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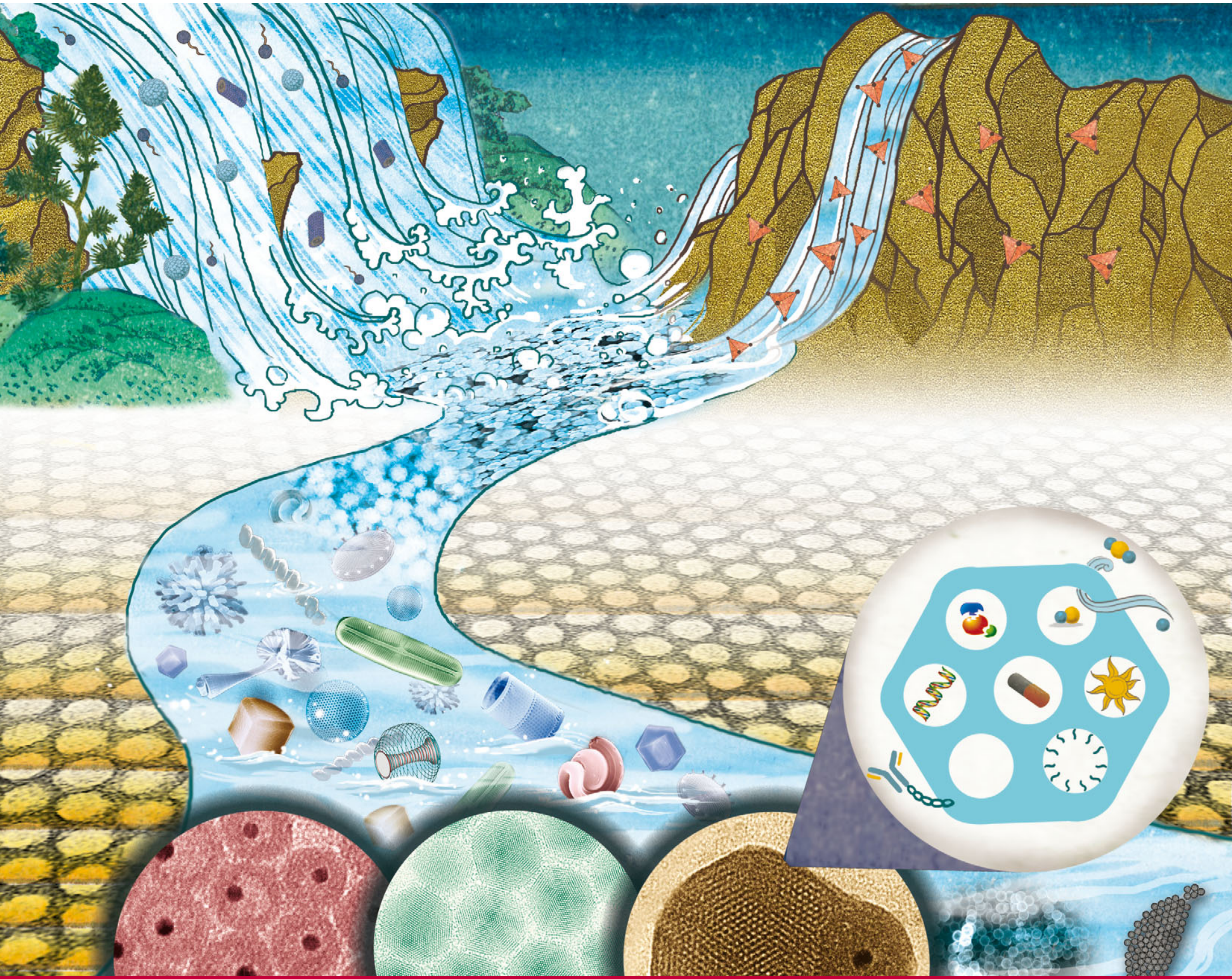

Themed issue: Mesoporous materials

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Synthesis of mesoporous silica nanoparticles†

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Good control of the morphology, particle size, uniformity and dispersity of mesoporous silica nanoparticles (MSNs) is of increasing importance to their use in catalyst, adsorption, polymer filler, optical devices, bio-imaging, drug delivery, and biomedical applications. This review discusses different synthesis methodologies to prepare well-dispersed MSNs and hollow silica nanoparticles (HSNs) with tunable dimensions ranging from a few to hundreds of nanometers of different mesostructures. The methods include fast self-assembly, soft and hard templating, a modified Stöber method, dissolving–reconstruction and modified aerogel approaches. In practical applications, the MSNs prepared by these methods demonstrate good potential for use in high-performance catalysis, antireflection coating, transparent polymer–MSNs nanocomposites, drug-release and theranostic systems.

1. Introduction

Since the discovery of mesoporous silicas synthesized using cationic surfactants as templates, the templating method has been widely applied to prepare mesoporous silicas with high surface areas, tunable pore sizes, large pore volumes and rich morphology.[1,2] Because of the existence of different liquid crystal mesophases and morphologies in the surfactant assemblies, surfactant-templated mesoporous silicas can be tailored to give various mesostructures (*e.g.* disordered, wormhole-like, hexagonal, cubic, and lamellar mesophases), morphologies (*e.g.* spheres, hollow spheres, fibers, tubules, gyroids, helical fibers, crystals and many hierarchical structures), and dimensions (nanometer to centimeter) by controlling the reaction conditions (such as reaction temperature, pH value, surfactants concentration, silica sources *etc.*).[3–5]

A large number of studies have focused on the interactions between surfactants and silica species in order to prepare specific mesoporous silicas. It is concluded that mesostructural surfactant–silica nanocomposites spontaneously assemble through interaction matching of the organic and inorganic components. In addition to thermodynamics of the surfactant–silica assembly,

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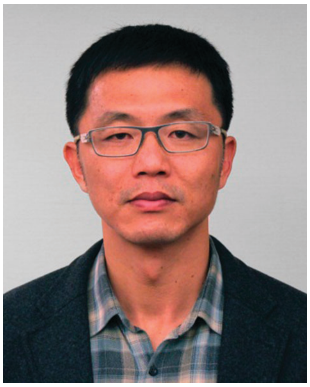
the morphologies and dimensions of the resulting materials are particularly dependent on the kinetics of sol–gel chemistry (such as the reaction temperature, water content, and pH value of the reaction solution). With a careful control of the self-assembly and silica condensation rate, it is possible to tailor the sizes, mesostructures and morphologies of the mesoporous silicas. Nano-sized mesoporous silicas, whose attributes include uniform mesopores, easy functionalization and significant biocompatibility, have gained much recent attention for their biomedical[6] and catalytic applications.[7]

Nano-sized mesoporous silicas were first successfully synthesized and reported by the groups of Cai,[8] Mann[9] and Ostafin.[10] Then the term MSN was popularized by Victor Lin to represent mesoporous silica nanospheres.[11] Over the past decade, MSNs with various morphologies, dimensions, pore sizes and pore structures have been synthesized and investigated systematically by many different groups. The synthesis of MSNs can be achieved by various adjustments of synthesis conditions, including the pH of the reaction mixture, the characteristics of surfactants or copolymers used, as well as the concentrations and the sources of silica. In this review, the principles of the various synthesis methods underpinning the formation of various MSNs will be introduced and explained. Taking advantage of rich silane chemistry, many multifunctional MSNs have been created and applied, and the MSN material is now one of the most widely studied nanomaterials in the field of nano-biomedicine.

In an ideal synthesis of MSNs, several good characteristics of the nanoparticle are desirable for versatile applications: well-suspended stable solution, controllable pore size, controllable uniform particle size and large pore volume. The solution-suspendability of MSNs is important for biomedical application as nano-carriers. In general, a well-suspended MSN solution allows it to be treated as a true solution in applying various solution spectroscopic techniques since light scattering can be largely reduced. Precise pore-size control may allow selective loading of biopolymers. Well-controlled particle size of the MSNs would allow good control in particle–cell interactions and precise quantitative dose in carrying cargos. The large pore volume, meaning thin silica wall, would allow better biodegradation. Furthermore, the unique topology provides MSNs with distinct domains (external and internal) that can be independently functionalized. These desirable properties demand a thorough understanding of the chemistry involved in the synthesis of MSN.



Hong-Ping Lin

Professor Hong-Ping Lin got his Bachelor and Master degrees in Chemistry from National Cheng Kung University, Tainan, Taiwan in 1991 and 1993. He obtained a PhD degree in Chemistry from National Taiwan University in 1997. He worked as a postdoctoral fellow in Institute of Atomic and Molecular Science and Institute of Chemistry, Academia Sinica, Taiwan for five years. Then he became an Assistant Professor at the Department of Chemistry in National Cheng Kung University. He was promoted to a full Professor in 2009. Professor Lin's research concerns the synthesis and applications of the mesoporous materials.

2. Control of reaction kinetics to prepare MSNs

Knowledge of nucleation and growth mechanisms is an important prerequisite for size control during synthesis of MSNs. Although for MSN systems the mechanism is not well-understood, it is appropriate we start from general principles for making uniform nanoparticles (metal or semiconductors). It is known that creating a burst of nuclei and subsequent growth can produce uniform nanoparticles.[12] It is desirable these two steps be completely separated because multiple nucleation events lead to a broadened size distribution. In addition to growth, aggregation of nanoparticles also affects the final size distribution. Methods for preventing aggregation are also important for maintaining a stable suspension of uniform MSNs.

Compared to metal or semiconductor nanoparticles, the building blocks of the mesostructured silica are complex, consisting of organic templates (such as surfactants) and silica species. Many experimental factors control the template–silica interactions, silica condensation rate, the assembly kinetics and thus the nucleation and growth rates. This then leads to a rich variety of synthetic methods for the construction of organized composites across a range of length scales and with complex morphologies of mesoporous silica. For MSNs, the many synthesis approaches are also somewhat perplexing.

Charge state and pH

The first important factor is the influence on the charges of silica species by the pH value of the synthesis solution. Both the rates of hydrolysis of silane and condensation of the siloxane bond depend strongly on the charge states. Hydrolysis of the Si–OR bond in silanes could be catalyzed by acid and base. Its rate is lowest near pH neutral conditions. The pH-dependence of charge density and silica condensation rate are shown in Fig. 1.[13] At pH below the isoelectric point (IEP = 2.0) of silica, the silica species are positively charged and the charge density increases as the pH decreases. When the pH is above silica's IEP, the silica species become negative, and the charge density of the negatively charged silica species (*i.e.*, silicates) increases along with the pH. At the same time (pH $\sim$ 2–7), the silicates with a negative charge density tend to assemble with the positively-charged surfactants or neutral polymers *via* electrostatic and hydrogen-bonding interactions. Under alkaline conditions (pH $>$ 7.0), silicates with a high negatively-charged density can only assemble with the cationic surfactants through strong electrostatic interaction.[14]

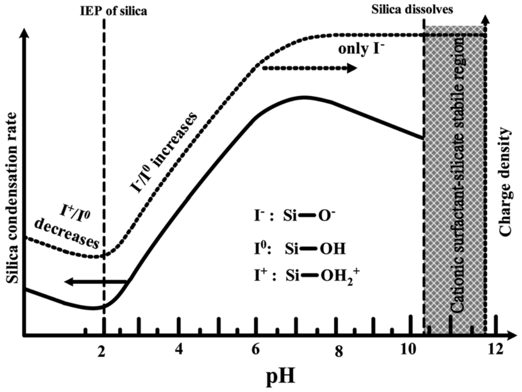


Fig. 1 Effects of pH value on the silica condensation rate, charge properties and charge density on the surface of the silica species.

In the silica condensation reaction,

$$-\mathrm{Si{-}O^-} + \mathrm{HO{-}Si{-}} \rightarrow -\mathrm{Si{-}O{-}Si{-}} + \mathrm{OH^-} \qquad (1)$$

the condensation rate would increase with the negatively charged silicates because of favored nucleophilic attack in eqn (1). Thus, the condensation rate shows parallel pH behavior as charge density in Fig. 1 for $\mathrm{pH} < 7.5$. However, the condensation rate reaches a maximum and decreases for $\mathrm{pH} > 7.5$ because of the gradual instability of silicates at higher pH. In most of the syntheses of MSNs, the reaction was performed above pH = 10.5 where silicates would have been dissolved in aqueous solution. Due to strong interactions between silicates and cationic surfactants, the surfactant–silicate composites can stably exist to a higher pH (up to 12) rather than silicate dissolving (Fig. 1). Consequently, Mann's group[9] and Lin's group[15] employed a fast pH-changing method using pre-hydrolysis tetraethyl orthosilicate (TEOS) to prepare MSNs. For example, at a pH around the isoelectric point of silica ($\mathrm{pH} \approx 2.0$), the slow silica condensation rate and weak interactions between silicate species and cationic surfactants provide appropriate conditions for the formation of silica–surfactant nuclei without precipitation (Fig. 2). By quickly raising the pH to the 6.0–9.0 range, the fast silica condensation and strong electrostatic interactions between silica and cationic surfactants induce the fast simultaneous assembling-growth of the silica–surfactant nuclei. The particle size of the MSNs can be controlled in the range of tens to a few hundred nanometers by tuning the reactants concentrations. In addition, mesoporous silica nanospheres and nano-rods can be synthesized by using different mixtures of the cationic surfactant and salts *via* this simple pH-changing process.[16] This synthetic method has been also used to prepare metal-incorporated MSNs with higher accessibility demonstrating a greater catalytic capability than the micrometer-sized mesoporous metal–silicates.[16]

Good suspension of MSN

There is a high tendency for the aggregation of surfactant–silica nanoparticles, in particular when surface silanols are active condensation reaction species for forming Si–O–Si bridging bonds between nanoparticles. Reducing aggregation is critical for the preparation of a stable colloid solution of MSNs. The high dilution method can be applied to prepare a stable colloid solution of the mesoporous silica nanoparticles in the range of tens to hundreds of nanometers.[9] However, collection of MSNs from a highly-diluted solution requires considerable time and energy. In order to reduce the irreversible aggregation of MSNs during synthesis, the direct contact of silanol groups should be prevented. Suzuki *et al.* used a binary surfactant mixture of a cationic surfactant as a mesostructural directing agent and a non-ionic triblock polymer (Pluronic F127, $\mathrm{EO_{106}PO_{60}EO_{106}}$) as a steric stabilizer (entropy effect) to synthesize MSNs.[17] Pluronic F127, anchoring to the cationic surfactant–silicate nanoparticles and suppressing grain growth, is a way to prepare a stable colloid solution of MSNs with a diameter below 50 nm in a relatively concentrated solution. The aggregation among the primary particles was reduced by coating them with the co-surfactant F127 (Fig. 3).[18] Other surface protecting agents, such as PEG,[19] triethanolamine (TEA)[20] and the amino acid L-lysine[21] have been used in stabilizing and reducing the size of MSNs.

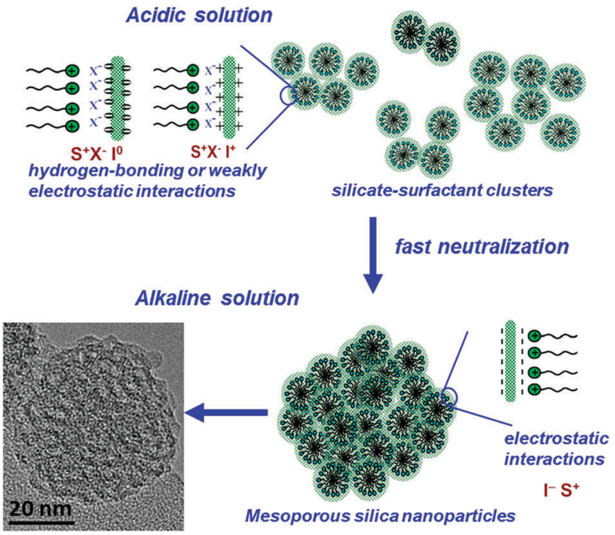


Fig. 2 Fast self-assembling method for the preparation of mesoporous silica nanoparticles by cationic surfactant as template.

Modified Stöber method

In 1968, Stöber *et al.* first discovered an effective method for the synthesis of monodispersed silica particles, which involves the hydrolysis of tetraalkyl silicates in a mixture of alcohol and water using ammonia as a catalyst.[22] The "Stöber method" has since been investigated widely, and subsequently particles with diameters ranging from tens of nanometers to a few microns have been obtained. With the Stöber method, excellent control can be obtained not only in the synthesis of silica particles but also in that of non-silica ones.[23,24] Based on a Stöber-like approach, it is possible to synthesize mesoporous silica nanoparticles of a uniform size by modifying the reaction compositions. Grun *et al.* first modified the Stöber synthetic compositions by adding a cationic surfactant to the reaction

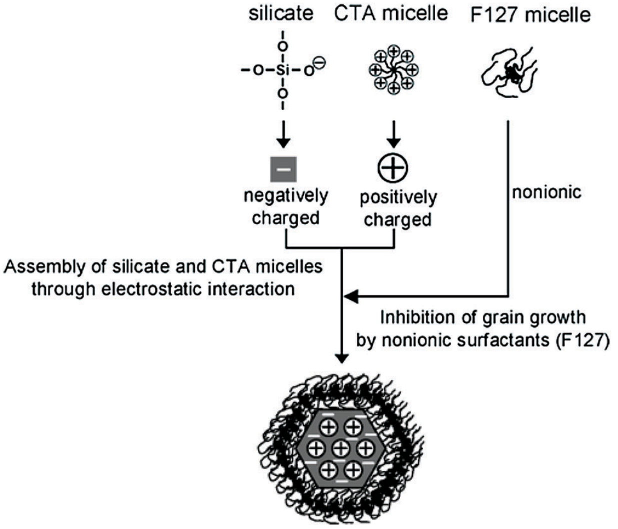


Fig. 3 Schematic representation of the functions of two surfactants for assembly of the mesostructure. (Reproduced with permission from ref. 18. Copyright 2006, American Chemical Society.)

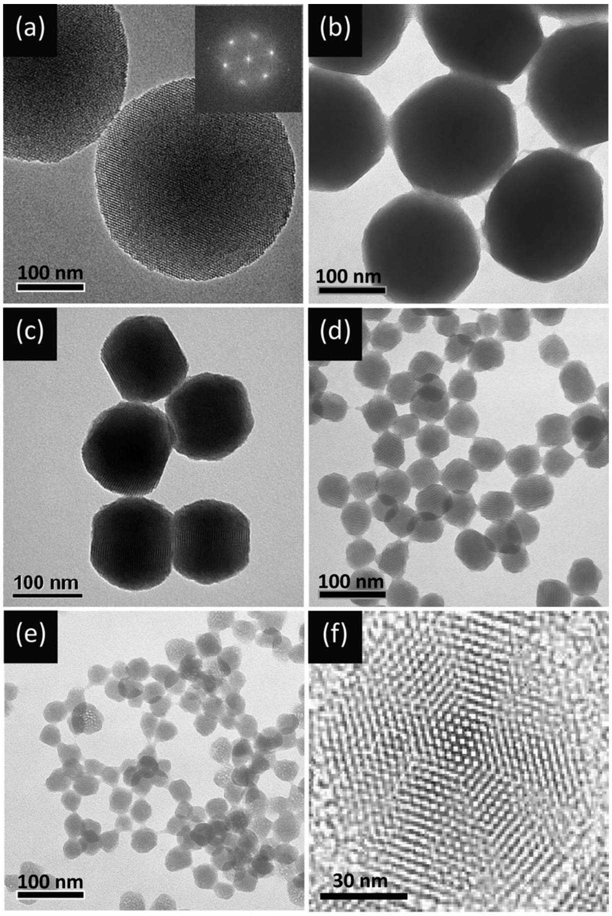


Fig. 4 TEM images of mesoporous silica with different average sizes: (a) 280 nm; inset: FFT analysis of the TEM image; (b) 170, (c) 110, (d) 50, (e) 30 nm. (f) High-resolution TEM image of a single particle in (c). (Reproduced with permission from ref. 29. Copyright 2009, Wiley Publishing Company.)

mixture and obtained the submicrometer-scaled MCM-41 spherical particles.[25] Since then, mixtures of alcohol, water and ammonia have been widely used with different template systems to prepare uniform MSNs with different pore sizes and mesostructures. Yano *et al.* synthesized mono-dispersed MSNs, with radially aligned mesopores, in the range of tens to a several hundred nanometers.[26] By changing the methanol–water ratio, MSNs with wide ranges of mean pore size were obtained with different alkyl chain length homologs of quaternary ammonium surfactants. In addition, according to their later study,[27] it was found that the monodispersed MSNs are formed through the sudden aggregation of small clusters in the initial stage of the synthesis, followed by preferential reaction of the residual silica precursors with the surface silanols on these existing particles. In fact, the size of the MSN can be easily expanded by an additional silica source (such as TMOS) which reacts preferentially with the surface silanol groups on the existing particles rather than generating new particles by reacting with each other.[27] This is the reason the Stöber-like process can generate uniform-sized MSNs. Later, Nooney *et al.* used both cationic surfactants (CTAB) and neutral surfactants (*n*-dodecylamine) as templates, and showed that MSNs with a wide range of diameters from 65 to 740 nm can be obtained by simply varying the TEOS–surfactant ratio under dilute conditions.[10] It is noted that when an aprotic cosolvent was used to create a homogeneous condition, spherical MSNs with smooth surfaces were formed. Mou and co-workers developed a strategy for synthesizing mono-disperse MSNs by separating the nuclei formation and particle growth into two steps,[28] and subsequently modulated the size of the MSNs by controlling the pH (10.86–11.52) of the reaction solution (Fig. 4).[29] A lower pH gave a smaller size of MSN because of the increased condensation rate and thus more nuclei. In contrast, Qiao *et al.* found that the size of MSNs increases from 30 nm to 85 nm with the decrease in pH from 10.0 to 6.0 presumably due to an decreased condensation rate (*c.f.* Fig. 1).[30] It is worth noting that Chiang *et al.* systematically investigated the effects of the key reaction conditions (*e.g.*, amount of TEOS, pH value, and reaction time) on the resulting MSNs, and concluded that the pH value is the dominant parameter influencing particle size.[31] Using the components of CTAB, Pluronic F127, TEOS and NH_4OH, Lin and co-workers obtained MCM-48-type MSNs based on a modified Stöber method. Moreover, they show that the phase transformation between 2D hexagonal *p6mm* and 3D cubic *Ia*3*d* can be controlled kinetically by tuning of the stirring rate, and the diameter of MCM-48-type MSNs can be controlled within the range of 70–500 nm by adding different amounts of Pluronic F127.[32]

Binary surfactants

The use of binary surfactants of different molecular weights in the synthesis of surfactant-templated mesostructure can lead to the formation of dual-mesoporous materials. For example, Niu *et al.* synthesized core–shell structured MSNs with bimodal mesopores consisting of smaller pores (2.0 nm) in the shell and

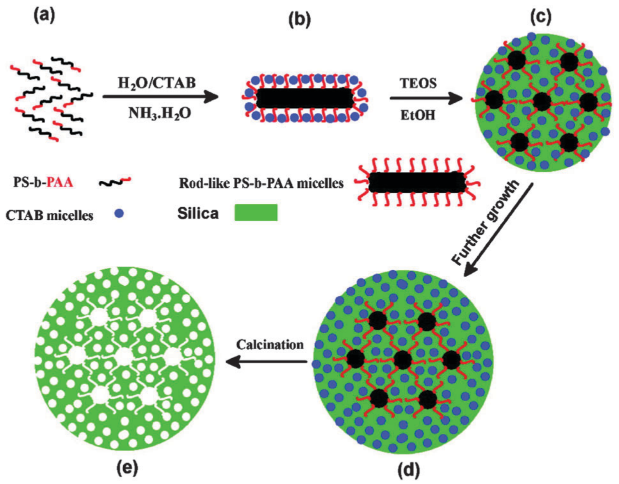


Fig. 5 (a) THF solution of PS-*b*-PAA; (b) CTAB-coated PS-*b*-PAA aggregates formed by the electrostatic interaction between CTA^+ and PAA^-; (c) core part formed from the assembly between CTAB-coated PS-*b*-PAA aggregates and TEOS; (d) mesoporous shell formation *via* the self-assembly between the remaining CTAB and the additional TEOS; (e) final core–shell structured dual-mesoporous silica spheres after calcination. (Reproduced with permission from ref. 33. Copyright 2010, American Chemical Society.)

larger tunable pores (12.8–18.5 nm) in the core by utilizing an amphiphilic block copolymer (polystyrene-*b*-poly(acrylic acid), PS-*b*-PAA) and CTAB as co-templates (Fig. 5).[33] In an aqueous ammonia solution, the hydrophilic PAA blocks of rod-like aggregates could couple with the CTAB micelles *via* electrostatic interaction between CTA^+ and PAA^- to form composite rod-like micelles. After the subsequent silicate deposition on the rod-like micelles, and cooperative self-assembly between the rich CTAB and additional TEOS, core–shell dual-mesoporous MSNs are obtained. Wiesner and co-workers synthesized highly aminated MSNs with cubic *Pm*3*n* symmetry and successfully controlled the sizes of particles. In contrast to previous studies, it is worth noting that using ethyl acetate in the aqueous ammonia solution could effectively elevate the amount of aminosilane incorporated in the MSNs, while still maintaining the mesostructural ordering.[34]

Sources of base and silica

Other than ammonia, other organic amines have also been used to provide the basicity in the synthesis of MSN. Bein *et al.* used the base triethanolamine (TEA) as a substitute for the more commonly used NaOH or NH_4OH to synthesize colloidal MSNs with diameters of 20–150 nm.[20] However, we note that uniform MSNs were not obtained until Kuroda's and Shi's laboratories modified this method.[35,36] Using a more dilute solution than that used by Bein *et al.*, Kuroda and co-workers obtained small MSNs ($\sim$20 nm in diameter) and subsequently applied dialysis for the removal of surfactants to avoid interparticle aggregation. Interestingly, four types of tetraalkoxysilanes ($Si(OR)_4$, R = Me, Et, Pr, and Bu) were selected to prepare MSNs of different sizes (*ca.* 20–80 nm) with smaller particle diameters correlating to shorter chain alkylsilane (TMOS) presumably due to faster intrinsic hydrolysis rates.[37] More recently, Shi *et al.* found the more TEA that is added, the smaller the particle size of the resulting MSNs,[36] and this is consistent with the results of a previous study,[20] where TEA was thought to act as a complexing agent for silicate species and additionally as a growth inhibitor for mesoporous particles, limiting the growth and aggregation of particles. Furthermore, Ma *et al.* successfully synthesized single-pore MSNs with sizes smaller than 10 nm by using PEG–silane to quench further silica condensation on the particle surface.[38]

Orientation of nanochannel

It appears the orientation of the nano-channels in MSNs could also be varied. Yano *et al.* synthesized mono-dispersed MSNs, with radially aligned mesopores, in the size range of tens to a several hundred nanometers by changing the methanol–water ratio.[26] The radial alignment of the nanochannels was found to be initiated by an MCM-48-like center seed.[39] Lebedev *et al.* disclosed a growth mechanism of the MSNs consisting of a cubic MCM-48 nucleus and radial cylindrical pores epitaxial growth on the surface of the nucleus as the added alcohol adopts different roles of cosurfactant (*i.e.*, increasing the packing parameter) for nucleation (of MCM-48) to cosolvent during growth to radial direction.[39] On the other hand, Mou and co-workers were able to obtain extremely uniform hexagonally shaped disks of MCM-41 structure (five XRD peaks observed for 100 nm sized particle).[40] In their synthesis, the seeds were a 2-D hexagonally arranged structure and the subsequent grown structure shows well aligned nanochannels perpendicular to the disk. In an aerosol-assisted surfactant self-assembly approach, Brinker and co-workers made MSNs with Brij-56 surfactant with worm-like nanochannels.[41,42]

Pore expansion

Although the pore size of MSNs could be controlled somewhat by varying the alkyl chain length of homologs of quaternary ammonium surfactants, the range is rather limited (1.8 to 2.3 nm). It would be desirable to further expand the pore size of MSNs to accommodate larger biopolymers. However, this is often difficult as most synthesis conditions for MSNs are tuned for surfactants such as CTAB. Recently, Fuertes *et al.* used *N*,*N*-dimethylhexadecylamine (DMHA) and 1,3,5-trimethylbenzene (TMB) as swelling agents to synthesize pore-expanded MSNs which can adsorb a large amount of protein.[43] Kim *et al.* synthesized MSNs using trimethylbenzene (TMB) and a hydrothermal method to obtain large pore sizes of MSNs for gene delivery.[44] Zhang *et al.* used TMB and decane to synthesize pore-enlarged magnetic MSNs as DNA carriers.[45] These pore-expanded MSNs usually possess large enough pore sizes but wormhole-like pore structure for loading small proteins. An alternative way to make MSNs of larger pore size is to use block-polymers as templates. Ying and co-workers employed non-ionic triblock copolymers (Pluronic P65, P123, and F127) as structure directing agents and a cationic fluorocarbon surfactant (FC-4) as a quencher of particle growth to synthesize IBN mesoporous silica materials.[46] Under mildly acidic conditions and a moderate reaction temperature, IBN-*n* mesoporous silica nanoparticles of several hundred nanometers can be obtained with 3D cubic, 2D hexagonal, foamlike and disordered pore structures and tunable pore sizes in the range of 5–30 nm.

Surfactant removal and surface functionalization

Finally, for the purpose of application, removal of surfactant and surface functionalization would be necessary. In general, the mesoporous silica nanoparticles are synthesized using a sol–gel reaction. However, like the silica gel, the MSNs are packed closely and shrink significantly when they are directly dried from a liquid. Because these nanoparticles come into contact with other nanoparticles and Si–O–Si bonds are formed between them by dehydration of the surface silanol groups, the shrinkage is essential irreversible, and their characteristics are lost.[35] Removal of surfactant by extraction is preferred over dry-air calcination. It is noted that Cauda *et al.* developed a method of ''liquid-phase calcination'' to remove surfactants at high temperatures in high boiling solvents, preventing agglomeration of MSNs.[47] Direct surface modification by refluxing the MSNs in a silane ethanol solution has been generally used for chemical removal of the reactive surface silanol groups. Because the surfactants can be dissolved very easy in the hot ethanol, silane-grafting and surfactant extraction from the nanopores are achieved simultaneously.[48] During the direct surface modification in the silane ethanol solution, the reactive surface silanol group can be changed to non-reactive Si–R, and thus the irreversible aggregation between the mesoporous silica nanoparticles can be reduced significantly. Without high-temperature calcination, the extent of the silane modification can be relatively high, and the surface properties can be easily adjusted. The colloidal MSNs functionalized with silanes are highly stable even after the removal of the organic templates. In the presence of the functional groups on the surface of MSNs, the irreversible aggregation between the MSNs can be reduced, which makes re-dispersion of the MSNs into the desired solution or matrixes relatively easy.[49] Furthermore, to avoid the need for further calcination or solvent-extraction processes, a thermosensitive polymer, poly(*N*-isopropylacrylamide), was used to act as a template to prepare the hollow silica nanospheres with mesoporous shells.[50] Because the temperature-sensitive polymers form aggregates at high temperature and dissolve at lower temperature in aqueous solution, the PNIPAm soft templates are recycled by simply regulating the reaction temperature (Fig. 6). This easy recovery of the organic template without using any organic solvent is attractive for the mass-production of MSNs.

3. Hollow silica nanoparticles synthesized by soft templating

In order to increase the pore volume to improve the loading capacity, efforts have been made to develop a simple synthesis method to prepare hollow MSNs, due to their potential biomedical applications in drug release and biosensing as well as their use as injectable nanovectors. Thus, hollow silica nanoparticles (denoted as HSNs) are a subclass of MSNs with a lot of recent research activity.[51] The encapsulation of agents of various functionalities, such as photoactive, magnetic or catalytic properties, inside the hollow spheres will give potential applications. Hollow silica particles have been prepared from many soft templates, such as micelles,[52] microemulsion droplets[53] or vesicular structures.[54] The rich variety of aggregates of amphiphilic surfactants, being well-studied,[55] can be explored for making hollow silica structures of various curvatures. The structure transformation of lyotropic surfactant organizations can be understood by the surfactant packing parameter, $g = V/la_0$, where V is the volume of the hydrophobic chains in surfactant, l is the surfactant chain length, and a_0 is the effective area of the hydrophilic head group of the surfactant at the interface. This simple parameter, g, can serve as a guiding rule to fine tune the reaction conditions and compositions (*e.g.*, temperature, concentration, pH value, counterion, salts, or addition of co-surfactant and oil phase) for the synthesis of MSNs in the desired morphologies and mesostructures. As predicted by the g-parameter, MSNs with a 3D cubic $Ia3d$ mesostructure (g = 1/2–2/3) were synthesized at a higher surfactant concentration than that for the 2D hexagonal $p6mm$ structure (g = 1/3–1/2).[32]

Single micelle-templating

We first discuss single micelle templating silica to form very small HSNs. In contrast to the normal micelle-templated

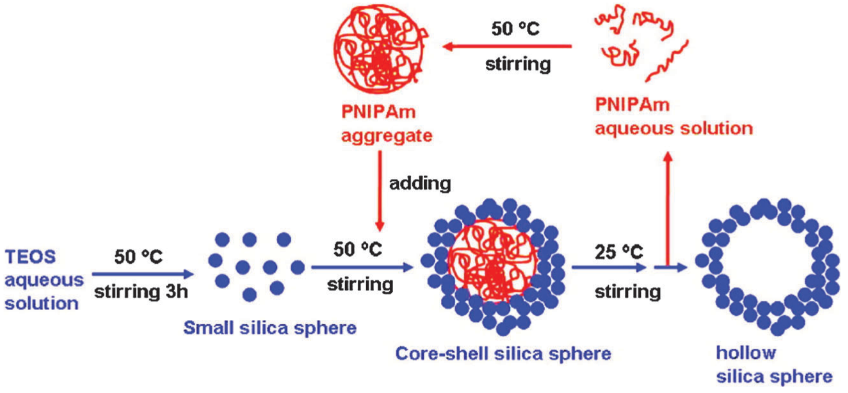


Fig. 6 Schematic illustration of the new strategy for the one-pot fabrication of hollow silica spheres with a mesoporous shell by using thermosensitive poly(*N*-isopropylacrylamide) as a recyclable template. (Reproduced with permission from ref. 50. Copyright 2009, American Chemical Society.)

periodic silica (MPS), here apparently the cross-linking of the micelle/silica spheres did not occur. Using Pluronic triblock copolymer with a different hydrophobicity (EO/PO ratio) and adding an appropriate amount of organosilica precursor, at *g*-values of resulting micelles, Yang and co-workers made distinct small hollow organosilica nanospheres and nanotubes.[52,56] Mandal and Kruk further used Pluronic F127 ($EO_{106}PO_{70}EO_{106}$) block copolymer templated synthesis of ethylene-bridged organosilicas in the presence of a swelling agent to produce HSNs of varying size.[57] Apparently, the lowering of the framework-precursor/surfactant ratio favors the formation of hollow nanoparticles templated by single micelles.[57] Cationic block copolymer micelles can also act as nanosized templates for the deposition of silicate in aqueous solution under ambient conditions (pH 7.2 and 20 °C).[58] Because of the positively charged surfactant, silica-cross-linking apparently still keeps the micelle/silica isolated and resulted in nanosized hollow silica particles after pyrolysis of the organic component. Because of the limited size of micelles, HSNs produced by micelle templating are generally limited to under 20 nm in size. However, Liu *et al.* could extend sizes of HSNs up to 40 nm by templating expanded micelles from asymmetric triblock copolymers and various hydrophobic expanding agents.[59]

Vesicle-templating

For further increasing the size of HSNs, vesicle-templating would be desirable. In addition to using a cationic surfactant, an anionic co-surfactant can be used to lower the curvature as mesostructural templates. Furthermore, a mixture of silanes and silicate has been used as a source of silica. Based on these synthesis concepts, mesoporous silica hollow spheres with mesostructural shells were prepared *via* the $S–N^{+}\cdots I^{-}$ interactions, which are advantageous for the direct incorporation of amino-functional groups into the silica framework after simple acid-extraction of the anionic surfactant (Fig. 7).[60] Uniform MSNs ranging in size from 25–105 nm have been obtained from a co-condensation process of tetraethylorthosilicate (TEOS) and organotriethoxysilanes in an alkaline aqueous solution containing triethanolamine and cationic surfactant cetyltrimethylammonium chloride (CTACl).[36] The mixture of oppositely charged single-tailed cationic and anionic surfactants produces a rich variety of aggregate microstructures (*e.g.* rod-like micelles, cylindrical, vesicles and lamellar phases) even at high dilution,[61] which can serve as novel organic templates for mesostructured silicas with various remarkable morphologies. As the ratio gradually increases to 1.0, a phase transformation from spherical micelles → cylindrical micelles → vesicles occurs. These mesostructural surfactants can be used as a template or co-template to generate mesoporous silica in the desired form. Then, at a suitable pH where soft templates and silica species have matching interactions, deposition and condensation across and around the curved external surfaces produce silica casts of the organic structures. For instance, individual silica nanofoams, mesoporous silica nanorods and hollow spheres can be templated from spherical micelles, rod-like micelles, and vesicles, respectively (Fig. 8). To introduce the mesostructure to the shell of the hollow MSNs, a ternary surfactant system has been utilized, where the neutral tri-block copolymers anchor on the cationic surfactant vesicles.[54] Due to the superior hydrophobic properties of fluorocarbons, a facile and stable vesicle template can be obtained from a mixture of

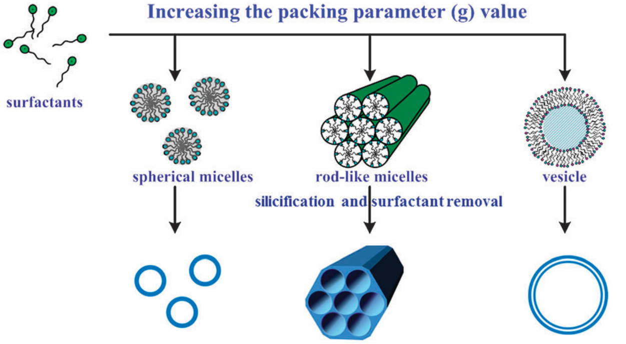


Fig. 8 Soft surfactant-templating approaches to synthesize mesoporous silica hollow nanospheres, nanorods, and hollow spheres from spherical micelles, cylindrical micelles and vesicles, respectively.

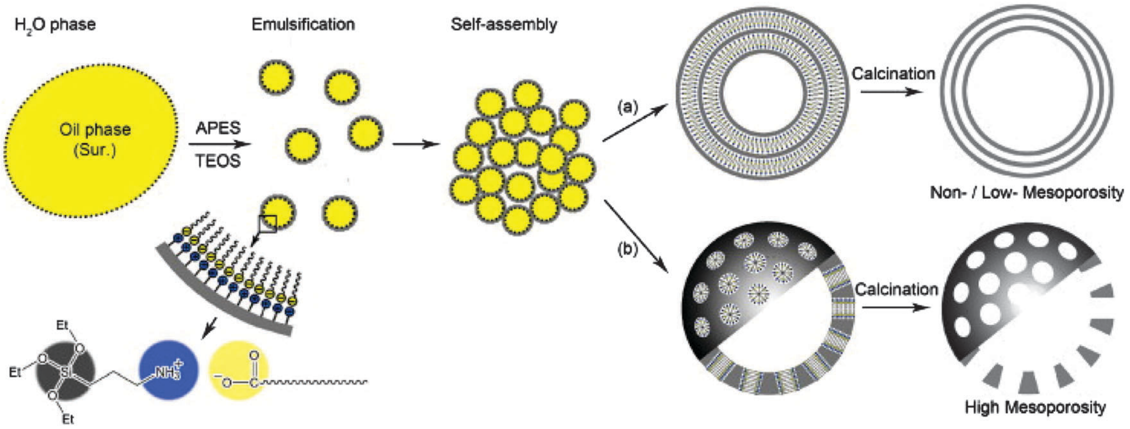


Fig. 7 A proposed formation mechanism of the nonporous/mesoporous silica hollow spheres. The lamellar structured (a) and mesostructured (b) silica hollow spheres were formed without and with adding an alcohol co-solvent, respectively. (Reproduced with permission from ref. 60. Copyright 2011, Elsevier Inc.)

cationic fluorocarbon surfactant $[C_3F_7O(CF)(CF_3)CF_2OCF(CF_3)$-$CONH(CH_2)_3N^+(C_2H_5)_2CH_3]I^-$ (FC-4) and Pluronic F127 $(EO_{106}PO_{70}EO_{106})$ tri-block copolymer.[62] Moreover, the flexible vesicles are capable of encapsulating the nanoparticles to generate the core–vesicle or yolk–vesicle templates.[63] The silica sources then hydrolyze and condense on the vesicle and core–vesicle templates through the attractive interactions and form hollow spheres and core–shell composites.

Microemulsion-templating

A stable oil-in-water (o/w) microemulsion system formed from a mixture of water, surfactant, oil and a small amount of aqueous alkaline solution can be used to prepare the hollow MSNs. With careful control of the silica shell thickness and extent of condensation of the silica framework, hollow silica nanospheres have been successfully synthesized.[64] To prepare silane-containing hollow MSNs in a one-pot reaction, a mixture of a hydrophobic silane and organic silica source (such as tetraethylorthosilicate, TEOS) is used as the silica source. After a slow hydrolysis reaction, the hydrolyzed TEOS and silane sources become hydrophilic, and gradually diffuse and co-condense on the surface of the microemulsions to solidify and form the hollow MSNs. The reverse water-in-oil (w/o) microemulsions have the advantage of ease of encapsulating other species (such as nanoparticles) in the hollow MSNs or making core–shell type MSNs.[65] Mou's group prepared a highly thermal stable single Au nanoparticle contained within a silica hollow nanosphere that serves as the catalyst for carbon monoxide oxidation by using w/o microemulsions consisting of water, cationic surfactant and hydrocarbons as the template.[66–68] Because only one Au nanoparticle of around 3.0 nm is confined within the nanospace of a silica hollow sphere, the aggregation of Au NPs is prohibited which preserves the high activity even at high reaction temperatures. On the other hand, an oil-in-water (o/w) type microemulsion has also been used to make HSNs. Microemulsion templates for mesoporous silica were first reported by Stucky's group.[69] Using the triblock copolymer Pluronic F127 as a template and 1,3,5-trimethylbenzene (TMB) as a swelling agent in the presence of an inorganic salt (KCl), Hao *et al.* made hollow silica nanospheres with large mesopores ($\sim$8 nm) on the shell.[70] In an interesting development, Kao *et al.* made Kippah-like mesoporous silica hollow spheres by collapsing the encapsulated oil in an oil-in-water type synthesis of MSN.[64] The oil in the core of oil-in-water escaped through the mesopore during synthesis before the silica shell became rigid. Thus the soft shell collapsed to form a kippah-like structure.

4. Hollow silica nanoparticles synthesized by hard templating

Many studies have examined the biomedical applications of MSNs. Discrete and monodisperse MSNs are essential for both high colloid stability in a physiological environment and are small enough in size to allow for long blood circulation. As noted above, the soft-templating method is widely applied to prepare MSNs, but the coexistence of mesostructures and low rigidity means that the resulting MSNs generally have a broad particle size distribution and mixed mesostructures and forms. Consequently, the synthesis of discrete, monodisperse, mesostructured, morphology-tunable MSNs for bio-applications remains a challenge.

Due to advances in the production of polymer lattices, silica colloids, and metal oxides in uniform sizes, these materials have been used as hard templates for monodispersed MSN products. There are three basic criteria for the achievement of a high-fidelity inorganic silica replica of hard templates. One is that the silicification at the surface of the organic template is faster than the self-condensation of the silica species in bulk solution. This requires that the surface possesses appropriate functional groups for interfacial recognition of the silicates under suitable reaction conditions. Second, the organic-template must be stable throughout the silicate deposition and condensation processes. Failed silica casting tends to occur when one of the components in the surface activated organic-template has a relatively stronger interaction with the silicates, and thus it prefers to leach out the original organic template to assemble with the silicates in solution rather than on the organic template surface. Third, the template has to be easily removed without fracturing the inorganic silica cast. For this reason, the sacrificial template approach has been widely applied, in which the dissolvable or combustible interiors can be simply removed after acid-dissolution, solvent extraction and calcination under mild conditions without destroying the mesoporous silica casting.

Polymer beads-templating

Colloidal hard template methods that have been explored in the literature include those that use gold, silver, CdS, ZnS, and polymer beads.[71] Among these, polymer latex particles (*e.g.* polystyrene, PS; polymethylmethacrylate, PMMA) in the size range of tens of nanometers to a few micrometers should be the most well-suited to make hollow MSNs because they are readily available in uniform size, inexpensive, and can be easily removed by calcination for the removal of the organic matter at 300–500 °C.[72,73] In contrast, the costly inorganic colloids must be removed in a corrosive acid solution that makes the procedure complex and hazardous.

To allow silicification on the surface of the polymer latexes, surface activation needs to occur by mediating the appropriate functional groups. A variety of surface activation methods have been employed to introduce these groups for silica gelation, including a chemical functionalization followed by a layer-by-layer deposition technique *via* electrostatic attractive interactions.[74] The strong interactions between the polymer latexes and functional groups can prevent the leaching of the capping agents during the silica deposition. However, such complex surface-modification procedures are likely to hinder the extensive use of the polymer latex templating method to prepare uniform silica hollow spheres. Therefore, a more convenient procedure to activate the surface of the polymer latexes for silicification is still required.

Both surfactants and block-polymer have been widely used as stabilizers of the hydrophobic polymer latexes to achieve good dispersion in an aqueous solution *via* hydrophobic interactions. By physically covering the surfactants or polymers with functional groups for silica gelation, the surface-activated polymer latexes can also directly act as a template for the hollow MSNs. Under optimal reaction conditions (with regard to the pH, temperature, and water content), the silicate species would prefer to condense on the surface-activated latexes without destroying the original structures. Although highly alkaline and acidic conditions are generally required to synthesize mesoporous silicas, it has been found that the MSNs can also be prepared at near neutral pH conditions (pH = 5.0–8.0), where the rate constant of the silica self-condensation is the greatest. In a highly dilute solution, the silicate self-condensation rate should be suppressed, and heterogeneous condensation on the favorable surface dominates. The silica deposition rate on the surface of the activated hard templates is supposed to be faster than that of self-condensation of the silica species. In addition, in the same neutral pH range, the silicate species are partially negatively-charged, and thus have weaker interaction with the cationic surfactant and polymer than those in alkaline and acidic solutions. It thus becomes possible to have an integral mesoporous-silica casting on the surfactant activated polymer latexes without leaching the surfactants. Here, the ultimate goal is not only to mimic silicification in nature at neutral pH but to go a step further and be able to preprogram mesoporous materials to produce a specific architecture with defined functionality.

The charge type, charge density and condensation rate constant of silica species are strictly dependent on the pH value. To achieve mesoporous silica replicas with high integrity, it is thus necessary to have a good control of the pH value. Given an appropriate pH value, other factors could be easily fine-tuned to be optimal. At an appropriate surfactant or polymer/latexes ratio, integral mesoporous silica replicas will be formed, while the mesostructure and pore size of the porous silica shell are dependent on the surfactants used (Fig. 9). At both lower and higher ratios, these broken silica replicas or mesoporous silica particulates would be generated along with the hollow MSNs. Due to their hollow interiors, hollow MSNs have a larger space to load more drugs, biomedicine, enzymes or nanoparticles, making them especially suitable for bio-medical applications.

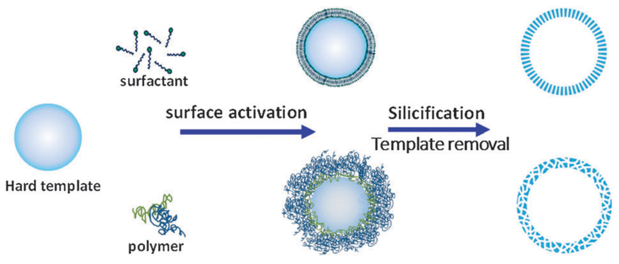


Fig. 9 Scheme of hard-templating methodology for the synthesis of hollow mesoporous silica spheres by using surfactant or polymer for surface activation.

Metal or metal oxide nanoparticles@MSN

The surface-activation on hard templates can further be extended to encapsulate other hard templates such as metal, metal oxides or semiconductor nanoparticles in the MSNs. Using a combination of self-assembled mesostructured silica together with a functional nanoparticle, a customized nanocomposite can readily be put together. With the versatile surfactant or polymers acting both as the capping agents of the nanoparticles and as the silica gelation agents, these nanoparticles embedded in the MSN (denoted as NPs@MSN) have been prepared by good control of the reaction conditions and composition. Therefore, the NPs@MSN has synergistically dual or multiple functions, and has some distinct advantages over those of the individual components. For example, coating the thermally stable and biocompatible mesoporous shell can reduce the clustering and aggregating of nanoparticles, prevent the direct contact of the nanoparticles with the organics, and provide a large surface area for surface modification and high porosity for increasing the loading amount of the drugs. After dissolving the core nanoparticles by acid etching, it is also possible to obtain hollow MSNs.

In previous literature, quaternary ammonium surfactants are generally used as the capping agents of many nanoparticles, and they are also the organic templates of the mesoporous silicas. Accordingly, Kim *et al.* proposed a simple and general method to prepare discrete and monodisperse single Fe_3O_4 nanocrystal@mesoporous silica, using cetyltrimethylammonium bromide (CTAB) both as a stabilizer and mesostructural directing agent.[75] After PEG surface modification, the Fe_3O_4@mesoporus silica can be simultaneously used as a T_2-weighting magnetic resonance imaging agent and a therapeutic one. In parallel work, Liong *et al.* reported another synthesis method to prepare multifunctional particles showing iron nanoparticles encapsulated within mesoporous silica, hydrophobic anticancer drugs stored inside the pores, and surface modification with phosphonate and folic acid targeting ligands.[76] To develop other multifunctional theranostic or highly stable nano-catalyst systems, Au or Pt nanoparticles, Au nano-rods and silver sulfide nanoparticles in quaternary ammonium surfactant aqueous solution have been successfully coated with mesoporous silica to form a core–shell structure under optimal conditions and compositions. The thickness of the mesoporous silica shells can be tuned by adjusting the ratio of nanoparticle : surfactant and the amount of silica source. Because single Au and Pt nanoparticles are confined within the mesoporous silica, these nanoparticle@mesoporous silicas show high thermal stability and catalytic activity even at high reaction temperature.[77] For cancer therapy, the Au nanorods nanoparticles embedded in MSNs have both high absorption of near infrared (NIR) radiation and large loading capacity needed to deliver chemotherapy drug.[78] When irradiated with a low power density laser, the chemotherapy drug will release from the Au nanorod@mesoporous silica matrix. Under high-power-density laser irradiation, the Au nanorod@mesoporous silica can be used for hyperthermia therapy. After surface-grafting of targeting ligands, such as arginine-glycine-aspartic acid peptides, the Au nanorod@mesoporous silica, able to enhance tumoricidal efficacy and decrease side effects, will explore its localized therapeutic potential *in vivo.* Due to the high electron-density of metal nanoparticles, the metal or metal sulfide@MSNs can also be used as bioimaging and biolabeling agents to track related digestion procedures.[79]

In addition to quaternary ammonium surfactants, the binary surfactant mixture of anionic and zwitterionic surfactants can form vesicle structures to encapsulate the nanoparticles. To match the interaction with the negatively-charged surface, the protonated amino-silane must be incorporated into the silica sources. After hydrolysis and condensation, various yolk–silica shell structures are prepared. The movable yolks can be silica beads, Au nanoparticles or Fe_2O_3 nano-spindles.[80] In addition, polymers with appropriate functional groups or a mixture of surfactants can also be used to prepare the core–shell nanoparticle@mesoporous silicas for desired applications. To combine varied functions, nanoparticles of different compositions, drugs, or enzymes can be embedded in a mesoporous silica nanoparticle. The resulting multifunctional nanocomposites can act as versatile tools for therapy and tracking, and such materials are attracting considerable attention with regard to the therapeutic potential of MSNs in medicine.

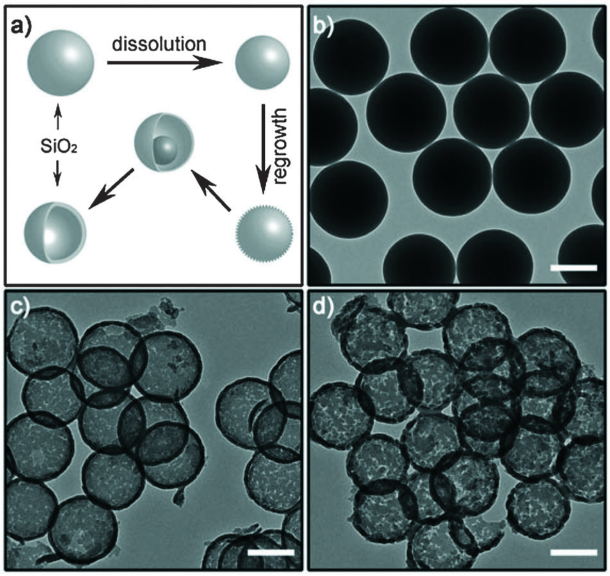


Fig. 10 (a) Schematic illustration of the spontaneous formation of hollow SiO_2 spheres. (b) TEM images of as-prepared SiO_2 spheres. (c and d) Samples after reacting with 0.06 g mL^{-1} $NaBH_4$ for 6 h at 51 °C (c), and 5 h at 56 °C (d). Scale bars are 200 nm. (Reproduced with permission from ref. 81. Copyright 2008, Wiley Publishing Company.)

5. Dissolving and reconstruction of silica nanoparticles to hollow mesoporous silica nanoparticles

As with biomineralization, the structural transformation usually occurs by surface dissolution of the precursor followed by nucleation of the second phase on the surface of the initially formed particles. Consequently, in addition to the aforementioned hollow MSNs in uniform sizes obtained from hard-templating and using a selective etching approach based on compositional differences, hollow MSNs can also be synthesized by dissolving and reconstruction of their corresponding preformed solid spheres based on structural differences. To achieve this, the preformed solid spheres are usually inhomogeneous in nature or can be partially dissolved in the subsequent treatments.

At relatively mild temperature, Yin and co-workers found that the uniform solid silica spheres prepared using the Stöber method can be transferred to rattle and finally to hollow structures using $NaBH_4$ solution (Fig. 10).[81] This self-templating strategy was performed *via* a silica dissolution–redeposition process. The uniformity and shape of the silica spheres are maintained during this simple structural transformation, and thus uniform hollow mesoporous silica spheres are generated. This organic template-free synthesis is desirable, because no surfactant-removal processes have to be employed. To precisely control the pore size and increase the surface area, hollow silicas with mesoporous shells can be obtained from the co-assembly of cationic surfactants and silicate species produced by etching of the preformed silicas in the presence of cationic surfactants using Na_2CO_3 solution.[82]

Utilizing the structural-difference etching approach, Mou and co-workers used a microemulsion system to prepare rather uniformly sized hollow silica nanoparticles by washing out the inner silica section of solid nanoparticles, which were less condensable due to the incorporation of organosilane in the synthesis.[66] A similar hollowing strategy was also used to fabricate silica nanorattles by means of selective etching of the middle organosilica region between the pure silica core and shell.[83] In addition, pure silica spheres with different diameters synthesized by various methods, such as the Stöber and microemulsion approaches, followed by various treatments, including acidic,[84] basic,[85] and neutral aqueous conditions,[86] have been demonstrated to form yolk–shell, hollow as well as hierarchical structures.[84–86] Although these syntheses are different and the etching methods might be sensitive to specific cases, it is noted that the hollowing processes are usually performed at high temperature, which can be explained by the significantly increased dissolution rate with increasing temperature.

Martin *et al.* developed a surfactant templating method to obtain mesoporous silica spheres by hydrothermal treatment of pre-shaped amorphous silica spheres in the presence of cetyltrimethylammonium bromide (CTAB) using NaOH solution, and introduced the term "pseudomorphic",[87] which is widely known in the mineral literature, to describe the transformation process. Because the pseudomorphic synthesis is a kinetically controlled process, optimization for each parent silica material is usually required to limit particle aggregation and suppress secondary nucleation.[88] However, these experimental conditions are usually costly and time-consuming. Recently, Dong *et al.* modified the pseudomorphic transformation process and claimed that the addition of a small amount of NH_4F could efficiently prevent the formation of secondary particles and aggregation of existing particles.[89] Consequently, a high yield of monodispersed silica core–shell particles (from 100 nm to 2 μm in diameters) with tunable porosities and various shell thicknesses were obtained.

6. Other novel approaches

Water is the most commonly used solvent to prepare MSNs *via* the sol–gel reaction. However, the large surface tension of the aqueous solution always induces a serious aggregation between the MSNs during the drying process. Although solvent exchange and direct silane modification have been shown to reduce the extent of irreversible aggregation, a synthesis procedure for the direct generation of dry MSNs is desired. Brinker and co-workers reported a rapidly modified aerosol-based procedure for the preparation of solid, silica spheres with well-ordered hexagonal and cubic mesostructures.[41] The process started with a homogeneous water–ethanol solution of the soluble silica source and mesostructure-directing agent (*e.g.*, surfactant or block copolymer), in which the template concentration is much lower than the critical micelle concentration. Using a commercial atomizer, as shown in Fig. 11, aerosol dispersion within a tubular reactor was achieved, and then the droplets were dried, heated and collected. The method relies on evaporation-induced interfacial self-assembly confined to the spherical aerosol droplets. Because this novel synthetic method possesses high compositional flexibility, various metal–silica, dye–silica, and polymer–silica composites can be prepared using the same procedure through addition of extra metal complexes, organic dyes and polymer precursors. In order to increase the high void ratio, adding an appropriate amount of ammonium salt, such as NH_4Cl or $(NH_4)_2SO_4$, to the stock solution can introduce a hollow interior into the MSNs to increase drug loading.[90] In the absence of water in the dry product, the resulting MSNs do not aggregate and can be well-dispersed in solvent or polymer matrixes.

Different from the typical hard-templating method, an inverse replica can also be used to prepare the MSNs. Stein and co-workers used the uniform and highly-ordered voids in the opal-like colloid crystals that occur in the assembly of monodisperse PMMA spheres as nanospaces to limit the size of the mesoporous silicas.[91] When creating the reverse opals, the mesoporous silica nanocubes and spheroids were obtained from infiltration of mesophase silicate–surfactant precursors into the nanospaces in 3D-ordered colloidal crystal templates in a face-centered-cubic structure, gelation and then calcination for disassembly of the PMMA colloid crystals template. Because the theoretical ratio of the octahedral (O_h) to tetrahedral voids (T_d) in a face-centered-cubic array of uniform spheres is 2.0, the number ratio of the larger nanocubes formed in the O_h voids to spheroids formed in T_d voids is relatively close to the theoretical value. Consequently, inverse casting of the organic or inorganic opal structures is an alternative method to prepare uniform MSNs in various morphologies and mesostructures with a careful control of the reaction composition and disassembly procedure of the opal structures.

7. Applications of the MSNs

In contrast to the mesoporous silica in micrometer or larger dimensions, MSNs have a number of unique characteristics in many promising potential applications. For example, their short channels can act as the solid supports for highly accessible active sites in catalysis. With regard to the synthesis of high-performance catalysts, MSN-based catalysts have been synthesized by grafting multiple functional groups, metal complexes, or metal oxides to the surface silanol groups.[7,92] Compared with mesoporous silica bulk materials, the MSNs have shorter channels, which can improve molecule transport especially for the large molecules (such as biodiesels, biomolecules). Therefore, the reactant and product molecules can avoid a long route through the nanochannels and possible blockages. Catilin Inc. (Albemarle Catilin) has developed a pilot-scale biodiesel plant that uses MSN-based catalysts to enable a clean biodiesel production.

Well-dispersed mesoporous silica nanoparticles of high-porosity and thermal and mechanical stability can be used as nano-fillers embedded in silica or polymer matrixes to produce nanocomposite films. Surface-modified MSNs in the 20–30 nm range can be applied to various substrates and used as a single layer antireflection coating by using simple wet deposition

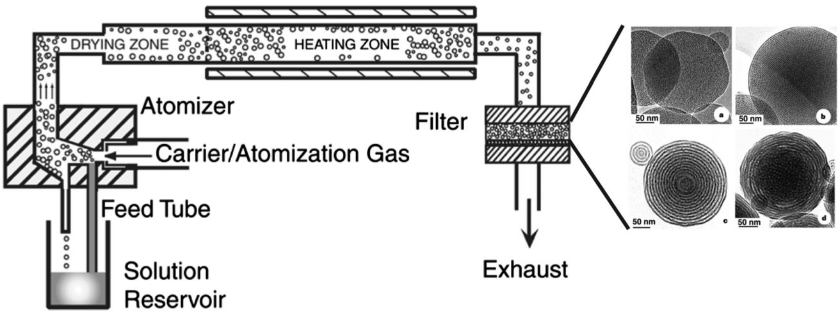


Fig. 11 Diagram of aerosol reactor. Silica/surfactant aerosols are generated using a commercial atomizer operated with nitrogen as a carrier/atomization gas. This atomizer produces aerosol droplets with a size distribution characterized by a geometric standard deviation of 2 (95% of the particles have diameters between 0.25 and 4 times the mean diameter). Representative TEM micrographs of mesostructured silica particles. (Reproduced with permission from ref. 41, Copyright 1999, Nature Publishing Group.)

techniques at ambient temperature.[93] With precise control of the thickness (around 100–150 nm) and porosity of the mesoporous silica (a reflective index of around 1.23), a perfect antireflective-coating window with a low reflectance (less than 0.1%) and high transparency ($>98\%$) in the visible light range (340–800 nm) has been demonstrated. In addition, MSNs with appropriate surface modification can also be well embedded in the polymer matrix for synthesis of a transparent silica–polymer composite with high mechanical strength and low linear thermal expansion.[94] These high-transparency MSN–polymer composites are promising for use in optoelectronic devices such as optical fibers, light guide films, and LED or solar cell covers.

In biomedical applications, Lin and co-workers first demonstrated the modified MSNs can be used as a stimuli-responsive controlled release system (Fig. 12).[11] The mercaptoacetic acid-coated CdS nanocrystals were synthesized as chemically removable caps to block the MSNs, encapsulating neurotransmitters and drugs. When the chemically labile disulfide linkages between MSNs and CdS caps were cleaved by various disulfide reducing agents, the contents entrapped within the channel of MSNs released. In addition, the biocompatibilities of MSN systems have also been demonstrated *in vitro* and *in vivo* in many studies. MSNs have been demonstrated as efficient carriers for various therapeutic agents. The functionalization of MSNs with molecular, supramolecular or polymer moieties, provides the material with great versatility while performing drug delivery tasks with cell-targeting and labeling, which makes the delivery process highly controllable. Since then, tremendous strides have been made in the field of nanotechnology.[95] Many reviews of these studies exist and reveal useful information with regard to choosing a synthesis method for MSNs associated with biological responses of interest.[6,96–98] Any discussion of the biomedical applications of MSNs would be outside the scope of this review. This emerging area at the interface of chemistry and the biosciences gives many opportunities for researchers with interests ranging from sol–gel science, synthesis of nanomaterials, controllable drug delivery to targeted theranostics in biomedicine.

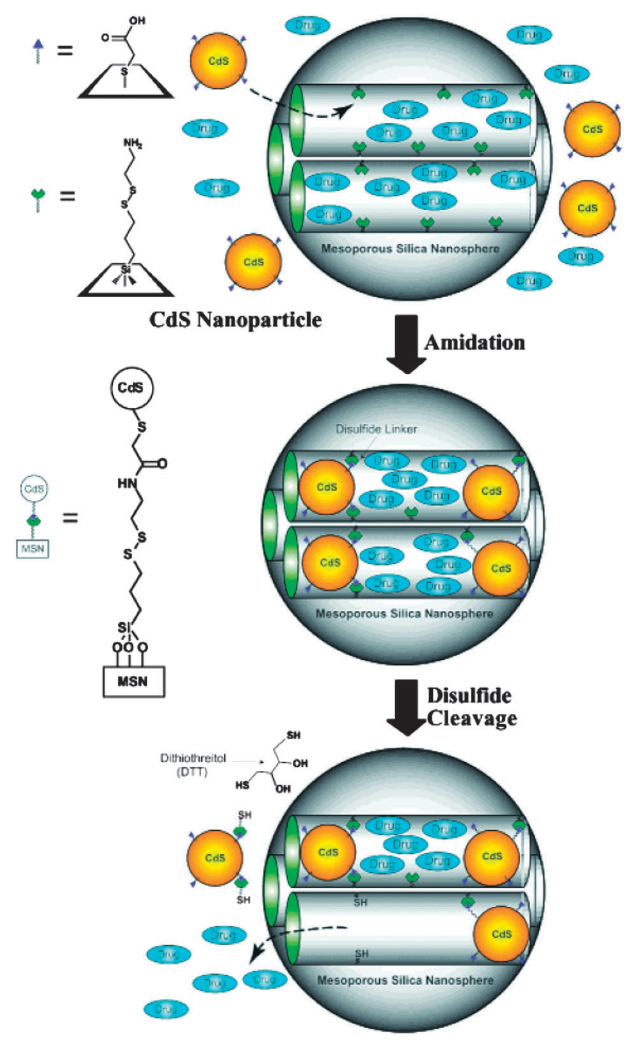


Fig. 12 Schematic representation of the CdS nanoparticle-capped MSN-based drug/neurotransmitter delivery system. The controlled-release mechanism of the system is based on chemical reduction of the disulfide linkage between the CdS caps and the MSN hosts. (Reproduced with permission from ref. 11. Copyright 2003, American Chemical Society.)

8. Conclusion and outlook

In the past two decades, great progress has been made in the synthesis of mesoporous silica nanoparticles. Many of these methods are based on the high dilution method, and the concentration of resulting products is usually low, typically in the millimolar range. Scaling-up the quantity to a commercial-scale (kilograms) for practical applications is expected to present major challenges with regard to collection, uniformity, and reproducibility. Moreover, the common template sources of cationic surfactants and block copolymer have aqueous toxicity, because of the slow degradation of the hydrophobic segments under ambient conditions. In addition, to avoid environmental damage, it is also necessary to develop biodegradable templates or template-free methods to synthesize MSNs. It is also necessary to develop cheap sources of silica and organic templates, reduce the number of synthetic procedures, shorten the time for reactions and hydrothermal treatment, avoid the production of large amounts of highly alkaline or acidic wastewater, and carry out synthesis under safe conditions, if mass production of mesoporous silica nanoparticles is to be achieved for industrial applications.

Mesoporous silica nanoparticles have the properties of high surface areas, large pore sizes and volumes, short diffusion reaction pathways, high biocompatibility and modifiable surfaces. However, the stability of MSNs of amorphous silica frameworks can be a problem for applications as catalysts at high temperature (>500 °C) or when used in steaming or alkaline solution. By carefully selecting the conditions under which MSNs are used, these materials are likely to have many potential applications in numerous fields.

Although various sizes, shapes, pore structures, functionalities and design strategies of MSNs have been created by various groups, the results of the biological effects of MSNs are sometimes conflicting, although this may be due to the different ways of preparing and treating the particles. For example, the dispersity of the MSNs, which is greatly affected by the methods used for template removal and particle collection, is highly correlated with particular biological responses. Therefore, some standardized methods to assess the biological impacts of MSNs should be developed before they are used in clinical trials.

In addition, the environmental impact of mesoporous silica nanoparticles should be also considered. MSNs with high surface areas could have a significant binding affinity toward proteins, and thus cause denaturation. The strong bonding of negatively charged mesoporous silica nanoparticles particularly to the surface of particular cells is due to the presence of quaternary ammonium ions in the membrane in the physiological pH range. Especially in powder form, inhalation of MSNs could have serious toxic effects in the same way as aerogels. To date, both *in vitro* and *in vivo* test results suggest that MSNs are not immunogenic or toxic, but their impact on human health and the environment still require further investigation. Studies on the potential hazards of MSNs will be helpful in establishing new guidelines on their use.

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