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Optimization of benzoyl peroxide concentration in an experimental bone cement based on poly(methyl methacrylate)

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The effect of the concentration of benzoyl peroxide in poly(methyl methacrylate) bone cement formulations on their setting characteristics, particularly peak temperature and setting time, were studied. An optimization of the concentration of benzoyl peroxide was made with respect to curing parameters and compared with the residual monomer content. The mechanical properties of the different formulations were also determined and the results indicated that a composition of 1.5% wt/wt and 0.82% wt/wt of benzoyl peroxide and N,N-dimethyl-p-toluidine concentrations, respectively, gave the highest yield strength. Studies on the preparation of bone cement formulations containing different amounts of barium sulphate were also performed to assess the effect on the polymerization process and mechanical properties of the cements.

1. Introduction

Conventional acrylic bone cements are usually based on poly(methyl methacrylate). The bone cements are generally obtained by free radical polymerization of methyl methacrylate monomer (MMA) mixed with a solid phase containing beads of poly(methyl methacrylate), PMMA. The polymerization is initiated in the presence of benzoyl peroxide which is incorporated in the solid polymer phase. N,N-dimethyl p-toluidine (N,N DMPTA) is constituted in the liquid phase which acts as an activator for the reaction.

Self-curing acrylic cements are commercially available and have been used in dentistry and orthopaedic surgery as filling agents and for the fixation of joint prostheses such as knee and hip replacements. One of the major problems is, however, fixation into bony structure, so that the most frequent long-term complication is loosening of the prosthetic components. This effect has been considered to be caused by both mechanical and biological factors. As a consequence, many attempts have been made in order to improve bone cement formulations, and most of the studies in this field have been carried out on commercial cements due to their use in surgery [1].

Commercial bone cements have been studied extensively in the past [2–6] and some of the variables which affect the properties of acrylic cements have been investigated, such as cementing techniques [7, 8], ambient temperature [9] and *in vivo* conditions [10]. The influence of intrinsic variables such as the polymer powder to monomer ratio [11, 12], and the addition of radiopaque agents to the cement formulations has been discussed [13]. However, very little is known about the variation of the initiator, benzoyl peroxide, and accelerator, N,N DMPTA concentrations and their effects on the properties of the bone cement. The concentration of BPO and N,N DMPTA play an important role in the kinetic parameters. In a previous paper [14] we reported the preparation of an experimental bone cement where the effect of particle size and size distribution on setting parameters and mechanical properties were determined.

An attempt to optimize the initiator concentration in the solid component, while keeping a low DMPTA concentration in the liquid phase, was carried out. Bone cement formulations containing different concentrations of BPO were prepared in the absence of radiopaque agent. In addition, radiopaque bone cements containing barium sulphate were formulated with an optimum amount of benzoyl peroxide. The effects on the curing parameters, residual monomer and mechanical properties of all formulations were determined.

2. Experimental procedures

2.1. Materials

Methyl methacrylate monomer, MMA (Bonar Polymers), benzoyl peroxide, BPO (Peroxidechemie) and N,N-dimethyl-p-toluidine, DMPTA (Merck) were used as received. Poly(methyl methacrylate) commercial samples in the form of beads were supplied by

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TABLE I Morphological characteristics, molecular weight, tacticity and glass transition temperature of the PMMA solid component used in the preparation of acrylic bone cements

Diameter, D (μm)	33.10
Interval of D (μm)	10–60
$M_n \times 10^3$	97
M_w/M_n	1.78
Tacticity (P_m)	0.26
T_g (°C)	103

Industrias Quirúrgicas de Levante, IQL. The PMMA beads did not contain any benzoyl peroxide. The morphological characteristics, average molecular weight, M_n, and tacticity of the PMMA component are given in Table I. The corresponding parameters were determined by optical microscopy (D, μm), size exclusion chromatography (M_n), ^{1}H-NMR spectroscopy (tacticity), and differential scanning calorimetry, DSC (T_g). These PMMA beads present a rather sharp distribution with more than 80% of particles within a diameter in the range 10–30 μm, which is quite similar to that present in the CMW commercial bone cement.

2.2. Methods

The experimental cements based on these PMMA beads were formulated by adding the liquid component to the solid component at room temperature. A typical solid:liquid ratio of 2:1 was used in all cases. The liquid component consisted of a 0.816% w/w DMPTA solution in MMA monomer in all cases. The solid component consisted of PMMA beads to which the corresponding amount of finely ground BPO was added. In the first set of experiments, four formulations of bone cement containing 0.75, 1, 1.5 and 2% wt/wt of BPO were prepared in the absence of radiopaque agent. In a second set of experiments acrylic bone cements were formulated with the optimum concentration of benzoyl peroxide in the presence of barium sulphate. The solid/liquid ratio of 2/1 was maintained in these formulations.

The exothermic polymerization temperature was recorded according to ASTM standard (F451). The components were mixed and approximately 25 g of the dough was packed into the plunger cavity of the mould. A thermocouple was positioned within its junction in the centre of the mould at a height of 3 mm in the internal cavity. The plunger was subsequently seated on the filled mould cavity and tightened with a G-clamp. Time was measured from the onset of mixing the powder with the liquid and the temperature recorded.

Residual monomer was determined by means of proton NMR spectroscopy. Residual monomer was measured in all cases after the specimens were kept for 7 days.

Tensile testing was carried out at crosshead speed of 5 mm/min at room temperature (21 ± 1 °C) in an INSTRON machine with a cell load of 100 kN. An extensometer was used to measure displacement.

TABLE II Values of peak temperature, setting and dough times, and residual monomer, M_r, for formulations prepared with 0.82% wt/wt of DMPTA and different concentrations of BPO

BPO concentration (%)	T_{max} (°C)	Dough time (min)	Setting time (min)	M_r (%)
0.75	76	4.50	13.17	3.56
1	78	4.00	12.08	3.00
1.5	83	3.66	10.33	2.75
2	86	3.50	8.50	2.33

M_r = Residual monomer

TABLE III Values of ultimate tensile strength, UTS, Young's modulus, YM, and strain to failure, ε, of different cement formulations based on PMMA beads and prepared with different concentrations of BPO. The DMPTA concentration was 0.82% wt/wt in all cases

BPO concentration (%)	UTS (MPa)	YM (GPa)	ε (%)
0.75	44.09 (1.87)	2.60 (0.26)	2.81 (0.12)
1	46.31 (1.96)	2.57 (0.18)	1.97 (0.21)
1.5	55.32 (1.95)	2.95 (0.18)	2.66 (0.27)
2	43.59 (2.5)	2.40 (0.12)	2.02 (0.37)

Standard deviations in parentheses

3. Results

The morphological characteristics of the solid component, i.e., the PMMA polymer, is presented in Table I. The range of the concentrations of benzoyl peroxide used were from 0.75 to 2.0% by weight (Table II), the concentration of the DMPTA being kept constant at 0.82% by weight. The doughing time, polymerization exotherm, setting time and residual monomer are shown for each BPO concentration. An increase in the concentration of BPO was accompanied by an increase in the polymerization exotherm with progressively shorter doughing time and less residual monomer.

Mechanical properties of all specimens were analysed by performing tensile testing according to standard specification ISO 527-1. The average values of ultimate tensile strength, Young's modulus and strain to failure for different formulations are shown in Table III. It is clear from these values that the use of a low concentration (0.75% wt/wt) of BPO did not affect the tensile properties of the set cement. Additionally, this formulation provided the maximum value of strain to failure. This could be ascribed to the highest residual monomer content present in the set mass, which would act as an internal plasticizer allowing the molecules to reach higher deformation before failure. The mean ultimate tensile strength and the Young's modulus were found to increase with increasing BPO concentration, reaching a maximum for the 1.5% concentration. Any further increase showed a

TABLE IV Values of peak temperature, setting and dough times, and residual monomer, M_r, for formulations prepared with 0.82% wt/wt of DMPTA, 1.5% wt/wt of BPO and different amounts of barium sulphate

$BaSO_4$ concentration (%)	T_{max} (°C)	Dough time (min)	Setting time (min)	M_r (%)
0	83	3.66	10.33	2.75
6.25	80	3.50	10.75	2.79
12.5	81	3.62	10.42	1.80
18.75	81	3.58	10.33	2.17

M_r = Residual monomer

TABLE V Values of ultimate tensile strength, UTS, Young's modulus, YM, and strain to failure, ε, of cement formulations based on PMMA beads prepared with 1.5% wt/wt and 0.82% wt/wt BPO and DMPTA concentrations, respectively, and different amounts of $BaSO_4$ as a radiopaque agent

$BaSO_4$ concentration (%)	UTS (MPa)	YM (GPa)	ε (%)
0	55.32 (1.95)	2.95 (0.18)	2.66 (0.27)
6.25	43.76 (3.20)	3.11 (0.07)	1.66 (0.25)
12.5	39.17 (1.83)	3.27 (0.16)	1.36 (0.18)
18.75	35.73 (2.03)	3.52 (0.14)	1.18 (0.11)

Standard deviations in parentheses

reduction of the tensile strength and modulus. The curing kinetics in the presence of varying quantities of the radiopacifier, $BaSO_4$ are shown in Table IV, with a peroxide content of 1.5% by wt. An increase in the amount of barium sulphate did not produce any appreciable changes in the exotherm or doughing times (see Table V). However, a reduction in the ultimate tensile strength was observed in comparison to the unfilled cement.

4. Discussion

The most important chemical event taking place in the preparation of an acrylic bone cement is the reaction between benzoyl peroxide and N,N dimethyl p-toluidine, a chain growth by free radical propagation and chain termination. During the initiation process the N,N DMPTA, the polymerization activator, is the active ingredient which induces reaction of the BPO giving rise to the "benzoyl" free radicals capable of initiating polymerization, although not all the "benzoyl" free radicals produced, actually initiate polymerization. The efficiency can be as high as 80% and as low as less than 50% [2]. Some of the "benzoyl" free radicals and the other species produced in the reaction can undergo side reactions and create new types of impurities in the solidified bone cement mass. These new impurities could appear long after the polymerization of MMA has essentially stopped, via propagation and termination reactions. These effects occur

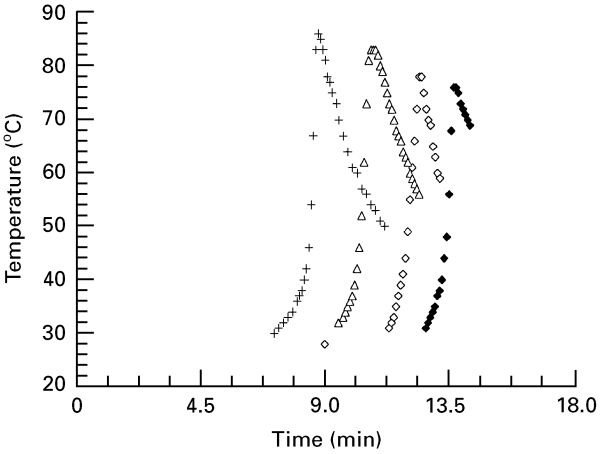

Figure 1 Polymerization exotherms of bone cement formulations prepared with 0.82% wt/wt of DMPTA and different concentrations of BPO: ◆ 0.75%, ◇ 1%; △ 1.5%, +2%.

due to the presence of residual BPO and N,N DMPTA, a highly reactive pair. On the other hand, BPO and N,N DMPTA concentrations are the variables controlling, to some degree, the rate of polymerization, which implies mainly differences in heat rise and heat dissipation. Peak temperature is expected to increase and the setting time to decrease by increasing both N,N DMPTA and BPO concentrations.

The BPO concentration of commercial bone cements ranges from 0.75 to 2.0% wt/wt while the N,N DMPTA concentration ranges from 2.0 to 2.75% wt/wt [2–6]. Most commercial formulations tend to contain an excess of N,N DMPTA in order to ensure total reaction of the initiator, an exception being the commercial CMW 1 cement with a N,N DMPTA concentration as little as 0.82% [15]. In this respect, it has been demonstrated in previous studies [14] that acrylic bone cements prepared by reducing the N,N DMPTA concentration to 1% v/v and the BPO concentration to 0.75% wt/wt possess adequate mechanical properties with values of tensile strength and elongation to failure higher than those obtained for formulations prepared with higher N,N DMPTA content. Subsequently, in order to optimize the initiator content a fixed N,N DMPTA concentration of 0.82% wt/wt was established and four formulations of experimental bone cement were prepared containing 0.75, 1, 1.5 and 2% wt/wt BPO concentration and 0.82% wt/wt DMPTA concentration. In the first set of experiments the cements were formulated in the absence of radiopaque agent to avoid the effect of particulate matter in the polymerization process.

In order to observe the variation in curing parameters with BPO concentration, exotherms were recorded, and are shown in Fig. 1. The exotherm curves obtained are the most representative curing parameters: peak temperature and setting time. The peak temperature is considered to be the maximum temperature reached during the polymerization reaction, and the setting time can be determined according to the ASTM standard (F451) as follows:

$$T_{amb} + (T_{max} - T_{amb})/2$$

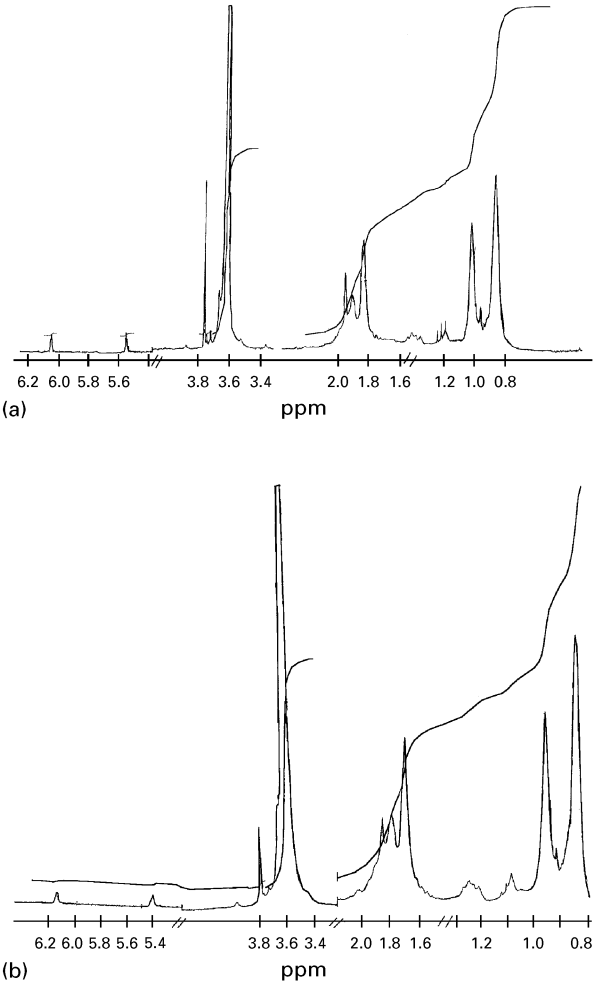

Figure 2 Proton NMR spectra of two formulations of bone cement prepared with (a) 0.75% and (b) 2% BPO concentration in the solid phase.

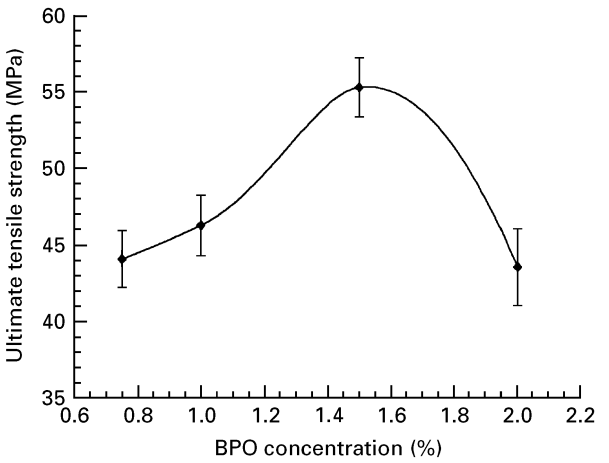

Figure 3 Ultimate tensile strength (UTS) versus BPO concentration for an acrylic bone cement based on PMMA beads.

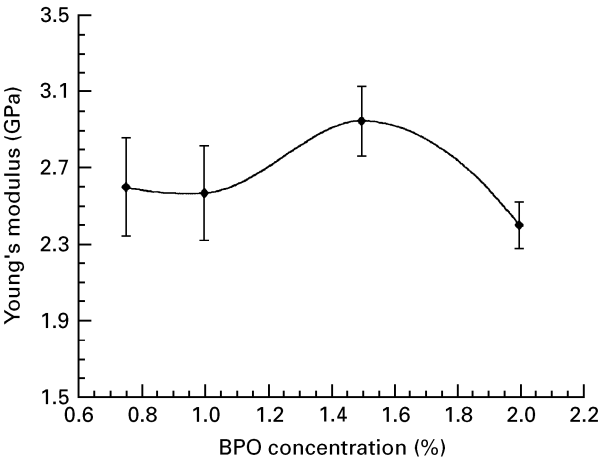

Figure 4 Young's Modulus (YM) as a function of the BPO concentration for an acrylic bone cement based on PMMA beads.

where T_{max} is the maximum temperature in °C and T_{amb} is the ambient temperature, 23 °C. As expected the peak temperature decreased with decreasing BPO concentration and it was found that the difference in peak temperature for the formulation prepared with the highest concentration of BPO and that prepared with the lowest concentration was approximately 10 °C. This fact should not be neglected as any decrease in the peak temperature is beneficial to the reduction of long-term necrosis, which is considered to contribute to loosening of the prosthesis [16]. On the other hand, the setting time increased with decreasing initiator concentration, with differences in the setting time of around 5 min for formulations prepared with the lowest and highest concentrations.

The residual monomer for each formulation was analysed by means of proton NMR spectroscopy. Fig. 2 shows the ^{1}H NMR spectra of two cements formulated with 0.75 and 2% wt/wt of BPO. The signals with chemical shift 3.78 δ can be assigned to the O–CH_3 groups of methyl methacrylate monomer and those at 5.58 δ and 6.10 δ to the acrylic methylene group, $=CH_2$. The very intense signal at 3.55 δ is assigned to the O–CH_3 group of methacrylate units incorporated into the polymeric chains. The percentage of monomer present in the total sample ($\%M_r$) was calculated using the following expression [17]:

$$\%M_r = (1.5 \times A_v/A_m)100$$

where A_m is the average of the methoxyl integral, A_v is the average of the vinyl integral and 1.5 is a factor relating the number of protons in the vinyl region (two) to those in the methoxyl group (three). The values of $\%M_r$ for formulations prepared with different BPO concentration in the solid phase are shown in the fifth column of Table II. These values lie in the range of those reported in the literature [2] and this shows that the use of low concentrations of initiator does not involve incomplete polymerization.

On the other hand, the cement prepared with 1.5% wt/wt BPO concentration gave rise to maximum values of ultimate tensile strength and Young's Modulus, and also to a considerably higher value of strain to failure (Figs 3–5). In this case this high value of strain to failure could not be explained by the residual monomer content since this is quite similar to that present in other formulations, e.g. the cement formulated with 1% wt/wt BPO concentration. The increase of the tensile properties when using 1.5% wt/wt BPO concentration could be due to obtaining an optimum average molecular weight of the PMMA

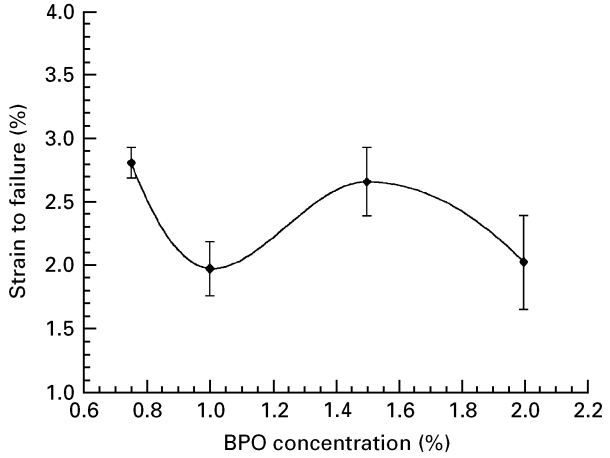

Figure 5 Strain to failure versus BPO concentration for an acrylic bone cement based on PMMA beads.

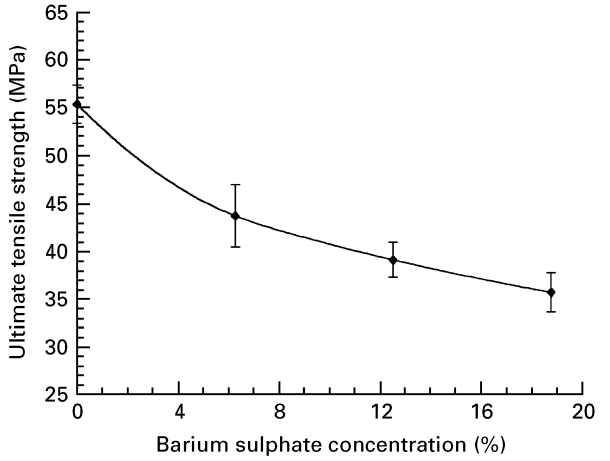

Figure 7 Ultimate tensile strength (UTS) versus barium sulphate concentration for an acrylic bone cement based on PMMA beads.

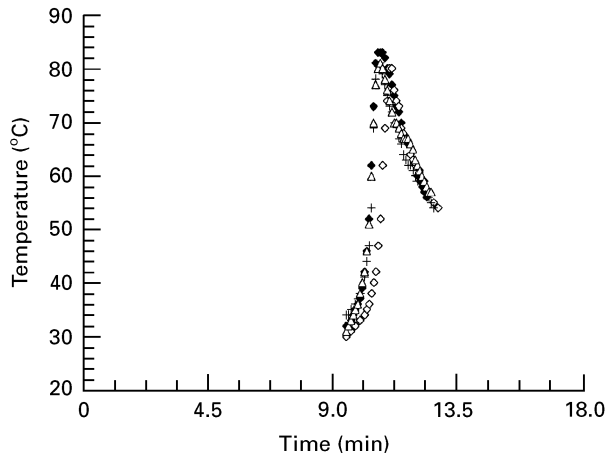

Figure 6 Polymerization exotherms of bone cements prepared with 1.5% wt/wt and 0.82% wt/wt of BPO and DMPTA, respectively, and different amounts of barium sulphate: ◆ 0%; ◇ 6.25%; + 12.5%; △ 18.75%.

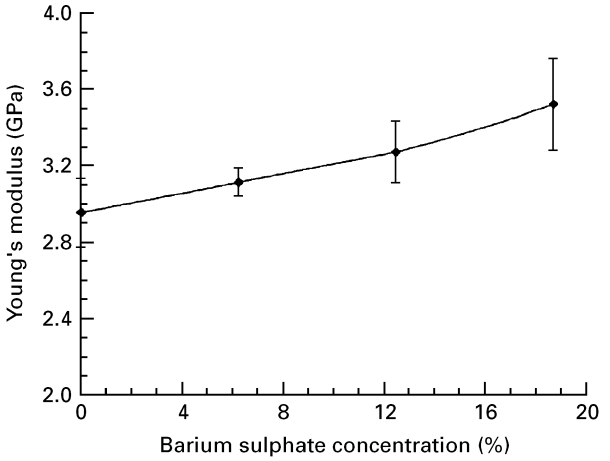

Figure 8 Young's modulus (YM) as a function of the barium sulphate concentration for an acrylic bone cement based on PMMA beads.

chains formed after the free radical polymerization promoted by the initiator BPO.

Finally, experiments were carried out on the effect of adding barium sulphate as a X-ray contrast material to the powder prior to mixing. The cements were formulated with the optimum BPO concentration. It can be seen from Fig. 6 that the addition of barium sulphate did not affect the curing characteristics of the cement, which is in agreement with the results reported in the literature [3, 4].

A decrease in both ultimate tensile strength (Fig. 7) and strain to failure (Fig. 9), and an increase of Young's modulus (Fig. 8) with increasing amount of barium sulphate particles in the formulation were observed. The increase of Young's modulus with increasing barium sulphate content could be a result of the addition of a second phase with elastic properties very different from those of the acrylic matrix, as some studies on poly(methyl methacrylate) bone cements modified with hydroxyapatite have shown [18, 19]. On the other hand, a decrease in the tensile strength with increasing concentration of the radiopaque agent is expected, and can be explained by

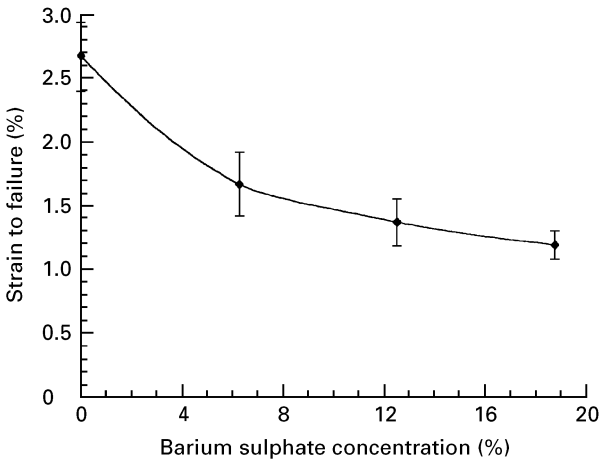

Figure 9 Strain to failure versus barium sulphate concentration for an acrylic bone cement based on PMMA beads.

the lack of adhesion between the organic polymer PMMA and the inorganic particulate matter: different commercial bone cements show similar behaviour after incorporation of radiopacifiers [4, 20]. Also, the work reported by J. Rudigier *et al.* [20] revealed that

the decrease in tensile strength is dependent on the type of radiopaque agent. They found that barium sulphate mixed with bone cement reduced the maximum tensile strength to a greater extent than zirconium dioxide in the same concentration, the decrease obtained by adding barium sulphate being twice as much. The substitution of barium sulphate by zirconium dioxide or another radiopaque agent will be the subject of further studies.

5. Conclusions

The present study revealed that the concentration of benzoyl peroxide had a marked effect on the setting kinetics of the cement and residual monomer content. Although the use of low BPO concentration resulted in a more ductile material, probably caused by internal plasticization due to the presence of higher residual monomers, the setting and doughing time were too long for ideal handling of the cement. An optimum of 1.5% by weight of benzoyl peroxide was found to yield suitable handling characteristics along with good mechanical properties. The inclusion of the radiopaque agent, barium sulphate did not affect the setting kinetics adversely, however, the tensile modulus progressively decreased with increasing concentration of barium sulphate.

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