Injectable Acrylic Bone Cements for Vertebroplasty with Improved Properties

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Abstract: Currently commercially available acrylic bone cements lack adequate radiopacity and viscosity when they are used in percutaneous vertebroplasty (PVP). In this work improved formulations of radiopaque and injectable poly(methyl methacrylate) bone cements were prepared with different amounts (10–50 wt.%) of $BaTiO_3$ or $SrTiO_3$ particles as the radiopaque agent. Two sets of cements were prepared by using untreated or silanated radiopaque particles, respectively. The influence of the content and nature of the radiopaque agent as well as its silanation with 3-(trimethoxysilyl) propyl methacrylate (γ-MPS), on the curing parameters, residual monomer content, radiopacity, mechanical properties, and injectability of the resulting materials, was examined. Doughing and setting times, maximum temperature, and compressive strength of all formulations fulfilled the requirements of standard specifications, with values of peak temperature in the range 57–72 °C and those of compressive strength between 114 and 135 MPa. Formulations containing at least 20 wt.% $BaTiO_3$ or $SrTiO_3$ had radiopacities equal to or greater than that corresponding to 2 mm of Al as required for surgical plastics. Injectability of any of the formulations provided 75–80 wt.% of the total mass manually injected through a conventional biopsy needle 4 min after mixing. Silanation of the $BaTiO_3$ or $SrTiO_3$ particles led to formulations with improved mechanical properties and injectability compared to those obtained with the untreated fillers.
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INTRODUCTION

Percutaneous vertebroplasty (PVP) is a therapeutic, interventional radiologic procedure that involves injection of a bone cement into a cervical, thoracic, or lumbar vertebral body lesion for the relief of pain and the strengthening of bone.[1–2] A large bore (10- to 15-gauge) needle is placed into the vertebral body lesion under radiological guidance from computed tomography scanning or fluoroscopy and the cement is then injected into the affected vertebra until the bone lesion is completely filled.

Currently, PVP is performed with commercially available PMMA bone cements, such as Simplex® P (Stryker-Howmedica-Osteonics, Rutherford, NJ), Osteobond® (Zimmer, Warsaw, IN), or Cranioplastic® (CMW, Blackpool, England). The United States Food and Drug Administration (FDA) approves only Simplex® P for use in treating pathologic fractures, including those in the spine. Simplex® P and Osteobond® contain 6.8 wt.% of $BaSO_4$ as the opacifier. However, this amount is insufficient for easy fluoroscopic visualization during PVP. Cranioplastic® contains no $BaSO_4$ and consequently is not intrinsically radiopaque. Other commercial radiopaque PMMA bone cements contain also $BaSO_4$ or ZrO_2, and their contents vary between 6.0 and 10.5 wt.%, still insufficient to provide the required radiopacity for PVP.[2,3] Therefore, all PMMA cements currently available require additional opacifier to ensure visualization under fluoroscopy. There are no reports on the value of radiopacity needed for cements used in PVP, although ASTM requires equivalent radiopacity of 2 mm of Al from plastic materials for medical use.[4] In Europe, tungsten and tantalum powders are commonly used as radiopacifiers in injectable acrylic bone cements, but the FDA has not yet approved them. In fact, the

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TABLE I. Values of Mass Absorption Coefficients for Various Radiopacifying Agents (in cm^2/g)

X-Ray Source		$BaTiO_3$	$SrTiO_3$	ZrO_2	$BaSO_4$	W	Ta
μ_0 (cm^2/g)[a]	$WK_{\alpha 1}$	5.43	1.86	2.94	5.33	3.87	3.71
	$MoK_{\alpha 1}$	33.02	52.12	12.69	29.3	102.46	98.95
	$RhK_{\alpha 1}$	20.63	34.60	53.02	18.2	64.74	62.43

[a]Calculated from the values of the mass attenuation coefficient, as a function of photon energy, for elemental media reported by the NIST.

risk associated with the corrosion products of finely powdered W and Ta particles has not yet been established. In the U.S., $BaSO_4$ is the predominant choice as the radiopacifier agent.[1,2] However, this material is considered potentially toxic, and it reduces the strength of the cement.[3]

An alternative to these traditional inorganic opacifiers is the use of radiopaque monomers incorporated in the liquid component of the cement. Bromine- and iodide-containing methacrylates and acrylates have been proposed for this purpose.[5] However, it appears that they do not provide adequate radiopacity to the cement when it is used in PVP.

Another disadvantage of the commercially available acrylic bone cements used in vertebroplasty is the lack of the adequate viscosity for injection. Consequently, the monomer–powder concentration ratio (MPR) must be increased. However, it should be noted that increasing a cement's MPR can lead to marked drops in some of its mechanical properties, such as elastic modulus, yield strength, and ultimate strength.[6]

In spite of the success claimed for PVP and the growing interest for this technique, there are only a few literature reports of studies dealing with injectable and radiopaque acrylic bone cement specially designed for this purpose.[7] Li et al.[7] reported excellent radiopacity and injectability of an acrylic bone cement containing strontium hydroxyapatite as the radiopaque agent.

A previous work prepared acrylic bone cements filled with $BaTiO_3$ and found a reinforcing effect of the filler for $BaTiO_3$ contents of 30 vol.-% or higher.[8] In addition, ferro- and piezoelectric properties exhibited by $BaTiO_3$ can potentially stimulate bone growth.[9] At the characteristic wavelength of the anodes that are most commonly used for X-rays of orthopedic implants *in situ*, the values of the mass absorption coefficients of $BaTiO_3$, $SrTiO_3$, and $BaSO_4$ are about the same (Table I). It should be kept in mind that μ_0 is a function of the energy of the X-ray photon and that the radiation emitted by commercial fluoroscopes and tomographs employed in PVP is unfiltered white radiation (polychromatic), so the values of μ_0 given in Table I for $K_{\alpha 1}$ lines may be used only as an approximation to the real picture. Finally, $BaTiO_3$ and $SrTiO_3$ are practically insoluble, and possess ferro- and piezoelectric properties.

Thus, the aim of this study was to develop novel injectable, radiopaque, and strengthened acrylic bone cements suitable for PVP, containing $BaTiO_3$ and $SrTiO_3$ as the radiopacifying agent. Such cements could also generate *in situ* electrical stimuli under biomechanical stress or polarize when submitted to an external electric field, thus increasing the rate of bone growth. The present article reports the preparation and characterization of the injectable formulations in terms of setting parameters, residual monomer content, and radiopacity. The study of these parameters are crucial to determine the further application of the formulations in PVP. Mechanical properties were analyzed through compression testing and SEM microscopy, because, as mentioned previously, the pain relief in PVP is mostly related with the stabilization of the vertebral body with regard to compressive forces. The radiopacifier was included in the formulation either untreated or silanated and the effectiveness of silane treatment was evaluated along with its influence on mechanical properties. Finally injectability of the developed formulations was evaluated according to the protocol currently applied by the surgeons.

MATERIALS AND METHODS

Poly(methyl methacrylate) (PMMA) beads (Plexigum M339, Rhom-Hass) with mean diameter of 33.10 μm and number and weight molecular masses of 64,000 and 130,000, respectively, were used. Benzoyl peroxide (BPO) (Fluka) was previously crystallized from methanol. 4-N,N-dimethylamino benzaldehyde (Fluka) and sodium borohydride (Merck) were used as received for the preparation of 4-N,N-dimethylamino benzyl alcohol, DMOH.[10] 3-(Trimethoxysilyl)propyl methacrylate (γ-MPS) (Acros Organics), methyl methacrylate (MMA) (Acros Organics), toluene (Acros Organics), tetrahydrofuran (Merck), deuterated chloroform (Merck), and tetramethylsilane (Merck) were used as received.

Opacifiers

Barium titanate ($BaTiO_3$) (Ticon® HPB, TAM Ceramics, Inc.) and strontium titanate ($SrTiO_3$) (Aldrich) with average particle size of 1.14 and 2.07 μm (water, Sedigraph, Micromeritics Instrument Co.), respectively, were used as received or after silane treatment with γ-MPS.

For silane treatment, 10 g of the opacifier, 0.35 ml of γ-MPS, 0.40 ml of water, and 200 ml of toluene were stirred and refluxed for 15 h. The treated powder was filtered and washed with fresh toluene in a Soxhlet apparatus for 24 h and then dried at 60 °C for 24 h.[11]

Preparation of the Cements

The powder component of the cements was prepared by mixing PMMA beads and the corresponding opacifier with

TABLE II. Composition of the Cements Prepared in this Work. Percentages Are Given with Respect to the Total Mass of the Cement

	Powder			Liquid		
Cement	PMMA (wt.%)	$MTiO_3$ (wt.%)	BPO (wt.%)	MMA (wt.%)	DMOH (wt.%)	P/L (parts in wt.)
M-10	59.52	10.00	0.89	29.29	0.30	2.38
M-20	49.52	20.00	0.89	29.29	0.30	2.38
M-30	42.53	30.00	0.80	26.40	0.27	2.75
M-40	34.25	40.00	0.75	24.75	0.25	3.00
M-50	27.11	50.00	0.67	22.00	0.22	3.50

Note: M for Ba or Sr

BPO. The liquid component consisted of dissolution of DMOH in MMA. The BPO and DMOH contents were always 3.0 wt.% and 1.0 wt.% of the weight of the liquid, respectively. Experimental cements were prepared by adding 0, 10.0, 20.0, 30.0, 40.0, and 50.0, wt.% of the opacifier, in accordance with the total weight of cement. The powder-to-liquid ratio was adjusted for each formulation, to ensure complete embedding of the powder by the liquid and allow greater than 4 min of dough time and 10–20 min of setting time. The compositions fitting these requirements are shown in Table II. In some experiments, a conventional nonfilled PMMA cement (PMMA, 65.67 wt.%; MMA, 33.00 wt.%; BPO, 1.00 wt.%; DMOH, 0.33 wt.%) was prepared and employed as control.

Setting Parameters

Setting parameters, that is, doughing time, $t_{doughing}$, setting time, $t_{setting}$, and maximum temperature, T_{max}, were measured as reported previously.[12] Samples weighing 3.0 ± 0.05 g were used. Both solid and liquid components of the cements were kept for at least 2 h at 23 ± 1 °C prior to the determinations. The average of two measurements was reported for each parameter.

Residual Monomer Content

Cured samples of radiopaque cements stored at room temperature (23 ± 1 °C) for 1 month were dissolved in deuterated chloroform (5 wt./vol.-%) containing tetramethylsilane as internal standard. The ^{1}H-NMR spectra were obtained with a Varian XL300 spectrometer and the residual monomer content was estimated from the signals of methoxyl protons of the MMA and the PMMA for the cements obtained with the untreated filler, and from the signals of vinyl protons of MMA and methoxyl protons of the PMMA for the cements containing the silanated fillers. For each cement formulation, three samples were tested.

Radiopacity Measurements

Radiopacity of the cements was determined as follows. Disks of 15 mm in diameter and 1.0 ± 0.1 mm in thickness were prepared by molding the cement dough in a Teflon mold pressed between two Teflon sheets by means of two screwed bronze plates. The mold with the specimens was kept at 37 ± 1 °C for 1 h at least, and the disks were grounded and finished with SiC-paper No. 400. Three disks of each material were glued on a sheet of paper next to an aluminum step wedge (0.5 mm steps, as in ISO 4049). The sheet of paper with samples and aluminium step wedge was placed on a Kodak PDS X-ray film sandwiched between Kodak Regular Screens, 100 cm below the exit window of an X-ray apparatus (Polymat 30M, Siemens). The film was irradiated during 2 ms (40 kV, 0.8 mA s) and then developed.

The absorbance of the developed films at the positions corresponding to sample and steps of Al determined by means of an ensemble composed by a cold light source (KL 1500, Schott) with a green filter, an optical conductor, a light detector (PT 171 C, International Light), and a radiometer (IL 700, International Light). A curve of absorbance versus mm of Al was plotted and the sample equivalent aluminum thickness was estimated from the curve and the sample absorbance. Radiopacity, expressed in equivalent mm of Al, was calculated as the quotient of the found equivalent Al thickness and the sample thickness, as in ISO 4049.[13]

Compression Testing

These tests were conducted using an Instron 4301 universal testing machine provided with a load cell of 5 kN, and at a cross-head speed of 20 mm/min. Cylindrical specimens of 6 mm in diameter and 12 mm high were prepared by forcing the cement dough into the holes of a Teflon mold. Both sides of the mold were covered with Teflon plates and secured with clamps. The specimens were cured for 1 h in the mold at 37 ± 1 °C, then removed from the mold, finished to a perfect cylindrical shape, and tested at least 1 week after aging in air at 23 ± 1 °C. For each cement formulation, six specimens were tested. The elastic modulus was calculated as the slope of the linear section of the stress–strain curve obtained.

SEM Microscopy

The external and fracture surface of M-50 cements were examined under an environmental scanning-electron micro-

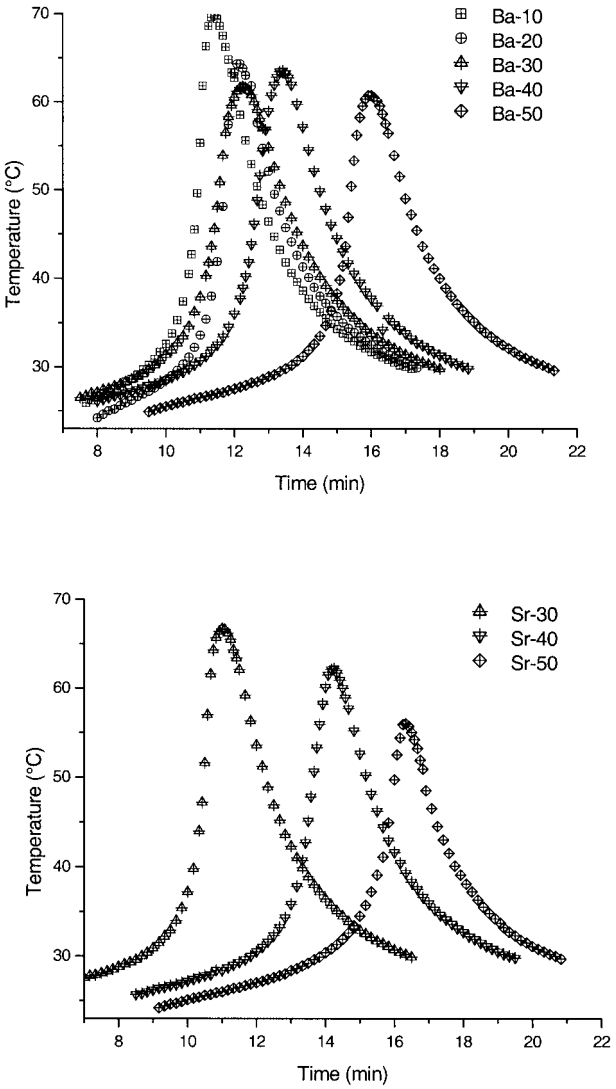

Figure 1. Typical time/temperature profiles for the curing of radiopaque cements charged with different amounts of untreated radiopacifying filler. Upper: $BaTiO_3$-charged cements; lower: $SrTiO_3$-charged cements.

scope ESEM XL30 (Philips). The external surface was polished with grinding paper No. 400, washed with distilled water, dried, and gold coated. The fracture surface of remaining pieces from the mechanical test was examined without any previous treatment.

Effectiveness of Silane Treatment

Samples of cements M-30 prepared with silanated and untreated opacifiers were extracted with tetrahydrofuran. The residue was filtered, exhaustively washed with tetrahydrofuran, and dried overnight at 60 °C. The remaining solid, along with silanated $BaTiO_3$ and $SrTiO_3$, were submitted to dynamic thermogravimetric analysis in a TGA7 thermogravimetric analyser (Perkin Elmer) coupled to a thermal analysis control unit TAC7/DX. Analysis was performed with 40–60 mg of sample in a platinum pan under nitrogen flow, at a heating rate of 10 °/min and in the range of 50–800 °C. For each cement formulation, three samples were tested.

Injectability

Solid and liquid components of the cements were kept for 2 h at 23 ± 1 °C before the determination. A total amount of 3.0 ± 0.1 cm^3 of cement was prepared and charged in a 2-cm^3 disposable syringe (Plastipak, Becton Dickinson). An 8-gauge needle (bone marrow biopsy/aspiration needle, Surecut BMB) of 150-mm length was fixed to the syringe and the cement injected to a Teflon recipient. Injectability was defined as the weight percent of cement injected into the recipient, expressed as a percentage of the total amount of cement charged in the syringe. The cement prepared with any of the untreated contrast agent was charged into the syringe and injected, 1 and 2.5 min, respectively, after the mixing of its components. For cements containing silanated contrast agents the charge and injection times were 2 and 4 min, respectively, except for the Ba-40 cement, which was charged into the syringe after 3 min, and injected after 5 min of the onset of the mixing. The injectability measurements were conducted in duplicate.

Statistical Analysis

The data obtained from mechanical testing, setting parameters, residual monomer content, and injectability measurements were analyzed by using multifactor ANOVA and multiple-range tests (Statgraphics Plus for Windows 2.1). The significance level considered in each case is indicated in the text.

RESULTS AND DISCUSSION

Setting Parameters

Exotherms of polymerisation are displayed in Figure 1. The values of the doughing times, setting times, and maximum temperatures for the cement formulations are presented in Table III. The maximum polymerization temperature of all

TABLE III. Values of the Doughing Times, Setting Times, and Maximum Temperatures of the Cements Formulated with Different Amounts of Untreated Radiopacifying Filler

Cement	$t_{doughing}$ (min)	$t_{setting}$ (min)	T_{max} (°C)
Ba-10	5.38 (0.53)	10.76 (1.55)	71.4 (2.3)
Ba-20	6.31 (0.31)	11.82 (0.35)	67.8 (4.7)
Ba-30	5.08 (0.63)	10.66 (0.94)	64.2 (3.9)
Ba-40	6.25 (0.50)	12.95 (1.55)	66.9 (3.0)
Ba-50	7.62 (0.18)	15.26 (0.09)	60.9 (0.3)
Sr-30	4.38 (0.18)	10.58 (0.31)	66.3 (0.6)
Sr-40	7.12 (0.53)	13.98 (0.79)	63.7 (2.1)
Sr-50	7.50 (0.00)	15.97 (0.62)	56.9 (1.3)

Note: Standard deviation in parentheses.

TABLE IV. Values of Residual Monomer Content of the Cements Prepared with Untreated or Silanated Radiopacifying Filler

	Residual Monomer Content (%)	
Cement	Untreated Filler	Silanated Filler
Ba-10	3.0 (0.2)	3.1 (0.6)
Ba-20	2.4 (0.1)	3.0 (0.3)
Ba-30	2.5 (0.2)	2.5 (0.2)
Ba-40	2.5 (0.2)	2.6 (0.2)
Ba-50	2.4 (0.3)	2.7 (0.3)
Sr-10	2.5 (0.7)	3.5 (0.1)
Sr-20	3.0 (0.5)	2.8 (0.5)
Sr-30	3.0 (0.6)	3.4 (0.4)
Sr-40	3.1 (0.4)	3.0 (0.3)
Sr-50	2.9 (0.6)	2.7 (0.3)

Note: Standard deviation in parentheses.

cements was below 90 °C, as required by ISO[14] and ASTM[15] standards, and lower than that obtained with commercially available formulations, for example, T_{max} of CMW 1RO was reported to be around 80 °C.[16] The ranges of the doughing and setting times were also within the limits specified in the standards,[14,15] and in the range of those presented in commercially available formulations.[16]

The higher the filler content of cements in Table II, the significantly higher the values of doughing and setting times (99% confidence level) and the lower the maximum temperature (95% confidence). No influence of the nature of the filler on the setting parameters was detected.

Setting time is a parameter related to polymerization rate. In the presence of fillers with small particle size and relatively large surface area, such as those employed in this work, part of the monomer liquid is immobilized on the filler surface. As a result, the effective viscosity of the monomer increases, and consequently, the polymerization rate decreases with the filler content.[17] On the other hand, the maximum temperature depends on the amount of heat produced as a consequence of the polymerization reaction of the monomer.[18] Therefore, the use of a lower amount of monomer in the formulation, that is, a higher P/L ratio, should give rise to a lower polymerization exotherm (see Table III and Figure 1). The observed maximum temperatures seem to be adequate according to ISO and ASTM standards; however, several authors relate pain relief in PVP practiced on vertebral tumors, to the malignant tissue necrosis and the destruction of sensitive nerve endings by the heat released during the exothermic polymerization reaction and the toxicity of the acrylic monomer.[19]

Although the setting parameters were only determined for cements prepared with untreated fillers, there are not firm

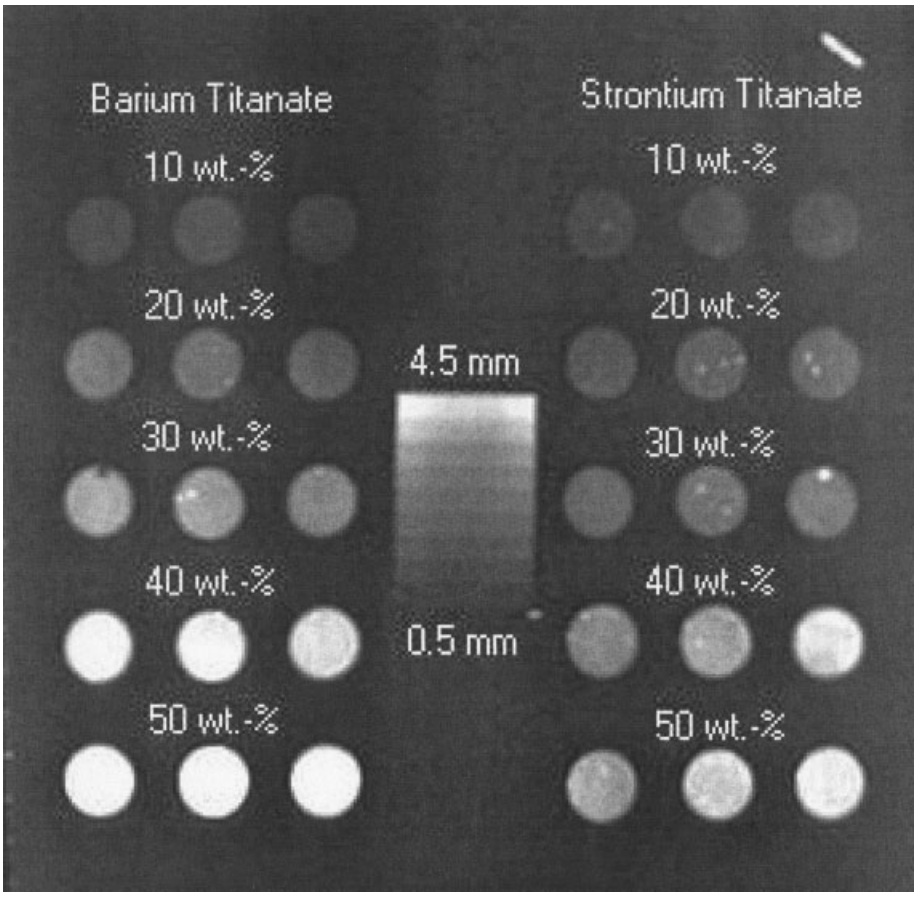

Figure 2. Radiography of cements containing different proportions of $BaTiO_3$ or $SrTiO_3$ along with aluminum step wedge.

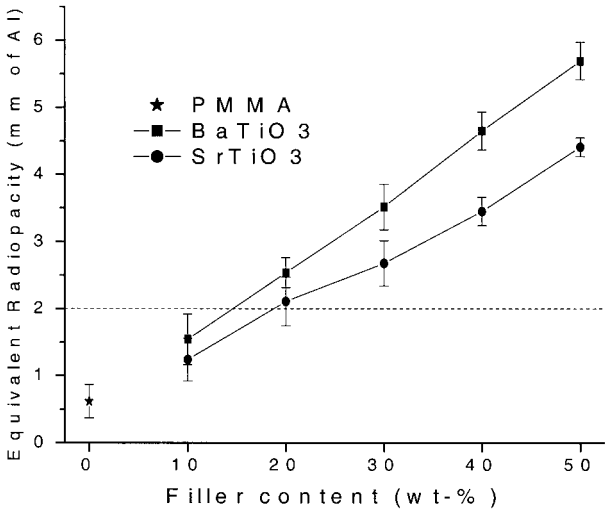

Figure 3. Variation of equivalent radiopacity of cements with the content of the radiopaque agent.

reasons to expect a significant change of their values when silanated fillers are used.

Residual Monomer Content

The content of residual monomer referred to the organic moiety for cements charged with untreated or silanated fillers is shown in Table IV. These values were within the range of those reported in the literature for acrylic bone cements.[20] No significant differences (95.0% confidence level) were obtained among the different formulations. Some workers[19] have attributed the efficacy of PVP for pain relief in tumored vertebral bodies to, in part, the toxicity of monomer released, both in the first stage of injection and after curing.

Radiopacity of the Cements

The radiographic images of samples of the untreated filler containing cements and the aluminium step-wedge, obtained after irradiating and developing films, are shown in Figure 2, with the equivalent radiopacity values being presented in Figure 3. Radiopacity was only determined for cements prepared with untreated fillers; however, because of the radiolucent nature of the silane agent no significant changes are expected for the radiopacity of cements prepared with the silanated fillers.

Presently, there is no radiopacity standard for cement preparations for PVP. Practitioners of PVP use several contrast agents and amounts, based on their own experience or empirical considerations. The present results (Figure 3) show that the radiopacities of formulations containing 20 wt.% or more of either $BaTiO_3$ or $SrTiO_3$ exceed the standard proposed by ASTM.[4]

Compression Properties

In spite of their brittle nature, the studied cements yielded under uniaxial compressive load and acquired a barrel shape and longitudinal cracks propagated parallel to the loading axis. Therefore, during the compressive testing, values of yield strength were obtained instead of ultimate strength. The results obtained for compressive yield strength are shown in Figure 4(a). All cements went beyond the minimum strength of 70 MPa required by ISO[14] and ASTM[15] standards. Multifactor ANOVA revealed no significant effect of the nature of filler ($BaTiO_3$ or $SrTiO_3$) on compressive strength. However, cements prepared with silanated filler exhibited significantly (99 % confidence level) higher strength than those prepared with untreated filler. The filler content also exerted a statistically significant effect at the same confidence level; however, this effect was only monotonically positive for silanated fillers (except for Ba-20). Among cements prepared with untreated fillers, only Ba-50, Sr-40, and Sr-50 had values of compressive strength significantly higher (95.0 % confidence level) than that corresponding to conventional unfilled acrylic bone cement. However, for cements contain-

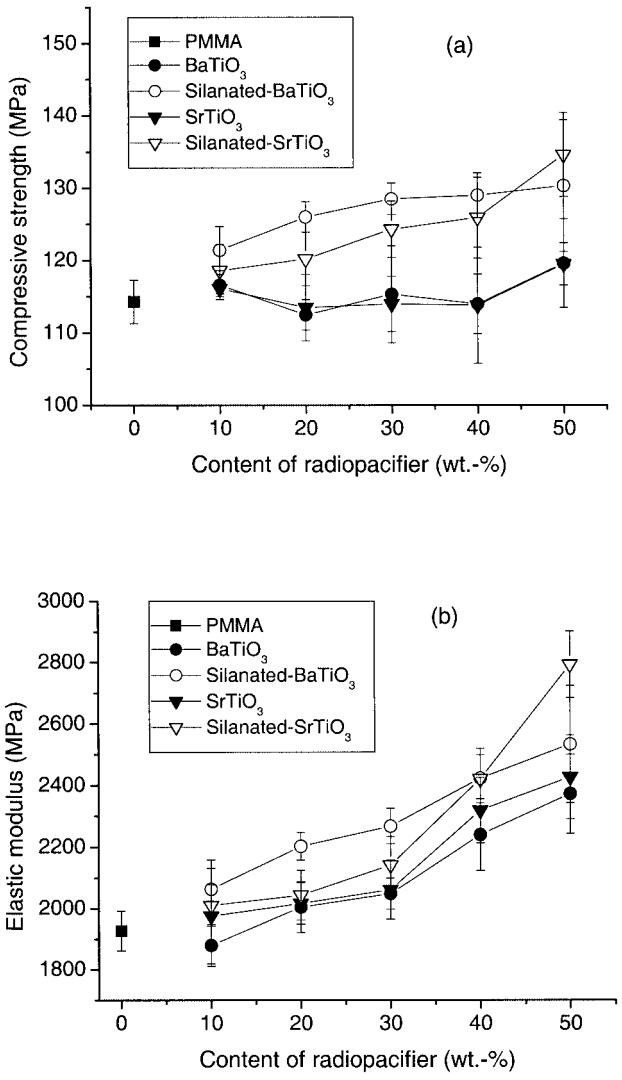

Figure 4. Variation of (a) compressive strength and (b) elastic modulus with the content of the untreated or silanated radiopaque agent for the cements in Table II.

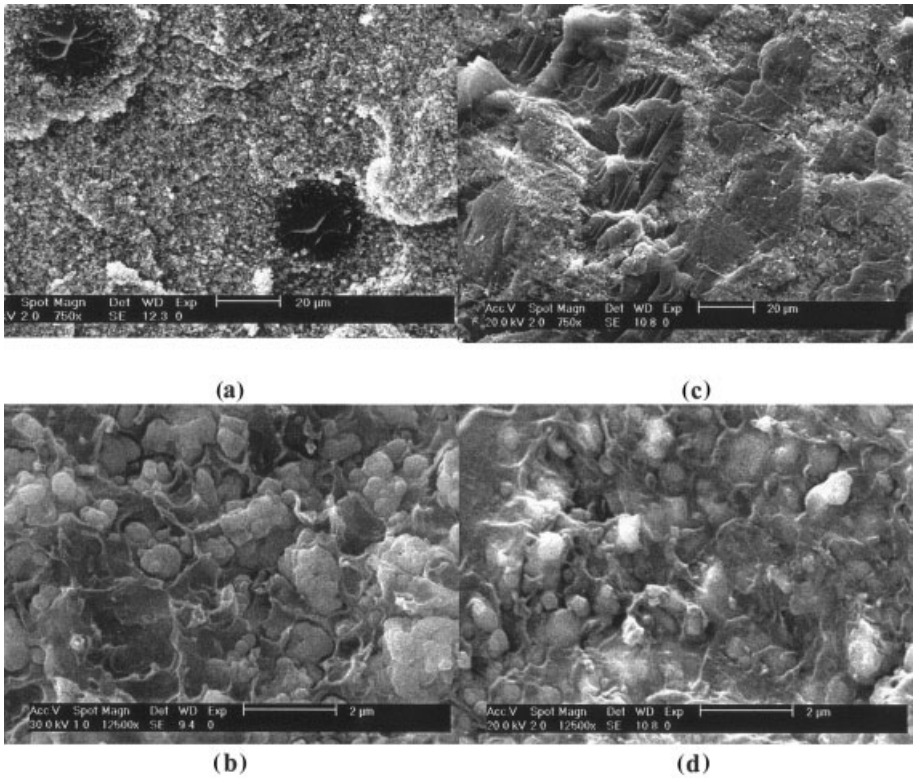

Figure 5. SEM micrographs of the fracture surface of cement Ba-50. (a) Filled with untreated $BaTiO_3$ (750 ×); (b) filled with untreated $BaTiO_3$ (12,500 ×); (c) filled with silanated $BaTiO_3$ (750 ×); (d) filled with silanated $BaTiO_3$ (750 ×).

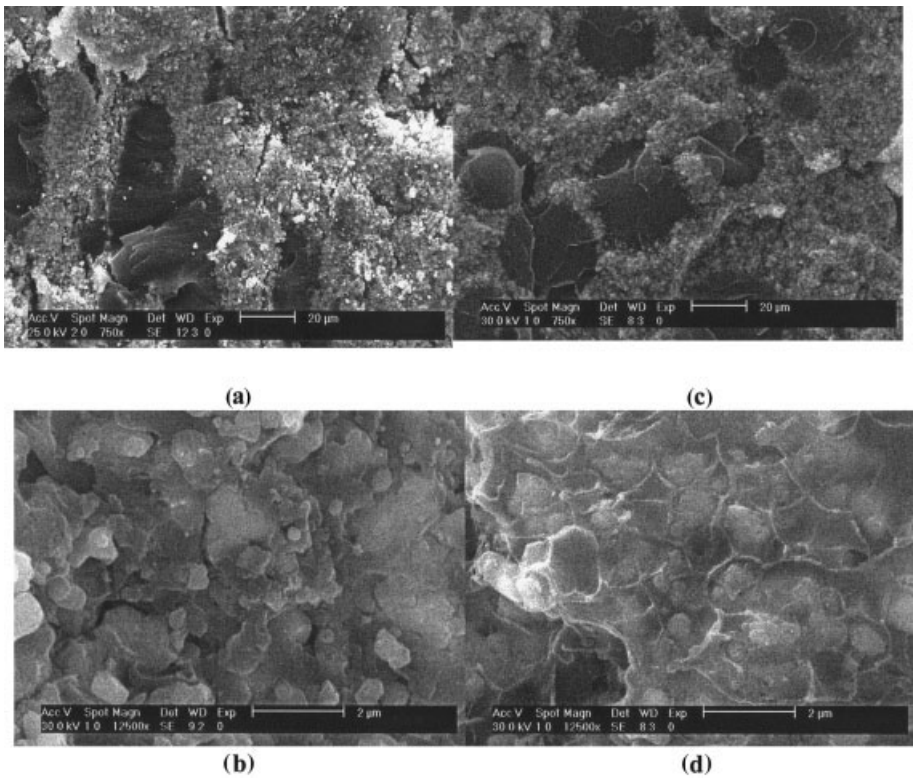

Figure 6. SEM micrographs of the fracture surface of cement Sr-50. (a) Filled with untreated $SrTiO_3$ (750 ×); (b) filled with untreated $SrTiO_3$ (12,500 ×); (c) filled with silanated $SrTiO_3$ (750 ×); (d) filled with silanated $SrTiO_3$ (12,500 ×).

ing silanated fillers, only Ba-20 and Sr-10 were not stronger than the conventional nonfilled PMMA cement.

Results of the variation of elastic modulus with the content of untreated or silanated radiopaque agent in the cement are plotted in Figure 4(b). Similar to compressive strength, elastic modulus is not significantly (95% confidence level) influenced by the nature of filler, but filler content and silanation do affect it positively (99% confidence level). Only for Ba-10 and Sr-10 charged with untreated fillers are the values of the elastic modules not significantly higher than that for the conventional nonfilled PMMA cement.

The elastic modulus of the selected filled cements significantly increased with filler content and silanation, as shown in Figure 4(b). The law of mixtures can predict the elastic modulus of a particulate composite on the basis of the mesophase concept:

$$E_c = E_f v_f k + E_m v_m + E_i v_i, \quad (1)$$

where E is the elastic modulus, v is the volume fraction, subscripts f, m, and i refer to filler, matrix, and mesophase, respectively, and k is a parameter describing the degree of bonding between filler and mesophase. The mesophase represents the zone of imperfections surrounding the filler particles and is considered to consist of a homogeneous and isotropic material of finite thickness.[21] According to this law, an increase in filler content (volume fraction of filler) and filler silanation (higher degree of bonding between filler and mesophase) should increase the elastic modulus, as shown in Figure 4(b).

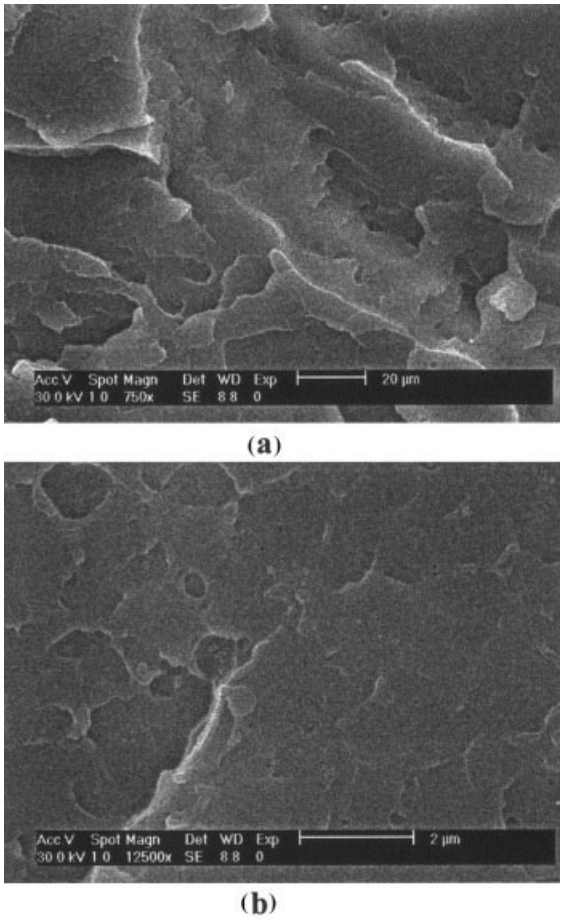

Figure 7. SEM micrographs of the fracture surface of conventional nonfilled PMMA cement. (a) 750 ×; (b) 12,500 ×.

SEM Microscopy

Selected images of the fracture surfaces of Ba-50 and Sr-50 specimens after compression testing are shown in Figures 5 and 6, respectively. For comparison purposes, in Figure 7 are presented micrographs of the fracture surface of conventional PMMA cement.

Examination of the micrographs of Figures 5(a) and 6(a), which were obtained at low magnification, reveals that cracks originating the fracture propagated through the composite matrix instead of PMMA beads for Ba-50 and Sr-50 cements prepared with untreated $BaTiO_3$ or $SrTiO_3$, respectively. However, when silanated fillers were employed [Figures 5(c) and 6(c)], the crack cut both composite and PMMA beads. These different behaviors can be explained in terms of the bonding strength at the interface between filler particles and polymer. Taking into account that a crack will travel through the route of lowest energy, the cohesion strength of the composite matrix for untreated fillers should be lower than that for unsilanated cement.

On the other hand, the fracture surfaces of charged cements, both untreated and silanated, were considerably rougher than unfilled PMMA cement (Figure 7). The increase in roughness implies longer crack path and greater fracture energy, which explain the reinforcing effect of fillers, both untreated and silanated.

At higher magnification [Figures 5(b) and 6(b)] the untreated filler particles seem to be pulled out from the polymeric matrix, and those remaining in the fracture surface are not bonded to the matrix. However, in the case of silanated filler [Figures 5(d) and 6(d)], the particles remained embedded and bonded to the matrix. This suggests that silanation of fillers effectively improves the bond strength at the filler–matrix interface. Similar microstructures have been described for the fracture surfaces of other charged acrylic bone cements.[22–23]

Effectiveness of Silane Treatment

The amount of volatile matter bonded to filler was determined by thermogravimetry, and the resulting weight-temperature curves are shown in Figure 8. The total weight losses were 0.58 wt.% for silanated $BaTiO_3$, and 3.24 and 0.83 wt.% for silane- and untreated $BaTiO_3$ recovered from cured cements. In the case of $SrTiO_3$, corresponding weight losses of 0.52, 2.65, and 0.71 wt.% were found. The weight loss of silanated fillers corresponds to desorption of physisorbed water and methacrylic acid and allylic radical loss.[24] For silanated fillers recovered from cured cements by dissolution of the polymeric matrix, the weight loss includes also the products of

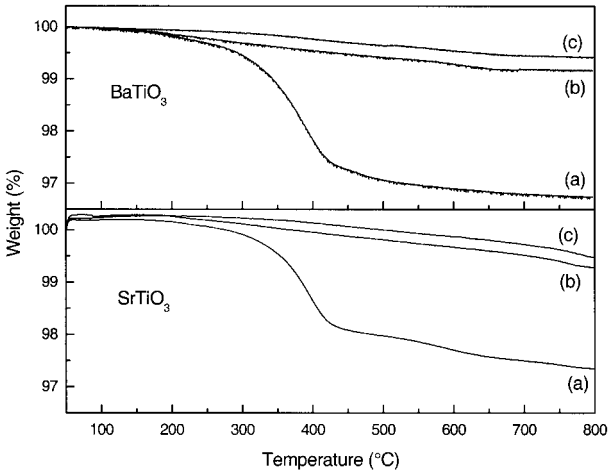

Figure 8. Thermogravimetric curves of (a) $MTiO_3$ silanated, extracted from M-30 cement; (b) $MTiO_3$ untreated, extracted from M-30 cement; (c) $MTiO_3$ silanated.

PMMA decomposition. The insoluble PMMA present in recovered fillers is covalently bonded to the filler surface, and its amount is considerably higher for silanated fillers. These results indicate that, for silanated fillers, a significantly higher amount of PMMA chains were covalently bonded to the surface of the filler through silane molecules. According to Abboud and co-workers[11,24,25] the silanation of Al_2O_3 filler with γ-MPS proceeds via hydroxyl groups corresponding to physisorbed water on the filler surface, as shown in the schematic representation of Figure 9. Before silane treatment, the filler surface is relatively hydrophilic and poorly wetted by the organic monomer. The grafting of γ-MPS onto the filler surface turns it hydrophobic and improves its wettability by organic liquids. Moreover, the acrylic group of the silane grafted onto the surface is able to copolymerize with the MMA monomer. Thus, grafted silane molecules act as bridges between the filler and the polymeric matrix. These silane bridges are covalently bonded to both the filler surface and the polymeric matrix, creating a strong interface and improving the reinforcing effect of the filler.

Similarly to silica,[26] glass,[27] alumina,[24] apatite-wollastonite glass ceramic,[27] and hydroxyapatite,[28,29] $BaTiO_3$ and $SrTiO_3$ powders were effectively silanated with γ-MPS, as evidenced by the thermograms in Figure 8. Silane treatment of the inorganic filler of the cement is a well-known approach in composite technology to achieve mechanically stronger composite cements. As a result of silanation, the inorganic filler can form stronger bonds with the organic matrix. Compression testing and SEM results showed that the silanated

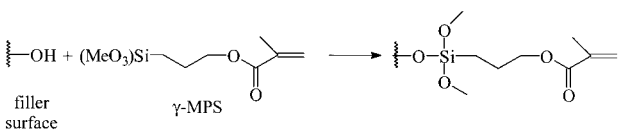

Figure 9. Schematic representation of silanation, according to Abboud and co-workers.[11,24,25]

TABLE V. Injectability of the Radiopaque Cements Prepared in this Work.

	Injectability (%)	
Cement	Untreated Filler	Silanated Filler
Ba-40	76.7 (0.6)	81.9 (0.0)
Ba-50	77.6 (3.8)	78.8 (2.4)
Sr-30	75.7 (4.2)	78.2 (2.2)
Sr-40	75.5 (3.7)	78.6 (0.1)
Sr-50	79.6 (1.0)	80.8 (0.5)

Note: Standard deviation in brackets.

fillers had a reinforcing effect, with values of compressive strength in the range 124.3–134.6 MPa [Figure 4(a)] and with their particles uniformly dispersed and intimately bonded to the organic matrix [Figures 5(d) and 6(d)]. The values of compressive yield strength were significantly higher than that corresponding to conventional unfilled PMMA bone cement (114.3 MPa).

INJECTABILITY

Injectability values measured for cements with equivalent radiopacity of 2 mm of Al or greater are given in Table V. Injectability significantly increased with silane treatment of the filler (95% confidence level). The positive effect of filler silanation on viscosity is the consequence of the better wetting of the filler particles by the organic moiety. Silanation of filler plays an important role during the mixing and precuring stages of the cements. The untreated particles of inorganic filler are hydrophilic because of the presence of hydroxyl groups or adsorbed water on their surface, and consequently are poorly wetted by the organic monomer. After silane treatment, surface hydroxyls condense with the Si-OH groups of hydrolyzed γ-MPS and form —O-Si-O— bonds with the silane molecule.[24] This surface modification permits the wetting of the particle by MMA monomer and explains the observed increase of powder embedding and fluidity and injectability of cement pastes with filler silanation (Table V), giving values of injectability in the range 78.2–81.9 wt%. Besides, a decrease in water uptake, referred to untreated fillers, should be expected for cements charged with silane-treated $BaTiO_3$ and $SrTiO_3$, according to results reported by Harper et al. for hydroxyapatite-reinforced PEMA bone cements. Water is able to bond to the hydroxyl groups available at the filler–organic matrix interfaces, via hydrogen bonding. In addition, the presence of the filler may introduce imperfections, which provide sites for water absorption. The presence of the silane inhibits the ability of the filler to absorb water by producing a hydrophobic surface upon it, and the better wettability minimizes the risk of imperfections at the filler–matrix interfaces. From a rheological point of view, this effect of silanation can be interpreted, as a deflocculant effect that reduces shearing stress and improves the flowing properties of the system.

In spite of the mentioned advantages of using silane-treated $BaTiO_3$ and $SrTiO_3$ in the formulations, further studies should be conducted to determine the effect of aging under simulated physiological conditions on the properties of the cements here described. In addition, the future work should also include a deeper study of the mechanical properties including flexural strength, and flexural and fracture toughness, along with determination of other relevant *in vitro* properties, such as osteoblast function or bone tissue formation.

Besides, simpler composite cements filled with 20–50 wt.-% untreated $BaTiO_3$ or $SrTiO_3$ also fulfilled with the requirements of ISO[14] and ASTM[15] standards. Thus, they should not be disregarded as potential bone cements for PVP, in spite of the improvements obtained with the use of the silanated filled composites.

CONCLUSIONS

Radiopaque and injectable barium and strontium titanate-filled bone cements were formulated and evaluated. Cements filled with 20–50 wt.% untreated or silanated $BaTiO_3$ or $SrTiO_3$ possess setting parameters (doughing time, setting time, and maximum temperature), compressive yield strength, radiopacity, and injectability that seem to be adequate for surgical procedures, such as PVP, where the injection of high contrast curable bone cements is required. The silanation of the $BaTiO_3$ or $SrTiO_3$ particles provides formulations with improved mechanical properties and injectability with respect to those obtained with the untreated fillers.

REFERENCES

1. Jensen ME, Evans AJ, Mathis JM, Kallmes DF, Cloft HJ, Dion JE. Percutaneous polymethylmethacrylate vertebroplasty in the treatment of osteoporotic vertebral body compression fractures: Technical aspects. Am J Neuroradiol 1997;18:1897–1904.
2. Mathis JM, Barr JD, Belkoff SM, Barr MS, Jensen ME, Deramond H. Percutaneous vertebroplasty: A developing standard of care for vertebral compression fractures. Am J Neuroradiol 2001;22:373–381.
3. Kühn KD. Bone cements. Up-to-date comparison of physical and chemical properties of commercial materials. Berlin: Springer; 2000.
4. American Society for Testing and Materials (ASTM). Test method F640-79. Standard test methods for radiopacity of plastics for medical use. Philadelphia: ASTM: 2000.
5. Vázquez B, Ginebra MP, Gil FJ, Planell JA, López Bravo A, San Román J. Radiopaque acrylic cements prepared with a new acrylic derivative of iodo-quinoline. Biomaterials 1999; 20: 2047–2053.
6. Jasper LE, Deramond H, Mathis JM, Belkoff SM. The effect of monomer-to-powder ratio on the material properties of cranioplastic. Bone 1999;25:27S–29S.
7. Li YW, Leong JCY, Lu WW, Luk KDK, Cheung KMC, Chiu KY, Chow SP. A novel injectable bioactive bone cement for spinal surgery: A developmental and preclinical study. J Biomed Mater Res 2000;52:164–170.
8. Carrodeguas RG, Vázquez B, San Román J, Madroñero A. Barium titanate-filled bone cements. I. Chemical, physical and mechanical characterisation. Int J Polym Mater 2002;51:591–605.
9. Feng J, Shao Q, Weng J, Li Y, Li J, Zhang X. An investigation on the ceramic composite of the biological piezoelectric implants. In: Feng H, Han Y, Huang L, editors. Proceedings of C-MRS International '90, Vol. 3: Polymers and biomaterials. Amsterdam: Elsevier; 1991.
10. Elvira C, Levenfeld B, Vázquez B, San Román J. Amine activators for the "cool" peroxide initiated polymerisation of acrylic monomers. J Polym Sci Polym Chem 1996;34:2783–2789.
11. Abboud M, Vol S, Duguet E, Fontanille M. PMMA-based composites materials with reactive ceramic fillers. Part III. Radiopacifying particle-reinforced bone cements. J Mater Sci Mater Med 2000;11:295–300.
12. Vázquez B, Elvira C, Levenfeld B, Pascual P, Goñi I, Gurruchaga M, Ginebra MP, Gil FX, Planell JA, Liso PA, Rebuelta M, San Román J. Application of tertiary amines with reduced toxicity to the curing process of acrylic bone cements. J Biomed Mater Res 1997;34:129–136.
13. International Organization for Standardization (ISO). ISO 4049: 2000: Dentistry-polymer-based filling, restorative and luting materials. Geneva: ISO; 2000..
14. ISO. ISO 5833:1992: Implants for surgery—Acrylic resin cements. Geneva: ISO; 1992.
15. ASTM. Specification F451-99a: Standard specification for acrylic bone cement. Philadelphia: ASTM.
16. Deb S, Vázquez B. The effect of cross-linking agents on acrylic bone cements containing radiopacifiers. Biomaterials 2001;22: 2177–2181.
17. Alvarez M, Davidenko N, García R, Alonso A, Rodríguez R, Guerra RM, Sastre R. Kinetic study of the photopolymerization of a bisphenol-A-bis(glycidylmethacrylate)/ triethyleneglycol dimethacrylate system in hydroxyapatite-filled composites. Polym Int 1999;48:699–704.
18. Pascual B, Gurruchaga M, Ginebra MP, Gil FJ, Planell JA, Goñi I. Influence of the modification of P/L ratio on a new formulation of acrylic bone cement. Biomaterials 1999;20: 465–474.
19. San Millán Ruíz D, Burkhardt K, Jean B, Muster M, Martin JB, Bouvier J, Fasel JHD, Rüfenacht DA, Kurt M. Pathology findings with acrylic implants. Bone 1999;25:85S–90S.
20. Willert HG, Frech HA, Bechtel A. Measurements of the quantity of monomer leaching out of acrylic bone cement into the surrounding tissues during the process of polymerisation. In: Biomedical applications of polymers. New York: Plenum; 1975.
21. Theocaris PS. The mesophase concept in composites. Berlin: Akademie; 1987.
22. Vallo CI. Influence of filler content on static properties of glass-reinforced bone cement. J Biomed Mater Res Appl Biomater 2000;53:717–727.
23. Ginebra MP, Albuixech L, Fernández-Barragán, Aparicio C, Gil FJ, San Román J, Vázquez B, Planell JA. Mechanical performance of acrylic bone cements containing different radiopacifying agents. Biomaterials 2000;23:1873–1882.
24. Abboud M, Turner M, Duguet E, Fontanille M. PMMA-based composite materials with reactive ceramic fillers. Part I. Chemical modification and characterisation of ceramic particles. J Mater Chem 1997;7:1527–1532.
25. Abboud M, Casaubieilh L, Morvan F, Fontanille M, Duguet E. PMMA-based composite materials with reactive ceramic fillers. Part IV. Radiopacifying particles embedded in PMMA beads

for acrylic bone cements. J Biomed Mater Res Appl Biomater 2000;53:728–736.
26. Davidenko N, García Carrodeguas R, Sastre R. Composites dentales: Efecto de la interfase y de otros factores sobre su durabilidad. Rev Plást Mod 2001;81:54–63.
27. Shinzato S, Kobayashi M, Mousa WF, Kamimura M, Neo M, Kitamura Y, Kokubo T, Nakamura T. Bioactive polymethyl methacrylate-based bone cement: Comparison of glass beads, apatite- and wollastonite-containing glass ceramic, and hydroxyapatite fillers on mechanical and biological properties. J Biomed Mater Res 2000;51:258–272.
28. Khorasani SN, Deb S, Behiri JC, Braden M, Bonfield W. Modified hydroxyapatite reinforced PEMA bone cement. Bioceramics 1992;5:225–232.
29. Dupraz AMP, Wijin JR, Meer SAT, Groot K. Characterization of silane-treated hydroxyapatite powders for use as filler in biodegradable composites. J Biomed Mater Res 1996;30:231–238.