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Fabrication and mechanical testing of porous calcium phosphate bioceramic granules

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Abstract Porous hydroxyapatite/tricalcium phosphate (HA/TCP) granules were fabricated by a novel technique of vacuum impregnation of reticulated polyurethane (PU) foams with ceramic slip. The resultant granules had 5–10% interconnected porosity with controlled pore sizes necessary to allow bone ingrowth combined with good mechanical properties. Using PU foams with a different number of pores per inch (ppi), porous HA/TCP granules in the size range of 2–8 mm were successfully manufactured. Dieplunger tests were used to compare the compression and relaxation properties of the granules with those of a commercially available bone graft product, BoneSave®. The results of the die-plunger testing showed that the experimental granules were stiffer than the BoneSave® materials and had less of a tendency to crumble to powder after testing. This therefore suggests that these experimental granules would be useful for impaction grafting and space filling applications.

Introduction

Bone stock loss represents a major challenge in orthopaedic surgery. As surgical techniques and medical knowledge continue to advance, there is an increasing demand for bone graft substitutes. This has become a problem as there is a limited supply of autograft material available and the use of allograft carries with it the risk of disease and infection [1]. A clinical need therefore exists for a synthetic material that can be used to either replace existing bone graft or be used alongside it as a bone graft extender. One particular area where such a material would have extensive use is for impaction grafting during revision hip arthroplasty.

The attention of some groups of researchers has focussed on porous calcium phosphate ceramic granules which are used widely as filler or packing materials [2–4]. The different forms of granular calcium phosphate include irregular multifaceted granules and round smooth granules, with solid or porous structures. However, the behaviour of granules in the body depends on their morphology and microstructure. Irregular morphology causes undesirable inflammatory reactions in the body tissues and the bone formation may be slower. Consequently, granules with a smooth geometry are superior [2]. TCP, HA and biphasic TCP/HA granules have been used as bone defect fillers with complete healing of the defects [3, 5–10], especially when mixed with human bone or marrow [8–10]. Calcium phosphate granules can also be impregnated with a drug, e.g. antibiotics, antimicrobial agent, growth factor etc. and used as a system for targetted drug delivery [11].

A number of studies have reported the development of calcium phosphate granules by various techniques such as crushing sintered blocks [12], hydrothermal conversion of natural corals [13, 14], dripping [4], drip casting [15], gelcasting [16] and stirring mixtures of immiscible liquids [2, 11, 17]. Granules made by crushing sintered blocks have irregular shapes and sizes. Further sieving and milling procedures are needed to obtain suitable sizes and a more regular shape. This increases the complexity of the process and wastes much of the material. Granules made by dripping, drip casting, gelcasting and stirring mixtures of

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immiscible liquids methods have good shapes which are spherical or near-spherical in form. Most of these granules exhibit controlled porosity however, in all of these materials the pores remain isolated, ie they are not interconnected. Although, some authors stated the porous network of these granules is highly interconnected, this may only appear in samples with a high porosity and in this case, the mechanical strengths may be compromised.

The aim of this research was develop a range of different size porous bioceramic granules using a novel technique that guaranteed interconnected porosity. The compression and relaxation properties of these granules were then compared with those of a commercially available bone substitute material, BoneSave®, which can be used clinically for impaction grafting. These properties influence mechanical stability against subsidence in impaction grafting, the compaction properties and the sensory feedback experienced by a surgeon during impaction. The protocol adopted in the current study was based on that of Grimm [18, 19] to analyse the performance of graft materials in terms of initial mechanical stability for the use in impaction grafting. There is a complex loading situation for the graft materials in impaction grafting but the die-plunger test is a simple, easily reproducible experiment to determine the fundamental mechanical properties of graft materials.

Experimental procedure

Manufacturing process for granular forms of porous calcium phosphate

Two grades of calcium phosphate powder, TCP 118 and TCP 130 (Thermphos), were used to produce the samples used in this study. The ratio of HA and TCP in the final sintered samples is controlled by varying the initial ratios of TCP 118 and TCP 130 and the sintering temperature. In this way, the long-term stability associated with HA and higher solubility and bioactive properties associated with TCP can be optimised in the samples produced. In this study, TCP 118 and TCP 130 powders (1:1) were gradually added to distilled water to prepare slips of 1000 g of powder per litre (100 wt%). The organic reticulated foams, which were completely burnt out during sintering, were made of polyurethane. Three grades were used with a different number of pores per inch (ppi)—20 ppi, 30 ppi and 45 ppi (Sydney Heath and Sons Ltd.). The PU foams were sectioned by scalpel and scissors to the desired shape and dimensions, then soaked in water for 24 h to remove dust and impurities. The manufacturing method developed can be used on PU foams in a full range of sizes, encompassing a range of geometries from small granules up to large blocks. Figure 1 shows cubes of foam with side lengths of 3.1, 6.3, 8.3 and 12.5 mm which were used to produce granules ranging from 2 to 8 mm in diameter.

The foams were substantially impregnated with ceramic slip by a vacuum impregnation method as described in an earlier publication [20]. This method ensures that the slip substantially fills the foams as opposed to just coating the walls. In the latter case, the resulting product would be a replica of the reticulated foam material and the ceramic parts of the structure would be hollow and therefore less strong. The dried green samples were sintered in a programmable furnace at 1280 °C. The final phase composition of the sintered samples was 75% HA and 25% TCP.

A commercially available synthetic material BoneSave® (Stryker Howmedica Osteonics, Limerick, Ireland), used clinically for impaction grafting and space filling, was used for comparative purposes; it is available in a range of sizes from 2 mm up to10 mm in diameter. Dieplunger tests were used to compare the compression and relaxation properties of 2–4 mm BoneSave® granules with those of experimental 4 mm and 6 mm diameter HA/TCP granules.

Die-plunger testing

A die-plunger device is normally used to press ceramic powder tablets prior to sintering and is commonly used in ceramic testing laboratories. Die-plunger testing was employed in this research to investigate the compressive and relaxation properties of different types of granule. The test was carried out using an Instron 1122 testing machine. A schematic of the die-plunger is shown in Fig. 2. It consists of a plunger cylinder of 20 mm diameter and 150 mm length which is pushed into a hollow cylindrical container of equivalent internal diameter. The bottom of the cylinder is closed with a 20 mm diameter disc which can be easily removed after the compression experiment to retrieve the granules.

The experimental procedure for the die-plunger testing can be described as follows. A measuring cylinder was used to measure a fixed volume of 10 cm^3 of loose and

Fig. 1 Macrographs of the foams after sectioning and before impregnation

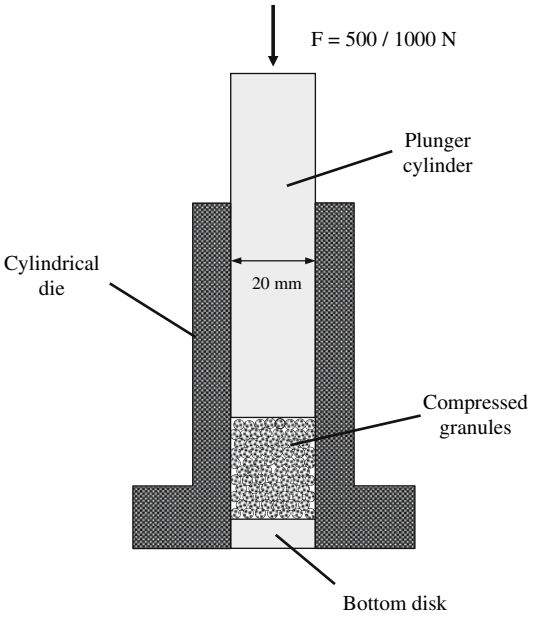

Fig. 2 Schematic representation of the die-plunger equipment

uncompressed granules. The granules were manually inserted into the die and pushed down slightly by the weight of the steel plunger cylinder. A volume of 10 cm^3 of granules converts to a theoretically filling height of 31.8 mm. However, for accuracy in converting absolute deformation into strain, the real height of the 10 cm^3 granules in the cylindrical die was recorded by measuring the starting position of the plunger cylinder. The cross-head speed of the Instron device was set to 2 mm/min. For each test, the following cycle, as shown in Fig. 3, was applied:

1. Loading to 500 N.
2. Position kept constant for a relaxation period of 120 s.
3. Releasing load to 0 N.
4. Loading to 1000 N.
5. Position kept constant for a relaxation period of 120 s.
6. Releasing load to 0 N and retrieving the granules.

The force and displacement values were recorded, converted into force (N) and strain (displacement/initial height) measurements and used to calculate compression and relaxation properties.

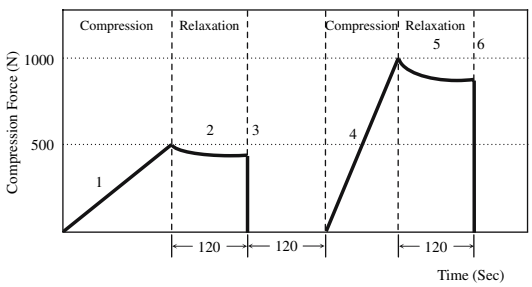

Fig. 3 Stages in the die-plunger testing

Results and discussion

Porous granular form of calcium phosphate

Figure 4 shows a range of porous HA/TCP bioceramics with various dimensions fabricated by the vacuum impregnation method. The largest sample shown in this figure was made from a foam template with dimensions of 30 × 30 × 25 mm; the others were made from 12.5 to 3.1 mm foams. Figure 5 shows 4 mm granules with a regular size and shape, made from 20, 30 to 45 ppi foams, Transverse sections of 6 and 8 mm cubic granules can be seen in Fig. 6. This demonstrates the method could be used to make HA/TCP granules in the size range of 2–8 mm with interconnected porosity and controlled size and shape. Image analysis revealed the porosities measured for three different PU foams were similar and in the range of 5.24–9.67 %. The macropore size of the HA/TCP bioceramics was 254 μm (for 20 ppi foam), 182 μm (for 30 ppi foam) and 126 μm (for 45 ppi foam). One of the methods currently used commercially to manufacture granules involves breaking up a large block into smaller pieces. Compared to this, the technique developed is efficient in manufacturing terms as particle size and shape can be controlled and waste minimised.

Die-plunger testing

Compression testing

Figure 7(a) shows the compression force versus strain curves for porous 4 mm HA/TCP granules made from 20, 30 to 45 ppi foams and BoneSave® materials during the first compression cycle (0–500 N). The compression force increased exponentially up to a maximum peak in the first

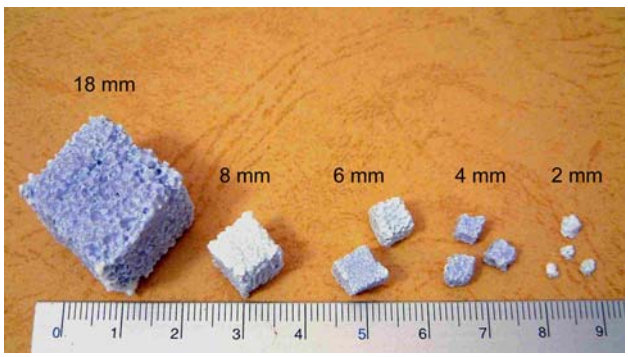

Fig. 4 Porous HA/TCP bioceramics with different dimensions

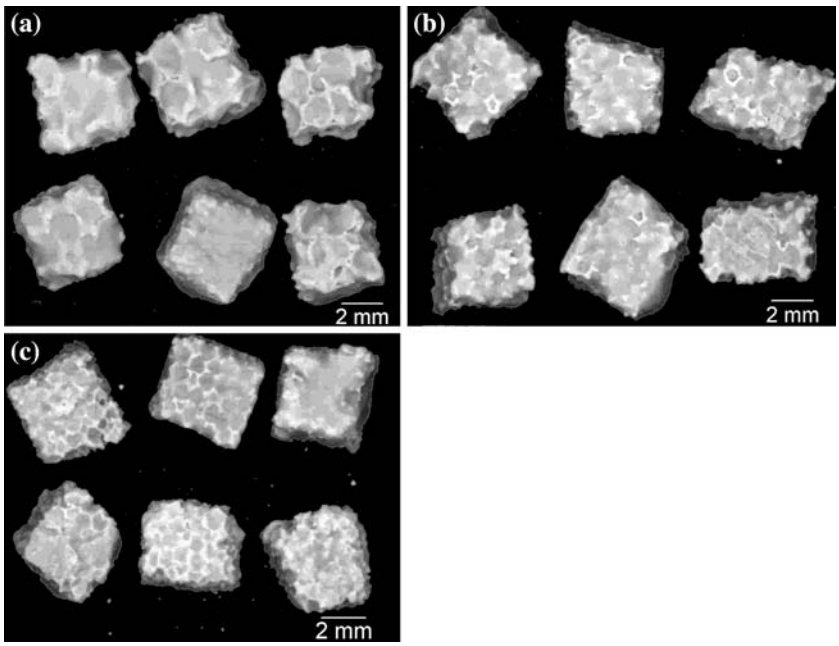

Fig. 5 Porous HA/TCP granules made from (**a**) 20 ppi (**b**) 30 ppi (**c**) 45 ppi foams

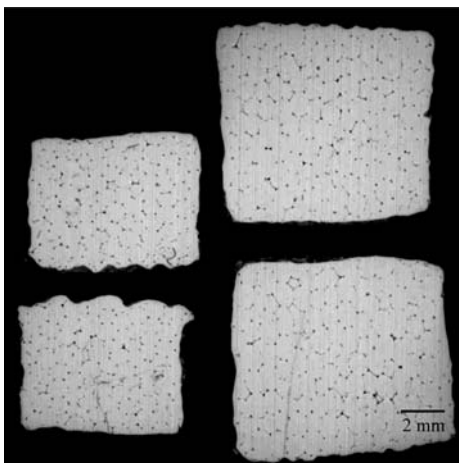

Fig. 6 A cross-section of porous granules fabricated by the vacuum impregnation method

compression cycle of up to the 500 N maximum load. The force-strain curves of the granules made by the vacuum impregnation method were quite irregular during the first compression from 0 to 500 N. In comparison, BoneSave® materials did not show this tendency. The shape and size of the particles will affect their packing efficiency. The experimental granules (4 mm cubes) had a more uniform shape compared to the BoneSave® materials, which ranged in shape and size, with an average diameter of 2–4 mm. BoneSave® granules with their broader range of geometries would be expected to have a greater initial packing density.

The granules made from 20 ppi foams had the highest average maximum strain of 0.088 up to 500 N compared to 0.067 for the granules made from 30 ppi foams to 0.061 the

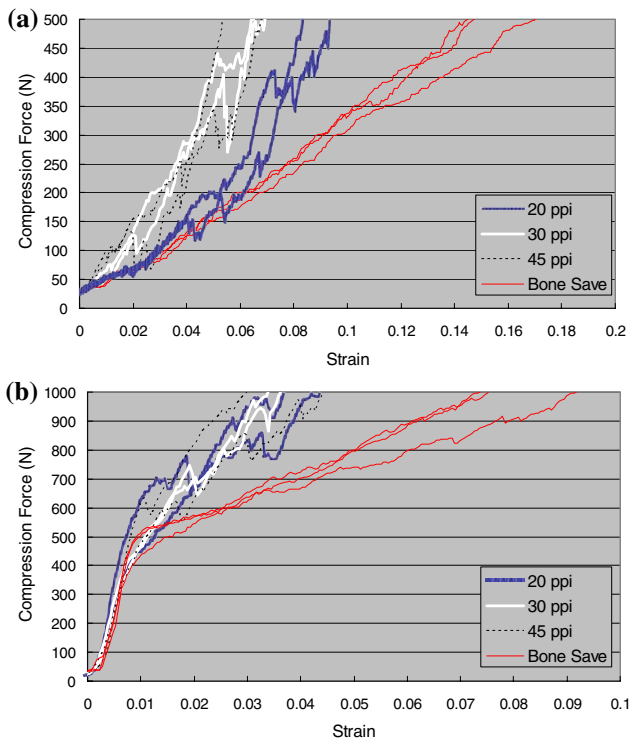

Fig. 7 Compression force versus strain diagram for die-plunger testing of 4 mm granules and 2–4 mm BoneSave®. (**a**) up to 500 N (**b**) up to 1000 N

45 ppi foams. This indicated that the larger macropore size resulted in a higher strain value in the first compression cycle. Figure 7(b) shows the compression force versus strain curves for porous HA/TCP granules made from 20, 30 to 45 ppi foams and BoneSave® materials during the

second compression cycle (0–1000 N). When the pre-compressed sample was loaded for the second time to 1000 N, the granules reacted in a stiffer manner than in the first compression cycle and the curves from 0 to 500 N were relatively smooth. When the force exceeded 500 N, a visible decrease in the gradient of the force-strain correlation was noticed. However, this gradient was still much higher than during the first 0 to 500 N compression. Once the original peak load was exceeded, the compression force-strain relation became irregular.

The average maximum strain measurements for the granules made from 20, 30 to 45 ppi foams were 0.040, 0.035 and 0.036, respectively indicating that the strain order in the second compression cycle was similar to that in the first compression cycle. Larger macropore size resulted in higher strain.

The granules made by the vacuum impregnation technique were stiffer than BoneSave® materials in both the first and second compression cycle and did not crumble to powder after the testing. By comparison, many of BoneSave® granules crumbled on compressing to become smaller diameter particles. The manufacturing process for the commercial material is such that the size and shape of the granules produced is not well controlled. The macropores in the commercial BoneSave® granules were found to be isolated and dispersed throughout the material, in contrast to the interconnected network of porosity in the experimental materials produced for the study.

Figure 8 shows results of testing the experimental granules with an average diameter of 6 mm. The curve in the first compression test from 0 to 500 N was extremely smooth and stable as seen in Fig. 8(a). However, the gradient of the curve was quite steep up to 600 N but dropped sharply and became unstable at 600–1000 N during the second compression cycle in Fig. 8(b). This may be explained in terms of the loose packing of the granules due to their geometry. The larger granules tended to have a particular stacking arrangement rather than a random packing arrangement; the results will be influenced by this. Figure 9 shows the likely distribution of these granules during the test. Smaller granules have a more uniform packing factor. Larger granules could have quite a different arrangement. Figure 9 (a) shows the large granules pile up compactly in the right hand side but loosely on the left hand side. These different packing configurations could result in a diversity of results.

The force used for the testing in the first stage of compression was low for these granules and almost none of the granules broke, this resulted in the smooth and stable curve in Fig. 8(a). Subsequently, for the test up to 1000 N, many of the granules were damaged or crushed. This resulted in the unsteady curve in Fig. 8(b). The results showed that the test conditions were only suitable for small granules, which

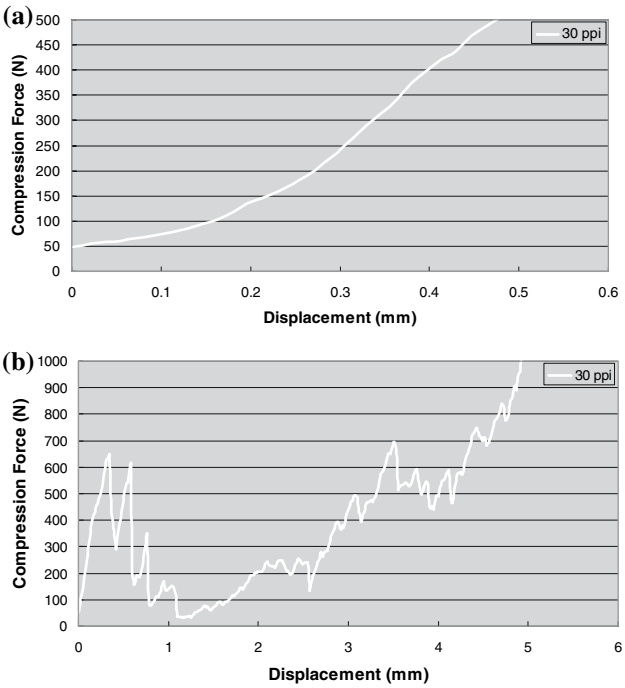

Fig. 8 Force-deformation diagram for die-plunger testing of 6 mm granules. (**a**) up to 500 N (**b**) up to 1000 N

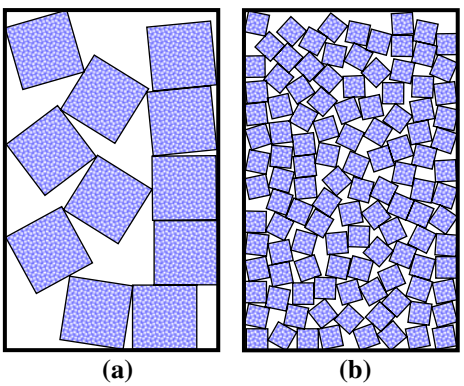

Fig. 9 Schematic representation of die-plunger testing for (**a**) large granules (**b**) small granules

were ***less*** than 4 mm in diameter due to the size of the granules in relation to the diameter of the die plunger. Furthermore, these granules were all regular cubic shapes which may exacerbate this problem. Using granules with a range of dimensions or a larger diameter die plunger may alleviate the problem.

Relaxation behaviour

The relaxation behaviour of the 4 mm granules made from various ppi foams and BoneSave® materials from the

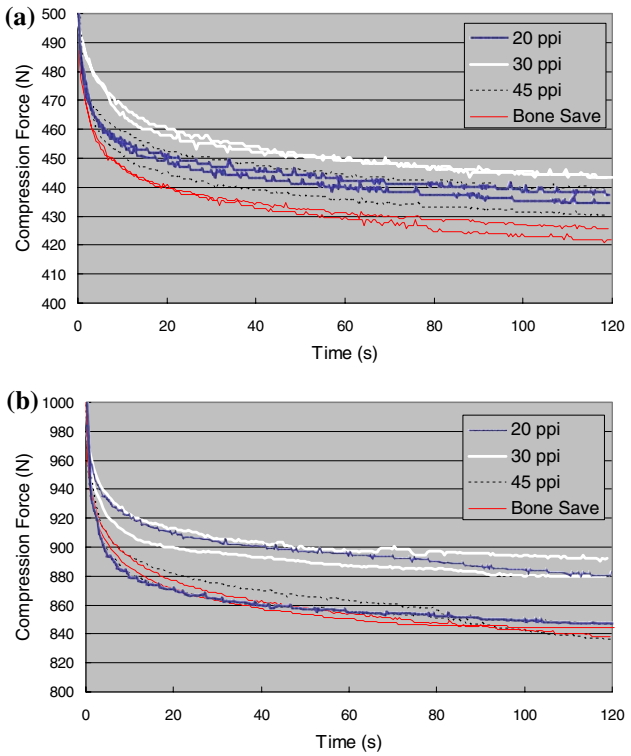

Fig. 10 Compression force versus time curves for relaxation of 4 mm granules from (**a**) 500 N (**b**) 1000 N

maximum load of 500 N is shown in Fig. 10(a). It can be seen that the BoneSave® granules have higher relaxation values than the experimental granules. The average relaxation values of granules from low to high are in the order of 30 ppi, 20 ppi and 45 ppi foams. This indicates the average relaxation values for the granules cannot be specifically related to macropore sizes.

The relaxation behaviour of the granules and BoneSave® from the maximum load of 1000 N is given in Fig. 10(b). The relaxation values from the maximum load of 1000 N are higher than those from the maximum load of 500 N but retain the same order from low to high of 30 ppi, 20 ppi and 45 ppi foams. Granules made from 45 ppi foam had similar relaxation behaviour to BoneSave® granules. As observed for loading up to 500 N, there was no particular order in relation to macropore size for the relaxation behaviour from the maximum load of 1000 N. BoneSave® granules seem to have higher values than the experimental granules for relaxation from the maximum loads of both 500 and 1000 N. However, the differences in relaxation behaviour between the granules and BoneSave® materials are not as great as the differences in the stiffness measurements. Further work needs to be carried out to establish more accurate correlations between relaxation and macropore size.

Conclusions

The method developed can be used to make porous HA/TCP granules in the size range of 2 to 8 mm with interconnected porosity and controlled size and shape—hitherto not possible using existing manufacturing techniques. The technique is efficient when compared to making a large block of material and subsequently breaking up the sintered product into smaller pieces, as size and shape can be controlled and waste minimised. The results of the die-plunger testing showed that the 4 mm granules made by the vacuum impregnation technique were stiffer than commercial BoneSave® materials and did not crumble to powder after the die-plunger test. By comparison, many of the BoneSave® samples crumbled to become smaller diameter particles. It can be concluded that the experimental 4 mm granules could be useful for impaction grafting and space filling, with an improved capacity for retaining structural integrity ensuring good graft stability. In addition, they have the added advantage of fully interconnected porosity which would improve their potential to encourage bone ingrowth in the long term.

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