

Review

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Smart mesoporous silica nanoparticles for controlled-release drug delivery

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Abstract: Stimuli-responsive controlled-release nanocarriers are promising vehicles for delivery of bioactive molecules that can minimize side effects and maximize efficiency. The release of the drug occurs when the nanocarrier is triggered by an internal or external stimulus. Mesoporous silica nanoparticles (MSN) can have drugs and bioactive cargos loaded into the high-capacity pores, and their release can be triggered by activation of a variety of stimulus-responsive molecular “gatekeepers” or “nanovalves.” In this mini-review, we discuss the basic concepts of MSN in targeted drug-release systems and cover different stimulus-responsive gatekeepers. Internal stimuli include redox, enzymes, and pH, while external stimuli include light, ultrasound, and magnetic fields, and temperature can either be internal or external.

Keywords: drug delivery systems; enzyme; light-responsive nanocarriers; magnetic; mesoporous silica nanoparticles; pH; redox; stimuli responsive; temperature.

1 Introduction

Advances in nano-biotechnology are providing many new concepts for targeted and controlled release of therapeutic molecules. Smart nanocarriers have been designed with stimulus-responsive moieties that can trigger cargo release only when and where it is required [1]. Mesoporous silica nanoparticles (MSNs) feature prominently in the range of nanocarriers used in Nanomedicine. MSNs were first introduced as drug delivery systems (DDS) in 2001 [2]. The unique properties of these inorganic nanomaterials, such as their nontoxic nature, high pore volume, no concerns with chemical or biological safety, the ability to functionalize the surface, and good biocompatibility, all combine to make them an ideal nanocarrier for DDS [3].

The presence of silanol groups on the silica surface allows good interactions with the phospholipid bilayers of living cells and stimulates endocytosis. The surface properties of MSN enhances their biocompatibility compared to other nanocarriers composed of metals or nanocarbon [4]. The surface properties of silica allow different types of functionalization to be applied in order improve the targeted delivery of therapeutic molecules [5]. Furthermore, the high stability of Si-O bonds protects the silica nanocarriers from biological degradation and lessens the requirement for other stabilizers such as the covalent cross-linking needed for proteins [6, 7].

The mesoporous spatial structure of silica leads to a high-capacity “honeycomb” structure that can be loaded with high concentrations of therapeutic compounds and can subsequently carry them higher to their targeted tissues, thereby reducing drug side effects by preventing drug leakage into the bloodstream [8]. Moreover, the surface properties of silica enable ready functionalization to enhance the loading and releasing of cargos [9]. A further advantage of MSN is that they can be generated through a simple and low-cost process, and their properties such as pore size and the diameter and shape of the nanoparticles can be controlled via the reversible

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condensation reaction that makes it possible to tailor the silica nanostructures [10–12].

Different types of precursors are used as a source of the silica in the synthesis procedure. Glyceroxysilanes and glyceroxysiloxanes are unaffected by pH, but are affected by ionic concentration and are not suitable for long-term storage [13]. Orthosilicic acid, owing to its slow reaction rate, requiring long preparation times, is not used anymore [14]. Tetraethyl orthosilicate and tetramethoxysilane, owing to their poor water solubility and a requirement for organic solvents and high temperatures, have only received limited use [15, 16]. Tetrakis (2-hydroxyethyl)orthosilicate has good biocompatibility, is water soluble, can form gels at relatively low temperatures, and has, therefore, been commonly used in many studies [17].

2 Design of MSN

The efficiency of drug loading and release of MSN depends strongly on the mesopore volume and diameter [18] and on chemical features characteristic of the surface functionalization [19]. The overall diameter of the nanovehicles is important because it governs the uptake into targeted cells, delivery of the drugs into the cytoplasm after uptake, and in the case of nucleic acid delivery into the nucleus [20]. As in many cases, the nanocarriers need to be small enough for endocytosis, the drug-loading capacity in each MSN is limited, but can be optimized by the preparation process and the chemical modification. Drug loading into MSNs mainly takes place via two methods: during synthesis of NPs or after synthesis of the nanocarrier, known as “post-sorption” [21]. Small drugs can be absorbed into the pores through physical adsorption. Surface Si-OH groups of the silica play a major role in this adsorption by providing two to four linking sites per nm. Positively charged water-soluble cargos can be loaded into the surface of the MSNs by ionic interactions, owing to the constitutive negative charge on MSN in physiological conditions. The efficiency of loading might be improved by the modification of the MSN surface by the addition of functional groups such as amines or carboxylic acids. On the other hand, hydrophobic drugs, which need to be dissolved in organic solvents, are transferred from the solvent into the MSN during the preparation process and are then fixed by removing the solvent by vacuum drying. The most important point to be taken into account in drug loading is the prevention of drug release prior to the vehicle reaching the active site. To this end, the drugs can be linked into the framework via a cleavable covalent linking bond, or the pore entrances

can be sealed by adding stimuli-responsive removable caps after loading [22].

Generally, the diameter of MSN varies from 50 to 450 nm. Studies have shown that MSN with diameters below 300 nm are favorable for delivery of therapeutic compounds through endocytosis [23], but in the case of larger particles, phagocytosis is the predominant mechanism of cell uptake. Larger nanoparticles may not be taken up into cells at all and are more likely to stimulate immune response [24].

According to the particular structure of the drug or other cargo, the dimensions and volume of the pores in the MSN would be different. The International Union of Pure and Applied Chemistry (IUPAC) has classified porous solid materials according to their pore diameter; if the diameter of pores is <2 nm, they are called “microporous,” in contrast, if the diameter of pores is >50 nm, they are called “macroporous,” and materials with a pore diameter between 2 and 50 nm are called “mesoporous” [25]. By increasing the mesoporosity, the loading efficiency and drug-carrying capacity will increase [26]. The honeycomb structure that can be tailored by preparation method and by functionalization is the most interesting feature of MSN [27].

To design a MSN with a desired morphology, structural components such as amphiphilic block copolymers and surfactant molecules play a major role. Broadly speaking, the morphology of MSN is spherical in shape. The overall structure of MSN can be divided into three distinct parts that can be independently functionalized for different purposes; the silica framework can be modified by attaching imaging agents to track the MSN for diagnostic purposes, the mesoporous structure and nanochannels can be linked to the bioactive molecules and drugs, and the outer surface possesses several silanol groups that can bind to different ligands to allow targeted delivery [28]. This basic overall structure is shown in Figure 1.

The surface of MSN contains a high number of Si-OH groups providing an attachment site for different types of functionalization [29]. These functional groups are important to control the charge present on the MSN surface, to allow loading with hydrophobic and/or hydrophilic drugs, and affect the loading efficiency of drugs. Some functional groups such as aromatic rings induce hydrophobicity on the surface of the MSN, thereby, preventing the loading with polar compounds into the mesopores [30, 31]. Additionally, the molecular dimensions of functional groups on the pore surface can directly influence the pore diameter; therefore, the size of the pores can be controlled by functionalization. On the other hand, these functional groups can be linked to other molecules such as fluorescent or

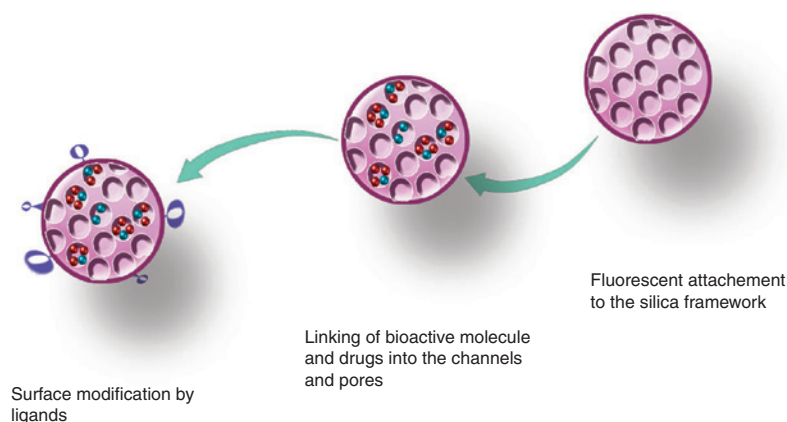


Figure 1: Basic structure of MSN.

other reporter molecules or to stimulus-responsive moieties [32]. The combination of these unique properties of MSN makes them promising vehicles for delivery of a variety of therapeutic compounds into targeted tissues and cells.

3 Smart MSN in drug delivery

After systemic administration of therapeutic drugs or other compounds, the molecules will distribute to all organs and parts of the body. Some natural protective systems such as the reticulo-endothelial system (RES) and the blood brain barrier are designed to prevent any damage to vital organs such as the liver, heart, kidney, and brain from these circulating exogenous compounds [33]. Therefore, in the design of a smart nanocarrier, two main requirements exist; first, the targeted delivery of an active compound with penetration through membranes and endocytosis to reach to the target site, and second, the ability of the carrier to escape from biological protective mechanisms such as opsonization and RES clearance. For smart nanocarriers, there is the need for modification and functionalization of their surface with moieties that are responsive to a range of different stimuli. These stimuli can be endogenous factors such as, redox [34], enzyme [35], and pH [36], or exogenous factors such as light [37], ultra sound, and magnetic fields [38, 39], or to temperature [40] that can either be endogenous or exogenous. Table 1 has summarized examples of different stimuli-responsive MSN.

3.1 Redox-responsive MSN

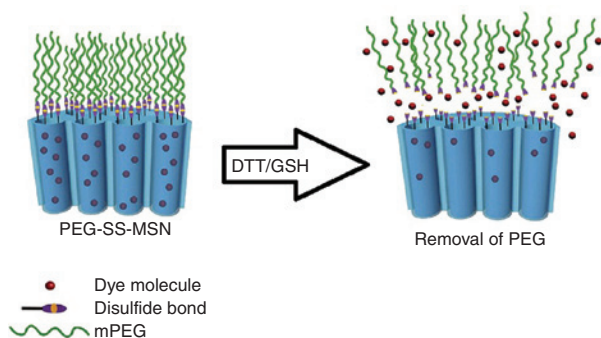
The difference between the reduction potential in the intracellular and extracellular environments provides

an opportunity to design nanoparticles that are specific for intracellular delivery [46]. The high concentration of glutathione in the intracellular milieu is the main reason for this difference; this is only 2–20 μM in the body fluids, while it is as high as 0.5–10 mM inside the cells [47]. Cancer tissues contain low concentrations of oxygen compared to normal tissue, and the concentration of GSH in cancer cells is at least four times higher than GSH in normal physiologic microenvironments [48]. In the presence of high concentration of glutathione, the thiol group of the cysteine residue acts as an electron donor and is responsible for the antioxidant scavenging activity of GSH. In reducing conditions, the thiol group donates an electron to the unstable disulfide bond of the gatekeepers in MSN. The reduced disulfide bond is broken down, the gatekeeper is removed, and two molecules of glutathione become joined together by a new disulfide bond as a GS-SG molecule [49]. Figure 2 illustrates the basic mechanism for the redox responsiveness of MSN.

The surface of MSN, due to the intrinsic property of silica, possesses an overall negative charge and can be easily noncovalently linked to cationic polymers or molecules such as the amphiphilic peptide RGD, IL13, collagen, polyethyleneimine (PEI), and poly (N-isopropylacrylamide) that can all act as a “cap” for sealing the MSN pores [50]. Wang et al. used amphiphilic polymers to function as a gatekeeper in doxorubicin (DOX)-loaded MSN. In this MSN, first, a stearic acid derivative (Cys-C1s) was attached through a disulfide linkage, to the surface of MSN, then an RGD sequence to target Integrin $\alpha_v\beta_3$ (C18-DSDSDSDSRGDS) was linked via a hydrophobic interaction with the octadecyl group, and finally, DOX was loaded into the modified MSN pores. RGD targeted the MSN to the tumor neovasculature, and then, the cap was removed due to cleavage of disulfide bound by

Table 1: Examples of stimuli-responsive MSN and some selected properties.

Stimulus	NP platform	Surface modification	Mechanism of action	Application	Drug loading method	Diameter	References
Redox	MSN-SS-PEG@RhB	Gatekeeper: polyethylene glycol (PEG) linked by disulfide bond to the MSN surface	Disulfide bond can be cleaved with high concentration of glutathione	Cargo release in reducing conditions	Stirring in the solution	100 nm	[41]
Enzyme	DOX@MSN-GFLGR7RGDS/ α -CD	Gatekeeper: azido-GFLGR7RGDS with tumor-targeting, membrane-penetrating, and cathepsin B-responsive functions	RGDS is tumor-targeting agent, and GFLG is a target for cathepsin B, which removes the cap, and drug is released	Growth inhibition toward α v- β 3-positive HeLa cancer cells	Free diffusion of the drug from solvent into carrier	130 nm	[42]
pH	FITC-Fe ₃ O ₄ -capped-MSNs	Cap: reversible boronate ester linker	The boronate ester is hydrolyzed and cap is removed	Drug tracking with FITC labeling and drug release in MC3T3-E1 cell model	Free diffusion of the drug from solvent into carrier	100 nm	[43]
Magnetic	MMSN-NIPAM	Gatekeeper: thermo-responsive copolymer of poly(ethyleneimine)-b-poly(N-isopropylacrylamide)	Remote magnetic field by increasing temperature changes the gate keeper and releases the drug	Remotely triggering the release of different therapeutic agents and contrast agents for MRI	Free diffusion of the drug from solvent into carrier	50–100 nm	[44]
Temperature	DOX-MSN-DNA-CuS	Gatekeeper: CuS bound to DNA strand, and the complementary strand on MSN provide reversible capping	Heating separates the two strands of DNA and cap is removed	Local drug release under control of heat stimulation	Free diffusion of the drug from solvent into carrier and capping by DNA hybridization	70-120 nm	[45]

**Figure 2:** Redox-responsive MSN: disulfide bonds are broken at a high concentration of GSH, and the caps (here PEG molecules) are removed, and the loaded dye is released. Reused from Reference [41] with the permission of Elsevier publisher.

intracellular redox conditions, and anticancer drug DOX was released inside the cells [51].

In a recent study, Li et al. [52] generated MSN-SH with a mesopore diameter of 2.64 nm by using a co-condensation method, then attached S-(2-aminoethylthio)-2-thiopyridine hydrochloride to produce MSN-S-S-NH₂. This structure was then reacted with propargyl bromide to obtain MSN-S-S-NH-alkyne. This particle was then attached to an azidopeptide via “click chemistry” to generate MSN-S-S-RGD. The MSN was then loaded with DOX that showed good responsivity to the presence of GSH in tumor cells. Furthermore, Sun et al. [53] used redox stimulus-responsive MSN to inhibit cancer by suppressing neovascularization and encouraging vascular normalization. For this purpose, they immobilized PEI through disulfide bond formation onto the surface of siRNA-loaded MSN to increase the RNA half-life and its penetration into targeted cancer cells. The MSN-siRNA/CrPEI showed an efficient intracellular gene delivery and

therapeutic effect on the vascular endothelial growth factor (VEGF) pathway.

3.2 Enzyme-responsive MSN

Enzymes have unique properties such as their isoelectric pH, exquisite substrate specificity, greater expression in particular organs and in subcellular organelles and can have large changes in concentration in inflammation and disease states. Proteases have a critical role in intracellular delivery [54], and matrix metalloproteinases (MMP) can be specific for the cancer microenvironment [55]. The concentration of elastase is increased in inflammation [56], and phospholipases are overexpressed in pancreatic cancer and can be used for antibiotic delivery [57]. Oxidoreductases also are taken advantage of in oxidase-responsive DDS [58]. MSN can be tailored to respond to these different enzymes by changing the linkers and capping agents on their functionalized surface.

Van Rijid's group [54] coated the external the surface of MSN with a hepatopeptide that contained a biotin group linked to the amino acid sequence SWMGLP, which can be recognized by MMP9. The enzyme MMP9 is a matrix metalloproteinase that breaks down the extracellular matrix in physiological conditions, and many basic functions of cells depend on this enzyme, such as embryonic and bone development, cell migration, and wound

healing responses. MMP9 is frequently overexpressed on malignant cancer cells, where it is responsible for tissue invasion and metastasis. After loading of the mesopores with the anticancer drug cisplatin, the protein avidin was attached to the biotin as a bulky gatekeeper to keep the loaded drug in the MSN pores. In the presence of MMP9 on the surface of lung cancer cells, the peptide sequence was cleaved by the enzyme, and the drug was released to the cancer cells. In a similar study, Xu et al. [55] coated MSN with a gelatin corona susceptible to degradation by MMP for delivery of DOX into HT-29 human colon carcinoma cells and suggested that the same MSN could be used for delivery of different drugs into different cells.

In an interesting study, Li et al. [59] attached an oligocationic TAT nucleus-penetrating peptide to the surface of drug-loaded MSN and neutralized it with a cleavable anionic peptide. In the cancer cells and in the presence of cathepsin B, the anionic peptide was cleaved, and the carrier was transferred into the nucleus by the penetrating peptide. Therefore, the anticancer drug was released directly into the nucleus. This strategy could be an efficient system for drug-resistant tumor therapy. Figure 3 depicts the basis of this strategy.

Mondragon et al. [60] used a nontoxic lysine polymer with an ϵ -amino group linkage for capping the MSN, which was biodegradable by amidases. They showed this gatekeeper had a zero cargo release when the protease was absent, but after it was taken up by HeLa cells, the cargo

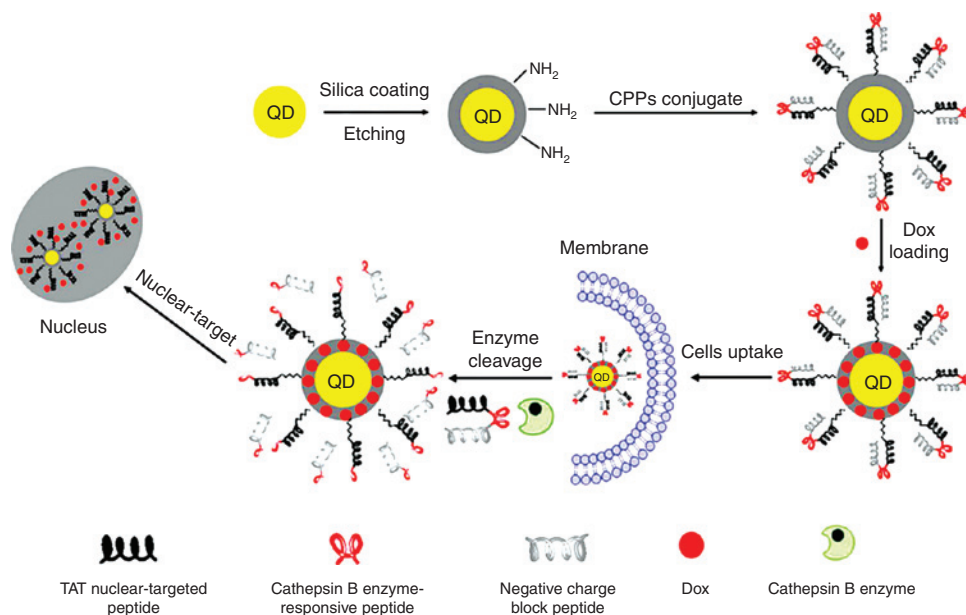


Figure 3: Schematic mechanism of nucleus-targeted drug delivery; MSN was synthesized by quantum dot method and TAT sequence along with cathepsin B-responsive peptide attached to its surface. Inside the cancer cell, the enzyme cuts the responsive peptide, and the nucleus-penetrating agent guided the carrier to the nucleus. Reused from Reference [59] with the permission of John Wiley and Sons' publisher.

was efficiently released into lysosomes under the action of proteases. Recently, Cheng et al. [42] designed a three-segment oligopeptide-conjugated rotaxane MSN. This oligopeptide consisted of a RGGGS tumor-targeting peptide, a sequence of seven arginine residues as a cell-penetrating peptide, and a GFLG enzyme-cleavable peptide. This nano-carrier bound to the integrin $\alpha v \beta 3$ that was overexpressed in cancerous cells and was internalized into the cells by the arginine sequence. Inside the cells, the GFLG peptide was cleaved by cathepsin B, and 80% of the loaded drug was rapidly released inside the cell.

3.3 pH-responsive MSN

The high rate of glycolysis in cancerous cells, leading to the production of lactic acid and carbon dioxide directly results in their having a relatively low pH that can be used as an endogenous stimulus for targeted drug release. This biochemical characteristic of abnormal cells has been utilized as a strategy to design an appropriate gatekeeper on the MSN surface and tunnels that could be triggered in response to an acidic environment.

Polyelectrolyte polymers formed from repeating monomer units bearing electrolyte groups can either be absorbed or covalently bonded to the surface of MSN. They act as stimulus-responsive release systems by virtue of their structural transformation in response to different pH values. The multilayered polyelectrolytes formed from PAH/PSS were used to modify MSN by Shi et al. [61]. The positive charge of PAH coated the negatively charged surface of the MSN. The negatively charged PSS, then, was added to PAH. Their results showed that gentamicin molecules could be stored within MSN pores and released in response to pH changes in the range of 2–8. The basic principle of pH-responsive drug release is shown in Figure 4.

Three different forms of MSN (carboxylated mesoporous silica (MSN-COOH), animated MSN (MSN-NH₂),

and hollow MSN (H-MSN)) were used by Gao et al. [62] to load anticancer drugs. Using cationic and anionic polyelectrolyte-coated MSN provided an opportunity for loading different types of bioactive molecules through the layer-by-layer method. Positive-charged drugs were loaded better into MSN-COOH, whereas MSN-NH₂ was more suitable for anionic drugs, while H-MSN exhibited a high capacity to load both types of drugs. Their results showed great potential as a pH-responsive DDS.

Supramolecular species such as β -cyclodextrin (β -CD) and proteins can act as another type of gatekeeper in pH-responsive MSN. An interesting study was carried out by Meng et al. in which a series of aromatic amines were used as a stalk to attach to MSN, and then, β -CD was attached to the stalk to prevent cargo release at normal pH. In acidic environments (pH < 6), however, the stalk lost its attachment due to protonation of the aromatic amines, and the cargo was released immediately upon opening of the nanovalves. The cell lines THP-1 and KB-31 were studied in their *in vitro* investigations. The THP-1 macrophages took up the ingested particles into the lysosomal compartment, and KB-31 was a cancer cell model to test the efficacy of the procedure [63].

pH-sensitive linkers such as acetal, ester, and hydrazine bonds have also been utilized in the design of smart MSN. These bonds can be used to attach bulky groups to cover the MSN pores, thus, preventing drug release at a pH about 7.4 as in the blood circulation. Recently, acetalated dextran (a polysaccharide with water-soluble characteristic achieved by hydrolysis of starch or glycogen) was used by Huang et al. to produce pH-sensitive MSN. The water solubility of the dextran could be modified by attaching cholesterol as a lipid soluble moiety. By modifying MSN with CaCO₃, another kind of pH-sensitive MSN was produced to produce acid-triggered release of the drugs, DOX and ibuprofen. Their results showed that the CaCO₃ coating dissociated in acidic conditions, and the drug was released rapidly. At physiological pH by contrast, the release of the loaded drug occurred very slowly [64].

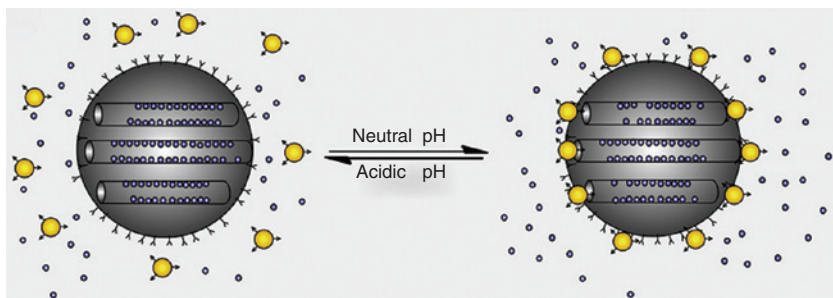


Figure 4: Basic concept of drug release under acidic conditions. Reused from Reference [43] with the permission of Elsevier.

3.4 Light-responsive MSN

Light responsiveness has been suggested to be a promising strategy for external stimulus-triggered drug release due to the noninvasive nature and the ability to remotely control it from outside. Near-infrared (NIR) light is a safe wavelength range and is able to deeply penetrate into tissue without any hazardous effect on the internal organs [65]. The main mechanisms of light-triggered drug release are (a) a photothermal increase of temperature at the site of irradiation with a corresponding change in the steric structure; and (b) photoisomerization of a light-sensitive molecule. Some studies have shown that the coating of the MSN with more hydrophobic materials can enhance its response to light [66].

Li's group constructed an NIR light-responsive nanovalve on the surface of MSN-coated gold nanorods by using sulfonatocalix [4] arene (SC [4] A) attached to a quaternary ammonium stalk as a capping switch. In this nanocarrier, the energy of NIR light was converted to heat by the plasmonic absorption by the gold nanorod core and the binding between the quaternary ammonium salt and the SC [4] A was weakened, leading to removal of the capping agent from the surface of the MSN pore, and drug was released [65]. In a similar approach, Lui et al. [67] used single-walled carbon nanotubes (SWCNT) as a light-absorbing agent attached to MSN. They found that the light absorbing material could absorb energy converting it to heat and cause drug release. They coated MSN with SWCNT and functionalized them with polyethylene glycol

(PEG) to enhance biocompatibility, solubility, and the stability of the nanocarrier in physiological conditions. The loaded drug was released after exposure of HeLa cells to NIR light. This strategy is depicted in Figure 5. Further studies indicated that noncovalent binding of the capping agents was able to prevent drug release and enhanced the light-mediated response. Reduced graphene oxide (RGO) noncovalently assembled onto the surface of alkyl chain-functionalized MSN could be disassembled by remote irradiation with NIR light [68].

In an interesting work, Wang's group designed a reversible nano valve that was responsive to near-UV irradiation. In this system, α -cyclodextrin was attached to the trans-form of azobenzene. Trans-azobenzene was isomerized under near-UV light to the cis-form, which forced the release of cyclodextrin, and the cargo was released during light irradiation. When the light irradiation ceased, the azobenzene returned to the trans-form, and as a result, the cyclodextrin again bound to the porous surface. This system represents the first reversible drug-release system triggered by light [69].

3.5 Magnetic-responsive MSN

This idea, that the use of an external magnetic field could be a stimulus for drug release, was first suggested by Freeman in 1960 [70]. The entrapment of magnetic materials within MSN can be carried out by three different mechanisms that control the diameter, morphology,

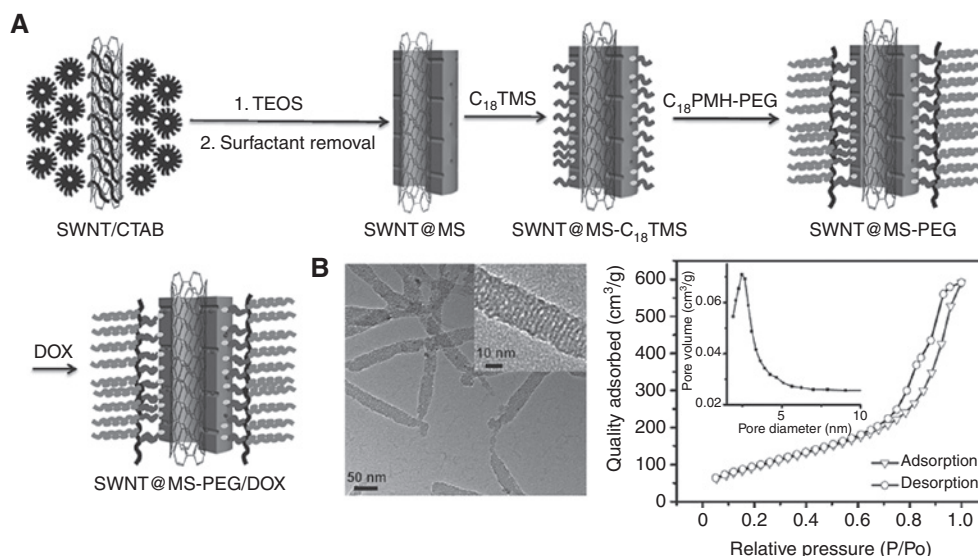


Figure 5: (A) Synthetic route to SWCNT@MS-PEG showing the preparation of mesoporous silica, its pegylation, and addition of CNT to construct the complete SWCNT@MS-PEG. (B) TEM image of the nanoparticles before pegylation. (C) Illustration of desorption and adsorption of cargo and its corresponding pore size. Reused from Reference [67] with permission of John Wiley and Sons' publisher.

and structure of magnetic MSN. These strategies are 1) magnetic nanocrystals are embedded in the core and surrounded by an MSN shell; 2) a large magnetic core is embedded in a sandwich-like structure with MSN surrounding it; 3) hollow MSN can contain magnetic nanocrystals like a baby's rattle [28]. These three mechanisms are depicted in Figure 6.

External magnetic fields are nontoxic, have a high ability to penetrate living organisms without any physical interaction with internal tissues [31]. As magnetic fields do not interact with living systems, they can be used for external guidance of magnetic nanocarriers, as contrast agents in magnetic resonance imaging (MRI), for tissue heating via application of alternating magnetic fields, and for triggering drug release. Application of magnetic fields can increase the cellular uptake of magnetic NP in a process known as “magnetofection” [44, 71]. Magnetic field-induced heating might increase the temperature of the surrounding environment and have a synergistic effect on drug release and cancer therapy. One strategy to use this hyperthermia property is the entrapment of magnetic materials in the core of MSN. Dong's group stabilized Fe_3O_4 NP within a silica layer. Then, hexadecyltrimethylammonium bromide (CTAB) was used as a surfactant, combined with mesitylene to cause swelling of the pores to generate M-MSN-CTAB. Next, the CTAB was removed by treatment with 3-(trimethoxysilyl) propyl methacrylate (MPS) to graft vinyl groups on the external

surface of the MSN nanoparticles. The removal of CTAB in an ammonia-ethanol solution led to pore formation in MSN. Finally, a smart thermoresponsive polymer, poly (N-isopropyl acrylamide) (PNIPAAm), was added as a gatekeeper to the pores. The Fe_3O_4 under an alternating magnetic field absorbed energy and generated heat. After the temperature was increased, the outer chains of PNIPAAm absorbed more water and became soluble, the pores became unblocked, and the loaded cargo was released [72]. The strategy is depicted in Figure 7.

In a similar approach, Thomas et al. covered zinc-doped iron oxide nanocrystals (ZnNC) inside the MSN and modified its surface by attaching pseudorotaxanes as a thermal-sensitive gatekeeper. The presence of ZnNC significantly improved the thermal responsivity four times, and the MRI contrast was increased 10 times compared to free iron oxide nanocrystals [73]. The unique structural properties of the MSN provided the possibility to combine magnetic sensitivity with temperature sensitivity as discussed above. This strategy has led to a generation of different MSN-based nanocarriers with magnetic cores and stimulus-sensitive nanovalves. For example, Lee's group [74] used three different reactions; sol-gel reaction, solvothermal reaction, and amide coupling reaction, to construct magnetic core MSN with nanovalves composed of crown-ether macrocycles as ultrasound responsive moieties and with CTAB as pH-responsive gatekeepers. This $\text{Fe}_3\text{O}_4@\text{SiO}_2@\text{CTAB}-\text{SiO}_2-\text{NH}_2$ MSN showed efficient

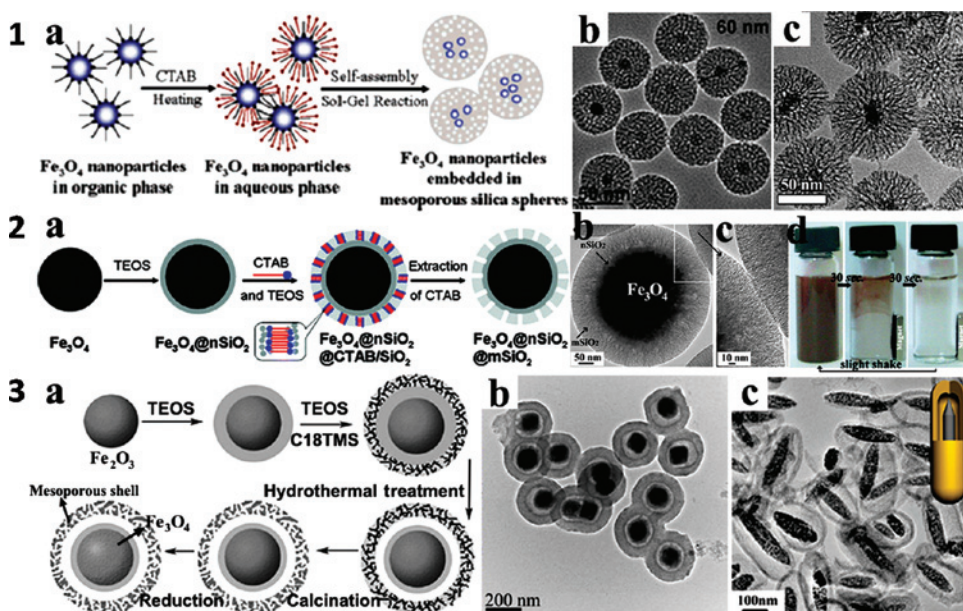


Figure 6: Mechanisms of magnetic core entrapment in MSN shells. (a) Schematic construction mechanism; (b) TEM image of magnetic core nanoparticles; (c) TEM image of nanoparticle after pore formation. Reused from Reference [28] with permission of John Wiley and Sons' publisher.

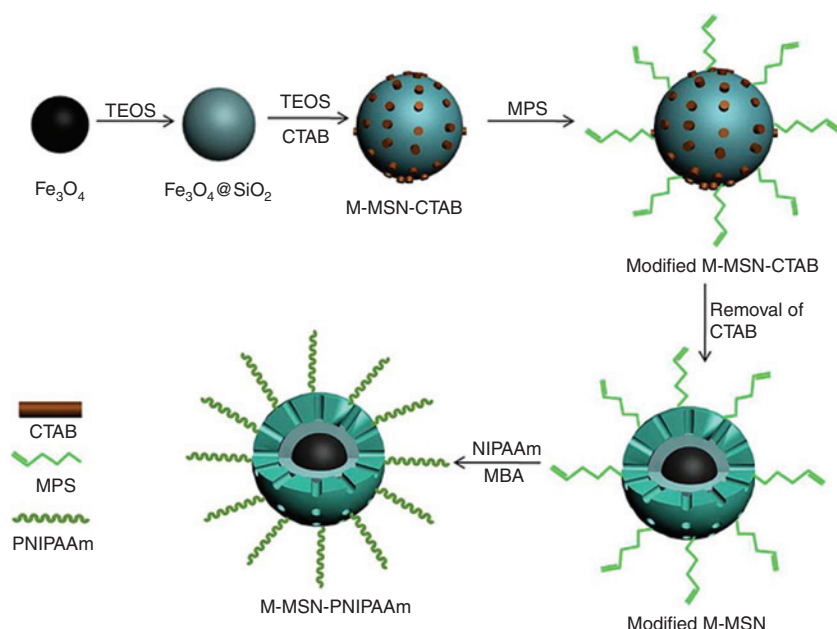


Figure 7: Schematic illustration of M-MSN-PNIPAAm preparation, functionalization, and drug release mechanism. Reused from Reference [72] with permission of John Wiley and Sons' publisher.

multiresponsive behavior (i.e. ultrasound, pH, and magnetic responsivity) when both internal and external stimuli could be used.

3.6 Temperature-responsive MSN

Utilizing thermoresponsive MSN is another approach for targeted release of the drug that can be triggered by both external and internal stimulation. This concept was reported in 2003 for the first time. One of the characteristic properties of tumor tissues (caused by high metabolism rates and inflammation) is their higher temperature compared to normal tissue. Therefore, using phase-change polymers with melting temperature (T_m) higher than normal conditions as gatekeepers would be an efficient strategy for smart temperature-responsive DDS. These polymers remain in a solid state at temperatures lower than their T_m but are converted to a liquid phase when the surrounding temperature is raised to T_m [75]. Poly (N-isopropylacrylamide-co-acrylamide) is a thermoresponsive polymer that is widely used in the design of these carriers. Russell et al. [76] used this polymer for capping the MSN pores with diameters of 2–5 nm through covalent binding. This study found that the density of the grafted polymers could directly influence the efficiency of the capping agent in loading and releasing the bioactive molecules. Linking thermosensitive polymers to the surface of magnetic core

MSN, as discussed above, has been used for generation of externally thermoresponsive MSN. Another strategy for the design of thermoresponsive MSN is capping the pores with paraffins. Different types of paraffins such as heneicosane (C21) and tetracosane (C24) with different T_m have been used. Solid paraffins reaching the T_m convert to the liquid phase and allow the loaded cargo to be released [75].

On the other hand, bioactive molecules can be used as thermosensitive materials on the surface of MSN. These molecules respond to a change in the temperature, by losing their conventional structure, either by opening of α -helix configuration or by altering hydrogen-linked subunits. This mechanism is depicted in Figure 8. Zhang's group [45] attached a single-stranded DNA at the MSN pore sites, and its complementary strand was attached to a copper sulfide (CuS) nanoparticles. CuS is a nontoxic semiconductor compound that shows the effective photothermal ablation behavior. By irradiation of the CuS NP with NIR light, the temperature was increased and the two strands of DNA became separated and CuS cap was removed leading to release of the cargo. Interestingly, after cessation of the irradiation and temperature decrease the cap returned to the pore site by annealing of the two complementary DNA strands thus providing reversible controlled release. Using a similar concept, Chang's group [77] utilized Au nanorods as a gatekeeper and a pair of oligonucleotides to form a temperature-responsive element under NIR light irradiation.

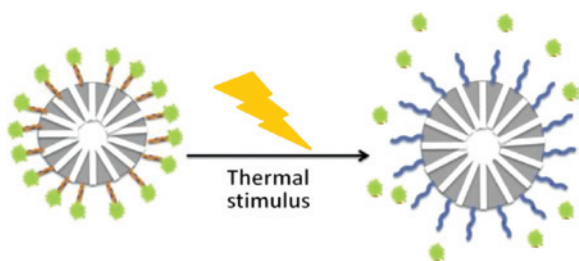


Figure 8: Schematic of thermally responsive MSN: the normal structure of a thermally responsive material is changed under temperature fluctuation. Reused from Reference [45] with the permission of the Royal Society of Chemistry.

Based on changing the configuration of an α -helix, Torre's group [78] used a 17-mer peptide anchored to a polymer as a gatekeeper. The α -helical structure of this peptide was converted to a random coil conformation at a raised temperature due to disorder arising in its structure. This transformation led to a reduction in the molecular crowding at the pore surface and led to the release of the cargo, whereas by reducing the temperature, the self-assembly property of the peptide covered the pore entrance and blocked the cargo release.

3.7 Toxicity of MSN

Silica materials, in general, are considered as being non-cytotoxic, but the silica nano-composite materials may possess different properties owing to alteration of the physicochemical characteristics at the nanoscale [79]. Previously, it was shown that MSNs have significantly lower cytotoxicity toward phagocytes and inflammatory cells in *in vitro* conditions compared to amorphous colloidal silica NPs [80]. Some literature has indicated that the properties of SiO_2 nanoparticles can influence their interaction with targeted cells. The surface modification of silica nanoparticles enhances their cellular uptake [81], the pore diameter increases the adsorption capacity [82], and the different geometry of the particles can disturb normal cell functions [83]. The fact that the properties of silica nanoparticles could influence their biodistribution and biocompatibility cautions us to consider different parameters in the design of these nanoparticles in order to reduce their possible toxicity.

Yu's group [84] focused on the impact of the charged surface groups, porosity, and geometry of the silica NPs on erythrocyte hemolysis and macrophage toxicity. They found that the toxicity of the SiO_2 was dependent on cell type, which is due to different physiological functions of different cells. Moreover, they suggested that the major

factor in the cellular interactions was the surface properties and porosity of the SNPs, and comparison of different structures on erythrocyte hemolysis indicated that amine modification of SiO_2 reduced the toxicity of these NPs.

Fu et al. [85] studied the effect of the administration route on MSN toxicity. They found that after systemic administration, nanosilica particles accumulated in the liver and their distribution was not the same in the body after other administration routes. According to their results, as the MSN are excreted via urine and feces, the most compatible routes for administration of MSN were oral and intravenous injection. They also indicated that MSN excretion by the kidney could not cause any micro-structural kidney damage.

Further studies suggested that *in vitro* assays might yield different results from assays after *in vivo* administration. *In vivo* interaction of SNPs with the reticuloendothelial system, (the major physiological system for blood purification) and interactions with complex serum protein concentrations could affect immune responses through the body. The presence of pores on the surface of SNPs could change the proliferation of splenocytes and increase immunoglobulin levels. MSN could possibly damage the immune system by disrupting the lymphocyte population patterns and produce alteration in lymph nodes [86].

4 Conclusion

Nanocarriers must play two main roles in DDS; first they must reduce the toxicity of the bioactive molecules and prevent their distribution throughout the body, especially highly toxic anticancer drugs, and second, the nanocarriers should be able to protect the drug from degradation and removal of the natural systems of the body and enable them to reach their targeted sites. Among all the presently available nanocarriers, MSN has an impressive capacity for carrying drugs, due to their high surface-to-volume ratio, and large pore volume. The presence of many free hydroxyl groups on the surface of the silica provides suitable attachment sites for modification in which either hydrophobic or hydrophilic compounds can easily attach to it. The diameter of the MSN pores is flexible and can be adjusted by the preparation methods used to make the nanocarriers. In order to fabricate smart stimulus-responsive nanocarriers, different types of gatekeepers can attach to the entrance of the pores. These structures affect the pore size, as well as tailoring the interaction properties of the MSN. Apart from magnetic responsiveness that relies on a magnetic core entrapped inside the MSN shell, all the other types of responsivity can be provided by tailoring the gatekeepers.

Polymers and other structures that cover the pores prevent premature drug release, while on application of the internal or external trigger, the gatekeepers are removed, and the targeted drug release takes place. In some cases, the drug release process is reversible, and the stimulus can be repeatedly applied, so that metered drug release is theoretically possible. In other cases, dual stimulus responsivity can be achieved, and even responsivity to three different stimuli. We suggest that MSN will continue to be studied as efficient, versatile, and tunable nanovehicles for targeted drug delivery. In the future, more *in vivo* studies need to be carried out to test their true utility in living whole organisms.

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