Functionalized Mesoporous Silica Particles for Application in Drug Delivery System

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Abstract: In these years, ordered mesoporous silica materials have shown promising applications in drug delivery system as drug carriers. These carriers with stable mesoporous structure, large surface area, good biocompatibility and tailored size of mesopores exhibit significant property of higher drug loading. However, silica-based mesoporous materials cannot control the release of the loaded drug without modifications. In this paper, we review the recent research work discussing functionalization of mesoporous materials by various components and methods for application in drug delivery systems. All the examples show that these functionalized mesoporous silica-based systems have great potential for a variety of drug delivery applications, specifically in the fields of the drug targeted and controlled delivery systems.

Keywords: Biocompatibility, drug delivery, mesoporous silica particles, modification.

1. INTRODUCTION

Over the past few decades, drug delivery system (DDS) has been developed rapidly in the field of modern medication and pharmaceuticals [1-3]. Compared with conventional dosage forms, controlled drug delivery system can precisely control the release rates or target drugs to a specific body site and offer numerous advantages, such as enhanced drug efficiency, reduced toxicity, and improved patient convenience [4,5]. Generally, biocompatible polymer particles are most employed as carriers in DDS, such as micelles, liposomes, and polymeric or co-polymeric particles [6-10]. However, DDS, especially targeted and controlled release system, still represent great challenges. For example, the release of many biodegradable polymer-based drug delivery systems relies on the hydrolysis-induced erosion of the carrier structure, which cannot well control the release rate of the drugs [11]. Also, it is still a problem to deliver a relatively large amount of drug molecules using a structure stable carrier. Among many structurally stable materials that have been investigated for drug delivery, mesoporous silica particles (MSPs) with well defined structures and surface properties are known to be an excellent candidate [5, 12-21]. It is demonstrated that MSPs can be efficiently endocytosed *in vitro* by a variety of mammalian cells [12]. What is more, they are biocompatibility and can be excreted through the kidneys in the urine [22]. The discovery of ordered mesoporous silica materials opens the possibility of new developments in the field of drug delivery.

Generally, MSPs are solid materials, which are comprised of a honeycomb-like porous structure with hundreds of empty channels (mesopores) that are able to absorb or encapsulate relatively large amounts of bioactive molecules [12]. In 2001, Vallet-Regi *et al*. firstly employed MCM-41 as a drug carrier in drug delivery system [23]. Since then, researches on mesoporous materials for biomedical purposes have experienced an outstanding increase. It has extensively bioapplications as delivery carriers for simultaneous magnetic resonance and fluorescence imaging, and as drug delivery carriers for anticancer drugs, DNA, and proteins [12,24-31].

Besides MCM-41, several other mesoporous silica structures, such as SBA-15 [16,17] and MCM-48 [18-20], are also used as drug carriers in controlled release system. The pore size of SBA-15 is usually 6 nm in diameter, larger than the 3 nm pore of MCM-41. In contrast with the unidirectional channels present in both MCM-41 and SBA-15, MCM-48 has a three-dimensional (3D) cubic Ia3d mesostructure, which consists of two interpenetrating continuous networks of chiral channels [21]. The synthesis of MSPs relies on the use of surfactants, which can self-assemble into a complete ordering of organic micelle, templating the inorganic component during synthesis. MSPs can be obtained after removing the surfactant template by calcination or dissolution with the appropriated solvent. MSPs have several attractive features as follows: (1) High surface area(>900 m^2g^{-1}) and large pore volume(>0.9 cm^3g^{-1}), which allow it to absorb or encapsulate large mounts of drug molecules; (2) Stable and ordered pore framework, which allows better control over drug loading and release; (3) The uniform and tunable pore size (2-10 nm) allows it to adjust the loading of different drug molecules and to study the kinetics of drug release with high precision; (4) There are silanol groups on both of the internal surface and external surface, which makes it simple to be modified; (5) Silica materials are non-toxic and biocompatibility, which is crucial for many biomedical applications[22,32]. It is demonstrated that MSPs can be excreted through the kidneys in the urine [22]. These unique features make MSPs

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1875-5607/12 $58.00+.00

Table 1. The Typical Reported Silica Systems for Drug Delivery Applications

Drug	Mesoporous matrix	Functional Groups	Max. load [%]	Ref.
IBU	MCM-48		29	[14]
IBU	SBA-15		32	[14]
IBU	SBA-15	Octadecyltrimethoxysilane	26	[14]
IBU	MCM-41	Trimethylsilyl	23.5	[15]
IBU	HMSN		48.5	[34]
IBU	HMSN	3-aminopropyltrieth-oxysilane	43	[34]
IBU	HMSN		23.2	[35]
IBU	SBA-15	Chitosan	1.5	[36]
IBU	HMSN	PAH/PSS multilayers	41.6	[37]
IBU	MCM-41	PMV	20.3	[38]
Doxorubicin	Fe_3O_4@SiO_2 HMSN		3	[26]
Doxorubicin	Fe_3O_4@SiO_2 HMSN	Folic acid	2.7	[28]
Doxorubicin	HMSN	PEG- b-PNIPAM	21.4	[39]
Doxorubicin	MCM-41	Cyclodextrin	4	[40]
Doxorubicin	MCM-41	starch derivatives	22	[41]
Vancomycin	MCM-41	CdS nanoparticles	3.7	[42]
Safranine O	MCM-41	Au nanoparticles	10	[43]
FITC	MCM-41	Fe_3O_4 nanoparticles		[44]
Vitamin B_2	MCM-41	polyamines	1.3	[45]
Fluorescein	MCM-41	Oligonucleotide		[46]
Rhodamine B	MCM-41	PDEAEMA		[47]
Captopril	MCM-41		34	[31]
Salicylic acid	SBA-15	poly(ethylene imine)		[48]
Gentamicin	SBA-15	PLGA	45.6	[49]
Atenolol	SBA-15	Collagen		[50]
Erythromycin	SBA-15	long alkyl chains	8	[51]
Atenolol	SBA-15	poly(N-isopropylacrylamide)	5	[17]
Paclitaxel	HMSN	Poly(ethylene glycol)	4.6	[52]
Fluorescent-PI	HMSN	α-cyclodextrin	4.8	[53]
Hoechst33342	HMSN	α-cyclodextrin	3.3	[53]

excellent candidates for controlled drug delivery systems. So the synthesis and modification of MSN have received much attention recently.

Silica-based mesoporous materials cannot control the release of the loaded drugs without modifications [33]. In this case, surface functionalization is one of the key steps toward the utilization of mesoporous materials in drug controlled delivery applications. Due to the importance and the quick development of functionalized mesoporous silica particles for application in controlled drug delivery system, it seems timely to review this field. In this review, we collect and analyze some of the most relevant milestones in the research of modification of MSPs for controlled drug delivery applications. We present some of the most-used methods for modifying MSPs with different materials, such as particles, organic molecules, and polymers. The functionalization strategies including amino-functionalized MSPs, gate keeper, magnetic mesoporous silica particles (MMSP) and polymer-MSP hybrid composites will be reviewed. Mesoporous materials exhibiting zero premature release seem to be an excellent alternative to conventional systems for the oral administration of highly toxic drugs [13]. Table **1** summarizes the typical reported silica systems for drug delivery applications.

2. TOXICITY AND BIOCOMPATIBILITY

Biodegradability and biocompatibility are the fundamental requirements that determine the possible therapeutic and surgical applications of mesoporous silica-based drug system. A lot of researches suggest that mesoporous silica nanoparticles are biocompatible and degrade over time in the body [22, 32, 42, 54]. *In vitro* and *in vivo* degradation studies of silica xerogel show that the implants dissolve with time at different rates. The dissolved

silica diffuses through the local tissue surrounding the implant, and then enter the blood stream or lymph, which is finally excreted through the kidneys in the urine [22,32]. *In vitro* cytotoxicity studies exhibit low toxicity at low concentrations, however, this toxicity appears to increase at higher concentrations. Zhu *et al*. prepared rattle-type Fe_3O_4@SiO_2 hollow mesoporous spheres and their *in vitro* cytotoxicity to HeLa cells was evaluated. The results show that there is no cytotoxicity for the concentration below 150 mg/ml, while a concentration of 200 mg/ml shows a small amount of cytotoxicity [26, 28]. Besides, the toxicity has been shown to depend somewhat on particle size [26, 55]. Hudson *et al*. studied the biocompatibility of mesoporous silicates of particle sizes ~150 nm, ~800 nm and ~4 μm and pore sizes of 3 nm, 7 nm and 16 nm, respectively [56]. *In vitro*, mesoporous silicates showed a significant degree of toxicity at high concentrations with mesothelial cells. Following subcutaneous injection of silicates in rats, the amount of residual material decreased progressively over 3 months, with good biocompatibility on histology at all time points. In contrast, intra-peritoneal and intra-venous injections in mice resulted in death or euthanasia. Microscopic analysis of the lung tissue of the mice indicated that death may be due to thrombosis. Liu *et al*. studied single and repeated dose toxicity of mesoporous hollow silica nanoparticles (MHSNs) in intravenously exposed mice [57]. For single dose toxicity, lethal dose 50 (LD_{50}) of 110 nm MHSNs was higher than 1000 mg/kg. Further repeated dose toxicity studies indicated no death was observed when mice were exposed to MHSNs at 20, 40 and 80 mg/kg by continuous intravenous administration for 14 days. These results suggest that there is low toxicity of MHSNs for intravenous injection at single dose or repeated administrations. This toxicity might be mitigated by modification of the materials.

The biocompatibility of silica nanospheres that interact with cellular systems has been demonstrated [42]. It is demonstrated that MSPs can be efficiently endocytosed *in vitro* by a variety of mammalian cells [12]. Also, surface functionalization of MCM-41 nanoparticles has been shown to regulate the material endocytosis, a key factor for intracellular delivery [58]. For example, folic acid receptor mediate the endocytosis of folic acid grafted MSN, amine and guanidinium functionalized MSN appear to enter cells by a clathrin and caveolae independent mechanism [42]. Besides, the particle size of MSN can be tuned from 50 to 300 nm allowing a facile endocytosis by living animal and plant cells without any significant cytotoxicity [12].

3. MODIFICATION OF MSPS

At present, one of the main problems for DDS is the loss of activity of several drugs before reaching the target tissue, which results in the premature degradation of the active agent. In this case, modification of the carrier surface is the key in the development of DDS. As for MSP, it can well control the release of the loaded drug after modifications. On one hand, selective functionalization of the particle surface is important for introducing responsive molecular functionality into porous particulate systems. On the other hand, usually the particle surface needs to be modified in order to prevent particle aggregation in solution under conditions relevant for the target application. Furthermore, targeting of specific cells in drug delivery applications requires additional functions, such as specific antibodies attached to the particle surface. Due to the rich Si–OH groups on the surface, the internal and external surface of the mesoporous silica materials are easy to be modified of desirable functionalities with organosilanes [34]. Therefore, functionalization is the key step for the applications of MSPs in DDS. The following will present the recent development of functionalized MSP for application in controlled drug delivery system by the strategies with amino-functionalized MSPs, gate keeper, MMSP and polymer-MSP hybrid composites.

3.1. Amino-Functionalized MSPs

The presence of amino functions on the outer particle surface is of special interest, as the linking chemistry is often relying on amine carboxylic acid interactions [59]. In general, amino-functionalization is mainly performed by the following methods: post-grafting method, co-condensation method or surface hyperbranching polymerization of poly(ethylene imine) (PEI) [60]. Amino-functionalization can not only remain the ordered mesoporous channels with the decreased of pore size to some extent, but also can strengthen the interaction force between functional groups and appropriate drug molecules [34, 61]. Besides, amino-functionalized MSNs can be further modified by covalent attachment of other functional groups and amino on the surface of silica.

3.1.1. Post-Grafting Method

Post-grafting is usually performed on the resultant mesoporous materials to incorporate amino functional groups. Organosilanes, mostly 3-aminopropyltrimetho-xysilane (APTMS) and 3-aminopropyl-triethoxysilane (APTES), are usually used to graft onto the pre-prepared mesoporous silica surfaces [48, 61-65]. Fig. (**1**) shows the typical schematic route of MCM-41 mesoporous silica functionalized by organosilanes [63]. For example, Babonneau *et al*. synthesized amino-functionalized MCM-41 through post-grafting method with APTES [61]. In their experiment, ibuprofen molecules were encapsulated into MCM-41 functionalized by amino groups to determine whether possible interactions between the confined ibuprofen and the silica matrix can restrict their mobility. The results revealed that amino-functionalization could be employed to enhance the interaction between the drug and the support. To further verify this conclusion, Rosenholm *et al*. prepared amino-functionalized MSPs by grafting APTES to SBA-15 particles and studied the structure–activity relationships [48]. Salicylic acid was chose as the probe rather than the more often studied ibuprofen. The results clearly showed that amino-functionalization could increase the drug loading degree and control the drug release rate by strong carboxylic acid–amine interaction. Li *et al*. synthesized MSPs grafted abundant amino groups by [1-(2-amino-ethyl)-3-amino-propyl]trimethoxysilane (AAPTS) to load Cr (VI) [62]. The adsorption experiment results showed that the functionalized mesoporous silica materials possessed an increased Cr (VI) adsorption capacity. Heidari *et al*. prepared MCM-41, nanoparticles of MCM-41, NH_2-MCM-41 (amino functionalized MCM-41 by APTMS) and nanoparticles of

NH_2-MCM-41 to investigate the application for the removal of Ni(II), Cd(II) and Pb(II) ions from aqueous solution [63]. It was found that NH_2-MCM-41 showed the highest uptake for metal ions in aqueous solution. To investigate the accessibility of amino groups in post-synthetically modified mesoporous silica, Ritter *et al*. prepared amino-functionalized MCM-41 MCM-48, and SBA-15 by APTMS, which acted with fluorescein isothiocyanate (FITC) [65]. As expected, increased accessibility was observed for materials with short channels or three-dimensional pore systems.

The above researches show that post-grafting method is effective for the introduction of amino groups into MSP matrix. However, it may result in inhomogeneous surface coverage due to organic moieties congregating near the external surface and the pore mouth, which may lead to the blocking of the pores [66,67]. Therefore the functionalization by post-grafting method should be carefully controlled in order to obtain the homogeneous surface modification.

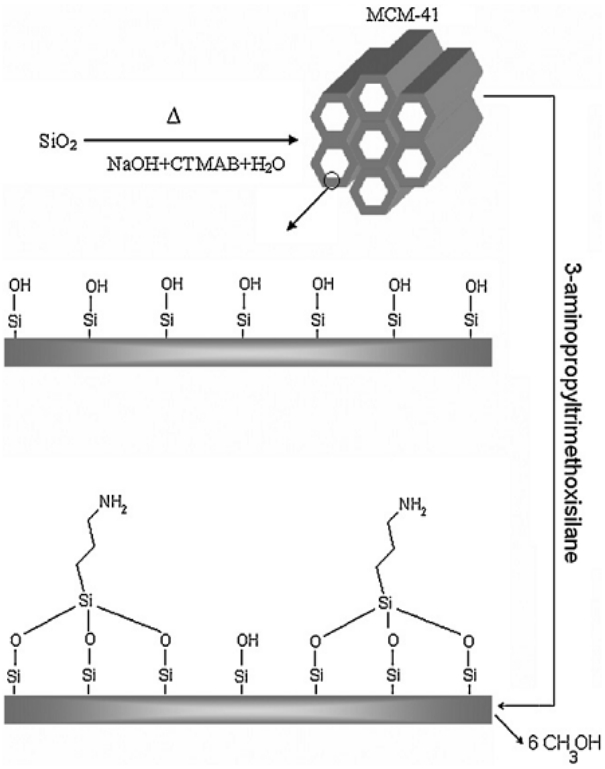

Fig. (1). Schematic functionalization route of MCM-41 by post-grafting method. (reproduced from Ref. [63]).

3.1.2. Co-Condensation Method

Direct synthesis of amino-functionalized mesoporous silica by co-condensation of trialkoxysilane with tetraethoxysilane (TEOS) is reported to be an effective way for a homogeneous distribution of organosilane functionalities [68]. The advantages of the method include the simple synthetic protocols involved in one-pot synthesis, the better control of the loading of the organosilanes, and a uniform distribution of organic groups [69]. However, co-condensation method may lead to a serious drawback: some of the functional groups are embedded in the silica network, which would restrict the applications of the functionalized mesoporous silica in DDS [60]. Nevertheless, it is still an effective way to homogenously incorporate organic functional groups onto the surface of MSPs. For example, the amino-functional MCM-41 materials were prepared by Zeng *et al*. through co-condensation method [70]. For comparison, post-grafting and solvothermal processes were also used. The results showed that the release properties of this system were affected by functionalization degree and the distribution of amino groups on the pore surface of mesoporous materials. The better delivery rate of MCM-41 materials would be obtained *via* co-condensation process. Wang *et al*. synthesized amino-functionalized SBA-15 directly by co-condensation of TEOS and aminopropyltriethoxysilane (APTES) using Pluronic P123 ($EO_{20}PO_{70}EO_{20}$) as pore-directing agent under acid condition [71]. The result showed that percentage of the loaded amino was up to 16%. Moreover, the long-range ordering of mesoporous structure of the modified materials decreased with the increase in APTES concentration in the initial mixture. Sujandi *et al*. reported the synthesis of amino-functionalized-SBA-15 materials by the direct co-condensation of sodium metasilicate and APTES in the presence of Pluronic P123 triblock copolymers as the structure-directing agent under strongly acidic conditions [72]. The results showed that 85% of the incorporated amino groups were easily accessible. Du *et al*. used both post-grafting modification and co-condensation to functionalize the hierarchically mesoporous silica nanoparticles (HMSNs) with primary amine groups, respectively [73]. Unfortunately, some unexpected sheets appeared when used the co-condensation method while the amino-HMSNs have a little aggregation for the modification using post-grafting methods.

3.1.3. Polymerization Approach

The surface density of the reactive amine group is a primary factor that determines the properties of the materials. Recently, hyperbranching surface polymerization shows a promising method for amino functionalization of mesoporous silica as the surface concentration of amino groups is much higher than post-grafting method and co-condensation method [59-60,74-75]. Hyperbranching polymerization of aziridine on silica solid substrates was investigated by Kim *et al*. [76]. It was found that the Si–OH group on the substrate was able to initiate the ring-opening polymerization of aziridine, resulting in highly branched PEI on the surface. Fig. (**2**) shows the formation of a hyperbranched PEI on mesoporous silica support using aziridine [75]. The thickness of the PEI layer can be well controlled simply by changing the aziridine/silica ratio in the surface functionalization step. Besides, the modified PEI can improve the hydrophobicity of the mesoporous silica material, which makes silica particles well dispersed in an aqueous media. Rosenholm *et al*. prepared amino-functionalized mesoporous SBA-15 silicas by different routes, including co-condensation, post-grafting of amino-silanes, and surface hyperbranching polymerization of PEI [60]. The result revealed that co-condensation route was the least efficient surface functionalization method. However, surface polymerization leads to the highest number of

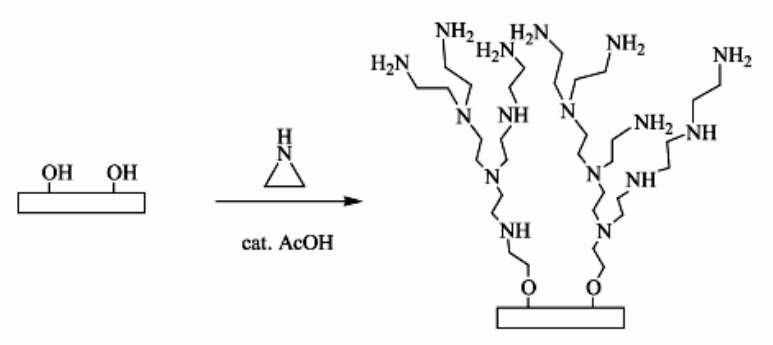

Fig. (2). Formation of a hyperbranched PEI on mesoporous silica support using aziridine. (reproduced from Ref. [76]).

accessible amine groups. Based on the modified silica particles, Rosenholm *et al*. further modified them using folic acid as the targeting ligand with the aim of specifically targeting cancer cells [24]. It was found that five times more particles were internalized by cancer cells expressing folate receptors as compared to the normal cells expressing low levels of the receptor. In addition, the hybrid PEI-silica particles were shown to be noncytotoxic, which was able to specifically target folate receptor-expressing cancer cells under coculture conditions. At the same time, they investigated the targeted intracellular delivery of hydrophobic agents using this hybrid carrier system [77]. It showed both cancer cell-targeting ability and capacity to retain a hydrophobic agent with subsequent specific release into the endosomal compartment, which revealed that the particles were promising candidates as carriers in targeted drug delivery for cancer treatment.

3.2. Gate Keeper

Gate keeper as a concept used in MSP-based stimuli-responsive systems is first developed by Lai *et al*. in 2003 [42]. In general, a variety of chemical entities (like nano-particles, organic molecules, or supramolecular assemblies) are used as "gate keepers" in DDS to regulate the encapsulation and release of drug molecules. Different stimuli-responsive strategies, such as pH [43,44], enzymatic [78], redox [40,42], and photo irradiation [43,79], have been applied as "triggers" for uncapping the pores and releasing the guest molecules from MSPs. Fig. (**3**) shows the representation of an MSP loaded with guest molecules and end-capped with a general gatekeeper [12]. This type of DDS with "zero premature release" performance is particularly useful when the cargo to be delivered is toxic, like anti-cancer drugs [12].

Recently, several MSP-based controlled-release systems with "zero premature release" property have been synthesized by using different kinds of pore-blocking caps as gate keeper. Lai *et al*. developed a redox-controlled drug delivery system that was based on MSP capped with cadmiumsulfide nanoparticles (CdS) [42]. In this system, CdS was chemically attached to MSP through a disulfide linker, which was chemically labile and could be cleaved

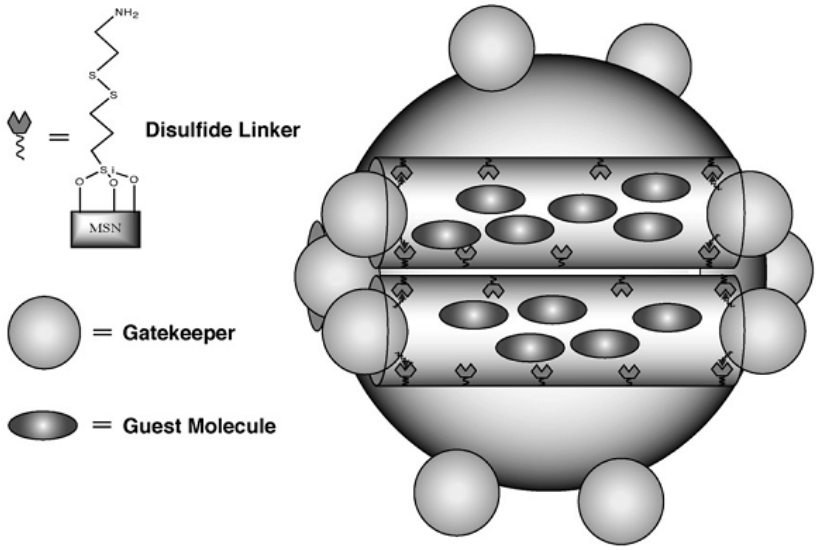

Fig. (3). Representation of an MSP loaded with guest molecules and end-capped with a general gate keeper. (reproduced from Ref. [12]).

with various disulfide reducing agents, such as dithiothreitol (DTT) and mercaptoethanol (ME). The drug molecules were encapsulated inside the porous framework by capping the openings of the mesoporous channels with size-defined CdS to physically block the drugs from leaching out. The CdS-capped MSN drug/neu-rotransmitter delivery system exhibited less than 1.0% of drug release in 10 mM PBS buffer solutions (pH 7.4) over a period of 12 h. When added DTT and ME to the release medium, CdS-capped MSNs triggered a rapid release with 85% of the total release within 24 h. The result revealed that this new MSN system could play a significant role in developing new generations of site-selective, controlled-release delivery nanodevices. Function-alized gold nanoparticles (AuNPs) [80] and superparamag-netic Fe_3O_4 nanoparticles [44,81] were also used as gate keepers. For examples, Zhu *et al*. reported the construction of a novel and general bioresponsive controlled-release mesoporous silica (MS) system that was based on MS nanoparticles capped with aptamer-modified gold nanoparticles, which was stimuli responsive to the aptamer-target interaction [80]. Gan *et al*. fabricated a magnetic and reversible pH-responsive, MSPs-based nanogated ensemble by anchoring superparamagnetic Fe_3O_4 nanoparticles on the pore outlets of MSPs *via* a reversible boronate esters linker [44]. This combination of controlled release properties with magnetic motor effects made the system very attractive for site-specific drug delivery applications.

In addition to solid nanoparticles, organic molecules and supramolecules also have been shown to be able to serve as gate keepers for mesoporous silicas. Bernardos *et al*. studied the controlled release of vitamin B_2 using mesoporous materials functionalized with amine-bearing gate-like scaffoldings [45]. In this system, the amine-based gate-like ensemble was anchored on the pore outlets as gate keeper to control the delivery of vitamin B_2. The *in vitro* release revealed that by choosing the suitable anion it was possible to control delivery of the vitamin at neural pH but completely inhibited its liberation in acidic conditions. Aznar *et al*. reported the development of an MCM-41 mesoporous support that was functionalized with saccharides at the pore outlets and contained the dye $[Ru(bipy)_3]^{2+}$ in the pores [82]. This control was selective in that only anion borate could act as a molecular tap and inhibit the delivery of the entrapped guest. Bernardos *et al*. also synthesized silica mesoporous supports capped with "saccharides" [41]. The gate-like functional hybrid systems consisted of nanoscopic MCM-41-based materials functionalized with different "saccharide" derivatives on the pore outlets and a dye in the mesopores. The suitable enzyme induced the hydrolysis of the glycosidic bonds in the anchored saccharides, which controlled the release of the cargo. It was demonstrated that the attachment of a hydrolyzed starch derivative as a gate keeper provided a new method for the design of mesoporous systems to deliver the entrapped guest in the presence of suitable enzymes. Climent *et al*. prepared oligonucleotide-capped mesoporous silica nanoparticles for controlled delivery applications [46]. The proposed paradigm was represented in Fig. (**4**). Solid S1-O1 is tightly capped, which shows a negligible release of fluorescein. In contrast, the presence of the complementary oligonucleotide O2 induced the hybridization between O1and O2. More than 95 % of the fluorescein had been released within 90 min. It was demonstrated that the use of oligonucleotides as caps on the surface of mesoporous supports was a suitable method for the preparation of "bio-gated" delivery systems that could be selectively opened in

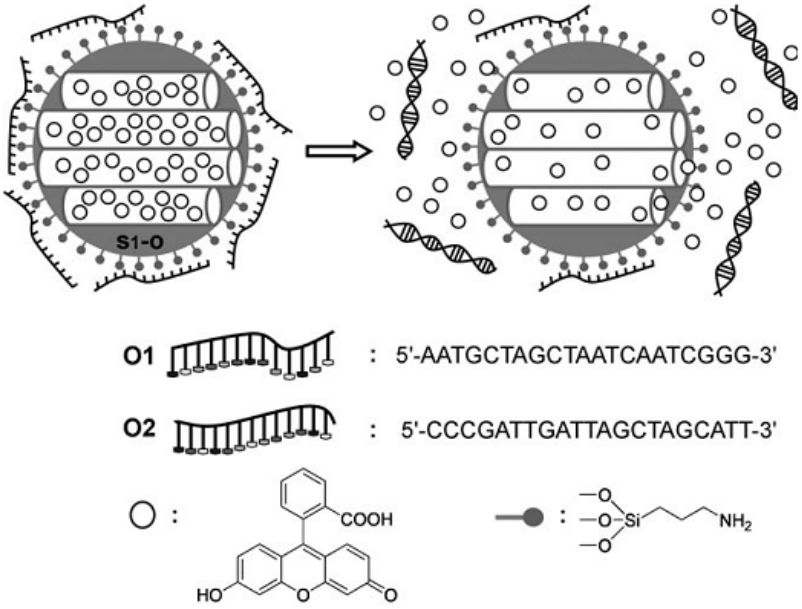

Fig. (4). Representation of the gated material S1 functionalized with 3-aminopropyltriethoxysilane and capped with a single-stranded oligonucleotide (O1). The delivery of the entrapped guest (fluorescein) is selectively accomplished in the presence of the complementary oligonucleotide (O2). The sequence of the oligonucleotides O1 and O2 is shown. (reproduced from Ref. [46]).

the presence of specific targets (i.e. the complementary oligonucleotide O2).

However, the development of real systems for controlled release is still in its infancy stage. For instance, some of the reported systems display gating features in non-aqueous solvents. Moreover, the used gate-like scaffoldings require large synthetic efforts. In some cases, external stimuli are difficult to apply to certain delivery applications [41]. Some efforts are then made to prepare MSP containing different gate-like scaffoldings [83-87], hoping that the using gate keeper for selective release applications opens a wide range of new perspectives in the development of DDS.

3.3. MMSP

Recently, there has increased interest in MMSP for the use as carriers in drug targeted delivery because of their high surface area and magnetic separability. The nanocomposite spheres, which combine the advantages of mesoporous silica and magnetic carrier technology, are likely to be applied in targeted delivery system [35]. Hollow mesoporous silica particle is the particle with penetrating pore channels from outside to the inner hollow cores [35]. As drug molecules can be absorbed into the pores and the interstitial hollow space, the drug storage capacity is much higher than that of conventional mesoporous particles [34,53,88,89]. Therefore, biocompatible mesoporous silica could be linked to the magnetic Fe_3O_4 nanoparticles forming a stable Fe_3O_4@SiO_2 core-shell structure. These multifunctional particles not only enable high drug loading but also can magnetically target drug delivery. As MMSP allows the drugs release at a defined target site with the aid of an external magnetic field, it has been widely investigated in DDS [89]. Hence studies on the synthesis of magnetism-functionalized mesoporous materials mainly focus on the structure with a magnetite core and a mesoporous shell [25-27,89,90]. For example, Kim *et al*. synthesized monodisperse and size-controllable core–shell mesoporous silica particles by using single Fe_3O_4 nanocrystals as cores and cetyltrimethylammonium bromide (CTAB) as template [25]. The surface of the particles was modified with PEG to render them biocompatible by preventing the nonspecific adsorption of proteins to the particles. The *in vivo* animal experiments revealed an accumulation of the Fe_3O_4@mSiO_2-PEG in tumor sites, even at 24 h after injection the particles still remained in tumors. The results demonstrated the successful multifunctional bioapplications of the core–shell particles for simultaneous magnetic resonance, fluorescence imaging, and for drug delivery. Zhao *et al*. fabricated a novel kind of rattle-type hollow magnetic mesoporous sphere (HMMS) with Fe_3O_4 particles encapsulated in the cores of mesoporous silica microspheres by sol–gel reactions on hematite particles followed by cavity generation with hydrothermal treatment and H_2 reduction [35]. Such a structure had the merits of both enhanced drug-loading capacity and a significant magnetization strength. The prepared HMMSs realized a relatively high storage capacity up to 302 $mg \cdot g^{-1}$ when ibuprofen was used as a model drug. Moreover, the IBU–HMMS system had a sustained release property. In the acidic solution (pH 2.4), it had a release rate of 63% within 30 h. Zhu *et al*. developed a targeted anticancer drug (Doxorubicin hydrochloride, DOX) delivery system based on folate-conjugated Fe_3O_4@SiO_2 spheres (Fe_3O_4@SiO_2-FA) combining receptor-mediated targeting and magnetic targeting [28]. The schematic procedure for preparation and folate conjugation of Fe_3O_4@SiO_2 hollow mesoporous spheres was shown in Fig. (**5**). The experiment showed that these spheres could be targeted under an external magnetic field. For *in vitro* cytotoxicity and cell uptake, these Fe_3O_4@SiO_2-FA spheres were nontoxic up to a concentration of 150 $\mu g \cdot mL^{-1}$. Furthermore, it could be specifically taken up by HeLa cells *via* FA receptor-mediated endocytosis. The release of DOX from Fe_3O_4@SiO_2-FA spheres had a sustained release pattern while the DOX-loaded Fe_3O_4@SiO_2-FA spheres exhibited greater cytotoxicity than free DOX. Therefore, they concluded that folate-conjugated Fe_3O_4@SiO_2 hollow mesoporous spheres had great potential application for targeted anticancer drug delivery for cancer therap. In addition, the magnetic particle could be loaded on the mesopores of the silica to result in MMSP for drug release. For example, Huang *et al*. synthesized magnetically functionalized mesoporous silica spheres by generating magnetic Fe_xO_y nanoparticles onto the mesoporous silica hosts using the sol-gel method [29]. The ibuprofen-containing spheres were then coated with biodegradable poly(DL-lactide-co-glycolide) (PLGA) by the S/O/W single-emulsion method. After coating PLGA, the initial burst release in 1 h was reduced greatly. The cumulative release amount in 1 day was 16.14%, and ~60% after 20 days. These composites with or without the PLGA could be used as potential vectors for drug targeting and controlled-release systems. However, the density of magnetic particles have to be well controlled, otherwise it may limit the pore volume of MSP, resulting in the relatively low drug content if the magnetic particles are loaded into the channel pores of the MSP.

Most of the above systems comprise magnetic nanoparticle "cores" coated with inorganic silica "shell" constituents. The core–shell systems are indeed attractive for the development of site-specific drug delivery systems [79]. However, they are not "zero premature release", which is greatly expected for the sustained site-selective delivery systems, especially for the highly toxic drugs and the drugs for antitumor, chronic and resistant diseases [44]. Fe_3O_4 nanoparticles have been very attractive as gate keepers for the development of site-directing and site-specific drug delivery systems. What is more, Fe_3O_4 nanoparticles can offer the MSPs magnetic property, which are attracted toward the magnet in the presence of an external magnetic field. As we have described this kind of system in the *gate keeper* section, we will not discuss here.

3.4. Polymer-MSP Hybrid Composites

Various types of nanoparticles, organic molecules, and biomolecules have been used as capping agents to block molecule transport from a silica mesopore. Recently, polymer–silica hybrid nanocomposites have attracted enormous attention because of their diverse potential applications in drug release systems [36,39,49,91,92]. These organic-inorganic hybrid materials are particularly attractive because they combine the functional versatility of organic chemistry with the advantages of thermal stability of

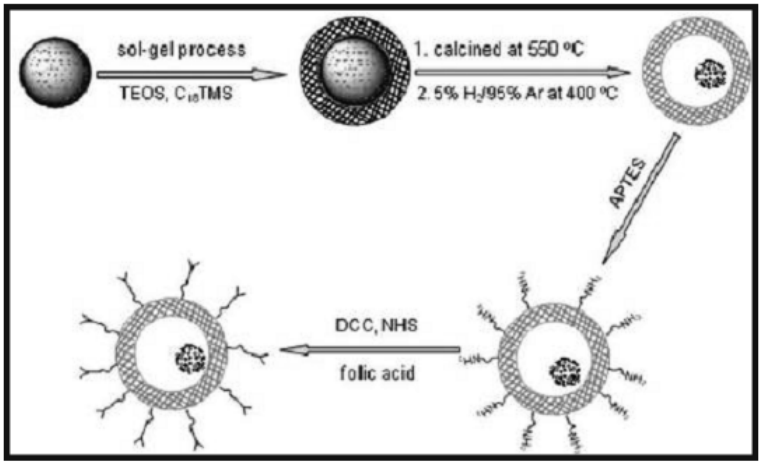

Fig. (5). Schematic procedure for preparation and folate conjugation of Fe_3O_4@SiO_2 hollow mesoporous spheres. (reproduced from Ref. [28]).

inorganic substrates [92]. Numerous polymers and methods have been developed to prepare these hybrid composites.

3.4.1. MSP Embed within the Polymer Matrix

The most simplest method to obtain the silica-polymer composites is to mix the drug loaded silica particles with polymer solution directly and then eliminate the solvent [49,50,93,94]. After mesoporous silica is embed in polymer matrix, the polymer layer caps the mesopore channels. In this case, the loaded drug molecules need to diffuse through the mesoporous channels and the polymer layers into the release medium, therefore the drug release rate is well controlled. For example, Xue *et al*. synthesized a PLGA/mesoporous silica hybrid structure (PS hybrid structure) *via* a novel sol-gel route assisted by single emulsion solvent evaporation [49]. The *in vitro* drug release properties of both the mesoporous silica and the PS hybrid structure were investigated. It was shown that the PS hybrid structure could realize a reduced initial burst with a plateau stage for nearly 3 weeks of slow release, followed by a sustained release stage lasting for nearly 2 weeks. The whole release period could last as long as 5 weeks. Fagundes *et al*. used collagen to prepare SBA-15-collagen hybrid material for drug delivery applications [50]. Significant differences were observed and the release rate was influenced by the presence of collagen in the mesopores. SBA-15 exhibited a release profile of almost 100% after 6 days of assays. On the other hand, for the hybrid system, the total cumulative release from SBA-15-collagen-drug (SBA-15-CD) at the end of immersion experiment was 80%. The experiment revealed that SBA-15-CD was a better drug release device as the collagen phase acted as a temporary barrier to prevent the rapid release of atenolol during assays.

3.4.2. Layer-By-Layer Technology

Polyelectrolyte capsules have been widely used in DDS recently. They are prepared by layer-by-layer (LbL) assembling of weak oppositely charged polyelectrolytes, such as poly(allylamine hydrochloride) (PAH) and polystyrene sulfonate (PSS) [37,95-97], poly(L-lysine) and poly(L-glutamic acid) [98,99], and poly(vinyl pyrrolidone) and poly(methacrylic acid) [100]. However, these hollow polyelectrolyte capsules are not mechanically strong and not freestanding. Due to its physical stability, MSP can be used as a container for drug molecules and a template for the polyelectrolyte multilayer coatings. Zhu *et al*. proposed a strategy to combine the advantages of hollow mesoporous silica (HMS) spheres with a 3D pore network and polyelectrolyte multilayers with a stimuli-responsive property. Fig. (**6**) showed the schematic illustration and the release profiles at different pH conditions [37]. The system (HMS@PEM) consisted of HMS spheres with an average sphere diameter of 300–400 nm and polyelectrolyte multilayer coatings (PAH/PSS) with an average thickness of 14 nm. The IBU storage capacity of the IBU-HMS system was 41.64% (918.6 mg_{IBU}/g_{SiO2}), while the IBU storage capacity in the IBU-HMS@PEM system was 34.60% (872.6 mg_{IBU}/g_{SiO2}). The cumulative drug release from the two systems in release media of pH 1.4 are very close to each other while the release rate of IBU-HMS@PEM system was very low with the released amount of only 10% over a period of 48 h. The reason was as follows. The PAH/PSS multilayers were compact, which had decreased permeability at the increased pH value. Therefore, the compact multilayers could easily cap the openings of the mesoporous channels. The result revealed that IBU release rate could be well-controlled by changing the pH value of the release medium. Moreover, the researchers reported an improved route based on the above mentioned strategy, which realized pH-controlled storage and release of water-soluble drug (gentamicin molecules as a model drug) [97]. Therefore, this type of material was of potentials for the controlled drug release applications.

MSP as sacrificial template can be used for adsorbing the therapeutic drug within the pores and polyelectrolyte multilayer capsule forms [101-104]. The sacrificial templates can be removed using conditions that do not significantly affect the activity of the loaded therapeutic drug, forming capsules with high drug loadings. The schematic illustration is illustrated in Fig. (**7**) [101]. Wang *et al*. reported the

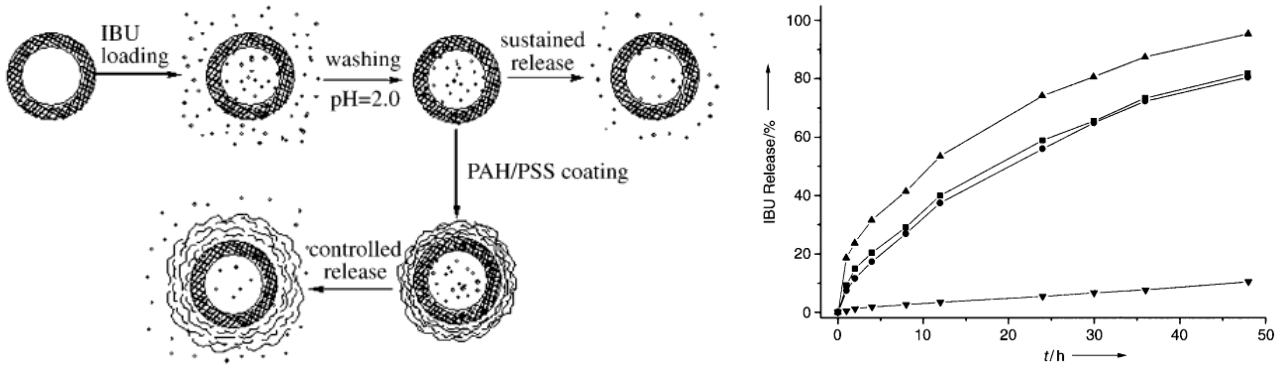

Fig. (6). The left shows the schematic illustration of the drug-delivery systems coated with PAH/PSS; the right shows cumulative drug release from the two systems in release media of different pH values. ■: pH 1.4 from IBU-HMS, ●: pH 1.4 from IBU-HMS@PEM, ▲: pH 8.0 from IBU-HMS, ▼: pH 8.0 from IBU-HMS@PEM. (reproduced from Ref. [37]).

immobilization of various enzymes in MSP followed by encapsulation *via* the layer-by-layer assembly of multilayered nanocomposite thin shells [104]. The enzyme possessed significantly enhanced reaction stability with increasing PDDA/PSS layer number, which might be caused by a reduced reaction rate. Yu *et al*. reported the stepwise formation of biocompatible poly(l-lysine)/poly(l-glutamic acid) (PLL/PGA) multilayer films on MS spheres *via* layer-by-layer (LbL) self-assembly technique [105]. Enzyme was preloaded into MS spheres and hollow polypeptide capsules could be obtained by subsequently removing silica cores in HF solution. The presented approaches provided a general strategy for the encapsulation of macromolecules in MSP materials.

3.4.3. Covalent Linking of Polymer Onto MSPs

Covalent linking of polymer onto pre-prepared mesoporous silica surfaces by co-condensation or post-grafting is an often used method to prepare mesoporous organic-silica composite materials [52,74, 106-108]. Significant advantages of these methods are the chemical stability arising from the strong covalent bonding between the organics and the silica walls [109]. Polymer-functionalized MSPs are promising for many applications, which can be obtained by tuning the chemistry and structures of the polymer and silica layers. Moreover, they can further be functionalized by reacting suitable molecular species with the mesoporous polymer surface. For example, Lay *et al*. prepared poly(ethylene glycol)-graft-hollow (PEG-g-hollow) silica vesicles by grafting PEG brushes through urethane groups formed by the reaction of the amino groups on the surfaces of hollow silica spheres and monomethoxy PEG (Mn: 5 kDa) 4-nitrophenyl carbonate [52]. The water insoluble drug paclitaxel (PTX) was loaded in PEG-g-hollow silica vesicles with a loading content of 4.6%. The release of PTX from PEG-g-hollow silica vesicles is 47 % after 330 h while only 5 % of PTX is from free PTX. Furthermore, PTX-loaded PEG-g-hollow silica vesicles showed a potent capacity to kill cancer cells while PEG-g-hollow silica vesicles showed a very low *in vitro* cytotoxicity in cells.

Stimuli-responsive polymer-grafted MSP carriers take advantage of the unique features of polymers which is employed as a stimuli-responsive switch [110]. Generally, the system is sensitive to physiological conditions (e.g., pH [37,38,47,110-112], temperature [113] and redox [114]), and therefore the necessary amount of drug could be released in response. As shown in Fig. (**8**), Liu *et al*. prepared responsive polymer-coated mesoporous silica as a pH-sensitive nanocarrier for controlled release [110]. In the responsive system, cross-linkable poly(4-vinyl pyridine) (PVP) was used as the responsive polymer because of its pH-triggered switching ability. They anchored PVP on mesoporous silica by simply grafting PVP with a bromo-functionalized silica surface. At high pH, the deprotonation of the polymer produced a hydrophobic shrunken state and inhibited the release of trapped molecules while at low pH, the swollen state of the protonated PVP was permeable to molecule transport, leading to the pH-controlled release. At pH 7.4, it needs 14 h to reach 70% release, indicating the capping effect of the coated polymeric barrier. The pH 5.5 environment induced the fast release of dye molecules. The release profile exhibited that the release reached 70% at 6 h

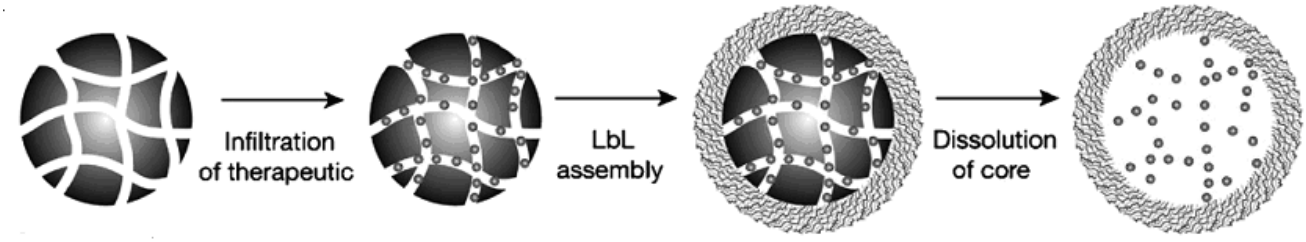

Fig. (7). Schematic representation of drug encapsulation using MSP as supports. (reproduced from Ref. [101]).

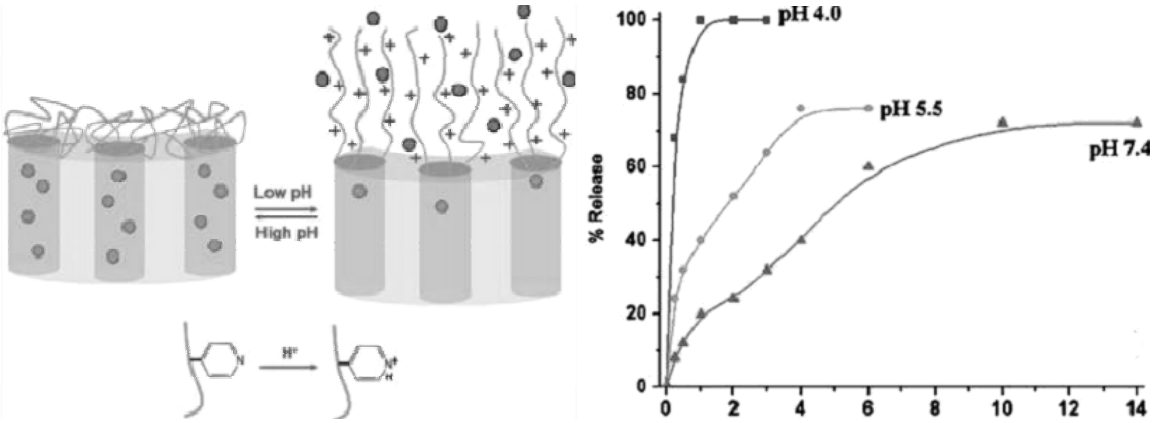

Fig. (8). Scheme of pH-controlled release from responsive polymeric nanoshell-coated MSP(the left), Cumulative drug release from the two systems in release media of different pH values(the right). (reproduced from Ref. [110]).

and no more release was observed after that. The release profile exhibited the fastest molecular transport at pH 4.0, in which 100% release was obtained within 1 h. The in-vitro release profile revealed that this system was a promising candidate in the formulation of a pH-sensitive vehicle in in-vivo delivery of therapeutic contents to low pH tissues, such as tumors and inflammatory sites. You *et al*. coated thermosensitive poly(N-isopropylacrylamide) on mesoporous silica to control the drug molecule release at specific temperature [115]. The resulting nanoparticle polymer composites showed an uptake and release of fluorescein at room temperature (below the lower critical solution temperature, LCST, of the polymer) and a low level of leakage at 38 °C (above LCST, 2% after 2 h). The results demonstrated that the phase state of a temperature-responsive polymer could control opening and closing of the pores.

CONCLUSION

This review highlights some of the recent advances in the modification of MSPs. The functionalization strategies including amino-functionalized MSPs, gate keeper, magnetic mesoporous silica particles, polymer-MSP hybrid composites, are discussed. It shows that functionalized MSPs are of great promise for the applications in drug controlled release system. Although the reported work shows great potential for future applications, new breakthroughs are still required for the functionalized MSPs as drug delivery systems. For example, the effective targeting of MSPs by specific chemical bonding or conjunction between the designed molecules or enzymes has not been well explored. Despite the emerging of stimuli-responsive silica systems, "zero release" in the delivery process and subsequent release after reaching the targeted cells or tissues are still difficulty to realize for the sustained site-selective delivery systems. What is more, the interactions between the drug and matrix surface can change when functionalized with different groups, which would result in the variation of drug loading and delivery rate. Therefore, much more work should be done to combat the increasing complications associated with particle property and physiological conditions. Further development and application of the functionalized MSPs will provide more research opportunities for the drug delivery community in future.

CONFLICT OF INTEREST

None declared.

ACKNOWLEDGEMENTS

This work is supported by National Natural Science Foundation of China (NSFC,No. 20803044, 21173127), the Natural Science Foundation of Shandong Province (ZR2011BQ003) and the Independent Innovation Foundation of Shandong University(IIFSDU).

ABBREVIATION

DDS	=	drug delivery system
MSPs	=	mesorous silica particles
MMSP	=	magnetic mesoporous silica particles
MHSNs	=	mesoporous hollow silica nanoparticles
LD50	=	lethal dose 50
PEI	=	poly(ethylene imine)
APTMS	=	aminopropyltrimethoxysilane
APTES	=	Aminopropyl-triethoxysilane
AAPTS	=	[1-(2-amino-ethyl)-3-aminopropyl]trimethoxysilane
LCST	=	lower critical solution temperature
PMV	=	poly(methacrylic acid-co-vinyl triethoxylsilane)
PEG-b-PNIPAM	=	poly(ethylene glycol)- b-poly(N-isopropylacrylamide)
PDEAEMA	=	poly(2-(diethylamino)ethyl methacrylate)
FITC	=	fluorescein isothiocyanate

TEOS	=	tetraethoxysilane
CdS	=	cadmiumsulfide nanoparticles
DTT	=	dithiothreitol
ME	=	mercaptoethanol
DOX	=	Doxorubicin hydrochloride
HMSNs	=	hierarchically mesoporous silica nanoparticles
MMSP	=	Magnetic mesoporous silica particles
CTAB	=	cetyltrimethylammonium bromide
HMMS	=	hollow magnetic mesoporous sphere
PLGA	=	poly(D,L-lactide-co-glycolide)
SBA-15-CD	=	SBA-15-collagen-drug
PAH	=	poly(allylamine hydrochloride)
PSS	=	polystyrene sulfonate
HMS	=	hollow mesoporous silica
PLL/PGA	=	poly(l-lysine)/poly(l-glutamic acid)
LbL	=	layer-by-layer
PEG-g-hollow	=	prepared poly(ethylene glycol)-graft-hollow
PTX	=	paclitaxel
PVP	=	poly(4-vinyl pyridine)

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Received: June 26, 2011 Revised: February 22, 2012 Accepted: February 28, 2012