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New acrylic radio-opaque cement

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Cements for orthopaedic or dental surgery are made radio-opaque by using Barium salts or Zirconium oxide particles. We have developed new radio-opaque acrylic cement without such inorganic materials. These cements were obtained by the partial replacement of poly(methyl methacrylate) from the standard cement composition with methacryloyl-oxyethylene phosphate as barium salt, or by the replacement with a copolymer made of methacryloyl-oxyethylene phosphate-barium salt with methyl methacrylate. The final cements were characterised by X-ray radio-opacity and mechanical resistance. The use of methacryloyl-oxyethylene phosphate-barium salt is the optimum solution for obtaining radio-opaque cements with improved mechanical properties.

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1. Introduction

Acrylic bone cements mainly consist in poly(methyl methacrylate) (PMMA) and have been used in orthopaedic surgery and dentistry for more than forty years [1-6]. In orthopaedic surgery, bone cements serve as a mechanical interlock between the metallic prosthesis and the bone. PMMA cements are usually composed of preformed PMMA beads being mixed with methyl methacrylate (MMA) monomer or a mixture of MMA and butylmethacrylate (BMA). The polymerisation process occurs as a result of the reaction between benzoyl peroxide in the polymer powder and N, N-dimethyl-p-toluidine in the monomer; the acrylics can be polymerised by a free radical chain reaction process. Prior to the application, the powder and the liquid parts are mixed until soft dough is obtained and then applied to the desired bone cavity. Acrylic bone cement hardens in the following minutes, due to the rapid polymerisation reaction.

To follow the healing process after surgery, it is important that the cement is radio-opaque. In the commercial bone cements, this is achieved by the addition of an inorganic compound, like barium sulphate ($BaSO_4$) or zirconium dioxide (ZrO_2) [7]. The addition of a contrast agent influences the mechanical behaviour of the acrylic cement. A weakened resistance has been attributed to several factors, for example, the agglomeration of X-ray opaque powder, weak interfaces between the filler materials and matrix, presence of bubbles, etc. Thus, it is desirable to find an alternative for the use of the radio-opaque additives. What was considered particularly promising was the synthesis of a radio-opaque monomer, or copolymers having covalently heavy atoms. In the first case, the copolymer is formed during self-curing, when the radio-opaque monomer reacts with MMA; in the second case, the radio-opaque copolymer is mixed in the powder component of the cement.

The aim of the present study was to develop such systems based on the use of methacryloyl-oxyethylene phosphate (MOEP), used to obtain biocompatible polymers able to induce hydroxyapatite formation [8-14], which can form salts with heavy radio-opaque metals such as barium and which can copolymerise with MMA.

2. Materials and methods

Materials. MMA (Merck) was purified by distillation *in vacuo* (T=47°C, p=100 mmHg). Its comonomer, MOEP (Aldrich) and also the precipitant polymerisation medium used, dibutylether of diethylene glycol (DBEDEG) (Merck) were used as such without further purification). Benzoyl peroxide (BPO), N,N-dimethyl-p-toluidine (DMPT) were also purchased from Merck. In order to obtain the methacryloyl-oxyethylene phosphate-barium salt (MOEP-Ba) salt, barium hydroxide $Ba(OH)_2 \cdot 8H_2O$ (Fluka) was used as saturated solution. PMMA pearls were obtained by suspension polymerisation in the presence of benzoyle peroxide and using poly(vinyl alcohol) (PVA) 88% degree of hydrolysis as a stabiliser. The kit for orthopaedic surgery used as standard was "Cerafixgenta BV''-Low Viscosity-CERAVER Department Biomatériaux-Paris.

Methods

I. Synthesis of copolymers MMA/MOEP (COP)

a) Copolymerisation in precipitant solution

The two monomers ([M1] + [M2]) = 2 moles/l were mixed together with the solvent (DBEDEG) and the initiator ([BPO] = 10^{-2} mole/l) in polymerisation ampoules. After conditioning under nitrogen atmosphere, the ampoules were sealed and kept at reaction temperature (80°C) for two hours to reach maximum possible conversion. After polymerisation, the content of the ampoules was diluted with methanol, filtered on filter crucible and washed with methanol. For the complete removal of the monomers and DBEDEG, the precipitant was subjected to methanol extraction at room temperature for 24 hours, followed by filtration and drying up to constant mass. For further use, the copolymer was grinded by gentle milling and sieved, then the fraction with particle size (d_m)<100 μm was retained.

b) Bulk copolymerisation

The monomers and the initiator [BPO] = 10^{-2} moles/l were dosed in glass ampoules with the dimensions 4×20 mm. They were introduced in sealed tubes under nitrogen atmosphere, which were immersed in the thermostatic bath (T=80°C) for six hours reaction time.

After observing the formation of the compact block copolymer by spontaneous detaching of the reaction mass from the interior walls (due to polymerisation shrinkage), the glass tubes were cooled, the ampoules were removed and broken to recover some cylindrical glassy rods. They were cut into cylindrical shapes of 10-15 mm length, which were then conditioned by extraction in methanol (24h) at low temperature and dried up to constant mass.

c) Suspension polymerisation

The polymerisations were performed in reactors (V=100 ml) equipped with stirring, reflux condenser, nitrogen bubble flask, and joint for samples evacuation. In the reactor heated at polymerisation temperature, water and PVA were introduced. After the complete dissolution of the stabiliser, the initiator solution was added to the mixture of the two monomers. The mixture was kept at the same temperature (70°C) until the samples extracted from the reaction mass proved the formation of the pearls with higher density than water ("sinking" sample) and glassy consistency. From this moment, a step-by-step increasing temperature programme up to 85°C was applied (10°C/0.5h), to consume the residual monomer. Finally, the reaction mass was immersed in a volume of cold water 10-20 times higher and the polymer suspension was purified by repeated water washing. After filtration and drying, the crusts and agglomerates were removed by coarse sieving, and then fractionated sieving was performed for granulometric distribution evaluation. For further processing, the fraction with d_m<100 μm was retained. Similarly, it was obtained the PMMA used for the final cements.

In the case of the suspension with barium hydroxide ($Ba(OH)_2$) treatment *in situ*, the PVA was replaced by $Ba(OH)_2$ so that the total neutralisation of MOEP from the monomers mixture was achieved.

The following reaction parameters were used in the case of suspension polymerisation:

- [BPO] in monomer = 2%
- [PVA] in water = 0.2%
- Organic phase/aqueous phase = ½ (vol/vol)

II. Treatment with $Ba(OH)_2$

a) Copolymers MMA/MOEP (COP-Ba)

The copolymers were kept at room temperature under gentle stirring in saturated solution of $Ba(OH)_2$ for 24 hours. The volume used was pre-established so that it contained twice of the stoechiometric quantity of $Ba(OH)_2$ vs. total concentration of MOEP from the copolymer. The COP-Ba copolymers were separated by filtration, washed with distilled water up to neutral pH and dried up to constant mass. The determination of the degree of Ba fixation was done either by the estimation from mass increasing or by the residual $Ba(OH)_2$ dosage from the filtration effluent. Titration was performed with 0.02 N oxalic acid solution, in the presence of phenolphthalein.

b) Treatment of MOEP with $Ba(OH)_2$ (MOEP-Ba)

The MOEP (2g) was added at 70°C in saturated solution of $Ba(OH)_2$ (3g $Ba(OH)_2 \cdot 8H_2O$ in 55 ml water) in a well-stirred crystalliser tank. The reaction mass was kept under continuous stirring during the spontaneous cooling at room temperature. The obtained precipitate was separated by filtration, washed with distilled water and dried (40-50°C) under vacuum. The possible structures of MOEP-Ba are presented below (Fig. 1).

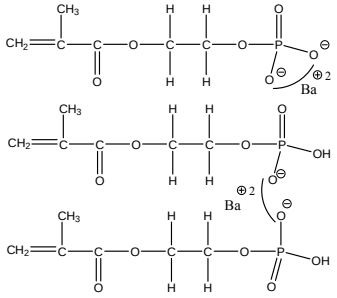

Fig. 1. The structures of MOEP-Ba

III. Cements' hardening at room temperature

The solid component of the cement was obtained through PMMA mixing with COP-Ba or MOEP-Ba and BPO (2.5% by weight from total mixture). The liquid component consisted of MMA and N,N-dimethyl-p-toluidine (1.5% by weight). The mass ratio between PMMA/MMA/COP-Ba was kept constant and equal to 3/2/1.

In order to make out the samples for X-ray analysis, the reaction mixture rapidly was obtained in the cylinder of a single use syringe, and after rapid homogenisation they were injected in a polyethylene tube with inlet diameter 3-4 mm. After complete hardening, the cement rods were extracted and subjected to X-ray analysis (degree of radio-opacity). As standard, the commercial product doped with ZrO_2 was used.

IV. Study of swelling kinetics by gravimetric method

The copolymer granules were immersed in MMA at room temperature. At pre-established time intervals, the liquid was completely separated and the granules were subjected to a rapid treatment to remove the unabsorbed residual liquid in copolymer (10 minutes at 40°C). After weighing, the cycle of operations was repeated until reaching saturation swelling.

V. Characterisation

The FTIR spectra of the copolymers were recorded using a SCHIMADZU 8900 apparatus in 4000-400 cm^{-1} range with a resolution of 2 cm^{-1}.The X-ray opacity of the samples was measured on 2D sections of cylinders examined with a X-ray microtomograph (Skyscan 1072, Skyscan Aartselaar, Belgium). The different polymers were fixed on a brass stub with plasticine and a piece of human cortical bone was used as control [15]. All specimens were scanned together at 80 kV, 100μA, 0.9° rotation. 2D sections were obtained after reconstruction from the projection images obtained in the cone beam mode. On each 2D section coded on 8 bits, the different polymer cylinders were evidenced in cross section. Five sections (separated by 200 μm) were transferred to Photoshop CS (Adobe Inc. software) and the mean grey level of each polymer sample was determined and ranged from 0 to 255. The X-ray absorbance was determined as A=1/grey level and ranged from 0 to 255 (100 % absorption), expressed in arbitrary unit.

Ba/P ratio was determined with EDX microanalysis system, Link ISIS (Oxford) model attached at SEM, JEOL 6301F (JEOL, France). The value of this gravimetric ratio was Ba/P=60/40; this value shows a 34 % yield of the reaction.

The compression resistance was evaluated with a press, WPM –60 model (F_{max} = 600 kN).

3. Results and discussion

The strategy of using MOEP for the manufacture of reactive cements implied in the first phase the testing of the following directions:

- obtaining statistical MMA-MOEP copolymers of different compositions;
- binding Ba^{2+} through neutralisation;
- replacing MMA in the final cement composition.

For the obtaining of a convenient granulation, the polymerisation procedure was tested in precipitant solution and the final conversions were determined at 2 hour reaction time (Fig. 2).

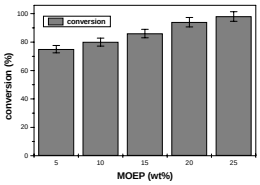

Fig. 2. Final conversion versus substrate composition

The final conversions, obtained at the same time, increased with MOEP weight (wt%) fraction from the substrate, a fact that seemed not explainable by the reactivity difference of the 2 monomers. Both monomers are methacrylates, so it is probable that the values of the reactivity ratios might be close to each other, subunitary and close to 1. In this case, the binary copolymer composition should be practically invariant with the conversion and almost equal to those of the resulted substrate. This effect could be explained by an autoaccelerated phenomenon whose amplitude increases progressively with MOEP fraction due to the existence of a residual tetrafunctional derivative in MOEP. The products of precipitant copolymerisation result as very fine powders whose granulometry is suitable for final compounding, (d_m)<100 μm.

Further step consists in the treatment with $Ba(OH)_2$ of the obtained copolymers in acidic form and in the determination of Ba retained on the surface of the polymer particle. As shown in Fig. 3, the quantities determined either by gravimetric analysis or by difference from volumetric analysis are in good concordance.

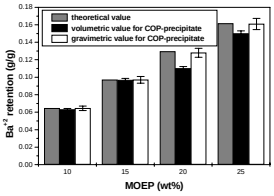

Fig. 3. Ba^{2+} retention.

As anticipated, the Ba quantity increased monotonously with the fraction of phosphate monomer and below maximum stoechiometric value.

Next stage consisted in testing COP-Ba copolymers, respectively of barium salt monomer for the manufacture of modified reactive cements. The cement-hardening interval varies between 7-20 minutes in the case of COP-Ba copolymers, respectively 6-8 minutes for the cement with Ba monomer. In both cases the rate of hardening decreased with the increasing of the fraction of Ba phosphoric structure.

The existence of a sufficiently long time for hardening in the case of COP-Ba copolymers proves the presence of limited compatibility among cements' components. The superficial swelling ability of the copolymer particles with MMA could constitute the major premise of the reinforcing action. This observation is valid both for the copolymers obtained through precipitant polymerisation and for the copolymers obtained in suspension. In the last case, the effect is more intense due to a lower specific surface. In order to verify this, some copolymer specimens with MOEP content identical to those used in the cement were obtained by bulk copolymerisation and a kinetic swelling study on MMA was done.

Fig. 4 shows the dependence of the swelling degree (x %) versus time both for COP-Ba copolymers and for copolymers without barium content. The swelling degree was determined by using the following formula:

$$x\% = \frac{m_i - m_0}{m_0} \cdot 100$$

where x = swelling degree; m_i = weight at time t; m_0 = initial weight.

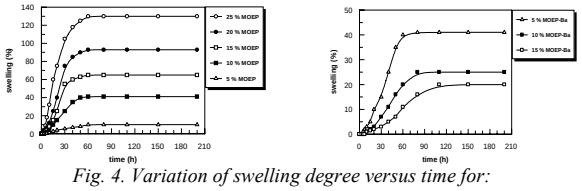

Fig. 4. Variation of swelling degree versus time for: a) non-Ba compounds b) Ba compounds.

The evolution of swelling degree allows the calculation of swelling constant accordingly to the following equations:

$$\frac{dx}{dt} = k \cdot (A - x) \quad \text{and} \quad \ln\left(\frac{A}{A - x}\right) = k \cdot t,$$

where k = swelling rate constant; $A = x_{max}$.

Considering for swelling process a first order kinetic, constant k measures the rate of diffusion of the micromolecular compound in the polymeric matrix (kinetic compatibility) and the maximum value of the swelling coefficient A measures the thermodynamical compatibility of the two substances (see Table 1).

The results of this study prove that the cross-linking degree influences the maximum values of swelling degree A, but it also influences, at a lower degree, the swelling rate.

The swelling rate decreased with the increasing of MOEP fraction as a consequence of immobilisation of the polymeric chains, both in the case of a compounds and non-Ba compounds. Of course, the affinity for MMA in the case of COP-Ba polymers decreases drastically, due to the formation on the surface of the granules of an inorganic pellicle.

Table 1. k and A values.

Copolymer MMA-MOEP (% MOEP)	Type of copolymer	A (%)	**k**
25 %	COP without barium	10	0.033
20 %		41	0.065
15 %		65	0.069
10 %		93	0.071
5 %		130	0.072
25 %	COP-Ba	No swelling	
20 %			
15 %		20	0.011
10 %		25	0.024
5 %		41	0.051

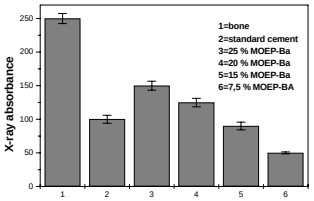

Fig. 5. X-ray radio-opacity.

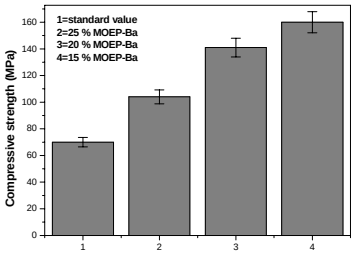

Fig. 6. Compression resistance tests.

In the case of using Ba salt of the monomer instead of the COP-Ba copolymer, the dependence of the hardening rate with the fraction of Ba component is very much attenuated. The only problem in this respect would be the ability of chemical bonding of this derivative by bulk copolymerisation with MMA. This fact was put into evidence by comparing the FTIR spectra for the monomer neutralised with Ba and respectively the MMA-based cement containing MOEP-Ba. The drastic decreasing of the peaks from 970 cm^{-1} and 1030 cm^{-1} characteristic to vinylic bond from Ba monomer proves its copolymerisation with MMA.

For post-surgery monitoring of the implant, it was imposed the X-ray scanning of the obtained cements in the case of Ba monomer. In Fig. 5 there are compared the X-ray opacities of the cortical bone, the standard cement and the cements with different compositions of the fraction of MOEP-Ba (wt%).

As it was expected, the X-ray opacity increased with Ba-MOEP fraction from the cement.

As regarding the mechanical properties, the compression resistance is presented in Fig. 6.

In the case of compression strength, all the samples are over the standard value specified by **ISO 5833 (σ=70 MPa)** [6].

4. Conclusions

This study was conducted in an attempt to develop new acrylic cements usable in bone or tooth surgery, by replacing PMMA from the cement composition with MOEP in as barium salt, respectively by replacing with its copolymer also as barium salt with MMA. The use of COP-Ba is limited and needs a complex study due to an insufficient compatibility with MMA, as compared to the use of MOEP-Ba that has the real key to be used in bone cements. This statement is sustained by mechanical resistance tests and the response of these compositions to X-ray scanner, superior to those of standard cement.

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