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Synthesis of Inorganic Hollow Nanospheres and their Application in Drug Delivery

Sudhina Guragain[l] and Bishnu Prasad Bastakoti[l] *

1Department ofChemistry, North Carolina TState University, New Science Building, 1601 East Market Street, Greensboro, NC, 27411
Email: bpbastakoti@ncat.edu

Abstract

Several approaches have been made to synthesize inorganic hollow nanospheres. A dual-template system is the most effective method, usually using surfactants to form mesoporous shells and rigid templates to form interior hollow structures. However, the removal of rigid templates is time consuming and uneconomical. The self-assembly of soft-templates is more convenient and is able to directly construct hollow mesoporous nanoparticles. The soft-templating approach especially the micelles of amphiphilic block copolymers are very helpfulfor creating hollow interiors andporous shell. The hollow void and thickness of shell can be easily tuned by changing either molecular weight of polymer or solution properties. This review focuses on the synthesis of inorganic hollow nanospheres and their application in drug delivery. The large hollow void space with thorough porosity are always beneficial for drug loading and release.

Introduction

The preparation of inorganic hollow nanoparticles of defined structures and composition is of immense scientific and technological interest. These hollow nanostructures have found to have diverse and fascinating applications, such as in catalysis, biomedicine, and energy storage. [I] The hollow voids provide space for payloads. The induction of porosity on shell is another challenge during synthesis. The thorough porosity on the shell helps to store drug molecules and promote the release when necessary. The interior hollow void is protected by inert porous shell. The hollow nanospheres of highly biocompatible calcium phosphate (CAP) are used to deliver the anticancer drug.[2] The pH sensitive solubility of CAP makes them intelligent carriers for anticancer drugs. The acidic pH of cancer tissue force the CAP to dissolve quicker to release the drug molecules. In addition, the porous shell can be tunctionalized with stimuli responsive organic molecules to control the drug release rate. The functionalization of silica shell with some stimuli responsive molecules/nanoparticles make the nanovalve while releasing the drug molecules.[3] Liu et al. conjugate peptide ligand with mesoporous silica to target tumor cells and angiogenic blood vessels.4

Corresponding author

Synthesis of Hollow nanoparticles

Several methods such as Ostwald's ripening: Kirkendal effects,[6] galvanic displacement,[7] surface protected etching[s] are used to synthesize the hollow architecture. However, this review only focuses on hard and soft templating method for the synthesis of hollow nanostructure.

Hard Template

Svnthesis of hollow structures by templating against hard particles is widely used method. In general, it comprises following steps as shown in Figure | .[9]

(l) synthesis of hard templates (2) functionalization/modification of template surface to achieve favorable surface properties (3) coating the templates with designed materials or their precursors by various approaches, possibly with post-treatment to form compact shells and (4) selective removal of the templates to obtain hollow structures.

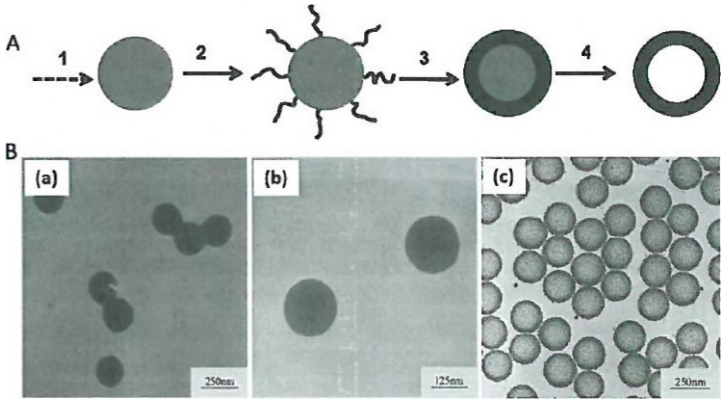

Figure I. (A) Illustration ofa conventional hard templatingprocessfor hollow sphere synthesis. Reprintedwith permissionfrom (9). (B)TEMpictures of(a) original PS particles, (b) PS/SiO,, and (c) hollow silica particles. Reprintedwith permissionfrom (10). Copyright 2007 American Chemical Society

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The commonly used hard templates are monodispersed silica particles, [IO] polymer latex colloids, carbon nanospheres.[12] Si02,[13] ZnS.[14] and CaC03 [15] and some metal nanoparticles are also used as hard templates. Polystyrene latex particles with different sizes are used for the fabrication of hollow inorganic oxide nanoparticles with controlled shell thickness and cavity size by the layer-by-layer techniques. [16] The sequential deposition of oppositely charged polymer species on substrates followed by removal of core gives rise hollow polymer particles. Caruso and coworkers synthesized hollow silica sphere by coating negatively charged silica precursors and positively charged polydiallyldimethylammonium chloride through sequential deposition of oppositely charged species. Hollow silica was obtained after removal of PS latex by calcination. The hollow silica spheres retained the spherical shape of the original PS particle templates. Li and coworkers synthesized the Ga203 and GaN hollow spheres by using colloidal carbonaceous polysaccharide microspheres as templates. This method involves the initial absorption of metal ions from solution into the functional surface layer of carbonaceous saccharide microspheres; these Chem.

are then densified and cross-linked in a subsequent calcination and oxidation procedure to form metal oxide hollow spheres.

The synthesis of hollow particles via hard templates is regarded as a very effective and most common method. However, hard templates have several intrinsic disadvantages, which include the complicated multi-

step processes, low productive yields, low structural robustness, difficulties for encapsulation and release of guest species. In this regard, the synthesis via soft templates has been developed as another fast growing method for the synthesis of hollow structures, with its own advantages such as simple procedures, variability of the template sources, encapsulation of guest species during the synthesis of hollow materials, and easy removal of the templates by washing at low temperature.

Soft Template

Soft templates typically include structures formed by biomoIecules, [18] Liquid crystal, [19] gas bubbles, [20] amphiphilic molecules such as surfactants,[21] and long-chain polymers.[22] Under certain conditions, these materials self-assemble into well-defined aggregating entities which restrict and direct the growth of inorganic precursors. Precursor species react in the confined space or on the outer surface of the soft assemblies, via a sol-gel process or hydrothermal method to form a shell.

Hollow nanospheres of calcium phosphate have been synthesized using cetyltrimethylammonium bromide (CTAB) as template. [23] Xu et al. have prepared novel multishelled Cu20 hollow spheres via CTAB vesicle templating route in aqueous solution.[24] Depending on the concentration of CTAB in the range of 0.1-0.15 M, the Cu20 hollow spheres are found to be dominantly single-, double-, triple-, or quadruple-shelled in the product.

Compared to the other strategies, one of the advantages of using templates of polymeric micelles is that the size and morphology of the micelles can be easily tuned by adjusting the block length and solution properties. Bastakoti et al. synthesized hollow nanospheres of CaC03 templating on laboratory synthesized triblock copolymer.[25] Poly(styrene-b-acrylic acid-b-ethylene glycol) (PS-b-PAA-b-PEG) block copolymer forms a spherical micelles with PS core, PAA shell, and PEG corona in aqueous solutions.26-28 In alkaline medium, PAA is negatively charged and can interact with positively charged metal ions. Calcium ion selectively interacts with PAA shell and provides space for mineralization reaction for calcium carbonate and calcium phosphate (Figure 2A). This method can be extended to several other composition. The use of micelles as template overcomes the problem of crystal overgrowth. allowing the formation of nanometer-sized hollow spheres with uniform void space. As the void space is formed after removing PS core, It can be tuned by changing the molecular weight of PS or using some swelling agent. Yamauchi et al. used a new dual soft-template system comprising high molecular weight block copolymer and the low molecular weight cationic surfactant cetyltrimethylammonium bromide (CTAB) to synthesize hollow mesoporous silica nanoparticles with a center void of around 17 nm. [29] The stable polymeric micelle serves as a template to form the hollow interior, while the CTAB surfactant serves as a template to form mesopores in the shells (Figure 2B) The positively charged P2VP interacts with positively charged CTA+ ions via negatively charged hydrolyzed silica species. Thus, dual softtemplates clearly have different roles for the preparation of the HMS nanoparticles. The surface area measurement revealed that the mesoporous silica shows high surface area (1160 $m^2g•l$) compare with that silica (478.0 m^2g^{-1}) prepared in the absence of low molecular surfactant. The hollow voids and thorough porosity in the shell are always beneficial in drug delivery application.

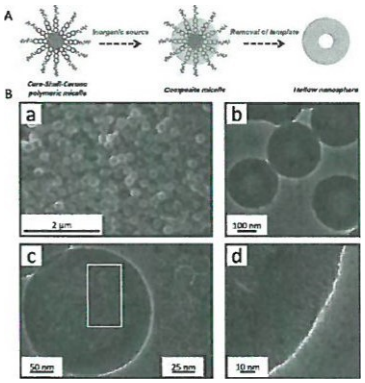

Figure 2. (A) Schematic formation route ofhollow nanospheres of inorganic materials using polymeric micelles. (B) (a) SEM and (b—d) TEM images ofhollow mesoporous bio-glass spheres. (d) Enlarged image ofthe shell region showing vertical mesochannels. Reprinted with permission from (29).

Hollow particles as drug carriers

The presence of void space in the hollow nanoparticles can be used to store different cargos. They could be drugs, imaging agents, contrast agents or reactants. The hollow polymer, silica, and several metal oxides are good candidates for drug delivery carriers. Calcium phosphate is highly biocompatible inorganic biomaterials. The natural occurrence of calcium phosphate in the human body is one of the primary advantages over other synthetic drug delivery systems. As a preliminary experiment, the safety and toxicological issues of the synthesized hollow calcium phosphate nanospheres were examined by MTT assays of a breast cancerous cell line. [2] The results shown in Figure 3 indicate that the cell viability was as high as the control sample (i.e., cells not treated with nanoparticles), even when the calcium phosphate concentration was up to 1000 mg.ml„-l , demonstrating an excellent biocompatibility in vitro.

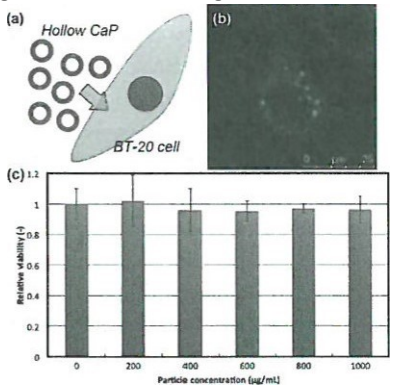

Figure 3. (a) Schematic illustration ofhollow calcium phosphate nanospheresfor biocompatibility test. (b) A confocalfluorescent image offluorescein adsorbed hollow calcium phosphate nanoparticles in BT20 cancer cells. (c) MIT assays ofBT-20 cells treated with hollow calcium phosphate nanoparticles with different concentrations. Reprinted with permission (2).

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Hollow silica nanoparticles (single composition) or yolk-shell type (double composition) serve as drug deliver carriers. 29,30 They are suitable for loading and releasing small drug molecules, si-RNA, enzymes and proteins. Hollow mesoporous silica was modified with poly(2-(diethyIamino)-ethyI methacrylate) (PDEAEMA) polymer. The conjugation of redox responsive disulphide bond and light cleavable onirobenzyl ester makes the mesoporous silica, a triple responsive drug carrier. [31] The multiresponsive drug delivery system could have greater potential for controlling drug delivery in complicated bold circulation and pathological environment. Hollow iron oxides and gold nanoparticles are used for drug delivery and hyperthermia cancer therapy.32,

Conclusion

The hollow structure have attracted wide research interest due their fascinating properties and application in biomedical sciences. Storing a payload and release at targeted sites with minimum side effects is a very demanding in targeted drug delivery. Some of the materials have already shown promising results. However, proper functionalization to make the hollow particles more friendly with human physiological environment is a current challenge. Specially, in biomedical application. the materials should be biocompatible.

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