School of Chemical and Petroleum Engineering

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Novel Hierarchically Structured Nanocomposites for Biomedical Applications

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Declaration

To the best of my knowledge and belief this thesis contains no material previously published by any other person except where due acknowledgement has been made. This thesis contains no material which has been accepted for the award of any other degree or diploma in any university.

Signature: _____ (Tingting Liu)

Date: 3 March 2017

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Abstract

Functional nanocomposites have attracted a great deal of attention from scientists and engineers for reasons well beyond the scope of their appealing structures, tuneable physical and chemical properties. Benefitting from their extraordinary properties such as small particle size, hierarchical nanostructures, controllable surface properties, multi-component nanocomposites can offer new opportunities for biomedical applications including disease diagnosis, drug/gene delivery, biosensors, tissue engineering, and cancer therapy. As an interdisciplinary research area that integrates biology, chemistry, materials science, engineering and nanotechnology, over the past decades, rapid advances have been made in nanomedicine. Currently, many research attempts have focused on the development new nanocomposites with tuneable surface properties and multiple functionalities, which have evolved new generation nanomaterials for biomedical applications. However, it is still desirable for the design of nanocomposites with multicomponents and controllable surface properties for intensive biomedical study; for example, engineering of nanocomposites for investigation of the nano-bio interface to mimic the natural system such as enzyme or virus. The aim of this thesis is to mimic the nanostructure in the natural system, to design and fabricate nanocomposites with suitable composition, and alter their surface properties and structure to suit the target biomedical applications. The main achievements obtained in this thesis are listed below.

In the first part, a facile method has been developed for preparation of magnetic mesoporous silica core-shell nanocomposites with large void pores and tuneable particle sizes. The spherical particle size can be tuned from 110 nm to 800 nm by tailoring the synthesis parameters such as ethanol to water volume ratio, while the large void pore on shell can be regulated from 8.0 to 20 nm by increasing the amount of ethanol. By further surface engineering with the NH_2 group, the NH_2-functionalized magnetic mesoporous silica nanospheres could be efficiently internalized into HeLa cell lines, which is potentially important for siRNA efficacy against cancer cells. The results would provide an application paradigm of magnetic mesoporous silica nanoparticles for cell labelling and drug delivery.

In the second part, a mild synthesis method has been developed for preparation of periodic mesoporous organosilicas (PMOs) through a condensation process of organosilicates 1,2-bis(trimethoxysilyl) ethane around inorganic-electrolyte-stabilized Pluronic F127 [$(EO)_{106}(PO)_{70}(EO)_{106}$] triblock copolymer micelles. It is found that the addition of inorganic sulfate salts in the synthesis is a crucial factor to ensure the formation of ordered mesostructures. The addition of Na_2SO_4 and $MgSO_4$ in the synthesis system can lead to the formation of ordered 2-D hexagonal (P6mm) and 3-D cubic (Im3m) mesostructures, respectively. The mechanism for PMOs formation has been proposed on the basis of inorganic salts assisted micelles-organosilicates closed packing under mild synthetic condition. The findings from this work contribute fundamental understanding towards a new formation route of these ordered mesoporous materials. This provides a new strategy to fabricate mesoporous silicas with controllable structures for emerging biomedical applications, for example, in-situly load the guest molecules such as enzyme or drug into the matrix.

In the third part, a facile and novel protocol has been developed to synthesise AgNPs in various microbe culture broths. The broth ingredients provide an ideal environment for the formation of AgNPs with uniform size distribution. The significant influences of some important parameters include light condition and broth pH values have been investigated systematically. Whilst sharing similar advantages with the conventional microbial processes to use non-hazardous chemicals, this method is of particular importance as it employs the culture broth alone without involving any specific microorganism.

In the fourth part, we have successfully prepared raspberry-like mesoporous silicas with particle size of 360 nm through an extension of the Stöber process. By precisely controlling the synthesis parameters, either decreasing the CTAB concentration or increasing the amount of TEOS, multi-compartment silicas with mesoporous silica spheres bridged with mesoporous silica rods can be fabricated. It is found that the particle size of mesoporous silica can be tuned from 100 to 600 nm with 2 nm hollow silica nanoparticles doped on the surface, which can be achieved by varying the water to ethanol ratio. Specifically, the present strategy allows an easy way to generate the hierarchical nanostructured silicas by mimicking the structures of diatom cells for the

potential application in catalysis and nanomedicine. Further studies are currently in progress in order to probe their efficiency in gene therapy and anti-aging applications.

In the fifth part, we have successfully prepared hollow colloidal carbon nanostructures with raspberry-like morphology. The developed method is highly reproducible and straightforward to synthesize uniform hollow colloidal carbon nanostructures with controllable surface properties and Janus particles. The water/ethanol ratio of the solvent is a critical factor in determining the different surface properties. After a thorough systematic investigation, we found the formation of different morphologies of silica@RF is due to the solubility difference of CTAB in different solvents. Furthermore, the as-prepared raspberry-like HCCNs display superior performance to smooth HCCNs in the LDI-MS detection of peptides, which has been ascribed to the different surface properties to capture the peptide molecule.

Publications by the Author

Published and Accepted Papers:

1. **Tingting Liu**, Lili Qu, Kun Qian, Jian Liu*, Qiao Zhang*, Lihong Liu and Shaomin Liu*, "Raspberry-like Hollow Carbon Nanospheres with Enhanced Matrix-free Peptide Detection Profiles" ***Chemical Communications***, **2016**, *52*, 1709–1712.

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3. **Tingting Liu**, Lihong Liu, Jian Liu, Shaomin Liu* and Shi Zhang Qiao*, "Magnetic Fe_3O_4 and Mesoporous Silica Core-Shell Nanospheres with Tunable Size and Large Void Pore for Cellular Uptake" ***Frontiers of Chemical Science and Engineering***, **2014**, *8*, 114–122.

4. **Tingting Liu**,† Xiaoyan Zhang,† Weidong Sun and Jian Liu*, "Mesoporous Organosilica Hollow Microspheres with Hierarchical Structures on the Shell" ***Journal of Nanoscience Nanotechnology*** **2013**, *13*, 3046–3053. (†**Tingting Liu** and Xiaoyan Zhang are contributed equally to this work)

5. **Tingting Liu**, Lihong Liu, Wenyi Gu, Jian Liu,* and Shaomin Liu* "One-pot synthesis of raspberry-like mesoporous silica nanospheres" ***Journal of Nanoscience Nanotechnology***, **2017**, *17*, in press, accepted on 22nd of January, 2017.

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Content

Chapter 1. Introduction

1.1 Significance of the project

In the past decade, with the progress in nanotechnology, biomedicine and nanopharmaceutics, “theranostics”, which is the combination of diagnosis and therapy, has received burgeoning scientific and clinic attention.[1-5] The target of “nanotheranostics” is to develop multifunctional nanocarriers with hierarchical structures and that can integrate diagnostic and therapeutic functions into one nanoparticle.[3-5] To achieve this goal, as shown in Figure 1.1[5], diverse type of organic (e.g., polymer, micelles, liposomes, vesicles and dendrimers) or inorganic (e.g., silicas, carbons, metal oxides) nanocarriers have been developed for loading or encapsulating biomedical “payloads”. These include therapeutic agents (anticancer drugs, DNA, small interfering RNA [siRNA], proteins, hyperthermia-inducing nanoparticles, ROS-generating agents, etc.) and imaging agents (e.g., organic dyes, quantum dots [QDs], upconversion particles [UCNPs], MRI contrast agents, CT contrast agents, etc.). The key requirements for the nanocarriers are as follows: 1). high loading capacity for the biological payloads; 2). sufficient physical protection for the imaging agents; 3). controlled release for the therapeutic agents; 4). high biocompatibility/low toxicity; 5). easy surface modification for additional properties of nanotheranostics.

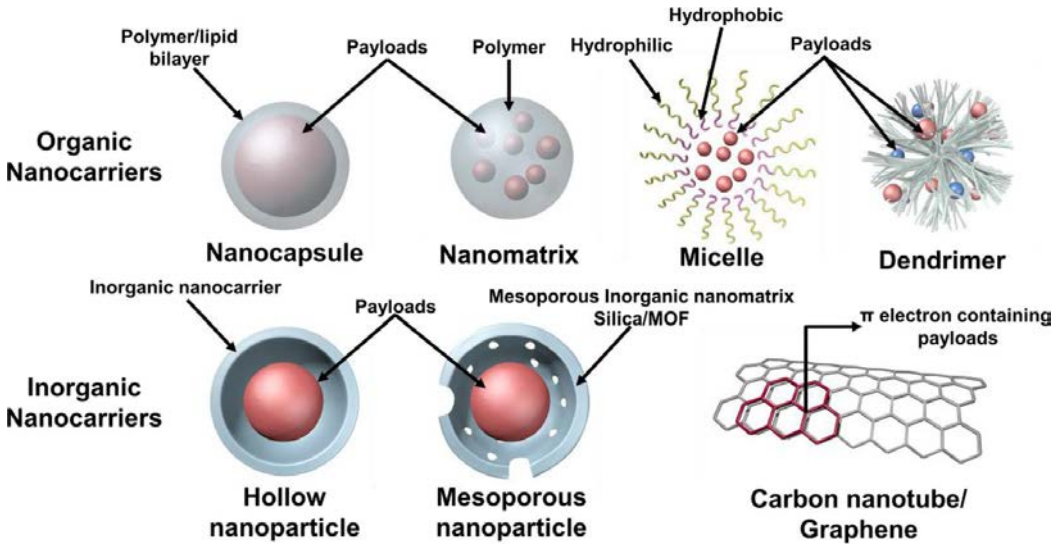

Figure 1.1 Various organic/inorganic carriers for biomedical applications. [5]

Compared to conventional nanocarriers, multicomponent silicas or carbons have 1). special porous structure and high surface area for loading higher amounts of biological payloads; 2). unique core shell, yolk shell, hollow structures for protection of the imaging agents; 3). rich surface chemistry for functionalization and stimuli-responsive releasing of therapeutic agents; 4). high biocompatibility/low toxicity; which is very promising as nanocarriers for theranostics applications.[6-16] With the aid of these nanocarriers, the performance of many imaging agents and therapeutic agents has been significantly improved.[6-10] However, current achievement is still as a proof of concept: 1). relatively few synthetic protocols can be used in-situ loading of biological payloads due to their harsh conditions; 2). there is still limited knowledge about the effects of chemophysical properties of the nanocarriers such as particle size, surface functionality, shape, structure on the toxicology and cell uptake; 3). labelling of nanocarriers for visualisation and tracking at ultra-low concentrations has been difficult; 4). less effective synthesis method for construction of nanocarriers with multicomponent and multifunctionality for realizing diagnosis and therapy simultaneously.[14-18] To address these key challenges, it is necessary to 1). develop innovative synthesis protocols for multicomponent nanocarriers; 2). develop innovative chemical approaches to label nanocarries for visualisation and tracking; 3). develop integrated nanotechnology platforms for diagnosis and therapy.

1.2 Research objectives

This thesis aims to develop an integrated multicomponent nanocomposites platform for effective diagnosis and therapy. A novel class of biocompatible nano-carriers with well-defined structures and surface properties will be developed for targeted and controlled drugs/genes delivery. The close correlation between particle morphologies and their cytotoxic effect will be studied by employing in vitro cell systems as well as *in vivo* studies with animal models. The mild wet chemistry synthesis method will be designed for in-situ immobilise biomolecules. This study will generate knowledge on the synthesis protocols for multicomponent nanocomposites, and give suggestions on how to design effective nanoparticles for biomedical applications. The specific objectives of this study are listed as follows:

1. Synthesising multicomponent mesoporous silicas, carbons (magnetic mesoporous silica nanocomposites, raspberry-like silica nanospheres, raspberry-like carbon

spheres) with desired shape, surface functionality, particle size and porous structures, which can provide specific affinity surface and large cages for the loading and easy diffusion of biomolecules;

2. Developing mild and greener synthesis methods for silicas or metal nanoparticles;

3. Providing novel insights in understanding the effects of particle size, shape, porous structure and surface chemistry on the deposition, uptake, translocation, and toxicity of nanoparticles;

4. Identifying emerging multicomponent nanocomposites platform on biomedical applications with mechanistic studies.

1.3 Thesis organization

This thesis consists of eight chapters, including introduction, literature review, results and discussions (five chapters), conclusions and perspectives for future studies.

Chapter 1 **—** *Introduction* **—** gives a brief introduction to the background, encountered issues, and solutions in regard to multicomponent complex nanoparticles for biomedical applications. This chapter also includes the objectives of the research and structural organization of the thesis.

Chapter 2 **—** *Literature review* **—** comprehensively summarizes the development of nanoparticles with multi-compartments, such as hierarchical porous structures, core-shell, yolk-shell, Janus structured particles for efficient diagnosis and therapy applications. Promising future directions of this active research field are also highlighted.

Chapter 3 **—** *Magnetic Fe_3O_4 and mesoporous silica core-shell nanospheres with tunable size and large void pore for cellular uptake. (**Frontiers of Chemical Science and Engineering**, **2014**, 8, 114–122.).* **—** reports a facile method for fabrication of magnetic core and mesoporous silica shell nanocomposites with hierarchical pores on the shell. The obtained nanocomposites combined magnetization response and large void pore, showed excellent cancer cells (HeLa cells) internalization capacity.

Chapter 4 — *Inorganic-salts assisted self-assembly of Pluronic F127-organosilica into ordered mesostructures. (****Journal of Nanoscience Nanotechnology*** **2016**, *16*, 9173–9179.*).* **—** develop a mild synthesis method and unravels the formation mechanism for mesoporous organosilicas with various mesostructures. The developed mild synthetic strategy provides the opportunity to in-situ load biomolecules into nanocarriers.

Chapter 5 — *Less is more, greener microbial synthesis of silver nanoparticles. (****Enzyme and Microbial Technology***, **2014**, *67*, 53–58.*).* **—** demonstrates that silver nanoparticles (AgNPs) can be synthesized in several types of microorganism culture broth without any specific living microbe involvement. The developed strategy dramatically simplifies the conventional microbial nano-synthesis process and thus provides a more eco-friendly way for nano-Ag preparation.

Chapter 6 — *One-pot synthesis of raspberry-like mesoporous silica nanospheres. (****Journal of Nanoscience Nanotechnology*** **2017**, *17*, 9173–9179.*).* **—** reports a one-pot synthesis method for raspberry-like mesoporous silica nanospheres with 2 nm hollow silica nanoparticles doped on the surface. A diverse library of multi-compartment mesoporous silicas networks consist of mesoporous silica nanospheres connecting with mesoporous silica branches has also been synthesized through this method. The synthesis method would enable one to synthesize hierarchical mesoporous silicas with complex architecture and different pore environments for the potential application in nanomedicine.

Chapter 7 — *Raspberry-like hollow carbon nanospheres with enhanced matrix-free peptide detection profiles. (****Chemical Communications***, **2016**, *52*, 1709–1712.*).* **—** synthesize hollow colloidal carbon nanostructures with raspberry-like morphology. This facile method is highly reproducible and straightforward to synthesize uniform hollow colloidal carbon nanostructures with controllable surface properties and Janus particles. The as-prepared raspberry-like HCCNs display superior performance to smooth HCCNs in the LDI-MS detection of peptides, which has been ascribed to the different surface properties to capture the peptide molecule.

Chapter 8 — *Conclusions and perspectives* **—** highlights the meaningful findings in this study and proposes suggestions for further research in the field.

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Chapter 2. Literature review

2.1 Introduction

As a multidisciplinary of chemistry, material science, biotechnology, and biomedicine, nanobiotechnology has received burgeoning scientific and clinical attention in the past decade.[1-11] One of these topics in nanobiotechnology is the development of multifunctional nanocarriers with hierarchical structures, which can integrate diagnostic and therapeutic functions into one nanoparticle for theranostic applications. To achieve this goal, diverse types of organic (e.g., polymer, micelles, liposomes, vesicles and dendrimers) or inorganic (e.g., silicas, carbons, graphene, metal oxides and semiconductors) nanocarriers have been developed for loading or encapsulating therapeutic agents and imaging agents. Among them, one particular class of nanocarriers namely mesoporous silica nanoparticles (MSNs), has attracted much attention for theranostic applications.

Since the discovery of mesoporous silica materials by Mobil scientists in 1992,[12,13] significant progress has been made toward the design and fabrication of mesoporous silicas with different structures, controlled morphologies and tailored properties. By using a soft templating or a hard templating approach, a range of MSNs including rods, tubes, plates, ellipsoids, spheres, cubes, raspberry-like, hollow, core-shell and yolk-shell structures, and Janus particles have been produced in the laboratory. With a series of extraordinary features, such as large surface area, highly diversified structures, controlled porosity, chemical functionality, low toxicity and high biocompatibility, MSNs are very promising for biomedical applications including bioimaging, drug/gene delivery, tissue engineering, cancer therapy and *in vitro* diagnostics.[1]

To further functionalize MSNs as a platform for biomedical applications, the development of multi-compartment mesoporous silica nanoparticles (MCMSNs) is crucial. MCMSNs offer great potential in theranostic applications because of their multi-functionality by the combination of therapeutic agents (e.g., anticancer drugs, DNA, small interfering RNA [siRNA], proteins, etc.) and imaging agents (e.g., quantum dots [QDs], upconversion particles [UCNPs], MRI contrast agents, etc.). They also have the possibility to selectively locate these functionalities onto different positions of the hierarchical structured particles by precisely controlling the surface chemistry. As summarized systematically in Figure 2.1, to date, MCMSNs with

various structures such as core-shell, yolk-shell, Janus, or raspberry-like particles have been synthesized by incorporating or encapsulating various imaging agents from organic dyes, QDs, UCNPs, MRI contrast agents, to CT contrast agents as a platform for biomedical diagnosis applications. Meanwhile, many different therapeutic agents including anticancer drugs, antiphlogistic drugs, antibacterial drugs, antihepatic fibrosis drugs, DNA, small interfering RNA [siRNA], proteins, etc. have been encapsulated and delivered by using MSNs as nanocarriers. Despite recent progress, the multifunctionalization of MSNs to fabricate MCMSNs and realize diagnosis and therapy simultaneously is still a major challenge for materials scientists and chemists. The nomenclature adopted in this review as demonstrated in Figure 1 is primarily including core-shell structured mesoporous silica nanoparticles (*cs*-MSNs), yolk-shell structured mesoporous silica nanoparticles (*ys*-MSNs), and Janus structured mesoporous silica nanoparticles (*j*-MSNs). The combination of the *cs*-MSNs, *ys*-MSNs, and *j*-MSNs for generating more complex structured MSNs with multi-pods are also reported in the literatures for a special biomedical application.

So far, there are many excellent reviews available on the synthesis and biomedical applications of mesoporous silicas.[1-3,14-28] However, these reviews have focused on the synthesis of spherical mesoporous silicas particles,[22,25,29] hollow structures,[2,24] core-shell structures,[18] dendritic structures,[27] surface functionalization and organosilicas,[20] and a specific application such as drug delivery and gene transfection,[15,23,26,28] *in vivo* bio-safety evaluations,[16] and cancer therapy.[3,14] Indeed, an up-to-date review on the protocols for the construction of multi-compartment mesoporous silica nanoparticles with multiple properties and tunable functionalities for theranostic applications is timely for guiding scientists to design MCMSNs for specific biomedical applications. In this review, however, the focus is placed on recent research progress in the systematic synthesis methodologies of multi-compartment mesoporous silica nanoparticles and their biomedical applications. This review is organised as follows: after a brief overview of synthesis of MSNs, the first part briefly covers various general methods developed for the synthesis of MCMSNs. By discussing some representative MCMSNs as examples, we present a summary of the key synthesis strategies for controlling the particle size, geometry, structure and functionalisation. Core-shell, yolk-shell, raspberry-like and Janus structured mesoporous silica particles, will be then discussed. The following section is devoted to review the potential biomedical applications. The chemophysical properties of

MCMSNs (*eg.* particle structure, particle size, pore size and geometry, surface property, and particle shape) effects on the *in vitro* cellular uptake, intracellular translocation and cytotoxicity, *in vivo* biodistribution, biodegradation, excretion, and toxicity will be discussed. We will closely examine the research on the combination loading of imaging agents and therapeutic agents into one particle to generate multifunctional MSNs based platforms for theranostic applications. Finally, the state of the art for this area is summarized and future perspectives are offered.

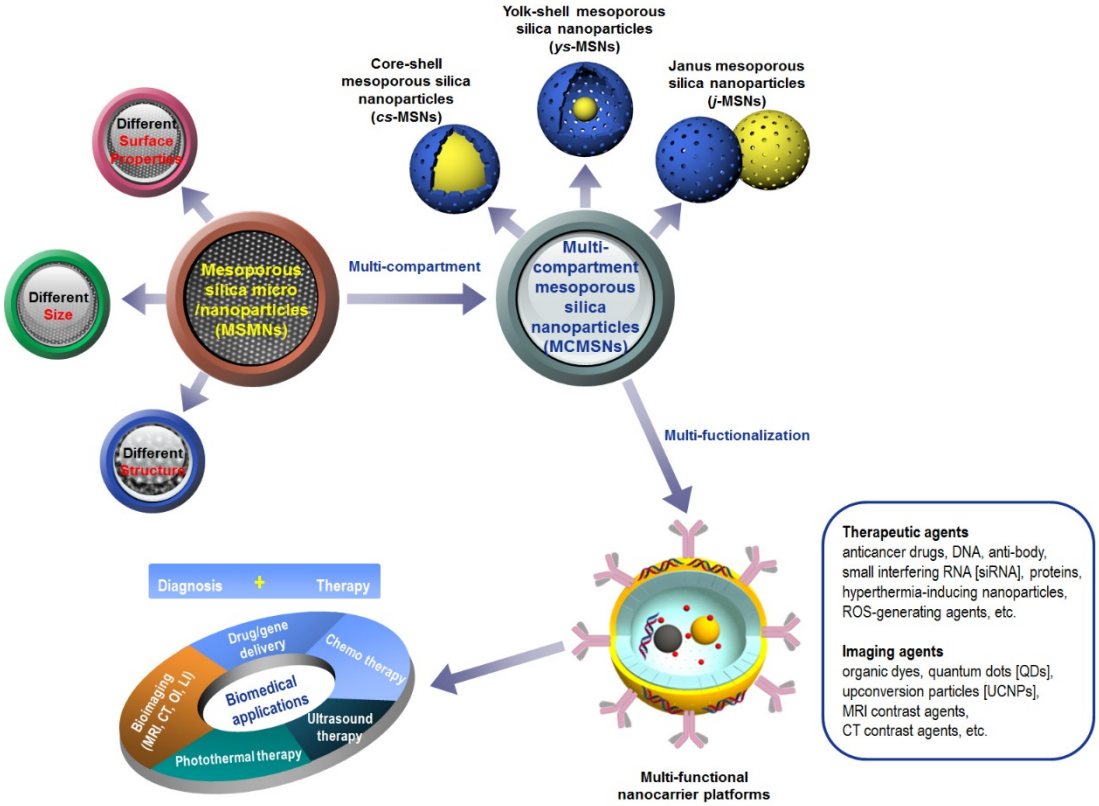


Figure 2.1 Schematic illustration for construction of multi-compartment mesoporous silica nanoparticles (MCMSNs) as a platform for diagnosis and therapy applications.

2.2 Categories and synthesis methods of multi-compartment mesoporous silica nanoparticles (MSNs)

After the early reports on mesoporous silica nanoparticles by the groups of Cai[30] and Mann,[31] independently, the term MSNs has been well popularized by several groups including Bein,[32-36] Kuroda,[37-44] Haynes,[45-48] Huo,[49-53] Hyeon,[3,54,55] Lin,[15,28,56,57] Mou,[58-60] Shi,[2,16,61-64] Tang,[17,21] Wiesner,[65-67] Vallet-Regi,[19,68,69] Zhao[70-75] and Zink[1,14,22,76,77] et al. Over the past decade, several research groups have reported

diverse synthesis protocols for MSNs as illustrated in Figure 2.2 with various pore sizes and pore structures, different morphologies including rods, cubes, plates, ellipsoid, and spheres, also the more complex structures derived from the above mentioned morphologies such as core-shell, yolk-shell and hollow structures, and Janus particles. The dominant synthetic methods developed for MSNs are the soft templating method and its derivative methods. By tuning the synthesis parameters such as pH value of the synthesis solution, the concentration of reagents and the template categories, a series of particles with different morphologies, pore size and particle size can be achieved.

As summarized in Table 2.1, Yu et al. first reported the synthesis of rod-like mesoporous SBA-15 1~2 μm in length through an inorganic salts assisted soft-templating method.[78] Later, Sayari and coworkers demonstrated 1.5 × 0.4 μm mesoporous SBA-15 straight rods can be prepared by adopting the synthesis method of SBA-15 but under static conditions without using salts.[79] Recently, Jang and coworkers modified the Stöber method to prepare MCM-41 type mesoporous silica rod-like nanoparticles (MSRNs) with different aspect ratios in a gram-scale by controlling the water to ethanol ratio.[80] As a special type of MSRNs, mesoporous silica helical rods nanoparticles (MSHRNs) have also been widely investigated.[81-84] As an example, by using perfluorooctanoic acid (PFOA) and cetyltrimethylammonium bromide (CTAB) as a dual template, Yang et al. reported the synthesis of MSHRNs and proposed an interfacial interaction mechanism.[82] In comparison with mesoporous silica rods, it is very difficult to synthesize mesoporous silica cube-like nanoparticles (MSCNs) using a soft-templating method. In most cases, hard templates such as hematite,[85-87] calcium carbonate,[88] and $Co_3[Co(CN)_6]_2$[89] have been employed for the preparation of hollow mesoporous silica cubes through an efficient mesoporous silica coating and template etching process. Alternatively, Stein and coworkers reported the fabrication of MSCNs through disassembling of ordered hierarchically porous structures derived from etching of the dense packing of colloidal crystal poly(methylmethacrylate) (PMMA) spheres. However, it is a challenge to control the purity of the resultant mesoporous silica cubes.[90] Soft-templating method was developed by Han et al. for MSNs, which were synthesized by using dual surfactants F127 and FC-4 in acidic conditions, part of the resultant IBN-1 also shows cubes morphology.[91] Compared to MSCNs, mesoporous silica ellipsoid-like nanoparticles (MSENs) are more popular and can be prepared using a soft-templating method.[34,92-

[95] Both MSENs with mesoporous channels oriented along the long axis and the short axis have been synthesized by using a water/oil emulsion templating method. By using an emulsion template formed from dibenzyl ether in water, Hao et al. reported the synthesis of 200 × 100 nm MSENs with 3.3 nm meso-channels running along the short axis.[94]

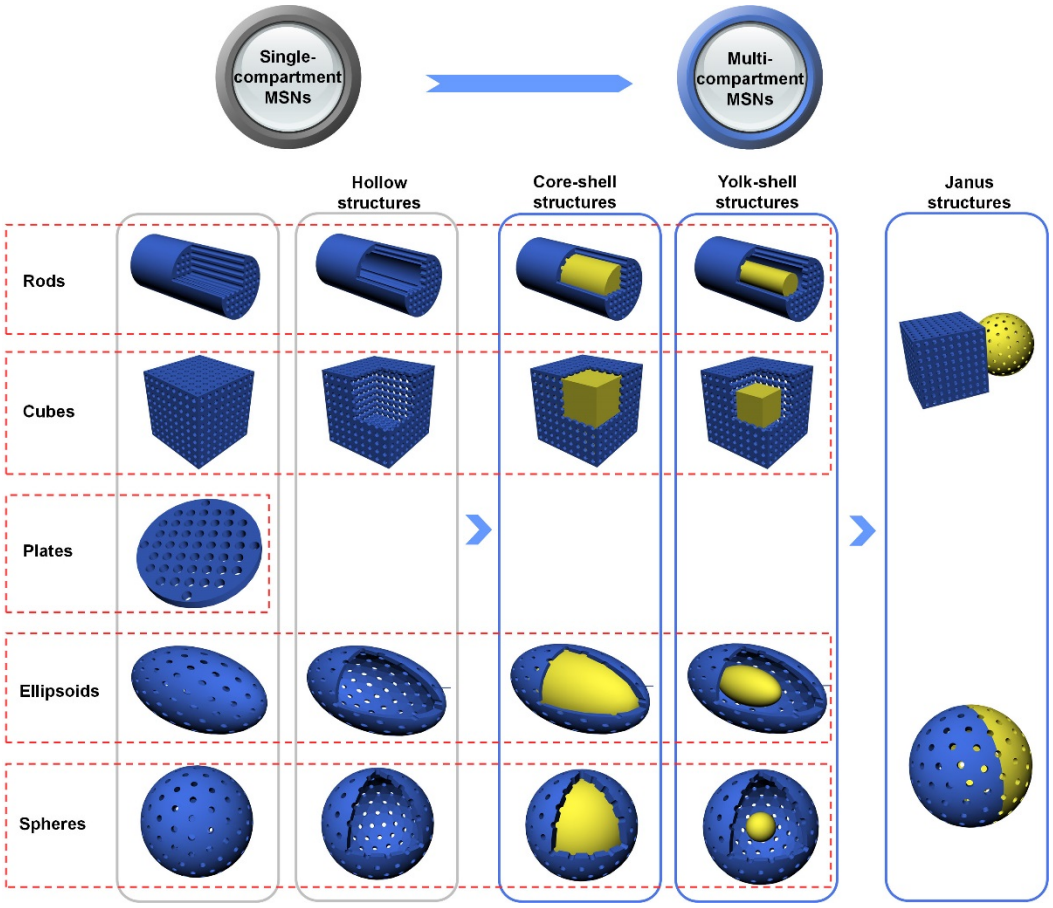
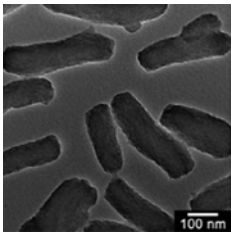
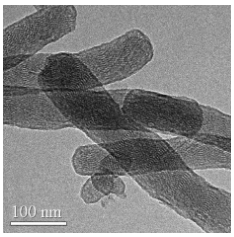
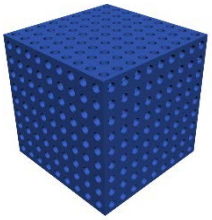
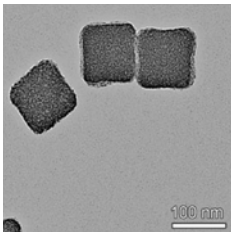
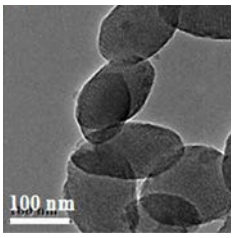
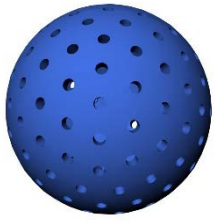
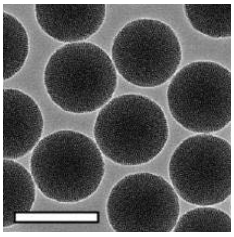


Figure 2.2 Schematic illustration for construction of MSNs with various pore sizes and pore structures, different morphologies from single-compartment to multi-compartment.

Among all MSNs, mesoporous silica spherical-like nanoparticles (MSSNs) are the most intensively investigated due to the well-developed methods and wide applications. There are many mature methods for preparing MSSNs with a particle size range from 20 nm to a few hundred nanometers, including hard and soft-templating, aerosol-assisted self-assembly, microemulsion templating, Stöber synthesis, and self-etching method. These synthesis methods have also been widely applied to prepare hollow mesoporous silica nanoparticles (*h*-MSNs), which will be discussed in the *ys*-MSNs section.

Table 2.1 Summary of the synthesis method for different mesoporous silica nanoparticles (MSNs) with various pore sizes and different morphologies.

Type	Schematic structures	Typical TEM images	Synthesis method	Composition	Ref.
Non-spherical morphology	Rod 		Soft templating method	Silica/organosilica	30,67,78-80,112-115
	Helical rod 		Soft templating method	Silica/organosilica	82,83
	Cube 		Hard templating method	Silica	90,116
	Ellipsoid 		Soft templating method	Silica/organosilicas	92-95
Spherical morphology	Sphere 		Stöber method	Silica/organosilicas	96,97,99-102,117
			Soft templating method	Silica/organosilicas	30,34,38-41,43,51,60,65,91,103,107-111,118
			Aerosol-assisted self-assembly	Silica/organosilicas	106,119-125

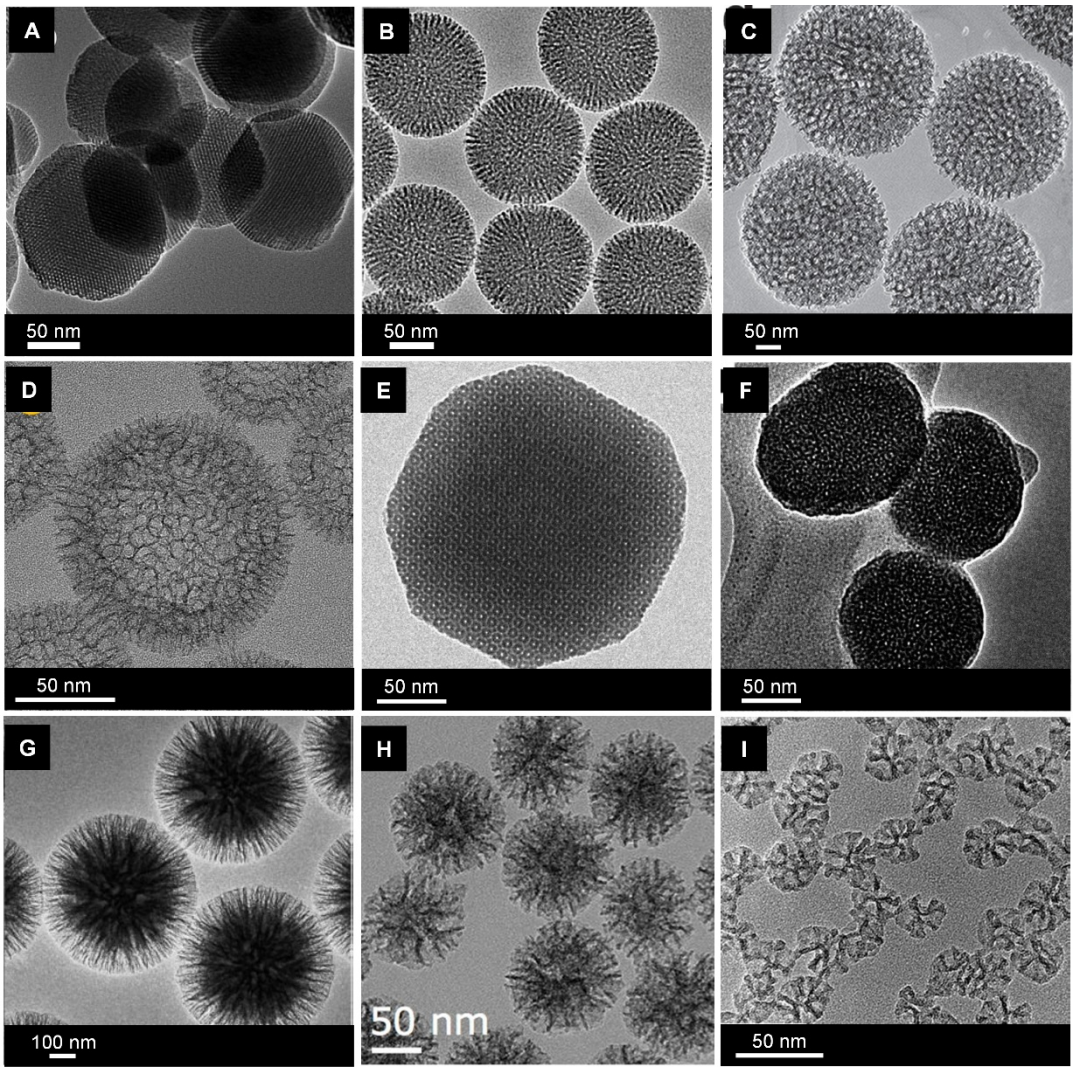


Figure 2.3 Gallery of MSSNs: Typical TEM images of various mesoporous silica spherical-like nanoparticles (MSSNs) synthesized by different methods, A-D, MSSNs with different pore size;[45,74,109,126] E, F, MSSNs with different porous structures;[51,65] G-I Dendritic MSSNs with different particle size.[109,118,127]

By utilizing water and ethanol as solvents, ammonia solution as the catalyst and a cationic surfactant such as CTAB as the soft-template, the modified Stöber method is extended to synthesize sub-micrometer MSSNs.[96] Yano and coworkers have widely investigated the modified Stöber method for the synthesis of MSSNs with radially aligned mesopores.[97,98] They also proposed the formation mechanism and explained why monodispersed MSSNs can be prepared by a Stöber method.[99-102] One of the most popular methods which has been widely adopted in the MSSNs and core-shell structured MSSNs preparation was developed by Cai and his colleagues by using a dilute surfactant solution.[30] Later, by varying the initial silicate/surfactant

concentration, Nooney et al.[103] further extended the above mentioned method to synthesize MSSN with particle size range from 65 to 740 nm. Since then, the research in this area has focused on controlling the particle size, pore size and dispersity of the MSSNs. The typical TEM images of MSSNs with different particle size, pore size, porous structures are summarized in Figure 2.3. Mou and co-workers synthesized MSSNs with tailoring particle size from 30 to 280 nm by tuning the pH of the reaction medium.[60] Dialysis process has been used for preparation of MSSNs with particle sizes below 50 nm.[38-40,42,43] Moreover, cubic *Ia3d* or *Pm3n* symmetry mesoporous structured MSSNs,[65,104,105] MSSNs with worm-like pores,[51,106] MSSNs with larger pore size[91,107-111] have also been synthesized either in basic or acidic conditions by employing different surfactants as templates. Using block copolymer polystyrene-b-poly (acrylic acid) (PS-b-PAA) and CTAB as dual templates, Niu et al.[109] reported the synthesis of MSSNs with interconnected open mesoporous channels larger than 12 nm. As a special type of MSSNs, dendritic MSSNs shown in Figure 3G-I with open large pore channels are of particular interest due to the highly accessible internal surface area for biomedical applications.[27,74,118,128,129] The used synthesis methods include microemulsion, biphase stratification and hard templating method. As Du and Qiao recently have provided comprehensive reviews on the synthesis and applications of dendritic MSSNs,[27] the current review focuses mainly on the synthesis and biomedical applications of complex MSNs including core-shell structured mesoporous silica nanoparticles (*cs*-MSNs), yolk-shell structured mesoporous silica nanoparticles (*ys*-MSNs), and Janus structured mesoporous silica nanoparticles (*j*-MSNs). In principle, as shown in Figure 2.2, the hollow, core-shell and yolk-shell structures with diverse morphologies and chemical compositions can be designed and synthesized by combining and modifying the schematic structures shown in Table 2.1. Only two typical examples of Janus structured silicas are illustrated in Figure 2.2, one represents a Janus particle with different properties on two faces, the second category is the combination of two or more different MSNs. In principle, more than 100 kinds of Janus structured MSNs can be created by the integration of the single and multi-compartment MSNs shown in Figure 2.2.

2.2.1 Core-shell structured mesoporous silica micro/nanoparticles

The combination of the diverse inorganic nanocrystals in the core with the unique properties of mesoporous shells creates the emergence of core-shell and yolk-shell structured mesoporous silica micro/nanoparticles as the first class of functional MSNs

as discussed in several excellent review papers.[18,75,130-133] However, in this section, we will begin by simply summarizing the most popular self-assembly coating methods. Separated MSNs and functional nanoparticles are normally formed rather than the core-shell composites, because of the lack of interaction between two particles. Therefore, the surface modification or the secondary growth is usually necessary to fabricate *cs*-MSNs.

Similar to the synthesis of MSSNs, the modified Stöber method has been widely adopted for coating and generating mesoporous silica shells. A cationic surfactant such as CTAB is commonly employed, which not only acts as a template for mesopores, but also as an agent to alter the surface charge of the core materials using "growth seeds". Ordinarily, to make better use of MSNs, mesoporous silicas have been used either as the core or shell materials. By selecting MSNs as cores, polymer such as polyethyleneimine,[134-136] poly(ethylene glycol) (PEG),[137,138] poly-L-lysine (PLL),[110] poly(N-isopropylacrylamide) (PNIPAM),[139,140] poly(methacrylic acid-co-vinyl triethoxylsilane) (PMV),[141] poly(N-vinylcaprolactam-co-methacrylic acid) (P-(VCL-s-s-MAA)),[142] polymer copolymer−lipid,[33,35,143] or layered double hydroxides (LDHs),[144] and metal organic frameworks (MOFs),[145] have been coated as shells for the applications of drug and gene delivery. In order to endow MSNs with unique optical, plasmonic, acoustic and magnetic properties for theranostics applications, the core particles used so far for spherical *cs*-MSNs with mesoporous silica shells including silica,[64,74,146-153] MOFs,[154] gold,[155-167] platinum,[168,169] silver,[72,170-172] UPCNs,[173-190] QDs,[128,163,191] photoluminescent nanodiamonds (NDs),[192,193] graphitic carbon,[63,194] magnetic nanoparticles (M NPs),[55,77,145,195-225] manganese oxide nanoparticles (MnO NPs),[226-228] Gd_2O_3:Eu nanocrystals,[229-231] AgS_2 nanocrystals,[232] copper chalcogenide (Cu_9S_5) nanocrystals,[233] and $Cu_{2-x}Se$ nanoparticles.[234]

Some typical TEM images of these *cs*-MSNs are summarized in Figure 2.4. The position of the core can be either eccentric or concentric, radial mesoporous silica shells can also be realized. It is also of vital importance to coat mesoporous silica shells to reduce the toxicity of the core functional nanoparticles and to avoid their aggregation during the therapy process. By employing the core materials with different morphologies, the self-assembly coating method has been extended to prepare *cs*-MSNs with rods,[157,159,161-164,166,167,223] cubes[154,158] and ellipsoids[150,200,205,235] shapes.

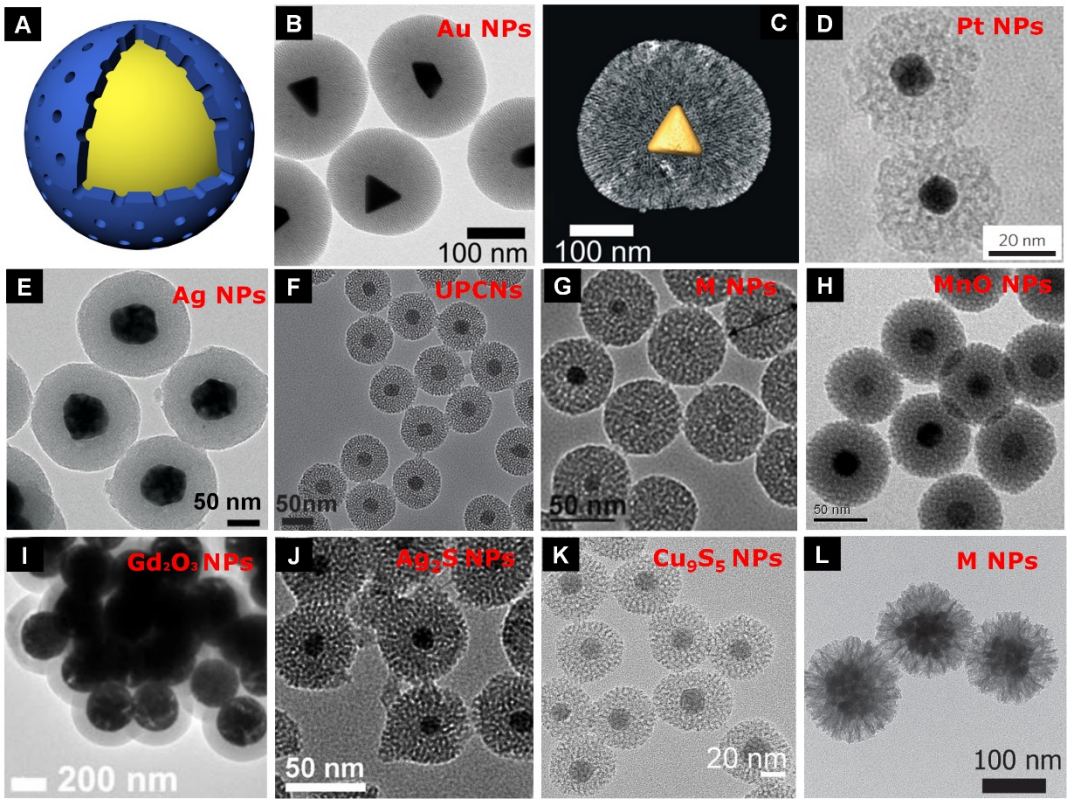


Figure 2.4 Gallery of *cs*-MSNs: A Schematic illustration and B-L typical TEM images of *cs*-MSNs with various core and different pore size of mesoporous silica shells. B, TEM image and C, 3D reconstructions of Au@meso-SiO_2;[155] D, TEM image of Pt@meso-SiO_2;[168] E, TEM image of Ag@meso-SiO_2;[170] F, TEM image of UPCNs@meso-SiO_2;[189] G, TEM image of Fe_3O_4@meso-SiO_2;[54] H, TEM image of MnO@meso-SiO_2;[226] I, TEM image of Gd_2O_3@meso-SiO_2;[231] J, TEM image of Ag_2S@meso-SiO_2;[232] K, TEM image of Cu_9S_5@meso-SiO_2;[233] L, TEM image of Fe_3O_4@dendritic meso-SiO_2.[225]

Coating of gold NPs, UPCNs, and magnetic Fe_3O_4 NPs with meso-silica shell is the most popular process for the development of biomaterials with plasmonic, optical, acoustic and magnetic properties, respectively for diagnosis and integrate treatments of chemotherapy, photodynamic therapy (PDT), and photothermal therapy (PTT). To date, due to their tunable localized surface plasmon resonance (LSPR) for adsorbing near infrared (NIR) radiation, many attempts have been carried out to prepare Au@meso-SiO_2 with a gold core and mesoporous silica shell for both cancer cell imaging and PTT application.[155-160,167,236-241] Additionally, UCNPs@meso-SiO_2 have been widely synthesized and applied in the field of bioimaging due to their unique ability of upconverting low-energy NIR light to high-energy ultraviolet (UV), visible

(vis) and NIR light.[174,175,178,180,181,189,221] For magnetic resonance imaging (MRI) and magnetic bioseparation applications, significant effort has also been devoted to prepare magnetic Fe_3O_4@meso-SiO_2 with controlled particle size.[18,109,131,133,197,198,207,214,216-219,223,225,242-245] Furthermore, multifunctional *cs*-MSNs with multiple cores or shells such as magnetic, UPCNs, plasmonic NPs, fluorescent dyes have been developed for multimodal imaging or theranostics.[174,182,186,189,195,200-205,209,212,246,247] For example, Chen et al. reported the synthesis of ellipsoidal Fe_3O_4@SiO_2@mesoSiO_2 coated with multi-layers of polyelectrolyte (PAH)/QDs to combine the merits of functional particles.[200] In addition, Sun et al. successfully synthesized Gd^{3+} ion doped UCNPs@meso-SiO_2-Ln(dbm)$_4$ (Ln = Eu, Sm, Er, Nd, Yb) with the combination of magnetic resonance imaging (MRI), upconversion, and downconversion luminescence imaging into one particle.[186] Therefore, multifunctionlization of *cs*-MSNs is crucial for their further applications in theranostics.

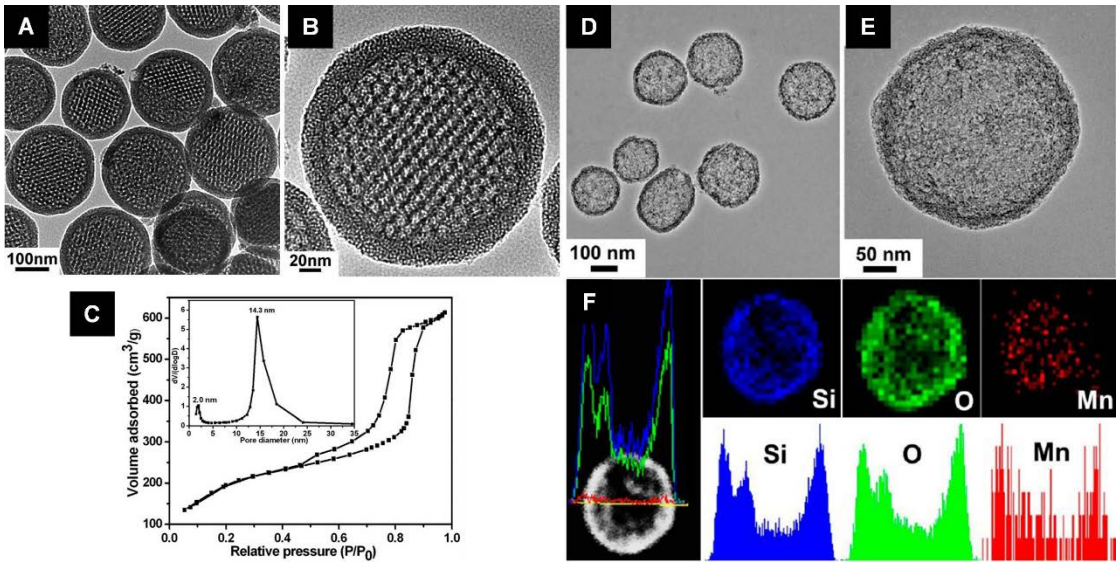


Figure 2.5 (A), (B) TEM images and (C) N_2 adsorption-desorption isotherms and BJH pore diameter distribution curve at adsorption branch (inset) of DMSSNs[64], (D), (E), TEM images of Mn- DMSSNs; (F) Scanning TEM image with high angle annular dark field (STEM-HAADF) and corresponding EDS elemental mapping images and EDS.[242]

In addition, great attention and effort have been devoted to the fabrication of dual mesoporous *cs*-MSNs (DMSSNs) with different pore size and structures with core and shells.[64,71,74,150-152,154,248] As shown in Figure 2.5A-C, core–shell structured DMSSNs

with 2 nm mesopores in the shell and 14 nm mesopores in the core were successfully synthesized from Shi's group by utilizing an amphiphilic block copolymer (polystyrene-b-poly(acrylic acid), PS-b-PAA) and CTAB as dual templates. They further extended the method to encapsulate ultrasmall manganese oxide nanoclusters and magnetic Fe_3O_4 into the pore channels of DMSSs to generate Mn@DMSSNs (Figs. 2.5D-F)[242] and Fe_3O_4@DMSSNs,[248] respectively. Moreover, Yang and coworkers reported the one-pot synthesis of *cs*-MSSNs with dual oriented mesochannels and controlled pore size (3.0 to 7.3 nm) by using CTAB as a template with the aid of 1,3,5-trimethylbenzene (TMB) in a basic medium.[152] Design and fabrication of *cs*-MSSNs with triple, and more hierarchical porous structure and size is expected in the future studies.

2.2.2 Yolk-shell structured mesoporous silica micro/nanoparticles

As a sub-class of core-shell particles, the yolk-shell nanoparticles (YSNs) or so called 'nano-rattles' with a distinctive core@void@shell structure, in principle, open a new platform for theranostic applications. The construction and applications of YSNs has already been well reviewed by the groups of Fromm,[249] Lee,[250] Lu,[29,251] Shi,[2] Song,[252] FQ Tang,[17] ZY Tang,[253] Yang,[254] Zeng,[255] Zheng,[256] and recently by Liu and Priestley,[130] Purbia and Paria,[257] Zhang and Yin et al.[258] Specifically, the synthesis of yolk-shell structured mesoporous silica nanoparticles (*ys*-MSNs) can be started from *cs*-MSNs by selective etching the core or shell, or etching the middle sacrifice layer. Different etching agents including HF,[259,260] KCN,[261] Na_2CO_3,[235,260,262] ammonia,[263,264] H_2SO_4 and Na_2SO_4[265] have been chosen to selectively etch the inner or middle sacrificial silica layer partially or completely; whereas the porous silica shell remained intact due to the structural differences in core and shell. Alternatively, it can be started from *h*-MSNs through the "ship-in-a-bottle" strategy.[266] For example, Chen and co-workers[266] have adapted this approach to synthesize UPCNs@meso-SiO_2 YSNs by encapsulating a trifluoroacetate precursor into *h*-MSNs and following a calcination step. A one-pot soft templating method has also been developed for the preparation of *ys*-MSNs.[267-270] Early work by Liu et al. reported the synthesis of *ys*-MSNs either with a mesoporous silica shell[268] or PMO shell[269] by a soft-templating method adapting FC4 and F127 as dual templates. Organosilane assisted etching method was also developed by Yang et al. for construction of *ys*-MSNs with PMO shell.[271,272] Applying the similar synthesis protocols, Teng et al. reported the triple-hybridized PMO YSNs with ethane, thioether-, and benzene-bridged moieties

simultaneously incorporated. It worth to noting nano-matryoshkas with multiple layers of yolk-shell can be obtained by either selective etching method or soft-templating method.[263,267] Similar to its *cs*-MSNs counterparts, to date, *ys*-MSNs with different cores such as silica spheres (SSs),[260,265,267-269,273,274] MSSNs,[268,272,275,276] Au,[53,165,240,263,264,268,274,277,278] ZnS,[278] Co_3O_4,[278] TiO_2,[278] Fe_2O_3,[150,279] Fe NPs,[280] UPCNs,[173,266,281-283] magnetic Fe_3O_4,[235,268,271,277,284-292] Ag/AgBr,[293] Gd_2O_3:Eu[294], BaFeO NPs,[295] have been prepared accordingly, and their corresponding TEM images are shown in Figure 2.6. By selecting core materials or *h*-MSNs with different morphologies, many yolk shell structured ellipsoidal particles,[150,235,280,282] nanoplates,[296] rod-like particles[159,166] have been fabricated through the above mentioned methods. In addition, *ys*-MSNs with polymer shells were synthesized by coating a sheddable thermo/pH-sensitive P-(VCL-s-s-MAA) polymer onto a carboxylic acid modified MSNs (MSN-COOH).[142]

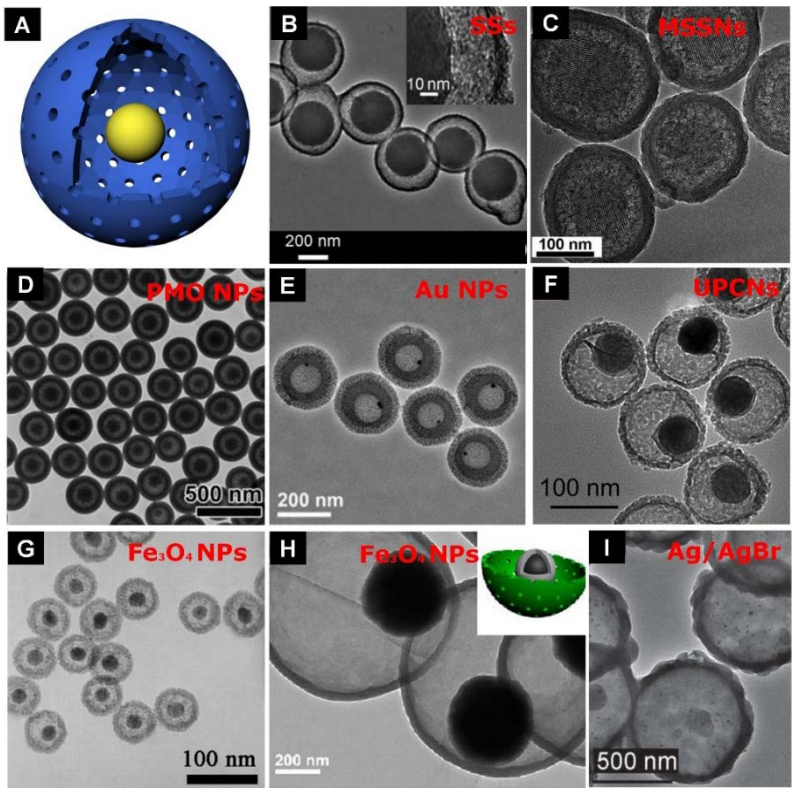


Figure 2.6 Gallery of *ys*-MSNs: A Schematic illustration and B-I typical TEM images of *ys*-MSNs with various core. B, silica spheres (SSs);[268] C, D, mesoporous silica spheres nanoparticles (MSSNs);[272] E, Au NPs;[53] F, UPCNs;[281] G, H, Fe_3O_4;[284,285] I, Ag/AgBr.[293]

Aiming at theranostics applications, similar to *cs*-MSNs, many research groups have focused on the design and synthesis of multifunctional *ys*-MSNs.[170,276,281,282,285,294,297] Lv et al.[282] demonstrated the synthesis of yolk-shell structured GdOF:Ln@mesoSiO$_2$ (Ln = 10%Yb/1%Er/4%Mn) with strong up-conversion luminescent (UCL) GdOF:Ln as the cores and mesoporous silica shells (Fig. 2.7). Then, PDT agent ZnPc and carbon dots (CDs) have been selectively located onto the core and outside the shell, respectively (Figs. 6a-c). The resultant multifunctional ellipsoidal particles with UCL imaging, MRI, and computed tomography (CT) imaging properties are excellent candidates for multimodal imaging guided multiple therapies. In addition, multifunctional *ys*-MSNs were simultaneously functionalized with photosensitizer Chlorin e6 (Ce6), photothermal agent CDs, and imaging agent Gd (III) ions, and a stimuli-responsive polymer (P(NIPAm-co-MAA)) have been coated on the out-layer for the integration of chemotherapy, PDT and PTT theranostic systems.[276]

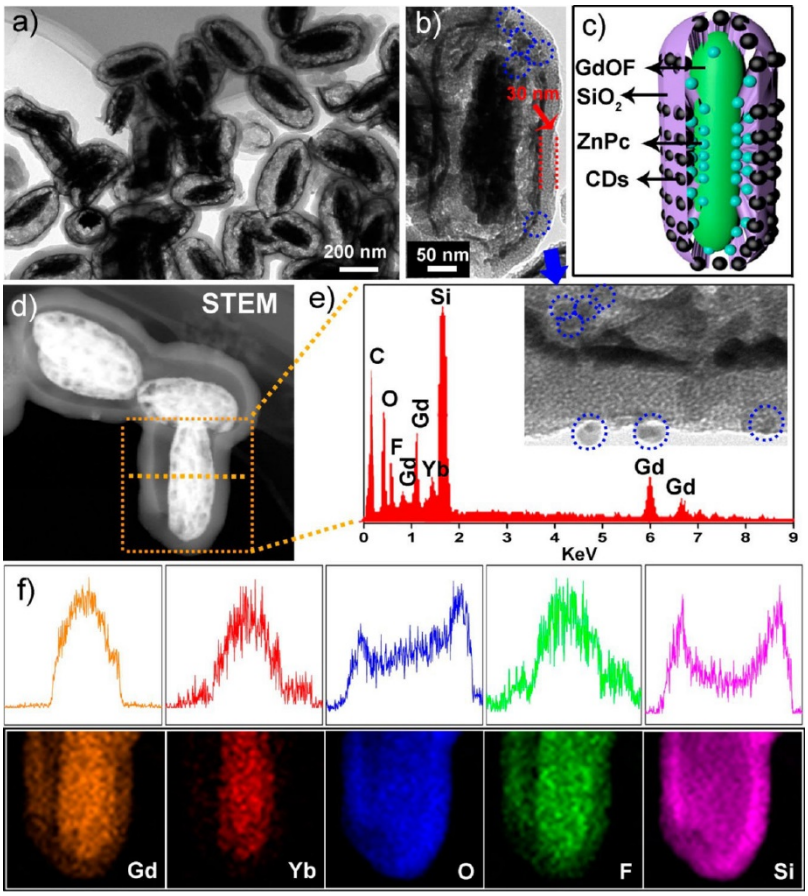


Figure 2.7 (a and b) TEM images with different magnification, (c) morphology sketch, (d)STEM image, (e) EDS, and(F) the cross-sectional compositional line profiles and elemental mapping images of GdOF:Ln@mSiO$_2$-ZnPC-CDs.[282]

2.2.3 Multipodal and Janus structured mesoporous silica micro/nanoparticles

Janus nanoparticles with asymmetric chemistry and structures in its two faces, have emerged as attractive nanomaterials. Owing to its unique structure in compartmentalizing multiple building blocks, Janus nanoparticles with controlled geometry and multiple compartments have shown many interesting properties in various potential applications including drug delivery, optical probes, self-propelled motors and solid surfactants.[298] To date, various methods have been reported to prepare Janus nanoparticles including emulsion, microfluidics, self-assembly assembly and one-step synthesis. It is well recognized that the properties of the obtained Janus particle strongly depend on their morphology and compositions.

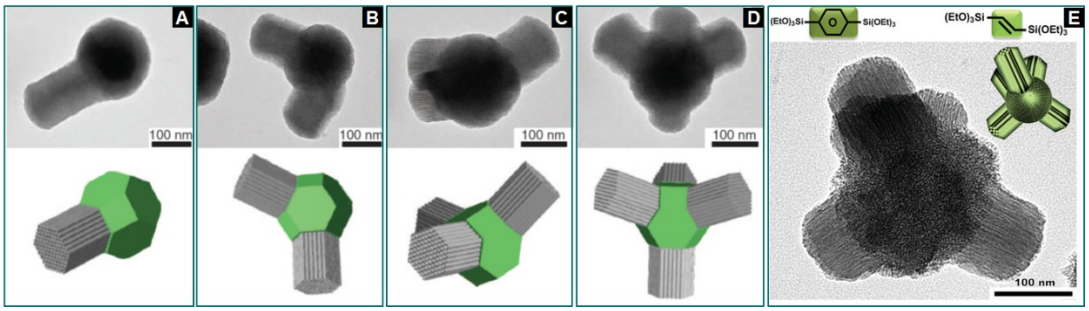


Figure 2.8 TEM images and schematic illustration of *j*-MSNs with multi-compartment. (A) one arm, (B) two arms, (C) three arms, (D) four arms[67] and (E) five arms.[49,299]

In 2013, Wiesner's group reported a one-pot synthesis method to obtain Janus structured mesoporous silica micro/nanoparticles containing both a cubic mesoporous structured core and hexagonal mesoporous structured branches within one particle.[67] As shown in Figure 2.8, the advantage of this method is that the amount of mesoporous cylindrical branches can be controlled with variations in ethyl acetate concentration [EtOAc] in the synthesis mixture. The key step in this method is to decrease the pH and change in the charge state of (3-aminopropyl)triethoxysilane (APTES) during the hydrolysis of EtOAc. Later, using NaOH as a catalyst and CTAB as a template, Croissant et al. also reported the synthesis of multipodal PMO *j*-MSNs with phenylene-PMO cores and ethenylene-PMO pods.[299,300] While phenylene-PMO nanospheres and ethenylene-PMO nanorods were obtained by using their sole corresponding precursor, multipodal PMO *j*-MSNs can be generated by the subsequent addition of the ethenylene precursor into a solution of freshly-prepared phenylene-PMO nanospheres. Through a two-step sprout-like growth method, Huo and co-

workers reported the *j*-MSNs consist of a PMO core and up to three branches with mesoporous pure silica nanorods growing out of the cubic core vertices.[49] Ujiie et al. synthesized less than 100 nm *j*-MSNs with MSNs asymmetrically capped with non-porous phenylsilsesquioxane by the post modification of MSNs with phenyltriethoxysilane.[37]

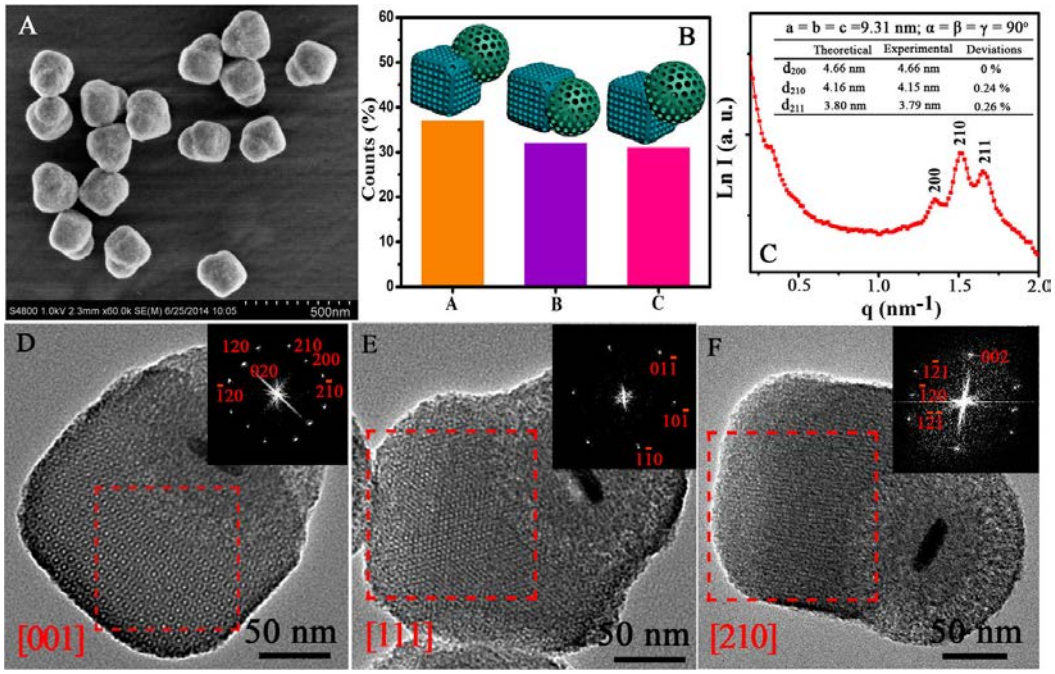


Figure 2.9 (A) SEM images of the obtained UCNP@SiO_2@mSiO_2&PMO Janus nanocomposites. (B) The statistic results of the relative positions between the core@shell@shell UCNP@SiO_2@mSiO_2 nanosphere domain and PMO single-crystal nanocube domain of Janus nanoparticles: the nanosphere attached on the vertex, edge, or face of the nanocube. (C) The SAXS pattern of the Janus mesoporous nanocomposites (inset: the theoretical and experimental d-spacing values of different planes obtained from the cell parameter and SAXS pattern). (D−F) The TEM images along with the corresponding fast Fourier transform of the Janus nanocomposite along [001] (D), [111] (E), and [210] (F) zone axis.[283]

For practical applications, significant efforts have been made to develop *j*-MSNs that simultaneously display multiple functions. For instance, as shown in Figure 2.9, Zhao and co-workers reported an anisotropic growth-induced approach to synthesize both Janus UCNP@SiO_2@mSiO_2&PMO and UCNP@SiO_2@mSiO_2@PMO with an up-conversion core and MSNs shell onto ethenylene-PMO cubic pods by varying the

H_2O to ethanol ratio in the synthesis mixture.[283] The formation of *j*-MSNs in solution involves nucleation of PMO onto the UCNP@SiO_2@mSiO_2 core followed by anisotropic island growth. By using $NH_3 \cdot H_2O$ as both a basic catalyst and an etching agent, a one-pot asymmetrical/symmetrical coating method has also been developed to prepare *j*-MSNs with gold an PMO, or yolk–shell Au@PMO nanostructures with different morphologies.[53] Furthermore, *j*-MSNs with magnetic Fe_3O_4,[301] Au,[241,302-305] Pt,[306,307] Ag,[308] and Ni,[309,310] heads and mesoporous silica body have been prepared through the asymmetrical coating method and electron beam deposition. Huo and co-workers also found that the length of growth of the mesoporous silica was able to be controlled by increasing and decreasing the ratio of TEOS to the head.[241,283,301] Noteworthy is that various *j*-MSNs nanomotors were synthesized by Sanchez and co-workers[306,307,309-311], and used for biomedical applications which will be discussed in the following section.

As a special type of *j*-MSNs, raspberry-like mesoporous silica nanospheres (RMSNs) with many small particles or pods decorating the surface of one large particle are of particular interest owing to their hierarchical structures and tunable surface properties.[132,312-314] Scherman and co-workers reported the synthesis of raspberry-like mesoporous hollow silica nanospheres (RHMSNs) with paramagnetic Fe_3O_4 nanoparticles decorating the shell by utilizing host–guest complexation of cucurbituril (CB).[313] By using a microfluidic approach, Zhao et al. demonstrated the synthesis of monodisperse raspberry-like hierarchical silica particles.[315] The one-pot synthesis of raspberry-like hierarchical siliceous hollow spheres has also been reported through a vesicle or emulsion template.[316,317] RHMSNs were also successfully synthesized by using carbon spheres as a hard template and CTAB as a soft template, respectively.[318]

2.3 Biomedical applications

MSNs have emerged as an excellent candidates for theranostic applications owing to their stable structure, tunable pore size, large surface area and well-defined surface. Recently, many kinds of MSNs with multi-components or multi-compartments have been successfully synthesized and adopted for biomedical application purposes due to their advantageous structural properties, such as hierarchical structures, selective functionalization sites, and colloidal stability. So far, these MSNs have been developed for targeted drug/gene/protein delivery, bioimaging for diagnosis, tissue engineering,

cancer therapy, or the combination of diagnosis and therapy for theranostic applications. In this section, we will first discuss the stimuli-responsive drug delivery systems (DDS)[319] and chemotherapy by loading drugs/gene into multi-component MSNs and surface functionalization of stimuli-responsive chemicals. The enhanced permeability and retention (EPR) effect can be improved to a certain level by adapting this strategy. Then we will introduce the bioimaging applications of MSNs with an emphasis on dual and multiple imaging application for disease accurate diagnosis. Phototherapies including photothermal (PTT) and photodynamic therapy (PDT) will be then discussed both for in vitro and in vivo applications. Recognizing that the theranostics using MSNs could offer a new approach to the treatment of degenerative diseases including cancer, the multiple components MSNs with bioimaging agents, tumor-targeting moieties, anticancer drugs, or siRNA, phototherapy agents for multimodal imaging, and dual therapy will be envisioned and discussed. The integration of treatments with chemotherapy, PDT, and PTT, in a single MSNs based nanoplatform is discussed for the potential in achieving super additive antitumor efficacy.

2.3.1 Stimuli-responsive drug/gene delivery and chemotherapy

Functionalization of MSNs with stimuli-responsive materials is emerging as a platform for "smart" stimuli-responsive drug delivery systems (DDSs) in order to improve the treatment efficacy and reduce the side effects of drugs during chemotherapy.[1-3,14,16,23,235] Meanwhile, molecular and supramolecular nanovalves functionalized MSNs so called mechanized MSNs have attracted substantial attention and widely used in controlled cargo/drug release. In the past decade, a library of stimuli-responsive MSNs vehicles has been fabricated for the controlled release of guests in response to external stimulus including, temperature,[140,143,176] pH,[141,143,176,177,187,195,202,265,308,320-330] light,[35,158,167,183,188,198,237,276,281,331-333] enzyme,[215,304,334] biomolecule,[137,142,175,335] redox,[322,336] competitive binding[337] and oscillating magnetic field.[138,309,321] For example, the polymer P(NIPAm-co-MAA)[176,276] has been widely used for thermal responsive controlled release; dibenzo-crown ethers,[321] polyethylene-imine (PEI), cyclodextrins (CDs),[323] acid-decomposable ZnO quantum dots[177] modified MSNs have been synthesized for pH-responsive controlled release; light-responsive azobenzene derivatives,[198] protoporphyrin IX (PpIX),[35] sulfonatocalix[4]arene (SC[4]A) supramolecular,[237] and gold NPs,[332] were used to functionalize MSNs for visible light triggering release of

guest molecules. Lee and co-workers described the development of a polypeptide-wrapped UCNP@MSNs as an adenosine triphosphate (ATP) biomolecules-responsive DDS for drug release (Fig. 2.10A).[175] Fe_3O_4[337] nanoparticles capped or disulfide-based[215,336] MSNs have been developed for redox-responsive controlled release. The controlled release processes are summarized in Figure 2.10 for different stimuli-responsive MSNs systems. With the concept of a nanovalve-gatekeeper system of MSNs, Leung and co-workers synthesized MCMSNs with superparamagnetic iron oxide (SPIO) core, mesoporous silica shell decorated with a series of crown ether macrocycles for controlled release with ultrasound waves.[321] It indicated that the crown ether-based nanovalves could be used to block Cs^+ and Na^+ ions for different modes of drug loading and release. The release profiles of DOX molecules were enhanced and triggered by ultrasound. In addition, dual responsive MSNs nanocarriers system with multiple functions, such as thermal and pH,[143,176,338] glucose and pH,[161,207,322] light and pH,[339,340] thermal and redox,[341] pH and redox,[342,343] have been also investigated for controlled DDSs. Qiu et al.[207] designed and synthesized core shell structured Fe_3O_4@MSNs@b-CDs for pH and sugar dual-responsive controlled release. Wu et al.[143] reported a pH- and thermo-dual-stimuli-responsive MSNs nanocarrier, which have potential applications in clinical anticancer drug. Wang and co-workers[342] reported dual responsive MSNs with an acid-dissolvable magnetic core and a redox-degradable poly(methylacrylic acid-co-N,N-bis(acryloyl)cystamine) (P(MAA-Cy)) shell, and the release of drug could be controlled by the pH value and redox-agents.

With the development of stimuli-responsive controlled release MSNs system, ultilization of these MSNs including core-shell, yolk-shell structure and Janus particles for chemotherapy has been investigated. Hydrophobic antitumor drug (docetaxel, DOC) was loaded into *ys*-MSNs for *in vitro* and *in vivo* liver cancer therapy. Efficient cellular internalization was achieved as fluorescein isothiocyanate (FITC)-labeled *ys*-MSNs monitored by fluorescence microscopy. The resulting *ys*-MSNs could successfully penetrate the plasma membrane of Hep-G2 cells and translocate into the cytoplasm with high efficiency. Moreover, the DOC-loaded *ys*-MSNs showed greater antitumor activity with about a 15% enhanced tumor inhibition rate compared to taxotere on the marine hepatocarcinoma 22 subcutaneous model.[344] The photostimuli-responsive *ys*-MSNs with an upconversion nanocrystal $NaYF_4:Tm^{3+},Yb^{3+}$–$NaLuF_4$ core and mesoporous silica shell have been used for the loading of aphototrigger-

conjugated prodrug (combined anticancer drug chlorambucil and phototrigger agent amino-coumarin).[281] These *ys*-MSNs possess the advantages of a high drug-loading capacity, zero premature release in nontargeted tissue, and sensitivity to NIR light with a wavelength that has a large penetration depth in tissue.

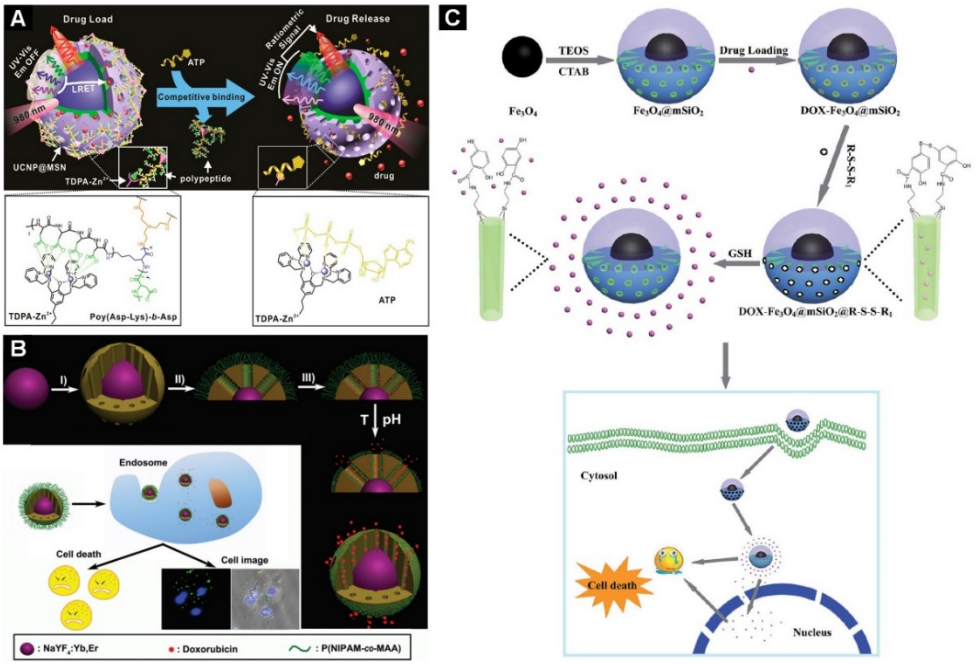


Figure 2.10 Schematic illustration of stimuli-responsive controlled release process of cargo molecules. A. Light-responsive;[175] B. pH-responsive;[176] C. Redox-responsive.[215]

As shown in Figure 2.11a-e, Li and co-workers demonstrated that Janus Ag-MSNs can be selectively endowed with the surface plasmon resonance (SPR) and mesoporous properties. The Janus Ag-MSNs have been used as an effective drug delivery system for easy endocytosis, pH-responsive drug release and simultaneous SERS imaging (Fig. 2.11f-h). By adapting a similar concept, multifunctional Janus particles containing MSNs and gold have been developed.[305] The fluorescence resonance energy transfer (FRET) pair and 6-mercaptopurine (6MP) either by pH or redox responsive bonds can be selectively functionalized onto the MSNs and gold, respectively. The Janus structured carriers have the potential for the real-time study of intelligent multi-drug delivery and release, as well as cellular responses to drug treatment. Villalonga et al.[304] also reported the Janus MSNs and gold containing MSNs part capped with a pH-responsive gate, whereas the gold surface was functionalized with the enzyme urease. Janus-type integrated nanoarchitecture opens new routes for

the development of novel biologically inspired smart nanomachines for drug delivery and sensing applications. The future development of design multifunctional MSNs for targeted delivery can be envisioned.

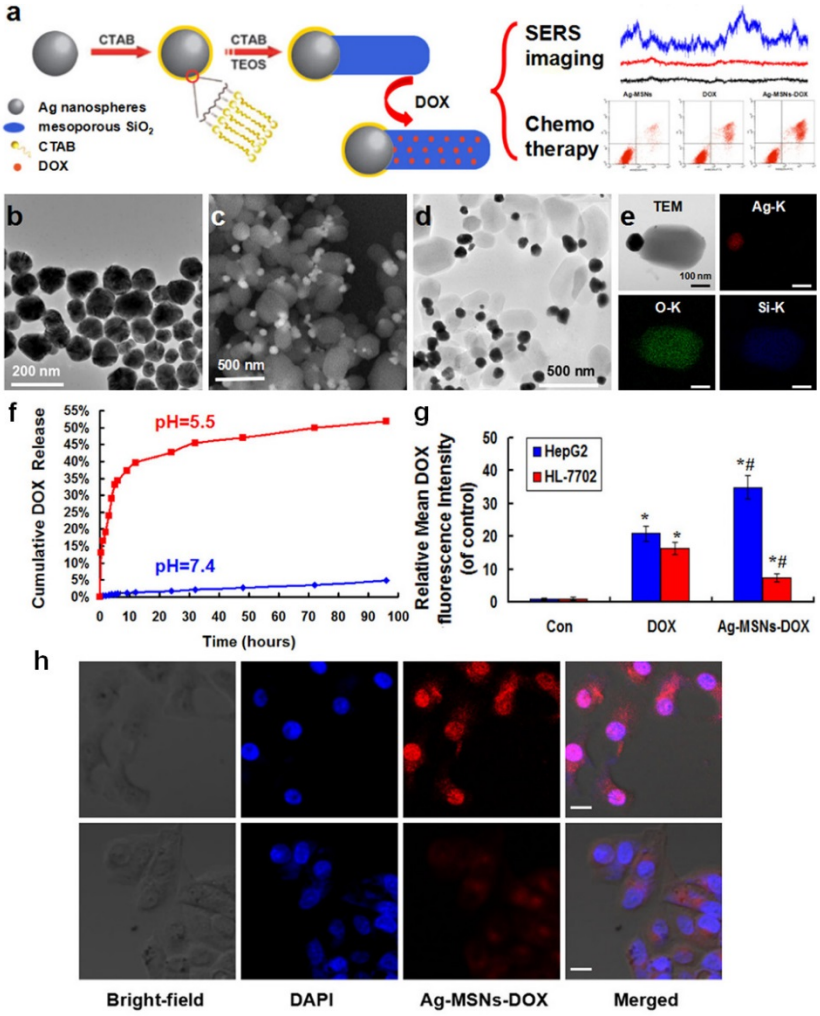


Figure 2.11 Synthesis and biomedical application of Janus Ag-MSN composites. (a) Schematic diagram of the fabrication procedure for the DOX-loaded Ag-MSNs and application for SERS imaging and pH-sensitive drug delivery in cancer therapy, (b) TEM images of Ag nanospheres, (c) SEM, (d) TEM images of Ag-MSNs, (e) Corresponding energy-dispersive X-ray spectroscopy (EDS) element mapping of Ag, Si, and O, respectively. (f) pH-dependent drug release profiles of Ag-MSNs-DOX. (g) Quantitative analysis of fluorescence intensity of DOX in free DOX or DOX-loaded Ag-MSNs treated HepG2 and HL-7702 cells for 3 h. These data represent three separate experiments and are presented as mean values ± SD *P < 0.05 versus control group, #P <0.05 versus DOX group. (h) CLSM images of HepG2 and HL-7702 cells incubated with DOX-loaded Ag-MSNs for 3 h, scale bars are 10 μm.[308]

2.3.2 Bioimaging

The introduction of various imaging techniques including magnetic resonance imaging (MRI), computed tomography (CT),[160,276] positron emission tomography (PET), upconversion luminescence (UCL) imaging,[176] and optical imaging[32,345] to the biomedical field has significantly improved the accuracy of medical diagnosis, especially for cancer. Semiconductor NPs[128] and gold NPs are generally used as fluorescence probes for cell labeling in optical imaging. MRI is one of the most representative imaging techniques to offer high-resolution and superior-contrast images between the specific tissues and their surrounding tissues. Typically, Gd-based complexes[276] or NPs[229,230] and manganese oxide NPs[226-228,346] have been used for T1-weighted imaging, and iron oxide-based NPs[77,202,204,235,239,290,347-349] have been used for T2-weighted imaging.

MnO@mSiO_2(Ir)@PEG with a manganese nanocrystal core and a functionalized mesoporous silica shell have been strategically designed for T1-weighted imaging.[226] Magnetic Fe_3O_4 NPs@mSiO_2 have been used as the contrast agents for T2-weighted MRI. Yolk-shell structured Fe_3O_4@mSiO_2 prepared through a ship-in-a-bottle method can achieve a 76.7% increase in its magnetic saturation value.[350] Shi's group reported the synthesis of multifunctional ellipsoidal MSNs by assembling CdTe quantum dots on the surface of Fe_3O_4@SiO_2@mSiO_2 via a novel layer-by-layer self-assembly technique.[200] The resulting nanoellipsoids integrated the merits of magnetic manipulation, intracellular delivery, and MRI showed a relatively high *r*2 value (143/mM·s) as contrast agents for simultaneous MRI/fluorescence imaging. By the combination of two different modes of imaging (T1- and T2- weighted MR imaging), the development of dual-mode contrast agents (DMCAs) has been widely studied to improve the accuracy of decease diagnosis.[242,294,351] Huang et al.[351] combined the T1 and T2-weighted imaging by the development of Gd^{3+}-chelated Fe_3O_4@mSiO_2, the resultant nanocomposites are endowed with enhanced transverse relaxation rates. Anker and co-workers also demonstrated a yolk shell structured Gd-DTPA-Fe@mSiO_2 for dual MRI contrast imaging.[280] For the high diagnostic requirements, a combination of multiple imaging probes into one single system for achieving multi-modality imaging is expected.[173,178,205,230,282,290] For instance, core-shell and yolk-shell structured Gd-UCNPs@mSiO_2 have been employed for both MR and UCL imaging.[178] As shown in Figure 2.12, Lin and co-workers synthesized yolk shell structured GdOF:Ln@mSiO_2-ZnPc-DCs for multiple imaging (CT, MRI, UCL,

photothermal) applications.[282] Similarly, Wang et al.[177] also prepared UCNPs@mSiO$_2$-ZnO as a nanotheranostic agent for the UCL/CT/MRI trimodality imaging.

Optical imaging techniques have also been widely used to monitor therapeutic release and distribution in real time. For example, a fluorescent dye like FITC has been combined with *ys*-MSNs via various methods such as absorption[352], covalent amidation conjugation[353], and in situ co-condensation [354]. FITC-labeled *ys*-MSNs have been tracked through the whole process of endocytosis: from cellular membrane penetration, to endosomes, then escape to the cytosol, and finally expulsion by lysosomes. Interestingly, the new-generation clinically approved NIRF molecule indocyanine green (ICG), has been successfully attached to *ys*-MSNs in Tang's group[355]. Since NIRF imaging has advantages such as high tissue penetration and low autofluorescence, it is applicable to noninvasive *in vivo* tracking for tumor-specific delivery and biodistribution in living animals.

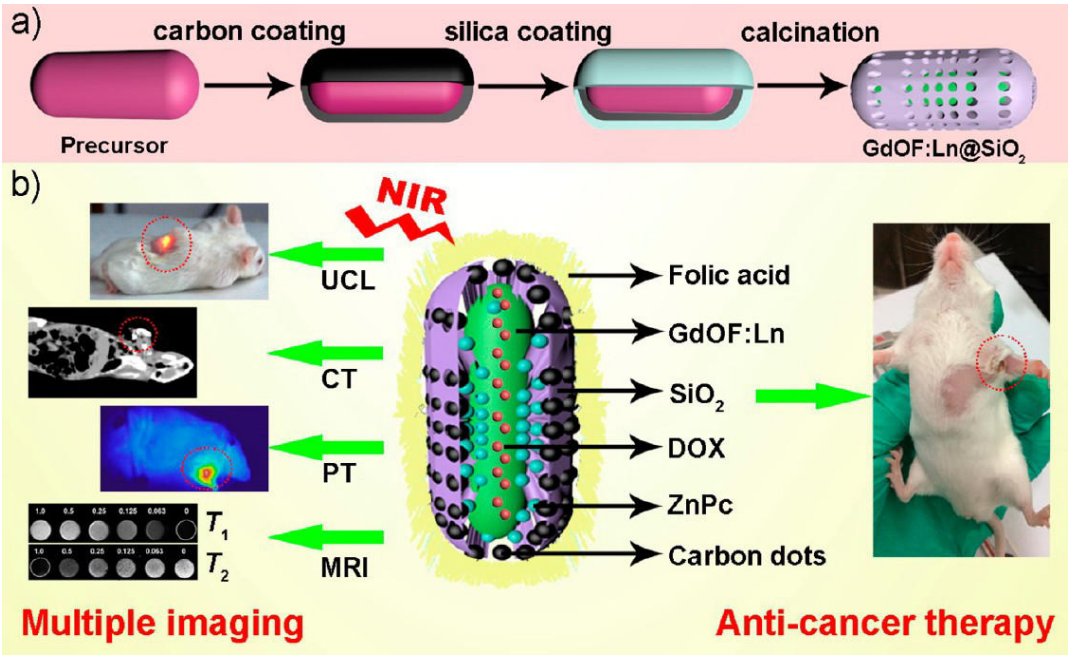


Figure 2.12 Schematic illustration for the synthesis of GdOF:Ln@mSiO$_2$-ZnPc-CDs microcapsule and bio-application for multiple imaging and anti-tumor therapy.[282]

2.3.3 Cancer therapy

Ultrasound therapy,[346] radiotherapy, chemotherapy,[204,333] phototherapy,[157,356] and magnetic hyperthermia-based therapies[357] have been developed for cancer therapy.

Both chemotherapy and phototherapy have been widely applied for cancer therapy by using synthetic nanomaterials.[8,10] Phototherapies including photothermal therapy (PTT) and photodynamic therapy (PDT) induced by light, preferably near-infrared (NIR) light with superior tissue penetration ability, can be used to selectively kill cancer cells under light irradiation. Generally, Au, Pt, and Ag can provide plasmonic properties and adsorb near infrared (NIR) radiation and have been proved to be effective PTT agents, though a mesoporous silica coating is necessary to reduce their cytotoxicity. Carbon nanomaterials also have been selected for PTT applications.[63,71,194] PDT relies on the fact that local light excitation of photosensitizer (PS) will generate highly reactive oxygen species (ROS) for irreversibly damaging of malignant cells.[184] Unlike PDT, PTT does not require oxygen, which is a hyperthermia (>41 °C) treatment of "cooking" tumorigenic cells, even hypoxic tissues. As illustrated in Figure 2.13A, Zhang et al.[156] demonstrated Au@mSiO_2 containing two-photon imaging (TPI) and hyperthermia agents can be used for cancer chemotherapy. Tang's group showed that *ys*-MSNs can be used for cancer therapy by binding monoclonal CD73 or CD90 antibody-conjugated with mesenchymal stem cells (MSCs), the laden MSCs could actively find and migrate to solid tumor tissues to achieve the targeted drug delivery as shown in Figure 2.13B.

MSNs based integration of photothermal- and chemotherapies[205,233,236] have been explored for combination therapy with reduced drug dosage and low laser power. Au NRs-capped magnetic Fe_3O_4@ mSiO_2 nanoellipsoids have been used for chemotherapy, photo-thermotherapy, in vivo MR-, infrared thermal and optical imaging into one single system.[205] As shown in Figure 2.13C, Luo et al.[236] developed a core-shell structured GNR@mSiO_2, in which a gold nanorod core and mesoporous silica shell have been used as the hyperthermal agent, and the reservoir of photosensitizer (Al(III)phthalocyanine chloride tetrasulfonic acid, $AlPcS_4$), respectively. CD gatekeeper and tumor targeting ligand (lactobionic acid, LA) were further loaded onto these MSNs for controlled drug release and chemotherapy. Under laser irradiation, the produced destructive heat/ROS would trigger the remarkable tumor cell death. As confirmed by *in vitro* and *in vivo* studies, the nanocomposite exhibits an obvious near-infrared induced thermal effect, which significantly improves the PDT and chemotherapy efficiency, resulting in a superadditive therapeutic effect. Furthermore, *ys*-MSNs with gold–nanoshell has been used to combine hyperthermia therapy with chemotherapy for cancer treatment.[358,359] *In vitro* experiments indicate

the combined hyperthermia and chemotherapy give a significantly enhanced cell-killing effect toward HepG2 cells. All these results demonstrate the importance of the synergetic effect of combined photothermal therapy and chemotherapy.

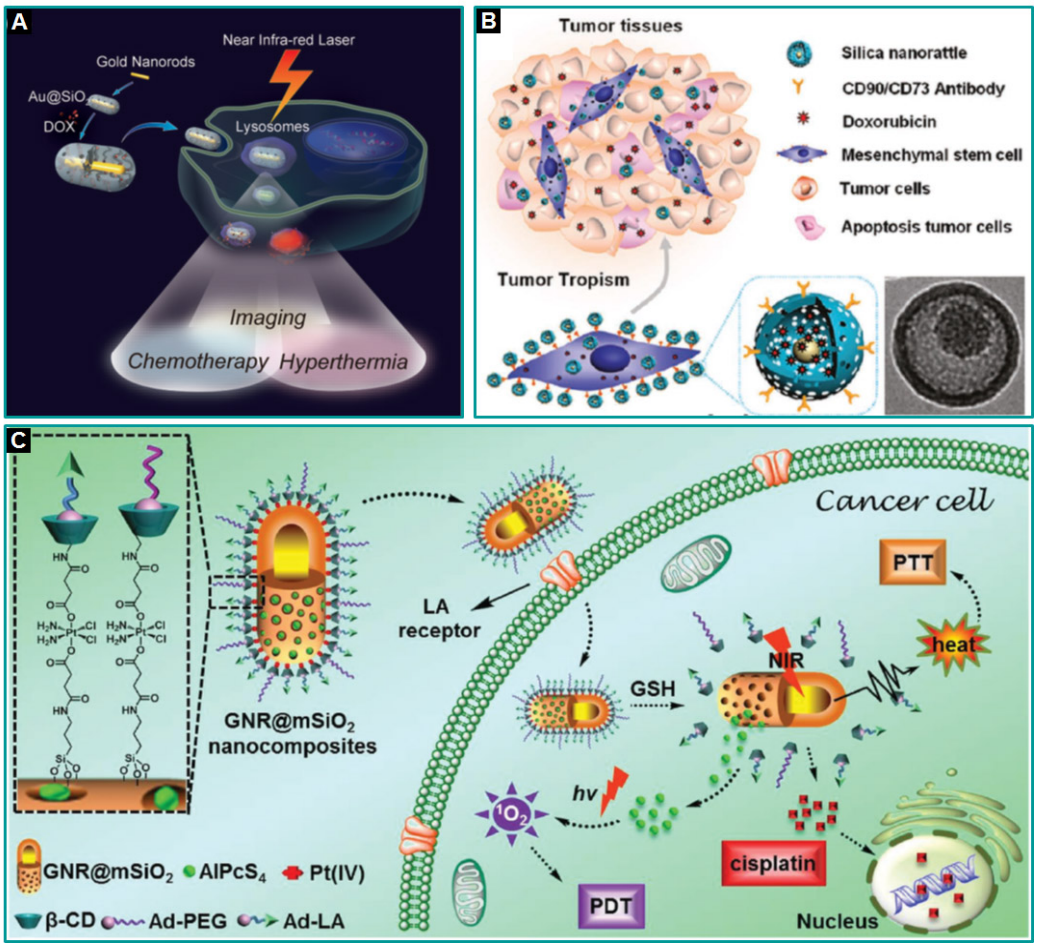


Figure 2.13 Schematic illustration A. Au@mSiO$_2$ as a multifunctional theranostic platform for cancer treatment;[156] B. *ys*-MSNs-DOX-anchored for tumor-tropic therapy;[360] C. MMSGNR-AlPcS$_4$ for tri-model high-performance tumor therapy.[236]

Theranostic applications with a combination of multimodal imaging, photothermal therapy, and chemotherapy is expected to offer better therapy effects on cancer cells than individual therapy approaches in vitro and in vivo. As demonstrated in Figure 2.14A, yolk shell structured Fe$_3$O$_4$@mSiO$_2$ were developed as multifunctional systems for MRI/NIRF bimodal imaging probe for cancer diagnosis, and chemotherapy of cancer.[290] Yang and coworkers[276] designed a multifunctional *ys*-MSNs with combined therapeutic effect (PDT/PTT/chemo) and dual imaging function (MRI/X-ray CT) (Fig. 2.14B). The *ys*-MSNs are surface modified by amino groups (-

NH_2) and then chelated with Gd-DTPA, doxorubicin (DOX) was chosen as the anticancer drug and encapsulated into the mesopores of *ys*-MSNs. Further modification with thermo/pH-sensitive polymer P(NIPAm-co-MAA)), which acted as a "gatekeeper" to control the release of the antidrug in *ys*-MSNs. Hu and co-workers report the anticancer drug of doxorubicin (DOX)-loaded core-shell nanostructured Cu_9S_5@mSiO_2-PEG can effectively delivery DOX into cancer cells with a pH sensitive release profile for the combination of photothermal- and chemotherapies.[233] As discussed earlier, yolk shell structured GdOF:Ln@mSiO_2-ZnPc-DCs prepared by Lin and co-workers have been well applied for both multiple imaging (CT, MRI, UCL, photothermal) and multiple therapies (PDT, PTT, and chemotherapy).[282] Similarly, Shi and co-workers also demonstrated an multifunctional Gd-UCNPs@mSiO_2 nanotheranostic for MR/UCL bimodal imaging and synergetic chemo-/radio-/photodynamic therapy.[178]

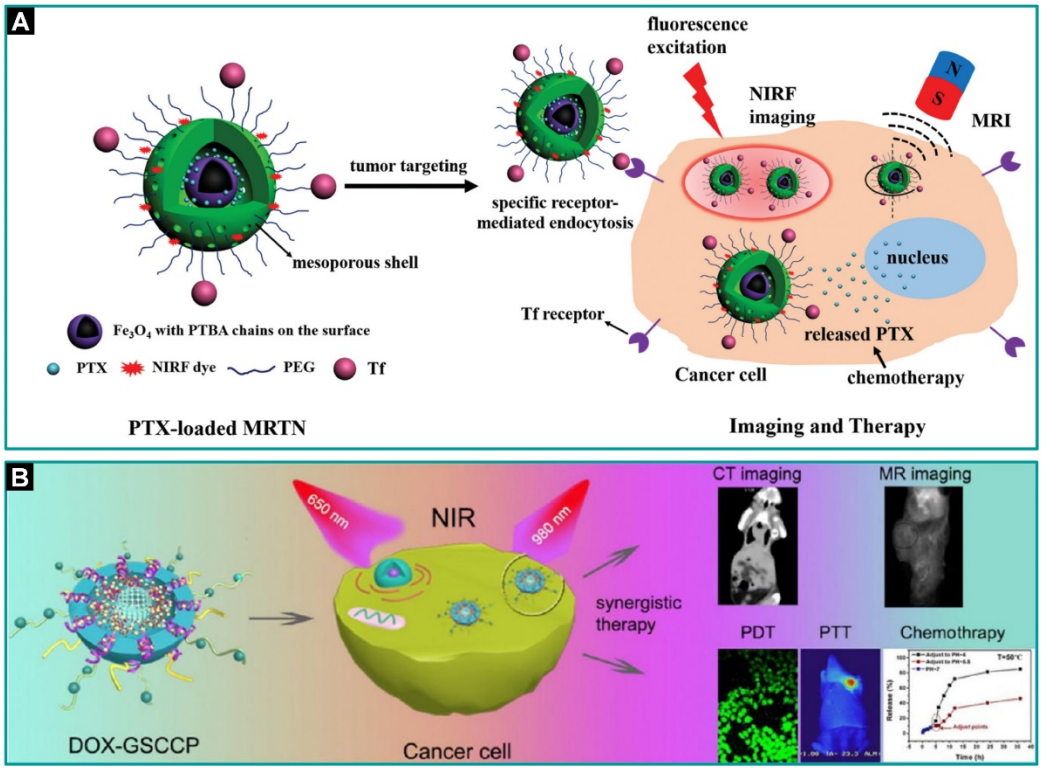


Figure 2.14 Schematic illustration for A. PTX-loaded yolk shell structured Fe_3O_4@mSiO_2 for tumor targeting, MRI, fluorescence imaging, and chemotherapy;[290] B. Chemo/photodynamic/photothermal therapy based on Gd (III) chelated *ys*-MSNs.[276]

2.4 Conclusion

Recent years have witnessed a blossoming research in the development of multicomponent mesoporous silicas nanoparticles for theranostics applications. We began humbly by the design and development of MSNs and their surface functionalization, particle size, morphological and structural control. The potential applications of these MSNs are in biomedical diagnosis and therapy including drug/gene/protein delivery, bioimaging and cancer therapy. Despite the great opportunity of MSNs for theranostic applications, the research is still in its infancy, and there are considerable challenges for the actual use of MSNs in clinical practices, as exampled below.

1. New facile, economic mild strategies for the synthesis of MSNs should be further explored for their large-scale production. Therefore, it is of great importance to design multicomponent nanocomposites for large-scale production and with a controlled structure and stable surface chemistry.
2. Multifunctional MSNs are expected to endow advanced properties such as long circulation time, controlled release, drug and gene co-delivery, and eventually, should be able to simultaneously realize diagnosis and therapeutics as a theranostic agent.

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Chapter 3. Fe_3O_4 encapsulated mesoporous silica nanospheres with tunable size and large void pore

Abstract

Magnetic Fe_3O_4 and mesoporous silica core-shell nanospheres with tunable size from 110 to 800 nm were synthesized via a one step self-assembly method. The morphological, structural, textural, and magnetic properties were well-characterized by scanning electron microscopy (SEM), transmission electron microscopy (TEM), X-ray diffraction (XRD), N_2 adsorption-desorption and magnetometer. These nanocomposites, which possess high surface area, large pore volume and well-defined pore size, exhibit two dimensional hexagonal (P6mm) mesostructures. Interestingly, magnetic core and mesoporous silica shell nanocomposites with large void pore (20 nm) on the shell were generated by increasing the ratio of ethanol/water. Additionally, the obtained nanocomposites combined magnetization response and large void pore, implying the possibility of applications in drug/gene targeting delivery. The cell internalization capacity of NH_2-functionalized nanocomposites in the case of cancer cells (HeLa cells) was exemplified to demonstrate their nano-medicine application.

3.1 Introduction

Magnetic nanoparticles have attracted a great deal of attention, not only for their fundamental scientific interest, but also for their many technological applications in bio-separation, diagnostic analysis, magnetic carriers for drug-delivery systems, magnetically separable catalysts, biosensors and so on.[1,2] However, due to the high ratio of surface to volume and magnetization, bare magnetic nanoparticles are usually prone to aggregation driven by the decrease of total surface energy.[2,3] Coating with ligands, polymers and silica can help to overcome this drawback.[2,4–6] Among these coating strategies, mesoporous silica-coated magnetic nanoparticles have become increasingly important because of the excellent properties of silica such as high

surface-to-volume ratio, high biocompatibility and biodegradability, easy functionalization, controllable porosity and low cytotoxicity.[6–15]

Since the early pioneering work in 1992, ordered mesoporous silicas with large surface area and porosity, narrow pore size distribution, controlled morphology, and high thermal and hydrothermal stabilities have gained much attention due to their wide potential applications.[16] The integration of mesoporous silica with magnetic particles to form core-shell nanostructures is undoubtedly of great interest for practical applications. Several groups have reported the synthesis of monodisperse magnetite (Fe_3O_4) nanocrystals embedded in mesoporous silica spheres.[7–15] The first reported magnetic mesoporous silica nanocomposites by Wu et al.[4] were irregular in shape and size. In order to improve their morphology, cationic surfactant such as cetyltrimethylammonium bromide (CTAB) was employed as not only a stabilizing agent for the transfer of magnetic nanocrystals to aqueous phase but also an organic template for the formation of highly uniform mesoporous silica spheres.[5,6,9–11] However, these materials either show low saturation magnetization values due to the difficulty in increasing Fe_3O_4 mass fraction or possess randomly aligned mesochannels. In addition, sandwich structured magnetic silica nanocomposites with large magnetite core (100~200 nm) and ordered mesoporous silica shell have been subject to extensive research due to their high magnetic response.[13–15] Especially, synthesis of superparamagnetic microspheres with Fe_3O_4 core and SiO_2 shell with perpendicularly aligned mesoporous channels and their application for water treatment were reported by Zhao's group[17] and Stucky's group[18] independently. However, there are rarely reports on the magnetic silica nanocomposites with well controlled particle size, shell thickness and pore size on shell, which is a major challenge in advanced materials science. Furthermore, the large-pore sizes on the shell would pave the way for hosting larger biomolecules compared with standard mesoporous silica-coated particles with 2 nm pores. Therefore, the core-shell magnetic mesoporous silica nanospheres with large pore size on the shell are highly desirable.

In this chapter, we report the synthesis of magnetic mesoporous silica core shell nanospheres by combination of microemulsion method and Stöber process as shown in Figure 3.1. The diameter and the shell thickness of mesoporous silica spheres can be readily adjusted by changing the synthetic parameters. More importantly, the pore structure on the shell can be tailored for multi-purpose applications by altering the ethanol/water ratio. To illustrate the core-shell nanocomposites for the potential

application in nanomedicine, the cell internalization capacity of NH_2-functionalized nanocomposites in the case of cancer cells (HeLa cells) was investigated.

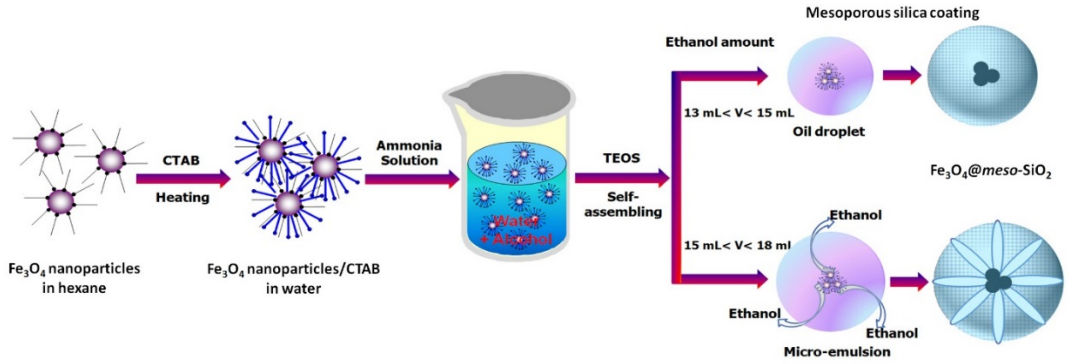

Figure 3.1 The formation of magnetic Fe_3O_4 and mesoporous silica core-shell nanospheres with tunable size (Fe_3O_4@*meso*-SiO_2-*n*).

3.2 Experimental section

3.2.1 Chemicals and materials.

All materials were of analytical grade and used as received without any further purification. Tetraethyl orthosilicate $Si(OC_2H_5)_4$ (TEOS) (>99%), aminopropyltriethoxysilane (APTES) (97%), 1-octadecene (90%), 1,2-hexadecanediol (90%), chloroform (99%), Iron stearic acid ($Fe(SA)_3$), anhydrous ethanol, ammonium hydroxide (25 wt% NH_3 in water), and cetyltrimethylammonium bromide (CTAB) were purchased from Aldrich. Water was purified by a Milli Q system and had an electrical resistance of 18 MΩ·cm.

3.2.2 Synthesis of monodisperse Fe_3O_4 nanocrystals

Monodisperse Fe_3O_4 nanocrystals were prepared according to the reported method.[9] In a typical synthesis, iron stearic acid ($Fe(SA)_3$, 2.0 mmol), 1,2-hexadecanediol (9.0 mmol), and 10 mL of 1-octadecene were heated and stirred until it became a homogeneous mixture. The resulting homogeneous mixture was heated and crystallized under static conditions at 240 °C in a Teflon-lined autoclave for 6–12 h. The synthesized mixture was then allowed to cool down to room temperature. Fe_3O_4 nanocrystals were washed with the mixture of ethanol and chloroform for three to four times. The precipitate was collected by centrifuging at 4750 rpm for 20 min and

suspended in 5 mL of hexane (The concentration of the magnetic nanocrystals is 30 mg mL^{-1}).

3.2.3 Synthesis of magnetic Fe_3O_4 and mesoporous silica core-shell nanospheres with tunable size

In a typical experiment, 2.0 mL of Fe_3O_4 nanocrystals dispersed in chloroform (30 mg mL^{-1}) was added to 20 mL of aqueous solution containing 0.16 g of C_{16}TAB. After vigorous stirring of the resultant solution, a homogeneous oil-in-water microemulsion was obtained. The solution was then heated at 65 °C for 30 min to induce the evaporation of chloroform and lead to the formation of aqueous phase dispersed nanocrystals.

The synthesis of magnetic Fe_3O_4 and mesoporous silica core-shell nanospheres with tunable size was achieved by the ammonia-catalyzed hydrolysis and condensation of TEOS in mixed ethanol–water solvents by using CTAB as a surfactant. Typically, 20 mL of the as-synthesized aqueous phase monodisperse Fe_3O_4 nanocrystals was added into the 61 mL mixture of water and ethanol and stirred at room temperature, and 0.16 g of CTAB was mixed. Then 1.0 mL of TEOS and 1.0 mL of ammonia solution (25 wt% NH_3 in water) were added under a stirring speed of 700 rpm at 25 °C. After 3 h stirring, the light brown product was collected by centrifugation, washed with water, and dried at room temperature. Finally, the surfactant was extracted by refluxing 1.0 g of as-synthesized material in 200 mL of ethanol for 24 h. This procedure was repeated twice. Six mixtures of water and ethanol with different ethanol-to-water volume ratios (V) (26 mL ethanol/35 mL water, V=0.74; 28 mL ethanol/33 mL water, V=0.85; 30 mL ethanol/31 mL water, V=0.97; 32 mL ethanol/29 mL water, V=1.10; 34 mL ethanol/27 mL water, V=1.26; and 36 mL ethanol/25 mL water, V=1.44) were used in this study. The samples synthesized using different ethanol/water ratio were denoted as Fe_3O_4@*meso*-SiO_2-*n*, (*n* = 110, 200, 420, 600, 650, 800), *n* is the particle size of the sphere as listed in Table 3.1.

3.2.4 Surface modification of magnetic Fe_3O_4 and mesoporous silica core-shell nanospheres

Typically, 0.6 g of core-shell nanospheres were suspended in toluene (50 mL) with 0.6 mL of 3-aminopropyltriethoxy silane (APTES; Aldrich), refluxed at 110 °C for 24 h,

the solid products were collected via the centrifuge and washed 5 times with acetone to remove toluene. The sample was then dried in oven at 50 °C and denoted as Fe_3O_4@*meso*-SiO_2-NH_2.

3.2.5 Cell uptake assay

The assays were carried out in 6-well cell culture plates. HeLa cells were seeded in plates at 2×10^5 cells per well the day before the assay. The particles (Fe_3O_4@*meso*-SiO_2-NH_2-*200*) were diluted in phosphate buffered saline (PBS) at a concentration of 1 mg/mL, and 100 μL of the resulting mixture was used for each well. A 21-nucleotide long (oligo) DNA conjugated with cyanine dye (Cy-3) was used as a template for short interfering RNA (siRNA) and was diluted in the 100 μL of particle solution to give final oligo DNA concentrations of 50 nM and 100 nM. The solution was mixed well and incubated at room temperature for overnight at 4 °C. After incubation, the particles were washed once with PBS, then centrifuged 3 min at 3000 rpm on a desktop microcentrifuge followed by two washes with Dulbecco's Modified Eagle's Medium (DMEM) supplemented with 10% heat-inactivated fetal calf serum, 100 units/mL penicillin G, 100 ug/mL streptomycin sulfate, and 0.29 mg/mL of L-glutamine (Gibco-Invitrogen), the complete DMEM. The nanoparticles were resuspended in 100 μL of complete DMEM and added to each well of 6-well plates containing 1 mL of complete DMEM. After 4 h of incubation at 37 °C, the cells were washed 2 times with PBS and fixed with 4% paraformaldehyde in PBS (4 °C for 30 min). The cells were washed again with PBS and the liquid was drained. A 200 μL portion of antifade fluorescent mounting medium with DAPI was added in for staining the nuclei, and the cells were viewed under the fluorescent microscopy.

3.2.6 Characterization

XRD measurements were performed on a Rigaku D/max-2550V diffractometer using Co Kα radiation at 30 kV and 15 mA. SEM images of samples coated with platinum were recorded on a JEOL 6400 microscope. TEM images were obtained by JEOL JEM2100 electron microscope. The powder samples for TEM measurements were suspended in ethanol and then dropped onto the Cu grids with carbon films. Nitrogen sorption isotherms of samples were obtained by a Quantachrome’s Quadrasorb SI analyzer at -196 °C. Prior to the measurement, the samples were out-gassed at 120 °C

for at least 6 h. The Brunauer-Emmett-Teller (BET) specific surface areas were calculated using adsorption data at a relative pressure range of P/P_0 = 0.05~0.25. Pore size distributions were derived from the adsorption branch using Barrett-Joyner-Halenda (BJH) method. The total pore volumes were estimated from the amounts adsorbed at a relative pressure (P/P_0) of 0.99. Magnetization measurements were carried out using a Magnetometer under magnetic fields up to 10000 Oe and at 300 K.

Table 3.1 Physicochemical properties of magnetic mesoporous silicas nanospheres/Fe_3O_4@meso-SiO_2 prepared under various synthesis parameters

Sample	Water (mL)	Ethanol (mL)	TEOS (mL)	$NH_3 H_2O$ (mL)	Average Particle size (nm)	BET surface area ($m^2 g^{-1}$)	Pore diameter (nm)	Void pore diameter (nm)	Total pore volume ($cm^3 g^{-1}$)
Fe_3O_4@*meso*-SiO_2-*110*	35	26	1.0	1.0	110	365	2.1	-	0.30
Fe_3O_4@*meso*-SiO_2-*200*	33	28	1.0	1.0	200	304	2.1	-	0.23
Fe_3O_4@*meso*-SiO_2-*420*	31	30	1.0	1.0	420	412	2.1	8.0	0.32
Fe_3O_4@*meso*-SiO_2-*600*	29	32	1.0	1.0	600	567	2.1	8.0	0.40
Fe_3O_4@*meso*-SiO_2-*650*	27	34	1.0	1.0	650	366	2.5	20.0	0.45
Fe_3O_4@*meso*-SiO_2-*800*	25	36	1.0	1.0	800	527	2.1	20.0	0.49

3.3 Results and discussions

The procedure for the synthesis of Fe_3O_4@*meso*-SiO_2-*n* with tunable particle size is shown in Figure 3.1. In brief, Fe_3O_4 nanoparticles in chloroform were firstly transferred to the aqueous solution using CTAB as the transferring agent. Secondly, CTAB-modified Fe_3O_4 nanoparticles were dispersed into water and ethanol mixture solution by adding ammonia solution. Subsequently, mesoporous silica shell was formed *via* an extension of Stöber method by adding TEOS in the system through the hydrolysis and condensation of TEOS around CTAB-modified Fe_3O_4 nanoparticles. Finally, the magnetic silica nanocomposites with large tunable particle sizes were obtained after removal of CTAB in a mild way by ethanol extraction.

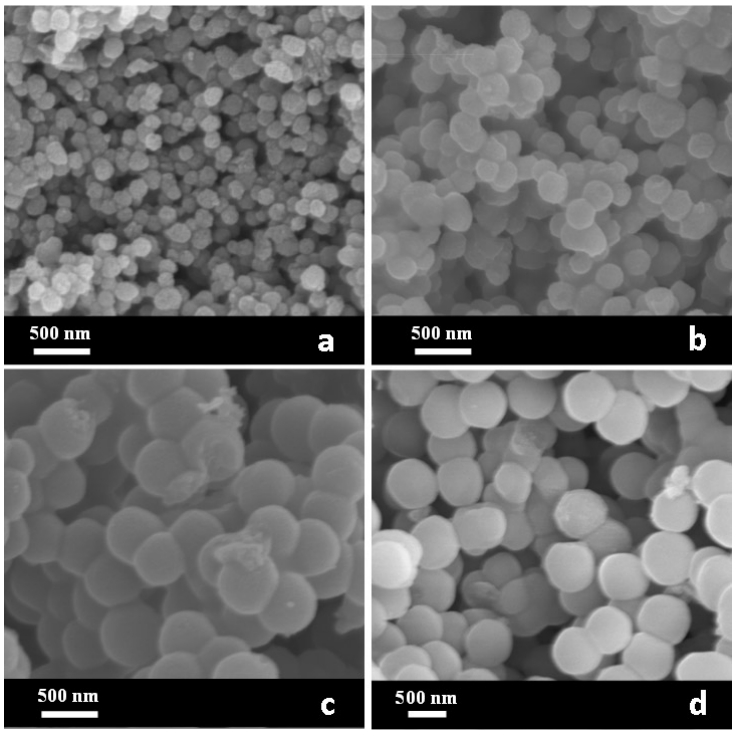

Figure 3.2 SEM images of Fe_3O_4@*meso*-SiO_2-*n* with different particle sizes: a/Fe_3O_4@*meso*-SiO_2-*110*; b/ Fe_3O_4@*meso*-SiO_2-*200*; c/ Fe_3O_4@*meso*-SiO_2-*420*; d/ Fe_3O_4@*meso*-SiO_2-*600*.

Figure 3.2 shows SEM images of the Fe_3O_4@*meso*-SiO_2 composites obtained after the removal of CTAB templates. The products have uniform spherical morphology and the diameters of the spheres increase with increasing ethanol-to-water ratio. The average sizes of Fe_3O_4@*meso*-SiO_2-*110*, Fe_3O_4@*meso*-SiO_2-*200*, Fe_3O_4@*meso*-SiO_2-*420*, and Fe_3O_4@*meso*-SiO_2-*600* vary in a range of ca. 110–600 nm as observed from SEM images. TEM images (Fig. 3.3) further confirm the spherical shape and uniform particle size. A typical core–shell structure with Fe_3O_4 nanoparticles as core and ordered mesoporous silica as a shell can be clearly observed. The mesoporous structure is uniform and accessible with unobstructed pore entrance on the rough silica surface. The physicochemical properties of the Fe_3O_4@*meso*-SiO_2 particles prepared under various synthesis parameters are summarized in Table 1. It can be seen that the sphere diameter increases significantly with the amount of ethanol. The samples synthesized with a low ethanol-to-water volume ratio (V=0.74~0.85) have ordered hexagonal mesoporous structures (Figs. 3.3a-d). The formation of large void pore on shell starts at V=0.97, which attributes to the transformation from oil droplets to microemulsion. At higher ethanol concentration, high charge density and large head groups of CTAB

is tend to form microemulsion, the large void pores are formed by the connecting of the small mesopore in the microemulsion. The Fe_3O_4*@meso*-SiO_2-*420* and Fe_3O_4*@meso*-SiO_2-*600* shown in Figs. 3.3e-h have a radially oriented 8 nm void pores around the hexagonal mesoporous structures. The nanocomposites synthesized with a large amount of ethanol (Figs. 3.3i–l) exhibit irregular particle size, randomly arranged small mesopores, and ellipsoidal shaped larger void pore around 20 nm.

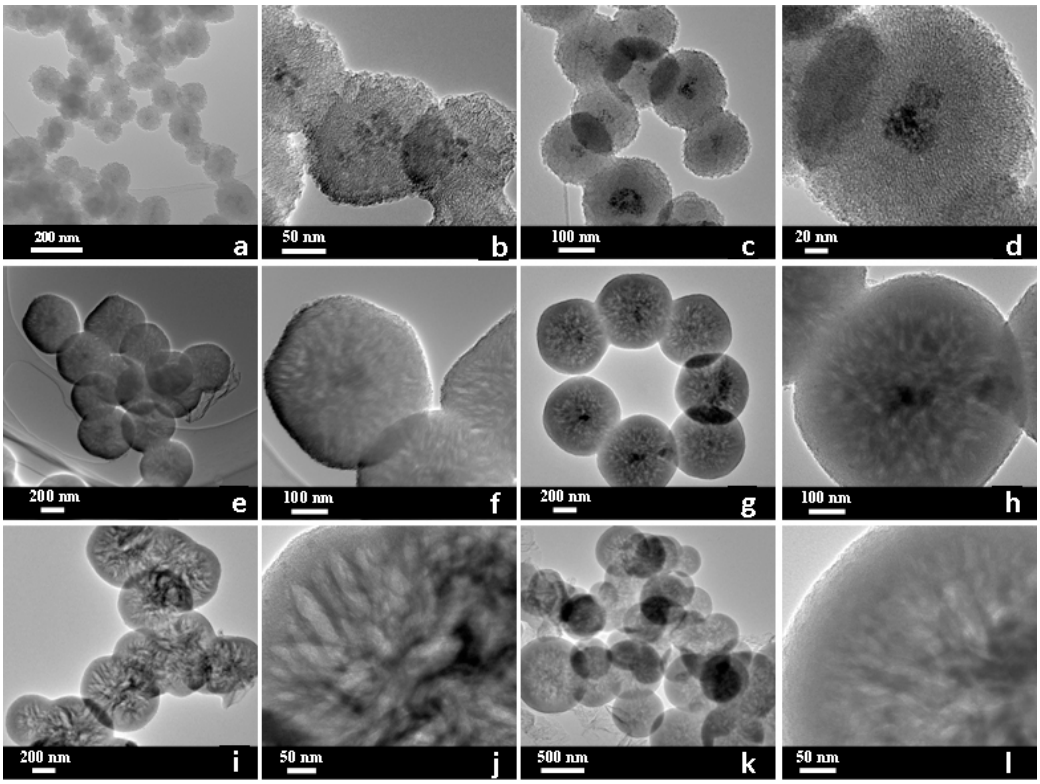

Figure 3.3 TEM images of Fe_3O_4*@meso*-SiO_2-*n* with different particle sizes: a, b/ Fe_3O_4*@meso*-SiO_2-*110*; c, d/ Fe_3O_4*@meso*-SiO_2-*200*; e, f/ Fe_3O_4*@meso*-SiO_2-*420*; g, h/ Fe_3O_4*@meso*-SiO_2-*600*; i, j/ Fe_3O_4*@meso*-SiO_2-*650*; g, h/ Fe_3O_4*@meso*-SiO_2-*800*.

According to the above results, we propose a possible mechanism for the formation of Fe_3O_4*@meso*-SiO_2 nanocomposites through a simple one-pot approach. After addition of TEOS, the electrostatic interactions between silicate oligomers hydrolyzed from TEOS molecules and CTAB-stabilized Fe_3O_4 nanocrystals quickly lead to formation of the core–shell Fe_3O_4 mesoporous silica nanospheres by the assembly of silica-surfactant micelles and CTAB-stabilized Fe_3O_4 nanocrystals.[6,9,15] As illustrated in Scheme 1, the effect of ethanol on the monodispersity and size variety of Fe_3O_4*@meso*-SiO_2-*n* can be explained. The presence of ethanol slows down the

hydrolysis reaction of TEOS and the condensation of silicate-surfactant aggregates on the Fe_3O_4 nanoparticles. At a low ethanol-to-water volume ratio, the particle aggregation process is fast and nanocomposites with small particle sizes were formed (Figs. 3.3a– d). With higher ethanol concentration, the slow hydrolysis rate of TEOS and condensation of silica-surfactant aggregates cause the monodispersity of mesoporous spheres with large particle sizes (Fig. 3.3e–h). The microemulsion is formed from the unhydrolyzed TEOS to generate large void pores. Too much ethanol could cause very slow silicate hydrolysis and condensation, which would decrease dispersity, increase the particle size of nanocomposites and induce the connection of spheres to each other, as shown in Fig. 3.3k. With increasing ethanol-to-water volume ratio, the enlargement of particle size was accompanied with the formation of large void pore.

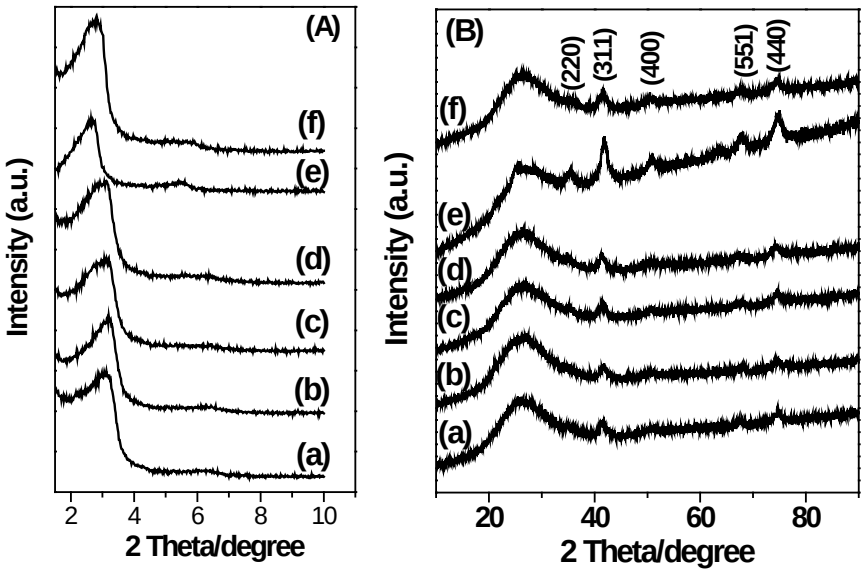

Figure 3.4 (A) Small angle and (B) wide-angle XRD patterns of Fe_3O_4@*meso*-SiO_2-*n* with different particle sizes: (a) Fe_3O_4@*meso*-SiO_2-*110*; (b) Fe_3O_4@*meso*-SiO_2-*200*; (c) Fe_3O_4@*meso*-SiO_2-*420*; (d) Fe_3O_4@*meso*-SiO_2-*600*; (e) Fe_3O_4@*meso*-SiO_2-*650*; (f) Fe_3O_4@*meso*-SiO_2-*800*.

The low-angle XRD patterns (Fig. 3.4A) of the resulted nanocomposites show one or two diffraction peaks, which can be assigned to the 100 and 110 reflections of a relatively uniform 2D-hexagonal (*P6mm*) mesostructure, confirming an ordered mesostructure of silica shells. Wide-angle XRD patterns of silica magnetic

nanocomposites present five resolved diffraction peaks (Fig. 3.4B), which can be indexed to 220, 311, 400, 511 and 440 and attributed to Fe_3O_4 with space group *Fd3m* according to the JCPDS Card Number 19-629 (JCPDS = Joint Committee on Powder Diffraction Standards), consistent with the presence of magnetite Fe_3O_4 core encapsulated in the nanocomposite. Fe_3O_4*@meso*-SiO_2-*650* has stronger intensities for all diffraction peaks, suggesting that more Fe_3O_4 nanocrystals are embedded in Fe_3O_4*@meso*-SiO_2-*650*. Additionally, the broad peak at around $2\theta = 21^o$ indicates the presence of amorphous silica in Fe_3O_4*@meso*-SiO_2-*n*. The characteristic diffraction peaks of Fe_3O_4 in XRD patterns (Fig. 3.4) together with TEM images (Fig. 3.3) confirm the existence of magnetic nanocrystals in mesoporous silica nanospheres.

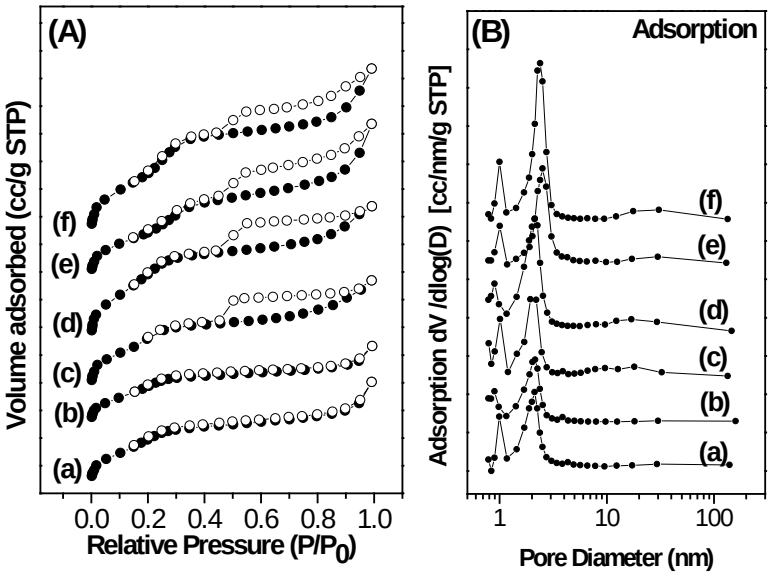

Figure 3.5 A/ Nitrogen-sorption isotherms, and B/ BJH pore-size distribution of Fe_3O_4*@meso*-SiO_2-*n* with different particle sizes: a/ Fe_3O_4*@meso*-SiO_2-*110*; b/ Fe_3O_4*@meso*-SiO_2-*200*; c/ Fe_3O_4*@meso*-SiO_2-*420*; d/ Fe_3O_4*@meso*-SiO_2-*600*; e/ Fe_3O_4*@meso*-SiO_2-*650*; f/ Fe_3O_4*@meso*-SiO_2-*800*.

The mesoporous feature of nanocomposites has been confirmed by nitrogen sorption measurement. The nitrogen sorption isotherms of core–shell Fe_3O_4*@meso*-SiO_2-*n* (Fig. 3.5A) show type IV isotherms with a capillary condensation step at low relative pressure ($P/P_0 = 0.2–0.4$), suggesting uniform cylindrical mesopores. The pore size distribution (Fig. 3.5B) exhibits a sharp peak centred at the mean value of ~2.1 nm, indicating a uniform mesopore. In addition to the capillary condensation step at

P/P_0 = 0.2–0.4, Fe_3O_4@*meso*-SiO_2-*n* where *n* = 420, 600, 650, 800, possesses a type-H4 hysteresis loop at P/P_0 values between 0.5 and 0.9. The existence of such a type-H4 loop might indicate that some void defects are formed in the core-shell nanocomposites. The surface area and the total pore volume are calculated to be as large as 567 m^2 g^{-1} and 0.49 cm^3 g^{-1}, respectively. The surface area and pore volume of the resultant Fe_3O_4@*meso*-SiO_2-*n* are changed irregularly by tunning the ethanol/water ratio. Thus, the relatively high specific surface area, large pore volume, and ease of functionalization make them attractive as delivery vehicles.

To investigate the magnetization properties of nanocomposites, the samples were studied by a magnetometer. Fig. 3.6 shows the field-dependent magnetisation curves of three typical nanocomposites, Fe_3O_4@*meso*-SiO_2-*200*, Fe_3O_4@*meso*-SiO_2-*420* and Fe_3O_4@*meso*-SiO_2-*650* measured from -20 000 to 20 000 Oe at 300 K. The saturation magnetization value is measured to be 2.6, 2.5 and 5.0 emu g^{-1}, respectively. The relatively low magnetization value is due to the presence of mesoporous silica shell and low concentration of magnetic particle, however, the particles show fast response toward external magnetic field. The magnetization value could be varied by tuning the magnetic particle concentrations. These characteristics are very beneficial to bioseparation, biocatalysis and drug/gene delivery applications.

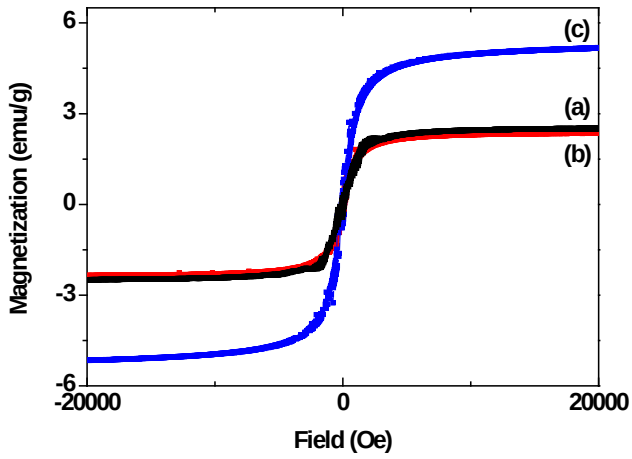

Figure 3.6 Field-dependent magnetization at 300 K of Fe_3O_4@*meso*-SiO_2-*n* with different particle sizes: a/ Fe_3O_4@*meso*-SiO_2-*420*; b/ Fe_3O_4@*meso*-SiO_2-*600*; c/ Fe_3O_4@*meso*-SiO_2-*650*.

Efficient cellular internalisation of nanoparticles is necessary for intracellular drug delivery and efficient therapy.[15,19-24] To further demonstrate the possible

application of Fe_3O_4@*meso*-SiO_2-*n* in nanomedicine, the outside surface of mesoporous silica shell of Fe_3O_4@*meso*-SiO_2 are modified by APTES (denoted as Fe_3O_4@*meso*-SiO_2-NH_2-*200*) to induce cationic charges which can promote the uptake of particles by negative charged cells. Fe_3O_4@*meso*-SiO_2-NH_2-*200* was then functionalized 21-nucleotide long (oligo) DNA (a model for siRNA) by adsorption. To adequately track adsorption and cell internalization process, oligo-DNA was labeled with cyanine dye (Cy3). Fig. 3.7 illustrates the cell uptake study of Fe_3O_4@*meso*-SiO_2-NH_2-*200*. It is observed that there is no Cy3 signal from the control experiment. The confocal microscopy image of Fe_3O_4@*meso*-SiO_2-NH_2-*200* shows that most red signals (Cy3) are within the cells, suggesting that a large amount of the Fe_3O_4@*meso*-SiO_2-NH_2-*200* particles were taken up by HeLa cells. The cell uptake results suggest the possibility and efficiency of magnetic mesoporous silica nanospheres to deliver drugs into cells for therapy, in addition, they can potentially serve as contrast agents in MRI because of their magnetic properties.[15,22-24]

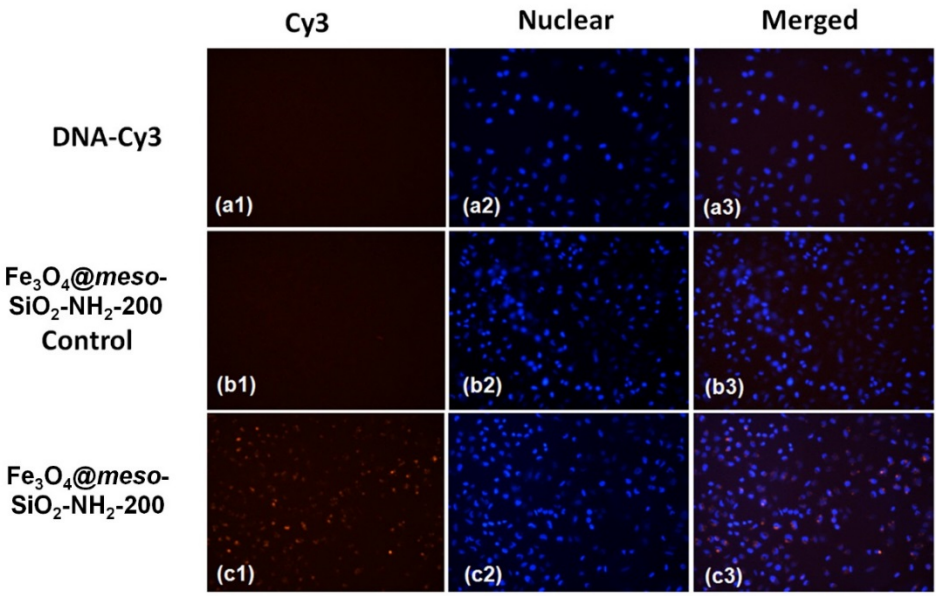

Figure 3.7 Confocal microscopic images of intracellular localization in HeLa cells: the cell up-take efficiency of Fe_3O_4@*meso*-SiO_2-NH_2-*200* was examined by labelling the particles with a 21-nt oligo DNA conjugated with Cy-3; the oligo DNA-Cy3 (DNA-Cy3) or Fe_3O_4@*meso*-SiO_2-NH_2-*200* alone is negative for Cy3 signal. Fe_3O_4@*meso*-SiO_2-NH_2-*200* with oligo DNA-Cy3 shows very strong orange fluorescence signal.

3.4 Conclusions

In summary, we have successfully designed and synthesized magnetic mesoporous silica core-shell nanospheres with large void pores and tunable particle sizes for gene therapy. The particle size can be tuned from 110 nm to 800 nm by tailoring the ethanol to water volume ratio, while the large void pore on shell can be regulated from 8.0 to 20 nm by increasing ethanol amount. Moreover, the NH_2-functionalized magnetic mesoporous silica nanospheres could be efficiently internalized into HeLa cell lines, which is potentially important for *si*RNA efficacy against cancer cells. The results would provide an application paradigm of magnetic mesoporous silica nanoparticles for cell labelling and drug delivery.

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Chapter 4. Inorganic-salts assisted self-assembly of Pluronic F127-organosilica into ordered mesostructures

Abstract

Periodic mesoporous organosilicas (PMOs) have been synthesized through the condensation of organosilicates 1,2-bis(trimethoxysilyl) ethane around inorganic-electrolyte-stabilized Pluronic F127 [$(EO)_{106}(PO)_{70}(EO)_{106}$] triblock copolymer micelles in a sodium bicarbonate ($NaHCO_3$)/sodium carbonate (Na_2CO_3) buffer solution (pH≈9.9). It is found that the addition of inorganic sulfate salts in the synthesis is crucial factor to ensure the formation of ordered mesostructures. The addition of Na_2SO_4 and $MgSO_4$ in the synthesis system can lead to the formation of ordered 2-D hexagonal (P6mm) and 3-D cubic (Im3m) mesostructure, respectively. The effects of other inorganic sulfate salts such as $CuSO_4$, $NiSO_4$, and $ZnSO_4$ have also been investigated. Apparently, the interaction between Pluronic F127 micelle and organosilica oligomers is enhanced by the presence of these inorganic salts. The mechanism for PMOs formation has been proposed on the basis of inorganic salts assisted micelles-organosilicates closed packing under mild synthetic condition. The findings from this work contribute understanding fundamental understanding towards a new formation route of these ordered mesoporous materials, thus providing a new strategy to fabricate mesoporous silicas with controllable structures for emerging applications.

4.1 Introduction

Since its first synthesis in 1990, mesoporous materials have attracted increasing research attention in materials science.[1-10] Periodic mesoporous organosilicas (PMOs) are one of the newly emerging organic−inorganic hybrid materials, which are composed of silica frameworks and organic bridging groups.[11-16] Since the

pioneering works reported in 1999 by three independent groups,[17-19] much research effort has been directed toward the design and synthesis of PMOs with different mesostructures, tailored pore sizes, controlled morphologies and functionalities to suit different applications.[11, 14, 16] With a series of extraordinary features, such as large surface area, uniform dispersion of the organic groups in frameworks, tailored properties by changing the bridging organic group, PMOs are becoming one of the important functional nanomaterials for a wide spectrum of potential applications in catalysis, optics, biomedicine, adsorption and separation.[11-16]

Similar to their mesoporous silicas (MPSs) counterparts,[20-25] significant progress has been made in understanding the formation mechanisms of PMOs and optimizing the synthesis strategy.[26-30] To date, various PMOs with different organic bridges have been successfully synthesized by involving different surfactants (i.e., cationic, anionic or non-ionic) such as Pluronic triblock copolymer (PTC).[11, 16] To explore the formation mechanism, cooperative self-assembly, colloidal phase-separation, and hard sphere packing routes have been proposed for PTC templating synthesis of mesoporous materials via diverse synthesis pathways such as S^0I^0, $S^0H^+X^-I^+$.[11, 22, 31] However, the formation process is difficult to be controlled due to the fast hydrolysis and condensation rate of silane precursors under strongly acidic conditions when involving PTC as a soft template. To overcome this shortcoming, other synthesis protocols have been developed by using buffered solutions (e.g. HAc/NaAc, NaH_2PO_4/Na_2HPO_4, citric acid/citrate) to purposely slow down the formation process so the formation mechanism could be easily tracked for fundamental understanding.[26, 28, 32-34] In most of these cases, the pH value of the buffer solution is controlled in the range of 3 to 5 after the addition of inorganic salts. Recently, Martens and coworkers have reported the packing formation mechanism by mastering the formation process of ordered cubic mesoporous silica material (COK-19) synthesized by using sodium silicate as silane precursor in a citric acid/citrate buffered micellar solution (pH≈3.0) of Pluronic F127 $[(EO)_{106}(PO)_{70}(EO)_{106}]$ triblock copolymer.[26]

Single PTC micelle templating is one of the most commonly used method to synthesize silica hollow nanospheres through silica cross-linking followed by PTC removal.[28, 31, 35, 36] For example, Liu et al. first demonstrated the synthesis of ethylene-bridged organosilicas hollow nanospheres through the cross-linking of 1,2-bis(trimethoxysilyl)ethane (BTME) onto F127 micelle under a mild buffer condition

(NaH_2PO_4-Na_2HPO_4, pH≈7.0).[28] Later, it has been confirmed that different organosilicas (*e.g.* methylene, $-CH_2-$, ethylene, $-CH_2-CH_2-$, ethenylene, $-CH=CH-$, phenylene, $-C_6H_4-$ bridged) hollow nanospheres can be obtained by using F127 micelle template under acidic condition in the presence of TMB.[29, 35] Furthermore, a transition from hollow nanospheres to ordered mesostructures can be achieved by varying the synthesis parameters such as category of silane, PTC or silane precursor concentration, reaction temperature, and addition of inorganic salts.[20, 21, 26-31, 35-38] For instance, sphere packing formation mechanism has been proposed based on these results.[25, 31, 35, 37] However, the effect of the presence of inorganic salts on the hollow nanospheres or the ordered mesostructures formation has not been systematically investigated and the role of cationic inorganic salts is still unclear. Moreover, all the buffer solution systems currently employed are in weak acidic condition, in particular, after the addition of inorganic salts, under which, the hydrolysis and condensation rates of silane are still too quick to be easily tracked to clarify the influencing factors of the process. It is still remains a challenge to develop a buffer synthetic strategy with a solution pH value close to neutral after the addition of inorganic salts.

Herein, we have adopted a single micelle templating synthesis strategy that was developed previously[35] to investigate the effects of inorganic salts on the formation of PMOs with different morphology and mesostructures. To our knowledge, this is the first time that the synthesis of ordered PMOs by using PTC template under a weak basic condition (sodium bicarbonate ($NaHCO_3$)/sodium carbonate (Na_2CO_3) buffer solution pH≈9.9) with the assistance of the inorganic salts has been reported. The effect of cationic sulfate on the physicochemical properties of PMOs is studied and accordingly, a new formation mechanism based on inorganic salts assisted micelles-organosilicates closed packing is proposed under moderate synthetic condition.

4.2 Experimental sections

4.2.1 Chemicals and reagents

Triblock poly(ethylene oxide)-b-poly(propylene oxide)-b-poly(ethylene oxide) copolymer $EO_{106}PO_{70}EO_{106}$ (Pluronic F127, M_w = 12600) and 1,2-bis(trimethoxysilyl)ethane (BTME, 96%) were purchased from Sigma-Aldrich

Company Ltd. All materials were in analytical grade and used without any further purification.

4.2.2 Synthetic procedure

In a typical synthesis, 1.0 g of F127, 1.0 g of 1,3,5-trimethylbenzene (TMB) and 40 mmol of different inorganic sulfate salts (Na_2SO_4, $MgSO_4$, $ZnSO_4$, $NiSO_4$, $CuSO_4$) were dissolved in 60 mL of $NaHCO_3$/Na_2CO_3 buffer solution (pH≈9.9, 0.050 mol/L $NaHCO_3$, 0.050 mol/L Na_2CO_3) at 40 °C under vigorous stirring. When the copolymer was fully dissolved, 2.70 g (10 mmol) BTME was added under stirring. The resultant mixture was stirred at the same temperature, which was taken as the reaction temperature for 24 h and aged at 100 °C under static conditions for an additional 24 h. The solid product was recovered by filtration and air-dried at room temperature overnight. Finally, the surfactant was extracted by refluxing 1.0 g of as-synthesized material in 200 mL of ethanol containing 1.5 g of concentrated aqueous HCl solution for 24 h. The surfactant-free sample was denoted as mesoporous organosilicas (MO-*n*) synthesized with addition of different inorganic salts as listed in Table 4.1.

Table 4.1 The synthetic conditions and physicochemical properties of mesoporous organosilicas MO-*n*, synthesized with addition of different inorganic salts

Sample	Inorganic salts	pH value	d spacing [nm]	BET surface area [m^2 g^{-1}]	Pore diameter [nm]	Total pore volume [cm^3 g^{-1}]	Mesostructures
MO-1	N/A	9.9	N/A	611	11.0	2.60	Hollow spheres
MO-2	Na_2SO_4	9.9	24.5	663	11.0	1.02	*P6m* hexagonal
MO-3	$MgSO_4$	9.9	16.3	1070	9.8	1.09	*Im3m* cubic
MO-4	$CuSO_4$	4.2	15.8	794	12.5	0.78	*Fm3m* cubic
MO-5	$NiSO_4$	6.2	17.7	1051	9.7	0.80	*Im3m* cubic
MO-6	$ZnSO_4$	6.5	14.8	1060	9.8	0.91	*Im3m* cubic

4.2.3 Characterizations

X-ray diffraction (XRD) patterns were recorded on a Rigaku RINT D/Max-2500 powder diffraction system using Cu Kα radiation of 0.15406 nm wavelength at 40kvX10mA. The nitrogen sorption experiments were performed at -196 °C using a Micromeritics ASAP 2020 system. Prior to the measurement, the samples were

degassed at 120 °C for at least 6 h. The Brunauer-Emmett-Teller (BET) specific surface areas were calculated using adsorption data in a relative pressure range of P/P_0 = 0.05~0.25. Pore size distribution was derived from the adsorption branch using the Barrett-Joyner-Halenda (BJH) method. The total pore volumes were estimated from the amounts adsorbed at a relative pressure (P/P_0) of 0.99. Transmission electron microscopy (TEM) was performed using a FEI Tecnai G^2 Spirit at an acceleration voltage of 120 kV. Scanning electron microscopy (SEM) was undertaken on a JEOL JSM-6360 scanning electron microscope operating at an accelerating voltage of 20-30 kV. The samples were deposited on a sample holder with an adhesive carbon foil and sputtered with gold prior to imaging.

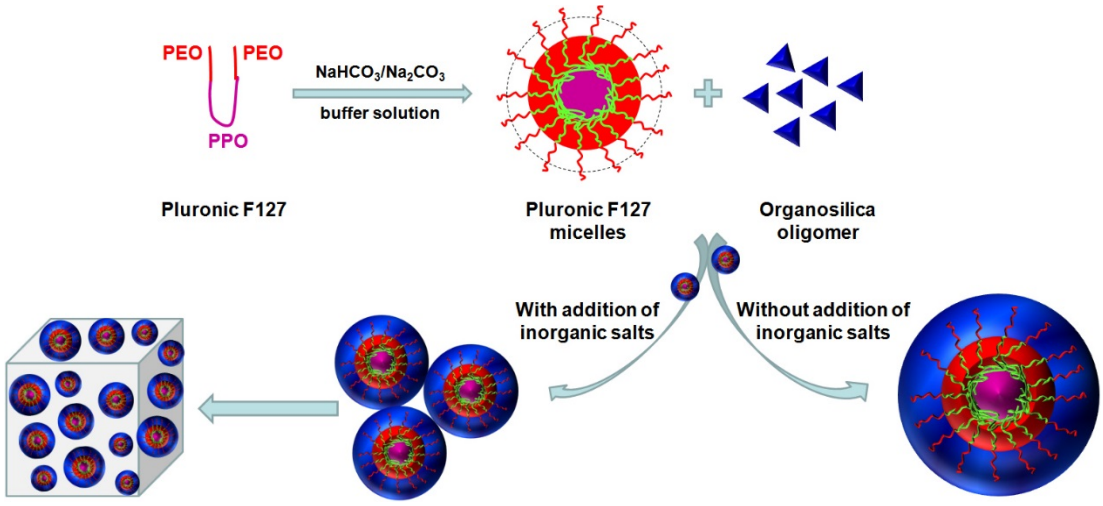

Figure 4.1 Schematic illustration of the formation of mesoporous organosilicas with different structures.

4.3 Results and discussions

4.3.1 Mesoporous organosilicas hollow spheres

The mesoporous organosilicas (MO-*n*) were synthesized under relatively mild conditions (sodium bicarbonate ($NaHCO_3$)/sodium carbonate (Na_2CO_3) buffer solution pH ≈ 9.9) with co-assembly of triblock copolymer F127 [$(EO)_{106}(PO)_{70}(EO)_{106}$] micelles with inorganic sulfate salts and organosilane [1,2-Bis(trimethoxysilyl)ethane (BTME)] condensation as shown in Figure 4.1. As shown in Figure 4.2a, MO-1 synthesized in absence of any sulfates displays irregular and aggregated hollow spheres. The size of the single hollow sphere is around 30 nm. The

non-uniform nanostructure formation might be related to the weak interaction between F127 micelles and organosilica oligomers under weak basic condition (pH≈9.9, 0.050 mol/L $NaHCO_3$, 0.050 mol/L Na_2CO_3) even with the assistance of sodium bicarbonate and sodium carbonate. The porous structure is further analyzed by the N_2 sorption measurement (Figures 4.2b and c). The isotherm curve of MO-1 shows two hysteresis loops at relative pressure from 0.65 to 0.80 and 0.80 to 0.98, respectively, which is the characteristic of hierarchical porous materials. The primary pore (11 nm) and secondary pore (31 nm) may be derived from the internal void of the hollow nanospheres and interparticle void, respectively (Figure 4.2c and Table 4.1). In order to enhance the interaction between F127 micelles and organosilica oligomers to obtain mesoporous organosilicas with ordered structures, the effects of different sulfates (Na_2SO_4, $MgSO_4$, $ZnSO_4$, $NiSO_4$, $CuSO_4$) on the co-assemble process was studied.

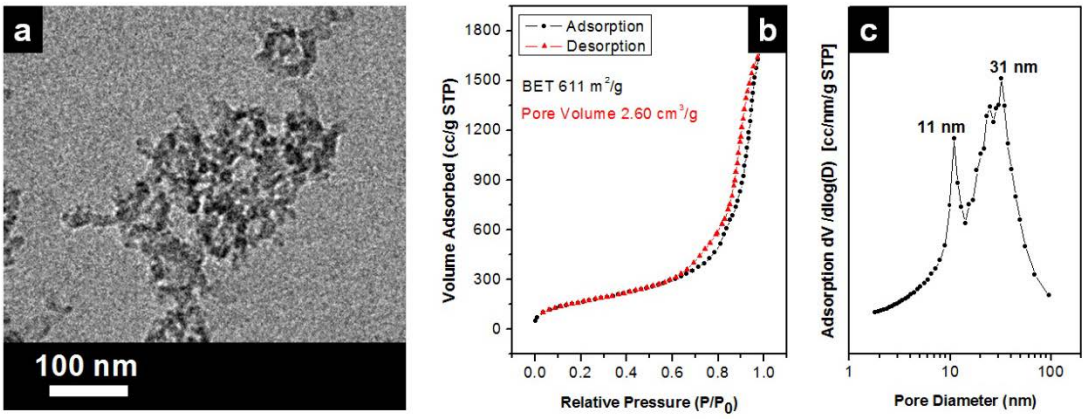

Figure 4.2 a), Representative TEM image; b), nitrogen adsorption-desorption isotherm curves, and c), pore size distributions of mesoporous organosilicas MO-1 synthesized without addition of inorganic salts.

4.3.2 Mesoporous organosilicas with ordered structures.

Small-angle X-ray diffraction (XRD) patterns of MO-2 synthesized in the presence of neutral Na_2SO_4 are shown in Figure 4.3a. One well resolved peak with lattice d spacing of 24.5 nm is recognized due to the (100) plane of the 2D hexagonal mesostructured (*P6mm*). Transmission electron microscopy (TEM) image of MO-2 shows the ordered hexagonal arrays of mesoporous channels (Fig. 4.3b) and that the size of mesopore is not very uniform. N_2 adsorption-desorption isotherm and the corresponding pore size distribution of MO-2 are shown in Figures 4.3c and 4.3d, respectively. Type IV

isotherm with a H1 type hysteresis loop at relative pressure between 0.60 and 0.95 is observed, which is a characteristic of mesoporous materials similar to SBA-15.[39, 40] The pore size distribution is broad with a maximum at 11 nm and further reveals non-uniform mesopores, which in good agreement with TEM images. The MO has a BET surface area of 663 m^2 g^{-1} and a pore volume of 1.02 cm^3 g^{-1} (Table 4.1). The above results demonstrate that ordered hexagonal PMOs (MOs-2) with average pore size of 11 nm have been obtained by the addition of neutral Na_2SO_4 as the auxiliary agents.

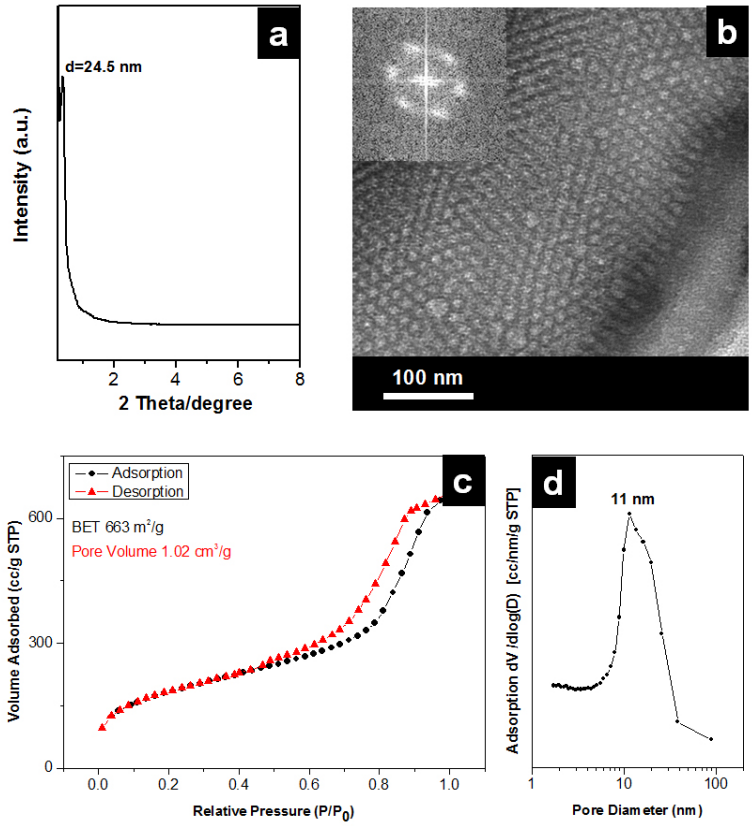

Figure 4.3 a), XRD pattern; b), representative TEM image, c), nitrogen adsorption-desorption isotherm curves, and d), pore size distributions of mesoporous organosilicas MO-2 synthesized with addition of 40 mmol Na_2SO_4.

Inorganic salt effect has been investigated for the formation of mesoporous silicas.[37, 41-44] It has been found that the addition of inorganic salts can alter the critical micelle concentration (CMC) of the surfactants, increase the ionic strength of the synthetic solutions, control the microporosity, morphology, hydrothermal stability of the resultant mesoporous silicas.[22, 45] However, only the effects of anions from

the Hofmeister's series have been noted by employing alkali metal salts as the auxiliary agents.[46, 47] In this study, we investigated the cationic effect of sulfates on the formation of mesoporous organosilicas. After the successful preparation of MO-2 with ordered hexagonal mesoporous structure by using Na_2SO_4 as the auxiliary agents, $MgSO_4$ has been selected as the additive for the preparation of MO-3.

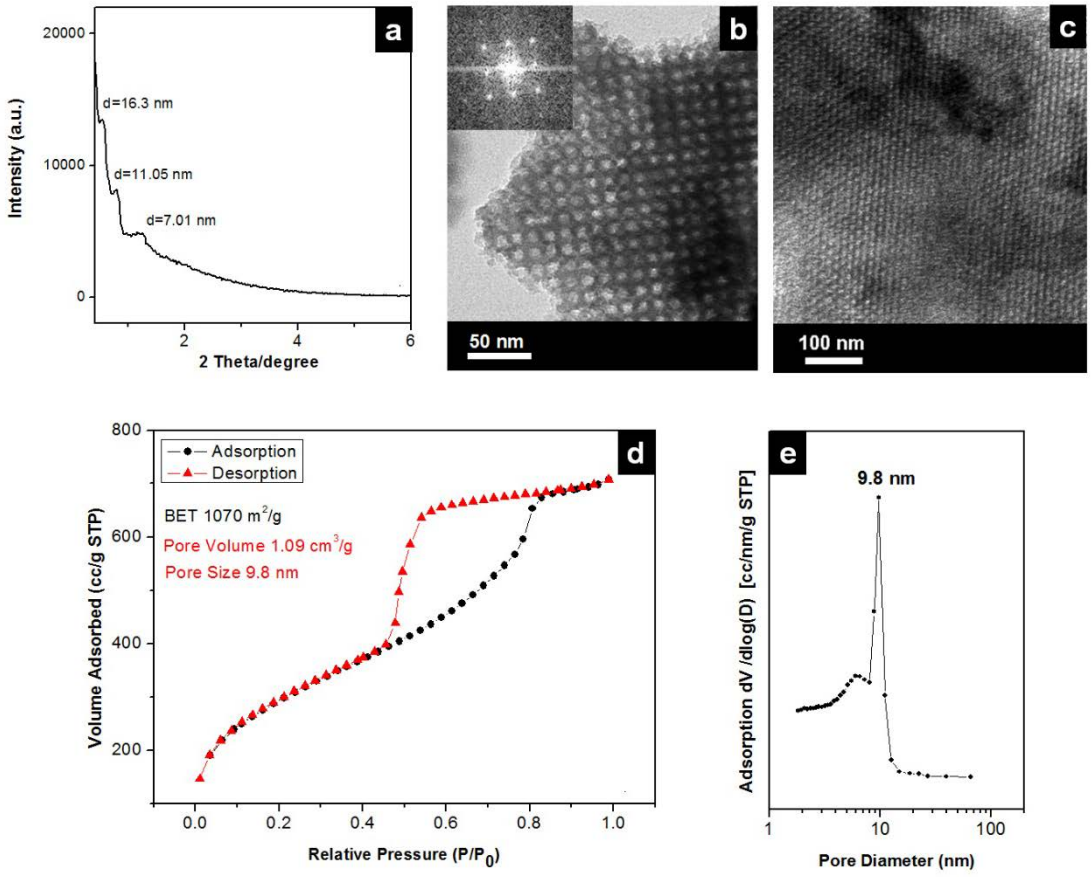

Figure 4.4 a), XRD pattern; b),c) representative TEM images; d), nitrogen adsorption-desorption isotherm curves, and e), pore size distributions of mesoporous organosilicas MO-3 synthesized with addition of 40 mmol $MgSO_4$.

Figure 4.4a shows XRD profile of MO-3, which reveal three clearly distinctive reflections in the range of 0.5–2°. These three low-angle reflections can be indexed properly to (110), (200) and (211) reflections of the SBA-16[40, 48] category of cubic structure (space group *Im3m*). TEM images further confirm that the MO-3 synthesized by using $MgSO_4$ as the auxiliary agent has cubic mesostructure. As shown in Figure 4.4b and 4.4c, the representative TEM images viewed along (110) and (111) directions reveal that MO-3 is consisted of ordered domains of body-centered cubic (*Im3m*)

structure (Table 1). As shown in Figure 4.4d, the nitrogen adsorption−desorption isotherms show a type IV isotherm with an H2-type hysteresis loop, indicating a cage-like pore shape. These results are in agreement with that previously reported SBA-16, [40, 48] suggesting MO-3 is ordered cubic mesostructured organosilicas. A narrow pore size distribution with a mean value of 9.8 nm is calculated from the adsorption branch (Figure 3e). The MO-3 has a very high BET surface area of 1070 m^2 g^{-1} and a pore volume of 1.09 cm^3 g^{-1} as listed in Table 1.

4.3.3 Mesoporous organosilicas synthesized by the addition of $ZnSO_4$, $NiSO_4$ and $CuSO_4$

Other sulfates such as $ZnSO_4$, $NiSO_4$ and $CuSO_4$ have also been used as auxiliary agents in current synthetic condition. It should be noted that the pH value of synthetic solution is changed from 9.9 to 6.5, 6.2 and 4.2 after the addition of $ZnSO_4$, $NiSO_4$, $CuSO_4$, respectively due to the transition metal ionic effect. As shown in Figure 4.5a, XRD patterns of the MO-4 and MO-5 show well-resolved pattern with (110), (200), and (211) reflections and characteristic XRD patterns of cubic mesostructured (*Im3m* plain group) with d_{110} spacing of 14.8 and 17.7 nm for MO-4 and MO-5, respectively. The PXRD pattern of MO-6 (Fig. 4.5a) shows two diffraction peaks with d-spacing ratios of $\sqrt{3}$: $\sqrt{11}$, which can be indexed as the (111) and (311) reflections of FDU-12 a face-centered cubic mesostructure (*Fm3m* plain group).[49, 50] Nitrogen adsorption isotherms of these samples are shown in Figure 4.5b. All the adsorption isotherms of MO-4, MO-5 and MO-6 showbroad adsorption–desorption hysteresis loops with capillary condensation steps centered at relative pressures of 0.75–0.85, and very steep capillary evaporation steps located at relative pressure around 0.49. These isotherms and hysteresis loops are similar to that previously reported mesoporous silicas (SBA-16, FDU-12) with cage-like mesopores by Zhao and coworkers.[40, 44, 49, 50] The average pore size of MO-4, MO-5 and MO-6 is 9.8, 9.7 and 12.5 nm, respectively (Table 1). All these organosilicas exhibit very high surface area in the range of 794 to 1060 m^2 g^{-1}, and large pore volume from 0.78 to 0.91 cm^3 g^{-1}. The systematic variation in XRD patterns and nitrogen adsorption isotherms suggest the occurrence of pore structure changes. Ordered mesoporous organosilicas (MO-3, MO-4, MO-5) with body-centered cubic *Im3m* structures has been obtained with the addition of inorganic salts such as $MgSO_4$, $ZnSO_4$ and $NiSO_4$, while MO-1 with

hexagonal structure and MO-6 with face-centered cubic *Fm3m* structure can be synthesized from the addition of Na_2SO_4 and $CuSO_4$, respectively.

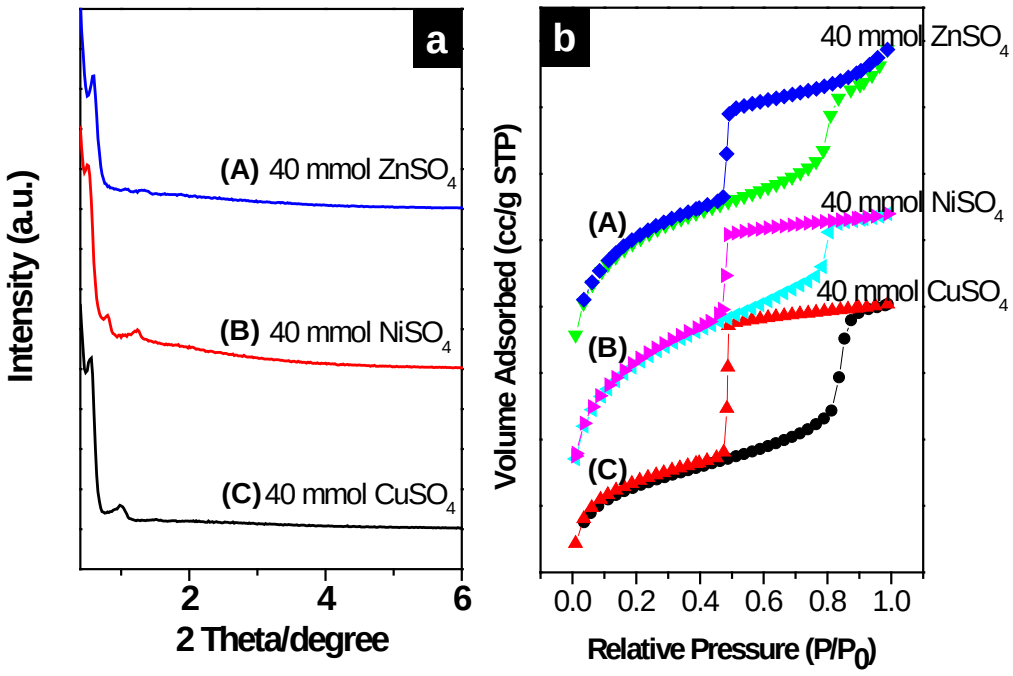

Figure 4.5 a), XRD patterns; b), nitrogen adsorption-desorption isotherm curves of mesoporous organosilicas MO-4, MO-5, MO-6 synthesized with addition of different inorganic salts: (A) 40 mmol $CuSO_4$, (B) 40 mmol $NiSO_4$, (C) 40 mmol $ZnSO_4$.

4.3.4 The effects of inorganic salts and the formation mechanism.

The above result suggests that the addition of inorganic sulfate can induce a transition from irregular aggregated hollow nanosphere to ordered mesostructure. It is interesting to note that the cationic of sulfate, appears to determine the structure of the final mesoporous organosilicas. As shown in Figure 4.1, F127 micelles with a hydrophobic PPO core and hydrophilic PEO shell can be formed in aqueous solution.[20, 26-29, 32, 35] It has been reported that the salting-out phenomenon can increase the hydrophobicity of the PPO block and reduce the hydrophilicity of the PEO block. Without addition of sulfates, aggregated hollow spheres were obtained from the crosslinking ethane silicas onto F127 micelles with the weak assembling interaction provided by the carbonate. The interaction between F127 micelles and ethane silicas can be significantly enhanced after the addition of sulfates due to the dehydration of

PEO shell, which will further facilitate the formation of ordered organosilica-F127 micelles mesostructures accompanied with organosilicas oligomers to penetrate into the PEO layer (Fig. 4.1). Lateral aggregation in a different mesophase results in the formed organosilicas with different mesostructures. According to Hofmeister series, the salting-out influence for anionic is following the sequence of $SO_4^{2-}>HPO_4^{2-}>F^->Cl^->Br^->NO_3^->I^->ClO_4^->SCN^-$,[47] therefore, sulfates have been selected in this study to investigate the cationic effect on the mesostructure formation. Cationic metal ions play an important role in the formation of different liquid crystal mesophase from micelles. Our results imply that mesophase transformation from hexagonal *P6mm* (by addition of Na^+), to body-center cubic *Im3m* (by addition of Mg^{2+}, Zn^{2+}, Ni^{2+}), and then to face-center cubic *Fm3m* (by addition of Cu^{2+}), occur with the addition of different sulfates. Thus, by changing the metal cationic, one can control the structure of liquid crystal mesophase, and further control the mesostructure of the resultant organosilicas.

4.4 Conclusions

In conclusion, PMOs with hexagonal, body-center cubic and face-center cubic mesostructures have been successfully synthesized in a $NaHCO_3/Na_2CO_3$ buffer solution with the assistance of inorganic sulfates. The influences of cationic metals of inorganic salts on the mesostructure of PMO materials have been systematically investigated. Sodium bicarbonate ($NaHCO_3$)/sodium carbonate (Na_2CO_3) buffer solution ($pH\approx9.9$) provide a mild synthetic medium to slow down the formation process. It has been found that ordered body-center cubic mesotructured PMOs can be obtained by the assistance of $MgSO_4$, $NiSO_4$ and $ZnSO_4$. The interaction between F127 micelles and organosilicas has been enhanced by the inorganic sulfates. The formation mechanism of mesoporous organosilicas has been explored and clarified on the basis of the micelles-organosilicates closed packing. Overcoming the problems encountered by the conventional method with fast hydrolysis and condensation process of organosilane, the present synthetic strategy can be more facilely applied to investigate, monitor, and understand the formation process of mesoporous materials.

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Chapter 5. Less is more, greener microbial synthesis of silver nanoparticles

Abstract

Microbial nano-synthesis has been well established as a green method for the sustainable development of nanotechnology. However, the mechanism of this biotechnology has to be reconsidered with the increasing realization that microorganism culture broth plays a vital role during the synthesis, which may obviate the dependence on microbes. Here, we demonstrate that silver nanoparticles (AgNPs) could be synthesized in several types of microorganism culture broth (an aqueous solution abundant in peptone, yeast extract from Saccharomyces cerevisiae, dextrose and other reducing and stabilizing agents) without any specific living microbe involvement. Light and high pH values of broth were identified as two critical factors in ensuring pure AgNPs formation. In broths containing NaCl at high concentration (0.5 w %), silver chloride was identified as the major intermediate and could be converted to AgNPs via one-pot photoreduction. Our broth alone strategy dramatically simplifies the conventional microbial nano-synthesis process by cutting the use of microorganisms and thus provides a more eco-friendly way for nano-Ag preparation. The fundamental understanding of the microbial synthesis mechanisms and implementing of complete green methods to fabricate technologically important nanomaterials will be further promoted by this study.

5.1 Introduction

Recently, silver nanoparticles (AgNPs) have been shown to find usage in a diverse range of research applications such as catalysis [1], nano-electronics [2], chemical sensor [3] and nanomedicine [4]. Additionally, the increasing demand for a wide range of consumer goods and apparel has promoted intense study on AgNPs synthesis. A multitude of methods have been established to synthesise AgNPs, including conventional chemical reduction [5], spray pyrolysis [6], physical vapour deposition [7] and irradiation route [8]. Since most processes described so far are associated with

high energy consumption or involvement of toxic chemicals, they are not environmentally benign. A green route based on pure biological molecules, such as peptide and enzyme, has been used successfully for the synthesis of AgNPs and controlling their properties [9-11]. Alternatively, extracts from algae and plants have been employed as green reactants for AgNPs preparation. Also, microorganisms such as bacteria, yeast and fungi are being rapidly exploited as nanofactories in producing various nanomaterials [12-15]. Biogenic AgNPs, either intra- or extracellularly fabricated have been intensively investigated due to their potent antimicrobial property [16-19]. In a typical microbial process, isolated or genetically engineered microbes were firstly cultivated in defined nutritional liquid such as LB [20,21] and GMYP media [22]. Most of these nutrient broths contain peptone, yeast extract, dextrose and other essential growth factors, some of which possess strong reducing and stabilizing capability as reported in the literatures [23,24]. After cell culture, the spent media were either discarded with the remaining biomass collected for nanoparticle synthesis; or silver salt precursors were added into the spent media with or without the presence of the microbes for nano-synthesis. It is generally recognized that specific enzyme(s) secreted by specific microbes are significant factors to determine the formation of nanoparticles, even though the real mechanism of biogenic AgNPs formation is still unclear [25]. We are surprised to see that all microbial approaches heavily rely on tedious microorganism maintenance rather than on facile broth environment optimization. Although the microbial process has been called “green approach” and is becoming a popular theme in current bionanotechnology [26], the conventional microbial process is apparently complex and non-economic. Furthermore, the synthesis mechanism needs to be reconsidered as the role of broth playing in the microbial synthesis has been largely ignored by researchers.

Contrary to these conventional methods involving tedious isolation of silver tolerant bacteria or manipulation of recombinant microbes, it is advantageous to use the culture media alone to prepare AgNPs in a more cost-effective way. We have successfully obtained gold nanoparticles (AuNPs) with controllable size and morphology in yeast mold broth. We point out that living microbes are not the indispensable factors for nanomaterial synthesis in this biological system. Peptone, yeast extract and dextrose are identified as more powerful players in reducing and stabilizing AuNPs with high yield and narrow size distribution. However, it was quite perplexing that silver nanoparticles could not be achieved by applying the similar

protocol for AuNPs synthesis mainly due to the AgCl intermediate formation; thus we started to suspect the versatility of this broth alone strategy to synthesize other noble metal nanoparticles. Until very recently, pure AgNPs were obtained after extensive efforts have been dedicated to clarify the significant effects of light condition and pH values. Furthermore, we performed AgNPs synthesis at the presence of unmodified Gram-positive and Gram-negative bacteria to verify that AgNPs formation is indeed microbe-independent. We are delighted to be able to confirm that the broth alone strategy also applies to the synthesis of uniform silver nanoparticles under appropriate light and pH conditions. We hope that the results of this research together with our previous publication will sufficiently alert the microbial nanosynthesis research community about the significant advantages or versatility of this novel microbe-free strategy.

5.2 Experimental section

5.2.1 General

Silver nitrate ($AgNO_3$), dextrose, hydrochloric acid and sodium hydroxide were purchased from Sigma-Aldrich. All chemicals were of at least analytical grade and used as received without further purification. Lysogeny broth (LB), nutrient broth (NB), tryptic soy broth (TSB), yeast mold broth (YMB), yeast extract (YE) and peptone in powder form were purchased from BD company. Aqueous solutions were prepared with deionized (DI) water.

5.2.2 Silver nanoparticle formation

Silver nitrate was dissolved in DI water to get a 20 mM stock solution. LB, NB, TSB, YMB, YE, peptone and dextrose were dissolved in DI water and autoclaved at 121°C for 15 min. It took ~ 10 minutes to heat up the autoclave (Siltex 250D) from room temperature to 80°C and took additional 15 minutes to reach 121 °C therefore the total autoclave operating time was about 1 hour. In a typical procedure for the nanoparticle preparation, 5 mL $AgNO_3$ solution was added to 5 mL broth to get final [Ag^+] concentrations from 0.125 to 2.0 mM. The pH of the broth was adjusted by HCl or NaOH. The mixture was then placed inside a shaker at room temperature or 37°C (100 rpm) to react for a period of up to 30 days or 24 h, respectively.

5.2.3 Structural characterization of Ag nanoparticles

The course of the AgNPs formation was monitored by UV-visible spectroscopy (GBC Scientific Equipment). The nanoparticles size and polydispersity were characterized by a dynamic light scattering (DLS) using Nano-ZS90 analyzer (Malvern). For transmission electron microscopy (TEM), a drop of solution was placed on carbon-coated copper grids and air dried. X-ray diffraction analysis was performed using a Bruker D8 Advance X-ray Diffractometer with Cu Kα ($\lambda = 1.54$Å) radiation. The diffracted intensities were recorded from 20° to 85° 2θ angles. Inductively coupled plasma optical emission spectroscopy (ICP-OES, Perkin Elmer ICP Optima 2000DV) was employed to determine the yield of AgNPs. After two days reaction at 37°C, 3 mL sample was dialyzed against 2 L DI water to remove free Ag^+ followed by 100 000-fold dilution before analysis by ICP-OES. Blank and standard solutions of silver nitrate were tested together.

5.2.4 Nanoparticle formation at the presence of unmodified bacteria

Bacterial strains of *Escherichia coli* (ATCC 25922) and *Bacillus subtilis* (ATCC 23857) were obtained from the American type culture collection (Rockville, MD). The bacterial cultures were maintained in trypticase soy broth at 37 °C. $AgNO_3$ was added at 0.03 mM. The incubation was carried out under light conditions for 3 h. *E. coli* cells for TEM ultrastructure study were centrifuged, washed, fixed and sliced into ~70-nm-thick specimen by using a Leica ultramicrotome.

5.3 Results and discussions

5.3.1 Light-dependent AgNPs formation

We firstly investigated whether or not Ag ions can be reduced by original broth in the dark. The pH values of the pristine lysogeny broth (LB), nutrient broth (NB), tryptic soy broth (TSB) and yeast mold broth (YMB) are 7.0 ± 0.2, 6.8 ± 0.2, 7.3 ± 0.2 and 6.2 ± 0.2, respectively. Detailed information on sample preparation condition is shown in Table 1. Unfortunately, at room temperature, the broth colour alternation caused by AgNPs formation was not visually observed even after one month incubation. Contrarily, in the presence of ambient light with normal fluorescent lamp, after 6 h, stable Ag nanoparticulates were gradually formed in all broths containing 1 mM Ag^+ as the colour of broth was altered from light yellow to brown as displayed in

Figure 5.1, indicating the dispersion of the formed nanosized Ag species in the broth system [27]. However, such colour variation was not observed when the negative control experiment was carried out using pure silver nitrate aqueous solution under the same condition. Moreover, with prolongation of incubation time, the colour of broth became darker due to the formation of larger and much more AgNPs. We also observed that AgNPs formation in NB and TSB were faster than in LB and YM broth as indicated by the broth colour.

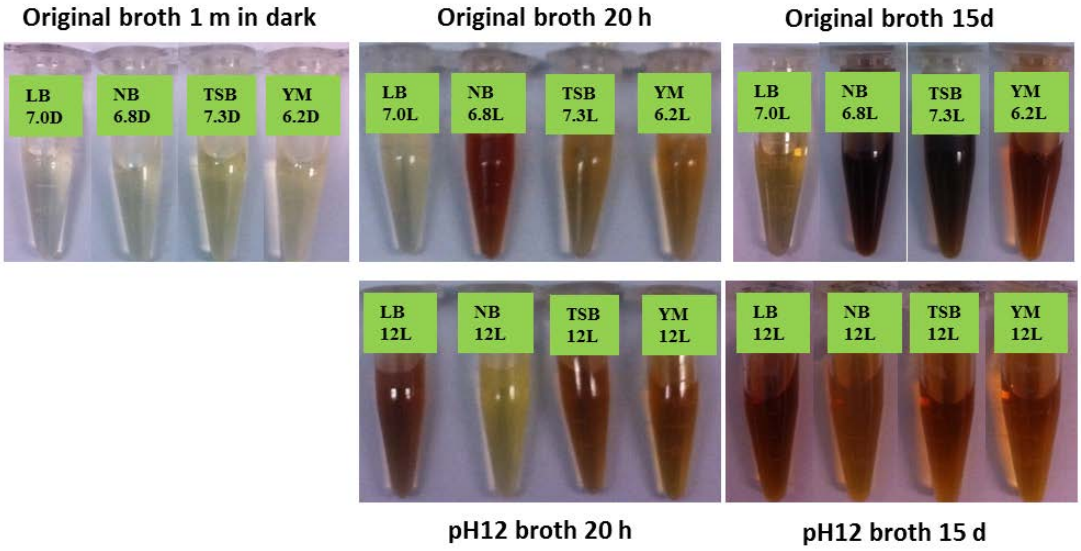

Figure 5.1 Digital images of 1 mM [Ag^+] in original or pH12 broths after incubation at room temperature for 1 month in dark (D) or under light (L) for 20 hours and 15 days, respectively.

In previous AgNPs microbial biogenic studies, some control experiments were conducted in the dark [28] and particles were not formed as compared to samples exposed to microbes. This is likely the major reason for the broth reducing capability to be often ignored and thus too much effort has been misled to engineer the special protein expression microbial strains. Even so, the importance of the presence of ambient light in reducing Ag^+ has been reported [29]. In their study, the authors firstly transformed the *S. cerevisiae* strain EBY100 which overexpressed the hexaglutamic acid (E6) peptide; then they employed the yeast cells as biological scaffolds for Ag^+ reduction. No AgNPs were detected in the E6 cells that being kept in the dark. In agreement with the hypothesis from Nam et al., we also speculate that photochemical

reduction of Ag may be facilitated after Ag ions bind with the reducing peptides in the broth [29].

Figure 5.2A shows the UV-visible absorption spectra of Ag nanoparticles formed in LB, NB, TSB and YMB after incubation for 15 days at room temperature under laboratory light. Two relatively narrow surface plasmon resonance (SPR) peaks at 404 nm and 416 nm indicated the obvious features of the Ag^0 in TSB and YMB, respectively. The reduction progress was further monitored by the SPR peak variation. The SPR peaks increased gradually in intensity as a function of time but with no significant peak shift (data not shown here). For Ag ion reduction in NB, the broader optical absorption peaks was shifted to the longer wavelength regime (~422 nm). Interestingly, the 1AgLBRT15D sample (X-Ag-Y-RT-Z, where X denotes the Ag^+ concentration in mM, Y is referred to as the broth name, RT is referred to as room temperature and Z denotes the reaction time) displayed a UV-vis spectrum similar to that of Ag@AgCl plasmonic nanocomposite [30,31]. These results suggested that in a broth containing high content of sodium chloride, AgCl could be formed immediately upon the addition of $AgNO_3$ [32] and served as the major intermediate compound during AgNP formation [33]. The XRD result is provided in Fig. 2B to understand the crystal structures of the samples. Figure 5.2B shows the XRD patterns of samples prepared under laboratory light at 37 °C for 24 h. For AgLB and AgTSB samples, they both show strong AgCl peaks with undetectable Ag peaks. The peaks at 27.7°, 32.1°, 46.2°, 54.7°, 57.4°, 67.4°, 74.4° and 76.6° correspond well to the (111), (200), (220), (311), (222), (400), (331) and (420) planes of the cubic phase of AgCl (JCPDS file: 31-1238), respectively. The diffraction peaks of Ag could be observed after extending the reaction time to 2 days. For AgNB samples, additional peak appeared at 38.2° corresponds to the typical cubic phase of metallic Ag (JCPDS file: 65-2871). AgYMB samples display major diffraction peaks of AgNPs. In agreement with the above Uv-vis spectra result, the light is implied as a key factor in transforming AgCl to AgNPs.

Apart from qualitatively verifies the formation of various noble metal nanoparticles, UV-vis spectroscopy is also a facile method to indicate the synthesis yield of nanoparticles. In Figure 5.2A, with the same final concentration of [Ag^+] (1.0 mM), the intensity of the maximum absorption band in our system is much larger than those of AgNPs synthesized by white rot fungal strain *C. versicolor* [34]. Further ICP-OES quantitation of silver reveals that after two days reaction at 37 °C, LB, NB, TSB and YM broth converted 70%, 30%, 55% and 40% of silver nitrate to silver colloids,

respectively. It should be noted that at original pH, silver nanoparticle decorated silver chloride (Ag@AgCl) was the major product in 1AgLB37C2D and 1AgTSB37C2D samples.

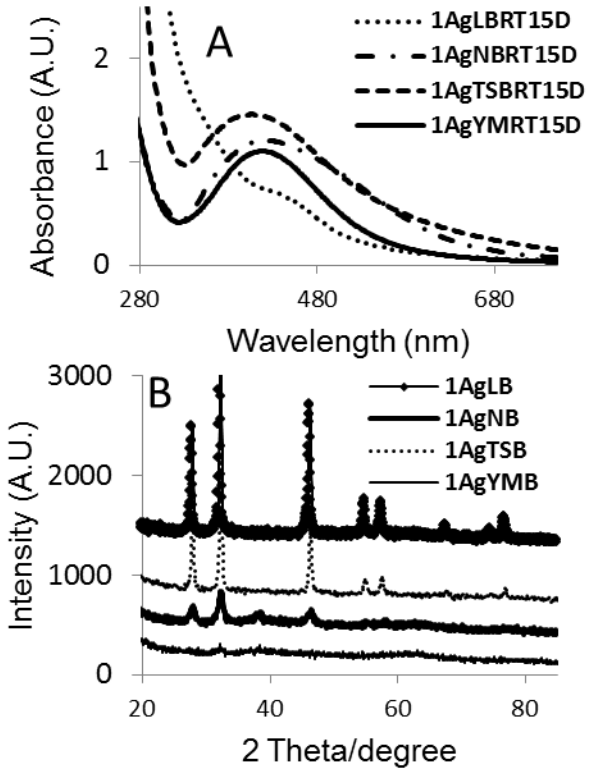

Figure 5.2 The UV/vis absorption spectra (A) and XRD patterns (B) of nano-Ag in various original broths after incubation at room temperature for 15 days. Detailed information regarding sample preparation condition is shown in Table 5.1.

Table 5.1 The individual ingredients concentration (w % in water) of broths employed in this study.

	Dextrose	Yeast Extract	Peptone	Malt Extract	Tryptone	Casein	Soybean Meal	NaCl	K_2HPO_4	Beef Extract
Yeast Mold Broth	1.0	0.3	0.5	0.3						
Tryptic Soy Broth	0.25					1.7	0.3	0.5	0.25	
Lysogeny Broth		0.5			1.0			0.5		
Nutrient Broth			0.5							0.3

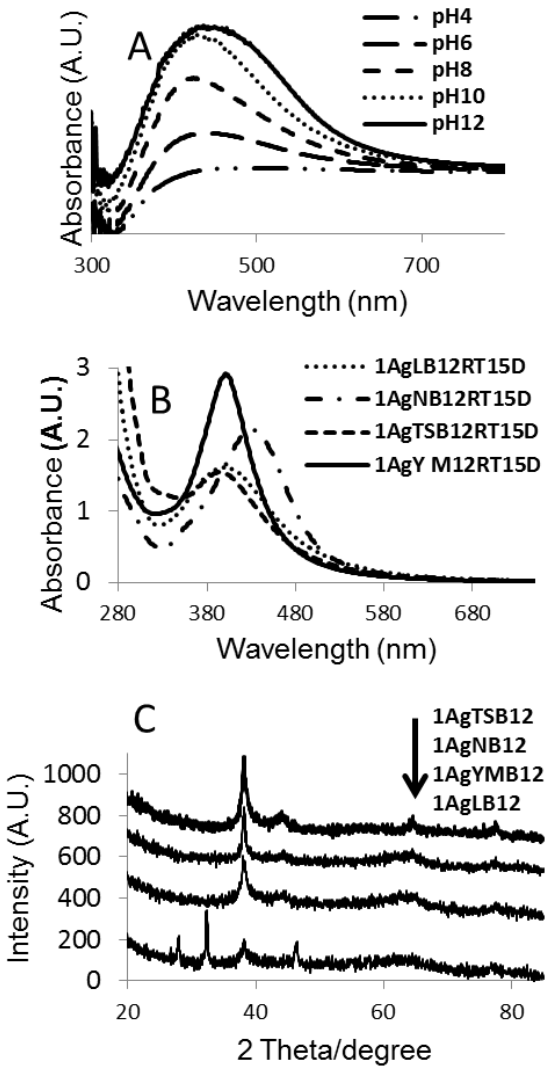

Figure 5.3 (A) pH-dependent UV-vis absorption spectra of 2.5 mM $AgNO_3$ reduced in TSB of various pH values for 6 h at room temperature. The UV/vis absorption spectra (B) and XRD patterns (C) of 1 mM $AgNO_3$ reduced in pH 12 broths.

5.3.2 pH-dependent AgNPs formation

We systematically investigated the Ag nanoparticle formation in broths with different pH values. For example, Figure 5.3A shows absorption spectra of 2.5 mM Ag ions reduced in TSB broth with pH value from 4 to 12. It is found that pH 10~12 broths enabled the quick particle formation with narrower size distribution (Fig. 5.4). Figure 5.3B displays the spectra of AgNPs formed in pH 12 of LB, NB, TSB and YMB. A strong plasmonic band appeared at ~ 400 nm for AgLB12, AgTSB12 and AgYM12 samples, which was shifted to 430 nm for AgNB12 sample. This is consistent with the observation of XRD patterns as displayed in Figure 5.3C. The diffraction peaks ascribing to Ag and AgCl are both clearly present for AgLB12

sample. As compared to AgLB12 sample, the XRD patterns of other samples signal the major phase of metallic Ag. It has been reported that Ag_2S phase and Ag phase coexisted in the product obtained by employing *C. versicolor* [34]. In our study, there was no peak observed at $2\theta = 33.3°, 39.2°, 46.2°$ that correspond to Ag_2S phase. In this sense, the broth-only process is promising due to its potential in providing relatively pure AgNPs.

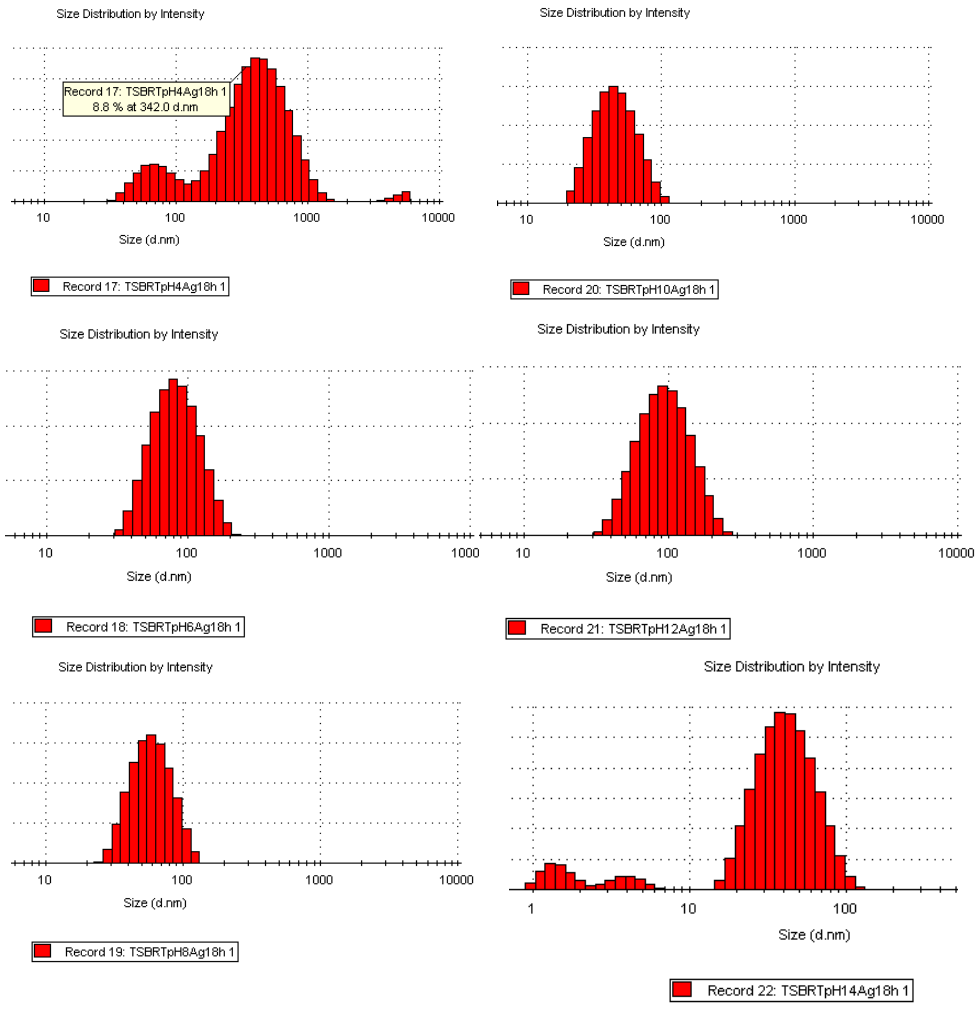

Figure 5.4 pH-dependent silver nanoparticle size distribution in TSB broth after 18 h incubation at room temperature. Dynamic light scattering results revealed that uniform and fast nano-silver formation was formed in pH12 TSB.

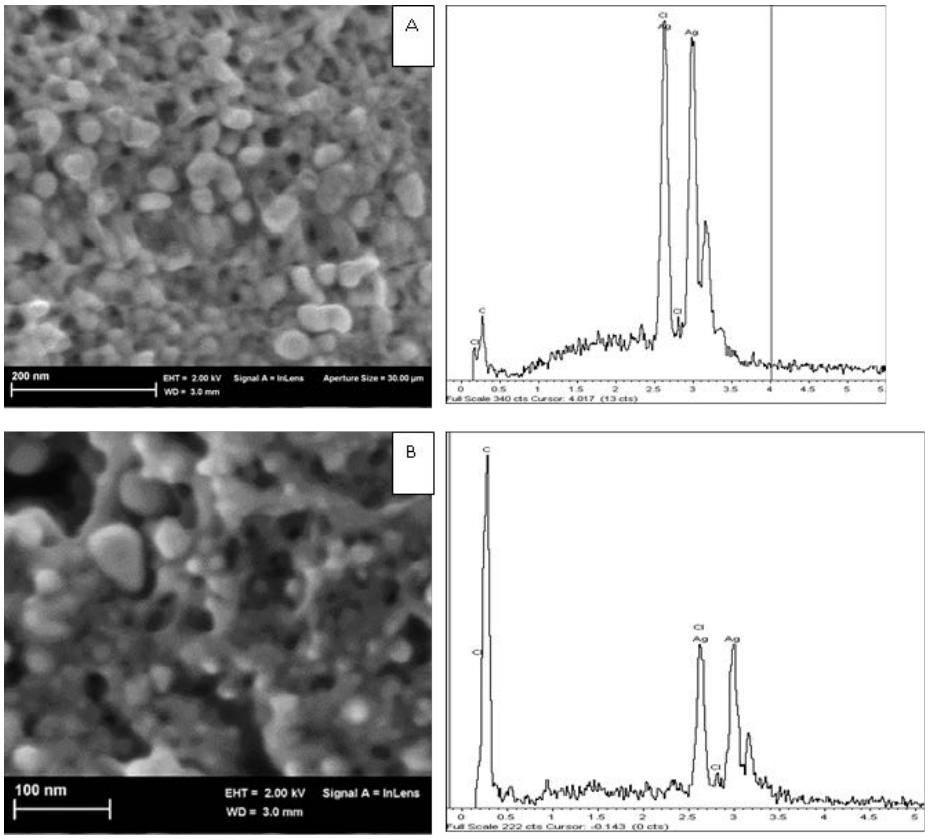

Figure 5.5 SEM and EDS results of colloidal silver particulates formed in original LB broth (A) and NB broth (B). Initial [Ag^+] = 1 mM and all the reactions were carried out in a shaker at 100 rpm, 37 °C for 24 h.

The morphologies of the particles obtained in pristine broths were observed using SEM. Taking 1AgLB37C24h and 1AgNB37C24h as examples, as shown in Figure 5.5, we can see that spherical nanoparticles with an average size of ca. 20 to 50 nm were synthesized. The composition of the NPs was determined by energy-dispersive X-ray spectroscopy (EDS), all of which show peaks of Ag and Cl. However, the SEM images could not be clearly taken because exposure of the Ag@AgCl particles to the electron beam caused a reduction of the AgCl to metallic Ag [35].

The most uniform AgNPs were formed in YM12 broth. Figure 5.6 displays the optical images and TEM image of 1AgYM12 and a magnified high-resolution (HR) TEM image of an isolated AgNP, respectively. The lattice fringes were separated by 0.23 nm, usually assigned to {111} plane of silver. EDS spectrum shows the occurrence of silver with phosphorous and sulphur, mirroring the important role of phosphorus and metallothioneins (MTs) or their fragments in the reducing and binding

of Ag^+ [36]. MTs could be originated from the autolyzed *Saccharomyces cerevisiae* yeast.

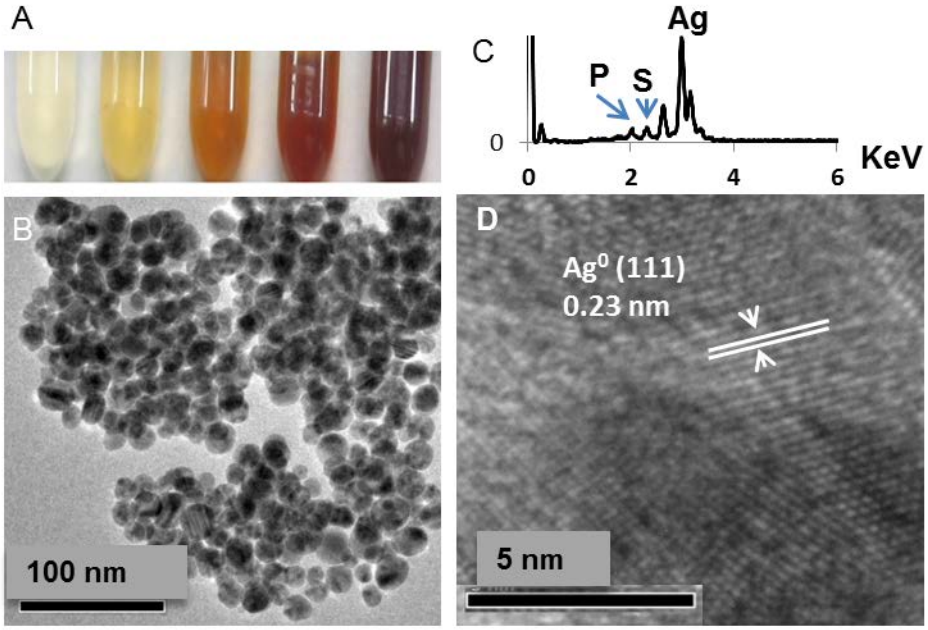

Figure 5.6 Silver nanoparticles formed in pH12 YM broth. (A) The optical images of nano-Ag in YM broth with initial [Ag^+] from 0.125 to 2 mM; (B) TEM image of the uniform silver nanoparticles and the corresponding EDS spectrum of nano-Ag(C); (D) HRTEM images of an isolated AgNP.

5.3.3 Identification of components in the broth for AgNP formation and possible biosynthesis mechanism

In our previous work, the reduction of Au^{3+} was completed by the active species in the broth like dextrose, yeast extract (YE) and peptone [24]. The aqueous solution of these components was individually or mixed together to reduce Ag^+ in this study. The UV-vis spectra recorded for a 1 mM Ag^+ after 2, 6 and 54 h of reaction at 37 °C with the presence of 0.25% dextrose (same dextrose concentration in TSB) showed no absorption in the 350-850 nm region, whereas the 0.5%YE, 1%YE+0.3% dextrose and 0.5%YE+0.25% dextrose produced a gradual increase in absorption band centered at ca. 420 nm. Notably, the position of major peak did not change at this wavelength (Fig. 5.7). These evidences implicate that yeast extract, concentrated from autolyzed *Saccharomyces cerevisiae*, is more powerful than dextrose in reducing Ag^+ under neutral pH.

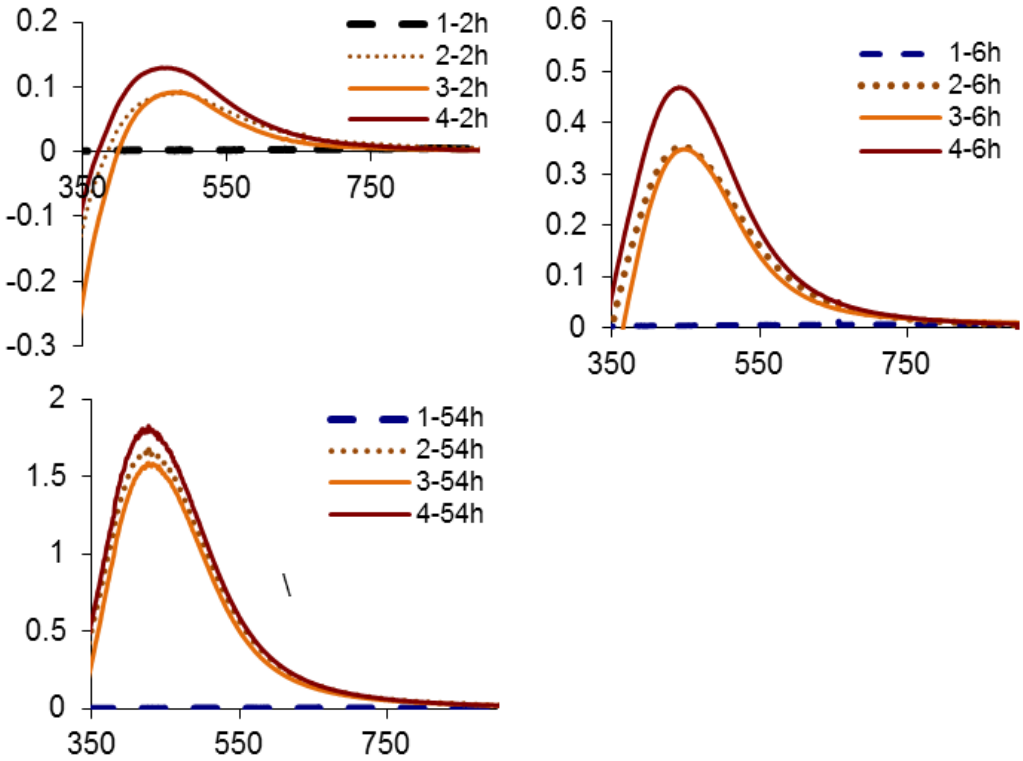

Figure 5.7 Nano-Ag formed in aqueous dextrose (DE), yeast extract (YE) or mixture of DE and YE. The compositions of 1, 2, 3 and 4 are: 1. 0.25% DE ; 2. 0.5% YE; 3. 1.0%YE + 0.3%DE ; 4. 0.5%YE + 0.25% DE.

In order to investigate the relationship between the AgNP formation and pH environment of the broth, pH of dextrose solution was adjusted to 12 by adding NaOH solution. Surprisingly, at room temperature, AgNPs were formed immediately as compared to dextrose solution at pH 5.5. Figure 5.8B recorded the continuous AgNP evolution from 10 s to 300 s. However, aggregation occurred within 2 h as indicated by DLS results (Fig. 5.8A). The SEM images clearly indicate the well dispersed AgNP fused together and formed microsized Ag plates (Fig. 5.8C-D). This is an important observation as we may explain the reason why in high pH broths, the major phase of nanohybrids was Ag but not AgCl. At high pH, both Ag and AgCl were instantly formed upon the addition of precursor solution. However, at neutral pH value, only AgCl was quickly yielded and it requires long time to change to AgNPs driven by the light. Also, it is clear from this result that yeast extract, peptone or other digested proteins play pivotal roles not only in the reduction of Ag^{+} but also in preventing the agglomeration of Ag particles during the reduction process.

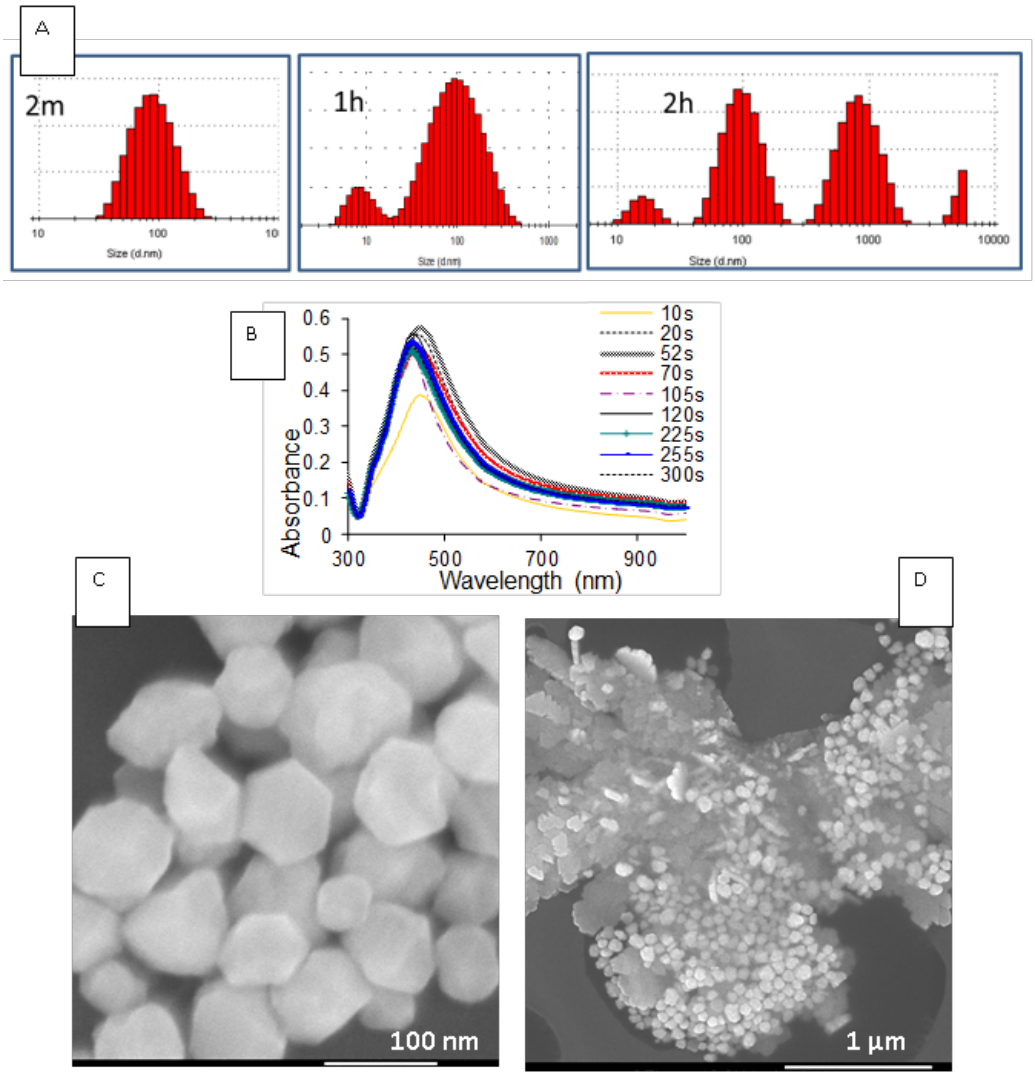

Figure 5.8 Nano-Ag formed in pH 12dextrose (DE). (A) DLS results of Ag nanoparticles; (B) UV-vis spectra of nano-Ag recorded from 10 seconds to 300 seconds. The initial well-dispersed nano-Ag (C) aggregated into Ag-nanoplate (D) in 2 h.

5.3.4 Microbe-independent formation of silver nanoparticle

To further verify that our greener process is microbe-independent, 0.03 mM silver nitrate was incubated with native *E. Coli* (ATCC25922) instead of the recombinant one. Silver nitrate of 0.03 mM was chosen because this is the maximum tolerable concentration of Ag ions to *E. coli* in the dark. After exposing the *E. coli* and Ag^{+} containing TSB broth to natural light, silver nanoparticles were synthesized extra-cellularly as indicated by the increased 420 nm absorbance intensity (Fig. 5.7C). To check whether or not AgNPs were formed inside the cells, the cell pellets were centrifuged and washed for ultrastructure study by TEM. In contrast to silver-resistant

Pseudomonas stutzeri AG259 cultured in the presence of 50 mM $AgNO_3$, for which the majority of the AgNPs were deposited in the periplasmic space of the cells [20], the size of the AgNPs in our study was smaller and distributed evenly all over the cell body (Fig. 5.9A). The control experiments without Ag^+ showed no AgNPs formation (Fig. 5.9B). Importantly, extracellular AgNPs were formed in TSB containing either *E. coli* or *B. subtilis*, thereby echoing that broth alone strategy is indeed microbe-independent (Fig. 5.10).

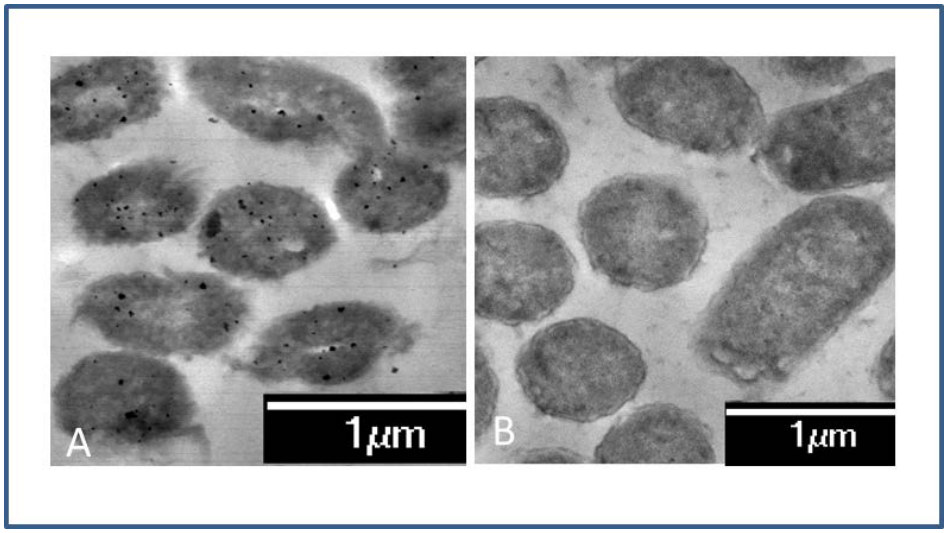

Figure 5.9 TEM images of thin sections of wild type *E. coli* (ATCC25922) cells after incubation with Ag^+ (A) and without Ag^+ (B) for 3 hours confirmed intracellular formation of silver nanoparticulates.

With all the above results in mind, we propose the following mechanism to explain the AgNPs formation in microbial cultivation broths in particular with high content of sodium chloride (0.5 w %), such as LB and TSB. When $AgNO_3$ solution was added drop-wise into broth, AgCl colloid could be formed immediately. UV photoconversion of AgCl to AgNPs mediated by DNA template has been reported by Wang et al. [37]. The authors have proposed the photosensitivity of AgCl towards the fast formation of AgNPs may be realized by visible light irradiation accelerated by specific dyes or color sensitizers. Along the same line, we speculate that on absorbing a photon, AgCl nanoparticle could generate an electron-hole pair, followed by e^- and Ag^+ combination and Ag cluster species evolution in the presence of peptide or protein:

$h\nu + Cl^- \rightarrow Cl + e^-$ (1)

$e^- + Ag^+ \rightarrow Ag^0$ (2)

Although further investigation is still needed, we propose that metallothioneins (MTs), having capacity of binding Ag species and scavenging superoxide and hydroxyl radicals [38], could accelerate the transformation of AgCl to AgNPs. To our knowledge, this is the first report about the broth-mediated AgNPs formation through the intermediate crystalline AgCl colloids.

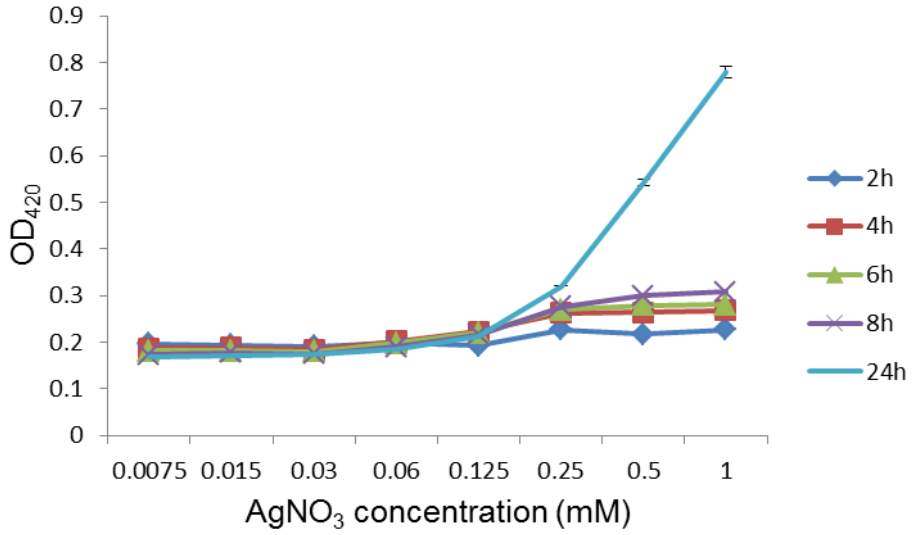

Figure 5.10 Nano-Ag formed extracellularly in TSB broth at the presence of *E. coli* is confirmed by recording the optical density at 420 nm.

Commonly accepted mechanism of extracellular AgNPs formation is the nitrate reductase enzymatic reduction [39]. Based on this assumption, much work has been dedicated to screening silver tolerant bacteria or genetically engineering special microbial species [17,21]. Our new findings have challenged these long-held viewpoints that microorganisms are predominantly responsible for the biogenic AgNPs. It is safe to affirm that the biomass including fungi and bacteria catalyse the AgNPs formation only when the reaction is conducted in broth-free system and in the dark condition [40]. AgNPs are formed in the minute to hour timeframe (depending on the pH, temperature and light condition, some of the data not shown in this manuscript) in our microbe-free process. However, it may take 3 days to obtain AgNPs by employing biomass as catalyst. The biomass must be maintained and cultured in different media, which are the starting materials that used in our microbe-free process. The high-yield and easier downstream particle separation apparently support that our technology is superior in producing uniform AgNPs faster, less labour-intensive and more eco-friendly.

5.4 Conclusions

Here we report a facile and novel protocol to synthesise AgNPs in various microbe culture broths. The broth ingredients provide an ideal environment for the formation of AgNPs with uniform size distribution. The significant influences of some important parameters include light condition and broth pH values have been investigated systematically. Whilst sharing similar advantages with the conventional microbial processes to use non-hazardous chemicals, this method is of particular importance as it employs the culture broth alone without involving any specific microorganism.

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Chapter 6. One-pot synthesis of raspberry-like mesoporous silica nanospheres

Abstract

Mesoporous materials with hierarchical morphologies have recently gained attention due to their structural versatility for various applications including catalysis, adsorption, energy storage and nanomedicine. However, it is still desirable for controllable synthesis of mesoporous particles with tunable surface properties and oriented hierarchical structures. Here, we report a one-pot synthesis method for raspberry-like mesoporous silica nanospheres with 2 nm hollow silica nanoparticles doped on the surface. We identify that the control over the concentration of cationic surfactant and silica precursor can be used to control the multiple morphological evolutions of mesoporous silica nanoparticles. This control enables the fabrication of a diverse library of multi-compartment mesoporous silicas networks consist of mesoporous silica nanospheres connecting with mesoporous silica branches. The synthesis method would enable to synthesize hierarchical mesoporous silicas with complex architecture and different pore environments for the potential application in catalysis and nanomedicine.

6.1 Introduction

Natural nanomaterials such as bone, cells, lotus, rose, fish skins, gecko feet exhibit multi-scale hierarchical structures.[1-6] Learning from nature, materials scientists and chemists have been developing different strategies to fabricate artificial nanomaterials with hierarchical structures for mimicking the functionality of natural nanomaterials.5-8 As one of the typical examples, mesoporous silica nanoparticles (MSNs) have attracted widespread interest because of their versatile applications in catalysis and nanomedicine.[4, 9-14] In the last decades, a variety of MSNs with different morphology have been explored, including rods, spheres, plate, hollow and yolk shell particles.[12, 15-24] Among them, raspberry-like mesoporous silica nanospheres (RMSNs) with many small particles decorating on the surface of one large particle are

of particular interest owing to their hierarchical structures and tunable surface properties.[16, 23, 25-31] By mimicking the surface of lotus leaves, raspberry-like silicas have been used as antifogging or self-cleaning coatings.[23, 32-36]

Many synthetic strategies have been developed for the fabrication of raspberry-like nanoparticles. The most common approach is the two step method by assembling smaller nanoparticles onto one large core particle through different types of complementary interactions. For example, Scherman and co-workers reported the synthesis of raspberry-like hollow silica microspheres with paramagnetic Fe_3O_4 nanoparticles decorating on the shell by utilizing host–guest complexation of cucurbit[8]uril (CB[8]).[25] Zhao et al. demonstrated the synthesis of monodisperse raspberry-like hierarchical silica particles through a microfluidic approach.[28] By using a vesicle or emulsion template, the one-pot synthesis of raspberry-like hierarchical siliceous hollow spheres has also been reported previously.[27, 29] Despite the existing library of geometrical variations of raspberry-like silica nanoparticles, in most of cases, it is focusing on the hollow silica particles, it is still necessary to exploit a simple and practical route for the synthesis of RMSNs.

In this chapter, we present a simple one-step extension Stöber method for the synthesis of raspberry-like and multi-compartment mesoporous silica nanoparticles. The effects of several synthesis parameters, such as the concentration of cetyltrimethylammonium bromide (CTAB) and silica precursor, water to ethanol ratio, on the morphology evolution of final mesoporous silicas particles have been investigated. The fundamental understanding of synthesis mechanisms reveals their potential for controllable synthesis multi-compartment mesoporous silica nanoparticles in the fields of catalysis and nanomedicine.

6.2 Experimental sections

6.2.1 Chemicals and reagents

All materials were of analytical grade and used as received without any further purification. Tetraethyl orthosilicate $Si(OC_2H_5)_4$ (TEOS) (>99%), anhydrous ethanol, aqueous ammonia solution (28 wt%), and cetyltrimethylammonium bromide (CTAB) were purchased from Aldrich. Water was purified by a Milli Q system and had an electrical resistance of 18 MΩ·cm.

6.2.2 Synthetic procedure

Monodisperse raspberry-like mesoporous silica nanospheres (RMSNs) was synthesized by extension of Stöber method. In a typical synthesis, 150 mg of CTAB was dissolved into a solution containing 30 mL of absolute ethanol (EtOH) and 50 mL of deionized water (H_2O), then, 0.5 mL of ammonia aqueous solutions (NH_4OH, 28 wt%) was added into the above solution. After stirring for 2h, 0.24 mL of TEOS was added to the solution and stirred for 24 h at room temperature, and subsequently heated for 24 h at 100 °C under static conditions in a Teflon-lined autoclave. The solid products were collected by centrifugation and washed with ethanol and water, respectively. The CTAB surfactant was removed by calcinations of the samples at 550 °C for 6 h.

6.2.3 Characterization

Field-emission scanning electron microscopy (FESEM) was undertaken on a HITACHI S-4800 microscope operating at an accelerating voltage of 1-30 kV. TEM images were obtained by JEOL JEM2100 electron microscope. The powder samples for TEM measurements were suspended in ethanol and then dropped onto the Cu grids with carbon films. Nitrogen sorption isotherms of samples were obtained by a Quantachrome's Quadrasorb SI analyzer at -196 °C. Prior to the measurement, the samples were out gassed at 120 °C for at least 6 h. The Brunauer-Emmett-Teller (BET) specific surface areas were calculated using adsorption data at the relative pressure range of P/P_0 = 0.05~0.25. Pore size distributions were calculated from adsorption branch using the Barrett-Joyner-Halenda (BJH) method. The total pore volumes were estimated from the amounts adsorbed at a relative pressure (P/P_0) of 0.99.

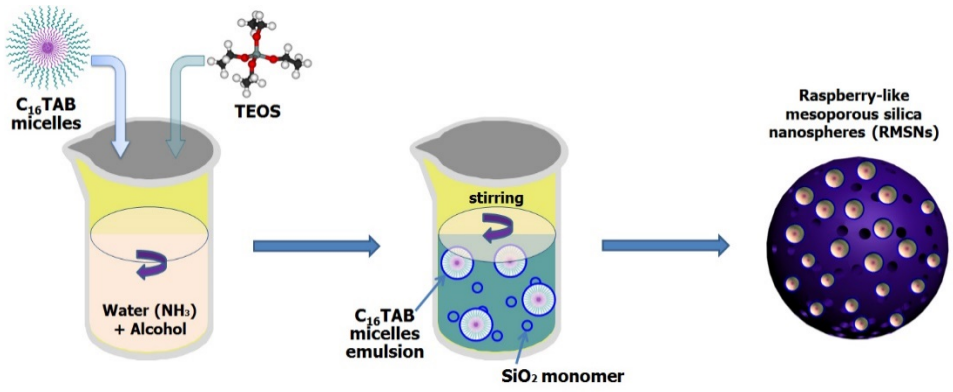

Figure 6.1 Schematic illustration of the synthesis process and formation mechanism of raspberry-like mesoporous silica nanospheres (RMSNs).

6.3 Results and discussion

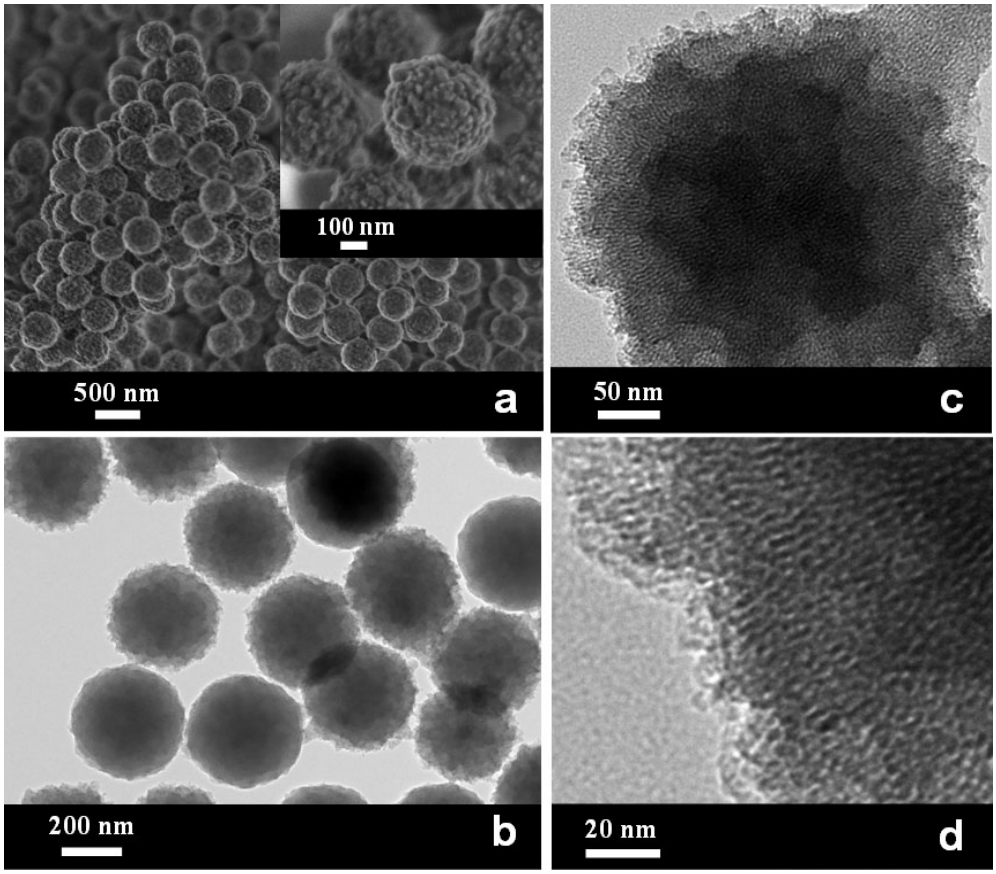

Figure 6.2 a) SEM and b)-d) TEM images of typical raspberry like mesoporous silica nanoparticles synthesized at CTAB concentration of 5.1 mM.

6.3.1 Synthesis of raspberry-like mesoporous silica nanospheres.

The well known Stöber method has been widely used for synthesis of silica and resorcinol formaldehyde resins spheres.[37] In this study, monodisperse raspberry-like mesoporous silica nanospheres (RMSNs) were obtained by extension of this synthetic strategy, the typical synthesis of RMSNs was schematically illustrated in Figure 6.1. Hollow silica nanoparticles are proposed to be formed on the surface of mesoporous silica spheres with the aid of an ammonium catalyst due to the different hydrolysis and condensation rates, forming a raspberry-like core–shell structure, denoted RMSNs. The typical scanning electron microscopy (SEM) and transaction electron microscopy (TEM) of RMSNs are shown in Figure 6.2. The spherical particle size of RMSNs is around 360 nm in diameter, these RMSNs are monodisperse, and the surface is rough with raspberry-like morphology (Figs. 6.2a and 6.2b). From the TEM images with high

resolution (Figs. 6.2c and 6.2d), a disordered worm-like mesoporous structure can be clearly seen. The surface of the raspberry-like shell is decorated with hollow silica nanoparticles with void size around 2 nm (Fig. 6.2d). Figure 6.3a displays N_2 sorption isotherms of RMSNs, which shows a type IV isotherm with capillary condensation at relative pressure P/P_0 between 0.15 and 0.30, indicating uniform mesopores, the narrow pore size distribution verifies the uniform pore size of RMSNs (Fig. 6.3b). RMSNs has a BET surface area of 435 m^2 g^{-1}, a pore volume of 0.24 cm^3 g^{-1}, and a pore diameter of 1.7 nm. The above characterizations suggest that raspberry-like mesoporous silica nanospheres has been successfully prepared.

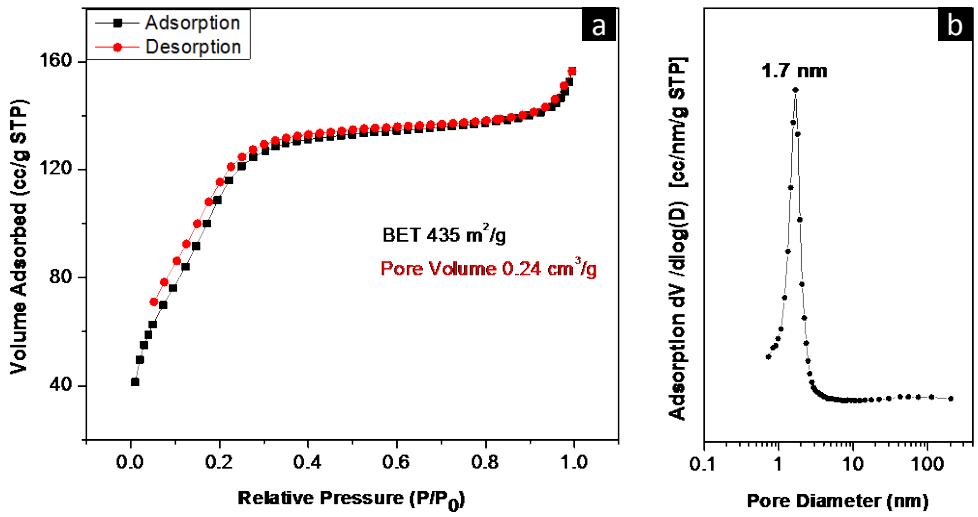

Figure 6.3 a) Nitrogen adsorption-desorption isotherms and b) pore size distribution of typical raspberry like mesoporous silica nanoparticles synthesized at CTAB concentration of 5.1 mM.

6.3.2 Effect of CTAB concentration

Cationic surfactant CTAB has been well recognized as micelle template for the formation of mesoporous silicas. In addition, it is well known that CTAB as a surfactant plays key role of the nanoparticle morphology. Therefore, the influence of different concentrations of CTAB on the formation of mesoporous silica nanoparticles has been investigated. As demonstrated in Figure 6.4, it was found that multi-compartment mesoporous silicas spheres connected by mesoporous silicas bridges are formed at low concentration of CTAB (3.4 mM). The spherical particle size is around

400 nm in diameter (Fig. 3). Moreover, higher magnification image reveals that the mesoporous silica bridges are around 150 nm in width. With increasing the concentration of CTAB to 5.1 mM, RMSNs were formed. While further increasing the concentration of CTAB to 6.8 mM, it is clearly observed that the particle size of resultant RMSNs is reduced to around 300 nm. More interestingly, large void pore of 20 nm is coexistence of mesopore as shown in the high magnification TEM image. The formation of void mesopores has also been reported in the previous reports with a similar synthesis system and higher CTAB concentration.[38, 39] These multi-compartment mesoporous silicas with hierarchical structures will be crucial for their further application in catalysis and nanomedicine, for example, to mimic cells, selectively loading different active sites onto different compartments in the silicas to construct nanoreactors.[21, 23, 31, 40, 41]

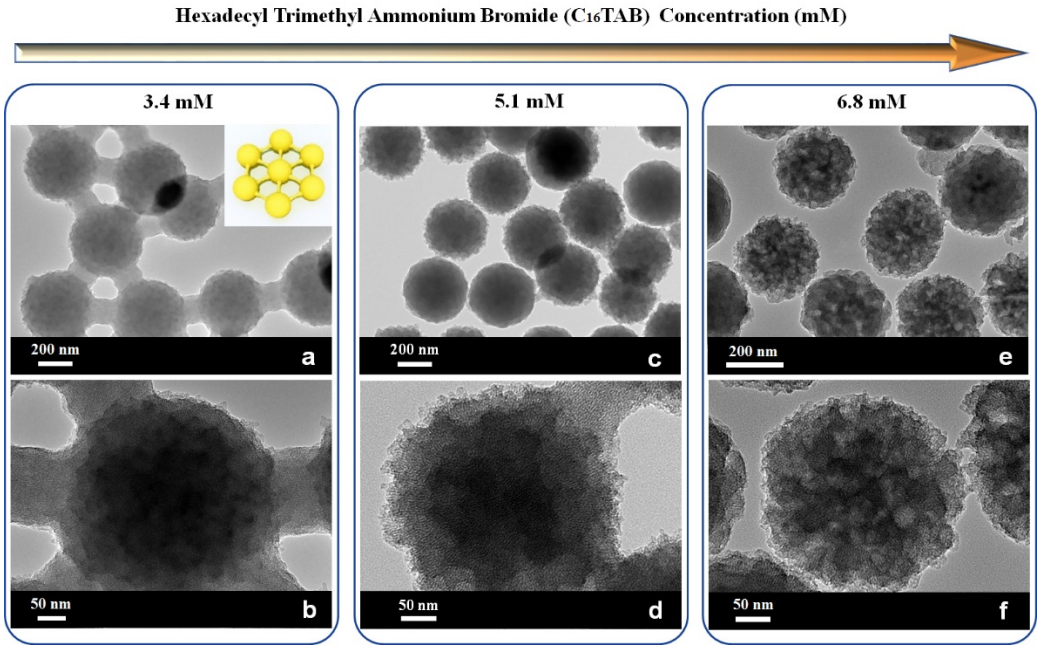

Figure 6.4 TEM images of mesoporous silica nanoparticles synthesized at different concentrations of CTAB.

6.3.3 Effect of TEOS concentration

Generally, it is believed that the silica precursor such as TEOS concentration also have a significant influence on the morphology and structure of final mesoporous silicas. In this study, the influence of different amounts of TEOS on the formation of mesoporous silicas has been studied. Figure 6.5 shows the TEM images of the samples prepared at

0.36 mL TEOS while keeping the other parameters consistence with RMSNs. Raspberry-like mesoporous silicas nanospheres with rough surface and larger particle size (~400 nm in diameter) are formed as the amount of TEOS increased. As the TEOS amount increased, mesoporous silica nanobridges were formed as presented in Figure 6.5, the nanobridges with 78 nm in width is thinner than the products formed with low CTAB concentration shown in Figure 6.3. Furthermore, no solid product can be obtained with reducing the TEOS amount less than 0.1 mL.

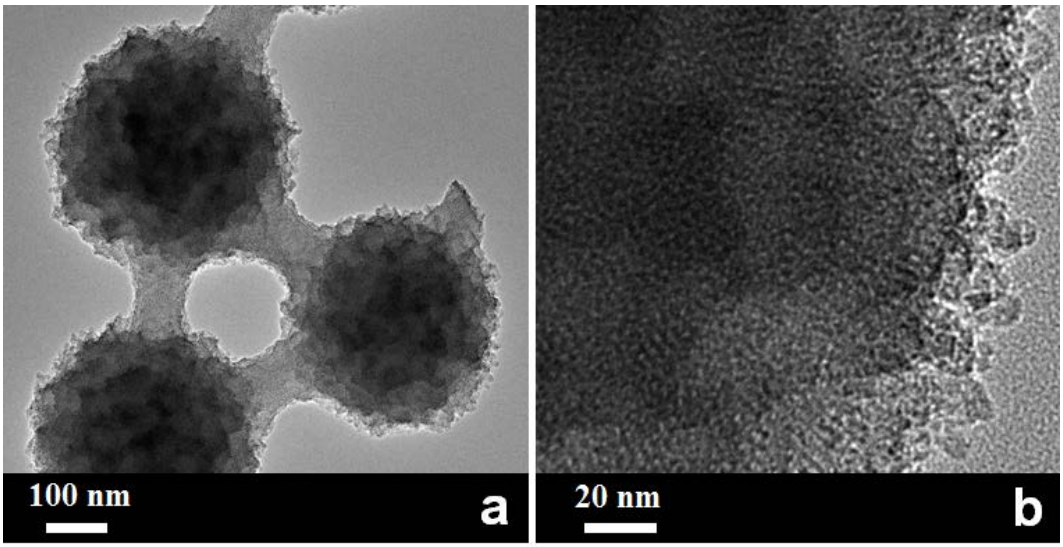

Figure 6.5 a), b) TEM images of mesoporous silica nanoparticles synthesized at concentrations of CTAB 5.1 mM and 0.36 mL of TEOS.

6.3.4 Effect of H_2O/EtOH ratio

In the Stöber process, the particle size can be varied by tuning the synthesis parameters such as ammonia solution concentration, precursor concentration, as well as water to alcohol ratio.[37] In addition, it is reported that the hydrolysis and condensation rates of a silane precursor can be accelerated by adding of alcohol. Therefore, the effect of the volume ratio of water to ethanol on the formation of RMSNSs has been investigated with other conditions fixed. Similar to other Stöber processes, the particle size is increased to around 600 nm as the volume ratio of water to ethanol was decreased from 1.67 to 1 (Fig. 6.6a, b). The resultant mesoporous silicas were composed of aggregated dendrimer-like porous spherical particles as shown in their corresponding TEM images (Fig. 6.6a). The enlargement of mesopore size by increasing the alcohol amount is in agreement with previous reports. While the volume ratio of water to ethanol was increased to 3, the particle size of the resultant mesoporous silicas spheres

is decreased to around 100 nm (Fig. 6.6c, d). The shape of spherical silica particles is irregular with aggregation can be observed (Fig. 6.6c). The worm-like mesostructured of silicas spheres is observed in the TEM image (Fig. 6.6d). The results shown above reveal that by increasing the ratio of water/ethanol, the particle size is gradually decreased, which is consistence with other Stöber processes.

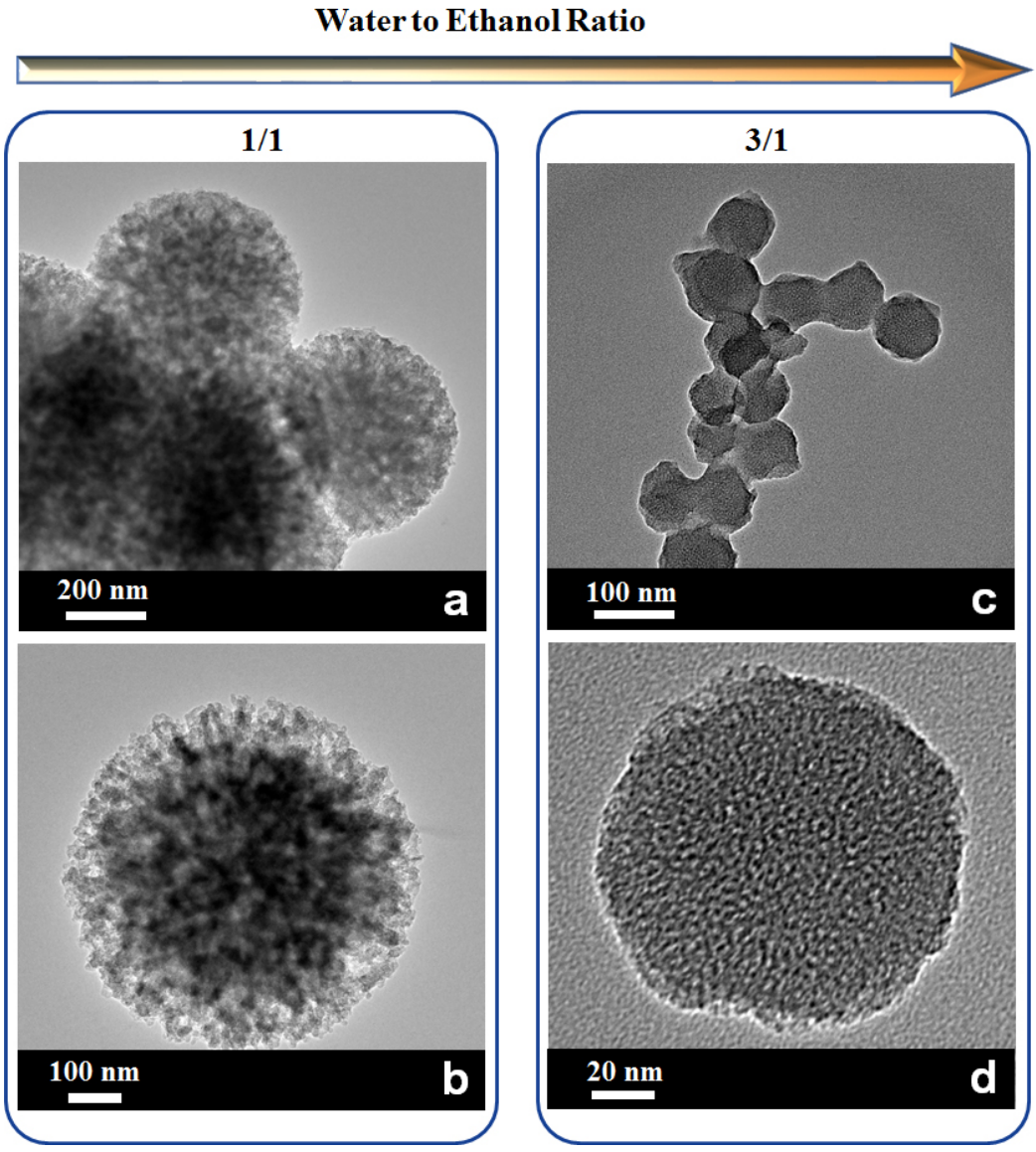

Figure 6.6 TEM images of mesoporous silica nanoparticles synthesized at concentrations of CTAB 5.1 mM and a), b) water to ethanol ratio of 1, c), d) water to ethanol ratio of 3.

It has been suggested by previous report that spherical particles can be formed through a Stöber process, in particular with suitable alcohol added. As depicted in Figure 6.1, the formation mechanism of mesoporous silica particles might be the

following four steps, i). 2 to 3 nm micelles of CTAB are formed; ii). after addition of TEOS, the hydrolysis and condensation of TEOS onto the CTAB micelles tend to generate silica monomers surrounding the micelles; iii). during the stirring and further reaction, silica monomers further condense onto the emulsion droplets derived from ethanol and water to generate mesoporous silicas spheres; iv). the formation of raspberry-like mesoporous silica spheres is possible due to the assembling of unreacted silica monomers onto mesoporous silica spheres. Decrease of the concentration of CTAB or increase of the amount of TEOS could promote the anisotropic nucleation and growth of silica monomer onto mesoporous silica spheres to connect the particles together.

6.4 Conclusion

In the present study, we have successfully prepared raspberry like mesoporous silicas with particle size of 360 nm through an extension Stöber process. By precisely controlling the synthesis parameters, either decreasing of CTAB concentration or increasing TEOS amount, multi-compartment silicas with mesoporous silica spheres bridged with mesoporous silica rods can be fabricated. It is found that the particle size of mesoporous silica can be tuned from 100 to 600 nm by varying the water to ethanol ratio. Specifically, the present strategy allows an easy way to generate the hierarchical nanostructured silicas by mimicking the structures of diatom cells for the potential application in catalysis and nanomedicine. Further studies are currently in progress in order to study their applications in gene therapy and anti-aging.

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Chapter 7. Raspberry-like hollow carbon nanospheres with enhanced matrix-free peptide detection profiles

Abstract

Utilising non solid nanoparticles and material design to create morphologies with special surface properties can lead to more advanced applications. Here, resorcinol formaldehyde (RF) polymer resins have been successfully coated on the silica spheres by the extension of Stöber method, to generate raspberry-like silica@RF core-shell particles with a rough surface. After carbonization of the shell and removal of silica, uniform raspberry-like hollow carbon spheres were obtained. A competitive process between homogenous nucleation and uniform surface coating is proposed as the mechanism for formation of the raspberry-like morphology. By finely controlling the water/ethanol ratio, a series of hollow carbon spheres with different surface properties and patchy structures can be synthesized with this method. The raspberry-like hollow carbon spheres demonstrate much better performance than hollow carbon spheres with a smooth surface in matrix-free peptide detection due to their high capability to capture the small peptide molecule.

7.1 Introduction

Colloidal materials have been studied in several research areas encompassing chemistry, materials science, condensed matter physics, applied optics, fluid dynamics, and biology because of their widespread applications such as in photonic crystal materials, optical sensing, and drug delivery.[1-3] In particular, hollow carbon colloidal nanospheres (HCCNs) with controlled diameters, shell thickness and surface properties have attracted a great deal of attention due to their unique properties, e.g., excellent chemical and thermal stability.[1, 3-10] HCCNs are promising materials with a variety of applications including adsorbents,[11-13] super-capacitors,[5, 10, 13-17] electrodes of fuel cells and lithium-ion batteries,[18-24] cell delivery[3] as well as supports for catalytic system.[9, 10, 14, 19, 25-27]

HCCNs have been synthesized either by hard or soft templating methods.[3, 4, 6, 7, 9, 11, 12, 14, 28-30] For instance, Lu and co-workers developed a confined nanospace pyrolysis method for the synthesis of discrete and highly dispersible HCCNs.[28] In their method, a dual core–shell structure particle was first synthesised by surface coating of monodisperse polystyrene (PS) nanosphere seeds with a phenol-containing polymer (PF), followed by a silica coating process. Dispersible and uniform HCCNs were obtained by subsequent pyrolysis of PF and removal of silica. Hollow carbon spheres with different particle size, shell thickness and layers have been also prepared through a hard templating method involving silica spheres as a template and PF as a carbon precursor.[4, 6, 8, 31] By ultilisation of a soft templating method through an aqueous emulsion co-assembly, Zhao and co-workers reported the synthesis of multi-shelled hollow carbon spheres.[7]

Most previous reports on HCCNs have focused on the sole aim to obtain hollow structural units and particle uniformity but little information has been provided with regards to the carbon surface properties. In fact, controllable synthesis of HCCNs with adjustable surface properties to suite more applications is still a challenge, for example, growing nanoparticles on the surface of cores rather than forming a fused shell. HCCNs with rough surface are of critical importance for both the fundamental study of carbon colloids and many practical applications such as colloidal catalysts, drug carriers, peptide enrichment, nanodevices and ink. However, to date and to the best of our knowledge, no raspberry-like HCCNs have been reported.

Carbon precursors have an important effect on the preparation and final physical and chemical properties of HCCNs prepared by the hard templating method. High carbon yield and uniform coating are two critical criteria for the carbon precursor selection. Phenolic resins are widely used as the carbon precursor for the synthesis of a variety of nanostructured carbons because of their high carbon yield and versatile chemical properties. For instance, Liu et al. successfully synthesized monodisperse polymer spheres from resorcinol–formaldehyde (RF) resin and carbon spheres by the extension of the “Stöber” method.[32] However, it is still a great challenge to precisely control the surface properties of the resultant polymer resin spheres due to the high concentration of the RF precursor used. In addition to the synthesis of colloidal silica spheres, Stöber method also has been widely used for uniform surface coating with silica. HCCNs can be synthesized through a hard template method by using either RF or dopamine as the carbon precursors. Inspired from this, herein, we report the

synthesis of hollow carbon spheres with different surface roughness by controlling the two competitive processes: the formation of free Stöber RF spheres and the uniform coating of RF on the silica surface. The essence of our method lies in the exploitation of 1) the controllable competitive process of homogeneous nucleation and surface uniform coating and 2) high carbonization yield of RF.

7.2 Experimental sections

7.2.1 Synthesis of Stöber spheres

In a typical procedure, 9 mL of ammonia aqueous solution (NH_4OH, 25 wt%) was dissolved in a mixture 16.25 mL of ethanol and 24.75 mL of water, stirred at room temperature for 5 mins to prepare the solution **A** and solution **B** was prepared by mixing 4.5 mL of TEOS in 45.5 mL ethanol and stirred at room temperature for 5 mins. The silica spheres were separated by centrifugation and rinsed thoroughly with water and ethanol.

7.2.2 Synthesis of silica@RF nanospheres

In a typical protocol, 200 mg 360 nm silica spheres were dispersed in a mixture of ethanol and water with a total volume of 28 mL; then 0.1 mL of ammonia aqueous solution (NH_4OH, 25 wt%) and 1 mL of 0.01 mol/L CTAB solution were added and stirred for more than 1 hour. Subsequently, 0.05 g of resorcinol was added and continually stirred for 30 mins. The 0.07 mL of formaldehyde solution was then added to the reaction solution and stirred for 24 h at 30 °C, and subsequently heated for 24 h at 100 °C under a static condition in a Teflon-lined autoclave. The silica@RF spheres were separated by centrifugation and washed three times with water.

7.2.3 Synthesis of hollow carbon nanospheres

The as-made silica@RF was heated at 5 °C /min from room temperature to 350 °C and held at this temperature for 1 h under a nitrogen flow. The temperature was then ramped at 5 °C /min to 600 °C and held at this temperature for 2 h. The pyrolyzed product was treated with aqueous 10% HF for 24 h to remove silica, thus generating HCCNs.

7.2.4 Enrichment tests

The as-prepared HCCNs show promising potential in the application of matrix-free LDI-MS detection of peptides. In a typical experiment, the carbon nanospheres were dispersed in ethanol at a concentration of 10 mg/mL and 1 μL of the slurry was deposited on the plain steel plate. After drying under ambient condition, 0.2 μL of diluted molecule solutions (N-[1-(2,3-dioleoyloxy)-propyl]-N,N,N-trimethylammonium methyl chloride, DOTAP) were added on the nanospheres followed by MS analysis. For MS analysis, the samples were directly analysed on a Bruker Autoflex TOF/TOF III Smart beam. All mass spectra were obtained in the RP-HPC-Proteomics mode via an accumulation of 500 laser shots at 10 different sites under a laser intensity of 36% for data collection. Two standard peptides, Angiotensin II (M.W. 1046.5) and ACTH-Clip (M.W. 2465.7), were used for calibration to reduce variability.

7.2.5 Characterization

Transmission electron microscopy (TEM) measurements were conducted on a JEM-2100 F microscope (JEOL, Japan) operated at 200 kV. The samples for TEM measurement were suspended in ethanol and supported onto holey carbon film on a Cu grid. Scanning electron microscopy (SEM) was taken with a JEOL-6400 electron microscopy operating at 8 kV. The surface area of the hollow carbon spheres was measured with the Brunauer−Emmett−Teller (BET) method using nitrogen adsorption and desorption isotherms through a Micrometrics ASAP 2020 system.

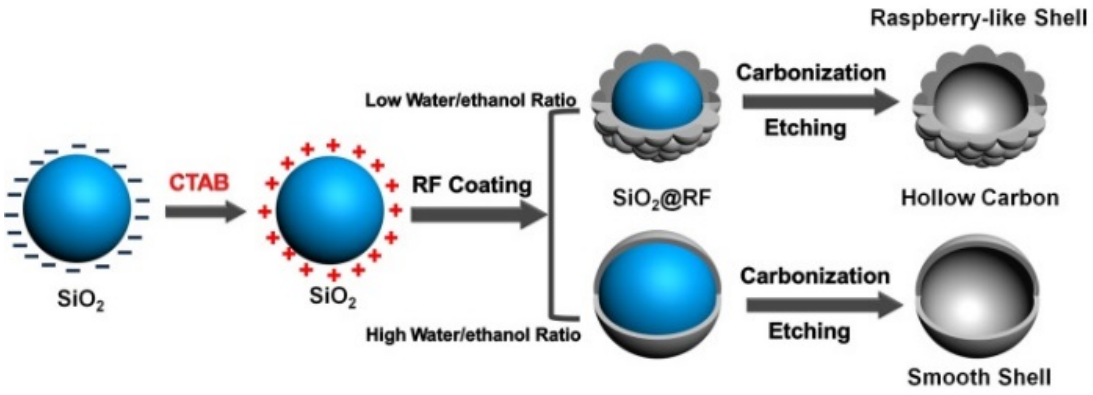

Figure 7.1 Schematic illustration of the synthesis process for hollow carbon spheres with different surface properties.

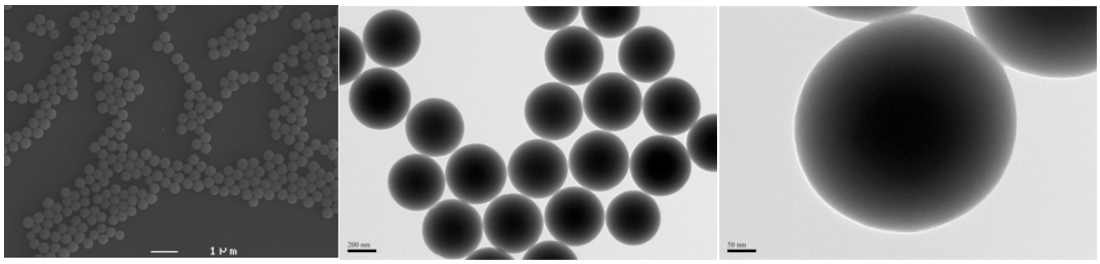

Figure 7.2 Typical large-scale SEM image and TEM images of silica nanospheres with an average size ~360 nm.

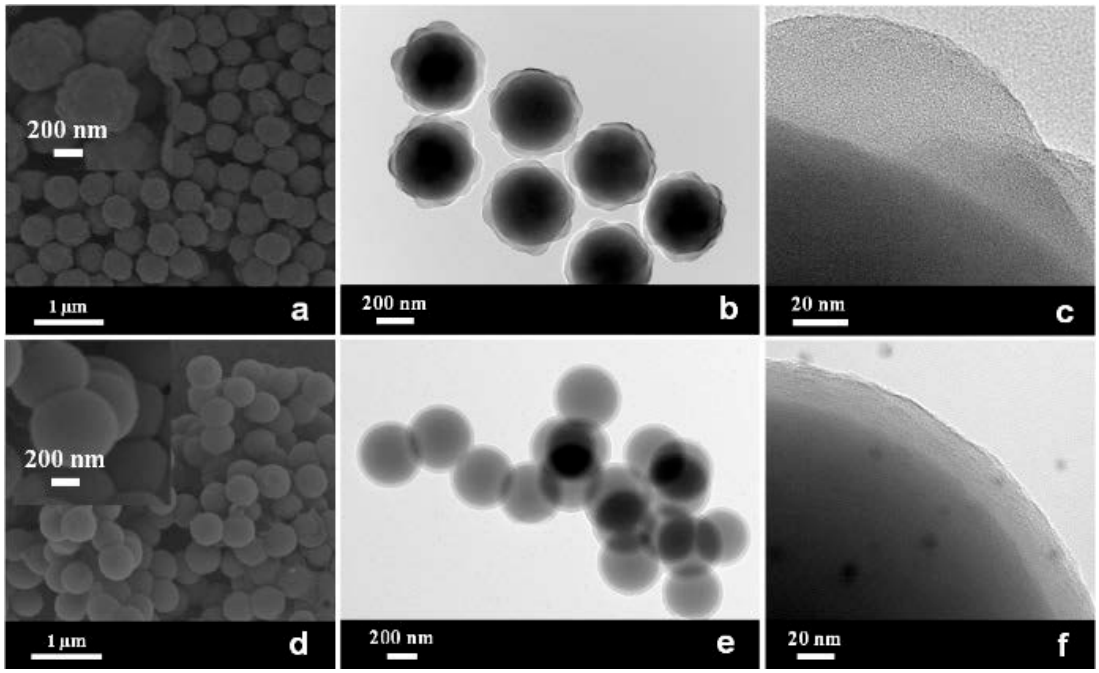

Figure 7.3 a,d. SEM images; b,e. TEM images and c,f. HRTEM images of the silica@RF resin core-shell nanospheres with rough (a-c) and smooth (d-f) surface prepared by tuning the ratio of water/ethanol.

7.3 The synthesis of raspberry-like hollow carbon spheres

The preparation process has been schematically illustrated in Figure 7.1. First, negatively charged silica spheres with uniform size of ~ 360 nm were synthesized through the well known Stöber method (Fig. 7.2). Cetyltrimethylammonium bromide (CTAB) was employed for alternating the surface charge of silica spheres to positive for efficiently coating of the negatively charged RF onto silica surface through an electrostatic attractive force in the mixture of water and ethanol. The surface properties

can be well controlled by tuning the water/ethanol ratio (R), a critical factor to ensure the homogeneous nucleation and surface uniform coating. After polymerization of resorcinol and formaldehyde catalysed by ammonium hydroxide on the outside of silica spheres, uniformly monodispersed core–shell silica@RF spheres with rough or smooth surface can be controllably prepared by varying the ethanol/water ratio. Finally, HCCNs with either rough or smooth surface are obtained after the pyrolysis of the silica@RF and subsequent elimination of the silica core by 10% HF as illustrated in Figure 7.1.

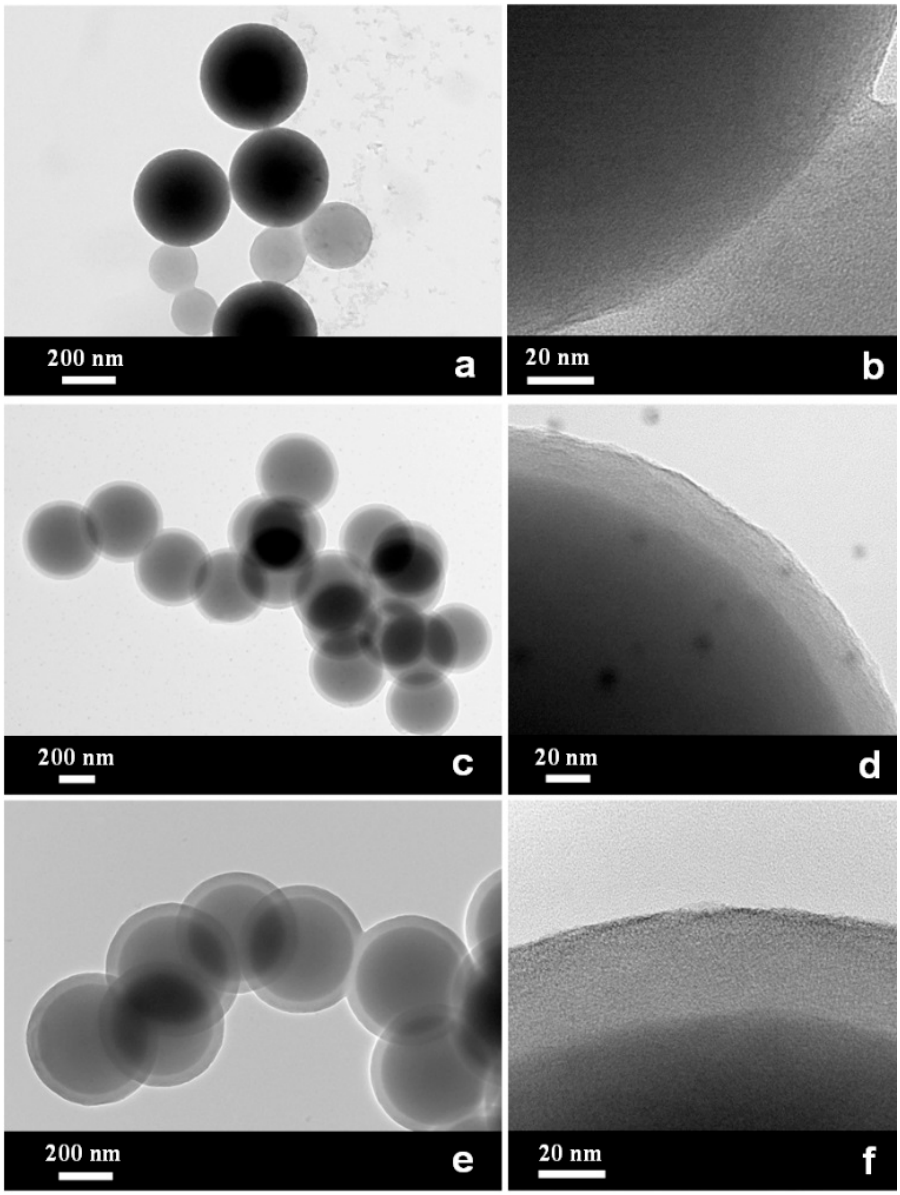

Figure 7.4 The effect of CTAB treatment to RF resin coating on the surface of silica. (a-b) no CTAB added; (c-d) 1 mL of CTAB added; and (e-f) 5 mL of CTAB added.

Figure 7.3 presents typical SEM and TEM images of the obtained core–shell structured silica@RF spheres. The silica@RF nanospheres prepared with R at 0.75 are highly monodisperse and spherical, with an average diameter of 470 nm and the surface is rough with raspberry-like morphology (Figs. 7.3a and 7.3b). The silica@RF composite particles possess a typical core–shell structure with a deep silica core and a light contrast of RF shell. The thickness of the raspberry-like shell is estimated to be about 20 nm for the concave surface and about 46 nm for the convex surface (Fig. 7.3c). The silica@RF spheres with smooth surface can be synthesized with R at 1.33 (Figs. 7.3d-f). The particle size is about 430 nm with shell thickness of 20 nm. The TEM image of silica@RF shows no free RF polymer nanospheres (Figs. 7.3b and e). CTAB plays a critical role to ensure the successful coating of RF resins on silica spheres for the formation of both smooth surface and rough surface.

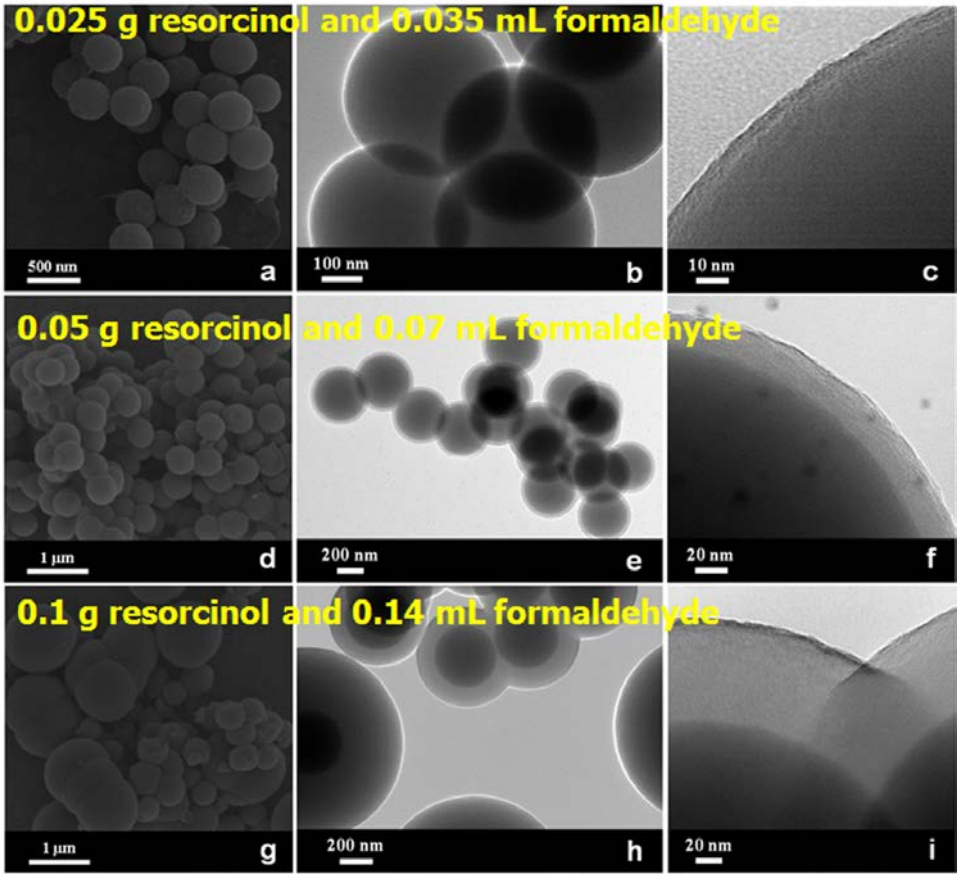

Figure 7.5 Shell thickness control by tuning the concentration of precursors. (a-c) shell thickness around 6 nm; (d-f) shell thickness around 20 nm; (g-i) shell thickness around 75 nm.

As shown in Figures 7.4a-c, without the addition of CTAB, only free RF resin particles can be observed. With increased concentration of CTAB, the RF resin shell is transferring to a more porous structure but the thickness of the shell has not been altered. Interestingly, we found that the thickness of the smooth shells of silica@RF increases gradually from 6 to 75 nm with increasing concentration of precursors (Fig. 7.5). This result indicates that the resultant HCCNs shell thickness can be easily adjusted by altering the concentration of precursor.

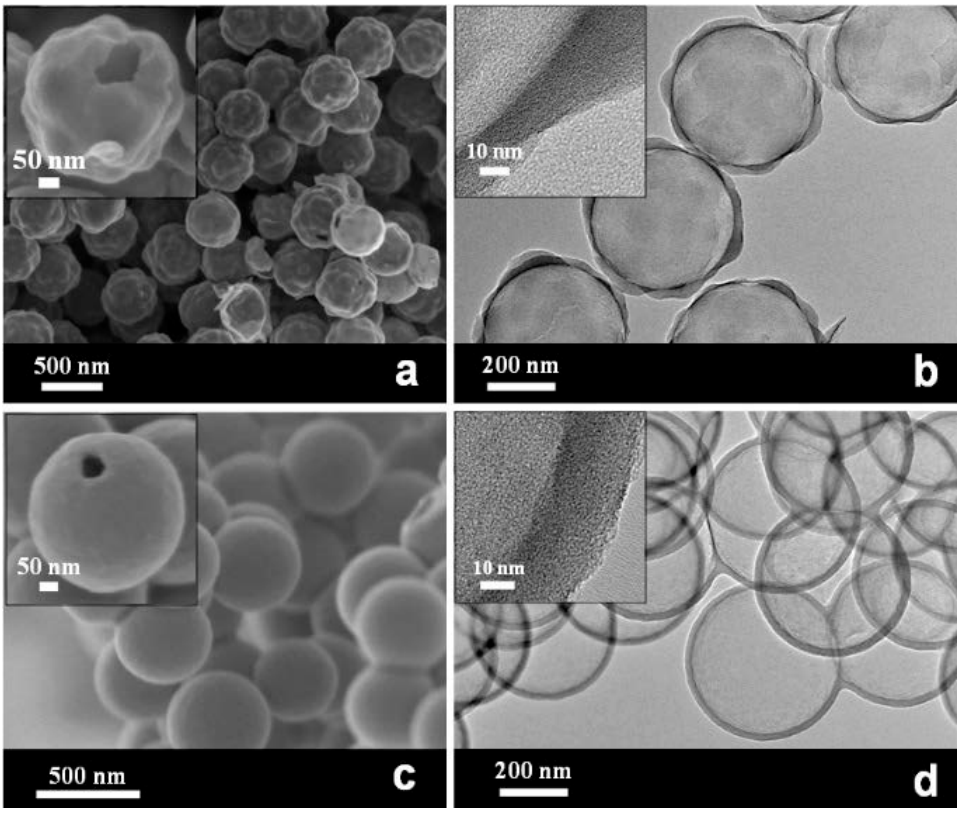

Figure 7.6 SEM (a, c), and TEM images (b, d) of hollow colloidal carbon nanostructures with either rough (a, b) or smooth surface.

A remarkable feature of the resorcinol-formaldehyde (RF) polymer is the high conversion yield to carbon (up to 62 wt%).[7, 9, 25, 32] Therefore, the as-obtained silica@RF core-shell nanostructures can be easily transformed to silica@C core-shell nanostructures after the carbonization process, which was completed by heat-treatment under N_2 atmosphere at 350 and 600 °C for 2 and 4 h, respectively. To obtain the hollow colloidal carbon nanostructure, silica was finally removed in a diluted HF solution. Interestingly, the raspberry-like rough surface of the HCCNs was well

maintained. As shown in Figures 7.6a and 7.6b, the final product is in a hollow structure with a raspberry-like rough surface. During the carbonization process, the shell thickness shrunk. The thickness of the raspberry-like shell is estimated to be about 20-25 nm for the concave surface (originally around 30 nm) and about 40-45 nm for the convex surface (originally around 50 nm). Accordingly, the smooth surface has also been well maintained, as evidenced by Figures 7.6c and 7.6d. Although some broken pieces could be detected after treatment with HF solution, the overall shape was well maintained in both raspberry-like and smooth HCCNs, implying the robust nature of the as-prepared structures. As shown in Figure 7.7, the nitrogen adsorption-desorption isotherms of both raspberry-like and smooth HCCNs are type I indicating their microporous structure. The measured surface areas of raspberry-like and smooth HCCNs are 456.62, and 387.71 m^2/g, respectively.

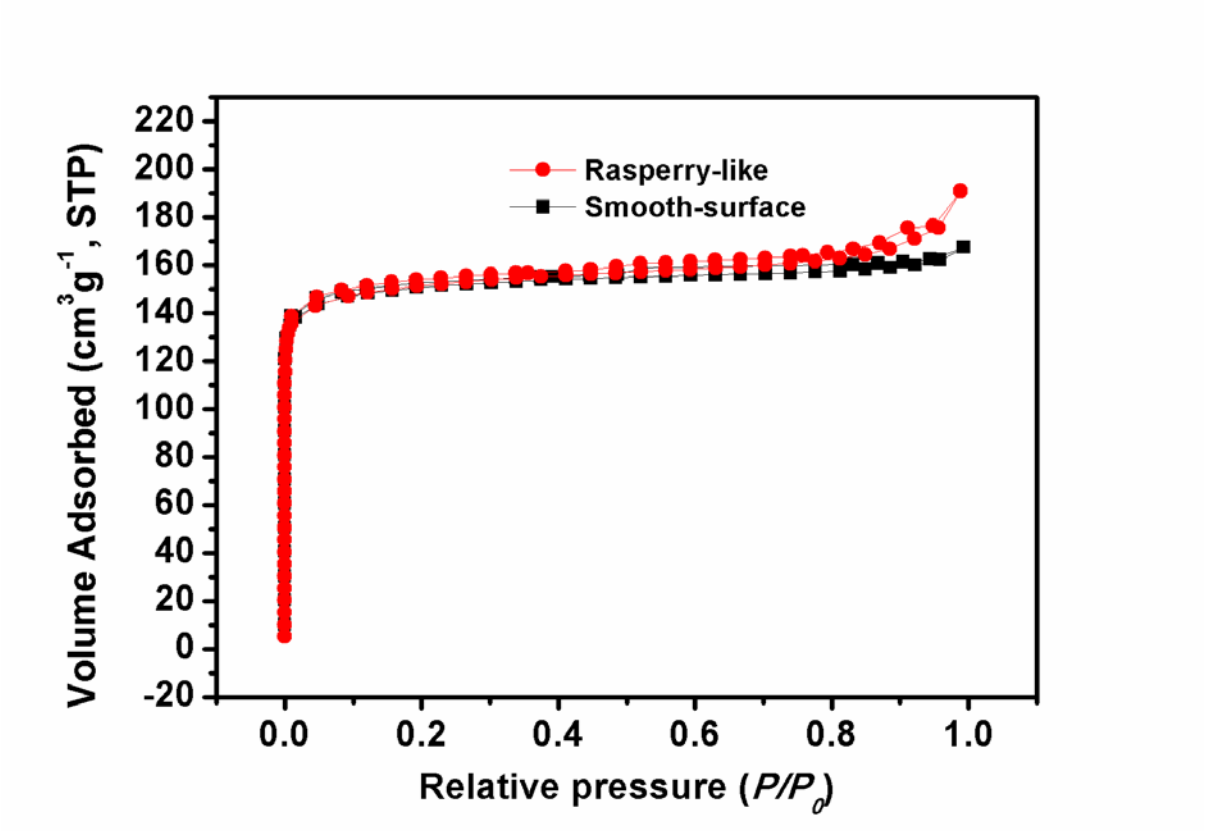

Figure 7.7 Nitrogen adsorption/desorption isotherms of the raspberry-like and smooth HCCNs.

7.4 Formation mechanism

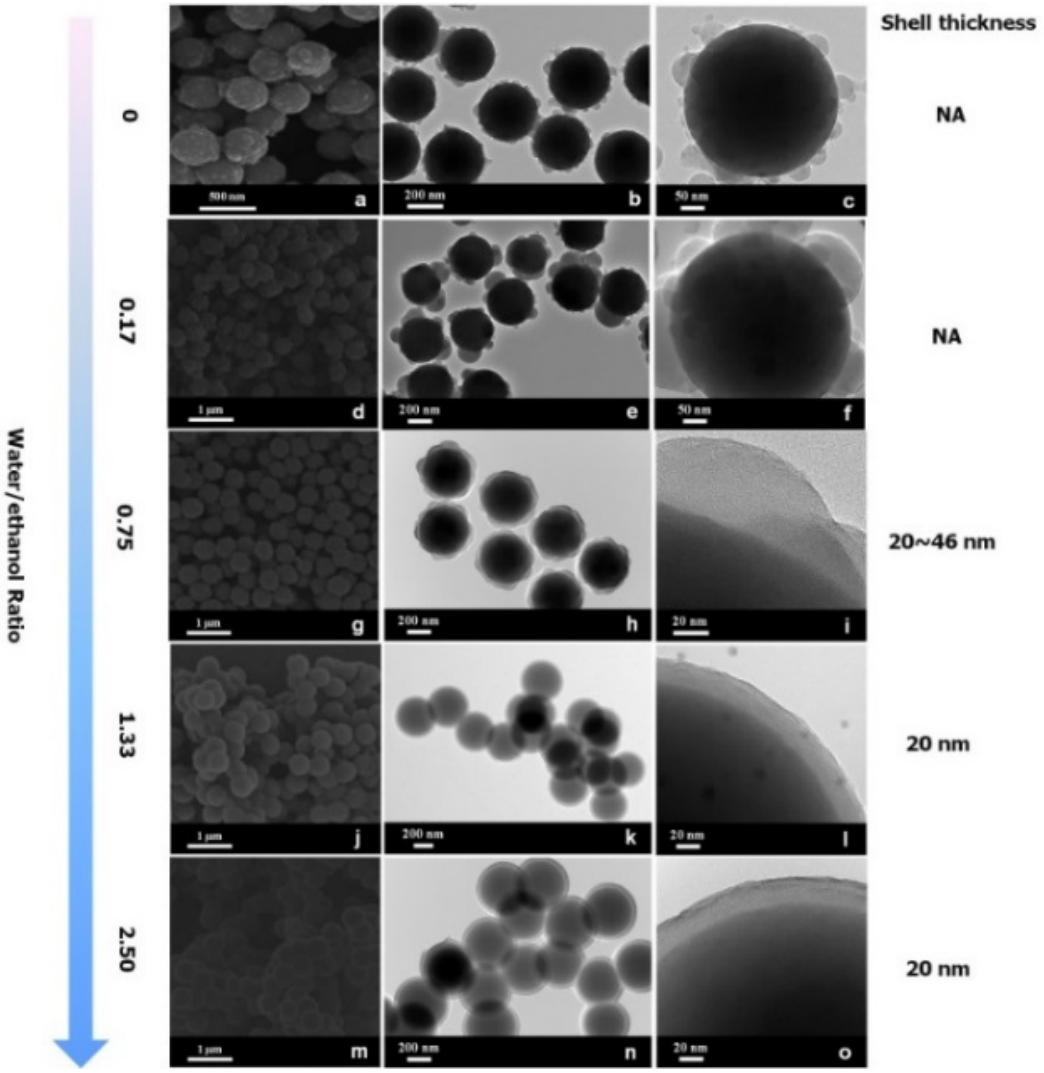

Figure 7.8 SEM and TEM images of the silica@RF resins composites obtained with different water/ethanol volume ratio: Water/ethanol volume ratio=(a, b, c) 0:28; (d, e, f) 1:6; (g, h, i) 3:4; (j, k, l) 4:3;and (m, n, o) 5:2.

To investigate the formation mechanism of a RF resin coating on silica surface with different morphologies, a series of experiments has been conducted. We found that the ratio of water/ethanol (R) is a critical factor in determining the final morphology of RF resins. As shown in Figures 7.8a-c, when the reaction was performed in a pure ethanol system, silica-RF anisotropic particles with patchy and Janus architectures can be obtained, in which the surface is partially coated with some RF islands. When the water/ethanol ratio was gradually increased from zero to 0.17, although a fully dense

coating on the surface was not achieved, the silica surface was deposited with larger patchy RF particles (Fig. 7.8d-7.8f). When the water/ethanol ratio was further increased to 0.75, a raspberry-like rough RF coating on the silica surface was observed (Figs. 7.3a, b and 7.8g-i). From both SEM and TEM characterizations, the as-prepared silica@RF is very uniform. Based on the high-resolution TEM observation, the shell thickness is around 20 nm (concave part) to 46 nm (convex part). A smooth RF coating on silica surface could be obtained when the water/ethanol ratio is increased to 1.33, and the shell thickness is around 20 nm (Figs. 7.8j-7.8l). Further increasing the water/ethanol ratio to 2.50 does not impact the shell roughness or the shell thickness, as inspected from Figures 7.4m-7.4o, which is different from the previous report that the particle size is gradually decreased with increasing of R.

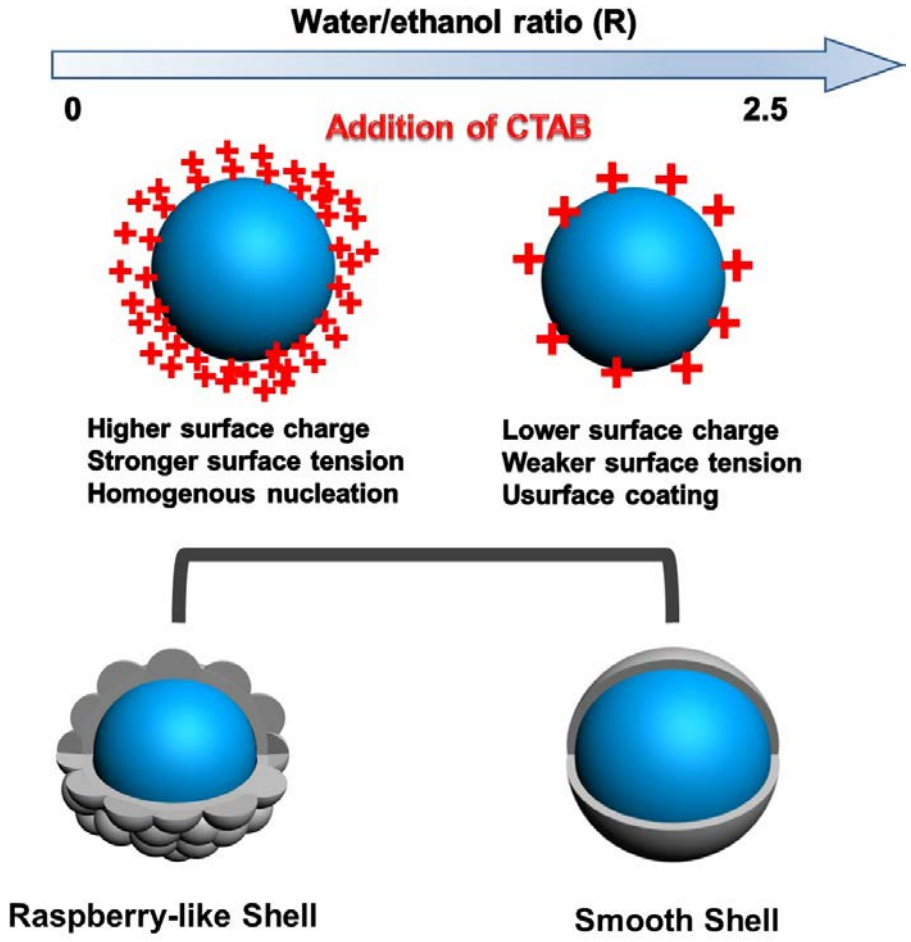

Figure 7.9 Proposed formation mechanism of RF coating process in mixture solution of water and ethanol with different ratios.

The different surface properties of the as-prepared silica@RF composite might be ascribed to the compatibility between the CTAB-modified silica surface and the solvent. After treatment with CTAB solution, the silica surface with negative charge was transferred to positive charge due to the adsorption of CTAB micelles. The optimized energies of CTAB tail in ethanol and water are -170.736 kJ/mol and -73.297 kJ/mol, respectively, which indicates the solubility of CTAB in ethanol is higher than that in water, and the surface tension is higher.[33,34] As suggested previously,[32] ammonia can supply the positive charges (NH_4^+) out of RF polymer spheres surface to prevent the aggregation. Therefore, a higher ethanol content in the solution would inspire a higher CTAB solubility and a stronger surface tension and the system would provide more positive charges, resulting in the partial coating of RF resin on the surface with the formation of the isolated RF particles. On the contrary, with the addition of more water inside the solvent system, positive charge concentration will be diluted, leading to the formation of fumed RF resins shell. As a result, the morphology of the final product would be evolved gradually from a partial coating with RF resins particle islands, to raspberry-like rough surface, and eventually to a smooth surface as proposed in Figure 7.9. A competitive process between homogenous nucleation and uniform surface coating is proposed as the formation mechanism for raspberry-like morphology. The strategy reported here also provides a facile way to design and synthesize the Janus architectures.

7.5 Biomedical applications

As ideal candidates for matrix-free laser desorption/ionization mass spectrometry (LDI-MS) analysis, carbon composites can eliminate background signals at low molecular range without the use of extra organic matrices thus providing better detection efficacy towards small bio-molecules (molecular weight < 1000 Da).[35-38] In order to investigate the performance of the prepared carbon nanospheres as substrates for LDI-MS analysis of small hydrophobic bio-molecules, a standard lipid molecule, DOTAP was employed (more details can be referred in the experimental section). As shown in Figure 7.10a, the fine-resolved ion peak of DOTAP (signal strength over 10,000) can be observed at the m/z of 662 ($[C_{42}H_{80}NO_4]^+$) consuming 30 fmol of lipids only by the use of carbon nanospheres with rough surface as LDI substrates. By comparison, the signal strength of DOTAP is less than 4000 using the

carbon nanospheres with smooth surface (Fig. 7.10b), while no signals could be detected from DOTAP in control on the plain steel substrates (Fig. 7.10c). The above desorption/ionization performance of the carbon nanospheres with rough surface is superior to previously reported graphene/silica nanocomposites[35] and comparable to the best current results.[36] The merits of the rough carbon nanospheres are dependent on the enhanced surface roughness to capture the lipid molecule (comparing favourably to the smooth surface), nano-scaled particle size (470 nm) and high surface hydrophobicity in the scale of fmol), these carbon nanospheres are anticipated to be promising alternatives for advanced MS detection/ imaging in bio-medical and forensic applications.

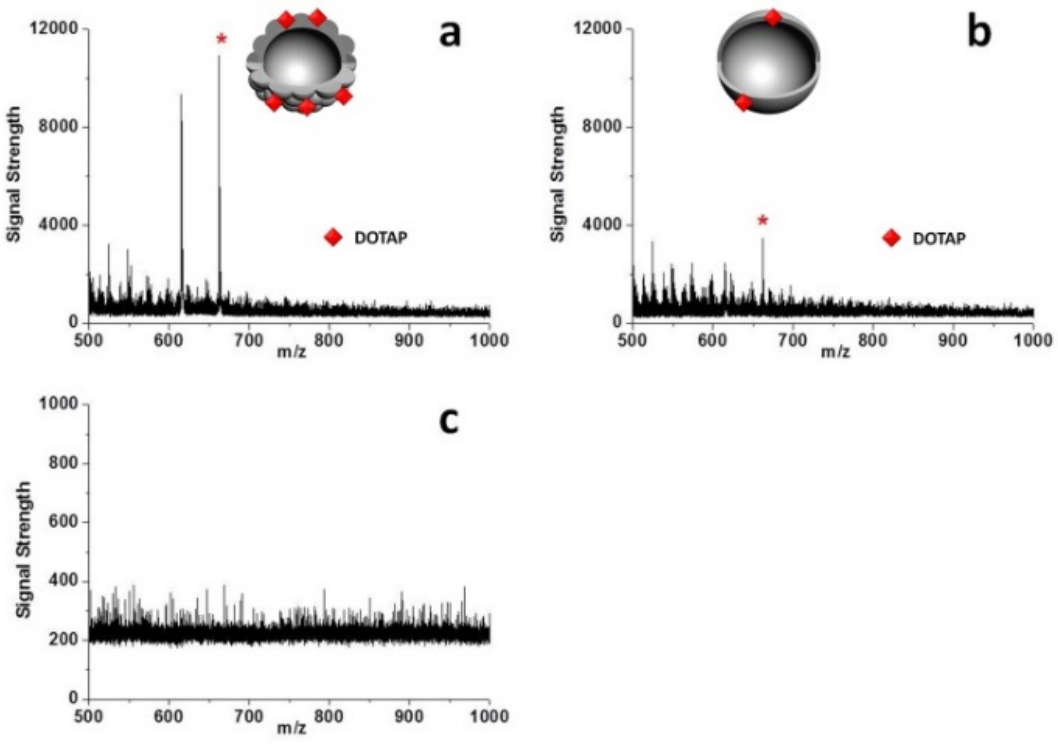

Figure 7.10 Laser desorption/ionization mass spectrometry (LDI-MS) analysis by using different materials as the matrix: (a) raspberry-like HCCNs; (b) smooth HCCNs; and (c) without carbon nanospheres.

7.6 Conclusions

In conclusion, for the first time, we have successfully prepared hollow colloidal carbon nanostructures with raspberry-like morphology. This facile method is highly reproducible and straightforward to synthesise uniform hollow colloidal carbon

nanostructures with controllable surface properties and Janus particles. The water/ethanol ratio of the solvent is a critical factor in determining the different surface properties. After a thorough systematic investigation, we found the formation of different morphologies of silica@RF is due to the solubility difference of CTAB in different solvents, i.e., a lower solubility of CTAB in ethanol induced the formation of discrete RF resins. The roles playing by ammonia and CTAB for polymerizations in such synthetic system need further investigation. With the high carbon yield from the carbonization of RF resin, the as-prepared silica@RF can be transformed to a hollow carbon nanostructure with well-maintained morphology. Furthermore, the as-prepared raspberry-like HCCNs display superior performance to smooth HCCNs in the LDI-MS detection of peptides, which has been ascribed to the different surface properties to capture the peptide molecule. However, the scaling up of current synthetic method is still a challenge due to the uncertainties brought in by the employed multi-step hard template processes. Future endeavour can be focusing on the development of a facile one step method for the synthesis of carbon nanomaterials with raspberry-like morphology. We believe that these carbon nanostructures could find their niche and contribute an added dimension in many possible application fields including sensors, capacitors, and catalysis.

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Chapter 8. Conclusions and perspectives

8.1 Conclusions

Multicomponent nanocomposites with tunable composition, structure, pore size, easy functionalization, possess many advantages for nanotheranostics applications. Although the design of multicomponent nanoparticles is still at its infancy, the formulation of multicomponent nanocomposite particles is particularly interesting and a crucial step for their administration. This thesis has been devoted to the development of the green and facile methods for the construction of multicomponent nanocomposites. Multicomponent nanocomposites with various compositions such as mesoporous silicas encapsulated Fe_3O_4 nanoparticles, Ag nanoparticles, silica and carbon spheres have been successfully prepared. In addition, porous silicas and carbons with hollow and raspberry-like spheres morphologies have been produced. Moreover, mild and green synthesis methods have been developed to fabricate silicas and silver nanoparticles. The developed multicomponent nanocomposites demonstrate a broad potential application in nanotherapeutics, for example, cellular drug/gene delivery, matrix free peptide detection and anti-bacterial. The major conclusions of this thesis can be summarised as following:

8.1.1 Magnetic Fe_3O_4 and mesoporous silica core-shell nanospheres with tunable size and large void pore for cellular uptake

- Multicomponent magnetic mesoporous silica core-shell nanospheres with large void pores and tunable particle sizes have been successfully synthesized by an extension of the Stöber process. The particle size can be tuned from 110 nm to 800 nm by tailoring the ethanol to water volume ratio, while the large void pore on shell can be regulated from 8.0 to 20 nm by increasing the amount of ethanol.

- The magnetic mesoporous silica core-shell nanospheres can be easily surface modified with an ammonia group; and the NH_2-functionalized magnetic mesoporous silica nanospheres can be efficiently internalized into HeLa cell lines, which is potentially important for siRNA efficacy against cancer cells.

- The resultant multicomponent magnetic mesoporous silica core-shell nanospheres would provide an application paradigm of magnetic mesoporous silica nanoparticles for cell labelling and drug delivery.

8.1.2 Inorganic-salts assisted self-assembly of Pluronic F127-organosilica into ordered mesostructures

- A mild synthesis method has been developed for PMOs with hexagonal, body-center cubic and face-center cubic mesostructures. Sodium bicarbonate ($NaHCO_3$)/sodium carbonate (Na_2CO_3) buffer solution (pH$\approx$9.9) provide a mild synthetic medium to slow down the formation process.

- The influences of cationic metals of inorganic salts on the mesostructure of PMO materials have been systematically investigated. It has been found that ordered body-center cubic mesotructured PMOs can be obtained by the assistance of $MgSO_4$, $NiSO_4$ and $ZnSO_4$. The interaction between F127 micelles and organosilicas has been enhanced by the inorganic sulfates.

- The formation mechanism of mesoporous organosilicas has been explored and clarified on the basis of the micelles-organosilicates closed packing. Overcoming the problems encountered by the conventional method with fast hydrolysis and condensation process of organosilane, our synthetic strategy can be more facilely applied to investigate, monitor, and understand the formation process of mesoporous materials.

8.1.3 Less is more, greener microbial synthesis of silver nanoparticles

- A green microbial synthesis method has been developed for silver nanoparticles (AgNPs). It is found that AgNPs could be synthesized in several types of microorganism culture broth without any specific living microbe involvement.

- Light and high pH values of broth were identified as two critical factors in ensuring pure AgNPs formation. In broths containing NaCl at high

concentration (0.5 wt%), silver chloride was identified as the major intermediate and could be converted to AgNPs via one-pot photoreduction.

- Our broth alone strategy dramatically simplifies the conventional microbial nano-synthesis process by cutting the use of microorganisms and thus provides a more eco-friendly way for nano-Ag preparation. The fundamental understanding of the microbial synthesis mechanisms and implementing of complete green methods to fabricate technologically important nanomaterials will be further promoted by this study.

8.1.4 One-pot synthesis of raspberry-like mesoporous silica nanospheres

- This study developed a facile one-pot strategy to successfully prepare raspberry like mesoporous silicas with particle size of 360 nm through an extension of the Stöber process. By precisely controlling the synthesis parameters, either decreasing the CTAB concentration or increasing the TEOS amount, multi-compartment silicas with mesoporous silica spheres bridged with mesoporous silica rods can be fabricated.

- We identify that by the control over the concentration of cationic surfactant and silica precursor can be used to manipulate the multiple morphological evolutions of mesoporous silica nanoparticles. It is found that the particle size of mesoporous silica can be tuned from 100 to 600 nm by varying the water to ethanol ratio.

- Our strategy allows an easy way to generate the hierarchical nanostructured silicas by mimicking the structures of diatom cells for the potential application in catalysis and nanomedicine. Further studies are currently in progress in order to study their applications in gene therapy and anti-aging.

8.1.5 Raspberry-like hollow carbon nanospheres with enhanced matrix-free peptide detection profiles

- For the first time, resorcinol formaldehyde (RF) polymer resins have been successfully coated on the silica spheres by the extension of Stöber method, to generate raspberry-like silica@RF core-shell particles with a rough surface. After carbonization of the shell and removal of silica, uniform raspberry-like hollow carbon spheres were obtained.

- A competitive process between homogenous nucleation and uniform surface coating is proposed as the mechanism for formation of the raspberry-like morphology. By finely controlling the water/ethanol ratio, a series of hollow carbon spheres with different surface properties and patchy structures can be synthesized with this method.

- The raspberry-like hollow carbon spheres demonstrate much better performance than hollow carbon spheres with a smooth surface in matrix-free peptide detection due to their high capability to capture the small peptide molecule.

In summary, multicomponent nanocomposites particles with various compositions, surface properties and morphologies have been successfully prepared in this thesis. More greener and mild synthesis strategies have been developed. The resultant multicomponent nanocomposites have tunable composition, structure, pore size, functionality, demonstrate high biomolecular loading amount, increased cellular uptake performance and high biocompatibility. The biomedical applications of these multicomponent nanocomposites particles in siRNA delivery, gene therapy, anti-bacteria and matrix-free peptide detection suggests the possibility to establish multicomponent nanocomposites platform for nanotheranostics.

8.2 Perspectives and suggestions for future research

The field of nanotheranostics, which is still in the early stages of its development, stands to benefit society greatly with the implementation of nanotechnology. We began

humbly by the design and development of multicomponent nanocomposites and their green and mild synthesis approaches. We have also shown that these multicomponent nanocomposites have potential applications in biomedical diagnosis and therapy. Although some progress has been achieved in the development of multicomponent nanocomposites for biomedical applications in this thesis. There are opportunities to extend the synthesis approaches to develop more complex multicomponent nanocomposites; and to exploit the multicomponent nanocomposites developed in this thesis for other biomedical applications, as exampled below.

1. New facile, economic mild strategies for the synthesis of multicomponent nanocomposites should be further explored for their large-scale production. Therefore, it is of great importance to design multicomponent nanocomposites for large-scale production and with a controlled structure and stable surface chemistry.
2. In future studies, by combination of computational simulation and theoretical modelling, combinatorial chemistry and high throughput screening experimental methods, the synthesis of multicomponent nanocomposites can be designed with precise located functionality.
3. Development of more precise in-situ techniques (in-situ Raman, in-situ FTIR, in-situ TEM) or even a combination of these techniques, for the deep understanding of the formation mechanism of multicomponent nanocomposites.
4. More insights in understanding the effects of particle size, shape, porous structure and surface chemistry on the deposition, uptake, translocation, and toxicity of nanoparticles can be developed.
5. Using inorganic nanocarriers as building blocks, integrating therapeutic agents (anticancer drugs, DNA, small interfering RNA [siRNA], proteins, hyperthermia-inducing nanoparticles, ROS-generatingagents, etc.) and imaging agents (e.g., organic dyes, quantum dots [QDs], upconversion particles [UCNPs], MRI contrast agents, CT contrast agents, etc.) to generate multifunctional nanocomposites systems while maintaining their individual functional characteristics. These multifunctional nanocomposites are expected

to endow advanced properties such as long circulation time, controlled release, drug and gene co-delivery, and eventually should be able to simultaneously realize diagnosis and therapeutics as a theranostic agent.

6. It should also be pointed out that the current experiments in this study are performed at a laboratorial scale. If the above issues are satisfactorily addressed in the future, clinical translations of multicomponent nanocomposites as a new platform for medical doctors for simultaneous diagnosis and the efficient and specific treatment of diseases.

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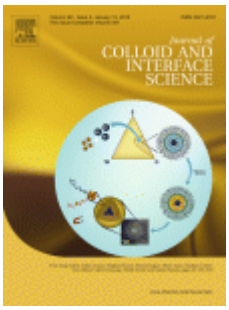

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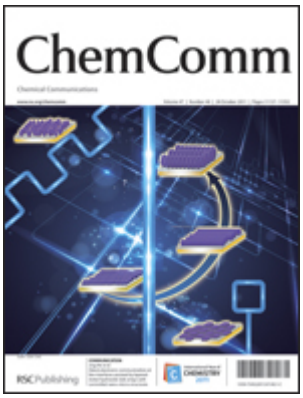

Title: Raspberry-like hollow carbon nanospheres with enhanced matrix-free peptide detection profiles

Author: Tingting Liu,Lili Qu,Kun Qian,Jian Liu,Qiao Zhang,Lihong Liu,Shaomin Liu

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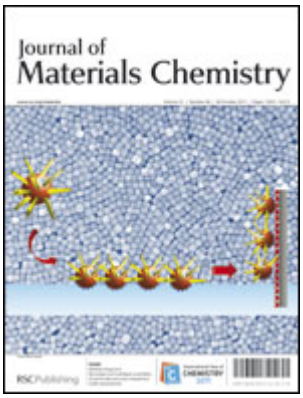

Title: Synthesis of nanorattles with layered double hydroxide core and mesoporous silica shell as delivery vehicles

Author: Jian Liu,Ryan Harrison,Ji Zhi Zhou,Ting Ting Liu,Chengzhong Yu,Gao Qing (Max) Lu,Shi Zhang Qiao,Zhi Ping Xu

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Publisher: American Chemical Society

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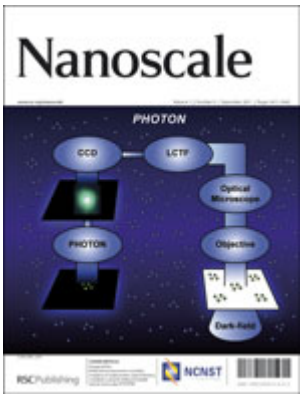

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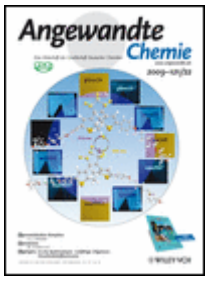

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Author: Jaeyun Kim,Hoe Suk Kim,Nohyun Lee,Taeho Kim,Hyoungsu Kim,Taekyung Yu,In Chan Song,Woo Kyung Moon,Taeghwan Hyeon

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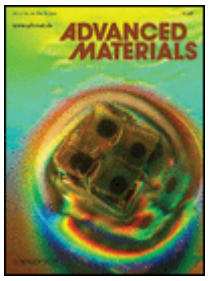

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Author: Dechao Niu,Zuojin Liu,Yongsheng Li,Xiaofeng Luo,Junyong Zhang,Jianping Gong,Jianlin Shi

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Date: Mar 1, 2009

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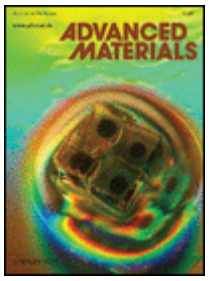

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Date: May 1, 2015

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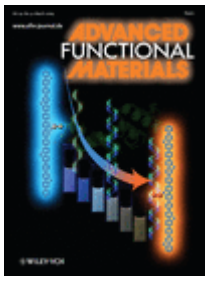

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Author: Xiao Zhang,Piaoping Yang,Yunlu Dai,Ping'an Ma,Xuejiao Li,Ziyong Cheng,Zhiyao Hou,Xiaojiao Kang,Chunxia Li,Jun Lin

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Author: Yung-Kang Peng, Chih-Wei Lai, Chien-Liang Liu, et al

Publication: ACS Nano

Publisher: American Chemical Society

Date: May 1, 2011

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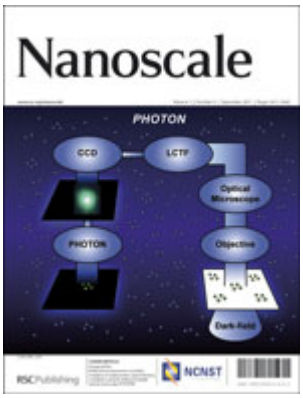

Title: Facile synthesis of an up-conversion luminescent and mesoporous Gd2O3:Er3+@nSiO2@mSiO2 nanocomposite as a drug carrier

Author: Zhenhe Xu,Chunxia Li,Ping'an Ma,Zhiyao Hou,Dongmei Yang,Xiaojiao Kang,Jun Lin

Publication: Nanoscale

Publisher: Royal Society of Chemistry

Date: Nov 22, 2010

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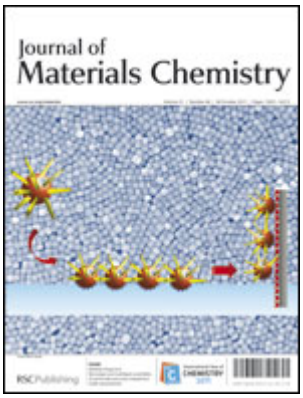

Title: Novel preparation and near-infrared photoluminescence of uniform core-shell silver sulfide nanoparticle@mesoporous silica nanospheres

Author: Lu Han,Yingying Lv,Abdullah M. Asiri,Abdulrahman O. Al-Youbi,Bo Tu,Dongyuan Zhao

Publication: Journal of Materials Chemistry

Publisher: Royal Society of Chemistry

Date: Mar 5, 2012

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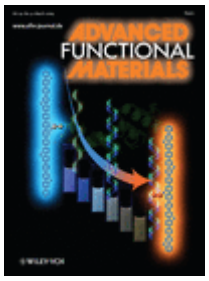

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Author:	Guosheng Song,Qian Wang,Yang Wang,Gang Lv,Chun Li,Rujia Zou,Zhigang Chen,Zongyi Qin,Keke Huo,Ronggui Hu,Junqing Hu
Publication:	Advanced Functional Materials
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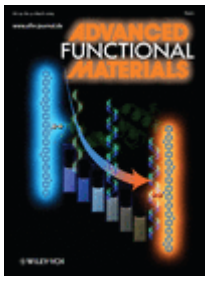

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Author: Guo-Feng Luo,Wei-Hai Chen,Qi Lei,Wen-Xiu Qiu,Yu-Xin Liu,Yin-Jia Cheng,Xian-Zheng Zhang

Publication: Advanced Functional Materials

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Author: Dechao Niu, Xiaofeng Luo, Yongsheng Li, et al

Publication: Applied Materials

Publisher: American Chemical Society

Date: Oct 1, 2013

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Author:	Jian Liu,Shi Zhang Qiao,Sandy Budi Hartono,Gao Qing (Max) Lu
Publication:	Angewandte Chemie International Edition
Publisher:	John Wiley and Sons
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Author: Yan Yang,Xiao Liu,Xiaobo Li,Jiao Zhao,Shiyang Bai,Jian Liu,Qihua Yang

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Author: Dan Yang, Guixin Yang, Shili Gai, et al

Publication: ACS Biomaterials Science & Engineering

Publisher: American Chemical Society

Date: Nov 1, 2016

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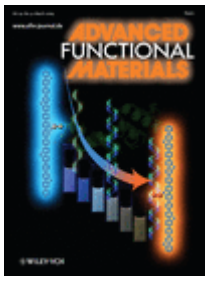

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Author: Lingzhi Zhao,Juanjuan Peng,Qi Huang,Chunyan Li,Min Chen,Yun Sun,Qiuning Lin,Linyong Zhu,Fuyou Li

Publication: Advanced Functional Materials

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Author: Ruichan Lv, Piaoping Yang, Fei He, et al

Publication: ACS Nano

Publisher: American Chemical Society

Date: Feb 1, 2015

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Title: Anisotropic Growth-Induced Synthesis of Dual-Compartment Janus Mesoporous Silica Nanoparticles for Bimodal Triggered Drugs Delivery

Author: Xiaomin Li, Lei Zhou, Yong Wei, et al

Publication: Journal of the American Chemical Society

Publisher: American Chemical Society

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Title: Mesoporous Silica Hollow Spheres with Ordered Radial Mesochannels by a Spontaneous Self-Transformation Approach

Author: Zhaogang Teng, Xiaodan Su, Yuanyi Zheng, et al

Publication: Chemistry of Materials

Publisher: American Chemical Society

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Title: General Route to Multifunctional Uniform Yolk/Mesoporous Silica Shell Nanocapsules: A Platform for Simultaneous Cancer-Targeted Imaging and Magnetically Guided Drug Delivery

Author: Lingyu Zhang,Tingting Wang,Lei Yang,Cong Liu,Chungang Wang,Haiyan Liu,Y. Andrew Wang,Zhongmin Su

Publication: Chemistry - A European Journal

Publisher: John Wiley and Sons

Date: Aug 21, 2012

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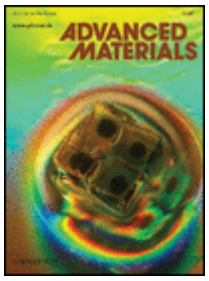

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Author: Linlin Li, Fangqiong Tang, Huiyu Liu, et al

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