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Macroporous synthetic hydroxyapatite bioceramics for bone substitute applications

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An improved strategy is described for the manufacture of macroporous hydroxyapatite bioceramics for bone substitute applications. This is based on a modified fugitive phase technique, which allows production of relatively open, high-strength devices. Properties of ceramics manufactured by this route are compared with those fashioned by two conventional methods. Aspects of design are discussed in terms of requirements for intrinsic osteoinductivity *in vivo*.

Macroporous hydroxyapatite [$Ca_{10}(PO_4)_6(OH)_2$, or HA] bioceramic implants are used in skeletal repair to allow bone and tissue ingrowth with eventual incorporation of the ceramic device in natural bone. In a companion paper, Ripamonti *et al.*[1] report that macroporous HA ceramics with specific geometric features exhibit intrinsic osteoinductivity (induces bone differentiation), rather than osteoconductivity (guides new bone growth) as is generally accepted. The osteoinductivity was extensively demonstrated using a primate model (Chacma baboon, *Papio ursinus*). The present paper describes an improved strategy for the manufacture of macroporous HA ceramics, based on a modified fugitive phase method, which incorporates the requirements for intrinsic osteoinductivity. The strategy largely eliminates common processing defects in the manufacture of more open, higher strength devices.

Macroporous HA bioceramics are intended to replace current bone graft materials, which are mostly derived from natural bovine (xenograft), human cadaver (allograft) and same-patient (autograft) sources. A major advantage offered by synthetic material is the overcoming of current concerns with regard to immune response, disease transmission and, in the case of autografts, limited quantity and morbidity of the donor site. Macroporous bone substitutes based on HA have been in clinical use for more than a decade, but reliable manufacture is difficult and commercial material is mostly derived from hydrothermal conversion of natural coral exoskeleton.[2,3] These materials are highly regarded but present disadvantages in that the source remains natural, the structure does not allow modification and the implants are considered too weak in certain applications.

The ability to manufacture entirely synthetic, highly porous and customized structures is a basic requirement in meeting emerging demands for partial resorption[4] and delivery of biomolecules[4,5] in bone tissue engineering.

Design criteria

Design criteria are summarized below, based on published data and the study reported in ref. 1, for macroporous HA bone substitute bioceramics that exhibit intrinsic osteoinductivity.

For the purposes of this work, the target chemical composition was phase pure hydroxyapatite corresponding to a Ca/P ratio of 1.67.

The role of microporosity is not fully understood.[6] One probable benefit of microporosity is an associated surface roughness, which should promote cell adhesion *in vivo*. An obvious disadvantage is reduced mechanical strength. The approach adopted here has been to minimize microporosity but to introduce surface roughness through post-sinter chemical etching.

Macropore size as reported in the literature is mostly in the range 100–400 μm, with indications that bigger is better.[3,6,7] With regard to the primate model, the preference has been for pore size in the range 400–800 μm. This is larger than recommended in some cases.[8] Even larger pore size up to 1600 μm has been tested for osteoinductive potential in heterotopic sites, but with no measurable benefit compared with 800 μm.[1] We found that the manufacture of highly porous ceramics becomes increasingly difficult with increasing pore size, in agreement with work conducted elsewhere,[8] so that an upper limit of 800 μm has been adopted.

Macropores should ideally be of substantially spherical shape. This is the most common shape reported in the literature, and is also a requirement for intrinsic osteoinductivity, as demonstrated by implanting solid hydroxyapatite disk specimens with hemispherical surface indentations in heterotopic sites.[1] New bone formed preferentially and consistently in concavities, as opposed to on the flat areas between indentations or the convex

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Table 1. Comparison of three ceramic manufacturing methods in terms of key properties.

Property	Foam method			Fugitive phase			Modified fugitive phase		
	$\bar{x}$	s.d.	*n*	$\bar{x}$	s.d.	*n*	$\bar{x}$	s.d.	*n*
Typical variability:									
Apparent density (g cm^{-3})	0.93	0.03	8	1.13	0.01	9	1.13	0.02	14
Closed porosity (%)	5.4	0.2	8	2.4	0.5	9	2.1	0.3	14
Crushing strength at 60 % porosity (MPa)	0.6	0.2	11	1.4	0.5	12	5.7	1.6	12
Modulus (MPa) at 60 % porosity	~30		11	132	47	12	463	51	12
Suitable porosity range (%)	60–75			60–70			55–70		

$\bar{x}$, average; s.d., standard deviation; *n*, number of samples.

edges of indentations.

High and complete connectivity of pores is generally indicated in the literature, although a scientifically justified specification has not been proposed. During the present work an indirect goal evolved, to achieve full connectivity of macropores with interconnecting holes of average diameter above 100 μm.

The level of porosity as reported in the literature is mostly in the range 50–70 %. All *in vivo* trials of the associated study[1] involved ceramics with porosity level in the range 60–70 %. Current preference is for a porosity near 60 %, provided that the connectivity of pores is high and complete. This level represents a reasonable compromise between the simultaneous but conflicting requirements for both high porosity and mechanical strength.

The properties in compression of commercial coral-derived material include a strength of 3.4 ± 1.1 MPa and modulus of 252 ± 100 MPa (Pro Osteon® Implant 500, Interpore International). At the reduced porosity level of 60 %, the properties in compression are almost double those of the coral-derived material at 6 ± 1.5 MPa ultimate compression strength (UCS) and 420 ± 75 MPa modulus.

Experimental

The phase purity of powders and ceramics was confirmed by X-ray diffraction. Chemical composition was determined by wet chemical methods and checked for conformity to ASTM F1185-88 specification. Ca/P ratio was determined by ICP. Chemical surface was verified by infrared absorption. Density and porosity were measured by Archimedes' method. Powder particle size and morphology were studied by laser scattering and SEM/image analysis.

Mechanical testing focused on ultimate compressive strength and modulus as indicators. Measurements were conducted using specimens of nominal dimensions 9 mm diameter and 18 mm height at a crosshead speed of 0.5 mm min^{-1}. The modulus was calculated between 25 and 75 % strain.

Ceramics were initially produced using a range of commercial hydroxyapatite powders, including fine-grained, ceramic grade powders and coarser powders obtained by ball-milling commercial plasma spraying feedstock to d_{50} ~1 μm. Sources included Product No. 1.02196 (Merck), Capital R P120, Capital R P147, Plasma Biotal No. 3 (Plasma Biotal, England), GR500P (Cam Implants, The Netherlands), Plasmatex A6020 (Plasma Technik, Switzerland) and Ch. No. 900727 (Friedrichsfeld via Tribo-Corr, South Africa). Following initial work, a proprietary bimodal powder was developed at the CSIR to improve the rheology of powder-polymer mixtures used as feedstock for the modified fugitive phase method.

Forming method 1: slurry impregnation of polymeric foam. A proprietary slurry was prepared by ball-milling powder, binder, plasticiser, deflocculant and solvent. This was aged for 24 hours before use. An open-cell polymeric foam with suitable density and cell size was cut to shape, allowing for expansion due to interaction with the slurry and shrinkage during sintering. The foam was impregnated with slurry and excess slurry removed by compression in a die. Specimens were then dried, debinded and sintered.

Forming method 2: conventional fugitive phase method. A granulated powder incorporating binder and pressing lubricant was mixed with stearic acid beads, sieved to the size range 600–1000 μm, and compacted. Compacts were heated to melt and decompose the binder, lubricant and stearic acid beads (hence the term 'fugitive phase') and eventually sintered. This was a sensitive process, since the structure had to withstand melting and decomposition of various components while in a brittle green state. A heating schedule based on a method of simultaneous mass loss and dilation rate control[9] was used to minimize deformation during this stage.

Forming method 3: modified fugitive phase method. A powder-polymer mixture with solids loading near 65 v/o was compounded, crushed and sieved. Stearic acid beads, sieved to the size range 600–1000 μm, were mixed with this feedstock and compacted. Compacts were heated to allow melting and decomposition of the polymer phases before sintering. The feedstock was designed to become soft and tacky before melting of the stearic acid fugitive phase, so as to minimize debris and crack damage arising from the sudden increase in volume. A rapid debinding process was further developed by which the molten stearic acid was largely extracted from the structure before further thermal processing.

Specimens were sintered under conditions ranging from 1200 °C for two hours to 1260 °C for four hours to achieve material density from 90–98 %, respectively.

Surface roughness was introduced by etching implants in dilute orthophosphoric acid. Typical conditions for etching were six minutes in 0.5 M H_3PO_4.

Results

Devices manufactured by the three different methods were tested *in vivo*. To date, only the results obtained from specimens produced by the foam route have been reported.[1] Biological response in this case was excellent but the mechanical strength of foam route specimens was considered inadequate.

The manufacturing methods are compared in terms of several key properties in Table 1, which highlights the favourable mechanical properties of specimens produced using the modified fugitive phase method.

The three methods resulted in distinctly different macrostructures (Fig. 1). Specimens created using the foam route exhibited pores that were either nearly spherical or resembled the original

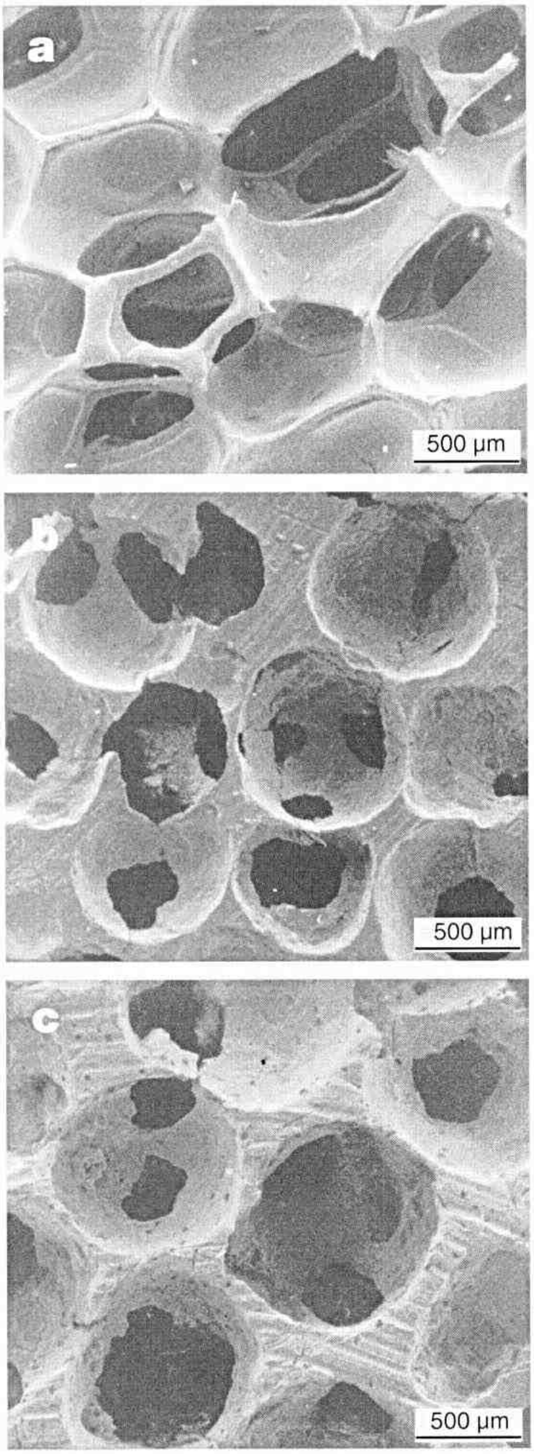

Fig. 1. Macrostructure of hydroxyapatite specimens produced by three different manufacturing methods; **a**: foam method; **b**: fugitive phase method; **c**: modified fugitive phase method.

foam with distinct struts and thin membranes spanning struts, depending on the preparation conditions. Interconnecting holes generally arose from cracked or missing membranes. Specimens produced using the conventional fugitive phase route exhibited largely spherical pores due to the original shape of the fugitive phase but interconnecting holes tended to be small. Specimens made using the modified fugitive phase route had a similar appearance but with large interconnecting holes between adjacent pores.

Distinctly different structural defects resulted from the three processing methods. Common faults in the foam route specimens included dense areas of incomplete connectivity, concentrations of spiky struts and crumbly struts and membranes. This outcome reflected the sensitivity of the process to slurry removal. Excess slurry resulted in incomplete connectivity while a deficiency led to spiky struts after sintering. Control is difficult since the slurry viscosity changes with the loss of volatiles during processing. Defects commonly associated with the conventional fugitive phase route include strut cracks, which arise during processing due to thermal expansion mismatch between the matrix and fugitive phase or the sudden expansion on melting and decomposition of the fugitive phase. Also, the size of connecting holes between adjacent pores are difficult to control and the connecting holes can remain partially blocked by highly defective, membrane-like debris. Defects associated with the modified fugitive phase method were generally minor and consisted of an occasional strut crack or small interconnecting hole.

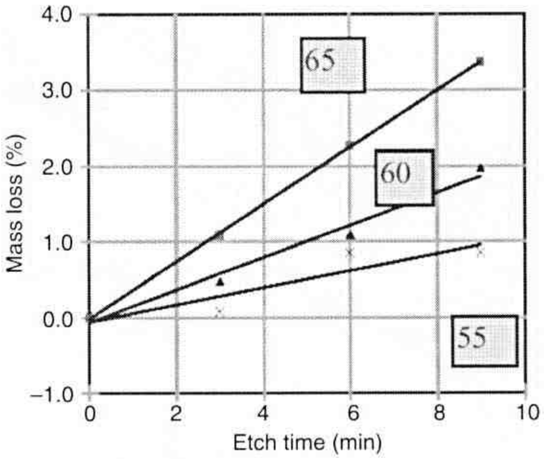

Fig. 2. Mass loss as a function of time during etching of specimens of 98 % bulk density and different macroporosity.

The sintered surface of specimens made by the three methods was similar on a microstructural level when using identical starting powder and sintering conditions. Etching was conducted to introduce surface roughness. The rate of etching varied with porosity as shown in Fig. 2; the desired effect of etching on the microstructure is shown in Fig. 3.

Two distinct types of crushing behaviour were observed for macroporous specimens produced by the methods described here. Low-strength specimens, which typically contained a high density of strength-limiting defects such as strut cracks, tended to fail locally during compression and gradually crumbled. High-strength specimens tended to fail catastrophically but at high load under the given test conditions. This difference in crushing behaviour is shown in Fig. 4 for two specimens of 60 % open porosity but 3 MPa and 9 MPa strength, respectively. Typical variation of strength and modulus in compression as a function of macroporosity level, with other material and processing parameters held constant, is shown in Fig. 5 for specimens manufactured using the modified fugitive phase method.

Conclusion

A modified fugitive phase method for the manufacture of macroporous ceramics for bone substitute applications, incorporating design criteria derived from the literature and *in vivo* studies, allows repeatable processing and structures of good mechanical strength and stiffness. Good control over defects is possible and full connectivity of macropores is consistently obtained. The strategy is generic and has been successfully used also in the manufacture of composite bioceramics (results not published).

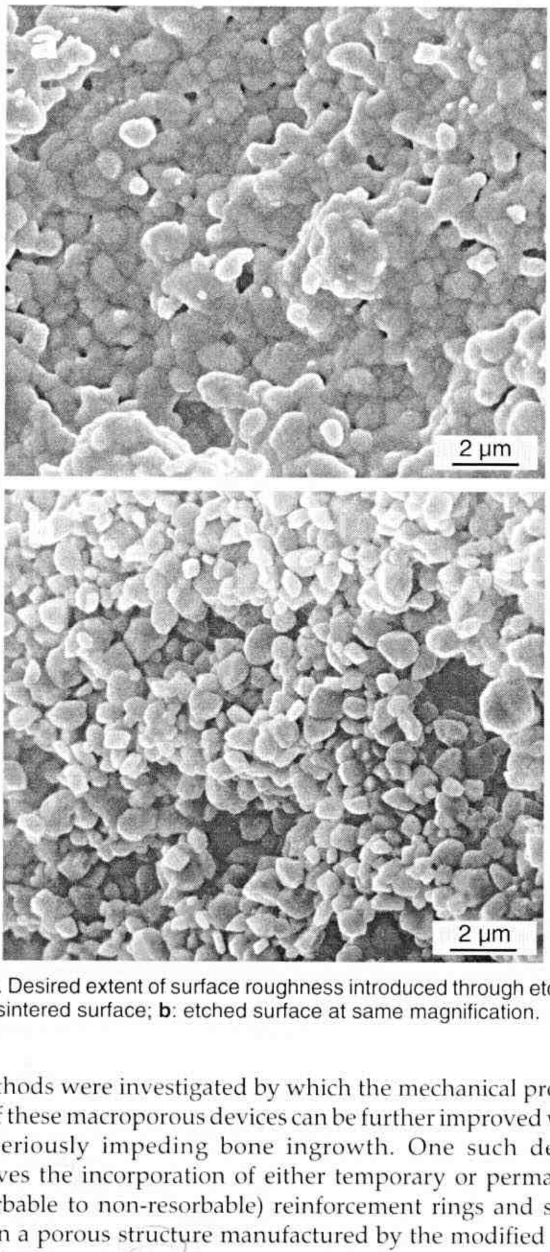

Fig. 3. Desired extent of surface roughness introduced through etching; **a**: as-sintered surface; **b**: etched surface at same magnification.

Methods were investigated by which the mechanical properties of these macroporous devices can be further improved without seriously impeding bone ingrowth. One such design involves the incorporation of either temporary or permanent (resorbable to non-resorbable) reinforcement rings and struts within a porous structure manufactured by the modified fugitive phase route.[10] Another approach has been to make structures by solid freeform fabrication, rendering the mechanical properties and essential features such as pores and channels adjustable.[11]

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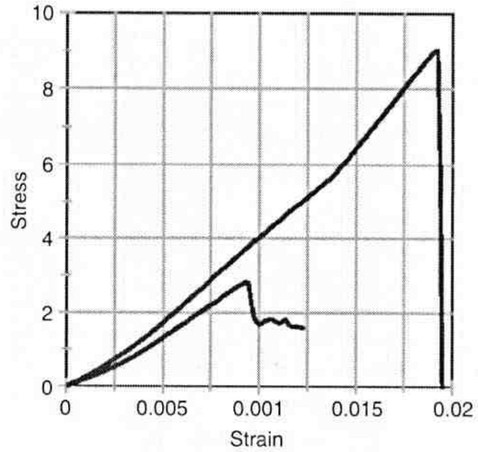

Fig. 4. Two types of crushing behaviour observed for specimens of 60% porosity.

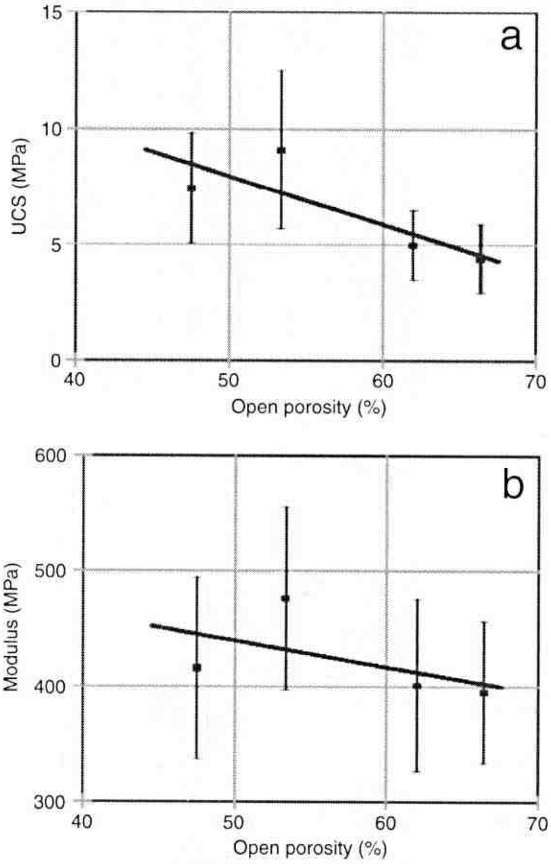

Fig. 5. Variation of (**a**) compressive strength and (**b**) modulus as a function of macroporosity level for hydroxyapatite specimens manufactured by the modified fugitive phase method.

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