Review Article

Wei Zhang*, Hongwei Liu, Xilong Qiu*, Fanjiao Zuo, Boyao Wang

Mesoporous silica nanoparticles as a drug delivery mechanism

Abstract: Research in intelligent drug delivery systems within the field of biomedicine promises to enhance drug efficacy at disease sites and reduce associated side effects. Mesoporous silica nanoparticles (MSNs), characterized by their large specific surface area, appropriate pore size, and excellent biocompatibility, have garnered significant attention as one of the most effective carriers for drug delivery. The hydroxyl groups on their surface are active functional groups, facilitating easy functionalization. The installation of controllable molecular machines on the surface of mesoporous silica to construct nanovalves represents a crucial advancement in developing intelligent drug delivery systems (DDSs) and addressing the issue of premature drug release. In this review, we compile several notable and illustrative examples of MSNs and discuss their varied applications in DDSs. These applications span regulated and progressive drug release mechanisms. MSNs hold the potential to enhance drug solubility, improve drug stability, and mitigate drug toxicity, attributable to their ease of functionalization. Furthermore, intelligent hybrid nanomaterials are being developed, featuring programmable properties that react to a broad spectrum of stimuli, including light,

* **Corresponding author: Wei Zhang,** Tianjin Medical University Cancer
Institute & Hospital, National Clinical Research Center for Cancer,
Tianjin's Clinical Research Center for Cancer, Key Laboratory of Cancer
Prevention and Therapy, No. 1 West Huan-Hu Road, Ti Yuan Bei,
Hexi District, Tianjin 300060, China, tel: +86-22-23359337,
fax: +86-22-23359337, e-mail: Zhang_wwwba@outlook.com
* **Corresponding author: Xilong Qiu,** School of Chinese Materia
Medica, Tianjin University of Traditional Chinese Medicine, No. 10
of Poyang Lake Road, Tuanpo Xincheng West District, Tianjin 301617,
China, tel: +86 13752409920, fax: +86 13752409920,
e-mail: xilongqiuqq@126.com
Hongwei Liu: Department of Pharmacy, First Teaching Hospital of
Tianjin University of Traditional Chinese Medicine, Tianjin, 300072, China
Fanjiao Zuo: School of Chinese Materia Medica, Tianjin University of
Traditional Chinese Medicine, No. 10 of Poyang Lake Road, Tuanpo
Xincheng West District, Tianjin 301617, China
Boyao Wang: School of Traditional Chinese Medicine, Tianjin University
of Traditional Chinese Medicine, Tianjin 301617, China

pH, enzymes, and redox triggers, through the use of molecular and supramolecular switches.

1 Introduction

Drug delivery systems (DDSs) represent significant advancements in contemporary pharmaceutical research, reflecting improvements in dosage forms and formulation development. These systems stand at the vanguard of current scientific and technological progress, characterized by substantial advancements in theoretical foundations, innovative formulation designs, manufacturing methodologies, and clinical applications [1–3]. DDSs have the potential to enhance medication bioavailability by increasing solubility and regulating the rates of degradation and absorption [4,5]. Furthermore, by modifying medication molecules with biocompatible compounds to prevent recognition by the body's immune system, these systems offer the potential to minimize drug-related adverse effects during medical treatment [6]. Nanomaterials have recently shown immense potential for use in biomedical fields, owing to the rapid advancement of nanotechnology and their exceptional physicochemical properties. Nanomaterials are extensively employed across various fields, including drug delivery [7], disease diagnostics and therapy [8,9], tissue engineering repair [10,11], among others, and have earned considerable recognition in the materials science domain for their contributions to controlled drug release systems. This acclaim is due to their inherent properties, which include easy synthesis, tunable size, chemical durability, large specific surface area, uniform and adjustable pore sizes, biocompatibility, surface modifiability, and effective loading capacity for poorly soluble pharmaceutical agents [12–14]. The rapid release of medications containing mesoporous silica nanoparticles (MSNs) is primarily attributed to the open pores of the MSNs.

The review provides an overview of MSNs, highlighting their advantages, slow-release, and controlled drug release system along with their applications. Our goal is to summarize

recent research progress in mesoporous silica and then offer insights into strategies for achieving desired chemical properties using this nanoplatform for future practical applications. We aim to stimulate new ideas and inspire continued efforts in this emerging research field [15–17].

2 Mesoporous silica nanomaterials

Mesoporous materials, characterized by a porous structure with pore sizes ranging from 2 to 50 nm, have seen significant advancements in recent years. This progress is particularly notable in the development of two-dimensional hexagonal mesoporous silica, various transition metal oxides not based on silicon, and diverse nanoparticle assemblies. The outcome of related research efforts is the discovery of innovative materials with promising applications [18,19].

A significant breakthrough occurred in 1992 when scientists at the American Mobile Company developed the MCM-41 series of novel mesoporous silicon materials. They utilized a cationic alkyl quaternary ammonium salt surfactant as a template, employing the concept of liquid crystal templates [20]. MCM-41 mesoporous silica, one of these materials, has garnered considerable interest within the biomedical research community. Its appeal lies in its robust structural integrity, extensive specific surface area, pores organized in a uniform hexagonal pattern, ease of surface functionalization and modification, adjustable pore diameters, and low cytotoxicity [21,22].

3 Mesoporous silica sustained-release drug systems

Leveraging MSNs as a delivery method allows for the loading of hydrophobic drugs into MSN pores using non-aqueous solvents. As these drug molecules transition from the pores to the cytoplasm, the phospholipid bilayer facilitates their entry into the hydrophobic intracellular environment. Notably, drugs such as camptothecin [23] and paclitaxel [24], known to be encapsulated within MSNs, are effectively released from these pores. Drawing on the biocompatibility and cell permeability of MSNs, Wang et al. succeeded in encapsulating the drug telmisartan in mesoporous silica. The integration of these two elements during the formulation process enhanced both the bioavailability and dissolution rate of telmisartan [25]. Compared to raw drug materials, this approach markedly improved both the drug dissolution rates and cumulative drug dissolution. To boost the bioavailability of medications with low solubility and enhance their permeability, Wang et al. embarked on a study aimed at examining the effects of different drug loading methods on drug loading efficiency and dissolution rates within MSNs. Qiu et al. demonstrated the successful synthesis of MSNs, dendritic mesoporous silica nanoparticles (DMSNs), and hollow mesoporous silica nanoparticles (HMSNs), with all three types exhibiting higher drug loading and encapsulation efficiency. Analysis based on the first-order release equation curve and Higuchi equation parameters revealed that the loaded puerarin exhibited sustained-release properties [26], Figure 1.

4 Mesoporous silica controlled drug release system

MSNs possess a large specific surface area, excellent biocompatibility, and a stable skeletal structure, making them a viable option for drug delivery. This has spurred significant research interest. In 2004, Hernandez et al. ventured into the field of nanoscale-controlled valve mechanisms by introducing the groundbreaking concept of a nanovalve based on macrocyclic receptor molecules [27]. For the nanovalve to function as intended, three key components are necessary: a nanocontainer for carrying drugs, an actuator capable of moving chains in response to specific stimuli, and a suitable control strategy to govern this chain movement. Designing a DDS that responds to particular environmental stimuli is crucial for achieving controlled medication release within the body, thereby minimizing drug leakage and adverse effects on healthy tissues. Examples of stimuli include light [27], pH fluctuations [28], enzyme activity [29], redox reactions [30], and combinations of these factors [31].

4.1 Light-responsive controlled drug release systems

Leveraging light to trigger reactions offers numerous benefits, such as the ability for remote activation, non-invasiveness, precise control, and extensive applicability in the biomedical sector. UV-visible and near-infrared light serve as the primary light sources in DDS [32].

In a noteworthy experiment, Nguyen et al. utilized mesoporous silica coated with the photosensitive substance anthracene formic acid [33]. This molecule-coated surface was encased by a ring of tetravalent ionic cyclophane –
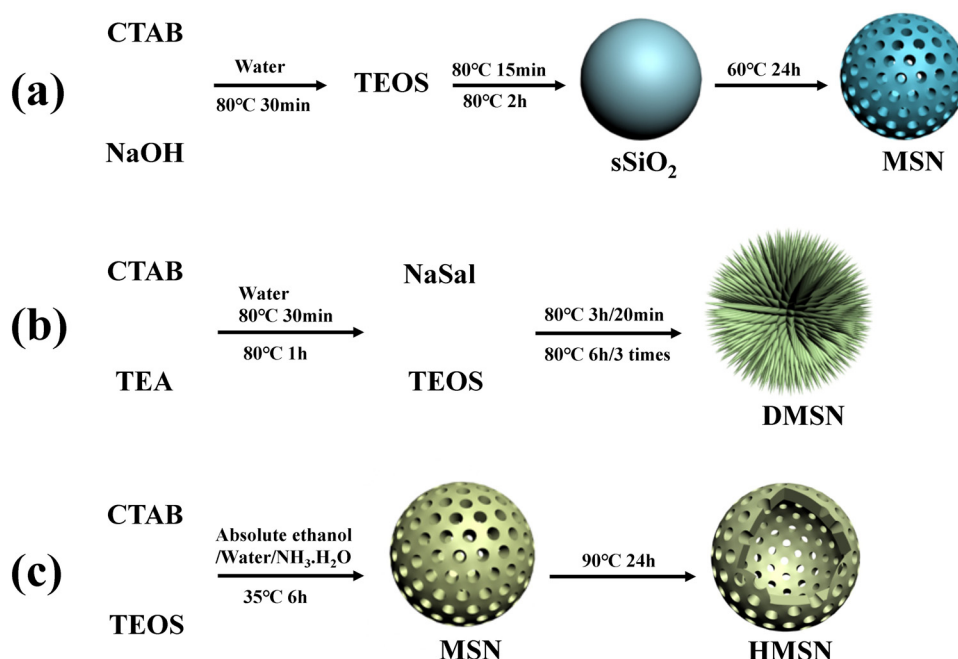
Figure 1: Schematic representation of the formation of MSN (a), DMSN (b), and HMSN (c), respectively.

$CBPQT^{4+}$. Upon exposure to light, the photosensitive molecule formed a covalent bond with the $CBPQT^{4+}$ ring, facilitating a light-induced electron transfer that ultimately resulted in the dissociation of the ring from the molecular bearing. This process enabled the development of a drug release mechanism responsive to light, simplifying the release of drug molecules from the mesoporous silica pores.

In a similar approach, Sierocki et al. incorporated azobenzene into the pores of mesoporous silica [34]. In its stable state, azobenzene adopts a trans configuration, which can be isomerized upon exposure to UV light. This exposure triggers the isomerization of azobenzene into the cis configuration. Further exposure to light at 450 nm induces continuous trans-cis and cis-trans photoisomerization of azobenzene. The oscillatory movements of the detached azobenzene head, resulting from this series of changes, trigger the release of drug molecules into the surrounding solution from the mesoporous silica pores.

Additionally, Li et al. employed host–guest interactions to attach trans-cinnamamide to the molecular bearing linked to the mesoporous silica surface, utilizing cucurbit[7]uril (CB [7]) [35]. Upon exposure to UV radiation at 300 nm, the trans-cinnamamide underwent isomerization into the cis structure. This isomerization induced spatial repulsion caused CB[7] to detach from the molecular bearing, thereby opening the mesoporous silica pores and allowing the release of drug molecules.

4.2 pH-responsive controlled drug release systems

pH-sensitive drug delivery methods are gaining prominence due to their capacity to release drugs in response to the varying acidic or alkaline environments present in different parts of the body, which have distinct pH levels [36,37]. This characteristic enhances therapeutic efficacy while minimizing adverse impacts on non-target tissues. A pH-responsive nanovalve system is designed to selectively release drugs at tumor sites, leveraging the pH differential between tumor tissues (typically pH 5.8–7.1) and normal tissues (pH 7.4) within the body's microenvironment [38]. This targeted approach facilitates cancer treatment without negatively affecting healthy tissues.

Stoddart et al. explored the interaction of CB[6] with amino groups on the molecular bearings of mesoporous silica as a potential drug release method. This interaction allows for binding or detachment based on pH variations. Under neutral and acidic conditions, the CB[6] ring securely encases the molecular bearings adorned with bisquaternary ammonium groups on the mesoporous silica surface, effectively trapping drug molecules within the mesoporous silica pores. Under alkaline conditions, deprotonation of the molecular bearings occurs, breaking the CB[6] binding and thereby enabling the release of drug molecules from the mesoporous silica [38].

Yang et al. investigated a pH-responsive, mesoporous silica-based drug release system functionalized with column[5] aryl hydrocarbon (CP[5]A) [39]. In this system, rotaxane molecules on the mesoporous silica surface are encased by electron-rich CP[5]A, effectively retaining drug molecules within the pores of the mesoporous silica under alkaline or neutral conditions. However, in acidic environments, CP[5]A dissociates from the rotaxane molecules, facilitating the easier release of drug molecules from the mesoporous silica.

Oiu et al. developed a method for delivering paclitaxel using carboxymethyl chitosan (CMCS)-functionalized dendritic fibrous nano-silica (DFNS). DFNS, characterized by a three-dimensional dendritic structure, was synthesized using a double-template method. A pH-responsive, nano-loaded vehicle system was then prepared by grafting CMCS onto DFNS through a covalent binding reaction. *In vitro* cellular experiments indicated that CMCS-DFNS significantly enhanced drug uptake efficiency in breast cancer MCF-7 cells. Crucially, *in vivo* and cellular pharmacokinetic results demonstrated that CMCS-DFNS could prolong circulation time and increase the relative bioavailability of paclitaxel. Therefore, this pH-responsive DDS holds potential for the delivery of anti-tumor drugs and offers a new pathway for enhancing the bioavailability of other compounds with low inherent bioavailability [40], Figure 2.

4.3 Enzyme-responsive controlled drug release systems

The variability in enzymes across different tissues in the human body highlights the importance of employing biomolecules as gatekeepers for controlled drug release within mesoporous systems *in silico*. E.g., a range of biomolecules – including antigen–antibody interactions [41], hybridized single-stranded DNA [42], enzymes [43], sugars [44], ribose [45–48], and proteins [49] have been engineered to function as gating elements at the entrances of mesoporous silica structures. This approach confers a high level of specificity, precision, and efficiency on the resultant mesoporous silica drug release systems.

In 2008, Stoddart et al. introduced a mesoporous silica drug release system designed to respond to enzymatic stimulation [50]. In this system, α-cyclodextrin (α-CD) wraps around the polyethylene glycol molecular bearings on the surface of the mesoporous silica, forming a bond with the upper ester linkage and thus securing drug molecules within the mesoporous silica pores. Upon introduction of porcine heparan esterase, which catalyzes the enzymatic hydrolysis of the ester bond, the molecular bearings break apart. This causes α-CD to detach from them, thereby facilitating the release of the drug from the pores.

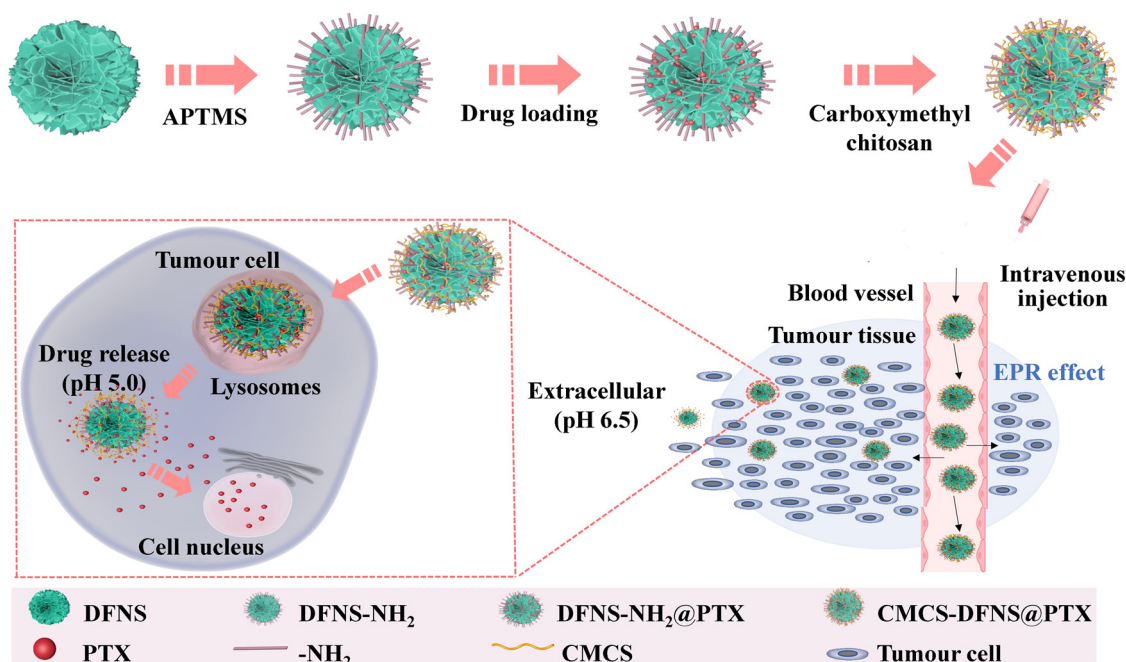Yang et al. developed organic–inorganic hybrid nanomaterials that leverage supramolecular interactions

Figure 2: Schematic illustration of the synthesis process of CMCS-DFNS@PTX and the pH-responsive release.

between hosts and guests. These materials not only showcase excellent biocompatibility but also exceptional controlled release capabilities in response to specific external stimuli. The release mechanisms, precisely regulated by cup-shaped aromatic-based nanogate systems enable the responsive release of acetylcholine – a neurotransmitter – into the environment. This approach facilitates timed, targeted, and quantifiable controlled release, exemplifying a significant advancement in the field of DDSs [51].

4.4 Redox-responsive controlled drug release systems

Recently, notable progress has been made in the development of controlled drug release systems that react to alterations in the body's redox environment. Studies have shown that the unique reducing conditions present within tumors act as a distinct trigger for the decomposition of redox-responsive delivery systems inside tumor cells, enabling the release of encapsulated medication. These redox-responsive systems present several benefits, such as stability in normal tissues and enhanced therapeutic efficacy compared to other controlled release mechanisms. Consequently, this can significantly diminish the toxicity and adverse effects associated with both the drugs and the nanocarriers [30,52].

Zink et al. developed molecular bearings known as rotaxanes, which were attached to the surface of mesoporous silicon. These rotaxanes featured a bistable state with two attachment sites: tetrathiafulvalene (TTF) and dioxynaphthalene (DNP). A CBPQT^{4+} ring, serving as a valve molecule, was positioned around the molecular bearings in their bistable state, demonstrating a strong affinity for TTF. In the absence of an oxidizing reagent, CBPQT^{4+} remained attached to the TTF site, distanced from the mesoporous silica pore, thus allowing the ingress or egress of drug molecules. Upon the introduction of Fe(ClO$_4$)$_3$·6H$_2$O, TTF was oxidized to TTF^{2+}, prompting the CBPQT^{4+} to migrate to the DNP site close to the pore entrance, effectively encapsulating the drug molecules within. The subsequent reduction of TTF to its original state by ascorbic acid caused CBPQT^{4+} to revert to the DNP site, facilitating controlled drug release [53].

Zink et al. further innovated by modifying the surface of mesoporous silicon with ferrocene dicarboxylic acid and β-cyclodextrin (β-CD) to engineer nanovalves. Upon application of an oxidizing voltage via cyclic voltammetry, the resulting positively charged oxidized ferrocenyl salt disrupted the stable inclusion complex formation with β-CD. This process led to the oxidation of the ferrocenyl dicarboxylic acid, prompting β-CD to detach, which in turn facilitated the release of drug molecules contained within the pore channels.

Zhao et al. utilized electrostatic interactions to attach negatively charged single-stranded DNA to positively charged disulfide bonds on the surface of mesoporous silicon. The introduction of reducing agents such as dithiothreitol and glutathione resulted in the cleavage of the disulfide bonds, enabling the single-stranded DNA to detach and thereby release the drug. Importantly, the intracellular concentration of the reducing agent glutathione is significantly higher (up to 10 mM) compared to extracellular concentrations (less than 10 μM). This difference in glutathione levels makes mesoporous silica an ideal storage microenvironment outside cells, offering considerable promise for the targeted delivery of therapeutic drugs, particularly in cancer treatment [54].

5 Challenges and opportunities

Leveraging the distinctive attributes of MSNs, multifunctional MSN nanocomposites emerge as potent agents for diverse applications. Nonetheless, significant opportunities remain to enhance the commercial production of MSNs. To boost yield, the development of new materials and synthetic strategies is crucial, particularly with a focus on efficiently synthesizing ultra-large-sized MSNs. Moreover, concerted efforts are required to ingeniously design smart theranostics that facilitate highly effective therapy under remote control and to establish correlations between experimental outcomes and therapeutic efficacy. This approach will pave the way for real-time monitoring of therapeutic results, thereby advancing personalized theranostics. The ongoing development of MSN-based theranostics for biomedical applications remains a vibrant and critical area of research. Continued in-depth investigation into MSNs promises to yield exciting and promising advancements for the chemistry and biomedicine communities by contributing novel discoveries and addressing existing challenges. Interdisciplinary collaboration is paramount to further refine the performance of MSN-based theranostics and ensure their successful clinical implementation.

6 Future trends

In conclusion, our review has highlighted recent advancements in MSNs that have led to the creation of novel smart materials with extensive applications across various fields.

MSNs have been endowed with numerous advantageous properties, establishing them as superior solid supports for constructing intelligent machinery. Significant strides have been made in developing biocompatible nanocarriers capable of controlled entrapment and release of cargo molecules in response to a wide array of internal and external stimuli. Consequently, MSNs hold a promising future in the pharmaceutical industry, presenting a broad spectrum of potential applications.

Author contributions: Wei Zhang and Hongwei Liu writed the paper. Wei Zhang and Fanjiao Zuo performed the literature search. Xilong Qiu and Boyao Wang critically revised the work.

Conflict of interest: Authors state no conflict of interest.

Data availability statement: Data sharing is not applicable for this article as no datasets were generated or analyzed during the current study.

References

[1] Beck JS, Vartuli JC, Roth WJ, Leonowicz ME, Kresge CT, Schmitt KD, et al. A new family of mesoporous molecular sieves prepared with liquid crystal templates. J Am Chem Soc. 1992;114(27):10834–43.

[2] Trewyn BG, Slowing II, Giri S, Chen HT, Lin VS. Synthesis and functionalization of a mesoporous silica nanoparticle based on the sol-gel process and applications in controlled release. Acc Chem Res. 2007;40(9):846–53.

[3] Serre C, Hervieu M, Magnier C, Taulelle F, Férey G. Synthesis and characterization of mesostructured titanium (IV) fluorophosphates with a semicrystalline inorganic framework. Chem Mater. 2002;14(1):180–8.

[4] Newalkar BL, Komameni S, Karsukl H. Rapid synthesis of mesoporous SBA-15 molecular sieve by a microwave-hydrothermal proeess. Chem Chem Phys. 2000;2:2389–90.

[5] Khan AM, Shafiq F, Khan SA, Ali S, Ismail B, Hakeem AS, et al. Surface modification of colloidal silica particles using cationic surfactant and the resulting adsorption of dyes. J Mol Liq. 2019;274:673–80.

[6] Tulyaganov DU, Fiume E, Akbarov A, Ziyadullaeva N, Murtazaev S, Rahdar A, et al. *In vivo* evaluation of 3D-printed silica-based bioactive glass scaffolds for bone regeneration. J Funct Biomater. 2022;13(2):74.

[7] Soler-Illia GD, Louis A, Sanchez C. Synthesis and characterization of mesostructured titania-based materials through evaporation-induced self-assembly. Chem Mater. 2002;14(2):750–9.

[8] Metosh NA, Davidson P, Chmelka BF. Monolithic mesophase silica with large ordering. J Am Chem Soc. 2000;122:823–9.

[9] Chatterjee M, Iwasaki T, Hayashi H, Onodera Y, Ebina T, Nagase T. Room-temperature formation of thermally stable aluminium-rich mesoporous MCM-41. Catal Lett. 1998;52:21–3.

[10] Newalkar BL, Komameni S, Karsuki H. Rapid synthesis of mesoporous SBA-15 molecular sieve by a microwave-hydrothermal process. Phys Chem Chem Phys. 2000;2:2389–90.

[11] Hoffmann F, Cornelius M, Morell J, Fröba M. Silica-based mesoporous organic-inorganic hybrid materials. Angew Chem Int Ed. 2006;45(20):3216–51.

[12] Guiotto A, Canevari M, Orsolini P, Lavanchy O, Deuschel C, Kaneda N, et al. Synthesis, characterization, and preliminary *in vivo* tests of new poly(ethylene glycol) conjugates of the antitumor agent 10-Amino-7-ethylcamptothecin. J Med Chem. 2004;47:1280–9.

[13] Lu J, Liong M, Zink JI, Tamanoi F. Mesoporous silica nanoparticles as a delivery system for hydrophobic anticancer drugs. Small. 2007;3:1341–6.

[14] Lu J, Liong M, Sherman S, Xia T, Kovochich M, Nel AE, et al. Mesoporous silica nanoparticles for cancer therapy: energy-dependent cellular uptake and delivery of paclitaxel to cancer cells. Nanobiotechnology. 2007;3:89–95.

[15] Wang TY, Zhao QF, Han X. Application of two kinds of mesoporous silica for preparation of nimodipine solid dispersion. Chin Pharm J. 2014;49(13):1139–45.

[16] Zhang Y, Wang J, Bai X, Jiang T, Zhang Q, Wang S. Mesoporous silica nanoparticles for increasing the oral bioavailability and permeation of poorly water soluble drugs. Mol Pharmaceutics. 2012;9:505–13.

[17] Vivero Escoto JL, Slowing II, Wu CW, Lin VS. Photoinduced intracellular controlled release drug delivery in human cells by gold-capped mesoporous silica nanosphere. J Am Chem Soc. 2009;131(10):3462–3.

[18] Aznar E, Casasús R, García-Acosta B, Marcos MD, Martínez-Máñez R, Sancenón F, et al. Photochemical and chemical two-channel control of functional nanogated hybrid architectures. Adv Mater. 2007;19(17):2228–31.

[19] Park C, Lee K, Kim C. Photoresponsive cyclodextrin-covered nanocontainers and their sol-gel transition induced by molecular recognition. Angew Chem Int Ed. 2009;121(7):1301–4.

[20] Liu M, Dunphy DR, Atanassov P, Bunge SD, Chen Z, López GP, et al. Photoregulation of mass transport through a photoresponsive azobenzene-modified nanoporous membrane. Nano Lett. 2004;4(4):551–4.

[21] Zheng YB. Light-driven artificial molecular machines. J Nanophotonics. 2010;4:042501.

[22] Sun YL, Yang BJ, Zhang SXA, Yang YW. Cucurbit[7]uril pseudorotaxane-based photo-responsive supramolecular nanovalve. Chem Eur J. 2012;18:9212–6.

[23] Angelos S, Khashab NM, Yang YW, Trabolsi A, Khatib HA, Stoddart JF, et al. pH clock-operated mechanized nanoparticles. J Am Chem Soc. 2009;131(36):12912–14.

[24] Xue M, Zhong X, Shaposhnik Z, Qu Y, Tamanoi F, Duan X, et al. pH-operated mechanized porous silicon nanoparticles. J Am Chem Soc. 2011;133(23):8798–8801.

[25] Park C, Oh K, Lee SC, Kim C. Controlled release of guest molecules from mesoporous silica particles based on a pH-responsive poly-pseudorotaxane motif. Angew Chem Int Ed. 2007;46(9):1455–7.

[26] Pour MM, Riseh RS, Ranjbar-Karimi R, Hassanisaadi M, Rahdar A, Baino F. Microencapsulation of Bacillus velezensis using alginate-gum polymers enriched with TiO_2 and SiO_2 nanoparticles. Micromachines. 2022;13(9):1423.

[27] Hernandez R, Tseng HR, Wong JW, Stoddart JF, Zink JI. An operational supramolecular nanovalve. J Am Chem Soc. 2004;126:3370–1.

[28] Giri S, Trewyn BG, Stellmaker MP, Lin VS. Stimuli-responsive controlled-release delivery system based on mesoporous silica nanorods capped with magnetic nanoparticles. Angew Chem Int Ed. 2005;44(32):5038–44.

[29] Bernardos A, Mondragon L, Aznar E, Marcos MD, Martinez-Mañez R, Sancenon F, et al. Enzyme-responsive intracellular controlled release using nanometric silica mesoporous supports capped with "saccharides". ACS Nano. 2010;4(11):6353–68.

[30] Nguyen TD, Tseng HR, Celestre PC, Flood AH, Liu Y, Stoddart JF, et al. A reversible molecular valve. Proc Natl Acad Sci USA. 2005;102:10029–34.

[31] Nguyen TD, Leung KC, Liong M, Pentecost CD, Stoddart JF, Zink JI. Construction of a pH-driven supramolecular nanovalve. Org Lett. 2006;8:3363–6.

[32] Leung KCF, Nguyen TD, Stoddart JF, Zink JI. Supramolecular nano-valves controlled by proton abstraction and competitive binding. Chem Mater. 2006;18:5919–28.

[33] Nguyen TD, Leung KCF, Liong M, Liu Y, Stoddart JF, Zink JI. Versatile supramolecular nanovalves reconfigured for light activation. Adv Funct Mater. 2007;17:2101–10.

[34] Sierocki P, Maas H, Dragut P, Richardt G, Vögtle F, Cola LD, et al. Photoisomerization of azobenzene derivatives in nanostructured Silica. J Phys Chem B. 2006;110:24390–8.

[35] Li QL, Sun Y, Sun YL, Wen J, Zhou Y, Bing QM, et al. Mesoporous silica nanoparticles coated by layer-by-layer self-assembly using cucurbit[7]uril for in vitro and in vivo anticancer drug release. Chem Mater. 2014;26:6418–31.

[36] Yuan L, Tang QQ, Yang D, Zhang JZ, Zhang FY, Hu JH. Preparation of pH-responsive mesoporous silica nanoparticles and their application in controlled drug delivery. J Phys Chem C. 2011;115:9926–32.

[37] Croissant J, Zink JI. Nanovalve-controlled cargo release activated by plasmonic heating. J Am Chem Soc. 2012;134:7628–31.

[38] Angelos S, Yang YW, Patel K, Stoddart JF, Zink JI. pH-responsive supramolecular nanovalves based on cucurbit[6]uril pseudorotaxanes. Angew Chem Int Ed. 2008;47:2222–6.

[39] Sun YL, Yang YW, Chen DX, Wang G, Zhou Y, Wang CY, et al. Mechanized silica nanoparticles based on pillar[5]arenes for on-command cargo release. Small. 2013;9:3224–9.

[40] Du L, Liao S, Khatib HA, Stoddart JF, Zink JI. Controlled-access hollow mechanized silica nanocontainers. J Am Chem Soc. 2009;131:15136–42.

[41] Cauda V, Onida B, Platschek B, Mühlstein L, Bein T. Large antibiotic molecule diffusion in confined mesoporous silica with controlled morphology. J Mater Chem. 2008;18:5888–99.

[42] Yu Z, Li N, Zheng P, Pan W, Tang B. Temperature-responsive DNA-gated nanocarriers for intracellular controlled release. Chem Commun. 2014;50:3494–7.

[43] Zhao W, Zhang H, He Q, Li Y, Gu J, Li L, et al. A glucose-responsive controlled release of insulin system based on enzyme multilayers-coated mesoporous silica particles. Chem Commun. 2011;47:9459–61.

[44] Feng W, Nie W, He C, Zhou X, Chen L, Qiu K, et al. Effect of pH-responsive alginate/chitosan multilayers coating on delivery efficiency, cellular uptake and biodistribution of mesoporous silica nanoparticles based nanocarriers. ACS Appl Mater Interfaces. 2014;6:8447–60.

[45] Gao L, Cui Y, He Q, Yang Y, Fei J, Li J. Selective recognition of co-assembled thrombin aptamer and docetaxel on mesoporous silica nanoparticles against tumor cell proliferation. Chem Eur J. 2011;17:13170–4.

[46] He X, Zhao Y, He D, Wang K, Xu F, Tang J. ATP-responsive controlled release system using aptamer-functionalized mesoporous silica nanoparticles. Langmuir. 2012;28:12909–15.

[47] Ozalp VC, Eyidogan F, Oktem HA. Aptamer-gated nanoparticles for smart drug delivery. Pharmaceuticals. 2011;4:1137–57.

[48] Hernandez FJ, Hernandez LI, Pinto A, Schäfer T, Özalp VC. Targeting cancer cells with controlled release nanocapsules based on a single aptamer. Chem Commun. 2013;49:1285–7.

[49] Yang Y, Li J. Lipid, protein and poly(NIPAM) coated mesoporous silica nanoparticles for biomedical applications. Adv Colloid Interface Sci. 2014;207:155–63.

[50] Patel K, Angelos S, Dichtel WR, Coskun A, Yang YW, Zink JI, et al. Enzyme-responsive snap-top covered silica nanocontainers. J Am Chem Soc. 2008;130:2382–3.

[51] Yang X, Pu F, Chen C, Ren J, Qu X. An enzyme-responsive nano-container as an intelligent signal-amplification platform for a multiple proteases assay. Chem Commun. 2012;48:11133–5.

[52] Zhang G, Yang M, Cai D, Zheng K, Zhang X, Wu L, et al. Composite of functional mesoporous silica and DNA: an enzyme-responsive controlled release drug carrier system. ACS Appl Mater Interfaces. 2014;6:8042–7.

[53] Khashab NM, Trabolsi A, Lau YA, Ambrogio MW, Friedman DC, Khatib HA, et al. Redox-and pH-controlled mechanized nanoparticles. Eur J Org Chem. 2009;11:1669–73.

[54] Ma X, Nguyen KT, Borah P, Ang CY, Zhao Y. Functional silica nanoparticles for redox-triggered drug/ssDNA co-delivery. Adv Healthc Mater. 2012;1:690–7.