JOURNAL OF MATERIALS SCIENCE: MATERIALS IN MEDICINE 13 (2002) 295–299

Porous hydroxyapatite ceramics of bi-modal pore size distribution

V. S. KOMLEV, S. M. BARINOV
Institute for Physical Chemistry of Ceramics RAS, Ozernaya 48, Moscow, 119361, Russia
E-mail: mnctk@cityline.ru

A route for the fabrication of porous hydroxyapatite ceramics having two populations of open pores is reported. The bodies are prepared by sintering the spherical gelatin/hydroxyapatite granules. As the result, ceramics containing intragranular small-size pores and intergranular large-size interconnecting pores are obtained. The pore size and content are dependent on the route. Ceramics can generally be applied as bone replacement materials where the interconnections in the intergranular pores are the pathway to conduct cells and vessels for the bone ingrowth, whereas the intragranular pores can be filled with a drug, e.g. to eliminate infections.

1. Introduction

The biocompatibility of hydroxyapatite (HA) and its osteoconductive behavior are well known. Bioceramics made of HA are available in dense and porous form. A number of porous hydroxyapatite ceramics were developed for application in both the tissue engineering [1–7] and the drug delivery systems [8–11]. The pores are known to have a direct influence on bone formation. Porous ceramic body function is to serve as a substrate for proliferation and differentiation of cells seeded or infiltrated from the surrounding tissues followed by the bone ingrowth into the pores. These processes are affected by pore size, morphology, volume content and connectivity [6, 7, 12]. In particular, it has been reported that the volume of bone ingrowth increases with an increase of pore size [13]. An optimal pore size occurs for cells infiltration and host tissue ingrowth: 5–15 μm for fibroblasts, 20–125 μm for adult mammalian skin tissues, and 100–350 μm for bone tissues [14, 15]. No unanimous opinion exists about optimal pores content in an implanted device. However, it became obvious that the pores' degree of interconnections directly influences the biological fluids, especially in cells and vessels, that favor tissue nutrition and condition of new bone formation [13]. As a consequence, some contradictions appeared concerning an optimal pore size if their degree of interconnection is not taken into account [6]. Generally, a minimum pore size of 100–135 μm for sustained healthy bone ingrowth is accepted [6].

On the other hand, it is supposed that the implant *in vivo* is probably first coated with plasma proteins and blood coagulation materials before the osteogenic cell adhesion takes place [16]. Therefore, smaller-size pores, of nano- and micro-scale dimension, have to effect the osteointegration process because such pores are similar in size to that of proteins, e.g. fibronectin, and the pores can promote the protein adhesion to the ceramic surface.

Another aspect of the problem is a combination of porous implant with a controled-in-time drug release system. In this case small-size pores can be impregnated with a drug like antibiotic, antimicrobial agent, growth factor, etc. to hinder the bacterial colonization of the implanted device, whereas the large-size interconnecting pores can functionally serve for the bone ingrowth. In this context, the aim of this work is to develop a route to prepare a porous hydroxyapatite ceramic containing the interconnected pores, the ceramic being of a bi-modal pore size distribution.

2. Materials and methods

As the starting materials, fine HA powder, gelatin and a vegetable oil are used. HA powder has been prepared from analytical grade $CaCl_2$, $(NH_4)_2HPO_4$ and NH_4OH by precipitation method described in detail elsewhere [17]. The powder was of 5.5 m^2/g BET specific area and of less than 1.0 μm particle size. The powder was mixed with 10% gelatin solution in distilled water. The slurry was dispersed in dispersion medium – oil at a room temperature with the use of a paddle stirrer. The stirring rate was 200–500 r.p.m. Spherical soft particles containing HA and gelatin formed due to the surface tension forces, the size of the particles being dependent on the HA/gelatin ratio in suspension and the stirring rate. Generally, the higher the stirring rate, the smaller is the particle size. The spheres were filtered, washed with ethanol and dried. The route allowed us to produce HA/gelatin granules of from 50 μm to more than 2000 μm in diameter and of perfectly spherical geometry. The granules were fractionated using standard test sieves,

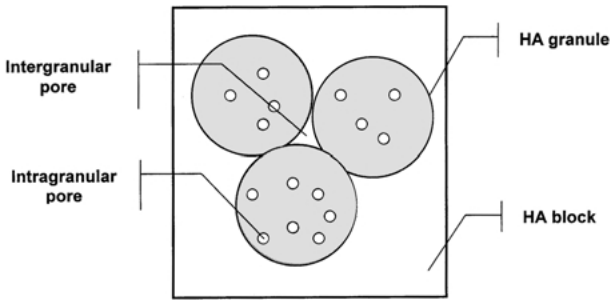


Figure 1 A structure model of the body sintered of porous spherical granules.

and those of 400–600 μm in diameter were used in further experiments.

Porous hydroxyapatite blocks were prepared by sintering of porous HA microgranules. Disc samples of 10 mm diameter and about 4–6 mm thickness were uniaxial pressed at 10–100 MPa pressure at a room temperature. Green bodies were further sintered at 1200 °C for 1 h in air.

Microstructure was monitored with a Neophot-32 microscope (Karl Zeiss, Jena, Germany) equipped with a Videolabs Desktop Color Video Camera (Videolabs Inc., USA), as well as by scanning electron microscopy (SEM) (a JEOL-3 microscope, Jeol Corp., Japan). Open pore size distribution (an Autoscan Qunatachrome Porometer, USA) was measured; their content was estimated by a common hydrostatic weighing in distilled water.

The disc specimens were tested for diametral compression loading to estimate the rupture tensile stress (Brazilian test) [18]. To calculate the strength, the following equation was used

$$\sigma = 2P/\pi dh \qquad (1)$$

where P is rupture load; d is diameter, and h is thickness of the disc. The samples were loaded in an UTS-100 stiff testing machine (UTS Testesysteme GmbH, Germany) at a cross-head speed of loading device of 1.0 mm/min. An error of the rupture load measurement was kept at $\pm$ 1%.

3. Results and discussion

Fig. 1 represents a structure model of porous bi-modal pore-size distribution ceramics. The bi-modality is due to the intergranular and intragranular pores in the body. Intragranular pore size and content are dependent strongly on the preparation route, e.g. on the gelatin/HA ratio in the initial suspension and on the heat treatment regime. Fig. 2 shows the mercury porometry data on open pore content versus the heat treatment temperature for the granules prepared with varied initial gelatin/HA content in the initial suspension. Porosity in the range from about 43 to 17 vol % can be obtained. Dominant pore size (effective diameter) is in the range 4–10 nm, the pore size increases within above range with an increase in the heat treatment temperature. These pores occupy from 34 to 68 vol % of the total open pores within the granules. Other pores are those of from 1 to 10 μm in diameter. The existence of the latest pore population is confirmed by microscopy observations. It

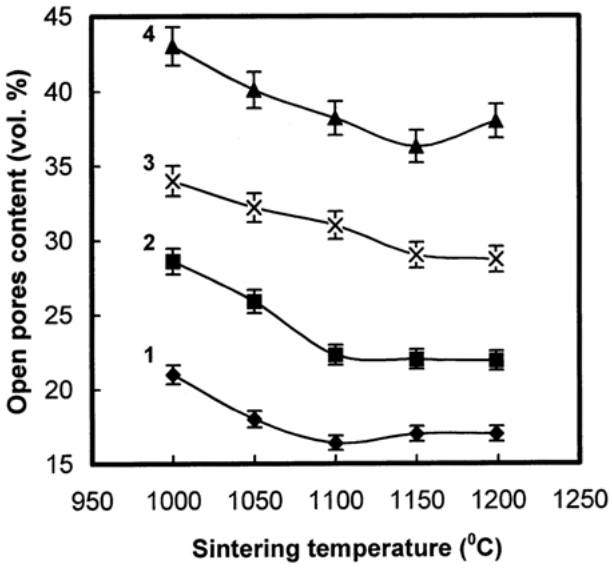


Figure 2 Open pores content versus heat treatment temperature of the granules: gelatin content in starting slurry 2.0 ml/g (1); 2.5 ml/g (2); 3.0 ml/g (3), and 3.5 ml/g (4).

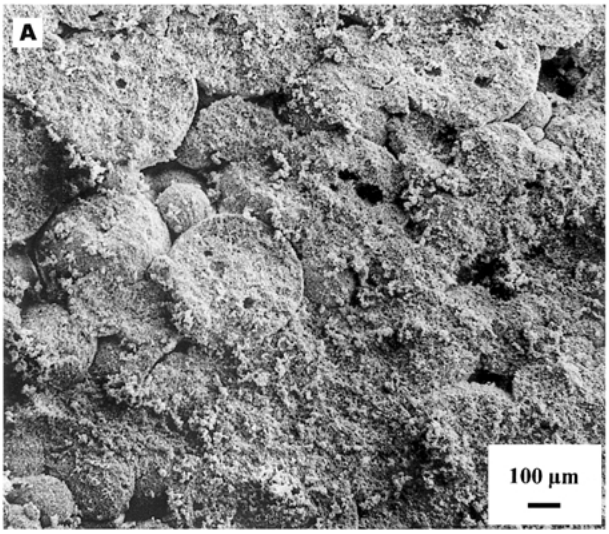
can be supposed, according to Strelov [19], that the pores of 10 μm diameter are connected either directly or by narrow slit-like channels. In the last case the mercury porometry data accounted for these channels size only, because the penetration of the mercury under the pressure is limited by the channel size.

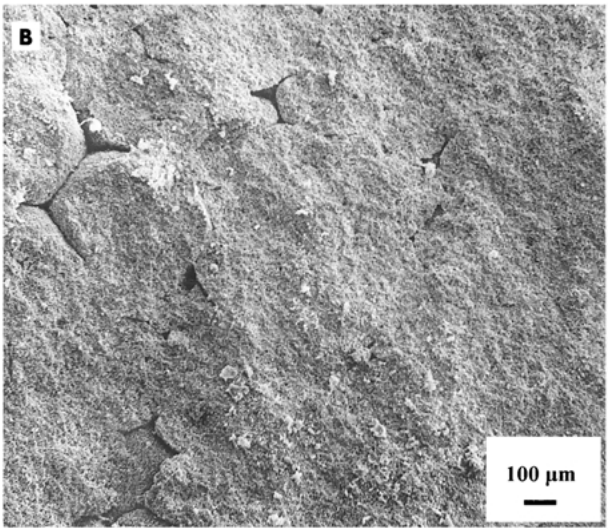
Intergranular pores result from the granule packing features. Monosize particles can be free packed into a green body having the relative open pore content 0.3–0.4 of the total body volume [20], if the packing is uniform and no arch effect of packing exists. Such packing density corresponds to the coordination number, N, of about 7 in the particles package

$$N = 11.6(1 - \Theta) \qquad (2)$$

where Θ is the pore content [21]. This N value is close to the coordination number of a body centerd cubic (b.c.c.) structure model. In the frame of this model, minimum pore cross-section can be evaluated from a simple geometric consideration of the packing density in the most dense-packed (110) plane of the b.c.c. structure. This minimum size is equal to about 0.2×0.4 of the spherical granule diameter. Therefore, the packing of monosize spherical glanules of 500 μm in diameter provides the open interconnecting pores of up to $100 \times 200\ \mu m^2$ cross-section. This size is in accordance to the requirement of a minimum pore dimension of 100–135 μm essential for sustained healthy bone ingrowth into implanted device [6]. To increase the pore size, coarser granules must obviously be used.

The situation becomes more complicated in the case of the polydisperse granule packing. A model of spherical granule packing for bi-size granule mixtures has been devised in Krasulin *et al*. [22]. It has been shown that the open intergranular pore percentage varies from 12.5 to about 35 vol %, the value being dependent on the granule dimension ratio and their relative contents in the mixture. If the granules of two diameters, d_1 and d_2, $d_1 \geq 5d_2$, are packed, a minimum of the intragranular pore content can be predicted as





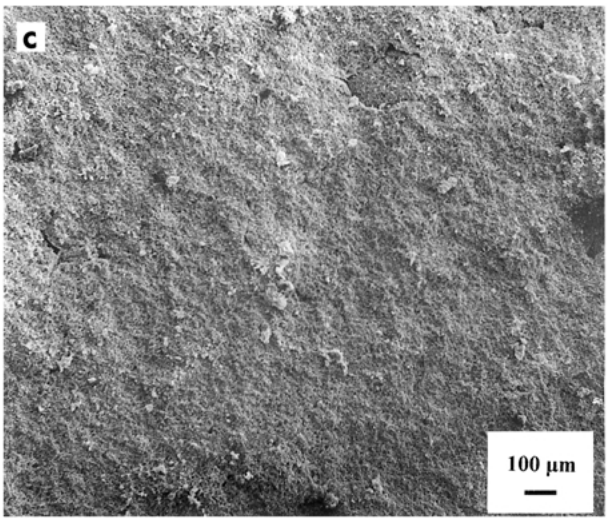


Figure 3 Scanning electron microscopy picture of ceramics sintered at 1200 °C being compacted at a pressure (a) 20 MPa (b) 80 MPa and (c) 100 MPa.

$$\Theta_{\min} = kV_2/[(1-k)V_1 + V_2] \qquad (3)$$

where k is a coefficient in the range from 0.3 to 0.4; V_1 and V_2 are the volumes occupied by coarse and fine spherical granules, respectively [22].

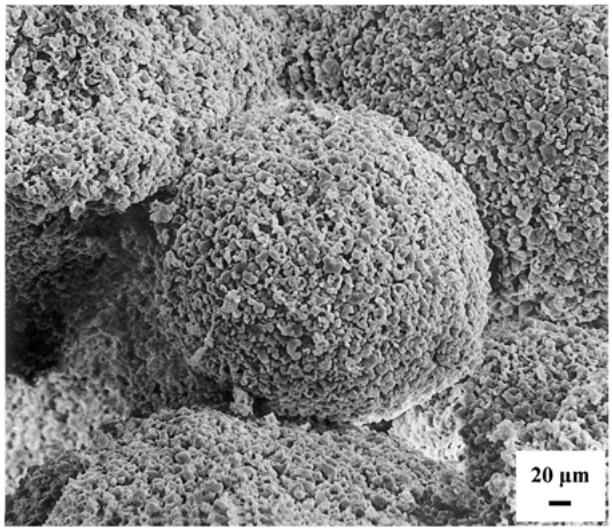


Figure 4 Scanning electron microscopy pictures of sintered at 1200 °C ceramics being compacted at 40 MPa.

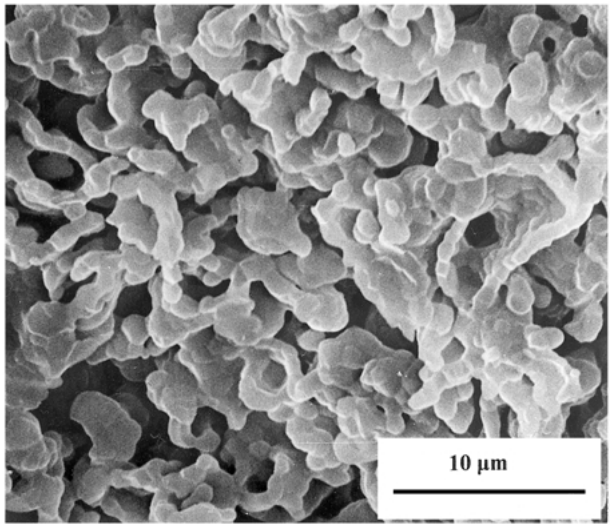


Figure 5 SEM micrograph of the granule surface in the sintered ceramics.

Microstructure of ceramics produced by sintering the granules depends on the green body compacting pressure. Fig. 4 shows SEM micrographs of the structure of ceramic blocks prepared by sintering at 1200 °C for 1 h of about mono-disperse batch of the granules having the mean size of 500 μm. The higher the compaction pressure, the lower is the interpore size and content, as can be seen from the micrographs of Figs 3(a)–(c). Shown in Fig. 4 is the pore view near an individual granule in the sintered ceramics, the green body being compacted at a pressure of 40 MPa. The pores size is up to 100 μm. Fig. 5 gives microstructure of the surface of the granule in the sintered ceramics. The pores of from 1 to 10 μm dimensions are clearly evidenced.

Mercury porometry measurements performed on individual 500 μm diameter granules after the heat-treatment at 1200 °C for 1 h revealed that the open pore content equals about 18 vol %. Shown in Fig. 6 is the total open pore content in sintered at 1200 °C body versus the compaction pressure plot. The open pore content decreases gradually with an increase of the compaction

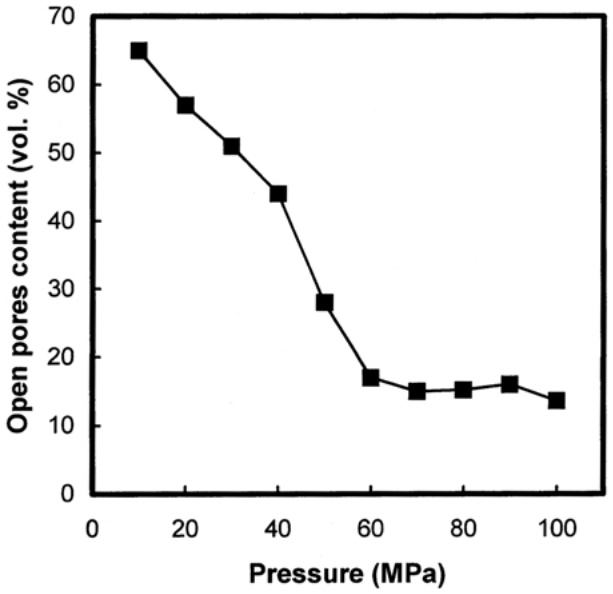


Figure 6 Total open pore content in sintered bodies versus compaction pressure.

pressure until the pressure of about 60 MPa is reached. This is due to the granule rearrangement and deformation because the granules contain gelatin which makes them plastic. Measured for the samples prepared at very low compaction pressure, the porosity is as high as 65 vol %. This value is higher than the sum of the intragranular porosity (18 vol %) and the predicted intergranular porosity for the uniform packing case (30–45 vol %). Therefore, a non-uniformity of the packing exists, probably resulting from the sticking of the granules together due to the gelatin. If the pressure exceeds 60 MPa, the pore content in sintered body becomes independent of the compaction pressure, being equal to about 18 vol %. This value corresponds to the open pore content in the granules themselves. Therefore, open porosity in the sintered bodies which are compacted at a pressure of 60 MPa and above is the intragranular porosity. Bodies prepared at the compacting pressure of 10 and 20 MPa are weak and may be crushed by hand easily. So, the ceramics obtained at 30–50 MPa densification pressure can only be considered as being of interest for practice.

Given in Table 1 are the mercury porometry measurement data on the open pore content and distribution within the sintered at 1200 °C blocks in dependence on the green body unaxial compacting pressure. The ceramics containing intragranular fine pores and intergranular coarse these, of about 100 μm effective diameter, can be produced with the use of the 500 μm size spherical granules batch compacted at 30 MPa pressure.

Fig. 7 gives the dependence of the rupture tensile stress of ceramics on the open pores content. The strength reduces drastically with an increase of porosity in the range from about 30–40 vol % reaching approximately constant level with the further increase of porosity. The strength is known to be influenced strongly by pores. Generally, an exponential dependence is used, $\sigma = \sigma_0 \exp(-\eta\Theta)$, where σ_0 is the strength of a non-porous body, $\eta = 7$–8 is a constant, to predict the pore effect [23]. The other common equation is $\sigma = \sigma_0(1 - \Theta)^m$, where exponent m equals to 3–10 for ceramics [23, 24]. Estimates give that a pore content of about 30 vol % decrease the strength by a factor of about 8–12. Therefore, the measured strength value seems to be a non-contradictory one, because the tensile strength of dense hydroxyapatite ceramics varies from 10 to 100 MPa [25].

Thus, the hydroxyapatite ceramics of bi-modal pore size distribution containing coarse interconnecting pores up to about 100 μm and above in size can be produced with the use of spherical HA/gelatin granules of 500 μm and above in diameter. These ceramics can further be impregrated under vacuum by different drugs [11], and the fine pores filled with drug will serve for drug delivery to hinder bacterial colonization, whereas the coarse interconnecting pores will invite ingrowth of bone into the implant, leading to more securely fixed and integrated repair, particularly in cancellous bone where the structure closely mirrors that of the host [6]. Besides, the increased amount of pores may enhance the formation *in vivo* of the biological carbonate-containing HA on the implanted device surface [26]. This should make the composition of the surface close to that of the human body mineral influencing the biointegration behavior.

4. Conclusion

A method is developed to produce porous hydroxyapatite ceramics of bi-modal pore size distribution. The route includes the preparation of gelatin-containing hydroxyapatite spherical granules followed by the compaction and sintering of the green body. Blocks of about 18 vol % fine pores content and of 25–52 vol % total open pore content are produced, the coarse pores being interconnected and of about 100 μm in size. These coarse

TABLE I Open pore characteristics of ceramics sintered at 1200 °C

Pressure (MPa)	Total open pore content (vol %)	Dominant open pore size and content			
		Intragranular pores		Intergranular pores	
		Size (nm)	Content: vol %	Size (μm)	Content vol %
10	67	2–10 and 5000–14 000	17–18	> 100	48–49
30	51	2–10 and 5000–14 000	17–18	about 100	33–34
50	28	2–10 and 5000–14 000	17–18	about 30	9–10

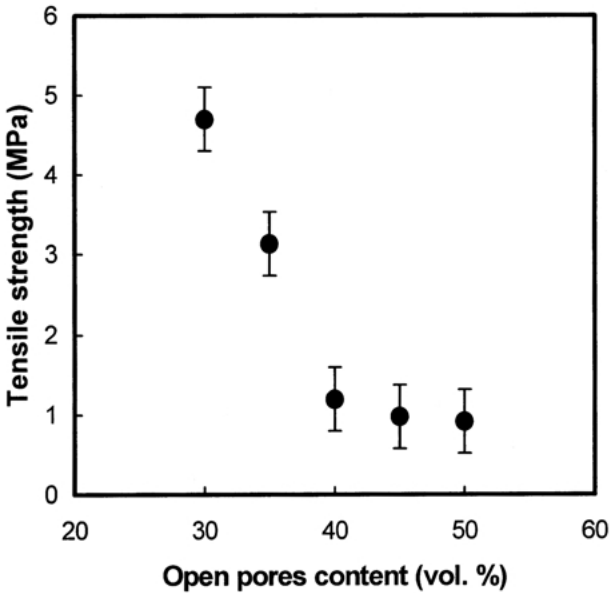


Figure 7 Tensile strength estimated by diametral compression test versus open pore content in ceramics.

pores can promote the bone ingrowth, whereas the fine pores can be filled with a drug, e.g. to reduce bacterial colonization of the implanted device.

Acknowledgment

One of the authors, S.M.B. is grateful to INTAS, grant N 97-30443, for the financial support for his participation in this work.

References

1. H. AOKI, ''Science and Medical Application of Hydroxyapatite'' (JAAS, Tokyo, 1991) p. 137.
2. L. L. HENCH, in ''Ceramics and Society'', edited by P. Vincenzini (Techna, Faenza, 1995) p. 101.
3. K. A. HING, S. M. BEST and W. BONFIELD, *J. Mater. Sci.: Mater. Med.* **10** (1999) 135.
4. Y. L. LIU, J. SCHOENAERS, K. DE GROOT, J. R. DE WIJN and E. SCHEPERS, *ibid.* **11** (2000) 711.
5. A. UCHIDA, S. M. N. NADE, E. R. MCCARTNEY and W. CHING, *J. Bone Joint Surg.* **66B** (1984) 269.
6. K. A. HING, S. M. BEST, K. E. TANNER, W. BONFIELD and P. A. REVELL, *J. Mater. Sci.: Mater. Med.* **10** (1999) 663.
7. P. S. EGGLI, W. MUELLER and R. K. SCHENK, *Clin. Orthop. Rel. Res.* **232** (1988) 127.
8. A. KRAJEWSKI, A. RAVAGLIOLI, E. RONCARI, P. PINSCO and L. MONTANARI, *J. Mater. Sci.: Mater. Med.* **11** (2000) 763.
9. W. PAUL and C. T. SHARMA, *ibid.* **10** (1999) 383.
10. W. PAUL and C. T. SHARMA, *J. Mater. Sci. Lett.* **14** (1995) 224.
11. M. ITOKAZU, M. ESAKI, K. YAMAMOTO, T. TANEMORI and T. KASAI, *J. Mater. Sci.: Mater. Med.* **10** (1999) 249.
12. J. X. LU, B. FLAUTRE, K. ANSELME, P. HARDOUIN, A. GALLUR, M. DESCAMPS and B. THIERRY, *ibid.* **10** (1999) 111.
13. R. E. HOLMES, V. MOONEY, R. BUCHOLZ and A. TENCHER, *Clin. Orthop. Rel. Res.* **188** (1984) 252.
14. M. YAMAMOTO, Y. TABATA, H. KAWASAKI and Y. IKADA, *J. Mater. Sci.: Mater. Med.* **11** (2000) 213.
15. J. J. KLAWITTER and S. F. HULBERT, *J. Biomed. Mater. Res. Symp.* **2** (1971) 161.
16. R. A. SMITH, M. W. MOSESSON, A. U. DANIELS and T. K. GARTNER, *J. Mater. Sci.: Mater. Med.* **11** (2000) 279.
17. V. P. ORLOVSKI, Z. A. EZHOVA, G. V. RODICHEVA, E. M. KOVAL, G. E. SUKHANOVA and L. A. TEZIKOVA, *J. Inorg. Chem.* **37** (1992) 881.
18. S. M. BARINOV and V. JA. SHEVCHENKO, ''Strength of Engineering Ceramics'' (Science, Moscow, 1996) p. 19.
19. K. K. STRELOV, ''Structure and Properties of Refractories'' (Metallurgy, Moscow, 1972) p. 216.
20. G. N. DULNEV and YU. P. ZARICHNJAK, ''Heat Conductivity of Mixtures and Composite Materials'' (Energy, Leningrad, 1974) p. 264.
21. M. G. KAGANER, ''Heat Insulation in Low Temperatures Technology'' (Mashinostrojenije, Moscow, 1966) p. 275.
22. YU. L. KRASULIN, V. N. TIMOFEEV, S. M. BARINOV, A. B. IVANOV, A. N. ASONOV and G. D. SHNYREV, ''Porous Structural Ceramics'' (Metallurgy, Moscow, 1980) p. 73.
23. R. A. ANDRIEVSKI, *Powder Metal.* **N1** (1982) 37.
24. R. A. ANDRIEVSKI and I. I. SPIVAK, ''Strength of Refractory Compounds and Related Materials'' (Metallurgy, Tcheljabinsk, 1989) p. 239.
25. W. SUCHANEK and M. YOSHIMURA, *J. Mater. Res.* **13** (1998) 94.
26. K. IOKU, K. YANAGISAWA, N. YAMASAKI, H. KUROSAWA, K. SHIBURA and H. YOKOZEKI, *Bio-Med. Mater. and Eng.* **3** (1993) 137.

Received 23 April
and accepted 7 September 2001