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A new process for the production of bone cement by gelled suspension polymerization of MMA

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A new suspension polymerization process, utilizing a water–agarose gel as suspending phase, is described. In the early stage of the process, the monomer is dispersed in the water–agarose solution by adequate stirring, then the solution gelifies and polymerization starts. By this technique, PMMA powders adequate for bone cement production were obtained. Several tests were performed on the polymer obtained in order to determine its basic physicochemical properties: viscometric tests, GPC tests, DSC tests, granulometric distribution analysis and SEM analysis. The measured properties show that the material obtained can be satisfactorily compared with the existing commercial powders for bone cements.

1. Introduction

Polymethylmethacrylate (PMMA)-based commercial bone cements are usually made of a solid phase, composed of a powder of polymeric microspheres and an initiator, and a liquid phase, composed by the monomer, an inhibitor and an accelerator. Eventually, radiopaque substances and antibiotics can also be added. Liquid and solid phases are usually hand mixed and placed *in situ* during the implantation of arthroprostheses.

Major problems involved with the use of the cement are due to the heat generation during polymerization and to shrinkage and toxicity. These problems strongly depend upon powder characteristics and upon powder/monomer weight ratio in the cement. High local temperatures reached owing to the exothermic chain propagation reactions are dangerous for the bone marrow cells. It can be seen that the resulting temperature peaks during *in vivo* polymerization give a decreasing straight line versus powder percentages. Another important problem is the cement matrix shrinkage (the specific gravity of the monomer being about 0.935 g/ml and that of the polymer about 1.19 g/ml) which can cause stem mobility. Finally, cement toxicity, due to residual monomer, can cause local or systemic damages. All those problems are reduced by adding to the monomeric phase as much powdered polymer and/or filler as possible.

In order to improve the final quality of the cement, a new process has been developed for producing polymeric powders with good characteristics. In the conventional process (called " dynamic" in the following), polymeric powders are obtained by means of suspension polymerization carried out in stirred reactors, to which many additives are added [1], such as polyvinylalcohol [2], hydrophobic modified celluloses [3], steric stabilizers such as hydrophilic and hydrophobic copolymers [4], soap solutions [5]. These substances, together with some degree of coalescence between the reacting particles, can compromise product purity and quality.

In the new process, patented in 1990 [6] and called "static", the monomeric phase polymerizes while suspended by a gelled aqueous phase, made of an agarose-type gel, which has good mechanical strength over a wide temperature range and is not toxic. The most important characteristic of this process is the absence of stirring during polymerization and, consequently, the absence of any potentially dangerous additive and of coalescence. So the reactor is filled only with the organic phase, containing the monomer and the initiator, and the aqueous solution of agarose. Polymeric microspheres with a high purity grade and dimensionally controlled have been obtained in such a way.

In the following, results regarding methylmethacrylate (MMA) polymerization will be reported and considered. The process consists of three steps: the mixing of the monomeric and aqueous phases, the formation of the gel and the polymerisation of the monomer. During the first step, the fundamental process parameters are viscosities, surface tensions of the phases and stirring speeds. By varying those parameters, pearl sizes and distribution can be varied widely. Stopping the mixing at a temperature 1 °C below the gelling temperature, pearl immobilization takes place in a few seconds. Polymerization is carried out in such a gelled condition by increasing the reactor

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temperature. The slurry is finally recovered after curing at 90 °C.

2. Materials and experimental apparatus

The suspending phase is a water–agarose solution with an agarose weight fraction varying between 0.25 and 4.00%. The agarose used is a Sigma–Aldrich product, obtained by agar desulfuration. The most interesting properties of gels obtained from water–agarose solutions by lowering temperature to below 42 °C (which is the gelling temperature of the particular agarose solution considered) are their thermal stability, their mechanical strength (they can suffer compression stresses up to 10 N/cm^2) and their ability to revert to an aqueous solution by simply stirring and warming over 90 °C [7–9].

The MMA used is an Aldrich Chem product with 99% purity. It has been purified by shaking with a 25% KOH aqueous solution, then dried with $CaCl_2$ and distilled under vacuum. The benzoyl peroxide used is an Aldrich Chem product with 97% purity.

A 1 l glass reactor with a hemispherical bottom was used. The reactor was equipped with a stirrer, a thermostatic water jacket, a system for obtaining nitrogen flux over the reacting mass and a reflux condenser. Monomer feeding was made drop-by-drop using a funnel.

The reflux condenser acts as a monomer damper in the case of reactor run away. Holes for a thermocouple and for feeding the dispersing solution are made in the head of the reactor.

3. Process description

In the above-mentioned reactor both dynamic and static polymerizations have been carried out in a discontinuous way. Dynamic polymerizations have been carried out at 70 °C, with several stirring speeds and with a final cure at 90 °C. Static polymerizations have been carried out as described in the following: the water–agarose dispersing solutions were prepared by adding agarose to boiling water (4 g agarose/400 g water); nitrogen circulation into the reactor to keep air away was then started. Water–agarose solutions, with three different stirring speeds (1000, 720, 500 r.p.m) were poured (in three different runs) into the reactor; the jacket was fed with water at 41 °C; the monomer (100 g), in which the initiator (3.75 g) was previously dissolved at room temperature, was added; the stirrer was left on for another 4 min to obtain a homogeneous suspension and then the suspending solution gelled. The nitrogen admitting valve was then locked, the jacket was fed with water at 70 °C and polymerization took place over about 90 min. Subsequently the jacket was fed with water at 90 °C and the reaction went to completion (cure); then the gel was collapsed by stirring again; the reactor was discharged and the polymer was separated by washing the slurry with hot water. Finally, water agarose solution was recycled to the reactor.

4. Results

Samples obtained with both static and dynamic methods were characterized by viscosimetry, gel permeation chromatography (GPC), differential scanning calorimetry (DSC), granulometric distribution analysis, scanning electron microscopy (SEM). The results of these measurements are reported in the following.

4.1. Viscosimetry

The viscometric tests were used for determining average molecular weight of the polymer, by measuring the intrinsic viscosity of acetone solutions of the polymer, at 25 °C, in a modified Ubbelohde viscometer. The Mark–Kuhn–Houwink relation ($\mu = K\ M^a$) was then used, with values of K and a parameters taken from literature [10]. A viscosity average molecular weight of about 570 000 was computed for the polymer obtained by the static process and a viscosity average molecular weight of about 260 000 for the polymer obtained by the dynamic process.

4.2. Gel permeation chromatography

The gel permeation chromatographic tests were used to evaluate the molecular weight distributions. The GPC curves confirm the average molecular weight values obtained by the viscometric tests. The curve for the static process is a little flatter than the one for the dynamic process, showing a greater dispersion of molecular weights in the former case.

4.3. Differential scanning calorimetry

Differential scanning calorimetry was carried out using a DSC 7 Perkin-Elmer. Samples prepared from both static and dynamic polymeric powders were submitted to two consecutive scans. In the static case, the first scan shows some exothermic phenomena beginning at about 120 °C, while the second scan shows a glass transition (T_g) at about 105 °C. The same happens in the dynamic case at about the same temperatures (Fig. 1).

4.4. Granulometric distribution

The polymers produced in three static runs with different stirring speeds during suspension formation, were sieved by using a nine-sieve cascade with apertures ranging from 530 to 38 µm. Curves were obtained (Fig. 2) which confirm the strong influence of the stirring speed used during suspension formation on the polymer granulometric distribution.

4.5. Scanning electron microscopy

Polymers obtained by both static and dynamic methods were submitted to SEM analysis (Jeol Mod. T 300). Particles obtained in the static process have quite different morphologies, according to the stirring speed used. Those obtained with a 1000 r.p.m. stirring speed have irregular shapes and look crumbly (Fig.3). Higher magnification shows that they are made of microspheres with diameters less than 1 µm.

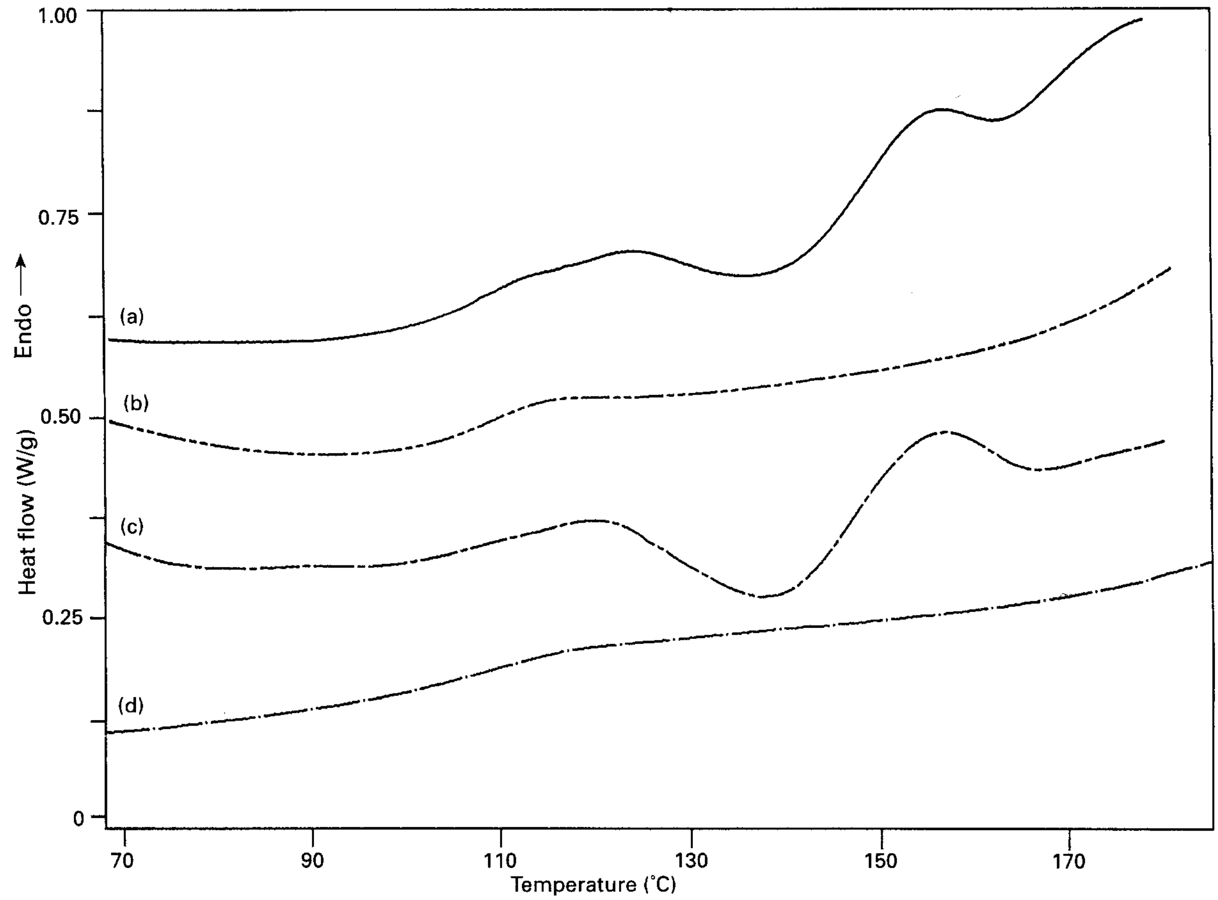

Figure 1 Normalized DSC curves: (a) dynamic polymer: first scan, scan rate 10 °C/min; (b) dynamic polymer: second scan, scan rate 20 °C/min; (c) static polymer: first scan, scan rate 10 °C/min; (d) static polymer: second scan, scan rate 10 °C/min.

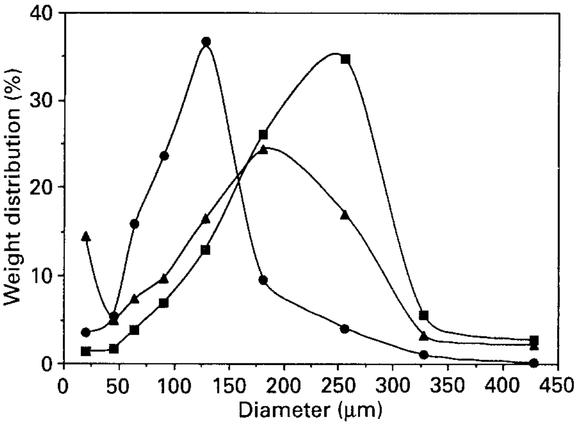

Figure 2 Weight distributions of static polymer for three different stirring speeds (● 100 r.p.m.; ▲ 720 r.p.m.; ■ 500 r.p.m.).

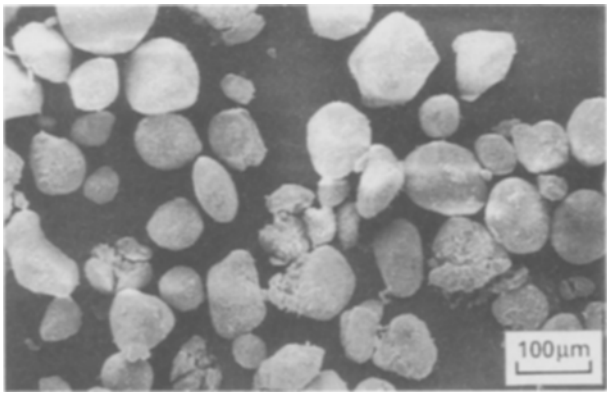

Figure 3 Scanning electron micrograph of a static-process powder (1000 r.p.m. stirring speed).

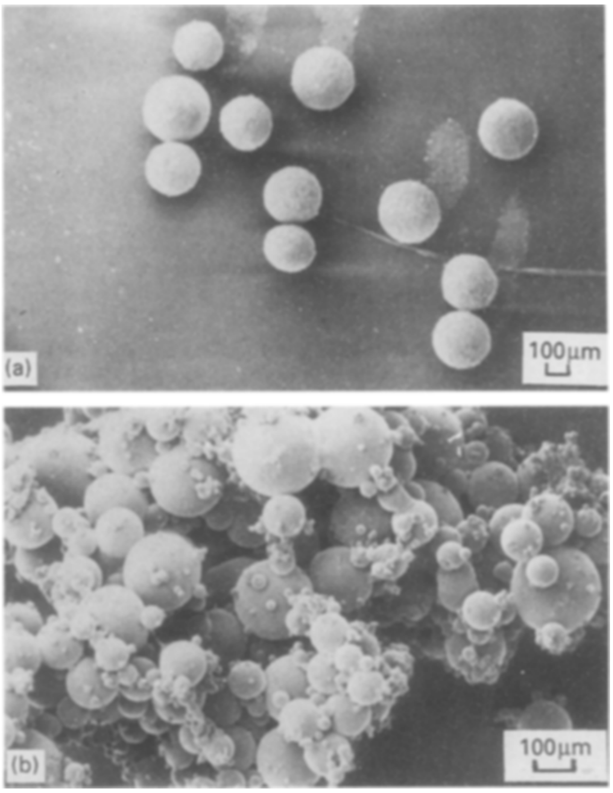

Figure 4 Scanning electron micrograph of: (a) a static-process powder (720 r.p.m. stirring speed); (b) a dynamic-process powder.

Particles obtained with 720 and 500 r.p.m. stirring speeds are spherical and do not look crumbly. A micrograph is shown for 720 r.p.m. stirring speed (Fig. 4a). This micrograph can be compared with the micro-

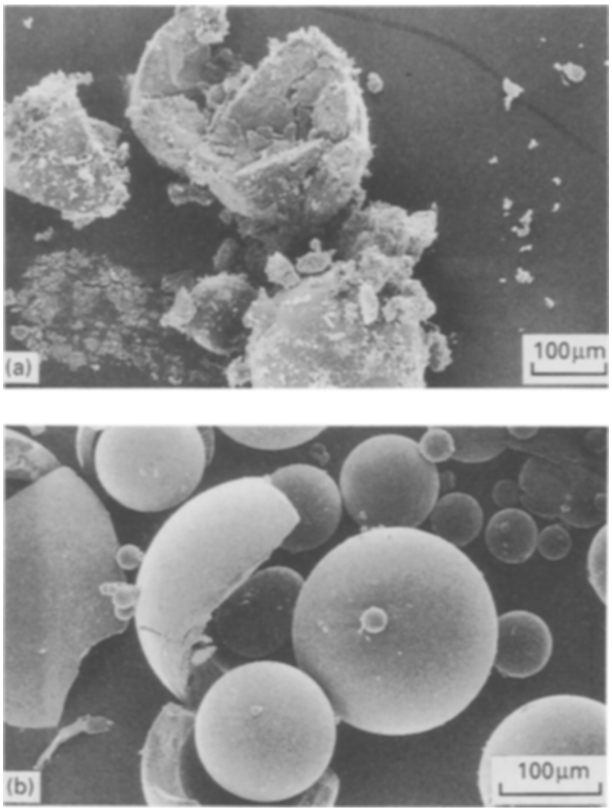

Figure 5 Scanning electron micrograph of freeze-fractured microspheres: (a) static process; (b) dynamic process.

graph for the same stirring speed in the dynamic process (Fig. 4b), in which aggregates due to coalescence between microspheres can be seen.

Particles were also fractured in liquid nitrogen. The particles obtained in the static process (Fig. 5a) show solid structures, while those obtained in the dynamic process show shell-like structures (Fig. 5b).

5. Discussion and conclusions

The static polymerization process described has several advantages over the dynamic process. The main features of the static process are the possibility of obtaining the desired particle distributions by means of an adequate stirring at the beginning of the process, the invariance of particle sizes during polymerization, the absence of any coalescence problem, and no need for additives. Consequently, product purity and quality are assured.

In the present case, the method has been used for producing a PMMA powder to be utilized for bone cement preparation. However, the process has general applicability and is being studied for accomplishing polymerization of water-insoluble monomers, or of water-insoluble monomers together with water-soluble or insoluble comonomers, with the aim of producing new bone cements with a lower temperature peak and reduced side-effects during and after implantation. In particular, the production of some bone cements based on MMA alone or on MMA copolymerized with N-vinyl pyrrolidone or diethylenglycol-bis-allyl carbonate is being studied.

The molecular weight of the PMMA obtained is quite high and this, in general, implies good mechanical properties. Molecular weight distribution is, in the static case, a little flatter than in the dynamic case: this can be adequately modified by temperature control on the reactor during polymerization.

DSC analysis shows that in both cases exothermic phenomena begin at about 20 °C above T_g. These are related to the polymerization of the residual monomer that is usually observed also in commercial bone cement powders.

Even if particle sizes obtained in the static case are somewhat greater than the optimal sizes for the usual bone cement powder, they can be reduced by changing the stirring speed, and by varying other parameters such as agarose concentration and water/monomer weight ratio, and by modifying the reactive system arrangement (stirrer shape, baffles, etc).

Using SEM analysis, single particle morphologies can readily be seen. Microspheres obtained by the static process show better shapes than those obtained by the dynamic process. Moreover, the latter, when fractured in liquid nitrogen, show morphologies that can significantly lower the cement quality. In fact, many of these particles have empty cavities and shell-like structures. Such kinds of defects have also been seen in some commercial bone cement powders.

Cements prepared by utilizing the powders obtained by the static process were satisfactory when tested according to the Draft International Standard Tests (ISO/DIS 5833-1) for "Implants for Surgery-Acrylic resin cement", 1989.

It can be concluded that high-quality powders for bone cements can be produced by the process described. Some problems in temperature control could arise in scaling-up the reactor. It should be observed, in this regard, that usual commercial quantities of the product do not require large reactors and that the present technology offers good possibilities for an optimal thermal control of the same.

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