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The effect of ethanol on acrylic bone cement

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Abstract

Prosthesis loosening is a major problem associated with the use of poly(methyl methacrylate) (PMMA) bone cement that may be related to a peri-implant vacuolisation commonly observed at bone–cement interface. Methyl methacrylate (MMA) monomer may be one of the cement components partly responsible for the mentioned vacuolisation due to a cytotoxic effect associated to this compound. Alcoholism has been related to bone necrosis in predisposed individuals. Furthermore, ethanol has been shown to clean material with adherent cement debris during cleaning procedure in laboratory. Consequently, we have decided to study whether ethanol will also be related to an increased liberation of MMA from the polymer matrix. 'In vitro' release studies using PMMA plates were conducted to access the role of ethanol on the liberation of the monomer. Contact angle measurements and surface tension estimation were also carried out in order to find a possible effect of ethanol on surface cement properties. Results suggest that ethanol, even in small quantities, enhances the leaching of the monomer from the polymer matrix, but does not considerably change the wettability properties of the cement surface. © 2002 Elsevier Science B.V. All rights reserved.

Keywords: Poly(methyl methacrylate); Methyl methacrylate; Bone cement; Ethanol; Release model; Surface tension

1. Introduction

Poly(methyl methacrylate) (PMMA) bone cement is commonly used in orthopaedic surgery for the fixation of endoprosthesis especially in cases of total hip replacement.

Painful, aseptic loosening is the most common problem limiting the long-term success of these cemented hip arthroplasties (Williams and McQueen, 1992). The late loosening phenomena may be related to a peri-implant vacuolisation commonly observed at bone-cement interface. This occurrence can compromise the prosthetic stability.

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In previous work, the authors (Vale et al., 1997; Bettencourt et al., 2000) found that residual methyl methacrylate (MMA) monomer may be one of the cement components partly responsible for the mentioned vacuolisation due to a cytotoxic effect that has been associated to this compound.

Alcoholism has been related to bone necrosis in predisposed individuals (Gold and Cangemi, 1979; Matsuo et al., 1988; Ritter et al., 1997), perhaps due to the toxicity inherent to ethanol. Furthermore, ethanol has been shown to clean material with adherent cement debris during cleaning procedure in laboratory. Consequently, we have decided to study whether ethanol will also be related to an increased liberation of MMA from the polymer matrix.

In the present paper we have conducted 'in vitro' release studies in phosphate buffer saline solution (PBS). These were performed to access the role of ethanol on the liberation of the monomer. In addition, contact angle measurements and surface tension estimation were also carried out in order to find a possible effect of ethanol on surface cement properties.

2. Materials and methods

2.1. Materials

CMW 1 Radiopaque, an orthopaedic bone cement, was obtained from DePuy CMW (DePuy International Ltd., UK); PBS (without $CaCl_2$ and $MgCl_2$) was obtained from GibcoBRL (Life Technologies); ethanol and 1,2-propanediol were reagent grade (Merck, Darmstadt, Germany); deionized water was obtained with the Milli Q-Water Purification System (Millipore).

2.2. Methods

2.2.1. Preparation of PMMA plates

Different batches of CMW 1 were used to obtain the acrylic cement plates. For each batch, PMMA dough was obtained by mixing the liquid component with the powder, at room temperature (24–25 °C), in a glass-mixing bowl. PMMA plates had an average thickness of 1.36 ± 0.02 mm, an average length of 23.48 ± 0.02 mm and an average width of 19.56 ± 0.02 mm.

2.2.2. Incubation media

Each PMMA plate previously prepared (Section 2.2.1) was exposed (in closed plastic flasks) to 25 ml of four different media. The media were: PBS (named C = control) and three ethanol solutions (30, 100 and 250 mg of ethanol per 100 ml of PBS named, respectively: E_1, E_2 and E_3).

2.2.3. MMA release studies

2.2.3.1. MMA release studies during 22 days. Twelve plates previously prepared (Section 2.2.1) were divided in four groups of three plates each. Each group was exposed to the above mentioned media (Section 2.2.2) and incubated for 22 days at 37 °C. The different media were replaced every 24 h to avoid reaching an equilibrium situation. Aliquots of supernatant were collected at days 1, 2, 3, 4, 6, 13 and 22 for MMA content determination.

2.2.3.2. MMA release studies during 24 h. Other twelve PMMA plates were divided in four groups of three plates each. Each group was exposed to the above mentioned media (Section 2.2.2) and incubated for 24 h at 37 °C. Aliquots of supernatant were collected at 0, 10, 20, 30, 40, 50, 60, 120, 240, 360, 480 and 1440 min for MMA quantification.

2.2.3.3. MMA content determination. All the aliquots collected were centrifuged. The supernatant were analysed by high-performance liquid chromatography (HPLC) according to the method described in Bettencourt et al. (2000).

2.2.3.4. Statistical analysis. Data analysis was performed using the Analysis Toolpak of Microsoft Excel 2000 and Curve Expert version 1.3 for Windows.

2.2.4. Contact angle and Surface tension determinations

Other twelve PMMA plates previously prepared (Section 2.2.1) were divided in four groups

of three plates each. Each group was exposed to the above mentioned media (Section 2.2.2) and incubated for 22 days at 37 °C (the media were changed daily). After 1, 6, 13 and 22 days of PMMA setting the plates were subjected to contact angle analysis and surface tension estimation.

Contact angle measurements were performed with the aid of a Kruss K121 tensiometer (Kruss GMBH, Hamburg, Germany) using the Wilhelmy plate method, by immersing the plates 2 mm into the test liquids (water and 1,2-propanediol) at a speed of 20 μm s^{-1}. Contact angle results refer to advancing contact angles and were measured at 25 ± 0.1 °C. Three replicates were carried out for each plate.

Equations for surface tension estimation were solved using the equation handling KRUSS-software program: Contact angle measuring system K121 (version 2.049).

3. Results and discussion

3.1. MMA release studies

3.1.1. MMA release studies during 22 days

Fig. 1 shows the mean daily amount of monomer released in the four tested media during 22 days of incubation. Data were evaluated for statistical significance by one-way analysis of variance (ANOVA).

Our results suggest that MMA liberation was influenced by ethanol. In fact, the amount of liberated monomer differed significantly (P-values less then 0.05 were considered as statistically significant) in the various ethanol media compared to control (C) from day 1 to day 6. Moreover, during the first 24 h of exposure the mean daily amount of monomer released was linearly related to ethanol's concentration($n = 12$; $r^2 = 0.9519$; $P < 0.01$; $[\text{MMA}] = 0.0663 + 0.000948 \times [\text{ethanol}]$).

In all tested media, MMA release declines over time being undetectable after 22 days of incubation (Fig. 1). In our opinion, this fact may suggest that ethanol does not have a depolymerization effect on the polymer matrix.

3.1.2. MMA release studies during 24 h

Fig. 2 shows the release profiles of the monomer during the first 24 h of exposure to the different media.

Ethanol seems to have no effect on MMA release pattern since in all tested media we have observed a rapid increase during the 1st h of incubation followed by a slower and steady release (Fig. 2).

The maximum amount of MMA released in C, E_1, E_2 and E_3 corresponds to the different values of a given in Table 1.

The a values were obtained by fitting the experimental results of the released MMA with time (Fig. 2) to the equation: $y = a(1 - e^{-k1t})$ (Donbrow, 1992) characterized by y (amount of the

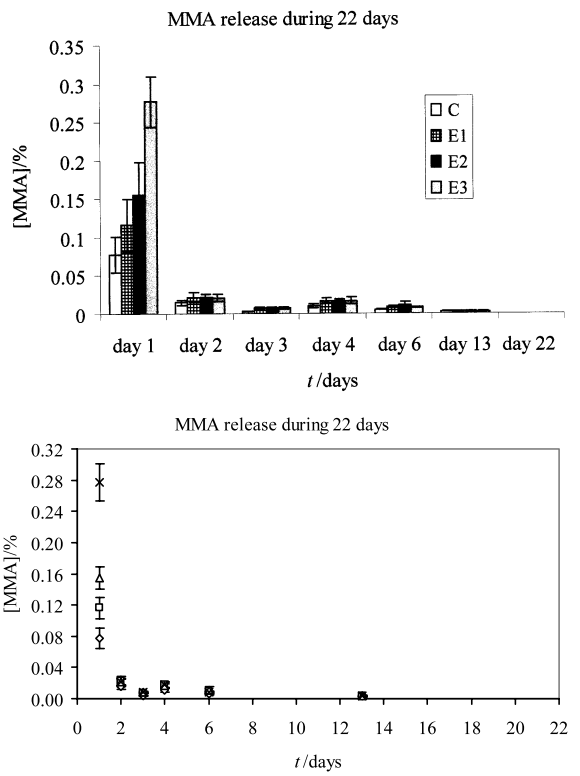

Fig. 1. (a) Mean daily amount content of MMA ($\pm$S.D.) in C, E_1, E_2 and E_3 media, during 22 days of incubation. (b) Mean daily amount content of MMA ($\pm$S.D.) during 22 days of incubation: ◇, experimental data for incubation in C; □, experimental data for incubation in E_1; △, experimental data for incubation in E_2; ×, experimental data for incubation in E_3.

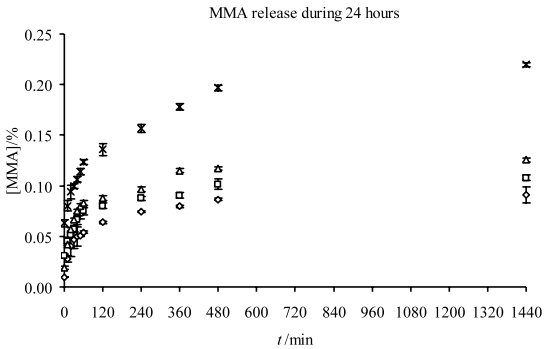

Fig. 2. Monomer release data ($\pm$S.D.) during 24 h: $\diamondsuit$, experimental data for incubation in C; $\square$, experimental data for incubation in E_1; $\triangle$, experimental data for incubation in E_2; $\times$, experimental data for incubation in E_3.

monomer released with time t), a (maximum amount of the monomer released in the medium) and k_1(first order release rate constant).

Furthermore, the 1st h dissolution data were also fitted by the equation: $Q = k_2 t^{1/2}$ (Higuchi, 1963) characterized by Q (amount of the monomer released per unit area after time t) and k_2 (release rate constant related with: diffusion coefficient of the monomer in the dissolution media, monomer's solubility, monomer's concentration in polymer matrix, porosity and tortuosity of the matrix).

The application of Higuchi model to this particular set of data is due to the reason that most of the monomer was released within the 1st h of incubation.

The differences in k_2 values (Table 1) can be associated to the higher amount of MMA liberated by ethanol and not by a different monomer release mechanism. In our opinion, the very good fit of cumulative release data to the square root of time, in all tested media (Table 1), suggests that ethanol does not change the mechanism of monomer release, being in accordance with a simple diffusion mechanism (Bettencourt et al., 2000).

From a clinical standpoint, the increase in the leaching of MMA due to the effect of ethanol may be relevant as it may enhance the toxic effects related to the use of this polymer.

3.2. Contact angle and surface tension determinations

Our release studies suggested that ethanol increases MMA liberation. Consequently, wettability studies were also conducted in order to evaluate a possible effect of ethanol on the polymer surface.

The underlying theory for the determination of surface tension (γ) of PMMA plates and its dispersive (γ^d) and polar components (γ^p) is based on the harmonic mean method proposed by Wu (1971), for calculating the interfacial tension between polymers or between a polymer and an ordinary liquid:

$$\gamma_{12} = \gamma_1 + \gamma_2 - \left(\frac{4\gamma_1^d\gamma_2^d}{\gamma_1^d + \gamma_2^d}\right) - \left(\frac{4\gamma_1^p\gamma_2^p}{\gamma_1^p + \gamma_2^p}\right)$$

where γ_{12} is the interfacial tension between phases 1 and 2, which each have a surface tension consisting of a polar and dispersive component. Essentially, if a contact angle (θ) is measured against two liquids of known surface tension and polarity (water and 1,2-propanediol in the present

Table 1
Parameters resulting from the application of mathematical models to experimental data in C, E_1, E_2 and E_3 media

Equations	C	E_1	E_2	E_3
$y = a(1-e^{k1t})$				
$k_1 \pm \sigma(k_1)$ (min^{-1})	0.024 ± 0.004	0.023 ± 0.007	0.024 ± 0.003	0.023 ± 0.005
$a \pm \sigma(a)$ (%)	0.080 ± 0.009	0.090 ± 0.002	0.107 ± 0.02	0.212 ± 0.06
R	0.904	0.900	0.901	0.903
$Q = k_2 t^{1/2}$ *(Higuchi model)*				
$k_2 \pm \sigma(k_2)$ ($\mu g\ mm^{-2}\ min^{-1/2}$)	0.042 ± 0.009	0.052 ± 0.008	0.056 ± 0.009	0.064 ± 0.006
R	0.974	0.981	0.980	0.982

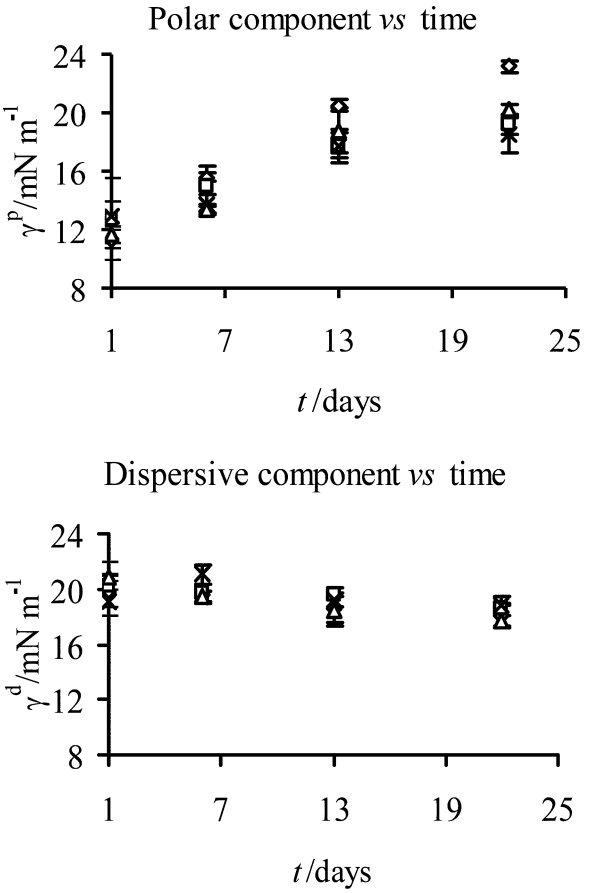

Fig. 3. Experimental polar ($\gamma^p \pm$ S.D.) and dispersive ($\gamma^d \pm$ S.D.) surface tension values of PMMA plates after exposure to different media conditions: ◇, experimental data for incubation in C; □, experimental data for incubation in E_1; △, experimental data for incubation in E_2; ×, experimental data for incubation in E_3.

study), then it is possible to estimate the surface tension and polarity of the solid.

Using the experimental values of contact angles measured with the reference liquids, the polar and dispersive values of PMMA plates surface tension were calculated.

Comparing these values (Fig. 3) it can be seen that in particular it is the polar component that changes with time. The dispersive component remains constant over the time.

The increase in the polar component of surface tension will correspond to an increase in hydrophilicity in all examined plates. Although the increase is slightly lower in the plates exposed to ethanol media it seems that ethanol will not change considerably the wettability behaviour of acrylic cement plates.

4. Conclusions

The results obtained in this work show that ethanol, even in small quantities, enhances the leaching of the monomer from the polymer matrix.

The leaching of the monomer in ethanol stops after 22 days of incubation suggesting that no depolymerization effect occurs. We have also found that ethanol does not considerably change the wettability properties of the polymer.

Although no direct correlation could be established between our 'in vitro' studies and clinical data (ethanol consumption), it is probable that 'in vivo' where the cement forms a thicker layer, less exposed to the surrounding media, MMA will be trapped for a longer period of time and the liberation process will be longer. The observed increase in the leaching of MMA due to ethanol, may then be relevant due to the inflammatory reactions possibly triggered or enhanced by this component of the acrylic cement!

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References

Bettencourt, A., Calado, A., Amaral, J., Vale, F.M., Rico, J.M.T., Monteiro, J., Lopes, A., Pereira, L., Castro, M., 2000. In vitro release studies of methylmethacrylate liberation from acrylic cement powder. Int. J. Pharm. 197, 161–168.

Donbrow, M., 1992. Microcapsules and Nanoparticles in Medicine and Pharmacy. CRC Press, Boca Raton, FL, pp. 193–210.

Gold, E.W., Cangemi, P.J., 1979. Incidence and pathogenesis of alcohol-induced osteonecrosis of the femoral head. Clin. Orthop. 143, 222–226.

Higuchi, T., 1963. Mechanism of sustained-action medication, theoretical analysis of rate of release of solid drugs dispersed in solid matrices. J. Pharm. Sci. 52, 1145.

Matsuo, K., Hirohata, T., Sugioka, Y., Ikeda, M., Fukuda, A., 1988. Influence of alcohol intake, cigarette smoking, and occupational status on idiopathic osteonecrosis of the femoral head. Clin. Orthop. 234, 115–123.

Ritter, M.A., Helphinstine, J., Keating, E.M., Faris, P.M., Meding, J.B., 1997. Total hip arthroplasty in patients with osteonecrosis. The effect of cement techniques. Clin. Orthop. 338, 94–99.

Vale, F., Castro, M., Monteiro, J., Couto, F., Pinto, R., Toscano, J.M.G.R., 1997. Acrylic bone cement induces the production of free radicals by cultured human fibroblast. Biomaterials 18, 1133–1135.

Williams, R.P., McQueen, D.A., 1992. A histopathologic study of late aseptic loosening of cemented total hip prostheses. Clin. Orthop. 274, 174–179.

Wu, S., 1971. Calculation of interfacial tension in polymer systems. J. Polym. Sci. Part C 34, 19–30.