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Preparation of acrylic bone cements for vertebroplasty with bismuth salicylate as radiopaque agent

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Dedicated to Cecilia Sarasola

Abstract

One of the problems of percutaneous vertebroplasty attributed to the use of acrylic cements is related to the radiopacity of the formulation. The use of bismuth salicylate as the radiopaque agent is proposed in this work, taking into account the high radiopacity of organobismuth compounds used in dental applications and the possible analgesic effect of salicylic acid. Various cements formulated with this compound (some of them modified with polyethylene oxide) were examined. Setting parameters, mechanical properties, rheological behaviour, injectability, radiopacity and biocompatibility were studied for a variety of formulations, showing that the cement formulations containing bismuth salicylate have a higher radiopacity and better injection properties than commercial bone cement preparations and present good mechanical properties.

Keywords: Acrylic bone cements; Rheology; Injectability; Radiopacity

1. Introduction

In the world of spinal surgery, the injection of bone cement by minimally invasive techniques for the treatment of spinal fractures or for stabilization of an osteoporotic vertebra is regarded as highly promising. Nowadays, percutaneous injection of poly(methyl methacrylate) (PMMA) is the most widely used technique [1]. Although it has been demonstrated that the relief of pain and the recovery of stiffness of the vertebral bodies is obtained, some problems arise when using this technique. The problems associated with the use of cement are basically its high viscosity and a radiopacity that is insufficient to adequately observe the injection process and ensure the perfect location of the reinforcement. Up to now, the surgeons have found their own solutions, i.e. changes in powder to liquid ratio [2] and addition of metallic powders [3] that enable the use of commercial cements in operating conditions. Given that the clinical significance of these changes is yet to be determined, there is a clear need for the controlled modification of these acrylic cement formulations. From the above, changes in rheological properties and an increase in the radiopacity of acrylic cements is the best way to obtain the sought performance.

The rheological properties have been dealt with in an other paper [4] and we propose to deal with the subject of radiopacity enhancement in this one. Taking into account the good results offered by bismuth compounds [5], we have chosen bismuth salicylate (BS) as the radiopaque agent. BS is a drug used to relieve indigestion and abdominal cramps, among other

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medical problems [6]. From the point of view of rheology, BS is an organic powder with small-sized particles which should not increase to a large extent the viscosity of the cement mixture. Other organobismuth radiopacifying additives, i.e. triphenylbismuth, have been used as radiopaque monomer-miscible agents for dental acrylic resins [7–9], producing homogeneous radiopaque materials which show enhanced mechanical properties over conventional formulations [5]. This led us to prepare cements in which BS was previously dissolved in the monomer. Finally, the interfacial behaviour of radiopaque particles has been another subject of research [10–12]. In this way, polyethylene oxide (PEO) was used as an interfacial agent to coat the organobismuth compound, since PEO seems to have bioactivity in contact with bone causing calcification within the near surface of the material [13].

Thus, the purpose of the current study was to measure the effect of replacing the radiopaque agent used in conventional cements with BS, incorporated in three different ways, on some properties of acrylic bone cement.

2. Materials and methods

2.1. Materials

The liquid component consisted of methyl methacrylate for synthesis (MMA) (Merck) stabilized with hydroquinone, used as received, and *N*, *N*′, dimethyl-4-toluidine for synthesis (DMT) (Merck), used as activator of the polymerization reaction. The solid component consisted of PMMA beads (mean diameter 118.4 μm, Colacryl-Bonar), benzoyl peroxide for synthesis (BPO) (Merck) as initiator and pure bismuth (III) salicylate basic (Fluka) as radiopaque agent. Barium sulphate for radiological examination (Merck) was also added in a number of samples and PEO (Hoechst) with $M_w = 20\,000$ was used to coat the BS particles.

2.2. Methods

2.2.1. Specimen preparation

The bone cements were formulated with a typical solid/liquid ratio of 2/1. In all cases 1% (v/v) of DMT in the liquid component and 1.25% (w/w) of BPO in the solid component were added. Specimens with 5, 10, 15 and 20% (w/w) of BS were prepared as follows:

(a) Adding the radiopaque agent as supplied in the solid component (BS formulations).
(b) Adding BS previously coated with PEO (BSPEO formulations) in the solid component. The coating was applied by dispersing the BS particles in a 5% (w/w) of PEO solution in distilled water.
(c) Dissolving BS in the monomer (BSDM formulations), i.e. in the liquid component.

Two cements were used as references, one in which the solid phase consisted only of PMMA beads and the initiator (radiolucent cement) and the other which included as well 10% of $BaSO_4$ in the solid phase (conventional cement).

The preparation of acrylic bone cement samples for the determination of residual monomer and mechanical testing was carried out following the method used for classical bone cements described in the ISO 5833 (1992) standard [14]. The components of bone cement were hand-mixed and before the dough state was reached the mass was placed in the corresponding Teflon mould and allowed to cure for 1 h at 37 °C.

2.2.2. Characterization

BS and BSPEO particle size analyses were carried out by means of a laser diffraction analyser (LS Beckman Coulter) using the Fraunhofer optical model with a run length of 90 s. Previously, samples were dispersed in *n*-heptane and 3 min of ultrasound was applied in order to prevent formation of clusters of the particles.

Setting parameters were determined according to the ISO 5833 Standard [14]. The maximum temperature (T_{max}) attained by the bulk was recorded and the setting time (t_{set}) was determined as the time taken to reach a temperature midway between room temperature and T_{max}. The given values are the mean of at least two determinations.

For the setting parameters and the characterization of physical and mechanical properties, mean and standard deviation values were calculated using the one-way ANOVA statistical technique. The error protection method used in this investigation was the Fisher PLSD method and the confidence interval used was 95%.

The residual monomer content was estimated by means of proton nuclear magnetic resonance (1H-NMR) spectroscopy as described in previous papers [15]. Samples were dissolved in deuterated chloroform containing tetramethylsilane as internal standard to obtain the spectra in an FT-NMR Bruker spectrophotometer operating at 300 MHz.

Water absorption of any polymeric material is of importance for surgical applications since it influences the mechanical properties of the cement and monomer release. Moreover, water absorption can lead to the hydrolysis of the salicylic salt and its subsequent release. Thus, specimens were immersed in a saline solution of NaCl 0.9% at 37 °C for one month. Water absorption (%*A*) and the percentage of elution (%*E*) of the cements were calculated using the following expressions (Eqs. (1) and (2)) [16]:

$$\%A = \frac{M_w - M_f}{M_0} \times 100, \tag{1}$$

$$\%E = \frac{M_0 - M_f}{M_0} \times 100, \tag{2}$$

where M_0 is the dry sample weight, M_f the dry weight after testing and M_w the weight at the equilibrium absorption point.

Due to the high tendency of the ester groups to hydrolyse and also, in this case, due to the potential clinical effects of salicylic acid, measurement of the released acid takes on a heightened importance. The salicylic acid was measured by means of UV spectrophotometry (UV CECIL CE2041) taking the signal at a wavelength of 297.0 nm, from an aliquot of