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Mesoporous Silica Nanoparticles: A Review

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Abstract

One of the greatest challenges in the field of medicine is the effective and efficient drug delivery to the defected cells or tumor cells with minimal toxic side effects. Due to lacking properties like specification and solubility of drug molecule, patient requires high doses of the drug to attain the desired therapeutic effect for the disease treatment. To overcome this problem various drug carriers are available in the pharmaceutical field, which help in delivering the therapeutic drug/ gene to the target site. For this purpose, mesoporous silica nanoparticles (MSNs) are found to be biocompatible, chemically and thermally stable nanoparticles. Their unique structural properties facilitate the loading of drug/gene and subsequent controlled delivery of drug to the target site. During recent years research on MSNs has been extensively increase. Since 2001, when MCM-41 was first proposed and later on SBA-15 and MCM-48 as drug carrier for controlled delivery system. Morphological characteristics like pore size, pore volume, particle size, surface area, pH and loading capacity of drug are widely effects the MSNs, when altered. Meanwhile, functionalization of MSNs using organic and inorganic group elaborates the delivery of drug to targeted site. This review article also deals with the recent research on synthesis methods of MSNs and their applications in the field of medicine, imaging, diagnosis, cellular uptake, target drug delivery, cell tracing and bio-sensing.

Keywords: Mesoporous silica nanoparticles; Target specificity; pH; Surface functionalization; Synthesis; Drug delivery

Introduction

In early 1990's, mesoporous silica materials have attracted special attention after the discovery of new family of molecular sieve called M41S. MCM-41, MCM-48 and SBA-15 are the most common mesoporous silica materials with the pore size ranging from 2 -10 nm and 2D-hexagonal and 3D-cubic structural characteristics [1]. The unique properties of mesoporous silica nanoparticles (MSNs) such as they have controlled particle size, porosity, morphology, and high chemical stability make nanoparticles highly attractive as drug carriers, diagnostic catalysis, separation and sensing [2-7]. Rapid internalization by animal and plant cells without causing any cytotoxicity inside the body, is another distinctive property of surface functionalized mesoporous silica nanoparticles [8,9]. In the synthesis of MSN's cationic surfactant micelle templates act as surface directing agents for polymerizing silica components due to electrostatic interactions as shown in Figure 1 [1].

In 2001, the first reported mesoporous silica material as a drug delivery system is MCM-41 [10]. Mesoporous silica materials are considering excellent carriers for drug delivery because of their textural properties which increase the loading amount of drug inside the pore channels. Similarly, drug diffusion kinetics can be controlled due to the functionalization of silanol group [11,12].

In the field of nanomaterial and nano-biomedicine, many multi-functional MSNs are widely studied due to their rich silane chemistry [13]. Diaz and Balkus [14] demonstrated that the large molecules like proteins can be immobilized in mesoporous material. Similarly, Vallet-Regi et al. illustrates the loading and slow release of ibuprofen (IBU) from mesoporous silica material in solution [10,15]. The interior pores of MSNs facilitate loading of organic molecules such as MRI contrast agents and fluorescent as well for delivery of drug DNA and RNA. Similarly, functionalization of their external surface provides site-specific targeting abilities [16-18]. In this review article, we discuss research towards general morphology, functionality, methods of synthesis and applications of mesoporous silica nanoparticles.

Morphology of Mesoporous Silica Nanoparticles

Particle size

Mesoporous silica nanoparticles can be synthesized by using surfactant in aqueous solution which may be charged and neutral. Silicates (an ester of ortho silicic acid) are polymerized by surfactant [19]. The variables that involve controlling the size and morphology of mesoporous silica nanoparticles include:

- Rate of hydrolysis.
- The level of interaction between assembled template and silica polymer.
- Condensation of silica source.

By controlling the pH, using different templates and co-solvent we control the above variables [20-22]. Stucky et al. synthesized hard mesoporous silica spheres having size ranging from hundreds of microns up to millimeters at oil-water interphase, by using high concentration of template and hydrophobic auxiliaries [23]. Stirring rate plays a key role in controlling the particle size of MSNs, if the rate is slow long fibers produced whereas upon fast stirring fine powder is formed [24]. The effect of pH on morphology of MSNs was studied by Ozin et al. and demonstrates that under mild acidic condition spherical mesoporous particles with the range of 1-10 μm are formed [25]. Brinker et al. used a technique to synthesize MSNs ranging from 100-500 nm by evaporating solvent from aerosol containing silica source and surfactant [26].

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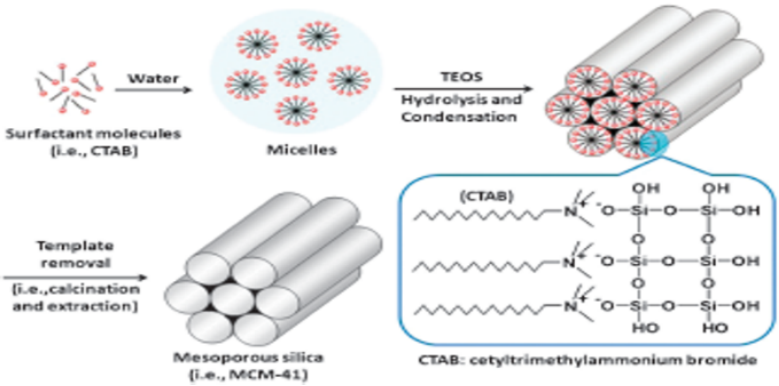


Figure 1: Diagrammatic representation of the formation mechanism of MCM-41 [1].

To determine the particle size of MSNs electron microscopy was used but a now-a-days dynamic light scattering is preferred [27]. MSNs are widely used in biomedical field because MSN's can work on sub-cellular level due to its smaller then eukaryotic cells. The interaction of MSN with living animals, plants and bacterial cells at extracellular [28] and intracellular levels [8,9,29] is demonstrated by Lin et al.. Lin et al. studied spherical and tubular MSNs on cancer and non-cancer cells and concluded that spherical MSNs has less ability to taken up by the cancer and non-cancer cells as compare to tubular one [30].

Pore size

The parameters that are used to control the pore structure of MSNs are:

- Amount of silica source and surfactant [31].
- Packing capacity of surfactant [22].

The aggregation of surfactant in solution depends on pH and concentration of the solution. MSNs are synthesized at both acidic and basic pH with different pore structures. For example, lamellar meso phases are synthesized at high pH (>12), while hexagonal structures are produced at basic pH (10-12) [20].

Lin et al. obtained different antibacterial effects in ionic liquid containing MSNs by changing the pore structure, cylindrical channels to twisted one [3].

Hydrothermal treatment during synthesis or post-synthesis is used to adjust the pore width. The selection of surfactant with different hydrophobic chain length or by using mesitylene as swelling agent plays an important role in production of desired pore size [32,33]. Pore expansion can be done by using additives during synthesis and for this purpose additional tuning is required because additives have a property to change the hydrophobic-hydrophilic balance. Mesitylene is used as a pore expander of MSNs from 3-5 nm without altering its particle size and these MSNs with enlarge pores are used as vehicle to deliver membrane impermeable protein in cancer cells [34].

In hydrothermal treatment during post-synthesis a freshly prepared material is subjected to autogenic pressure at temperature ranging from 373 K to 423 K with or without additives, is done to increase the pore size without changing the morphology of pre-formed particles [22,35-37]. A group of Ying, Botella and Corma demonstrated the control of pores size and particle size by using fluorocarbon-based surfactant with polymer-based surfactant [38,39].

X-ray diffraction and transmission electron microscopy (TEM) are used to measure pore structure of MSNs while nitrogen sorption is used to measure the pore width. The 2D hexagonal *p6m* (MCM-41), the 3D cubic *Ia3d* (MCM-48) and the lamellar *p2* (MCM-50) are the common mesophases in silicas with pore sizes between 2 and 5 nm [31]. Similarly, 2D hexagonal *p6m* is reported in MSNs with large pore size 6-20 nm [33].

Surface area

The surface area of the MSNs is the most determining factor for the quantity of adsorbed pharmaceutical products. To control the amount of incorporated drug in the matrix two different approaches are used increasing or decreasing the surface area and modifying the surface drug affinity. This demonstrates that the surface area is directly proportional to the amount of drug adsorbed. MCM-41 is synthesized by surface area (S_{BET} value) 1157 m^2g^{-1} and SBA-15 with surface area value of 719 m^2g^{-1}. When alendronate is loaded in MSNs under same conditions, 139 mg g^{-1} of drug is loaded in MCM-41 while 83 mg g^{-1} in SBA-15. It indicates that surface area value closely related with maximum loading of the drug [40,41].

In another study of Lin et al., biocompatibility of MSNs with RBCs study concluded that large surface area of MSNs is rich in hemolytic silanol group which cause high toxicity [42].

Pore volume

Generally, the pore volume in the range 2 cm^3g^{-1} when the pore size is less than 15 nm and surface area is about 1000 m^2g^{-1}. The interaction of drug with mesopores is surface phenomenon while poor drug-drug interactions may lead to the pore filling. The amount of drug adsorbed can be determined by pore volume. In ordered mesoporous material many consecutive loading of the drug cause large filling of mesopores due to which drug-intermolecular interactions within pore wide is increased. It indicates that pore volume and amount of drug loaded are directly proportional to each other [43].

Functionalization of Mesoporous Silica Nanoparticles

Surface functionalization of mesoporous material by using organic groups is a mile stone in the development of mesoporous silica nanoparticles [44-48].

The functionalization with organic groups, involves in controlling drug absorption and drug release. High density silanol groups are synthesized by grafting organic silanes ($(RO)_3SiR'$) on the surface of mesoporous silica material. The comparison of the several drugs with the use of various functional groups is shown in the Figure 2.

Increased drug-surface interaction is most useful method to control drug release. For this, modification with chemical groups on the surface of MSNs is done which link the drug molecule through ionic bonds/ ester groups [49]. Adsorption of ibuprofen (IBU) is extensively studied on functionalized matrices. Incorporation of IBU on the surface of mesoporous silica nanoparticles is done on the assumption that carboxy group links to silanol group as shown in the Figure 3.

But in case of non-functionalized matrices, drug-drug interactions lead to the formation of IBU dimer [50] by an intermolecular hydrogen bond through carboxy group. Babonneau et al. [51,52] study the behavior of mesoporous silica particles with IBU by using NMR and demonstrate the incompatibility of IBU with molecules situated on the pore wall of the mesoporous silica and it occurs due to their high mobility.

Maria Vallet-Regi et al. and Song et al. explained the release of IBU from MCM-41 and SBA-15, respectively, which is functionalized with amino groups, can be controlled due to the ionic interaction between the carboxy group present in IBU and amino group present on the matrix surface [53,54]. After NMR analysis, it was concluded that IBU dimer hydrogen bonds had weak bonding at the surface of MSN as compare to drug-surface ionic interactions.

Maria Vallet-Regi et al. incorporated alendronate drug in amino-functionalized MCM-41 and SBA-15 mesoporous silica material as shown in Figure 4.

Initially, amino group was added to functionalize the surface of pore wall. After 24 hours, it was observed that modification in the pore wall of mesoporous silica material increase the drug loading capacity by almost 3 times as compare to the unmodified material. In case of

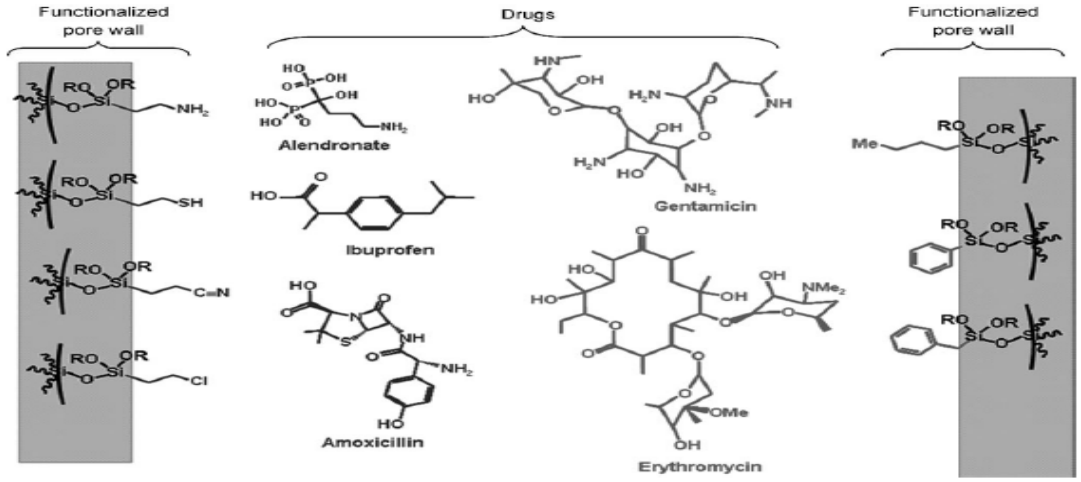
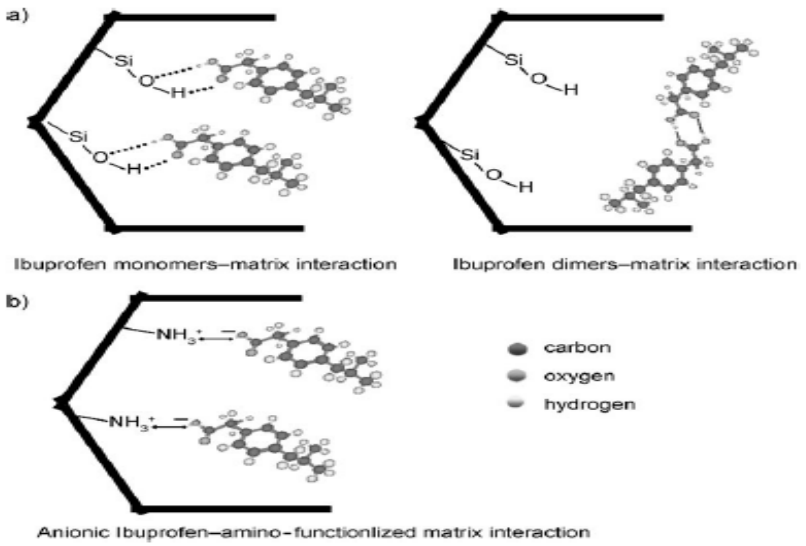


Figure 2: Functionalization of the wall of MSNs and the use of different drugs with various functional groups [40].



(a) *Non-functionalized matrix:* The weak hydrogen bonding between carboxylic acid and silanol groups present in IBU is shown which form physisorbed dimer molecule at the surface.
(b) *Amino-functionalized matrix:* Strong ionic bond between carboxylate and ammonium groups linked IBU to the pore wall [41].

Figure 3: Linkage of silica mesoporous material of Ibuprofen (IBU).

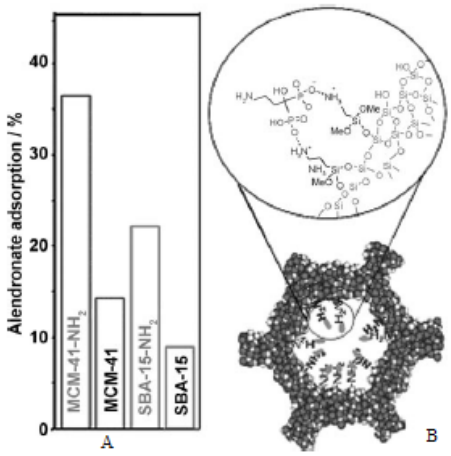


Figure 4: A: Loading of drug (alendronate) in ordered mesoporous materials. **B:** Illustration of chemical bonding present between the drug amino-functionalized mesoporous material [40,41].

unmodified material, phosphonate groups of alendronates chemically interact with silanol group but in case of modified material phosphonate groups react with amino groups present on the mesopores surface.

The interaction between amino groups and phosphonate groups is stronger as compare to silanol groups and phosphonate groups at pH 4.8. 22% of alendronate can be adsorbed on the amino-modified material i.e., SBA-15-NH_2 and 37% of alendronate adsorbed on MCM-41-NH_2. While 8% of drug can be adsorbed on unmodified material SBA-15 and 14% of drug adsorbed on MCM-41. The drug slowly released at physiological pH (7.4) occurs because of the weakening of the adsorbed molecule due to the differences in polarity between silica surface and the bisphosphonate [41].

Surface functionalization of mesoporous silica material by using hydrophobic species is another effective method to control the drug release. By using this method, drug release from the matrix is increased because of inability of aqueous medium to penetrate into the pores but the drug-surface interactions remain same. Maria Vallet-Regi et al. incorporate erythromycin in SBA-15 material containing hydrophobic species [15]. Treatment of the mesoporous silica material with trimethoxyoctylsilnane and trimethoxyoctadecylsilane resulted into functionalized surfaces of octyl and octadecyl moieties, respectively. The modified SBA-15 has decrease pore size and decrease wetting property by aqueous solution as compare to non-functionalized SBA-15.

Similarly, mesoporous material can be functionalized by silylation, which resulted into decrease loading of captopril [55] and ibuprofen [56]. By regulating the degree of silylation well-defined controlled drug release will occur [41].

Another attractive targeted drug delivery application is magnetic nanoparticle. It works by providing the desired location to the particle and hold it until the therapy is completed [57]. Mostly this system of drug delivery helpful in cancer-therapy drugs because of their toxic effects. In order to minimize the limitations in the field of drug delivery, mesoporous silica matrix combined with iron oxide particles [58-61]. The construction of iron-oxide based mesoporous silica-based drug delivery system has got much interesting in recent studies. Piaoping Yang et al. grouped the iron-oxide based magnetic mesoporous silica material into 4 basic structures as shown in Figure 5.

Core-shell structure

For core-shell structure so called bottom-up approach is used as synthetic strategy. In this strategy, core and shell are fabricated in an inside to outside order. These specialized core-shell structures provide high magnetization up to 50 $emug^{-1}$ [62,63]. This mesoporous silica shell act as a good drug carrier by providing sufficient surface area and pore volume to store and release the drug [1].

Embedded structure

The example of embedded structure is fibrous mesoporous silica mesosphere i.e., Fe_3O_4/FMSMs which hold sustain drug release profile sufficient magnetic response and redispersibility to the external magnetic field as shown in Figures 6A and 6B. Figures 6C-6E illustrate that DOX is present into the cytoplasm and nucleus of cell so that it means DOX-Fe_3O_4/FMSMs has the ability to reach the cytoplasm as well as nucleus to kill the cell. This DOX delivery could be used as therapeutically effective system only when DOX have increased intracellular delivery and extracellular protection by DOX-Fe_3O_4/FMSMs.

Rattle-type particles

In previous few years rattle-type particles are used as controlled drug delivery carriers with large hollow interior spaces mesoporous silica shells and functional cores. A series of rattle-type Fe_3O_4/Fe_2O_3@$mSiO_2$ hollow spheres are synthesized with either single double mesoporous silica shell by Shi et al. [64-68]. In their study, they prove that due to the removal of in-between silica layer, the saturation magnetization value of rattle type hollow structure is higher as compare to corresponding pore structure with intact middle silica layer [65]. The calculated surface area of rattle type structure is 435 m^2g^{-1} and pore volume is 0.58 cm^3g^{-1} while for intact middle silica layer the surface area is 274 m^2g^{-1} and pore volume is 0.38 cm^3g^{-1}. Due to this reason rattle-type structure is more appropriate for targeting drug delivery as compare to core shell and embedded structures.

Magnetite (Fe_3O_4) capped $mSiO_2$

In this system, drug molecules in mesopores are capped by different types of "gatekeppers" includes nanoparticles, liner molecules macrocyclic organic molecule and polymer multilayer are investigated. To avoid any premature release drug molecule are blocked inside the

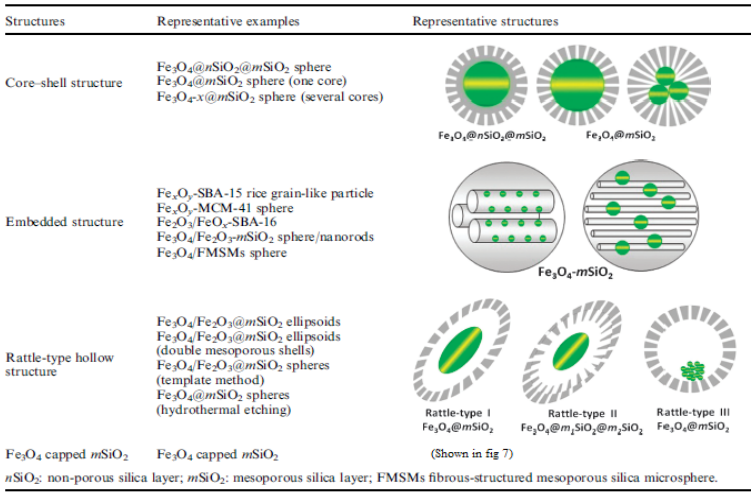


Figure 5: Functionalized structures of Fe_3O_4/ Fe_2O_3 mesoporous silica particles [1].

mesoporous silica host. The release of drug molecules can only be possible upon exposure to the stimuli which has ability to release pore-entrapped drug. The major types of gatekeppers include:

Structure I: *(NPs-gatekeeping system)* In this system, modified surface of mesoporous silica is covered with solid NPs and these can be removed with different external stimuli like pH, temperature, redox potential by destroying the chemical bond.

Structure II: *(Macrocyclic organic molecule gatekeeper)* Macrocyclic organic molecules (a- or b-cyclodextrin, cucurbit [6] uril, and dibenzo-24-crown-8) holds on immobilized stalk to form a cap on the pores. This supramolecular is dismissed by external stimuli to release the entrapped drug.

Structure III: *(Liner molecules)* For structure 3 stimuli responsive linear molecule are attached to the external surface of mesopores due to which a "close/open" mechanism of liner molecule is arouse.

Structure IV: *(Multi-layers shell coating)* In this structure, to cap the mesopores channels a stimuli responsive polymer layer, biomolecule or polyelectrolyte multilayer is coated on the surface of mesoporous silica particles. The drug molecule diffuses out of the matrix when the system is stimulated.

Structure V: *(Pores modification)* In structure V, multi-responsive polymer or nano-impellers are used to functionalize the pore interior. As shown in Figure 7 [1].

Synthesis of Mesoporous Silica Nanoparticles

Initially, the groups of Cia [69], Mann [70] and Ostafin [71] successfully synthesized and reported mesoporous silica nanoparticles. After that the term "MSNs" became familiar when Victor Lin introduces mesoporous silica nano spheres [28]. In last, few years mesoporous silica nanoparticles have been synthesized with multiple dimensions, pore sizes, pore structure and morphologies. MSNs can be synthesized by multiple adjustments in synthesis conditions like pH change, using different surfactants or co-polymers, and with different concentrations and sources of silica. In the synthesis of an ideal MSNs the characteristics like well suspended stable solution, controlled and uniform particle size, controlled pore size and large pore volume must be considered [13]. Furthermore, two conditions need to be satisfied during synthesis of MSNs (a) Well controlled nucleation and growth rate of MSNs. (b) Non-sticky nature of MSNs [72]. Various synthesis methods of MSNs are discussed below.

Growth-quench approach

To quench the silica condensation reaction, Mann et al. [70] firstly used dilution and pH change method to prepare sub-100 nm MSNs. The particle size of MSNs may vary from 23-100 nm by using in different time-delays between dilution and neutralization steps [72]. Triethanolamine [73] and alcohol co-solvents [74] are used as reaction slowing agent due to their silicon-chelating capability. Recently, Suteewong et al. [75] reported MSNs with cubic pore structure having high laminated functionality, are synthesized in which to quench the growth of MSNs ethyl acetate is used.

Limitations: From pH quench approach, less ordered and less stable MSNs materials are resulted due to poor condensation of silica. Similarly, in dilution quench approach scaling up may occur [72]. Considerable time and energy is required to collect MSNs from highly diluted solution [13].

Separation of nucleation and growth

Mou et al. introduce a process to prepare mono-disperse MSNs in a dilute alkaline solution in two steps i.e., by separating the nuclei formation and particle growth [76]. La Mer diagram clearly explains nucleation and growth steps. In the first step of nucleation (Figure 8A), a transparent solution of micelle/ silicate clusters containing nuclei are formed by adding the whole quantity of surfactant (CTAB) and small quantity of TEOS. In second step to initiate the growth process (Figure 8B), a large quantity of TEOS is added. Uniform finite size of particles is obtained due to the exhaustion of material in growth acceleration process.

The resultant MSNs possesses ideal structure order and showing 4 XRD peaks for 100 nm size of MSNs. No aggregation of MSNs occurs when it shows hexagonal facets. Small particle size can be achieved at low pH [77], and by decreasing the amount of ammonia use (i.e., 280 nm to 30 nm). This method is considered to be size-focusing [78] as it gives very sharp size and shape distribution. Lin et al. obtain regular hexagons having 2D photonic crystal-like structure [79].

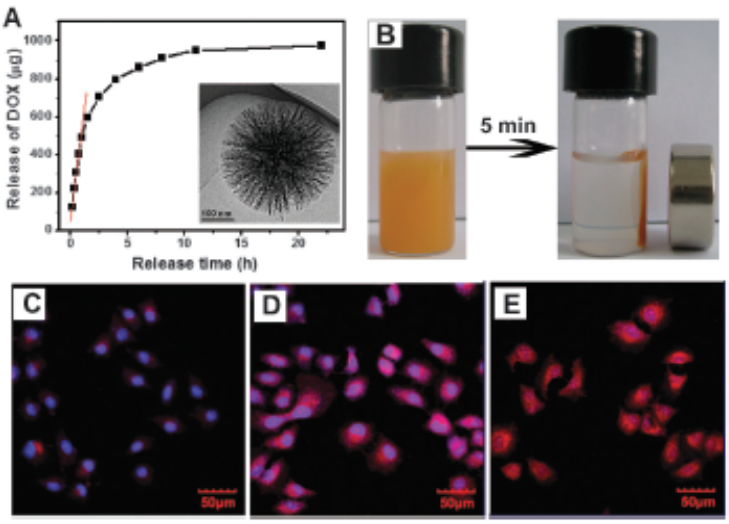


Figure 6: (A) Illustration of Drug-release profile of DOX–Fe_3O_4/FMSMs in PBS buffer in TEM image. **(B)** By using magnet separation process of Fe_3O_4/FMSMs. Images of incubated HeLa cell with DOX–Fe_3O_4/FMSMs ([DOX]=2 mM) for 10 min using Confocal laser scanning microscopy (CLSM) **(C)**, 60 minutes **(D)**, and 6 hours **(E)** at 37°C, blue colour being dyed by Hoechst 33324=the merged images of both the nuclei of cells and red=DOX fluorescence in cells [125].

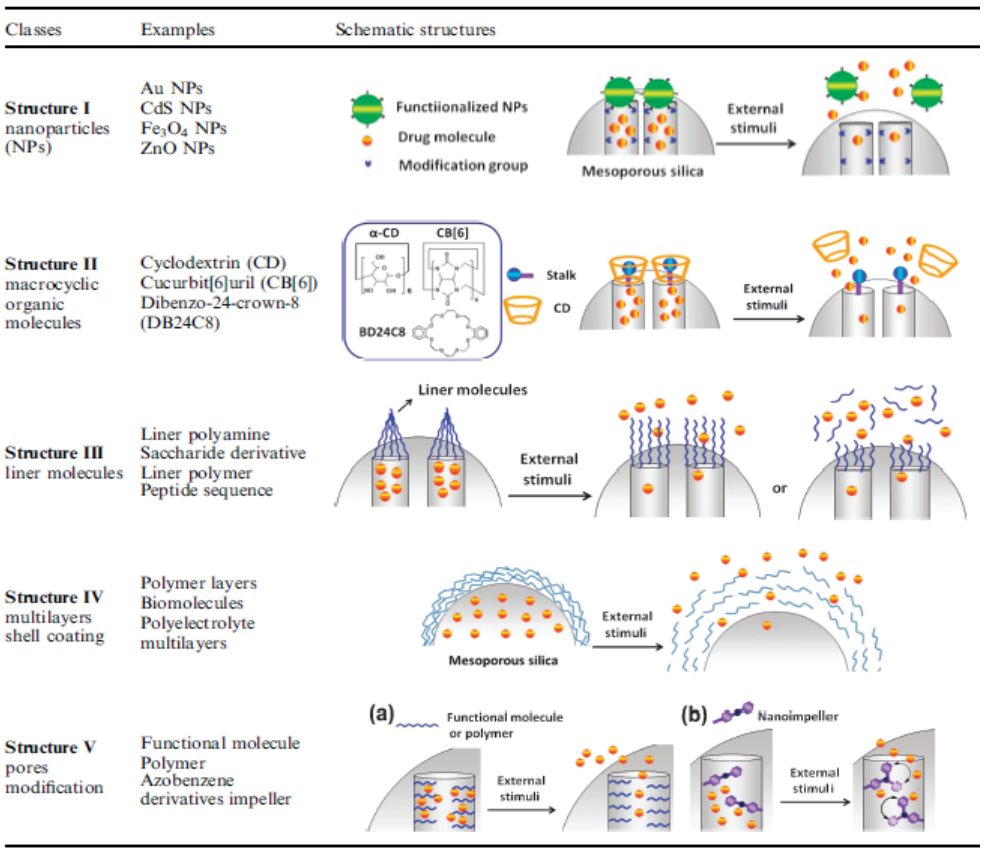


Figure 7: Fusion of different gatekeepers on the pores of MSNs in stimuli-responsive CDDSs [1].

Stober method and its modifications

Stober et al. discovered "Stober method" which is used to synthesis monodispersed silica particles. By using this method silica and non-silica particles can be synthesized. The particles having diameter from tens of nanometers to a few microns can be obtained. In this method hydrolysis of tetraalkyl silicates in a mixture of alcohol and water is involved using ammonia as a catalyst [80-82].

Grun et al. redesign stober method by changing the composition

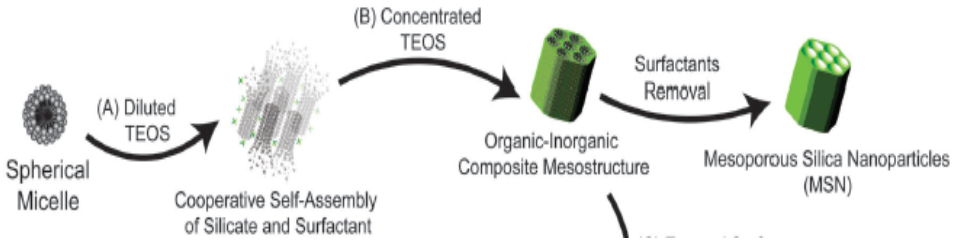


Figure 8: Schematic representation of MSNs synthesis [77].

of stober synthetic method. They obtained sub-micrometer sized MCM-41 spherical particle by using cationic surfactant in the reaction mixture [83]. Likewise, uniform MSNs with different pore sizes and pore structures are obtained by using mixture of alcohol water and ammonia [84].

In later studies, it was discovered that at the initial stage of synthesis, the sudden aggregation of small clusters leads to the synthesis of MSNs. And then residual silica precursors react with the surface silanols on MSNs particles [85].

Nooney et al. prepared mesoporous silica nanoparticles with the size ranging from 65 to 740 nm by using different ratio of tetraethyl orthosilicate (TEOS) surfactant under dilute conditions. They also used neutral (*n*-dodecylamine) and cationic (CTAB) surfactants as templates in their experiment [71].

Qiao et al. found that decrease in pH from 10.0 to 6.0 lead to increase the size of MSNs from 30 nm to 85 nm due to decrease condensation rate [86].

Furthermore, Chiang et al. studied all the parameters that can influence the particle size of MSNs and concluded that pH value played a key role in controlling the size of MSNs as shown in Figure 9 [87]. Moreover, Lin et al. demonstrated that the MCM-48-type MSNs diameter ranging from 70-500 nm can be obtained by adding different amounts of Pluronic F127. They also used CTAB, Pluronic F127, NH_4OH and TEOS to synthesis MCM-48-type MSNs [88].

Hollow silica nanoparticles synthesis

Soft templating method: Hollow silica nanoparticles, is a sub-class of mesoporous silica nanoparticles and is denoted by HSNs. Because of the important MSNs applications in drug release and bio-sensing, hollow MSNs are prepared which increases the drug loading capacity and pore volume of the MSNs [89]. Soft templating method for the preparation of mesoporous silica nanoparticles (MSNs) includes:

- Single micelle-templating.
- Vesicle-templating.
- Micro-emulsion-templating.

***Single micelle-templating*:** Yang et al. synthesized small hollow organosilica nanotubes and nano-spheres by using sufficient amount of organosilica as a precursor and Pluronic triblock copolymer with the different hydrophobicity [90,91]. Mandal and Kruk produced HSNs of varying size by using Pluronic F127 block copolymer template synthesis of ethylene-bridged organosilicas in the presence of swelling agent [92]. Cationic block copolymer micelle used under conditions i.e., pH 7.2 at 20°C. For the deposition of silicate in aqueous solution [93].

***Vesicle-templating*:** Vesicle templating method is used to further increase the size of HSNs. As a source of silica, mixture of silanes and silicates are used as well as cationic surfactant and anionic co-surfactants are involved to lower the curvature as meso-structural templates [94]. Co-condensation process is used to synthesis uniform MSNs with the size of 25-105 nm. This process involves the co-codensation of tetraethylorthosilicate (TEOS) and organotriethoxysilanes in an alkaline aqueous solution containing triethanolamine and cationic surfactant cetyltrimethylammonium chloride (CTACI) [95].

Another important method to prepare mesoporous silica nano-rods and hollow spheres are to use a mixture of single tailed anionic and cationic surfactants. These surfactants lead to the formation of a variety of meso-structures like cylindrical micelles, spherical micelles and vesicles as shown in Figure 10. These micelles have various remarkable morphologies and act as organic templates or the synthesis of desired forms of mesoporous silica nanoparticles. Then, at a pH where templates and silica species have matching interactions, condensates around the curved surfaces produce silica nanoparticles with organic structures [96].

***Micro-emulsion-templating*:** For the preparation of hollow mesoporous silica nanoparticles, a stable micro-emulsion of oil-in-water (o/w) is used. This emulsion is prepared by mixing oil, water, surfactant and small amount of alkaline solution. These hollow silica nano-spheres are prepared by controlling condensation of silica framework and silica shell thickness [97].

Mou et al. introduced another method in which they used water-in-oil (w/o) emulsion consisting of water, hydrocarbons and cationic surfactants, and prepared thermally stable nanoparticles [98,99].

Hollow silica nanospheres with relatively large mesopores on its outer surface are synthesized by Hao et al. In this method 1, 3, 5-trimethylbenzene (TMB) act as a swelling agent and triblock copolymer Pluronic F127 act as a template in the presence of an inorganic salt i.e., potassium chloride [100].

Hard templating method: In biomedical field, both discrete and mono-dispersed MSNs plays a key role in providing enough stability in physiological environment and its nano-size provides effective distribution of a drug in the body. Because of their hollow interior, MSNs have large capacity to load biomedicines, enzymes, or nanoparticles and ligands.

In mono-dispersed MSNs, products polymer lattices, metal oxides and silica colloids are used in hard template method. High-fidelity inorganic silica replica of hard template method requires 3 basic measures:

- Saturation of silica at the surface of organic template is a fast process as compare to self-condensation of silica species in

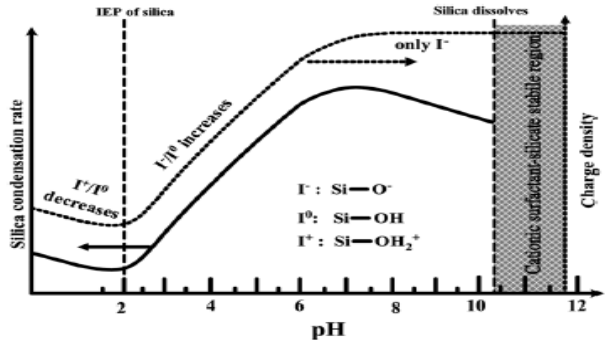


Figure 9: Graphical representation of effect of pH on the charge density and silica condensation rate on the surface of the silica species [87].

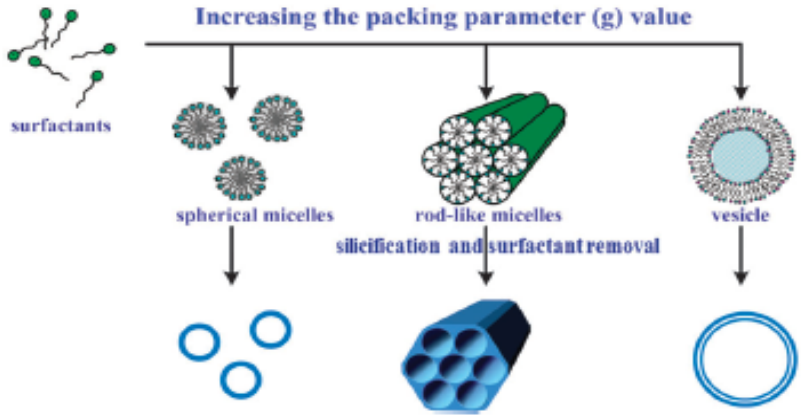


Figure 10: Synthesis of mesoporous silica hollow nanospheres, nano-rods and hollow spheres from spherical micelles, cylindrical micelles and vesicles, respectively by using soft surfactant-templating approaches. Adapted from reference [96].

bulk solution. For this silicate surface must have a suitable functional group for its recognition under appropriate reaction conditions.

- In the whole process of silicate deposition and condensation, stability of organic template is essential. The stronger interaction of any of the components of surface activated template with silicates may lead to the failure of silica casting. Due to this, the original organic template leaches out and gathered at the surface of silicates rather than the organic template surface.
- The sacrificial template approach is used to remove template without breaking inorganic silica cast. In this approach, dissolvable or combustible internal part can be removed after solvent extraction, acid-dissolution and calcination under mild conditions [13].

Hard templating method for the preparation of mesoporous silica nanoparticles (MSNs) includes:

- Polymer latexes-templating.
- Metal or metal oxide nanoparticles.

***Polymer latexes-templating*:** On the surface of polymer latex, silicification occurs through surface activation by using suitable functional group. A layer-by-layer deposition technique *via* electrostatic attractive interaction is used to introduce functional group for silica gelation, as surface activation method [101].

To avoid the leaching of capping agents during the process of silica deposition, the strong interaction between functional group and polymer latex is needed. However, polymer latex templating method is avoided because it is a complex procedure for surface modification.

By controlling the pH values, we can achieve high integrity of MSNs. Meso-structure and pore size of silica shell depends on type of surfactant used. Likewise, mesoporous silica replicas can be synthesized by using appropriate ratio of surfactant or polymer/ latex as shown in Figure 11. Along with hollow MSNs broken mesoporous silica particulates are formed at both lower and higher ratio [13].

Metal or metal oxide nanoparticles: Discrete and mono-dispersed single Fe_3O_4 nanocrystals@ mesoporous silica are prepared by Kim et al. For this purpose cetyltrimethylammonium bromide (CTAB) is used as stabilizer and mesostructural directing agents [102]. In another similar study, Liong et al. proposed a method to synthesis MSNs in which mesoporous silica surround the iron nanoparticles, pores contain the hydrophobic anti-cancer ligand, whereas, folic acid and phosphonate are used for surface modification [59]. The thickness of mesoporous silica shells can be controlled by adjusting the ratio of surfactant and amount of silica source [13].

Furthermore, a mixture of anionic and zwitter ionic surfactant is used to form vesicles in order to encapsulate the MSNs. The protonated amino-silica is added into the silica source to match the interaction with negatively charge surface. Different yolk-like silica shell structures synthesized after hydrolysis and condensation. These yolks can be Fe_2O_3 nano-spindle or silica beads [103].

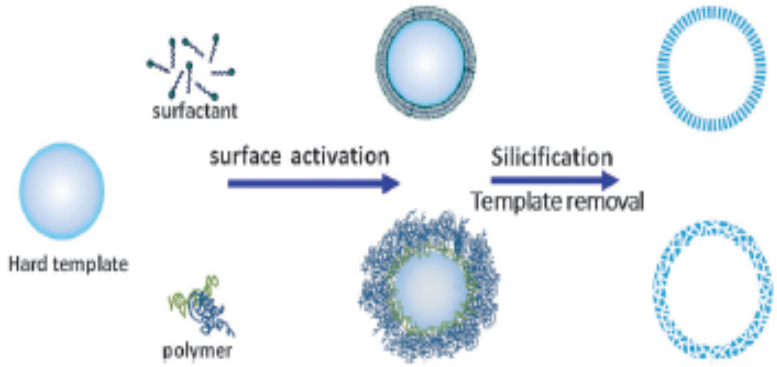


Figure 11: Synthesis of HSN spheres by using surfactant or polymer for surface activation through hard-templating method. Adapted from reference [13].

Applications of Mesoporous Silica Nanoparticles

Mesoporous silica nanoparticles (MSNs) have a number of potential applications depending upon the nature of pore, size, shape and connectivity of mesoporous silica particles as we discussed earlier in detail [41]. In catalysis, the short channels of mesoporous silica nanoparticles support solids for highly accessible active sites [13]. By changing surface morphology mesoporous silica nanoparticles based catalysts can manufactured by inserting different functional group as well as different metal oxides and metal complexes [104,105]. Mesoporous silica nanoparticles contain small channels as compare to mesoporous silica bulk material which improves transport of large molecules for example, biomolecule and biodiesels. That's why reactant and product molecule use nano-channels and do not attain long route [13].

The biological application of mesoporous silica nanoparticles includes imaging and diagnostic agents, specificity, dispersibility and capability to load and deliver of high concentration of different molecules [106].

Imaging and diagnostic agents

Mesoporous silica nanoparticles are used for quantitative imaging for a longer time period, when use in small dosage and it has ability to eliminate from the body when the imaging process is complete. For this purpose, silica-based imaging nano-probes are extensively used for optical resonance imaging and magnetic resonance imaging (MRI) or a combination of both [107]. Bio-distribution, cancer cell targeting efficiency, cytotoxicity, internalization pathway and the progress of the therapy is observed well by direct method of imaging of mesoporous silica nanoparticles. The core material can be filled with therapeutic agents, quantum dots and fluorescent dyes like Fluorescein isothiocyanate (FITC) and rhodamine B isothiocyanate (RITC). The most commonly used Near-IR dyes for imaging includes AlexaFluor 700 and DyLight 680. The fluorescent mesoporous silica nanoparticles that are resulted have the ability to generate high resolution, provide quantitative data and multichannel images.

Target specificity

Mesoporous silica nanoparticles can be used on the intended areas to reduce non-specific binding and to increase specific binding to target cell or tissue. Both passive and active targeting specificity plays a major role in increasing bioavailability [106]. Target specificity of mesoporous silica nanoparticles decreases the dosage of drug and eliminates the harmful toxic effects of drugs after administration [108].

Passive targeting increases permeability of tumor blood vessels and allow the accumulation of nanocarriers at tumor site. But decrease therapeutic efficacy, drug expulsion and multiple drug resistance occurs due to the lack cell specificity [109]. Binding and internalization of nanocarrier can be increase by selective targeting i.e., specific interaction of drugs with receptor site [110]. This could only be happen when cancer cells or tumor cells are highly exposed with receptors (10^4-10^5 copies/cell) as compare to normal healthy cell [106]. Xia et al. manifested that if mesoporous silica nanoparticles coated with cationic polymer (PEI), it will increase the uptake of MSN [111]. Meng et al. proved that increase EPR effect can be achieved on xenograft model by both controlling the size and addition of PEI/PEG copolymers as a coating material [112].

In active targeting, surface modification of MSN with cancer specific targeting drugs increase the specificity of drug to the cancer cells as compare to normal healthy cells [113]. For this purpose biologically active drug like folate, RGD peptide and transferrin are used [114]. For instance, folic acid as folate receptors are extensively use in many types of human cancers includes endometrial breast colorectal, lungs and ovarian [113,115]. More efficient drug delivery requires high specificity and binding affinity which can be achieved through high concentration of surface conjugated drug molecule that ultimately enhances multivalent binding effects as shown in Figure 12 [111].

Capability to load and deliver of high concentration of different molecules

The loading of high concentration of various classes and multiple cargos is achieved by large surface area and through controlling the surface chemistry of MSNs, and it enter into the cell through the process of endocytosis and macropinocytosis as shown in Figure 12 [116-118]. Initially, drugs having low solubility in water like ibuprofen and aspirin were used for drug delivery through MSNs [10]. Lu and Liong et al. latterly worked on mesoporous silica nanoparticles for the delivery of hydrophobic chemotherapeutic agent, camptothecin, into cancer cells [119]. The mesoporous silica nanoparticles have large surface area and pore volume which permit hydrophobic ligands to enter into the pores, from non-aqueous environment and retained in aqueous environment. But in case of hydrophilic drugs further changes of MSNs is required. Such as, Meng and Liong et al. enables loading and retention of positively charge hydrophilic drug, doxorubicin (DOX) by using negatively charge group on the surface of MSNs [120]. The capacity of doxorubicin in MSNs is 1000 times greater than FDA approved Doxil because of its attractive electrostatic interaction and high surface area [117].

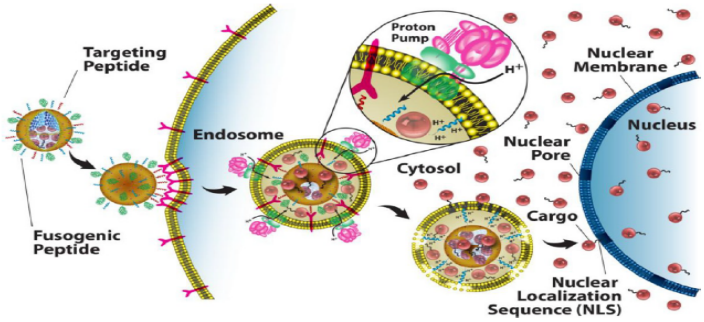


Figure 12: Schematic diagram shows (1) enhanced multivalent binding, (2) internalization of targeted MSNs-supported lipid bilayers, (3) endosomal escape and (4) nuclear localization of MSNs-encapsulated cargo. Adapted from reference [111].

Dispersibility

For biomedical application MSN must remain dispersed for its stability and its aggregation must be avoided because due to this cell internalization suffers, its distribution in body become difficult to control and enlarge particle size causes high toxicity [106]. By chemical modification of the surface of MSNs, [119] coating with proteins and polymers [112] and lipid bilayer coating particle aggregation can be decreased [117,118,121]. By using these methods steric hindrance and electrostatic repulsion is achieved, as a result stable saline dispersion of MSNs is formed [106].

Other applications include bio-sensing and cell tracing, use in optoelectronic devices, CdS nanoparticle-capped MSNs use for delivery of drug molecules/ neurotransmitters.

Bio sensing and cell tracing

The versatile surface chemistry and small particle size of MSNs work as a sensor system for the detection of target within individual cell both *in vivo* and *in vitro* [122]. Nanoparticles have the ability to avoid fluorescence, self-quenching and other diffusion related issues. This capability of mesoporous silica nanoparticles to functionalize its surface with greater amount of cell recognizing agents or other site-directing compounds make MSNs an excellent cell tracing agent [123].

Use in optoelectronic devices

A transparent silica-polymer, having high mechanical strength and low thermal expansion, can be synthesis by accurate surface modification of MSNs [124]. These high transparency MSNs-polymers are used in optoelectronic devices like optical fibers LED or solar cell covers, and light guide films [13].

CdS nanoparticle-capped MSNs

Lin et al. explained the stimuli-responsive controlled release system in MSNs as shown in Figure 13 [28]. The CdS nanocrystals with mercaptoacetic acid coating were chemically prepared as removable caps to block MSNs and encapsulated drugs/ neurotransmitters. With the help of various di-sulphide reducing agents, the di-sulphide linkage between MSNs and CdS caps were cleaved and the entrapped contents released from the channel [13].

Conclusion

In conclusion, this review highlighted many exciting progresses of researchers on mesoporous silica-based nanoparticles. Due to the discovery of this novel drug delivery system, has shown greater potential and encouragement for the researchers to work on it. These particles with diverse nature and even size smaller than eukaryotic cell have capability to cross the cell. Moreover, it is an excellent alternative to conventional systems for oral administration, due to zero premature release. For long term therapies, by changing external stimuli there is a possibility to control the kinetic release of drug more efficiently.

MSNs are promising nanocarriers to transport highly toxic drugs like chemotherapeutic agents with site specific characteristics to kill only tumor cells. MSNs have stimuli responsive drug release which enhances and minimizes the side effects of anti-cancer drugs in therapy.

Morphological changes help in modifying mesoporous silica material to produce diversified forms of material. By changing pH and stirring rate produces hundreds of microns up to milliliters of particle size and different pore structures. Mesitylene, as a pore expander of MSNs has the best capability to increase pore size without affecting the particle size. Two approaches required to control the amount of incorporated drug i.e., by increasing or decreasing the surface area and by modifying the surface drug affinity of the MSNs. Modification in the pore wall of MSNs increases the drug loading capacity by many times as compare to the unmodified material.

Hydrophobic species also explains the effective control of drug release. Similarly, functionalization with silylation decreases the loading of drug. Above all attractive targeted drug delivery application is magnetic nanoparticles. A synthetic strategy, core-shell structure provides high magnetization up to 50 $emug^{-1}$, which gives sufficient pore volume and surface area to store and release the drug.

Animal cell studies although successful on MSNs but there are still unsettle questions before practicing in vivo such as long-term stability, acute and chronic toxicities, bio-distribution, circulation properties and targeting efficacy. Particularly, detail study of bio-distribution and toxicology of this delivery system is needed before starting to be used in human beings.

In our review, different approaches are discussed of researchers for synthesizing the MSNs. Many of the methods are on high dilution and the concentration of the product is low typically in millimolar. Commercial production of such materials will be the major challenge for pharmaceutical industries due to their highly specific characteristic nature, collection, uniformity and reproducibility. There is still needed to focus on developing biodegradable templates to avoid it from environmental damage and cheaper sources of silica and organic templates to minimize the number of synthetic procedures, time saving for reactions, carry out synthesis under safe condition and also avoid the production of highly acidic or basic pH waste.

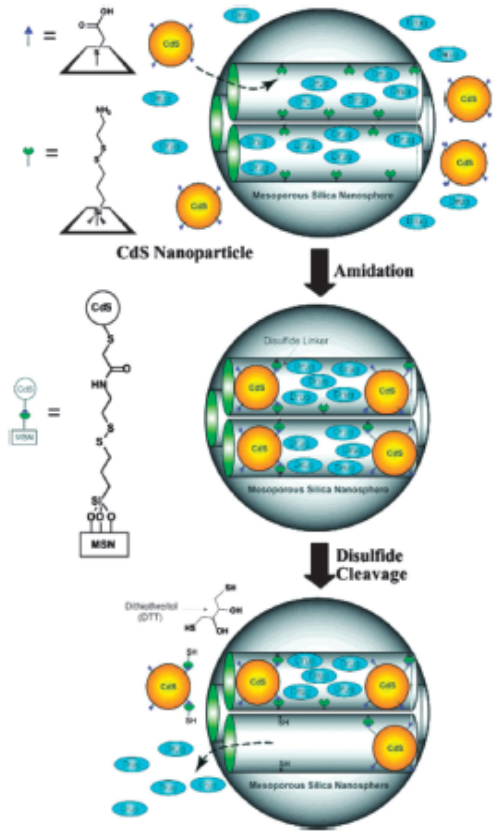


Figure 13: Diagrammatic representation of the CdS nanoparticle-capped MSN-based drug/ neurotransmitter delivery system. The chemical reduction of the disulfide linkage between the CdS caps and the MSN hosts provides controlled-release effect of the system. Adapted from reference [28].

Diversified nature of MSNs has a wonderful approach for applications like drug/ biomolecules/ gene delivery, targeted drug delivery for cancer drugs, as diagnostic and imaging agent, bio-sensing and cell tracing and many more.

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