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Strength of hollow hydroxyapatite microspheres prepared by a glass conversion process

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Abstract Hollow hydroxyapatite (HA) microspheres (diameter = 100–800 μm) were prepared by reacting solid Li_2O–CaO–B_2O_3 glass spheres in 0.25 M K_2HPO_4 solution at 37°C. The influence of subsequent heating on the microstructure, surface area, and compressive strength of the HA microspheres was evaluated using scanning electron microscopy, the BET method, and nano-mechanical testing. The surface area and rupture strength of the as-prepared microspheres were 135 m^2/g and 1.6 ± 0.6 MPa, respectively. On heating for 8 h at 600°C, the surface area decreased to 27 m^2/g, but there was no increase in the compressive strength (1.7 ± 0.4 MPa). Heating to 800°C (8 h) resulted in a marked decrease in the surface area (to 2.6 m^2/g) and a sharp increase in the compressive strength (to >35 ± 8 MPa). These hollow HA microspheres may be useful as devices for drug or protein growth factor delivery or as scaffolds for engineered tissues.

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1 Introduction

Microspheres of biodegradable polymers, bioceramics, and glass have been widely studied over the past few decades for biomedical applications such as drug delivery devices for proteins [1, 2], radiation delivery devices to treat liver cancer and rheumatoid arthritis in humans [3], and scaffolds for bone tissue engineering [4, 5]. Biodegradable polymer microspheres, both synthetic and natural, have been the most widely studied drug delivery devices because of several favorable characteristics, including degradation in vivo to produce biocompatible or non-toxic byproducts, relatively simple fabrication, and facile administration to a variety of locations in vivo [1, 6–8]. Degradation of the microspheres leads to controllable, sustained delivery of the encapsulated protein drug. Microspheres of poly lactic acid (PLA), and copolymers of PLA and poly glycolic acid (PGA), find considerable use because they are among the few synthetic biodegradable polymers approved for human clinical use.

Bioinert glass microspheres, with an yttria aluminosilicate composition containing Y^{89}, have been developed by Day and Day [3] to deliver localized doses of radiation for the treatment of liver cancer. Prior to use, the microspheres are bombarded by neutrons to create Y^{90}, a radioactive isotope which undergoes beta-decay, with a short half-life (64 h), and with a short range (2–3 mm) in the liver. Localization of the radiation at the site of the tumor decreases the radiation dosage required to kill the cancer cells, thereby reducing toxic side effects. Biodegradable borate glasses containing rare earth oxides such as Dy_2O_3 have been investigated for use as radiation delivery vehicles to treat rheumatoid arthritic joints [3, 9] in much the same way as the bioinert yttrium aluminosilicate glass microspheres are used to deliver large doses of localized beta radiation to treat liver cancer.

Microspheres and microparticles of biocompatible phosphates such as hydroxyapatite (HA) and tricalcium phosphate (TCP) are being considered for use in controlled drug delivery [1] and for the formation of scaffolds in bone repair [10]. HA is the main mineral constituent of bone, so it should produce no systemic toxicity or immunological reactions. Because of its inorganic structure, HA devices might provide higher strength than similar devices prepared from biodegradable polymers. However, synthetic HA resorbs slowly or undergoes little conversion to a bone-like material after in vivo implantation [11]. The toxicity of HA, particularly in the form of fine particles, is the subject of some debate. Some studies have shown that HA in the solid or particulate form produced a favorable substrate for adhesion, proliferation, and differentiation of osteoblasts and, thus, to more efficient growth of new bone [12, 13]. On the other hand, fine particles or particulate debris of HA have been reported to produce an adverse effect on cells and an enhanced inflammatory reaction [14, 15]. The biological response depended on the size, morphology, and structure of the HA particles.

Methods used to prepare porous HA microspheres include spray drying of particulate suspensions [16], oil-in-water emulsions [17], plasma spraying [18], and gelling of suspensions [19]. Hollow HA microspheres, consisting of a hollow core and a porous shell, have been prepared by coating chitin microspheres with a composite layer of chitin and HA, followed by thermal decomposition of the chitin and sintering of the porous HA shell [20]. Day and Conzone [21] invented a process for the preparation of HA microspheres or fibers, hollow or porous, at near room temperature by converting borate glass with special compositions in dilute phosphate solution [9, 22, 23]. The conversion reaction was pseudomorphic, so the product retained the same external shape and dimensions as the starting glass object. The as-prepared product typically consisted of nanostructured HA with a surface area as high as 200 m^2/g.

The objective of the present work was to determine the compressive strength of hollow HA microspheres prepared by the borate glass conversion method. The strength of individual microspheres was measured using nano-mechanical testing equipment which permitted small loads (<500 mN) to be applied to the microspheres and the measurement of small displacements. The influence of calcination on the surface area and strength of the as-prepared HA microspheres was also investigated. Data on the surface area and strength of these HA microspheres are important for evaluating the use of these materials as devices for controlled drug or growth factor release, or as scaffolds for the repair of bone.

2 Experimental procedure

The composition of the borate glass (in wt%) was $10Li_2O \cdot 10CaO \cdot 80B_2O_3$, which was within the range of compositions known from previous work to be capable of producing hollow HA microspheres [21–23]. Microspheres of two different diameters, 106–125 and 500–800 μm, were prepared. The smaller microspheres were used for microstructural and surface area characterization, whereas the larger spheres were used for strength measurement because they could be manipulated more easily in the instrument.

The preparation of glass microspheres of diameter 106–125 μm and their conversion to hollow HA microspheres are described in detail elsewhere [21–23]. Briefly, glass microspheres were prepared by melting Li_2CO_3, $CaCO_3$, and H_3BO_3 in a platinum crucible for 1 h at 1,100°C, casting the melt onto steel plates, grinding the quenched glass in a hardened steel mortar and pestle, sieving to give the required size range, and spheroidization in a flame at ~1,400°C. Conversion to hollow HA microspheres was achieved by reacting 1 g of glass microspheres for 5 days in 100 cm^3 of 0.25 M K_2HPO_4 solution at 37°C and pH 9.

Glass microspheres of diameter 500–800 μm were prepared by pouring the molten glass onto a stainless steel plate, thereby creating droplets that solidified to form nearly spherical particles. Conversion of these larger glass spheres to HA was achieved by reacting them for 14 days under the aforementioned conditions. The as-formed HA microspheres were dried for more than 24 h at 90°C. Some HA microspheres were calcined for 8 h at 600 or 800°C.

Scanning electron microscopy (SEM) (S-4700; Hitachi, Tokyo, Japan) and X-ray diffraction (XRD) (XDS 2000; Scintag, Cupertino, CA) were used to examine the structural characteristics of the as-formed and heat-treated HA microspheres. XRD was performed using CuK_α radiation at a scan rate of 1.8° 2θ per min, in the range 10–80°. Prior to XRD, the microspheres were ground in an agate mortar and pestle to form a powder, and sieved through a 325 mesh sieve (aperture <45 μm). The surface area of the HA microspheres was measured using N_2 adsorption at the boiling point of liquid N_2, by the BET method (Nova-1000; Quantachrome, Boynton Beach, FL).

The compressive strength of individual HA microspheres was measured using a nano-mechanical testing machine (Nano Bionix; MTS Corp., Eden Prairie, MN). Except for the greater precision of measuring small loads and displacements provided by this equipment, the general methodology was similar to those used previously to determine strength by direct unidirectional compression tests on individual pelletized spheres (8–20 mm in diameter) using an Instron testing machine [24], or on individual

granules (100–2,000 μm) using laboratory-designed equipment [25]. For each group of HA microspheres studied in the present work (as-prepared or heated at 600 or 800°C), 5–6 microspheres were tested and the mean strength and standard deviation were determined.

A schematic of the important functional elements of the machine is shown in Fig. 1. The two significant components of the machine are the crosshead and the Nano Mechanical Actuating Transducer (NMAT), both of which are controlled by software using a personal computer. The crosshead is actuated by a precision lead screw and has a relatively large range of motion (150 mm) with a resolution of 35 nm. The NMAT column has a maximum displacement of 750 μm with a displacement resolution of <1 nm, and a maximum load of 500 mN with a resolution of 50 nN.

In the measurement of the rupture strength, a single microsphere was placed on the NMAT column. The crosshead was moved slowly toward the NMAT column until the NMAT column was negatively displaced a distance of 1 μm. The crosshead was then backed away 5 μm to ensure slight separation between the microsphere and the crosshead. The NMAT column was then moved toward the crosshead at a rate of 50 nm/s until the slope of the raw electro-mechanical force signal versus the raw NMAT column position signal reached a threshold of 250 N/m. When this threshold was reached, the microsphere was assumed to have just reached intimate contact with the crosshead, at which point the crushing force on the microsphere was assumed to be zero. The electromagnetic force on the NMAT column was increased, to increase the crushing load at a rate of 0.3 mN/s. The force was increased until the sphere experienced catastrophic failure, identified by an instantaneous jump in the position of the NMAT column. During each test, data from each signal was captured at 10 Hz. After each test, the data were stored and retrieved in a text format for analysis.

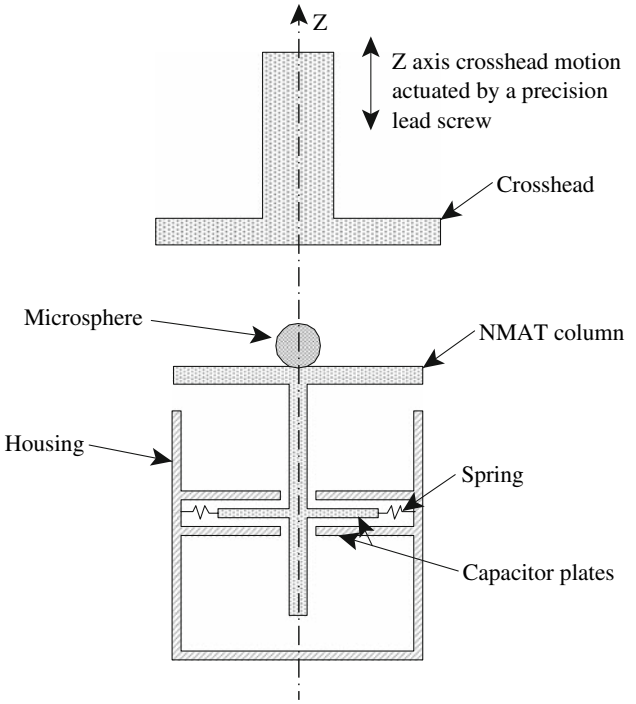

Fig. 1 Schematic of the functional elements of the MTS Nano Bionix universal testing machine

3 Results and discussion

XRD patterns (Fig. 2) confirmed that the phase composition of the as-prepared and heat-treated microspheres corresponded to that of a reference HA (JCPDS 72-1243). The broad peaks of the as-prepared microspheres indicated that the HA consisted of nanosize crystals, was incompletely crystallized, or a combination of these two. Heating to 600 or 800°C caused a reduction in width of the peaks and an increase in the intensity (peak height), indicating coarsening of the HA crystals or more complete crystallization of the material. BET surface area data (Table 1) showed that the as-prepared HA microspheres had a high surface area (135 m^2/g), which decreased by a factor of 5 (to 27 m^2/g) after heat treatment at 600°C. Heating the as-prepared microspheres at 800°C produced a more drastic reduction in surface area to 2.6 m^2/g, which is more than 50 times smaller than the surface area of the as-prepared microspheres. This drastic reduction in the surface area of the heat-treated microspheres was presumably caused by coarsening of the HA particles, densification of the microspheres, or a combination of these two processes.

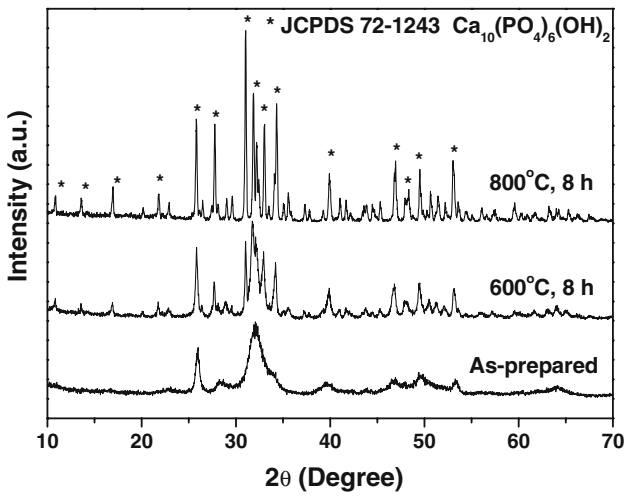

Fig. 2 XRD patterns of powders formed from three groups of hollow HA microspheres: as prepared, heat-treated for 8 h at 600°C, and heat-treated for 8 h at 800°C. The peaks correspond to those of a reference HA (JCPDS 72-1243)

Table 1 Surface area and compressive strength of as-prepared and heat-treated hollow HA microspheres

Sample	Surface area (m^2/g)[a]	Compressive strength (MPa)[b]
As-prepared	135	1.6 ± 0.6
8 h at 600°C	27	1.7 ± 0.4
8 h at 800°C	2.6	>35 ± 8

[a] Microsphere diameter = 106–125 μm

[b] Microsphere diameter = 500–800 μm

Figure 3a–c shows SEM images of as-prepared HA microspheres dried at 90°C, and subsequently heated for 8 h at 600 or 800°C. Observations of deliberately fractured microspheres showed that the shell wall consisted of a porous multilayered structure (Fig. 3d–f), in which the layers differed in microstructure. The outer layer (a few microns thick) was smooth, and apparently less porous than the inner layers. Higher magnification SEM of the shell walls (Fig. 3g–i) showed that heating to 800°C caused densification and separation of the layers in the shell.

Within the limits of detection (<0.5 wt%), the powder diffraction patterns (Fig. 2) showed that the hollow microspheres consisted of the HA phase only. Furthermore, energy-dispersive X-ray (EDS) analysis in the SEM showed no significant difference between the surface and inner region of the microsphere wall. It appeared that the separation of the layers in the shell wall observed for the microspheres heated to 800°C was not caused by compositional differences, which could lead to differences in the thermal expansion coefficient of the layers, and therefore to differential stresses during heating. Instead, structural differences in the layered microsphere wall, caused by the conversion reaction [26], may lead to differences in shrinkage (or densification) between the layers and, therefore, to differential stresses and separation of the layers, upon heating to sufficiently high temperatures.

A typical load versus displacement curve obtained from the measurement of the rupture strength of the hollow HA microspheres is shown in Fig. 4. The load increased with displacement, following the curve A to B. Prior to collapse of the sphere, when the load was released, the relationship between load and displacement followed the curve B to C. In the case of purely elastic deformation, the load versus displacement curve would return to its original position (A) along the path B to A as the load was released. On the other hand, if the deformation were purely plastic, the load versus displacement curve would follow the path B to D. In these experiments, the curve followed the path B to C, so the deformation was neither purely elastic nor purely plastic. It was difficult to determine the contact area between the HA microsphere and the crosshead during application of the load, so the elastic deformation model was not used. The compressive strength was determined from the purely plastic deformation model. Because the contact area for purely plastic deformation is larger than that for purely elastic deformation, the compressive strength (which is inversely proportional to the contact area) determined from the plastic deformation model is commonly lower than the value determined from the elastic deformation model. Therefore, the actual rupture strength of the HA microspheres should be higher than the values determined in these experiments.

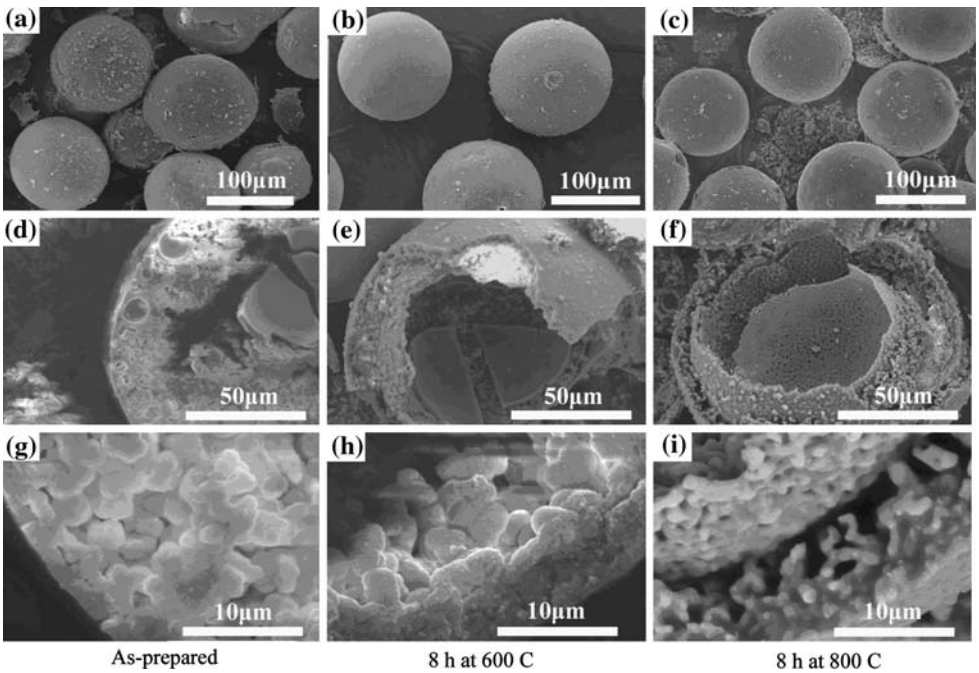

Fig. 3 SEM images of the surfaces and fractured sections of hollow HA microspheres (106–125 μm): as-prepared (**a**, **d**, **g**); heat-treated for 8 h at 600°C (**b**, **e**, **h**); heat-treated for 8 h at 800°C (**c**, **f**, **i**)

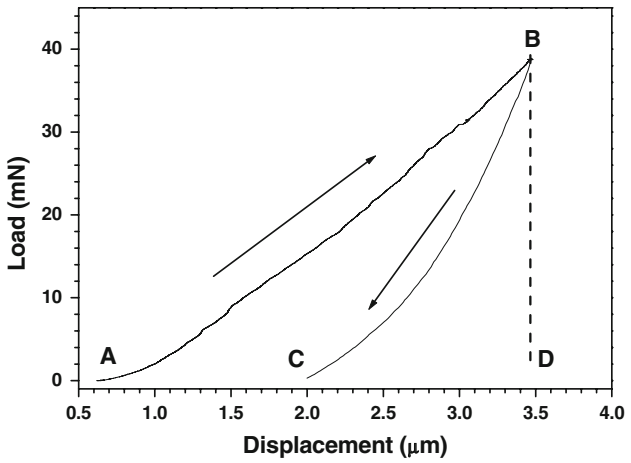

Fig. 4 Load versus displacement for an individual hollow HA microsphere tested below the point of rupture

Figure 5 shows load versus displacement data for the as-prepared and heat-treated HA microspheres. Two typical curves are shown for each system. For the as-prepared microspheres and the microspheres heated at 600°C (Fig. 5a, b), the load increased approximately linearly with displacement until rupture, but in some cases, a short constant-load region preceded rupture. In the case of the microspheres heated to 800°C (Fig. 5c), the load versus displacement data also followed an approximately linear relationship, but the curve contained several small peaks and valleys. Rupture of the microspheres in Fig. 5c did not occur at the highest load that could be applied with the instrument, so the actual compressive strength was higher than the value determined in the test.

Data for the mean strength and the standard deviation are given in Table 1 for the as-prepared and heat-treated HA microspheres. Within the limits of experimental error, there was no difference in the compressive strength of the as-prepared microspheres dried at 90°C (1.6 ± 0.6 MPa) and the microspheres heated at 600°C (1.7 ± 0.4 MPa). However, the surface area of the microspheres decreased considerably (from 135 to 27 m^2/g) on heating at 600°C. Presumably the coarsening of the HA particles which caused a reduction of the surface area at 600°C did not alter the strength-limiting flaws present in the as-prepared HA microspheres. In the case of the HA microspheres heated at 800°C, enhanced coarsening coupled with densification, as observed in Fig. 3i, may be responsible for the considerable strengthening (compressive strength >35 ± 8 MPa) and low surface area (2.6 m^2/g).

Microspheres of diameter 106–125 μm were used in the characterization of the microstructural and surface area changes produced by the glass conversion reaction, whereas microspheres of diameter 500–800 μm were used in the compressive strength tests. This is because the smaller microspheres (106–125 μm) are more desirable for some biomedical applications such as drug delivery and are easier to prepare but, because of their small size, they are difficult to manipulate and position correctly in the nano-

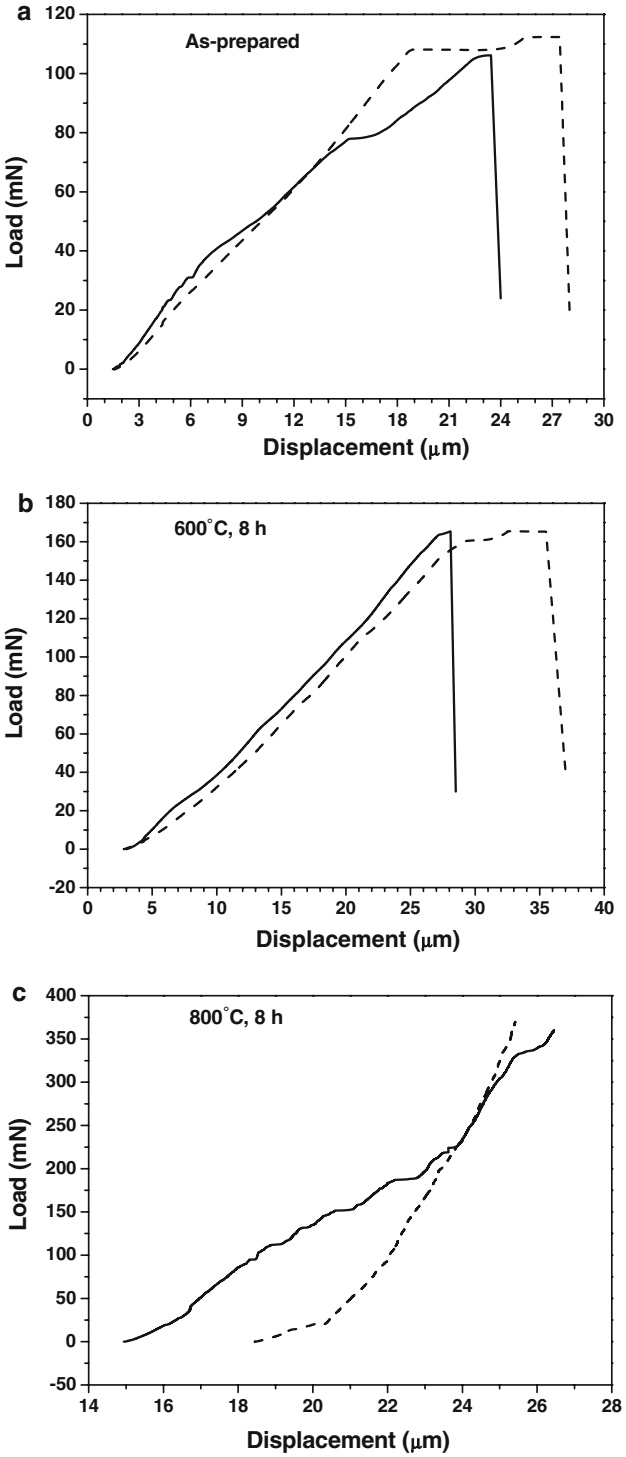

Fig. 5 Examples of load versus displacement data for individual hollow HA microspheres (500–800 μm): (**a**) as-prepared (dried at 90°C); (**b**) heated for 8 h at 600°C; (**c**) heated for 8 h at 800°C

mechanical testing machine. For porous spheres which are compositionally and structurally homogeneous, the compressive strength should be independent of size, as observed for Al_2O_3 and SiO_2 granules (100–2,000 μm) [25]. In the present work, testing of two groups of HA microspheres with diameters of ~500 and ~800 μm, respectively, showed no size effect on strength. Since the microspheres were assumed to be spherical in determining the contact area between the microsphere and the crosshead of the testing machine, deviation from a spherical geometry would also influence the measured strength of the HA microspheres. Corrections for deviation from the spherical shape would require additional data, such as the lengths of the long and short axes of each individual microparticle.

Hollow HA microspheres could be used as devices for delivery of drugs or protein growth factors. Previous work [22] with hollow HA microspheres prepared by a similar technique showed that the release of a protein, bovine serum albumin (BSA) from the microspheres into a surrounding medium of phosphate buffered saline (PBS) was dependent on the calcination temperature of the microspheres. The release of BSA was most rapid from the as-prepared microspheres dried at 90°C, presumably because these microspheres had the highest porosity and surface area as well as the largest pores. More sustained release of BSA was observed from hollow HA microspheres heated to 600°C, presumably because of the reduction in porosity. An even smaller release rate was observed from hollow microspheres heated at 900°C, presumably because nearly all the pores were closed off. The small amount of BSA released from the hollow HA microspheres heated at 900°C might also be caused by residual BSA adsorbed on the external surface of the microspheres which were not removed after repeated washing.

The results indicate that the strength of the as-prepared HA microspheres (~1.6 MPa) did not increase after heating for 8 h at 600°C. For some biomedical applications, hollow HA microspheres with higher strength coupled with the ability to provide sustained release of drugs or growth factors may be required. While a marked increase in strength occurred upon heating for 8 h at 800°C, this was achieved at the expense of a drastic reduction in surface area and porosity. Further studies are required to develop microstructure–strength relationships for these hollow HA microspheres in order to provide a better basis for achieving a combination of enhanced strength and sustained drug or growth factor release.

Fine particles or particulate debris of HA, as outlined earlier, have been reported to produce an adverse effect on cells and an enhanced inflammatory reaction [14, 15]. In the present system, the as-prepared HA microspheres consisted of a porous three-dimensional network in which nanosize HA particles were bonded together, so the HA did not exist as free particles. Furthermore, when heated to higher temperatures, the HA particles coarsened (with a reduction in surface area), leading to enhanced connectivity. Toxic effects caused by the dispersed state of free HA particles are therefore expected to be absent in the present system.

4 Conclusion

Hollow HA microspheres prepared by converting Li_2O–CaO–B_2O_3 glass microspheres in dilute (0.25 M) K_2HPO_4 solution at 37°C had a high surface area (135 m^2/g) and a rupture strength of 1.6 ± 0.6 MPa. Heating for 8 h at 600°C caused a substantial reduction in the surface area of the microspheres to 27 m^2/g but no change in the strength of the microspheres (1.7 ± 0.4 MPa). Upon heating for 8 h at 800°C, a drastic decrease in the surface area (to 2.6 m^2/g) was accompanied by a considerable increase in the rupture strength (>35 ± 8 MPa). These changes in the surface area and strength of the heat-treated HA microspheres may be caused by densification, coarsening, or a combination of these two processes.

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