REVIEW

Mesoporous silica nanoparticles for drug and gene delivery

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Abstract Mesoporous silica nanoparticles (MSNs) are attracting increasing interest for potential biomedical applications. With tailored mesoporous structure, huge surface area and pore volume, selective surface functionality, as well as morphology control, MSNs exhibit high loading capacity for therapeutic agents and controlled release properties if modified with stimuli-responsive groups, polymers or proteins. In this review article, the applications of MSNs in pharmaceutics to improve drug bioavailability, reduce drug toxicity, and deliver with cellular targetability are summarized. Particularly,

Abbreviations: AO, acridine orange; APTES, 3-aminopropyltriethoxysilane; APTMS, amino propyl trimethoxysilane; BCL-2, B-cell lymphoma-2; BCS, Biopharmaceutical Classification System; Bio-TEM, biological transmission electron microscopy; C dots, Cornell dots; CMC, critical micelle concentration; CPT, camptothecin; CTAB, cetyltrimethyl ammonium bromide; EPR, enhanced permeability and retention; FDA, Food and Drug Administration; GI, gastrointestinal; GNRs@mSiO2, mesoporous silica-encapsulated gold nanorods; LHRH, luteinising-hormone releasing hormone; MDR, multi-drug resistance; MTT, 3-[4,5-dimethylthiazol-2-yl]-2,5-diphenyl tetrazolium bromide; MRP1, multidrug resistance protein 1; MSN-Dox-G2, Dox-loaded and G2 PAMAM-modified MSNs; MSNs; mesoporous silica nanoparticles; MSNs@PDA-PEG-FA, poly(ethylene glycol)-folic acid-functionalized polydopamine-modified MSNs; MSNs-HA, hyaluronic acid-conjugated MSNs; MSNs-RGD/TAT, RGD/TAT peptide-modified MSNs; MSNs-TAT, TAT peptide-modified MSNs; NIR, near-infrared; PAMAM, polyamidoamine; PDEAEMA, poly(2-(diethylamino)ethylmethacrylate); PDMAEMA, poly(2-(dimethylamino)ethylmethacrylate); pDNA, plasmid DNA; PEG400, polyethylene glycol 400; PEI, polyethylenimine; P-gp, P-glycoprotein; PLL, poly-L-lysine; PTX, paclitaxel; Q-MSNs, quercetin encapsulated MSNs; RGD, arginine-glycine-aspartate; TAT, trans-activating transcription; TMB, 1,3,5-trimethybenzene

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1. Introduction

In recent years, there has been a rapid growth in the area of biomedicine, particularly in exploring new drug/gene delivery systems. More recently, nanotechnology emerged as a promising approach which has motivated researchers to develop nanostructured materials. Among various integrated nanostructured materials, mesoporous silica nanoparticles (MSNs) have become a new generation of inorganic platforms for biomedical application.

MSNs with uniform pore size and a long-range ordered mesoporous structure were first introduced by Mobil corporation scientists in 1992. In general, supramolecular assemblies of surfactants are necessary in the synthesis of MSNs. Usually, the surfactant will self-aggregate into micelles at a concentration higher than the critical micelle concentration (CMC). Then, the silica precursors can condense at the surface of the micelles forming an inorganic-organic hybrid material. Finally, the template surfactant can be removed either by calcination or by solvent extraction to generate pores (Fig. 1). The resulting silica-based mesoporous matrices may offer the following unique structural and biomedical properties:

1) Ordered porous structure. MSNs have a long-range ordered porous structure without interconnection between individual porous channels, which allows fine control of the drug loading and release kinetics (Fig. 2).

2) Large pore volume and surface area. The pore volume and surface area of MSNs are usually above 1 cm³/g and 700 m²/g, respectively, showing high potential for molecular loading and dissolution enhancement.

3) Tunable particle size. The particle size of MSNs can be controlled from 50 to 300 nm, which is suitable for facile endocytosis by living cells.

4) Two functional surfaces. MSNs have two functional surfaces, namely cylindrical pore surface and exterior particle surface. These silanol-contained surfaces can be selectively functionalized to achieve better control over drug loading and release. Moreover, the external surface can be conjugated with targeting ligands for efficient cell-specific drug delivery.

5) Good biocompatibility. Silica is “Generally Recognized As Safe” by the United States Food and Drug Administration (FDA). Recently, silica nanoparticles in the form of Cornell dots (C dots) received FDA approval for stage I human clinical trial for targeted molecular imaging. It was reported that MSNs exhibited a three-stage degradation behavior in simulated body fluid, suggesting that MSNs might degrade after administration, which is favorable for cargo release. Several in vivo biodistribution studies of MSNs have been reported recently. Liu et al. evaluated the systematic toxicity of MSNs after intravenous injection of single and repeated dose to mice. The results of clinical features, pathological examinations, mortalities, and blood biochemical indexes indicated low in vivo toxicity of MSNs. It was also reported that MSNs were mainly excreted through feces and urine following different administration routes.

These unique features make MSNs excellent candidate for controlled drug/gene delivery systems. Since the first report using MCM-41 type MSNs as drug delivery system by Vallet-Regi et al. in 2001, the research on biomedical application of MSNs has steadily increased, with an exponential rise in last decade. Various mesoporous materials with different porous structure and function- ability have been developed for controlled and targeted drug/gene delivery. Here, we give an overview of the recent research progress and future development of MSNs in biomedical applications, particularly focused on the practical applications of MSNs as delivery systems for poorly soluble drugs, anticancer agents, and therapeutic genes. Based on the review, we have also included our perspectives on the further applications of MSNs.

2. Mesoporous silica-based system for poorly soluble drugs

With the increasing numbers of innovative new drugs in development, almost 70% of new drug candidates exhibit low aqueous solubility, ultimately resulting in poor absorption. In an attempt to overcome this solubility obstacle and to improve the oral bioavailability, a growing number of drug delivery technologies have been developed. Presently, nanotechnology is attracting increasing attention as it can be applied in two aspects: processing the drug itself and eventually resulting in poor absorption. In an attempt to overcome this solubility obstacle and to improve the oral bioavailability, a growing number of drug delivery technologies have been developed. Presently, nanotechnology is attracting increasing attention as it can be applied in two aspects: processing the drug itself and subsequently enhancing their absorption.

When water-insoluble drug molecules are contained in mesoporous silica, the spatial confinement within the mesopores can reduce the crystallization of the amorphous drug. Compared with the crystalline drug, the amorphous drug can reduce the lattice
energy, subsequently resulting in improved dissolution rate and enhanced bioavailability\(^2\,^3\). Moreover, the huge hydrophilic surface area of mesoporous silica facilitates the wetting and dispersion of the stored drug, resulting in fast dissolution\(^4\). In one example, the poorly water soluble drug clotrimazole was loaded into MSU-H type mesoporous silica through supercritical CO\(_2\)\(^5\,^6\). The experimental and theoretical results indicated that clotrimazole was not crystalline and drug molecules were homogenously distributed in the mesopores. He et al.\(^7\) also reported that the solubility of paclitaxel was significantly enhanced after loaded into MSNs. The 3-[4,5-dimethylthiazol-2-yl]-2,5-diphenyl tetrazolium bromide (MTT) assay revealed that paclitaxel loaded mesoporous silica nanoparticles exhibited obvious cytotoxicity on HepG2 cells as compared with paclitaxel. SBA-15 mesoporous silica was successfully used to accelerate the dissolution rate of furosemide which is a representative class IV drug according to the Biopharmaceutical Classification System (BCS)\(^8\). About 71% of the drug was released from SBA-15-based preparation at 2 h dissolution, whereas only 49% of drug release from the commercial product Lasix. In addition, when the dissolution medium was changed from pH 3.0 to pH 6.8, the drug was rapidly and completely released from the inclusion preparation against the incomplete release of 83% drug from the commercial product during the whole test.

There are several factors which can influence drug release rates from MSNs. Pore size plays an important role in the release rate since the drug release is mainly controlled by diffusion\(^9\). Jia et al.\(^10\) prepared paclitaxel-loaded MSNs with different pore sizes from 3 to 10 nm. The in vitro drug release test showed that the release rate decreased as the pore sizes changed from 10 to 3 nm, which might be attributable to the reason that paclitaxel loaded in relatively small pores has less opportunity of escaping from pores and diffusing into the release medium. The effect of pore size on the drug release rate was further verified in the celecoxib loaded mesoporous silica system. The release rate of celecoxib from mesopores increased with the increase of the pore size (3.7–16.0 nm)\(^11\). In addition, the surface chemistry is another factor which can influence the drug release rate. Ahmadi et al.\(^12\) loaded ibuprofen into amino-modified SBA-15. Compared with SBA-15, the release rate from amino-modified SBA-15 was much slower. This was due to the interaction between carboxyl groups of ibuprofen and amino groups of the amino-modified SBA-15. Hollow structure was also reported to retard drug release from mesoporous silica nanoparticles\(^13\). Furthermore, during the degradation, highly ordered hexagonal mesoporous structure will be degraded into a disordered network where the walls have been partly destroyed\(^14\), which might affect the release of drug cargo loaded in MSNs.

To obtain a suitable release rate and high bioavailability of poorly soluble drugs from mesoporous silica, mesoporous silica were combined with other materials into different kinds of formulations. Chen et al.\(^15\) constructed a liquisolid formulation in which liquid polyethylene glycol 400 (PEG400) and model drug carbamazepine were absorbed into mesoporous silica to achieve improved adsorption capacity and high drug loading. The obtained liquisolid system was mixed with starch slurry, then granulated, and filled into gelatin capsules. The in vivo study demonstrated that the bioavailability of the liquisolid capsules was improved to 182.7% compared with the commercial carbamazepine tablets. Hu and his co-workers\(^16\) encapsulated felodipine-loaded MSNs using chitosan and acacia through layer by layer self-assembly method. The release rate of felodipine decreased with the increase of the number of chitosan/acacia bilayers coated on MSNs. The production of immediate-release carbamazepine pellets was reported by Wang et al.\(^17\) based on mesoporous silica SBA-15 using extrusion/spheronization method. The dissolution results showed that the incorporation of drug-loaded SBA-15 into pellets did not change the in vitro release behavior. Moreover, the oral bioavailability of pellets was 1.57-fold higher than that of fast-release commercial tablets in dogs (\(P<0.05\)). In another study, MSNs were formulated into hydrogel beads with polysaccharides matrix, resulting in a sustained drug release profile maintaining for 24 h\(^18\).

3. Mesoporous silica-based system for cancer therapy

Recently, the combination of nanotechnology with drug delivery in the field of cancer therapy has been a research hotspot. The defective vascular architecture and impaired lymphatic drainage/recovery system of tumors allow small nanocarriers and macromolecules to extravasate the endothelial barrier and accumulate in the tumor tissues\(^19\). Owing to this so-called enhanced permeability and retention (EPR) effect, the passive targeting of nanocarriers can be partially achieved\(^20\). Though organic nanocarriers such as nanocapsules\(^21\), liposomes\(^22\), polymeric micelles\(^23\), and nanoparticles\(^24\) can easily encapsulate anticancer drugs, their physicochemical instability and unexpected drug leakage have severely impeded their application. In contrast, inorganic silicate (SiO\(_2\)) carriers have several merits, such as excellent biochemical and physicochemical stability, biocompatibility, and degradability\(^25\). Among the recent breakthroughs that brought new exciting possibilities to this area, MSNs have commonly been suggested as effective carriers for anticancer drugs because of their excellent drug delivery and endocytotic behaviors\(^26\). In this part, we review the applications of MSNs in cancer therapy.

3.1. Intracellular uptake mechanism of MSNs

3.1.1. Pathways for the cellular internalization of MSNs

Since the cell membrane is the biggest barrier for intracellular anticancer drug delivery, it is important to thoroughly investigate the cellular internalization and intracellular trafficking of MSNs as drug carriers.

Generally, the uptake pathways can be divided in two groups: phagocytosis and pinocytosis (macropinocytosis and endocytosis)\(^27\). Phagocytosis usually occurs in specialized cells (professional phagocytes) such as monocytes, neutrophils, macrophages, and dendritic cells, for particles with minimum size of 1 \(\mu\)m\(^2\). Small
nanoparticles (<200–300 nm) are usually taken up by cells via endocytic pathways, which involve various routes such as clathrin-mediated, caveolae-mediated, or the clathrin and caveolae independent mechanism, depending on the cell type, particle size, particle shape, particle surface charge, and even culture conditions.

Since most endocytic pathways are energy dependent, use of an inhibitor or a method of energy depletion can directly identify an endocytic pathway. It was reported that incubating KB cells with MSNs at 4 °C significantly impeded the cellular uptake and the internalization also markedly decreased in the presence of sodium azide. These findings demonstrated that the uptake of MSNs by KB cells was an energy-dependent endocytic process. To further investigate the role of specific endocytic pathways involved in the cellular internalization of MSNs, KB cells were pre-incubated with a series of metabolic inhibitors, including chlorpromazine (inhibits the formation of clathrin vesicles), nystain (binds sterols and disrupts the formation of caveolae), cytochalasin D (inhibits clathrin- and caveolae-independent endocytosis). Finally, the authors proposed that the uptake of MSNs into KB cells was predominated by clathrin-mediated endocytosis and required energy. Similar results were found in A549, PANC-1, and 3T3-L1 cells. Other researchers also reported that MSNs were taken up by Hela cells through caveolae-mediated endocytosis.

3.1.2. Intracellular trafficking of MSNs

After penetrating the cell membrane barrier, MSNs need to reach the cytoplasm to release therapeutic drugs. Biological transmission electron microscopy (Bio-TEM) is usually adopted to observe the intracellular distribution of MSNs after endocytosis. It was found that MSNs were transported to large vesicular endosomes after internalization, and then fused with lysosomes. The membranes of endosomes/lysosomes eventually disrupted, suggesting that the nanoparticles could escape from the endosomes/lysosomes. In addition, a large number of nanoparticles were observed in the cytoplasm maintaining their spherical morphology. No particles were found in the nucleus.

The trafficking of MSNs inside cells also can be studied by confocal fluorescence microscopy using transferrin and fluorescently labeled MSNs. Lu et al. used acridine orange (AO) to specifically stain acidic organelles (endosomes and lysosomes) red but stained other cellular regions green. The green fluorescence of labeled MSNs overlapped mostly with the red fluorescence of AO exhibiting yellow fluorescence, which indicated that MSNs were mainly internalized into the acidic organelles. Lin et al. stained the endosomes by a red endosome marker (FM 4–64) and observed the Hela cells after incubating with green fluorescent FITC-cytochrome c-labeled MSNs using confocal fluorescence microscope (Fig. 3). Interestingly, after 24 h of incubation, no yellow spots were observed, indicating there was no overlap between the red endosomes and the green MSNs. This suggested that MSNs could escape from the endosomal entrapment. Recently, Tang and co-workers showed that different shaped MSNs-PEG were internalized into cells and partially located in the acidic organelles, and the green fluorescence observed inside the cytoplasm also suggested the nanoparticles could successfully escape from the endosomes/lysosomes.

3.2. MSNs as anticancer drug delivery vehicles

With porous interiors and large surface areas, MSNs can be used as reservoirs to store different molecules with high loading capacity and tunable release mechanisms. As a promising drug delivery system, the pore size of MSNs can be tailored to selectively load either hydrophobic or hydrophilic anticancer agents, and their size and shape can be controlled to maximize cellular internalization. The cytotoxic effect of camptothecin (CPT)-loaded MSNs on several cancer-cell lines was evaluated, and the clear growth inhibition was found in three pancreatic cancer-cell lines (Capan-1, PANC-1, AsPc-1), one stomach cancer-cell line (MKN45) and one colon cancer-cell line (SW480). Tao et al. reported when loaded into MSNs, transplatin, an inactive isomer of cisplatin, exhibited enhanced cytotoxicity similar to that of cisplatin on Jurkat cells after 24 h exposure. This work indicated that even less potent anticancer drugs could become biomedically effective after proper combination with MSNs.

3.2.1. Active targeting therapy using MSNs

Over the last decade, the development of MSNs as anticancer drug delivery systems has been mainly based on the premise that the tailored nanoparticles can store high volume of chemotherapeutics in their pores and accumulate in tumor tissues achieving passive targeting via EPR. To enhance the uptake of MSNs in targeted cells, MSNs have been conjugated with various targeting ligands, which have specific affinity to the receptors over-expressed on the surface of cancer cells, including folic acid, monoclonal antibody, galactose derivatives, lactobionic acid, hyaluronic acid, arginine-glycine-aspartate (RGD), transferrin, and others (Table 1).

Figure 3 Confocal microscopy images of Hela cells incubated with FITC-cytochrome c at incubation time of (a) 2 h; (b) 14 h; and (c) 24 h. Endosomes were stained red with fluorescent FM 4-64, and FITC was shown as green fluorescence. Reproduced with permission from Slowing et al. Copyright (2007) American Chemical Society.
Successful specific drug delivery to cancer cells has been reported by Sarkar and coworkers. Quercetin encapsulated MSNs (Q-MSNs) modified with folic acid exhibited increased cellular uptake and higher cytotoxicity in breast cancer cells. In another study, significant improvement of tumor suppression in vivo was also achieved by folic acid modified MSNs. Ma et al. synthesized hyaluronic acid-conjugated MSNs (MSNs-HA) by a facile amidation reaction. The cellular uptake study showed that MSNs-HA were more effectively endocytosed by CD44-positive cancer cells (Hela cells) through receptor-mediated endocytosis mechanism. In contrast, no selective endocytosis of MSNs-HA was found in CD44-negative cells, such as L929 and MCF-7 cells. Model drug CPT loaded in the nanoparticles exhibited enhanced cytotoxicity to Hela cells.

3.2.2. Environment-responsive therapy using MSNs

Although vast effort has been devoted to active targeting therapy using MSNs, the delivery efficacy still needs to be strengthened. During the blood circulation and penetration into tumor matrix, anticancer drugs may leak from mesopores of MSNs, leading to insufficient drug concentration at the tumor site. To overcome this obstacle, “smart” MSNs-modified with environment-responsive gatekeepers were designed. Since the microenvironment of tumor tissue differs from that of normal tissue (e.g., acidic pH [4.5–6.5], high concentration of glutathione [2–10 mmol/L] and high temperature [40–42 °C]), environment-specific drug release at a tumor site is envisioned upon removal of gatekeepers.

According to the microenvironment of cancer cells, the “smart” environment-responsive gatekeepers of MSNs can be divided into pH-responsive gatekeepers, redox-responsive gatekeepers, temperature-responsive gatekeepers, and enzyme-responsive gatekeepers. Cheng et al. designed poly(ethylene glycol)-folic acid-functionalized polydopamine-modified MSNs (MSNs@PDA-PEG-FA) for controlled delivery of doxorubicin (Dox). As illustrated in Fig. 4, when MSNs@PDA-PEG-FA were dispersed in acidic conditions, the PDA film would be destroyed and the loaded doxorubicin would be released rapidly. The in vivo experiments indicated that this system exhibited superior antitumor effects. Li and his coworkers developed a glutathione-responsive MSNs system. The gatekeeper (RGD containing peptide) was conjugated on the surface of MSNs by disulfide bonds which could be cleaved by the high concentration of glutathione at tumor site, leading to a burst release of doxorubicin.

To improve the control release of anti-tumor drugs, MSNs were designed to be sensitive to multi-stimulus. Zhao and colleagues developed a redox and enzyme-responsive doxorubicin delivery system based on MSNs. The in vitro experiments demonstrated that the release of doxorubicin was dependent upon glutathione and hyaluronidase. Moreover, the anticancer effects of doxorubicin were enhanced in HCT-116 cells as compared with free doxorubicin. MSNs based on photodynamic and photothermal therapy have also shown great potential in cancer therapy, which exerts a therapeutic effect following irradiation with a near-infrared (NIR) laser. Compared with microenvironment-responsive systems, NIR-responsive systems can achieve remote spatiotemporal control and in-demand drug release. Qian et al. synthesized mesoporous-silica-coated zinc oxide nanoparticles for drug and gene delivery.
phthalocyanine nanoparticles. Zinc phthalocyanine, a photosensitizer, can convert NIR light to visible light, then release reactive singlet oxygen to kill cancer cells. It was demonstrated that the photosensitizers loaded into mesoporous silica were protected from degradation in the biological environment and could continuously produce singlet oxygen with NIR irradiation. Yang and colleagues\textsuperscript{89} developed mesoporous silica-encapsulated gold nanorods (GNRs@mSiO\textsubscript{2}) as a doxorubicin delivery system as well as a photothermal conversion system. The results showed that the combined treatment had a higher therapeutic efficacy for cancer therapy compared with either chemotherapy or photothermal treatment alone.

3.2.3. Overcoming multidrug resistance

Multidrug resistance (MDR) is a major obstacle in cancer chemotherapy and severely impedes the efficacy of anticancer drugs. Drug resistance at tumor tissues is complicated, and usually involves multiple dynamic mechanisms. MDR can commonly be divided into two categories, pump and non-pump resistance. Pump resistance mainly refers to the expression of drug efflux pumps, such as P-glycoprotein (P-gp) and multidrug resistance protein (MRP1), which expel many anticancer agents to decrease the intracellular drug concentration. The main non-pump resistance refers to the activation of cellular antiapoptotic defense pathway, such as drug-induced expression of B-cell lymphoma-2 (BCL-2) protein, leading to a decrease in drug sensitivity. Moreover, these two resistance mechanisms can mutually interact.

Several design strategies based on the unique properties of MSNs have been utilized to overcome drug resistance. First, nano-scaled MSNs can facilitate cellular uptake, increase intracellular accumulation, and improve drug efficacy. The energy-dependent endocytosis of MSNs can bypass the drug efflux pumps\textsuperscript{40,90,91}. Recently, Shi and co-workers\textsuperscript{91} confirmed the enhanced cellular uptake and nuclear accumulation of DOX-loaded MSNs in MCF-7/ADR cells, which may have resulted from bypassing the drug efflux mechanism and/or down-regulation of P-gp by MSNs. The IC\textsubscript{50} of Dox-loaded MSNs against MCF-7/ADR cells was 8-fold lower than that of free DOX, which demonstrated that MSNs increased the suppression of cell proliferation by DOX in ADR cells.

Another advantage of MSNs is the ability to co-deliver different agents, such as antitumor drugs and MDR reversal agents. Jia et al.\textsuperscript{92} fabricated MSNs for co-delivery of paclitaxel (PTX) and tetrandrine (TET) to overcome MDR of MCF-7/ADR cells. As shown in Fig. 5, TET could inhibit the efflux of P-gp to enhance the antitumor effect activity of PTX. Many researchers also used MSNs to deliver chemotherapeutic agents and nucleic acids. Nucleic acids provide the opportunity to silence the genes responsible for drug resistance, such as drug efflux transporter gene P-gp\textsuperscript{93,94} and antiapoptotic protein gene BCL2\textsuperscript{95}, thereby

![Figure 5](image_url)
restoring the intracellular drug concentration required for effective apoptosis and cytotoxicity. In another study\textsuperscript{94}, MSNs were functionalized to effectively deliver anticancer drug DOX as well as P-gp siRNA to MDR cells (KB-V1 cells). It was found the dual delivery system significantly increased the intracellular and intranuclear drug concentrations as compared with free DOX or DOX delivered alone by MSNs.

In addition, MSNs have been designed as stimulus-responsive drug delivery systems to control drug release and increase the accumulation of antitumor agents in nuclei of cancer cells. Wang and coworkers\textsuperscript{96} prepared sericin-coated MSNs with pH accumulation of antitumor agents in nuclei of cancer cells. drug delivery systems to control drug release and increase the delivered alone by MSNs.

It is currently thought that an ideal nuclear-targeted nanoparticle drug delivery system can effectively overcome MDR. Recently, MSNs were modified with trans-activating transcriptor (TAT) peptide to construct a nuclear-targeted anticancer drug delivery system\textsuperscript{97–99}. This novel TAT peptide-modified MSNs (MSNs-TAT) system facilitated intranuclear localization in multidrug resistant MCF-7/ADR cancer cells and released the drug directly into the nucleoplasm. As illustrated in Fig. 6, the authors also constructed a MSN-based vasculature-membrane-to-nucleus sequential drug delivery strategy exploiting RGD and TAT dual-peptides as targeting ligands\textsuperscript{99}. RGD/TAT peptide-modified MSNs (MSNs-RGD/TAT) first bound to the tumor vasculature and then to the cell membrane. Finally, the TAT served as a nuclear targeting ligand for enhanced nuclear uptake. This sequential targeting system remarkably enhanced the therapeutic efficacy in vivo.

4. Mesoporous silica-based system for gene delivery

Besides conventional drug delivery, mesoporous silica can also be applied as carrier for gene transfection. It is well known that carriers play an important role in gene delivery, since the naked nucleic acids show little penetration of cell membranes\textsuperscript{100}. There are two main gene delivery systems, namely viral and non-viral systems. The more effective viral systems face significant safety concerns, such as immunogenicity, gene recombination\textsuperscript{101}, and nonspecificity\textsuperscript{102}. The non-viral systems, including cationic compounds\textsuperscript{103}, recombinant proteins\textsuperscript{104} polymeric\textsuperscript{105,106} and inorganic nanoparticles\textsuperscript{107}, have been widely studied in recent years. However, cationic materials are often associated with high toxicity, and the recombinant proteins show a low cost-performance ratio\textsuperscript{108}. Though liposomes have attracted much attention and can provide efficient gene transfection, their main drawback is instability. Inorganic nanoparticles possess several advantages over the others, such as simple preparation and surface-functionalization, good biocompatibility, and excellent physicochemical stability. Among various materials, MSNs are particular attractive due to their unique properties. Therefore, MSNs are considered to be a promising vehicle for gene delivery to increase the cell uptake and transfection efficiency.

4.1. Gene delivery by positive charge-functionalized MSNs

Untreated MSNs often possess a negative charge due to the ionization of surface silanol groups which reduces binding to negatively charged nucleic acids, such as DNA. Therefore, silica nanoparticles are usually modified to express net positive charges by methods including amination-modification, metal cations co-delivered vector and cationic polymer functionalization. Use of these modified MSNs promotes gene loading by enhanced electrostatic interactions with nucleic acids.

Amination modification is a simple and common attempt to enhance the gene loading capacity of MSNs, 3-aminopropyltriethoxysilane (APTES)\textsuperscript{109–112} or amino propyl trimethoxysilane (APTMS)\textsuperscript{113,114} have been commonly used to modify MSNs. Yang et al.\textsuperscript{111} also analyzed and reported the positive correlation between the adsorption amount of plasmid DNA (pDNA) and amination degree.

Metal cations which can enhance the interactions between DNA and the silica surface have also been used to facilitate MSNs-mediated gene delivery. Solberg and Landry\textsuperscript{115} investigated the effect of metal counter ions on gene adsorption, and found Mg\textsuperscript{2+} had a higher affinity with DNA vs. Na\textsuperscript{+} or Ca\textsuperscript{2+}. However, DNA
seemed to bind less strongly with MSNs through metal cations as compared to the case with the presence of amino group.

Furthermore, cationic polymers, such as polyamidoamine (PAMAM)\textsuperscript{95,116}, polyethyleneimine (PEI)\textsuperscript{93,117–121}, poly-l-lysine (PLL)\textsuperscript{122,123}, and poly-l-arginine\textsuperscript{124}, can bind to and deliver genes with high transfection efficiency. Radu et al.\textsuperscript{125} successfully employed PAMAM (second generation, G2) dendrimer-capped MSNs to simultaneously deliver Dox and BCL-2 siRNA into multidrug-resistant cancer cells. As shown in Fig. 7, strong florescence was observed in almost every cell after incubation with Dox-loaded and G2 PAMAM-modified MSNs (MSN-Dox-G2) and BCL-2 siRNA together. This indicated BCL-2 siRNA significantly silenced the expression of BCL-2 and MSNs, genes or plasmids were found to primarily be adsorbed on the outer surface of MSNs rather than loaded in the pores, leading to burst leakage of genes. In addition, genes located on the outer surface of MSNs cannot be protected from nucleases or lysosomes. Therefore, nanoparticles with large pores have been synthesized to facilitate the internal gene storage and protection\textsuperscript{100,142}.

The production of MSNs with expanded pores is mainly realized by temperature control\textsuperscript{115,123,142,143} or pore-enlarging agents\textsuperscript{100}. Kim et al.\textsuperscript{100} simply synthesized MSNs with ultra-large pores (~23 nm) using the swelling agent 1,3,5-trimethylbenzene (TMB). The resulting MSNs efficiently protected plasmids from nuclease degradation and exhibited higher transfection efficiency compared to MSNs with small pores (2.1 nm). Meka et al.\textsuperscript{144} fabricated MSNs with large pores (9 nm) using ethanol as co-solvent and fluorocarbon-hydrocarbon as template. After conjugation with hydrophobic octadecyl group, this type of MSN showed high loading capacity and efficient delivery siRNA into cancer cells, leading to inhibition of cancer cell proliferation.

4.2. Gene delivery by pore-enlarged MSNs

To date, MSNs with small pores (< 3 nm)\textsuperscript{94,116,140,141}, such as MCM-41 (pore size about 2–3 nm), have been studied as potential vectors to deliver genes. However, limited by the small pore size of MSNs, genes or plasmids were found to primarily be adsorbed on the outer surface of MSNs rather than loaded in the pores, leading to burst leakage of genes. In addition, genes located on the outer surface of MSNs cannot be protected from nucleases or lysosomes. Therefore, nanoparticles with large pores have been synthesized to facilitate the internal gene storage and protection\textsuperscript{100,142}.

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4.3. Gene delivery by multifunctional MSNs

As briefly mentioned above, nanocarriers provide a great potential for delivering drug-nucleic acid combinations to overcome MDR in cancer treatment\textsuperscript{145}. As such, there is an increasing focus on the development of multifunctional delivery systems based on MSNs and other multiple components, including drugs, genes, specific targeting and imaging agents.

Besides modification with cationic materials to enhance the loading of biomolecules and cell uptake, MSNs have been functionalized with various targeting agents to achieve better applications. Park et al.\textsuperscript{118} coupled MSNs with mannoseylated polyethylenimine to target macrophage cells with mannose receptors as well as to enhance the plasmid DNA expression. Peptides, like luteinising-hormone releasing hormone (LHRH)\textsuperscript{146} and SP94\textsuperscript{138}, have been reported to form multifunctional delivery systems. Ashley et al.\textsuperscript{147} developed a new type of nanocarrier (the “protocell”) based on mesoporous silica particles and liposomes, modified with a targeting peptide (SP94), a fusogenic peptide (HSWYG), and PEG. These nanocarriers can hold multiple cargos like doxorubicin, 5-fluorouracil, cisplatin, and siRNA, forming “cocktails”. This system showed significant advantages in stability, targeting specificity, high delivery efficiency of multicomponents, as well as dosage reduction.
Magnetic nanoparticles have also been widely used to effectively deliver vehicles to target organs or tissues, and even permit magnetic response imaging. PLL functionalized magnetic silica nanospheres with large mesopores (13–24 nm) were synthesized by Gu and co-workers. This platform showed strong adsorption capacity for DNA and efficient cellular delivery capability for miRNA, respectively. Yiu et al. prepared PEI-Fe3O4-MCM-48 particles, which showed 4-fold higher transfection efficiency compared with the commercial reagent Polymag™. Zhang et al. synthesized a multifunctional fluorescent-magnetic polyethyleneimine functionalized platform with mesoporous silica, which satisfied the fluorescent tracking and magnetically guided siRNA delivery simultaneously.

5. Conclusions and perspectives

During the last decade, MSNs have exhibited many attractive features which can be synergistically exploited in the development of drug/gene delivery systems. It has been demonstrated that MSNs can improve the dissolution rate and bioavailability of the water insoluble drugs based on the following features: 1) non-crystalline state of drug entrapped in the mesopores; 2) high dispersibility with large surface area; 3) wettability enhancement by the hydrophilic surface of MSNs. Moreover, several factors can influence the drug release rate from MSNs, including pore size, surface chemistry and hollow structure.

Especially for cancer therapy, MSNs have shown obvious advantages for delivery of chemotherapeutic agents over other nanocarriers, such as excellent drug loading capacity and endocytosis behavior. The external surfaces of MSNs can be further modified with various tumor-recognition molecules and stimuli responsive molecules to enhance the therapeutic effect of anti-tumor agents. Moreover, the energy-independent endocytosis and co-delivery ability of MSNs can overcome the MDR in cancer cells.

As for gene delivery, MSNs possessing large pores have been designed to encapsulate abundant genes and protect genes from nuclease. Through cationic modification, MSNs are able to complex with genes and successfully be transfected into various cells. In addition, multifunctional systems based on MSNs also show great potential in controlled drug/gene delivery.

Despite the recent extensive research into the development of MSN-based carriers for drug/gene delivery, there are critical issues that need to be addressed to facilitate their further development. In particular, the biocompatibility, degradability and pharmacokinetics of these materials should be systematically investigated. The in vivo therapeutic benefits of MSNs-based systems in vivo should be rigorously and extensively demonstrated. The essential information regarding the circulation properties in blood, clearance time in body, possible immunogenicity and accumulation in tissues should be obtained before the clinical translation of MSNs. Given the satisfactory resolution of these issues, MSNs-based formulations may make exciting breakthroughs in the treatment of many important diseases and disorders.

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