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Synthesis of porous hollow silica nanostructures using hydroxyapatite nanoparticle templates

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Abstract

Porous hollow spherical and rod like silica nanoparticles were obtained *via* a surfactant templating method adopting hydroxyapatite (HAp) nanoparticles as an etchable core material.

Mesoporous silica has attracted significant interest since the discovery of surfactant templating methods.^{1,2} Having large surface areas and high capacity to adsorb a variety of biological molecules, mesoporous materials offer an ideal platform for application in various fields such as drug delivery,³ catalysis,⁴ sensing,⁵ separation⁶ and electrical insulation.⁷ Mesoporous silica particles with hollow interiors have also attracted attention, and have a number of useful attributes including low density, high surface area, thermal and mechanical stability, and potentially unique optical and chemical properties.

The most successful synthetic approaches to hollow shell particles are based on template methods, involving latex,⁸ gold,⁹ silica,¹⁰ polystyrene¹¹ and carbon¹² templates. Other routes include emulsion¹³ or vesicle-based¹⁴ systems, in which the emulsion droplets act as templates, and use of co-solvents.¹⁵ The preparation of hollow nanoporous silica shells *via* surfactant templating methods has been investigated, and the effects of varying solvent composition, hydrolysis catalyst and surfactant reported.^{16–18} Existing methods have employed calcium carbonate,^{19,20} polystyrene¹¹ and latex⁸ particles as core templates to produce hollow silica nanostructures. These methods often require strictly controlled synthetic conditions and produce large particles with poor monodispersity and uncontrolled morphology. The morphology and properties of hard core template methods can be exploited to generate hollow structures in a variety of shapes and sizes.²⁰ The Stober²¹ method has been further modified by employing organic surfactant templates to produce nanoporous materials with controlled dispersity and morphology.^{16,18}

Hydroxyapatite ($\text{Ca}_{10}(\text{PO}_4)_6(\text{OH})_2$) has several properties that lend themselves to application as a template material for nanoparticles synthesis. It is a simple, low cost material that can be prepared in nanoparticulate form with a high level of monodispersity and reproducibility. It can be etched easily *via* dissolution with dilute acids. It is highly biocompatible and has been applied as a bone substitute in orthopaedic and orthodontic

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implants, exploiting its osteoconductive properties.^{22,23} It has high adsorbability and affinity for various biological molecules. Exploiting these properties, hydroxyapatite has been used in drug delivery systems for proteins,²⁴ antibiotics,²⁵ anti-cancer drugs.²⁶ It is also well known for its use in protein purification and extraction *via* column chromatography.²⁷

Herein we investigate the use of various hydroxyapatite nanoparticles as templating materials for hollow silica nanostructures, defining effects of particle morphology, size and surface properties. We report a simple route to mesoporous spherical and rod-like hollow silica particles, using cetyltrimethylammonium chloride (C₁₆TAC) as a directing agent for the formation of mesoporous channels.

Several different hydroxyapatite nanoparticle preparations were compared (see Fig.1, table 1 and supporting information) including commercially available HAp1 (Fig. 1A) and samples prepared in our laboratory: HAp2 (prepared *via* wet chemical synthesis and calcination, Fig. 1B), HAp3 (*via* wet chemical synthesis with hydrothermal treatment, Fig. 1C), and HAp4 (citrate-treated particles, Fig. 1D).

The preparation of samples HAp2,^{28,29} HAp3^{30,31} and HAp4³² was adapted from literature procedures and is detailed in ESI. A simple and versatile method for hydroxyapatite nanoparticle production is wet chemical precipitation, described herein for HAp2. Ammonium dihydrogenphosphate (0.3M) was added to a calcium nitrate (0.5M) solution dropwise. These concentrations were chosen to achieve a 1.67 Ca/P ratio. The reaction was allowed to proceed at 60°C for 4 h followed by an overnight aging period during which the suspension was allowed to stand at room temperature. After washing and drying at 60°C overnight the precipitate was heated in a furnace at 550°C for 6 h, to produce nanocrystalline HAp2. X-ray diffraction studies show that the predominant crystalline phase is indeed hydroxyapatite, confirmed by comparison with standard JCPDS files (see ESI). The material is highly crystalline, as indicated by the presence of a peak corresponding to the (300) Miller plane, and the high peak intensity and narrow peak width. The TEM images of HAp2 reveal particles with an irregular morphology, in transition between spherical and needle-like shapes (Fig. 1B).

HAp3 was formed *via* wet chemical precipitation (as in HAp2) followed by hydrothermal treatment, as follows: after washing and drying at 60°C overnight the HAp powder was suspended in water, placed in an acid digestion bomb, and heated in an oven at 200°C for 24 h, followed by freeze drying. TEM analysis revealed a needle-like morphology (Fig. 1C). The citrate treated particles of HAp4 were prepared by suspending HAp1 in a solution of sodium citrate (0.2 M) at pH 6 overnight, followed by washing. FT-IR spectra show a new band at ca. 1382 cm⁻¹ and zeta potential measurements show a large increase in negative charge, indicating presence of the citrate anion in the sample.

All hydroxyapatite materials were subjected to the same silica encapsulating and core etching processes (see ESI). In a typical synthesis hydroxyapatite nanoparticles were dispersed in ethanol and sonicated. C₁₆TAC 25% was added and the suspension stirred vigorously for 10 min before adding water, ammonium hydroxide 28%, and finally tetraethyl

orthosilicate (TEOS) dropwise. The suspension was stirred for 3 h, and the particles washed with ethanol and left to dry in air. The surfactant was removed by calcination of the silica-HAp composites at 550°C for 6 h. TEM analysis of the resultant composite material revealed its porous nature; an example is shown in Fig. 2. Energy dispersive X-ray spectroscopy (EDX) for elemental analysis confirmed the presence of Ca, P, Si and O. FT-IR spectroscopy (ESI) was consistent with the presence of both silica and hydroxyapatite phases.

To prepare the hollow shells, the core-shell composites were suspended in dilute HCl (0.1 M) overnight, for complete dissolution of the hydroxyapatite core. The suspension was centrifuged, washed with water, and freeze dried. The resulting hollow silica particles are referred to as HSP1-4, corresponding to their respective template materials HAp1-4. Particle sizes and shell thicknesses are displayed in Table 1.

The contrast between the dark outer rings and light inner circles seen in TEM images (see Fig. 3) is convincing evidence for the hollow nature of the particles. The spherical and rod-like shapes of the light inner core voids correspond well to the morphology of their hydroxyapatite templates. The TEM of well defined porous hollow nanorods HSP3 provides compelling evidence that shell morphology is controlled by HAp morphology. Elemental analysis using EDX established the disappearance of Ca and P leaving only Si and O detectable in all HSP samples (ESI). FT-IR spectroscopy confirmed the removal of surfactant and inner core templates for all samples (ESI).

Dynamic light scattering (DLS) was used to monitor the colloidal behaviour of the hollow silica shells in solution. Suspensions of the particles were prepared by dispersing 1 mg/mL in deionised water followed by sonication for 10 min. Samples were then analysed at 25°C and pH 7.4 at a measurement angle of 90°. Particle sizes thus measured were found to be within the range of 500-2000 nm, suggesting that the nanoparticles form large aggregates in solution. These results are in agreement with the TEM analysis showing large aggregates of particles.

Previous studies have suggested that formation of nanoporous silica occurs initially *via* the development of small irregular clusters of silica/surfactant aggregates which then aggregate further or collapse and form larger spherical particles. The surfactant micelles eventually align themselves perpendicular to the particle/solution interface, resulting in radially orientated pores.³³ In the dual templating method, Tan and Ranking have suggested that the small silica/surfactant clusters adsorb on the template surface and subsequently adopt hexagonal close packed ordering, with the micelles aligning parallel to the shell surface as the particles age.⁸ However, Wang *et al.* describe the positively charged C₁₆TAC surfactant adsorbing on a negatively charged particle surface followed by deposition of silicate species and self-assembly of a 2D hexagonal silica layer on the particle surface.¹⁹ To investigate the formation of nanoporous silica, citrate coated HAp4 was used as a template. It was thought that the inherent unstable colloidal nature of hydroxyapatite may cause aggregation of the core template and subsequent deposition of silica/surfactant on the core aggregates. The adsorption of citrate ions on the HAp surface has been shown to reduce aggregation, allowing formation of stable colloidal solutions.³² However, formation of silica shells on the

colloidally stable HAp4 did not result in stable suspensions or improved dispersion, indicating that HAp agglomeration may not be the cause in this instance. Other factors that may also contribute to the colloidal stability are sonication prior to silica deposition and the positively charged surfactant C₁₆TAC acting as a dispersing agent. Similar problems have been observed by Tan and Ranking⁸ using latex as a core template, suggesting that aggregation occurs during the aging process.

In conclusion, a novel method for synthesis of porous hollow silica structures utilising hydroxyapatite nanoparticles as templates has been developed. Most interestingly, the morphology of the hollow silica structures can be well controlled and tailored according to the nature of hydroxyapatite template. Due to the large surface areas, porous nature, and the control that can be exercised over their size and shape, these hollow silica shells may have applications in fields such as catalysis and drug delivery and release.

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

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Fig. 1.
TEM images of hydroxyapatite used in this study; A) commercially available (HAp1); B) calcined (HAp2); C) hydrothermally treated (HAp3); D) citric acid treated (HAp4).

Fig. 2.
TEM of HAP1-silica porous composite.

Fig. 3.
TEM images of hollow silica nanoparticles prepared using different templates
(corresponding to those in Figure 1); A) HSP1 B) HSP2 C) HSP3 D) HSP4

Table 1
Particle dimensions as measured by TEM.

Material	Particle size/nm	Shell thickness/nm
HAp1	54.8 ± 2.1	-
HAp2	41.6 ± 1.8	-
HAp3	107.5 ± 6.3 x 25.8 ± 0.9	-
HAp4	59.8 ± 2.2	-
HSP1	68.0 ± 2.8	6.5 ± 0.3
HSP2	54.5 ± 2.1	8.9 ± 0.4
HSP3	140.9 ± 5.5 x 44.2 ± 1.1	12.2 ± 0.4
HSP4	71.3 ± 2.3	18.6 ± 0.9