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Functionalisation of porous hydroxyapatite for bone substitutes

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Abstract

Calcium phosphate ceramics such as hydroxyapatite (HA) have been widely used to repair and reconstruct damaged parts of the human skeleton. This material is currently available as injectable cements, granules or macroporous blocks. The most common materials are granules because of their ability to be implanted in the human body. In this study, a new manufacturing procedure to fabricate either dense or microporous or macroporous hydroxyapatite spherical granules based on a lost wax method and leading to beads with a fully controlled porosity was developed. The as-obtained HA granules porous structure was impregnated by gentamicin and lambda phage and the antibiotic and phage releasing kinetics were studied as a function of time and porosity.

Keywords: B. Porosity; Hydroxyapatite; Beads; Functionalisation; Drug releasing; Phage therapy

1. Introduction

Bioceramic materials such as calcium phosphate ceramics, and in particular hydroxyapatite (HA) and β tricalcium phosphate (β-TCP) because of their excellent biocompatibility, bioactivity and osteoconduction properties, have been widely used to repair and reconstruct damaged parts of the human skeleton and especially as bone substitutes in the filling of bone defects.[1] These materials are available in the form of injectable cements, granules or macroporous blocks. Calcium phosphate granules have been generally selected for classical bone filling.[2] However, such granules present irregular shapes and do not allow for optimal filling of bone cavity or defect. To overcome this problem, adjunction of a binding agent such as fibrin glue has been found to stabilise the granules in the implantation site and produce a composite that can be moulded into the defect without empty spaces.[3]

Many processing routes have been used for fabrication of porous hydroxyapatite granules, such as hydrothermal conversion of natural corals,[4] crushing of sintered blocks, granulation by vibration and rolling,[5] dripping procedure, casting in plaster mould, emulsion methods[6] and spray-drying. A new method similar to the lost wax process has been developed by our team. This method consists in building a calcium carbonate scaffold around a template constituted of piled up calibrated PMMA poly(methyl methacrylate) beads. Thermal treatment led to the removal of the organic beads, thus resulting in a porous calcium carbonate scaffold. This empty space could then be filled by a HA powder aqueous slurry and subsequent elimination of the carbonate scaffold allowed to obtain controlled size and shape HA beads.[7]

Besides their use as bone filling material, microporous HA beads could be used in the orthopaedic field as drug delivery carriers for substances such as growth factors, anticancer drugs and antibiotic agents. Microporous HA (i.e. with a pore size around the micrometer) could be obtained by partial sintering of the ceramic material. It was thus possible to impregnate them by active substances like gentamicin antibiotic for its prophylactic action[8] or phages used for phage therapy in case of nosocomial diseases.[9]

In this study, we present the fabrication process for dense, micro- and macro-porous HA beads from our lost wax process and we give comparative results of drug loading and release rate of gentamicin antibiotic and lambda phage in the microporous HA beads.

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2. Experimental

2.1. HA powder synthesis

HA powder was prepared by an aqueous precipitation technique using a diammonium phosphate solution and a calcium nitrate solution. After successive steps of precipitation–calcination–milling, the as-obtained powder displayed a surface area of 5 m^2/g, a mean particle size of 1 μm and a Ca/P ratio of 1.667.[10] A complete densification was achieved by pressureless sintering after 3 h at 1250 °C.

2.2. Fabrication of ceramic beads

The porous ceramic beads were fabricated through the lost wax process. The first step consisted in building a template of organic beads, infiltrating it by a calcium carbonate slurry and burning the organic species by thermal treatment. The as-resulting voids were then filled with a HA powder slurry and the carbonate surrounding carapace was destroyed by another thermal treatment (Fig. 1).

2.2.1. Preparation of the organic skeleton

An organic skeleton was built by stacking PMMA beads (Diakon TM Ineos Acrylics Holland, Saluc Belgium) with diameters in the range from 100 μm to 3 mm. Bridging between polymeric beads was obtained by a chemical treatment under pressure using acetone (RPE 99.8% Carlo Erba, France) which partially dissolved the PMMA bead surfaces and induced welding of the individual bodies (Fig. 1a).

2.2.2. Preparation of the calcium carbonate scaffold

The as-prepared organic skeleton was then impregnated by the calcium carbonate suspension in order to fill the voids between polymeric PMMA beads.

A $CaCO_3$ powder (Mikhart 2, Provençale s.a, France) showing a surface area of 3.3 m^2/g, a mean particle size of 3 μm and a purity level superior to 99% was used.

A 64 wt.% dry matter $CaCO_3$ aqueous slurry was prepared. Slurry deflocculating was assured by adding Darvan C (R.t.Vanderbilt. Co) in an amount corresponding to 1.5 wt.% of the $CaCO_3$ content. An organic binder (Duramax B1001, Rohm and Haas) in an amount equal to 4 wt.% of the $CaCO_3$ content was also added to ensure a consolidation of the green material during the thermal treatment necessary for PMMA elimination. Slip preparation was carried out using a planetary ball mill with agate container and balls. Milling duration was fixed to 1 h with a 180 rpm rotation speed. After the infiltration process (Fig. 1b), the sample was dried in a plaster mould and then underwent a two-dwell thermal treatment (220 °C during 20 h followed by 250 °C for 10 h). The elimination of PMMA beads created a controlled size macroporosity within the ceramic. After this thermal treatment, the 3% residual organic ensured enough mechanical strength for the handling of samples during the later stages and the sample was constituted of macropores, the size of which was equal to that of the used PMMA beads. These cavities were interconnected. Fig. 1b shows macroscopic and microscopic

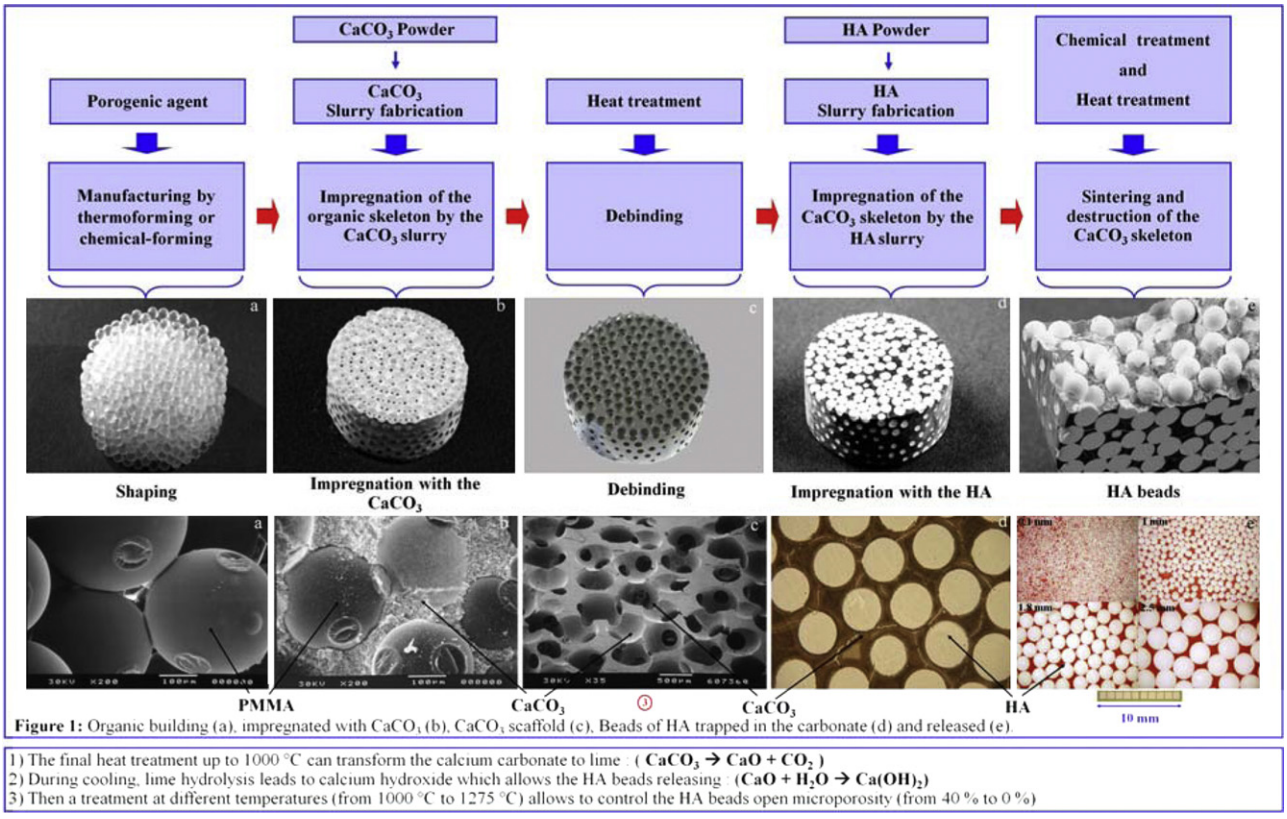

Figure 1: Organic building (a), impregnated with $CaCO_3$ (b), $CaCO_3$ scaffold (c), Beads of HA trapped in the carbonate (d) and released (e).

Fig. 1. HA spherical granules elaboration procedure.