

Available online at www.sciencedirect.com

ScienceDirect

journal homepage: www.jfda-online.com

Review Article

Cell microenvironment stimuli-responsive controlled-release delivery systems based on mesoporous silica nanoparticles



Chun-Ling Zhu^{a,*}, Xian-Wei Wang^a, Zhen-Zhen Lin^a, Zeng-Hong Xie^a,
Xiao-Ru Wang^b

^aDepartment of Chemistry, Fuzhou University, Fuzhou, PR China

^bXiamen Huaxia Vocational College, Wenjiao Aera, Jimei Xiamen, Fujian, PR China

ARTICLE INFO

Article history:

Received 30 September 2013

Accepted 27 December 2013

Available online 1 February 2014

Keywords:

Cell environmentally responsive mechanisms

Controlled-release delivery system

Mesoporous silica nanoparticles

Stimuli-responsive

ABSTRACT

To develop novel tumor cell microenvironment stimuli-responsive smart controlled-release delivery systems is one of the current common interests of materials science and clinical medicine. Meanwhile, mesoporous silica nanoparticles as a promising drug carrier have become the new area of interest in the field of biomedical application in recent years because of their unique characteristics and abilities to efficiently and specifically entrapp cargo molecules. This review describes the more recent developments and achievements of mesoporous silica nanoparticles in drug delivery. In particular, we focus on the stimuli-responsive controlled-release systems that are able to respond to tumor cell environmental changes, such as pH, glucose, adenosine-5'-triphosphate (ATP), glutathione (GSH), and H₂O₂.

Copyright © 2014, Food and Drug Administration, Taiwan. Published by Elsevier Taiwan LLC. Open access under [CC BY-NC-ND license](https://creativecommons.org/licenses/by-nc-nd/4.0/).

1. Introduction

The development of stimuli-responsive nanomaterials for cancer treatment has been receiving extensive attention in recent years and now has become a principal field in medical research [1–4]. In cancer therapy, to achieve the complete eradication of tumors, anticancer drugs must be administered systematically in high doses to ensure sufficient and sustained therapy. However, sustained drug delivery systems will cause severe side-effects because of the nonspecific uptake of anticancer drugs by healthy tissues/organs such as liver,

kidney, bone marrow, and heart before reaching the targeted organs or tissues [5]. Therefore, it is highly desirable to design stimuli-responsive controlled drug delivery systems (CDDSs). In this system, the vehicles loaded with drug molecules can be capped by various “gatekeepers.” Being blocked, drug molecules are unable to be leached out from the host, thus preventing any premature release. The release is triggered only upon exposure to stimuli, which induce the removal of gatekeepers and then the release of the entrapped drug molecules. Among the various dedicated materials for drug delivery applications, multifunctional mesoporous silica nanoparticles (MSNs) are particularly interesting candidates for powerful

* Corresponding author. Department of Chemistry, Fuzhou University, Fuzhou 350108, PR China.

E-mail address: clzhu@fzu.edu.cn (C.-L. Zhu).

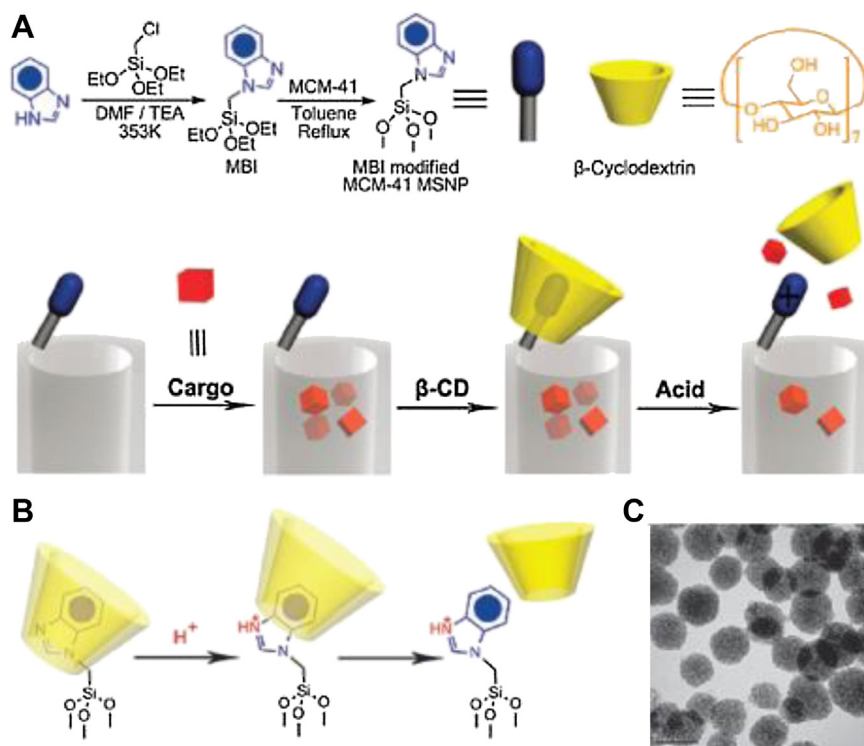


Fig. 1 – A graphical representation of the pH responsive MSN nanovalve. (A) Synthesis of the stalk, loading of the cargo, capping of the pore, and release of the cap under acidic conditions. Based on previous calculations, the maximum number of stalks per nanopore is six and the maximum number of fully assembled nanovalves per nanopore is four. The average nanopore diameter of the MSN is around 2.2 nm, and the periphery diameter of the secondary side of b-cyclodextrin is about 1.5 nm. Thus, for a cargo with a diameter 40.7 nm, a single nanovalve should be adequate to achieve effective pH-modulated release. (B) Details of the protonation of the stalk and release of the b-cyclodextrin. (C) TEM image of capped MSN. The scale bar is 100 nm. MSN = mesoporous silica nanoparticle; TEM = transmission electron microscopy. Note. From “Autonomous in vitro anticancer drug release from mesoporous silica nanoparticles by pH-sensitive nanovalves,” by H. Meng, M. Xue, T. Xia, et al, 2010, *J Am Chem Soc*, 132, p. 12690, Copyright 2010, American Chemical Society. Adapted with permission [23].

drug carriers because of their unique characteristics and abilities to efficiently and specifically entrap cargo molecules. The unique features of MSNs for high surface areas (900–1500 m²/g), tunable pore size, large accessible pore volumes (0.5–1.5 cm³/g), less toxicity, and biocompatibility make them attractive vehicles for drug delivery. Since 2001, María Vallet-Regí's research group proposed MSNs as drug delivery systems for the first time [6]. A series of MSN-based stimuli-responsive systems have been reported [7,8]. The drug release is subsequently to be triggered by some external stimuli. These external stimuli include: (1) physical signals such as temperature [9,10], electric field [11], magnetic field [12], and photo [13–15]; and (2) chemical signals such as ionic strength [16], redox potential [17–19], and enzymatic activities [20,21]. However, in the past years, design of novel bio-responsive nanocarriers that release drugs in response to an intracellular signal, in particular acidic pH and redox potential, has received great interest.

In this review, we critically discuss the recent developments related to the use of MSNs for drug delivery, with special focus on cell environmentally responsive mechanisms and highlight the use of pH-responsive, glutathione (GSH)-responsive, adenosine-5'-triphosphate (ATP)-

responsive, glucose-responsive, and H₂O₂-responsive mechanisms in drug delivery. We also give our view on some of the open challenges that need to be addressed in order to bring the highly promising MSNs to practical use as drug delivery vehicles.

2. pH-responsive CDDSs

Among vigorous stimuli-responsive CDDSs, biological pH-responsive drug delivery systems received the most investigation since the human body exhibits variations in pH along the gastrointestinal tract from the stomach (pH = 1.0–3.0), to the small intestine (pH = 6.5–7.0), then to the colon (pH = 7.0–8.0) [22]. In addition, cancer cells have a more acidic environment compared with normal cells. Furthermore, tumor and inflammatory tissues are more acidic than normal tissues and blood. Consequently, the pH-responsive nano-DDSs based on MSNs have been designed to achieve a site-selective controlled release. There are three main methods to design pH-responsive drug delivery. The caps such as polyamine and DNA were linked on the surface of MSNs through electrostatic

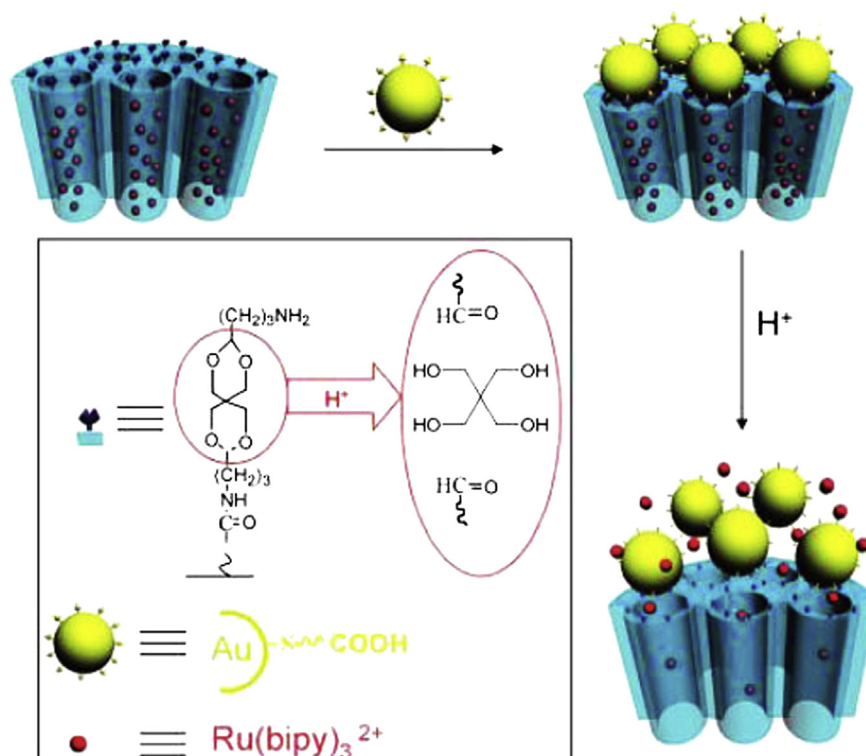


Fig. 2 – Schematic illustration of pH-responsive nanogated ensemble based on gold-capped mesoporous silica through acid-labile acetal linker. Note. From “pH-responsive nanogated ensemble based on gold-capped mesoporous silica through an acid-labile acetal linker,” by R. Liu, Y. Zhang, X. Zhao, et al. 2010, *J Am Chem Soc*, 132, p. 1500. Copyright 2010, American Chemical Society. Adapted with permission [26].

attraction and were uncapped from MSNs under low pH condition. By contrast, the caps including supramolecular stoppers and inorganic nanoparticles were anchored on the surface of the MSNs by acid-labile bonds such as in acetals. The third gating mechanism involves the reversible reaction between polyalcohols and boronic acids to form boronate esters. While at pH 2.0–4.0, the hydrolysis of the boronate ester bond took place and thus resulted in a rapid release of the entrapped drug.

Zink and coworkers developed several pH-responsive mesoporous silica CDDs utilizing the pH-dependent pseudorotaxanes, rotaxanes, or other analogues [23–25]. In these systems, the aromatic amines/ammonium stalks were immobilized on the surface of the MSNs, and macrocyclic movable gates were introduced to encircle the stalks for controlling the flow of the drug models loaded in the pore channels. For instance, the efficient macrocyclic movable gate β -cyclodextrin (β -CD) was developed by Zink and coworkers [23]. The nanovalve formation and cap release mechanism is given in Fig. 1. The β -CD rings encircle aromatic amine stalks as a result of noncovalent bonding interactions under neutral pH conditions, and effectively block the nanopore openings, and trap the included drug molecules. Decreasing the pH under mildly acidic conditions leads to the protonation of the aromatic amines and dissociation of β -CD caps, following drug models diffusion from the nanopores.

Feng's group has reported another pH-responsive nanogated ensemble by capping the gold nanoparticle onto the

mesoporous silica through an acid-labile acetal linker. As shown in Fig. 2, at neutral pH, the linker remains intact and pores are blocked with gold nanoparticles to strongly inhibit the molecular diffusion from the pores. At acidic pHs, the hydrolysis of the acetal group will remove the gold cap and allow escape of the entrapped molecules in a pH-dependent controlled release.

A magnetic, reversible pH-responsive nanogated ensemble based on Fe_3O_4 nanoparticle-capped mesoporous silica, which was capped onto the outlet of the mesoporous silica via an acid-labile boronate ester linker was reported by Shi and coworker. As shown in Fig. 3 [27], at neutral pH, the linker remains intact and the entry of the pores on the MSNs are blocked with Fe_3O_4 nanoparticles to strongly inhibit the molecular diffusion from the pores. At acidic pHs (pH < 4), the Fe_3O_4 cap is removed due to the hydrolysis of the boronate ester, allowing the release of the entrapped molecules. Moreover, owing to the inherent reversibility of the boronate ester reaction, a sustained, pulsatile release controlled by pH value is realized easily.

Climent et al [28] modified MSNs with amino groups to create a positively charged surface that interacts with negatively charged DNA molecules. Thus, the interaction of single-stranded DNA molecules with the surface attached positively charged amino groups resulted in an effective capping of the pores. The nanoparticle cargo can be released when complementary DNA strand binds and displaces the adsorbed oligos on the surface of nanoparticles (Fig. 4).

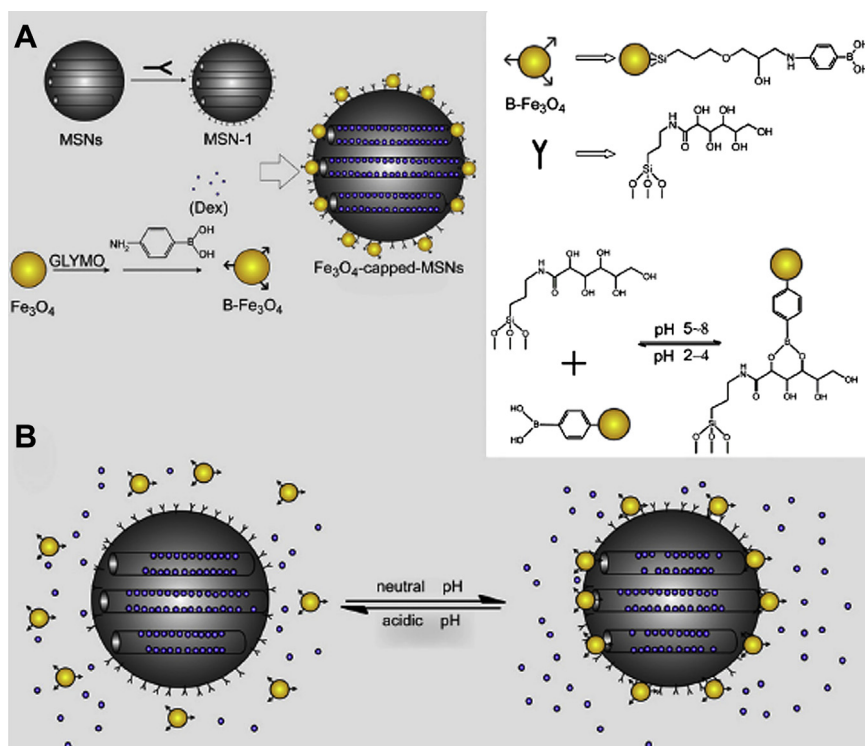


Fig. 3 – Schematic of (A) synthesis of the pH-responsive delivery system based on MSNs capped with Fe₃O₄ nanoparticles and (B) reversible release system based upon pH. MSN = mesoporous silica nanoparticle. Note. From “Magnetic, reversible pH-responsive nanogated ensemble based on Fe₃O₄ nanoparticles-capped mesoporous silica”, by Q. Gan, X. Lu, Y. Yuan, et al., 2011, *Biomaterials*, 32, p. 1932. Copyright 2011, Elsevier Science. Adapted with permission [27].

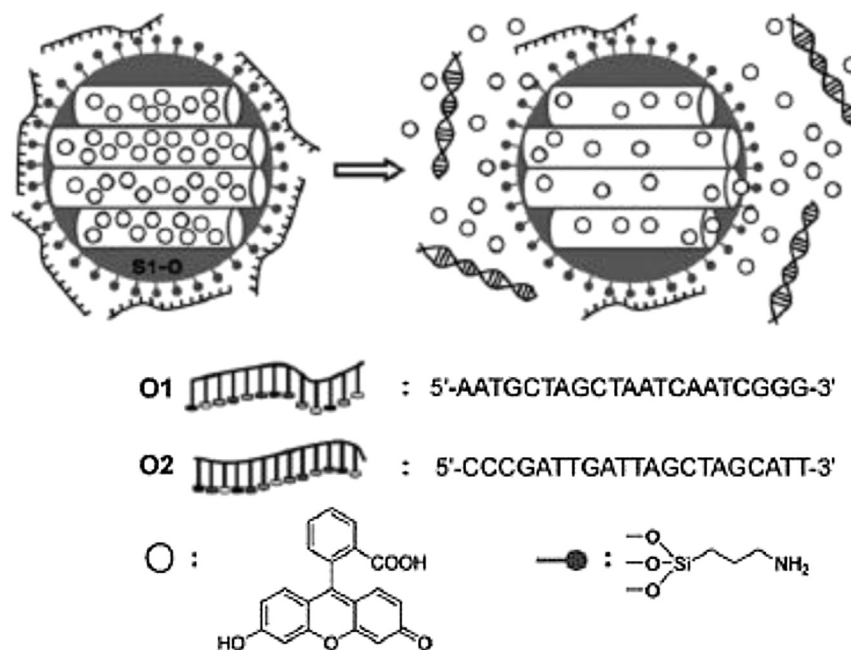


Fig. 4 – Schematic representation of a valve system based on MSNs functionalized with amino groups and capped with a single-stranded oligonucleotide (O1). Release of the trapped dye molecules is accomplished upon the addition of the complementary oligonucleotide (O2). The sequence of the oligonucleotides O1 and O2 is shown. MSN = mesoporous silica nanoparticle. Note. From “Controlled delivery using oligonucleotide-capped mesoporous silica nanoparticles”, by E. Climent, R. Martinez-Manez, F. Sancenon, et al., 2010, *Angew Chem Int Ed Engl*, 49, p. 7281. Copyright 2010, Wiley. Reprinted with permission [28].

3. GSH-responsive CDDSs

The development of glutathione-responsive nanovehicles for targeted intracellular drug and gene delivery is very efficient. Several intracellular compartments such as cytosol, mitochondria, and cell nucleus contain a high concentration of GSH tripeptides (about 2–10 mM), which is 100–1000 times higher than that in the extracellular fluids and circulation (about 2–20 μM) [29]. Therefore, glutathione has been recognized as an ideal and ubiquitous internal stimulus for rapid destabilization of nano-carriers inside cells to accomplish efficient intracellular drug release [30]. To establish GSH-responsive drug delivery system, disulfide bonds were absolutely necessary. The gatekeeper inorganic nanoparticles such as CdS, Au, Fe_3O_4 , and the organic part as the polyelectrolyte are chemically attached to MSN through a disulfide linker, which is chemically labile and could be cleaved with various disulfide reducing agents, such as dithiothreitol (DTT) and mercaptoethanol (ME).

Lin and coworkers have creatively developed a series of redox-responsive mesoporous silica CDDSs, in which CdS nanoparticles [17], Fe_3O_4 nanoparticles [18], and poly(amido amine) dendrimers [31] were used as the gatekeepers to cap the pores, and various disulfide reducing agents as release triggers. As an example of CdS nanoparticle-capped mesoporous silica nanopores (MSNs) redox-responsive CDDS (Fig. 5), 2-(propylthiol) ethylamine groups on the surface of the open mesopores covalently capture the water-soluble mercaptoacetic acid derivatized CdS nanocrystals, resulting in disulfide linkages. The linkages are chemically labile in nature and can be cleaved with various disulfide-reducing agents, such as DTT and ME. Hence, the release of the CdS nanoparticle caps from the drug-loaded MSNs can be regulated by introducing various amounts of release triggers.

Feng and coworkers reported redox-responsive nanogated MSNs by grafting poly(N-acryloxysuccinimide) (PNAS) to the pore entrance of MSN particles followed by cross-linking with cystamine (Fig. 6) [32]. The release studies demonstrated that the release rate of rhodamine B was dependent on the

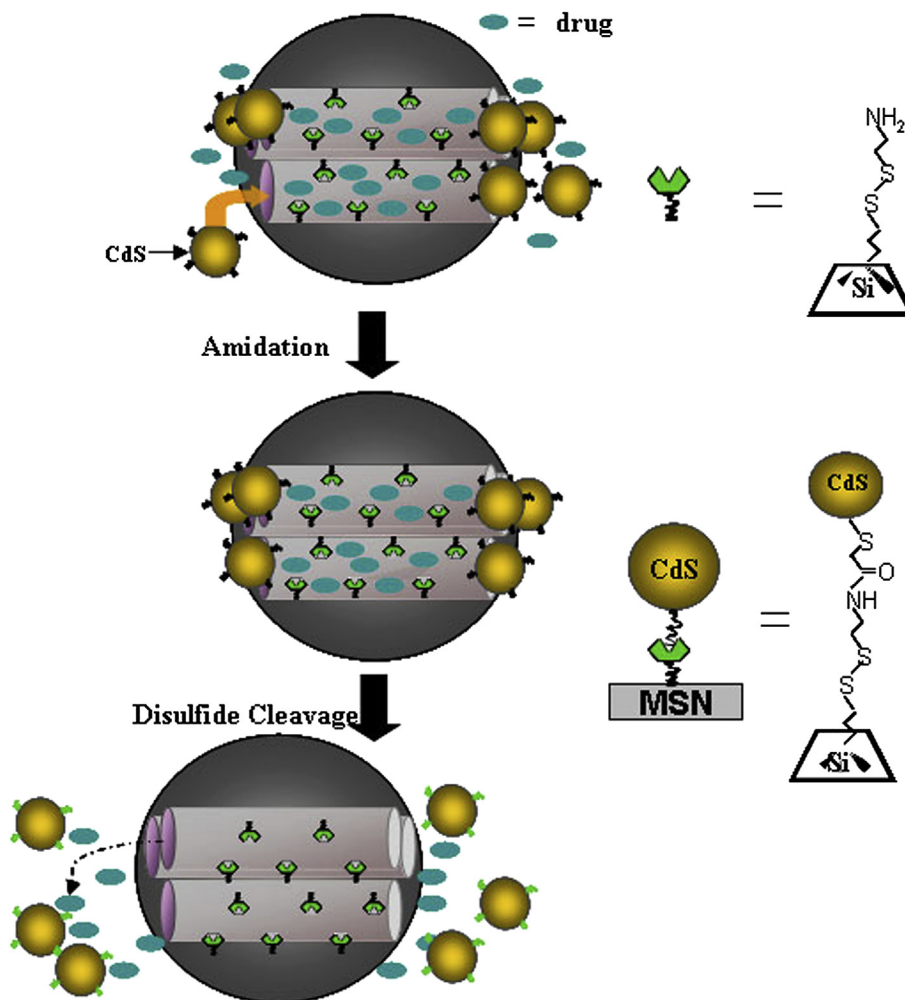


Fig. 5 – Schematic representation of the CdS nanoparticle-capped MSN-based drug/neurotransmitter delivery system. The controlled-release mechanism of the system is based on chemical reduction of the disulfide linkage between the CdS caps and the MSN hosts. MSN = mesoporous silica nanoparticle. Note. From “A mesoporous silica nanosphere-based carrier system with chemically removable CdS nanoparticle caps for stimuli-responsive controlled release of neurotransmitters and drug molecules”, by C.Y. Lai, B.G. Trewyn, D.M. Jeftinija, et al., 2003, *J Am Chem Soc*, 125, p. 4451. Copyright 2003, American Chemical Society. Adapted with permission [17].

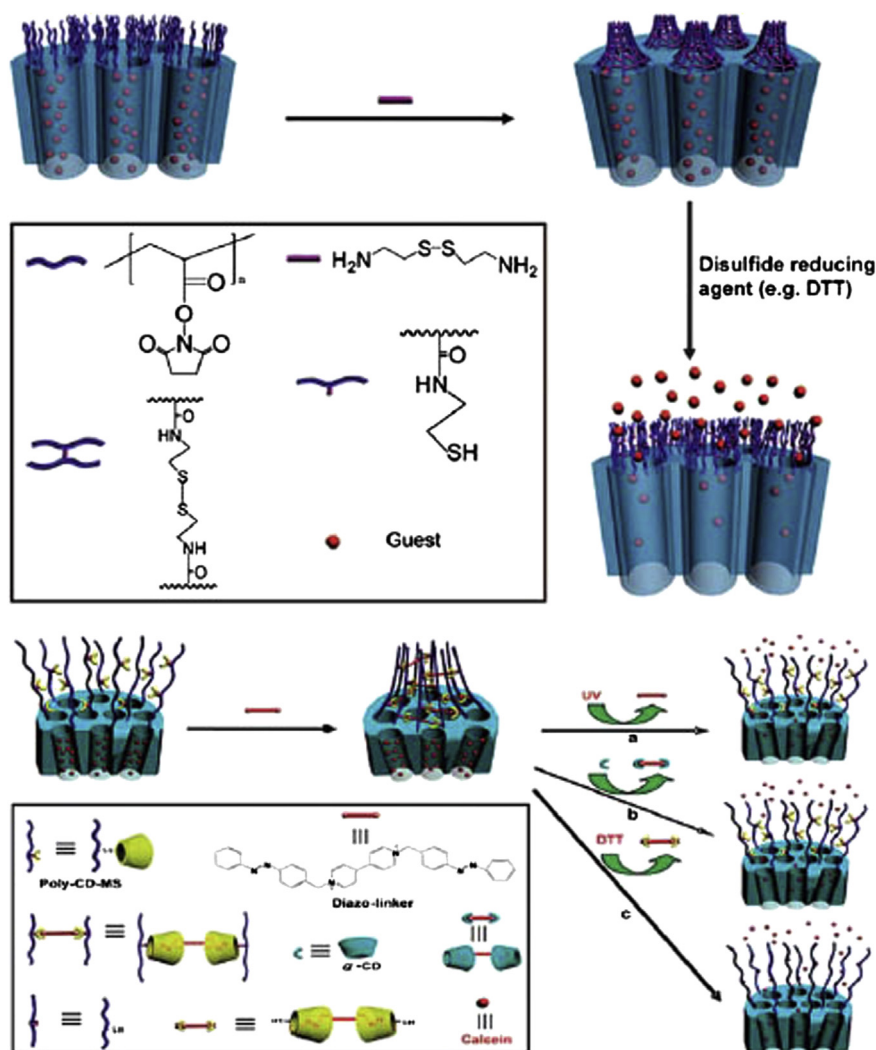


Fig. 6 – Schematic representation of redox-responsive nanovalves based on polymeric network-capped MSNs (top) and multi-responsive nanovalves based on supramolecular polymeric network-capped MSNs (bottom). In the first system, PNAS-coated MSNs are first loaded with dyes, then their valves closed with the cross-linking of the polymer chains by the addition of a disulfide-based cystamine. The polymeric network formed can then be reopened by cleaving the disulfide bond of cystamine in the presence of DTT, leading to the cargo release. In the second system, poly-CD-MS filled with cargos are blocked by adding diazo linker to cross-link the β-CD-bearing polymer chains. Release of cargo molecules calcein is achieved by the cleavage of the polymeric network using UV irradiation, competitive binding, or the addition of disulfide reducing agent DTT. DTT = dithiothreitol; MSN = mesoporous silica nanoparticles; PNAS = poly(N-acryloxysuccinimide); UV = ultraviolet; CD-MS = cyclodextrin-mesoporous silica. Note. From “Tunable redox-responsive hybrid nanogated ensembles”, by R. Liu, X. Zhao, T. Wu, et al., 2008, *J Am Chem Soc*, 130, p. 14418. Copyright 2008, American Chemical Society. Reprinted with permission [32].

DTT concentration. In comparison, irreversibly cross-linked ensembles (with 1,6-hexdiamine) showed no induced release with the addition of DTT.

4. ATP-responsive GDDSs

Although many of the internalized carriers will release the drug within the lysosome, some of the drug delivery vehicles may escape from the lysosome before drug release. Hence, there is also a need for a stimulus in the cytosol to trigger drug

release. ATP is a multifunctional nucleotide, which plays a vital role in many biological processes, including muscle contraction, cells functioning, synthesis and degradation of important cellular compounds, and membrane transport. Owing to ATP being predominantly present in the cytosol [33] and assuming the concentration of ATP inside cells is high enough to release the drug (concentration range of 1–10 mM) [34], it is considered as an important stimulus for drug release in the cytosol. Thus, the development of ATP-responsive controlled-release system for bioorganism application is very significant. Our group has first reported a novel bio-responsive controlled-release system

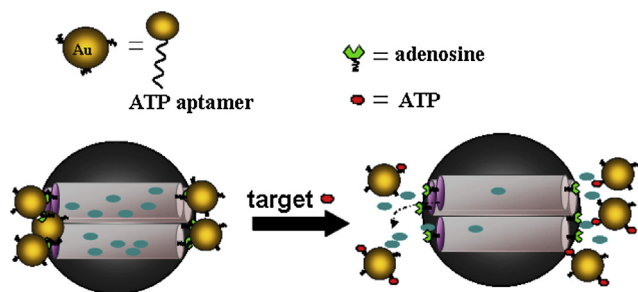


Fig. 7 – Schematic illustration of aptamer–target-interaction-responsive controlled-release system.

AuNPs–aptamer is capped on the MSA surface because of the binding reaction of the ATP aptamer to the adenosine molecule. The delivery of the entrapped guest (fluorescein) is selectively triggered by an effective displacement reaction in the presence of the target molecule (ATP).

ATP = adenosine-5'-triphosphate. Note. From “Bioresponsive controlled release using mesoporous silica nanoparticles capped with aptamer-based molecular gate”, by C.L. Zhu, C.H. Lu, X.Y. Song, et al., 2011, *J Am Chem Soc*, 133, p. 1278. Copyright 2011, American Chemical Society. Reprinted with permission [35].

based on MSNs gated with aptamer-modified gold nanoparticles (Fig. 7), which is stimuli-responsive to the aptamer–ATP interactions [35]. In this work, MCM-41 tailed with amino group was selected as support, and further functionalized with adenosine-50-carboxylic acid (adenosine–COOH)—a derivative of the ATP target to give MSA. Gold nanoparticles were functionalized with ATP aptamer through Au–S bond to

form AuNPs–aptamer. As the binding reaction of ATP aptamer with adenosine resulted from the recognition of ATP aptamer to the adenine and ribose moieties, upon mixing AuNPs–aptamer with MSA, AuNPs would block the pores of MSA. The release of cargo molecules' fluorescein isothiocyanate (FITC) dye from these AuNPs-gated MSNs was triggered by the addition of ATP molecules, which resulted in a competitive displacement reaction to the adenosine–aptamer interaction to uncap the pores of MSNs. The selectivity of this delivery process was tested with the ATP analogs CTP, GTP, and UTP, but a characteristic release of the dye similar to the release of ATP was not observed.

Another ATP-based controlled-release system was published by Özalp and Schäfer's group. They directly used ATP-aptamer gated MCM-41 nanoparticles for the selective and reversible detection of ATP by release of fluorescein [36]. The aptamers were immobilized on the surface of the MSNs containing the dye in the pores. The release of the dye was induced by the denaturation of the double-strand region of the aptamer close to the pore gates by specific complexation of ATP (Fig. 8). The pores of the mesoporous material have a diameter of 2.6 nm and a double DNA helix has a thickness of 2 nm. Therefore, it is supposed that the similar diameter of the hairpin-type aptamers on the material's surface blocks the pores of the nanoparticles. Accordingly, opening can be achieved by denaturation with ATP and the formation of a single-stranded neck region, which permits the dye to diffuse out of the pores.

Jiang et al developed an efficient, smart gating system based on ATP molecules-ATP aptamer and its complementary DNA, which exhibited extremely high ON-OFF ratios and nearly perfect electric seals in its closed state [37]. The open-to-closed process is achieved by self-assembling super-sandwich

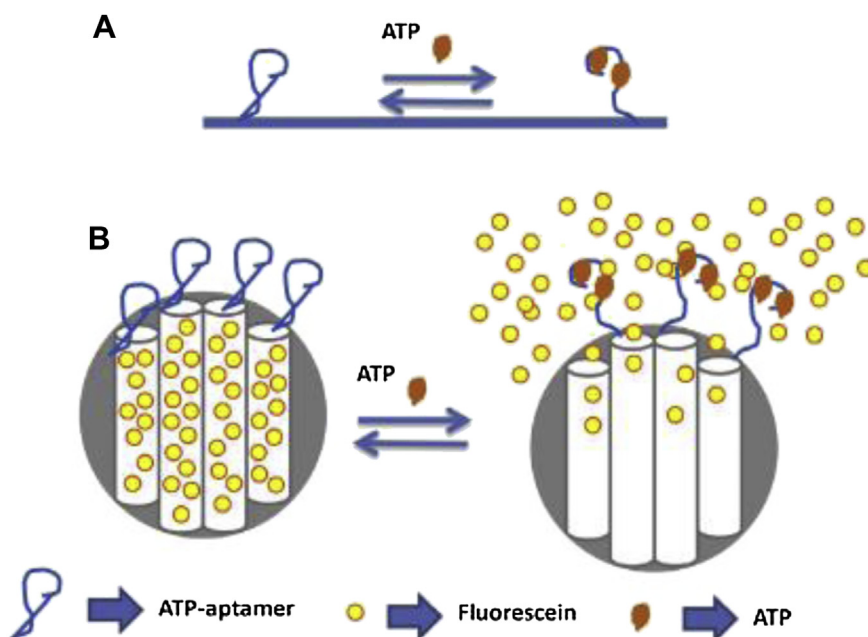


Fig. 8 – Aptamer-based switchable nanovalves. (A) symbolically shows changes in the secondary and tertiary structure of the hairpin of the ATP-binding aptamer in the presence or absence of ATP. (B) ATP-triggered release of fluorescein from MSNs. ATP = adenosine-5'-triphosphate; MSN = mesoporous silica nanoparticle. Note. From “Aptamer-based switchable nanovalves for stimuli-responsive drug delivery”, by V.C. Özalp and T. Schäfer, 2011, *Chem Eur J*, 17, p. 9893. Copyright 2011, Wiley. Reprinted with permission [36].

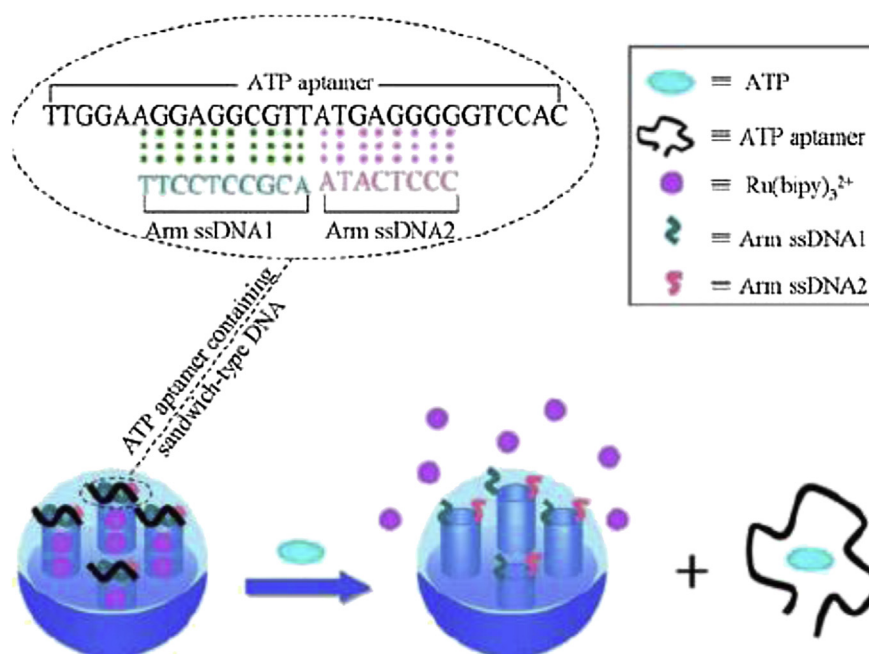


Fig. 9 – Schematic illustration of aptamer-based ATP responsive MSN system. ATP = adenosine-5'-triphosphate; MSN = mesoporous silica nanoparticle. Note. From “ATP-responsive controlled release system using aptamer-functionalized mesoporous silica nanoparticles”, 2012, by X.X. He, X.Y. Zhao, D.G. He, et al., *Langmuir*, 28, p. 12909. Copyright 2012, American Chemical Society. Reprinted with permission [38].

structures consisting of an ATP aptamer and its complementary DNA into solid-state nanochannels, while the closed-to-open process is realized by the disassembly of ATP-ATP aptamer binding. He and coworkers reported another example that they developed an ATP-responsive controlled-release system using aptamer-functionalized MSNs [38]. In this system, as shown in Fig. 9, the ATP aptamer is first hybridized with arm single-stranded DNA1 (arm ssDNA1) and arm single-stranded DNA2 (arm ssDNA2) to form the sandwich-type DNA structure and then grafted onto the MSN surface through click chemistry approach, resulting in blockage of pores and inhibition of guest molecules release. In the presence of ATP, the ATP aptamer combined with ATP and got away from the pore, leaving the arm ssDNA1 and ssDNA2 on the surface of MSN. The guest molecules can be released because single-stranded DNA is flexible. The release of the guest molecules from this system then can be triggered by the addition of ATP.

5. Glucose-responsive CDDs

Glucose-responsive materials have attracted great attention in recent years because of their potential application in drug delivery [39]. Saccharides are also a suitable target because of their unique interaction with boronic acids. According to this principle, Lin and coworkers have described on the synthesis of a glucose-responsive MSN-based double delivery system for both insulin and cAMP with precise control over the sequence of release [40]. As depicted in Fig. 10, gluconic acid-modified insulin (G-Ins) proteins are immobilized on the exterior surface of MSN and also serve as caps to encapsulate cAMP molecules inside the mesopores of MSN. The release of both G-Ins

and cAMP from MSN can be triggered by the introduction of saccharides, such as glucose. Moreover, they have demonstrated that the uncapped MSN can be efficiently endocytosed by live mammalian cells, leading to the effective intracellular release of the cell-membrane-impermeable cAMP. This glucose-responsive controlled-insulin-release system (GRCIRS) was expected to be a new and highly promising therapy approach to replace the frequent insulin injections to cure diabetes, one urgent medical challenge worldwide.

Another glucose-responsive controlled-release system based on the competitive combination between glucose oxidase (GOD), glucosamine, and glucose has been reported by Zhu's group [41], which exhibits perfect controlled-release properties and high selectivity for glucose over other monosaccharides. The design strategy relies on the unique interaction between an inhibitor, an enzyme and a substrate (Fig. 11). The external surface of MCM-41 was first functionalized with D-(+)-glucosamine, an effective inhibitor of GOD. Rhodamine B (RB) was utilized as a model drug for convenient detection. GOD was selected as the capping agent because it can combine with D-(+)-glucosamine anchored outside the pores to form an enzyme inhibitor (EI) complex, which acts as a “bio-gate,” resulting in the closing of the mesopores. The opening event will occur by a highly effective competitive combination of glucose (substrate) and GOD, which forms the enzyme–substrate (ES) complex, then uncaps the pores and releases the entrapped guest molecules.

More recently, a glucose- and pH-responsive controlled release of cargo from protein-gated carbohydrate-functionalized mesoporous silica nanocontainers was reported by Du's group [42]. MSNs were functionalized with mannose ligands at optimized surface densities. Tight concanavalin A (Con A)

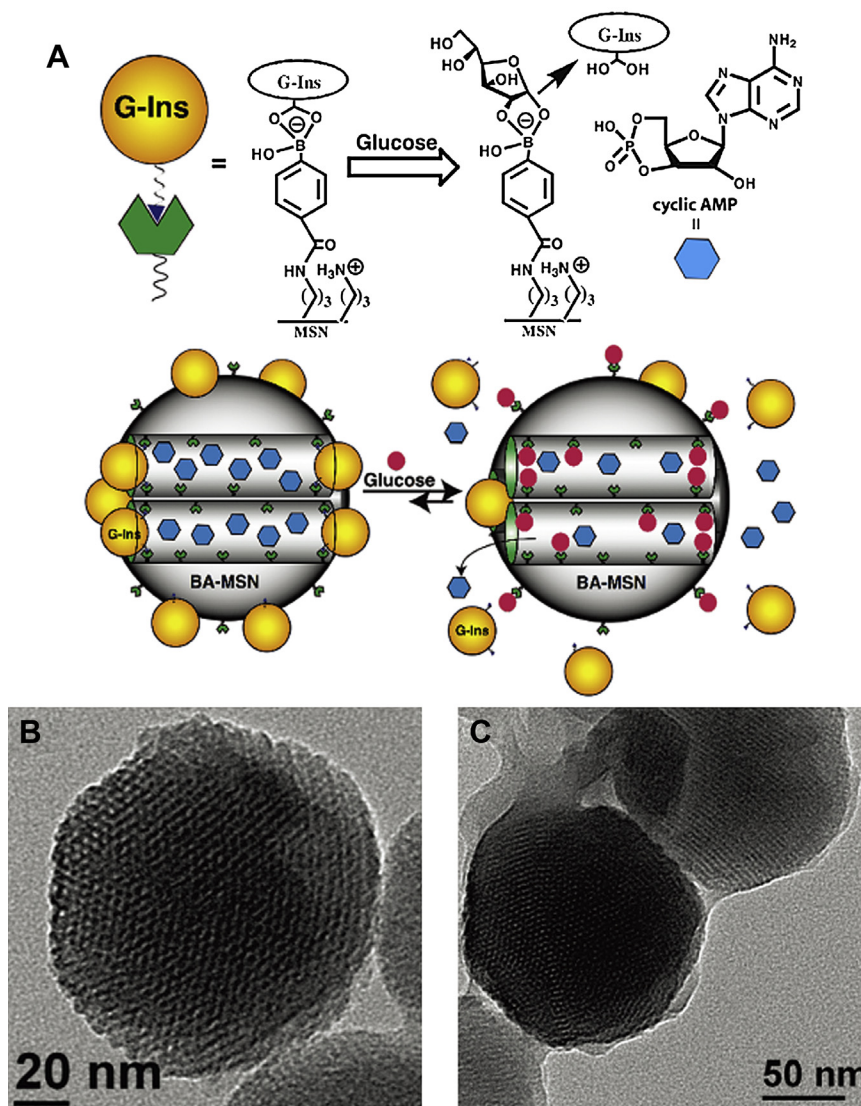


Fig. 10 – (A) Schematic representation of the glucose-responsive MSN-based delivery system for controlled release of bioactive G-Ins and cAMP. Transmission electron micrographs of (B) boronic acid-functionalized MSN and (C) FITC-G-Ins-capped MSN. FITC = fluorescein isothiocyanate; G-Ins = gluconic acid-modified insulin. Note. From “Mesoporous silica nanoparticle-based double drug delivery system for glucose-responsive controlled release of insulin and cyclic AMP”, by Y. Zhao, B.G. Trewyn, I.I. Slowing, et al., 2009, *J Am Chem Soc*, 131, p. 8398. Copyright 2009, American Chemical Society. Reprinted with permission [40].

nanogates were then constructed using multivalent carbohydrate–protein interactions to encapsulate the cargo within the pores, and the cargo was released by competitive binding of glucose when the normal blood-glucose concentration becomes elevated, which would have potential applications for diabetes therapy. In addition, the drug could also be released by introducing an acidic environment, such as is found in tumor cells and inflammatory tissues.

6. H₂O₂-responsive CDDS

A biocompatible delivery platform by using H₂O₂-responsive controlled-release system to realize target delivery of AD therapeutic metal chelator was reported by Qu’s group [43]. As

shown in Fig. 12, the advantage of this novel strategy is that metal chelator can only be released by the increased levels of H₂O₂; thus, it would not interfere with the healthy metal homeostasis and can overcome strong side effects of metal chelator after long-term use. By taking advantage of the good biocompatibility, cellular uptake properties, and efficient intracellular release of metal chelators, the delivery system is promising for future *in vivo* controlled-release biomedical applications.

7. Conclusion

In this review, we have highlighted some exciting research progress on mesoporous silica-based materials as cell

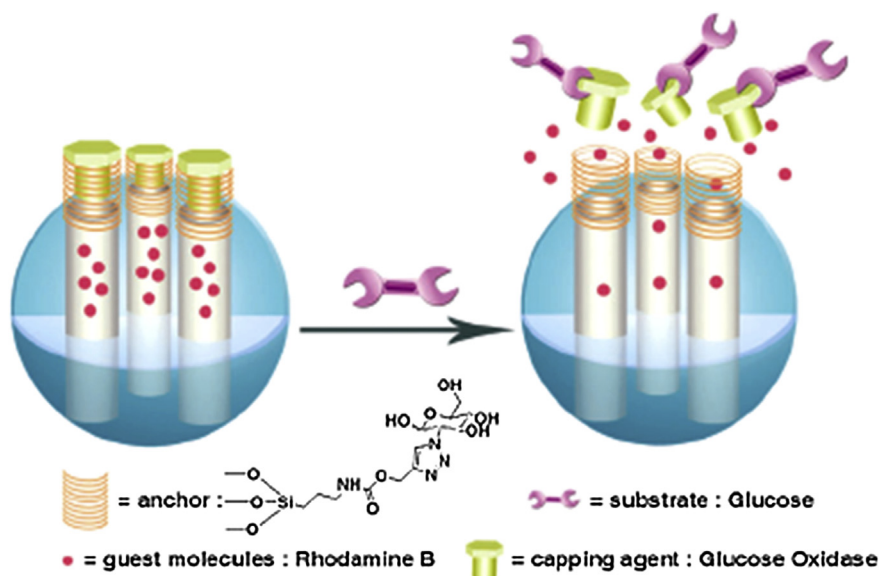


Fig. 11 – Schematic illustration of enzyme-inhibition-mechanism-triggered release of guest molecules from the pores of functionalized mesoporous silica materials. Note. From “Glucose-responsive controlled release system using glucose oxidase-gated mesoporous silica nanocontainers”, by M.J. Chen, C.S. Huang, C.S. He, et al. *Chem Commun*, 48, p. 9522. Copyright 2012, The Royal Society of Chemistry. Reprinted with permission [41].

microenvironment stimuli-responsive controlled-release systems. These smart nano-CDDs can be delivered into targeted organs or cells and release drugs in some controlled manner by the virtue of various internal triggers, such as pH,

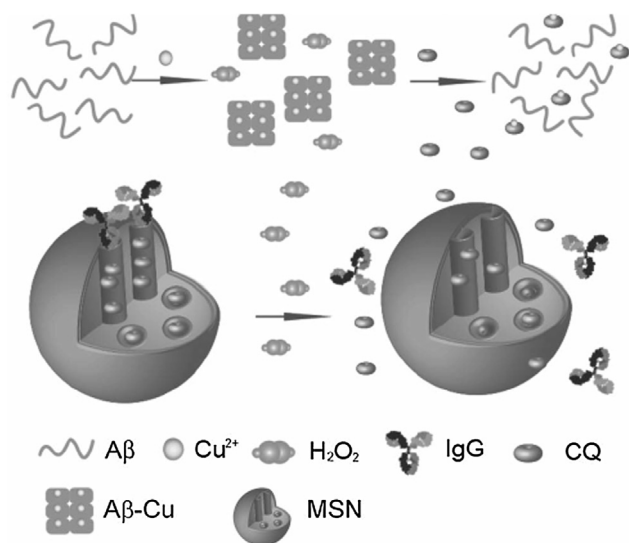


Fig. 12 – Schematic representation of H_2O_2 -fueled release of guest molecules CQ from the pores of MSN capped with IgG. CQ can chelate Cu^{2+} to disassemble $\text{A}\beta$ plaques and inhibit H_2O_2 production. CQ = clioquinol; MSN = mesoporous silica nanoparticles. Note. From “Mesoporous silica nanoparticle-based H_2O_2 responsive controlled-release system used for Alzheimer’s disease treatment”, by J. Geng, M. Li, L. Wu, et al., 2012, *Adv Healthcare Mater*, 1, p. 332. Copyright 2012, Wiley. Reprinted with permission [43].

ATP, GSH, glucose, and H_2O_2 , which is encouraging and shows great promise in biomedical applications. However, there are still a great many challenges, especially the *in vivo*-applicable stimuli-responsive mechanisms, which need to be understood and investigated more comprehensively and thoroughly. In addition, the challenging goal to these nanocarriers of releasing the guest molecules *in vivo* in a site- and time-specific manner still has to be demonstrated. Some biomolecules such as peptide sequences, enzymes, DNA or collagen as “bio-gates” are still in their infancy.

Acknowledgments

Financial support from the National Natural Science Foundation of China (NSFC 21001033, 21271044), the NSF of Fujian (2011J01039), and Research Foundation for Talented Scholars in Fu Zhou University (022330) is greatly acknowledged.

REFERENCES

- [1] Slowing II, Vivero-Escoto JL, Wu CW, et al. Mesoporous silica nanoparticles as controlled release drug delivery and gene transfection carriers. *Adv Drug Delivery Rev* 2008;60:1278–88.
- [2] Descalzo AB, Martínez-Máñez R, Sancenón F, et al. The supramolecular chemistry of organic–inorganic hybrid materials. *Angew Chem Int Ed Engl* 2006;45:5924–48.
- [3] Angelos S, Liang M, Choi E, et al. Mesoporous silicate materials as substrates for molecular machines and drug delivery. *Chem Eng J* 2008;137:4–13.
- [4] Rosenholm JM, Sahlgren C, Lindén M. Towards multifunctional, targeted drug delivery systems using

- mesoporous silica nanoparticles – opportunities & challenges. *Nanoscale* 2010;2:1870–83.
- [5] Chen Y, Chen H, Zeng D, et al. Core/shell structured hollow mesoporous nanocapsules: a potential platform for simultaneous cell imaging and anticancer drug delivery. *ACS Nano* 2010;4:6001–13.
- [6] Vallet-Regí M, Ramila A, Del Real RP, et al. A new property of MCM-41: drug delivery system. *Chem Mater* 2001;13:308–11.
- [7] Wang YW. Towards biocompatible nanovalves based on mesoporous silica nanoparticles. *Med Chem Commun* 2011;2:1033–49.
- [8] Manzano M, Vallet-Regí M. New developments in ordered mesoporous materials for drug delivery. *J Mater Chem* 2010;20:5593–604.
- [9] Aznar E, Mondragón L, Ros-Lis JV, et al. Finely tuned temperature-controlled cargo release using paraffin-capped mesoporous silica nanoparticles. *Angew Chem Int Ed Engl* 2011;50:11172–5.
- [10] Schlossbauer A, Warncke S, Gramlich PM, et al. A programmable DNA-based molecular valve for colloidal mesoporous silica. *Angew Chem Int Ed Engl* 2010;49:4734–7.
- [11] Zhu Y, Liu H, Li F, et al. Dipolar molecules as impellers achieving electric-field-stimulated release. *J Am Chem Soc* 2010;132:1450–1.
- [12] Thomas CR, Ferris DP, Lee JH, et al. Noninvasive remote-controlled release of drug molecules in vitro using magnetic actuation of mechanized nanoparticles. *J Am Chem Soc* 2010;132:10623–5.
- [13] Yang XJ, Liu X, Liu Z, et al. Near-infrared light-triggered, targeted drug delivery to cancer cells by aptamer gated nanovehicles. *Adv Mater* 2012;24:2890–5.
- [14] Zhu YC, Fujiwara M. Installing dynamic molecular photomechanics in mesopores: a multifunctional controlled-release nanosystem. *Angew Chem Int Ed Engl* 2007;46:2241–4.
- [15] Ferris DP, Zhao YL, Khashab NM, et al. Light-operated mechanized nanoparticles. *J Am Chem Soc* 2009;131:1686–8.
- [16] Casasús R, Marcos MD, Martínez-Máñez R, et al. Toward the development of ionically controlled nanoscopic molecular gates. *J Am Chem Soc* 2004;126:8612–3.
- [17] Lai CY, Trewyn BG, Jęftinija DM, et al. A mesoporous silica nanosphere-based carrier system with chemically removable CdS nanoparticle caps for stimuli-responsive controlled release of neurotransmitters and drug molecules. *J Am Chem Soc* 2003;125:4451–9.
- [18] Giri S, Trewyn BG, Stellmaker MP, et al. Stimuli-responsive controlled-release delivery system based on mesoporous silica nanorods capped with magnetic nanoparticles. *Angew Chem Int Ed Engl* 2005;44:5038–44.
- [19] Kim H, Kim S, Park C, et al. Glutathione-induced intracellular release of guests from mesoporous silica nanocontainers with cyclodextrin gatekeepers. *Adv Mater* 2010;22:4280–3.
- [20] Schlossbauer A, Kecht J, Bein T. Biotin–avidin as a protease-responsive cap system for controlled guest release from colloidal mesoporous silica. *Angew Chem Int Ed Engl* 2009;48:3092–5.
- [21] Bernardos A, Aznar E, Marcos MD, et al. Enzyme-responsive controlled release using mesoporous silica supports capped with lactose. *Angew Chem Int Ed Engl* 2009;48:5884–7.
- [22] Khan MZ, Prebeg Z, Kurjaković N. A pH-dependent colon targeted oral drug delivery system using methacrylic acid copolymers. I. Manipulation of drug release using Eudragit L100-55 and Eudragit S100 combinations. *J Controlled Release* 1999;58:215–22.
- [23] Meng H, Xue M, Xia T, et al. Autonomous in vitro anticancer drug release from mesoporous silica nanoparticles by pH-sensitive nanovalves. *J Am Chem Soc* 2010;132:12690–7.
- [24] Zhao YL, Li Z, Kabehie S, et al. pH-operated nanopistons on the surfaces of mesoporous silica nanoparticles. *J Am Chem Soc* 2010;132:13016–25.
- [25] Angelos S, Khashab NM, Yang YW, et al. pH clock-operated mechanized nanoparticles. *J Am Chem Soc* 2009;131:12912–4.
- [26] Liu R, Zhang Y, Zhao X, et al. pH-responsive nanogated ensemble based on gold-capped mesoporous silica through an acid-labile acetal linker. *J Am Chem Soc* 2010;132:1500–1.
- [27] Gan Q, Lu X, Yuan Y, et al. Magnetic, reversible pH-responsive nanogated ensemble based on Fe₃O₄ nanoparticles-capped mesoporous silica. *Biomaterials* 2011;32:1932–42.
- [28] Climent E, Martínez-Manez R, Sancenón F, et al. Controlled delivery using oligonucleotide-capped mesoporous silica nanoparticles. *Angew Chem Int Ed Engl* 2010;49:7281–3.
- [29] Schafer FQ, Buettner GR. Redox environment of the cell as viewed through the redox state of the glutathione disulfide/glutathione couple. *Free Radic Biol Med* 2001;30:1191–212.
- [30] Cheng R, Feng F, Meng FH, et al. Glutathione-responsive nano-vehicles as a promising platform for targeted intracellular drug and gene delivery. *J Control Release* 2011;152:2–12.
- [31] Gruenhagen JA, Lai CY, Radu DR, et al. Real-time imaging of tunable adenosine 5-triphosphate release from an MCM-41-type mesoporous silica nanosphere-based delivery system. *Appl Spectrosc* 2005;59:424–31.
- [32] Liu R, Zhao X, Wu T, et al. Tunable redox-responsive hybrid nanogated ensembles. *J Am Chem Soc* 2008;130:14418–9.
- [33] Cook DL, Satin LS, Ashford MLJ, et al. ATP-sensitive K⁺ channels in pancreatic beta-cells Spare-channel hypothesis. *Diabetes* 1988;37:495–8.
- [34] Fitz JG. Regulation of cellular ATP release. *Trans Am Clin Climatol Assoc* 2007;118:199–208.
- [35] Zhu CL, Lu CH, Song XY, et al. Bioresponsive controlled release using mesoporous silica nanoparticles capped with aptamer-based molecular gate. *J Am Chem Soc* 2011;133:1278–81.
- [36] Özalp VC, Schäfer T. Aptamer-based switchable nanovalves for stimuli-responsive drug delivery. *Chem Eur J* 2011;17:9893–6.
- [37] Jiang Y, Liu N, Guo W, et al. Highly-efficient gating of solid-state nanochannels by DNA supersandwich structure containing ATP aptamers: a nanofluidic implication logic device. *J Am Chem Soc* 2012;134:15395–401.
- [38] He XX, Zhao YX, He DG, et al. ATP-responsive controlled release system using aptamer-functionalized mesoporous silica nanoparticles. *Langmuir* 2012;28:12909–15.
- [39] Traitel T, Cohen Y, Kost J. Characterization of glucose-sensitive insulin release systems in simulated in vivo conditions. *Biomaterials* 2000;21:1679–87.
- [40] Zhao Y, Trewyn BG, Slowing II, et al. Mesoporous silica nanoparticle-based double drug delivery system for glucose-responsive controlled release of insulin and cyclic AMP. *J Am Chem Soc* 2009;131:8398–400.
- [41] Chen MJ, Huang CS, He CS, et al. Glucose-responsive controlled release system using glucose oxidase-gated mesoporous silica nanocontainers. *Chem Commun* 2012;48:9522–4.
- [42] Wu SS, Huang X, Du XZ. Glucose- and pH-responsive controlled release of cargo from protein-gated carbohydrate-functionalized mesoporous silica nanocontainers. *Angew Chem Int Ed Engl* 2013;52:5580–4.
- [43] Geng J, Li M, Wu L, et al. Mesoporous silica nanoparticle-based H₂O₂ responsive controlled-release system used for Alzheimer's disease treatment. *Adv Healthcare Mater* 2012;1:332–6.