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# Gated supramolecular chemistry in hybrid mesoporous silica nanoarchitectures: controlled delivery and molecular transport in response to chemical, physical and biological stimuli

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This review presents and discusses recent advances in the emerging field of "gated nanochemistry", outlining the substantial progress made so far. The development of hybrid mesoporous silica with complex tailored pore nanoarchitectures bridges the gap between molecular materials and the requirements of nanodevices for controlled nanoscale chemistry. In the last decade, membranes, particles and thin film porous architectures have been designed, synthesized and selectively modified by molecular, polymeric, organometallic or biologically active groups. The exquisite manipulation of mesopore morphology and interconnection combined with molecular or supramolecular functionalities, and the intrinsic biological compatibility of silica have made these materials a potential platform for selective sensing and drug delivery. The wide *répertoire* of these hard–soft architectures permit us to envisage sophisticated intelligent nano-systems that respond to a variety of external stimuli such as pH, redox potential, molecule concentration, temperature, or light. Transduction of these stimuli into a predefined response implies exploiting spatial and physico-chemical effects such as charge distribution, steric constraints, equilibria displacements, or local changes in ionic concentration, just to name a few examples. As expected, this "positional mesochemistry" can be only attained through the concerted control of assembly, surface tailoring and, confinement conditions, thus giving birth to a new class of stimuli-responsive materials with modulable transport properties. As a guiding framework the emerging field of "gated nanochemistry" offers methodologies and tools for building up stimuli-sensitive porous architectures equipped with switchable entities whose transport properties can be triggered at will. The gated nanoscopic hybrid materials discussed here not only herald a new era in the integrative design of "smart" drug delivery systems, but also give the reader a perspective of the promising future in the development of mesoporous platforms that can control mass transport on command through the combination of flexible supramolecular routes, with implications on health, environment and energy.

## 1. Introduction

Hybrid mesoporous architectures combining the properties of inorganic and organic materials constitute a remarkable category within the field of materials science.[1–4] Although very sophisticated advances in supramolecular material science have been achieved, the blend of concepts from "sol–gel chemistry" and "soft matter", a concept often referred to as "integrative chemistry",[5,6] stands in its own right as an attractive route towards the flexible realization of heteroarchitectures[7] and hierarchical nanosystems[8] with unprecedented control over functional tailoring.[9,10]

Part of the appeal of hybrid mesoporous materials is the unique and thorough molecular control of their intrinsic topological and chemical characteristics, *i.e.*, composition, pore size, mesopore architecture, and morphology.[11,12] A significant advancement in controlling the composition of mesoporous silica materials has been the integration of organic groups into the pore wall to create mesoporous organosilicas displaying derivatizable sites.[13–15] With the correct choice of building blocks and self-assembly conditions, it is possible to produce nanostructured materials *via* sol–gel processes with precisely defined and tunable chemical functions incorporated into well-defined ordered mesostructured frameworks. By way of example we should mention the topo-chemical molecular engineering of mesoporous silica that enables

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us to specifically change the chemical nature of the internal pore surface *versus* the outer surface of the mesoporous silica.[16–18]

In this context, the combination of supramolecular concepts with nanoscopic mesoporous solids has found incredible resonance within the last few years.[19–23] Supramolecular chemists enjoy the luxury of having a large collection of building blocks at their disposal for preparing organized assemblies of different specific attributes in which the harmony of noncovalent and covalent interactions leads to "smart" and adjustable functions.[24–26] Inorganic chemists, on the other hand, have shown an increased mastery in construction of functional nanoscopic solids, multifunctional materials and hierarchical structures by learning ways to merge concepts and tools from self-assembly and "sol–gel" chemistry of inorganic precursors, leading to precise positioning of chemical or nanoderived functions in the surfaces or spaces of nanocavities.[4,9,27–30] Exciting opportunities are revealed when we think in this manner. The synergism arising from the integration of molecular functional units on the pore outlets of mesoporous scaffolds brings to bear a startling range of ideas related to controlled delivery of substances hosted in the mesoporous frameworks.[31,32] In this way, the chemically modified mesopores act as supramolecular-based nanoscopic gates able to control mass transport that can be opened and/or closed by specific chemical, physical or biological signals. This conceptual framework based on nanoscopic supramolecular architectures incorporating chemical entities that act as functional gate-like scaffoldings is currently known as "gated nanochemistry".[33] The deliberate and predictable control of the molecular transport properties of nanomaterials is at the heart of drug delivery systems, a burgeoning research field which holds immense implications for human health.[34,35] One early benchmark in the field of gated molecular systems has been the pioneering work of Vallet-Regí and coworkers[36] who demonstrated the potentialities of mesoporous particles as drug delivery vehicles. The porous framework can serve as a nanoreservoir for hosting drug molecules due to its uniform pore size and highly ordered nanochannels whereas the chemical functionalization with different organic molecules can allow the diffusion-controlled drug release under specific conditions,[37,38] or even "on command" delivery, by including responsive groups or molecular machineries.[39,40] As mentioned above, mesoporous silica matrices exhibit a set of singular features that render them ideal building blocks to design nanocarriers for controlled delivery of substances.[41,42] Current knowledge in sol–gel chemistry permits the straightforward preparation of mesoporous materials displaying homogeneous and controllable pore size and functionalization that

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allows attaining reproducible loadings and release kinetics. We should bear in mind that the pore size of these mesoporous materials determines the dimensions of the cargo molecules that can be hosted into the mesopores provided that the loading is not only governed by diffusion into the pores but also by size selectivity. With much of the synthetic effort in nanochemistry relating directly or indirectly to controlled-delivery nanosystems, it is not surprising to find gated supramolecular chemistry driving much of the current efforts in hybrid mesoporous materials. One of the main problems of drug delivery systems is the loss of activity before reaching their targets as a result of premature release of the active agent. Here is when ''gated nanochemistry'' comes into the picture as a valuable concept to engineer the gating properties of mesoporous delivery vehicles in order to attain ''zero premature release'' or full release of cargo molecules at will.[18]

The ability of mesoporous channels to command molecular transport functions would be greater if one could equip them with additional, artificial gating mechanisms. Pioneering examples showed a photoregulation effect in molecular transport due to the photomechanic response of grafted molecular azo functions.[43,44] However, organic–inorganic hybrid mesoporous materials presenting molecular functions at the pore surface have a limited offering due to the small occupation of the total pore space. Thus, a clever integration of stimuli-responsive units through soft chemistry routes could overcome these limitations and produce active channels with novel gate-like entry/release mechanisms. For this reason, a distinguishable facet of the revolution in ''gated nanomaterials'' has been the integration of specific properties of polymeric, supramolecular and biological materials to benefit from the excluded volume effects, charge distributions and specific functions that these building blocks can confer to the mesoporous scaffolds.

Biological assemblies and supramolecular units are of high potential because of their unique characteristics such as flexibility, self- and hierarchical-organization and responsiveness towards various stimuli. All these features are highly desired in practical applications of mesoporous materials with modulated transport properties. Considering the chemical diversity of polymers, the integration of macromolecular building blocks on the pore entrances can endow the mesoporous scaffold with built-in responses to a myriad of environmental chemical and physical stimuli. As our array of synthetic tools and building blocks grow, so does our repertoire to ''engineer'' gating mechanisms on the mesoporous scaffolds. Hence, the utilization of weak intermolecular forces for the construction of ''gatekeepers'' with controlled dimensionality and responsiveness plays a central role in this research field.

Typical configurations of gated nanoscopic ensembles are represented by mesoporous scaffolds functionalized on the outer surface with switchable/responsive/adaptive units. The gate opens upon application of an external stimulus or trigger such as light, pH, changes in redox potential, temperature or the presence of certain ions, molecules or biomolecules. Concomitantly, the hybrid material either releases the molecules hosted in the mesoporous framework or permits the entrance of molecular species from the bulk solution. The relevance of this strategy blending supramolecular concepts and tailored mesoporous scaffoldings is mainly due to the almost infinite tuning of their gating properties by conventional chemical synthetic methods through soft routes, from organic chemistry to coordination chemistry to supramolecular chemistry. Ultimately, this powerful combination opens unprecedented possibilities for the design of gate-like nanoensembles with the desired size, charge, polarity, responsiveness, bioactivity, *etc.* It is evident that gated nanochemistry is of major significance in the molecular design and development of drug delivery systems, where the expected added value of highly dispersable matrices with selective gated sensing and delivery properties is enormous. This explains why most of the gated mesoporous systems reported so far have been developed for cargo delivery. Notwithstanding this utilization, the applications of gated materials can expand beyond drug delivery to virtually any area of advanced applications in energy, environment or agriculture, in the shape of selective sensor/actuator systems, gated membranes, molecule or ion scavengers, novel series catalysts, *etc.*

The goal of this work is thus to assess recent progress in the field, to identify fruitful new research directions, and to summarize the substantial progress that has thus far been made with hybrid mesoporous nanoarchitectures displaying gated supramolecular chemistries. In this way, the practitioner (novice or expert) may gain knowledge or inspiration to innovate as well as to explore the utilization of the vast array of approaches given herein to the solutions of their scientific problems. We should note that in this era of exploding scientific information, it is difficult to keep abreast of the latest developments regarding a particular research field. This is even more difficult when dealing with popular and enthralling topics, as is currently the case with gated supramolecular chemistry in mesoporous materials – the corpus of experimental findings grows on a daily basis. Within this context, we present here an overview of the most relevant works that help to identify the emerging trends in this area so as to raise awareness of their potential. Special emphasis has been devoted to very recent explorations (*i.e.*, studies reported during the past three years). In the most optimistic sense, the gate-like mesoporous ensembles described herein not only in themselves provide novel approaches to accomplish controlled drug-delivery systems, but also may lead to the exploration of new avenues to integrative design of hybrid mesostructured materials exhibiting strictly controlled structure, topology and function. We hope this portrait of a very dynamic field will contribute to give the reader a feeling of the multiple possibilities and the many promising trends behind the development of gated mesoporous systems.

## 2. Chemical signals that trigger nanogating processes in mesoporous systems

A variety of routes and procedures have been developed in order to produce gated supramolecular mesoporous systems with tailored response. However, the essence of responsiveness relies

in controlling the ''mesoporous nanospace'',[45] understood as the accessible cavities with highly controlled architecture, surface chemistry and the whole pore volume enclosed. The gating responses are the consequence of a combination of charge, local interactions and steric effects of the different components that occupy the pore. These structural/architectural features can be externally controlled by designed synthesis, and are programmable taking into account an adequate stimulus coded in the molecular, supramolecular or nanoscopic regions of the materials. Among the most relevant controllable features of mesoporous hybrid silica are (a) the control of surface charge, related to the acidity of surface silanol groups, which can be changed by grafting organic groups, by the interactions with molecular or polymeric residues (*i.e.*, surface charge tuning), or by shielding the electrostatic interactions through changes in ionic strength; (b) the creation of hydrophilic, lipophilic or charged pockets in the mesopore volume, leading to preconcentration or exclusion of species (*i.e.*, pore volume tuning); (c) the inclusion of reactive species in the pore or particle surface that can lead to programmed functions detached through acid–base, redox or other specific reactions (*i.e.*, reactivity tuning). Another important development is related to the ability to achieve distinct functionalization in different regions of the materials, for example, differentiating between the inner mesopore and the particle surfaces, and by the selective deposition of nanosized objects such as nanoparticles or pre-formed polymers on the particle surface. In the following sections, the different systems will be presented according to the stimuli exploited. We stress that despite this arbitrary classification, it is useful to observe the basic physico-chemical principles beneath the production and behaviour of each system (charge development or interplay, conformation changes, swelling/solvent expulsion, local hydrophilicity/hydrophobicity changes, bond creation/rupture, *etc.*), which should permit to grasp a unified picture of this research field.

### 2.1. Proton-gated molecular transport in mesoporous architectures

One of the first examples of pH-gated release platforms was proposed by Xiao and co-workers[46] that utilized electrostatic interactions between carboxylic acid modified mesoporous silica rods and poly(dimethyldiallylammonium chloride), a cationic polyelectrolyte, to create the pH-responsive capping layer. The mesoporous nanosystem was able to store and release vancomycin from the pore voids by changing pH values at will. Polycations (PDDA) absorbed to anionic pore walls by electrostatic interactions acted as closed gates for storage of vancomycin in the mesopores. When anionic carboxylate groups ($COO^-$) were transformed into protonated carboxylic groups (COOH) by changing of the pH value, the attractive electrostatic interactions were strongly weakened and polycations were removed from the mesopore surface, leading to the opening of the gates for the release of vancomycin from the inner environment of the particle. Mesoporous architectures modified with multilayered polyelectrolyte assemblies have been proposed as pH-responsive nanosystems compatible with the delivery of cargo molecules. The effect of pH on the interaction between polyelectrolyte multilayers has been addressed by several authors.[47] Yang *et al.*[48] described the use of poly(allylamine hydrochloride)(PAH)–sodium poly(styrene sulfonate)(PSS) and alginate (ALG)–chitosan (CHI) as assembly pairs to create pH switches for controlled delivery of anionic doxorubicin hydrochloride (DOX) and cationic sodium fluorescein (FLU). The delivery process is controlled by the protonation–deprotonation process that governs the physicochemical properties of the multilayers capping the mesopores. For example, in the case of PAH–PSS-modified mesopores at neutral pH charge, compensation between positive and negative monomer units ($NH_3^+$ and $SO_3^-$) operates in the whole assembly. With decreasing pH the amino groups of PAH gradually become charged and counterion uptake takes place to compensate for the excess charge of PAH, leading to an increase in the osmotic pressure. Subsequently, water molecules diffuse into the multilayer from the bulk solution, driven by this osmotic pressure difference. As a result, the multilayer gradually swells to develop a porous architecture that facilitates the permeation of drug molecules. A similar effect can be observed when the multilayer-capped mesoporous material is subjected to strong ionic strength variations. At high salt concentrations, the high ionic strength weakens the electrostatic binding between the oppositely charged layers, which results in the loosening of the PAH–PSS multilayers. As a result, multilayers can no longer cap the openings of the mesoporous channels and provide the pathways for drug molecules to diffuse into the medium.[49] Later on, Liu's group[50] integrated the concept of charge conversion polymers into the construction of mesoporous architectures capped with pH disintegrable polyelectrolyte multilayers. pH-triggerable charge-conversion polymers typically possess amide functionalities linked with β-carboxylic acid moieties *via* α,β-unsaturated bonds (Fig. 1). Rhodamine-loaded mesoporous silica particles were modified with polyelectrolyte multilayers constituted of PAH and negatively charged polyelectrolyte, P(DMA-*co*-TPAMA), consisting of *N*,*N*-dimethylacrylamide (DMA) and THPA-functionalized *N*-(3-aminopropyl)-methacrylamide (TPAMA) monomer units.

During the layer-by-layer (LbL) deposition process, cisplatin was incorporated into the multilayers by forming complexes with the negatively charged polyelectrolyte possessing charge conversion characteristics. It was found that the pH-triggered co-release of cisplatin and RhB can be achieved at pH 5–6, whereas their release at pH 7.4 is quite slow. These results indicate that subtle alteration of environmental pH from 7.4 to ~5–6 can lead to the disintegration of outer polyelectrolyte multilayers, accompanied with the co-release of cargo molecules hosted in the mesoporous core and the shell layer. Using a rather similar approach Gao and co-workers[51] modified COOH- and $NH_2$-terminated mesoporous silica nanoparticles preloaded with doxorubicin hydrochloride (DOX) with polyelectrolyte multilayers constituted of poly(acrylic acid) (PAA) and linear or star-shaped amino-functionalized polycations. Experimental results revealed that the loading capacity of nanosystems based on negatively charged mesoporous particles was superior to that based on $NH_2$-terminated samples owing to its electrostatic interaction with cationic DOX molecule. Nanoassemblies constructed from star-shaped polymers exhibited better loading capacity

 

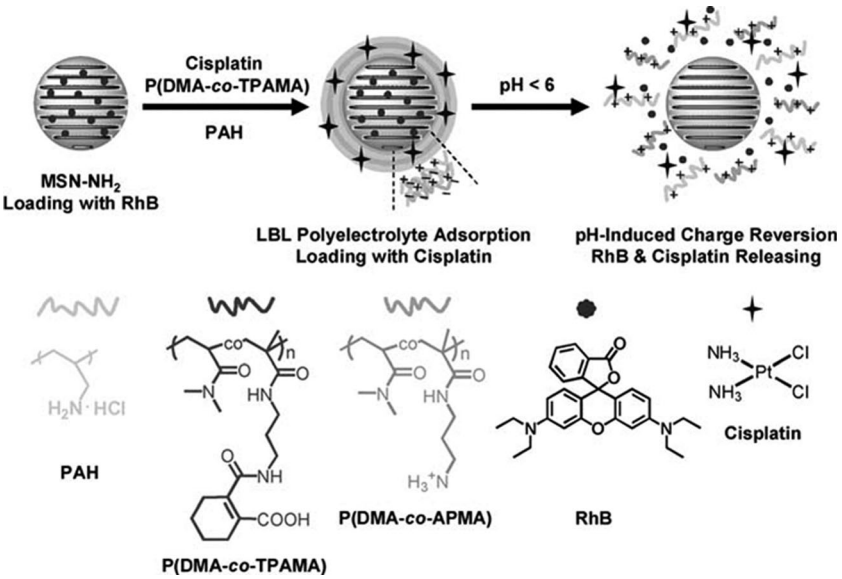


Fig. 1 Scheme describing the fabrication mesoporous silica particles coated with P(DMA-*co*-TPAMA)/PAH polyelectrolyte multilayers via the layer-by-layer technique and the pH-stimulated release of cisplatin trapped in the multilayers and rhodamine B encapsulated within the mesopores framework as a result of the pH-induced disintegration of the multilayer. Reproduced with permission from Wan *et al.*, *Macromol. Rapid Commun.*, 2011, **32**, 1082–1089. Copyright 2011 Wiley-VCH Verlag GmbH & Co. KGaA.

and sustained release. *In vitro* release tests showed that DOX release was triggered under acidic conditions but remained confined within multilayer-modified mesoporous systems under neutral pH conditions. Along these lines, Minati *et al.*[52] explored the functionalization of DOX-loaded mesoporous silica with poly(acrylic acid) (PAA)–poly(allylamine hydrochloride)(PAH) complexes with the aim of investigating the *in vitro* drug release in cellular environments. The carboxyl groups of PAA bind the amino groups of the PAH polymer through acid–base interactions forming a stable polyelectrolyte complex. The release profiles of DOX from modified particles obtained at pH 5.0 and 7.4, confirmed the pH-controlled delivery properties of the mesoporous particles. The observed pH-dependence in the drug release rate was attributed to the protonation of $-NH_2$ groups of DOX, which reduce the interaction between DOX and the silanols groups. On the other hand, the polyelectrolyte-complex-coated nanoparticles exhibited slower release kinetics as compared to the bare counterparts. This behavior was ascribed to the electrostatic repulsion between the doxorubicin and the protonated amino groups of the PAH layer in this pH range. The presence of the positively charged polyelectrolyte on the surface of the nanoparticles was able to prevent the fast doxorubicin release from the nanoparticle, decreasing the release rate of drug from the nanoparticles.

In order to achieve enhanced chemotherapy efficacy through targeted drug/siRNA co-delivery, Zhao and co-workers[53] designed and fabricated drug/siRNA co-delivery mesoporous nanovehicles stimulated by pH changes. Folic acid conjugated polyethyleneimine (PEI–FA) was electrostatically assembled on phosphonate-modified mesoporous silica particles preloaded with DOX. Folic acid plays a role as the targeting ligand that enables the nanosystem to selectively bind with and enter into target cancer cells. Under neutral conditions electrostatic interactions between the partially charged amino groups of PEI–FA and the exposed phosphonate groups conduct to the blocking of the nanopore outlets preventing the leakage of the drug. siRNA was then assembled onto the PEI–FA-coated silica though electrostatic interactions. The entire capping layer, including the siRNA, was held together through electrostatic interactions. Upon the cellular uptake, the acidic intracellular environment led to further protonation of the amino groups on the PEI–FA layer that concomitantly affected the electrostatic balance within the capping shell. Strong swelling of the polymeric layer due to strong Coulombic repulsion between the polymer chains led to the release of siRNA and DOX from the mesoporous nanoparticle.

Grafted polymers forming brush-like layers on the outer region of the mesopores may also serve as gatekeepers to control the delivery of cargo molecules on demand. Hong and co-workers[54] synthesized a pH-sensitive nanosystem based on the surface-initiated atom transfer radical polymerization of poly(2-(diethylamino)ethyl methacrylate) (PDEAEMA) brushes from mesoporous silica particles. The tertiary amine in PDEAEMA is easily protonated under acidic conditions, thus leading to swollen polyelectrolyte chains tethered on the outer surfaces of the mesopores. Conversely, in neutral or alkaline solution polymer chains adopt a collapsed (insoluble) state due to the hydrophobic interaction of polymer chains with the aqueous environment. The pH-dependent open–close mechanism of this hybrid material was confirmed by a set of experiments using rhodamine B as the cargo molecules hosted in the interior of the mesopores. Release of guest molecules was conducted at different pH values, and the results showed rapid release in acidic aqueous solution but very little leakage in alkaline solution. By adjusting the pH of the solution repeatedly, the release of

encapsulated molecules could be switched on and off at will. The same operation principle was explored by Liu *et al.*[55] through the coating of mesoporous silica particles with pH-responsive poly(4-vinyl pyridine) (PVP) brushes in such a way of manipulating the pH-controlled release of $Ru(bipy)_3^{2+}$ and calcein from the mesopores. On the other hand, the permselective transport of ionic species diffusing from the aqueous environment into mesoporous thin films modified with pH-responsive polymer brushes was thoroughly investigated by Brunsen *et al.*[56] The modification of these thin films with phosphate-bearing polyprotic polymer brushes led to a hybrid interfacial architecture displaying arrays of pH-responsive mesochannels whose ionic transport properties were finely tuned in the presence of protons and calcium ions (Fig. 2). In the case of protons, the electrostatic characteristics arising from the multiple protonation states of phosphate groups were responsible for tuning the ionic transport of anionic and cationic redox probes across the mesoporous framework over a wide range of pH values. Increasing pH from 4 to 8 led to a significant increase in (anion) permselectivity and (cation) preconcentration, thus reflecting the ability of the PMEP brush-modified mesopores to act as a selective ''electrostatic nanovalve'' precluding and boosting the anionic and cationic transport, respectively. Experiments demonstrated that the hybrid interface at pH 8 reversibly switches from low to high anionic conductance states depending on the formation of stable $Ca^{2+}$–phosphate complexes in the mesochannels. As a result, at high pH values, MEP-modified pores were strongly permselective, preventing the transport of anionic probes; on the other hand, once $Ca^{2+}$ were bound to the monomer units, the ionic mesochannels reached the open state.

In a recent development, Brunsen *et al.*[57] performed a systematic investigation on the role of the polymer content in the permselective response of hybrid architectures modified with cationic poly(2-(methacryloyloxy)ethyl trimethylammonium chloride) (PMETAC) brushes as a function of pH. PMETAC contents from 5 to 100% pore volume filling were obtained by different polymerization routes and varying polymerization times. A gradual variation of ionic permselectivity from a silanol-regulated to a PMETAC-regulated permselectivity was observed, ranging from ion exclusion to pre-concentration. The experimental observations are correlated with theoretical calculations that provide quantitative insights into the organization of the ions and polymers within the pore. This work sheds light into the understanding of the interplay between charge density and space on molecular transport.

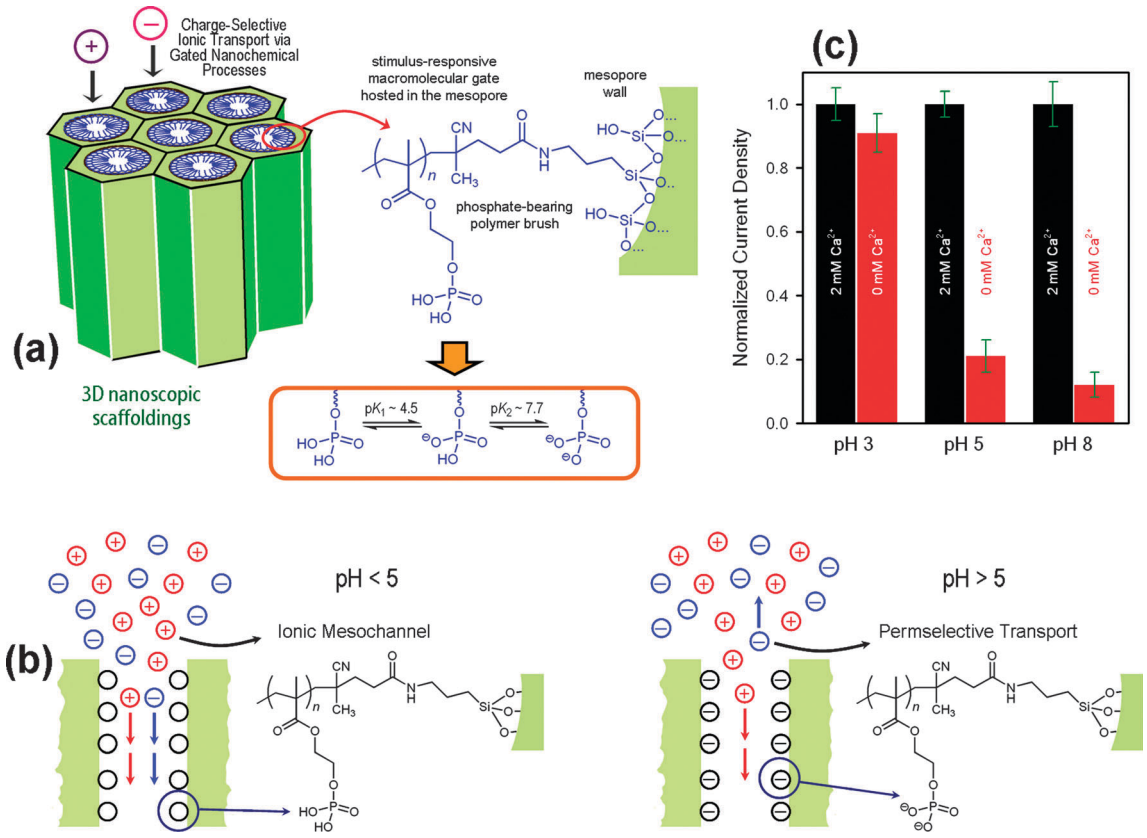


Fig. 2 (a) Scheme describing the hybrid polymer–inorganic mesostructured material constituted of phosphate-bearing polymer (PMEP) brushes grafted on mesoporous silica supports. (b) Schematic depiction of the ionic transport processes taking place in the hybrid polymer–inorganic interfacial assembly at different pH values. (c) Histograms showing variations in electrochemical current densities arising from the influence of pH and the presence of $Ca^{2+}$ ions on the molecular transport of $Fe(CN)_6^{3-}$ redox probes through the PMEP-modified mesopores. Reproduced with permission from Brunsen *et al.*, *Langmuir*, 2012, **28**, 3583–3592. Copyright 2012 American Chemical Society.

 

A completely different situation was observed when zwitterionic polymer brushes were integrated into mesoporous materials. Calvo *et al.*[58] described the creation of hybrid organic–inorganic assemblies displaying unique pH-dependent ionic transport properties originating from the combination of zwitterionic poly(methacryloyl-L-lysine) (PML) brushes ($pI_{brush} \sim 5$) and silica mesoporous matrices ($pK_a \sim 2$). In the pore walls the grafted polyzwitterionic chains coexist with silanol sites, which are negatively charged at pH > 2. At pH > 5 both the zwitterionic moieties and the $SiO^-$ groups bear negative charges. As a result, the hybrid mesoporous film shows a remarkable cation-permselective behavior (Fig. 3). Then, at pH lt; 5 the zwitterionic monomers bear positive charges while the silanol groups are still negatively charged. This experimental scenario leads to the emergence of a zwitterionic, "bipolarly charged" mesopore in the $pI_{brush} > pH > pKa$ silica range. In contrast to the typical Donnan exclusion phenomenon, which refers to confined negative charges repelling anions and confined positive charges repelling cations, the confinement of both negative and positive charges leads to a very particular exclusion condition. Initially the anions are attracted to the pore by the positive charges in the "bipolar" wall. However, the negative charges in the "bipolar" wall are very close to the positive ones, and as a result, repulsion of the anions occurs simultaneously. In a similar way, the diffusing cations exhibit the same electrostatic behavior due to their interaction with the "bipolar" environment.

Designable coordination bonding has been proposed by Che and collaborators[59,60] as a strategy to attain pH-responsive release from mesoporous systems. This method takes advantage of the pH sensitivity of the formation and cleavage of coordination bonding between metal ions like $Cu^{2+}$, $Zn^{2+}$, and $Fe^{3+}$ and amino-containing functional groups, such as guanidine. The working principle is based on the fact that the formation and cleavage of metal ion–ligand coordination bonds are sensitive to external pH variations, because both metal ions and protons are Lewis acids and compete among them to combine with the ligand, which is a Lewis base. In this way aminopropyl-functionalized mesoporous silica nanoparticles were employed as carriers for hosting metal ion binders and guest molecules to form "host–metal–guest" architectures. The cleavage of either the "host–metal" or the "metal–guest" coordination bond, in response to pH variations, gives rise to a significant release of guest molecules under preset pH conditions. These authors demonstrated the elegance and versatility of the method by hosting and delivering anticancer drug bearing binding groups. Hosting of mitoxantrone (MX) and daunorubicin hydrochloride (DNR) into the mesoporous carriers on the basis of "$NH_2$–$Cu^{2+}$–MX/DNR" coordination bonding was employed for the pH-responsive uptake and release. Experimental results revealed that no significant release of MX or DNR nanoparticles was detected under the physiological conditions; however, under mildly acidic conditions, drugs were released in significant amounts from the carrier into the external environment. In the same vein, self-assembly strategies using supramolecular motifs have been recently developed with the aim of conferring pH-dependent properties to mesoporous silica thin films. Mixed charge-transfer complexes have been introduced by covalently fixing viologen to the silica walls and subsequent exposure to pyranine solutions. This simple two step process leads to the formation of charged surface complexes due to strong non-covalent charge-transfer interactions between the dicationic viologen (acceptor) and the trianionic pyranine (donor). By varying the exposure to pyranine solution, the pore charge can be adjusted, exploiting the charge-transfer directed assembly between the molecular building blocks, which is stronger than electrostatic interactions. Both molecular components show pH-dependent speciation, thus permitting to achieve charge reversal of the surface and hence pH-gated ion transport.[61]

A similar concept was applied to the development and use of mesoporous silica particles modified with coordination polymers as drug delivery vehicles.[62] Mesoporous silica particles were modified with amino groups by grafting aminopropyl-triethoxysilane on the outer surface of the mesopores. After loading the anticancer drug, topotecan (TPT), pores were capped by coordination polymers of zinc and 1,4-bis(imidazol-1-ylmethyl) benzene (BIX) grown on the mesoporous surfaces. The amino groups on the mesoporous surface facilitate the growth of the coordination polymer layer *via* coordination chemistry. These coordination bonds between BIX and Zn in the capping layers are labile and prone to cleavage under acidic conditions to

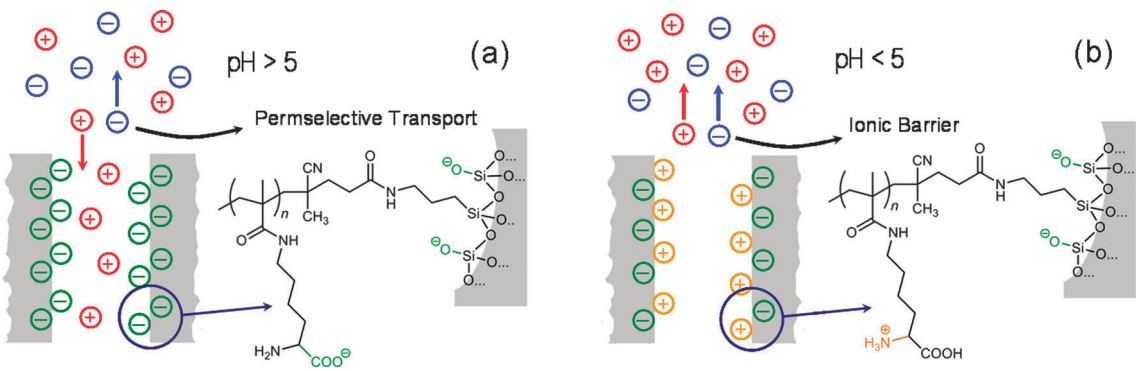


Fig. 3 Schematic illustration of the ionic transport processes taking place in the mesoporous silica film modified with the zwitterionic polymer brushes at different pH values: (a) pH > 5, permselective transport of cations and (b) pH < 5, ionic barrier (exclusion of ionic species). Reproduced with permission from Calvo *et al.*, *J. Am. Chem. Soc.*, 2009, **131**, 10866–10868. Copyright 2009 American Chemical Society.

release the encapsulated guest molecules from the pores. Release experiments confirmed good storage and sealing effects of the coordination polymer coating on TPT-loaded nanoparticles in PBS solution (pH 7.4) and favorable TPT release under acidic conditions (pH 4). The use of pH-responsive linkers between the substance to be delivered and the mesoporous host has also been investigated by Bein and co-wokers.[63] This research group has shown that acetals can be applied as pH-sensitive linkers for the delivery of melittin, a small peptide containing 26 amino acids, from mesoporous silica. Zink's group developed acid-responsive nanogated mesoporous ensembles on the basis of the pH-dependent chelating properties of iminodiacetic acid (IDA) molecules.[64] IDA can form stable complexes with different transition metal ions, so these chelating systems can function as molecular gates with a variety of different metal latches, including $Co^{2+}$, $Ni^{2+}$, and $Ca^{2+}$. However, if pH varies from neutral to mildly acidic, IDA binding constants exhibit an $\sim 10^3$ decrease resulting from the protonation of the Lewis base chelating groups.[65] This property is the conceptual framework for the operation of pH-responsive nanogates based on IDA-grafted mesopores. Pore openings derivatized with IDA were loaded with Hoechst 33342 as the probe cargo molecule and then were latched shut by forming a bis-IDA chelate complex with $Co^{2+}$, $Ni^{2+}$, and $Ca^{2+}$ ions, respectively. No cargo release was observed in a neutral aqueous environment, but acid stimulation and/or the addition of 2,2′-bipyridine (bipy) as a competitive binding ligand prompted the release of the chelated ions and the dye from the mesoporous particles.

Recently, Gooding and his collaborators[66] proposed an interesting strategy to manipulate the gating properties of mesoporous particles using pH-dependent ion-mediated metal nanoparticle assembly. In this hybrid interfacial architecture the release process is controlled by the removal of metal nanoparticles that act as capping agents of the nanopores. The capping was accomplished through sequential chelation/ligation of amino-functionalized mesoporous silica nanoparticles, $Cu^{2+}$ ions and L-cysteine derivatized gold nanoparticles. The working principle is associated with the switch in the $\zeta$ potential of the cysteine-coated AuNPs from negative to positive under acidic conditions (pH $< 5$). The pH-induced alteration of the affinities and electrostatic balance between counterparts triggers the disassembly of the interfacial architecture that ultimately leads to the delivery of the cargo molecules entrapped in the mesopores. It is interesting to note that ATP can also trigger the disruption of the nanoparticle assembly due to the strong interaction with $Cu^{2+}$ ions. In this particular modular setting both low pH and ATP can be exploited as chemical triggers to release the cargo. The pH-triggered release of fluorescein sodium hosted in the mesopores was confirmed by fluorescence emission spectroscopy at 520 nm. The system has no observable release of the drug at pH $> 5$ indicating that the nanoensembles exhibit well-defined ''on–off'' gating properties.

pH-induced labilization of capping moieties has been successfully employed for the case of mesoporous supports functionalized with thymidine derivatives which were capped with poly-adenine (polyA) units.[67] The surface of mesoporous silica nanoparticles was modified with a thymidine derivative in order to expose nucleobases capable of complementary base pairing with adenine. After loading rhodamine B into the mesopores, the particles were capped with poly-adenine *via* hydrogen bonding with the anchored thymidine groups on the mesoporous surface. The capping layer inhibited the release of the fluorescent dye at neutral pH; however, exposure to low pH triggered the release of the cargo molecules as a consequence of the destabilization of the intermolecular interactions between the oligonucleotide capping moiety and the tethered thymidine groups (Fig. 4).

Mesoporous silica nanoparticles functionalized with acid-labile thymine-based oligonucleotide switches were employed as proton-gated nanoensembles.[68] Selective interaction between mismatched thymine (T) bases in DNA strands and mercury ($Hg^{2+}$) ions results in the formation of duplex DNA containing T–$Hg^{2+}$–T base pairs that act as nanoscopic caps. In this configuration the nanogates remain closed at neutral pH but environment acidification triggers the uncapping mechanism through the dissociation of T–$Hg^{2+}$–T structures and the subsequent melting into single-stranded oligonucleotides.

Chen *et al.*[69] constructed a gate-like delivery system using i-motif quadruplex DNA as caps onto pore outlets of mesoporous silica nanoparticles. I-motif DNA is a four-stranded DNA structure that undergoes a precise structural change driven by a pH change with significant force (8–10 pN). Hence, conformational transformations triggered by changes in environmental pH can open and close the pore system. One attractive feature of this ensemble is the reversibility of the opening–closing mechanism as a function of pH. Delivery experiments showed that the release of rhodamine is strongly hindered at pH 5, whereas there is significant release of the fluorescent dye from the mesopores at pH 8. A partial cargo delivery can be easily manipulated due to the reversible and rapid structural switch between the i-motif quadruplex and random coil DNA.

The use of acid-sensitive chemical bonds integrated within extended weblike supramolecular capping layers was comprehensively studied by Zink and Stoddart and collaborators[70] as a mechanism for operation of pH-stimulated nanogates. Amine-modified cyclodextrin stalks were grafted onto mesoporous supports *via* imine bond formation. Imine bonds are acid-sensitive and prone to cleavage under acidic conditions. To attain better gating control these authors designed a set of weblike capping agents bearing adamantine units. These adamantine groups bind strongly to the exposed cyclodextrin units on the mesopore surface leading to the nanogate closing and preventing the leakage of the hosted probe molecules. When the pH of the solution was lowered, the imine bonds in the stalks were cleaved, promoting the removal of the cyclodextrin groups and the extended supramolecular capping layer bound to them. As a result, the pH drop led to the depletion of the capping layer and the subsequent release of cargo molecules from the nanoparticles.

The use of complex supramolecular architectures based on synthetic macrocyclic receptors to confer pH-responsive properties to mesoporous materials has been pioneered by Stoddart and Zink and co-workers. Rather than consisting of monolithic

 

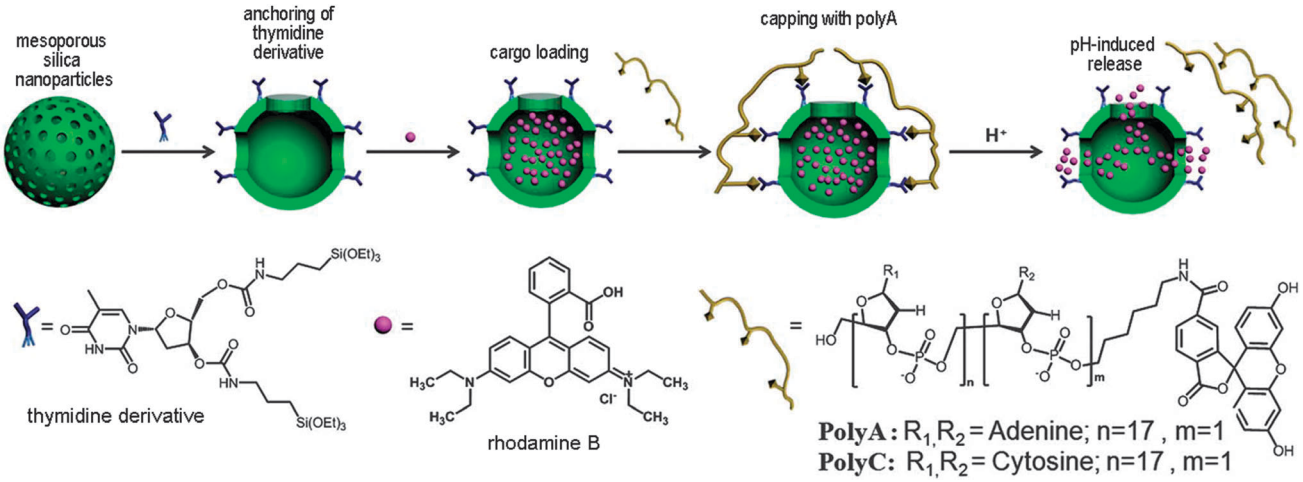


Fig. 4 Schematic depiction of the pH-responsive delivery system based on polyadenine-capped mesoporous silica particles. Reproduced with permission from Choi *et al., J. Mater. Chem.*, 2012, **22**, 9455–9457. Copyright 2012 Royal Society of Chemistry.

architectures, these supramolecular structures are spatially organized assemblies of different specific functions in which the harmony of noncovalent and covalent interactions leads to adjustable functions. One of the first examples was a supramolecular mesoporous nanovalve based on α-cyclodextrin forming pH-dependent host–guest complexes with anilinoalkane stalks that were grafted on the mesopore outlets.[71]

Complexation of the α-CD ring with the stalk at neutral pH locate the bulky unit near the pore openings, thus blocking the release of any preloaded probe molecule hosted in the interior of the particle. The binding affinity between α-CDs and the tethered anilinoalkane groups strongly decreases upon protonation of the aniline when the solution is acidified, thus bringing about the dissociation of the α-CD from the surface and the release of the cargo molecules. Importantly, the pH at which the valves open can be tuned by changing the substituents on the stalk. These supramolecular concepts were further extended to nanosystems constituted of cucurbit[6]uril (CB[6])[72] and cucurbit[7]uril (CB[7])[73] in combination with (*N*-(6-aminohexyl)-aminomethyl-triethoxysilane) and 1,4-butanediamine, respectively, as stalks tethered to the mesoporous silica. These stalks have two amino groups separated by long alkyl chains. Under acidic or neutral conditions, the amino groups are protonated and interact favorably with bulky CB[*n*] units. In an alkaline environment, the amino groups become deprotonated and the interaction between the CB[*n*] molecules and the stalks is strongly weakened, causing the removal of cucurbituril molecules from the mesoporous surface and the subsequent uncapping of the mesopores. Recent research suggests that the integration of cucurbit[6]uril-based reversible bistable [2]pseudorotaxanes in mesoporous architectures would enable multistage pH-controlled delivery platforms (Fig. 5).[74] Within this framework, Stoddart and co-workers[75] have also shown that the complexation of negatively charged carboxylatopillar[5]arene (CP[5]A) with stalks terminated by positively charged pyridinium units offers a new set of supramolecular tools to fabricate pH-sensitive nanovalves for on-demand cargo release. Under neutral or alkaline conditions the negatively charged CP[5]A units strongly interact with the pyridinium stalks grafted on the pore outlets, thus forming surface-confined [2]pseudorotaxanes and blocking the passage of molecules stored in the interior of the particle. On the other hand, acidification leads to neutralization of the charged CP[5]A units and the weakening of the attractive interactions between the ring and stalk components of the [2]pseudorotaxanes, *i.e.*: a pH-triggered unblocking process.

Finally, a new paradigm in pH-gated mesoporous materials was recently proposed by Kleitz and co-workers[76] through the integration of ''responsive'' protein architectures on mesoporous ensembles. Succinylated β-lactoglobulin was grafted onto amino-functionalized mesoporous silica nanoparticles pre-loaded with ibuprofen and acridine as hydrophobic and hydrophilic model drug candidates. At pH $< 5$, β-lactoglobulin undergoes a gelation process that has pronounced effects on its secondary structure. This conformational change is associated with lower solubility of the protein in acidic media resulting in a pH-dependent gel-like ''shell'' capping layer that prevents the release of the cargo molecule from the mesopores. However, when pH increases to the isoelectric point (pH $> 5$) or physiological conditions, the b-lactoglobulin remains permeable even for the case of hydrophobic drugs, allowing the entrapped drug to diffuse into the environmental solution.

### 2.2. Cargo delivery from mesoporous materials triggered by redox reactions

If we consider that intracellular concentration of glutathione (GSH) is two to three orders of magnitude higher than in the extracellular environment[77] and the tumor tissues show higher concentrations of GSH levels compared with normal tissues,[78] then, the creation of redox responsive drug release strategies based on the cleavage of disulfide bonds induced by disulfide-reducing agents seems to be a promising avenue in nanomedicine. This explains why a large number of research groups devoted considerable research efforts to build up delivery platforms utilizing the rupture of disulfide bonds between the cap and support.

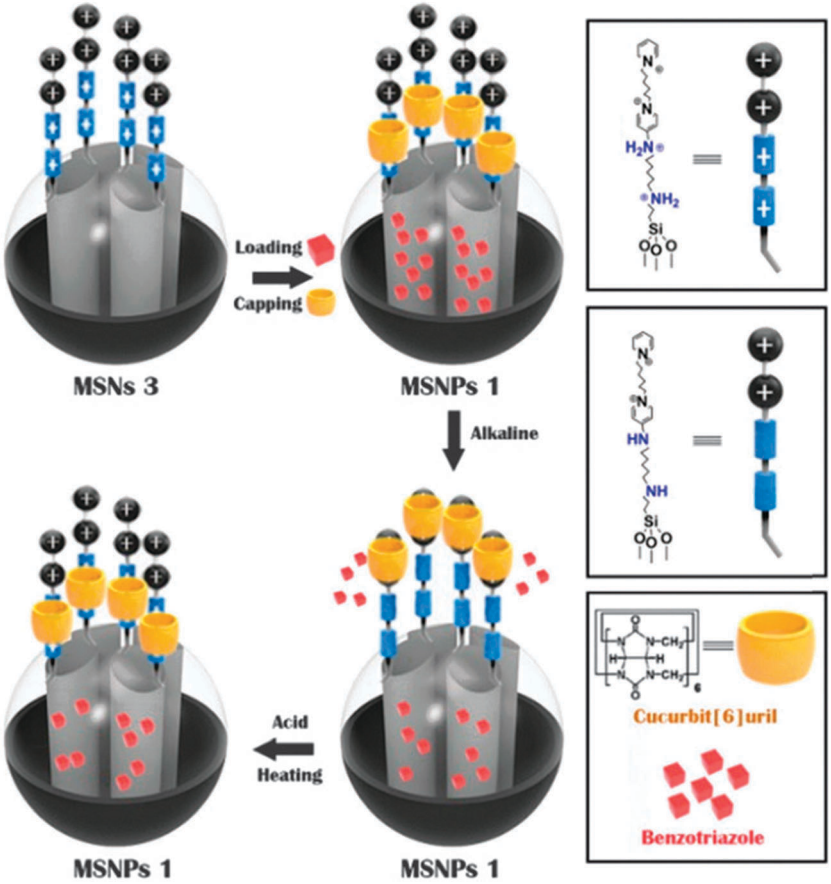


Fig. 5 Scheme of silica nanoparticles reversibly capped by bistable [2]pseudorotaxanes for multistage pH-controlled release. Reproduced with permission from Wang *et al., Chem. Commun.*, 2014, **50**, 5068–5071.Copyright 2014 Royal Society of Chemistry.

Seminal works of Lin and his collaborators introduced this general concept in which nanoparticles anchored to the surface of the mesoporous silica particles through redox-responsive linkers were cleaved upon addition of specific redox agents, allowing the release of the cargo molecules.[79] Mesoporous particles were loaded with vancomycin- and adenosine triphosphate (ATP) using surface-derivatized cadmium sulfide (CdS) nanocrystals as chemically removable caps. The addition of reducing agents such as dithiothreitol (DTT) or mercaptoethanol triggered the rupture of the disulfide bridges that linked the CdS nanoparticles to the porous framework and ultimately led to the delivery of the cargo molecules. The same group also explored creation of stimuli-responsive delivery systems based on mesoporous silica nanorods capped with superparamagnetic iron oxide nanoparticles. The controlled-release mechanism of the system was based on reduction of the disulfide linkage between the $Fe_3O_4$ nanoparticle caps and the linker grafted on the mesoporous surface by introducing dithiothreitol as a reducing agent in the nanoparticle environment (Fig. 6).[80]

The redox responsiveness of disulfide bonds was also exploited by Feng and co-workers[81] by creating an interesting class of the mesoporous delivery system based on cross-linked polymeric networks as macromolecular gatekeepers (Fig. 7). The gate operation was based on redox reactions in which the cross-linked polymeric network worked as an off–on switch in response to redox signals. After loading the probe molecules into mesoporous framework, the pore outlets were modified with poly(*N*-acryloxysuccinimide) followed by the addition of cystamine, thus promoting the cross-linking of the polymer chains through the reaction between cystamine and *N*-oxysuccimide groups along the polymer chain. The polymeric network formed around the pore opening could be unblocked by cleaving the disulfide bond of cystamine in the presence of dithiothreitol (DTT), leading to the redox-controlled release of the cargo molecules.

Zink and Stoddart and coworkers[82] proposed the modification of mesoporous silica nanoparticles with surface-bound rotaxanes incorporating disulfide bonds in their stalks, which were encircled by cucurbit[6]uril or α-cyclodextrin rings. Reductive chemistry in the presence of a large excess of dithiothreitol (DTT) resulted in the complete ''snapping'' of the stalks of the rotaxanes tethered to the pore entrances, thus leading to the cargo release from the nanoparticles. A versatile one-pot strategy for the preparation of reversibly cross-linked polymer-coated mesoporous silica nanoparticles *via* surface reversible addition–fragmentation chain transfer (RAFT) polymerization was recently proposed by Sun *et al.*[83] The oligo(ethylene glycol) acrylate (OEGA) and the cross-linker *N,N′*-cystaminebismethacrylamide (CBMA)

 

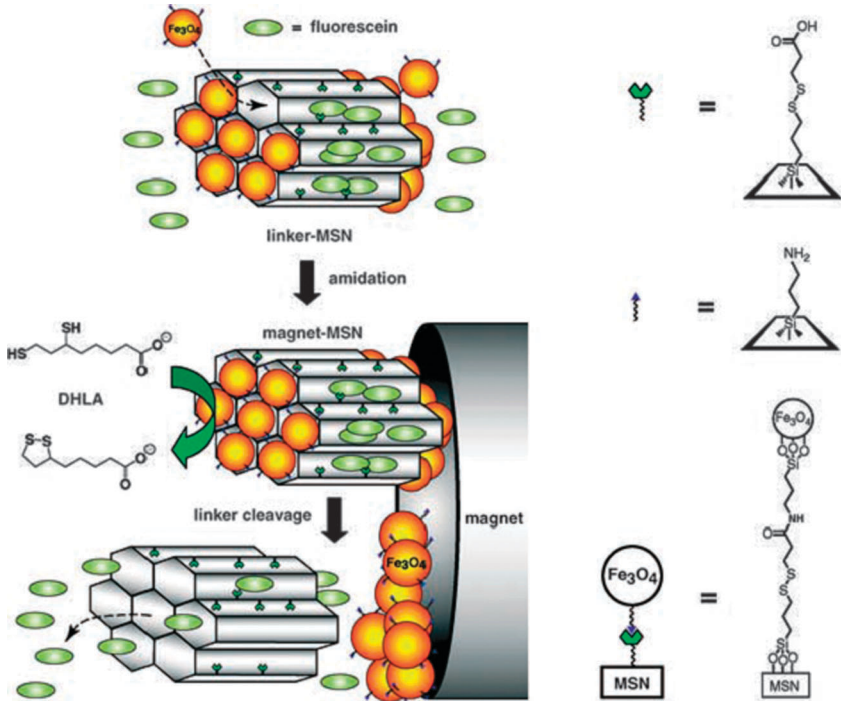


Fig. 6 Illustration of mesoporous particles capped with superparamagnetic iron oxide nanoparticles that work as gatekeepers. The nanoparticles are attached to the mesopores through disulfide-based linkers that in the presence of dihydrolipoic acid (DHLA) (reducing agent) are disrupted to release the cargo molecules. Reproduced with permission from Giri *et al., Angew. Chem., Int. Ed.*, 2005, 44, 5038–5044. Copyright 2005 Wiley-VCH Verlag GmbH & Co. KGaA.

were copolymerized on the external surfaces of RAFT agent-derivatised mesoporous nanoparticles in order to form a cross-linked hydrogel-like polymer shell. The reversible cleavage/formation of disulfide bonds through reduction/oxidation reactions on the hydrogel shells was used to control the on/off switching of the nanopores and regulate the drug loading and release of doxorubicin. Considering that the cleavage and formation of disulfide bonds are reversible *via* reduction and oxidation reactions, this strategy seems plausible to load drugs in the nanopores after cleaving the disulfide bonds and then oxidize the mercapto groups to block the leaching of the entrapped drugs. In the same context, Kim and collaborators[84] described the creation of stimulus-responsive mesoporous particles using cyclodextrin (CD) gatekeepers covalently grafted to the nanopore entrance *via* disulfide tethers and demonstrated that glutathione can be used as a redox trigger to induce the controlled release of doxorubicin from the inner environment of the particles. These results demonstrate that cell-expressed glutathione could cleave disulfide bonds for the controlled release of drugs hosted in the mesopores. The use of cell-produced antioxidants as redox triggers of chemically-modified mesoporous delivery platforms has been thoroughly studied by Lin and his collaborators.[85] This research group studied the effect of nicotinamide adenine dinucleotide hydride (NADH), dihydrolipoic acid (DHLA), glutathione (GHS) and dithiothreitol (DTT), as the chemical triggers for the controlled release of cysteine (Cys) molecules tethered to mesoporous particles through disulfide bonds. Experiments showed that after 30 min of the addition of NADH, DTT, DHLA and GHS, 99, 90, 70 and 60% of mesopore-loaded Cys was released, respectively. The different rates of release were attributed to the different reducing power of each reducing agent.

Yang and co-workers[86] reported the fabrication of nanoreservoirs with excellent biocompatibility and cellular uptake properties based on mesoporous nanoparticles that were end-capped with collagen. The strategy relied on the use of collagen, which is one of extracellular matrix (ECM) components, as a capping agent to encapsulate fluorescent probes within the mesoporous network of the nanoparticles. Collagen was grafted on the outer surfaces of the particles *via* disulfide linkages, which could be cleaved in the presence of dithiothreitol (DTT). Peptide modified mesoporous silica nanovalves were also proposed as redox-triggered release systems (Fig. 8).[87] In this case the peptide units were integrated on the mesoporous surface to ensure an efficient cellular uptake. The release of the drugs from the mesoporous silica nanocontainer occurred when the disulfide bond between the tether and the peptide was cleaved under reducing conditions in the presence of dithiothreitol (DTT). A rather similar strategy was recently implemented by Rosenholm *et al.* to deliver electrostatically assembled oligonucleotides from mesoporous platforms modified with amino-terminated disulfide bridge tethers.[88]

A different approach was proposed by Stoddart and Zink and co-workers[89] who explored the use of redox processes as triggers for controlling molecular transport in mesoporous materials modified with supramolecular nanovalves. This elegant approach is based on the stabilization/destabilization

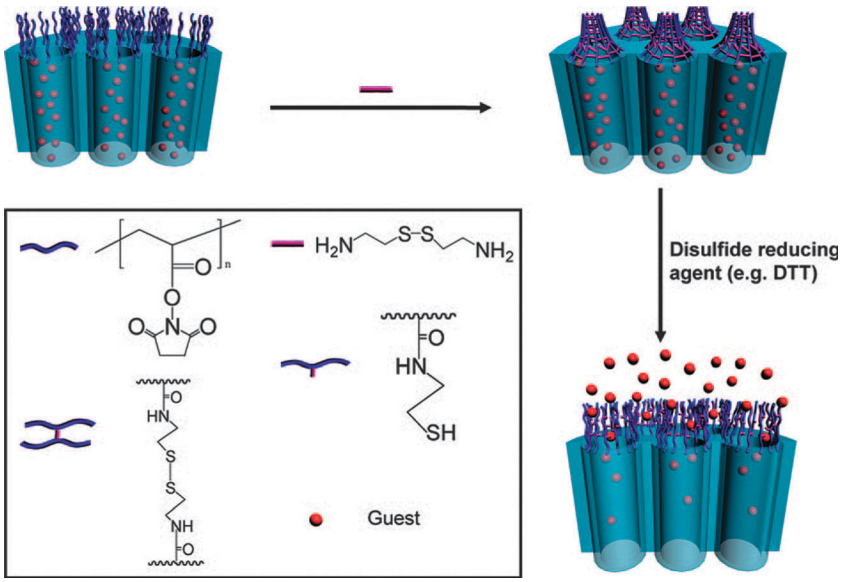


Fig. 7 Redox-responsive nanogated ensemble based mesoporous silica capped with redox-active cross-linked polymeric networks. Reproduced with permission from Liu *et al.*, *J. Am. Chem. Soc.*, 2008, **130**, 14418–14419. Copyright 2008 American Chemical Society.

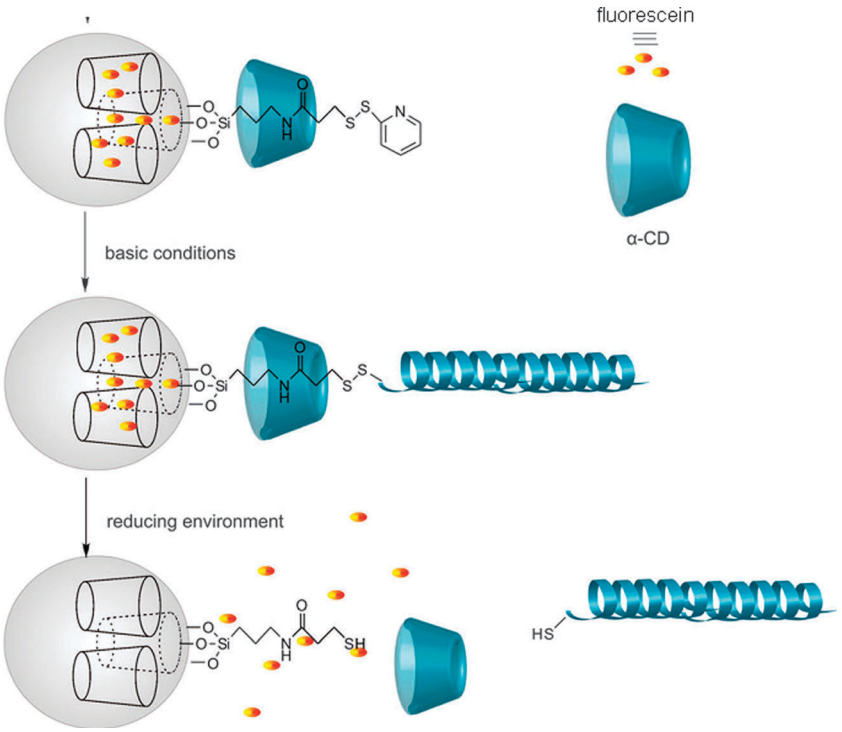


Fig. 8 Redox-triggered release systems based on peptide modified mesoporous silica. The release of the drugs takes place when the disulfide bridge linking the mesopore outlet and the peptide is cleaved in the presence of dithiothreitol. Reproduced with permission from Porta *et al.*, *Phys. Chem. Chem. Phys.*, 2011, **13**, 9982–9985. Copyright 2011 Royal Society of Chemistry.

of supramolecular complexes through oxidation/reduction of particular molecular components of the supramolecular nanovalve. The operation principle of this fascinating supramolecular array relies on the molecular-level actuation of a pseudorotaxane composed of two components – a long thread containing a 1,5-dioxnaphthalene donor unit, which is attached to the pore opening, and the moving part which is constituted of a tetracationic cyclophane acceptor/receptor, cyclobis(paraquat-*p*-phenylene). This moving building block is responsible for controlling the access to the interior of the nanopore. The operation sequence of the supramolecular nanovalve involves filling of the pores with the host molecules, closing the

 

nanovalve and opening the gate to release the probe molecules on demand. Nanopore closing takes place during pseudorotaxane formation; however, the presence of an external reducing reagent, like $NaCNBH_3$, can prompt the dethreading of the pseudorotaxane so as to unlock the nanopores and allow the release of the host molecules. Along these lines, the same group further developed this supramolecular concept using a reversible molecular valve based on a redox-activated, bistable [2]rotaxane tethered to the surface of mesoporous silica.[90] In this case the moving part of the molecular valve is a $CBPQT^{4+}$ ring, which shuttles between a tetrathiafulvalene (TTF) station and a dioxynaphthalene (DNP) station under redox control. The openings of the cylindrical pores on the silica are blocked by the $CBPQT^{4+}$ ring when the valve is closed. Loading of the host molecules takes place by diffusion when the $CBPQT^{4+}$ ring is located on the TTF station. Then, the closing of the nanogates is accomplished by oxidation of the TTF unit to its dication, causing the $CBPQT^{4+}$ ring to move to the DNP station, which is much closer to the openings of the pores. Finally, the valve can be re-opened to release the host molecules by adding ascorbic acid in order to reduce the TTF dication back to its neutral state, whereupon the $CBPQT^{4+}$ ring moves back from the DNP station to the TTF station. According to these authors, the efficient functioning of these supramolecular nanovalves is highly dependent on the distance between the movable ring component (*i.e.*, $CBPQT^{4+}$) on the bistable [2]rotaxane molecules and the nanopores' orifices.[91] Willner's group[92] reported the creation of reversible redox-gated molecular valves associated with mesoporous silica particles modified with chloronaphthoquinone units. These authors showed that the integration of 2-amino-3-chloronaphthoquinone derivatives in the mesoporous surface enabled the retention of eosin Y through donor–acceptor interactions. The reduction of the quinone units to the hydroquinone state by ascorbic acid resulted in the formation of electron donor groups displaying increased hydrophilicity. This redox-induced chemical change disrupted the original donor–acceptor interactions, resulting in the opening of the pores and the release of eosin Y.

Very recently, Brunsen and co-workers[93] reported the integration of electroactive polymer brushes in mesoporous materials as a blueprint for controlling the charge-selective transport through redox-controlled chemistries. These authors showed a set of experiments in which poly(2-(methacryloyloxy)ethyl ferrocenecarboxylate) (PFcMA) brushes were grafted from mesoporous films whereas the permselective transport was investigated using cyclic voltammetry of cationic ($Ru(NH_3)_6^{2+/3+}$) and anionic ($Fe(CN)_6^{3-/4-}$) redox probes. Oxidation of the grafted PFcMA polymer chains resulted in the chemical transformation of the ferrocene-bearing monomers into cationic ferrocenium pending groups. The redox-induced formation of positive charges in the mesopore walls led to the exclusion of $Ru(NH_3)_6^{2+/3+}$ probe ions from the mesoporous film due to electrostatic repulsion and, concomitantly, the response for the anionic $Fe(CN)_6^{3-/4-}$ probe molecules showed a signal increase owing to the electrostatic attraction between the oxidized cationic polymer and the negatively charged probe molecule.

### 2.3. Small organic molecules and ionic species as chemical stimuli activating gated mesoporous ensembles

Lin and co-workers[94] reported the use of boronic acid-functionalized mesoporous silica nanoparticles to attain glucose-responsive controlled release of insulin and cyclic adenosine monophosphate (cAMP). Fluorescein isothiocyanate-labeled, gluconic acid-modified insulin (FITC-G-Ins) proteins were immobilized on the exterior surface *via* reaction of phenylboronic acid moieties on the mesopore surface with the carbohydrate groups in the periphery of the proteins. The release of both G-Ins and cAMP was triggered by the introduction of saccharides. The selectivity of FITC-G-Ins release towards a series of carbohydrate triggers was determined to be fructose > glucose > other saccharides. On the other hand, the incorporation of cyclodextrin gatekeepers on the surface of mesoporous silica nanoparticles modified with boronic acid moieties has demonstrated to be a very efficient approach to entrap and release guest molecules from the pore in the presence of D-fructose and D-galactose as chemical stimuli.[95] Calcein-loaded mesoporous particle surface-modified with phenylboronic acid units were reacted with cyclodextrin to form the boronate ester on the nanopore outlets. Hence, the CD groups anchored on the pore surface *via* boronate ester linkers act as gatekeepers of the silica nanocontainers. D-Fructose and D-galactose bind to the boronic acid moiety more strongly than CD. As a consequence, the presence of D-Fructose or D-galactose triggers the removal of the CD groups from the pore entrances and induces the release of the cargo molecules from the mesoporous particle. Martínez-Máñez and his collaborators[96] exploited the synergy arising from the combination of the enzymatic process and supramolecular assemblies to manipulate the uncapping process of mesoporous materials in the presence of glucose. The working principle was based on the used of $[Ru(bpy)_3]^{2+}$-loaded mesoporous silica particles which were surface-modified with propylbenzimidazole moieties on the pore outlets. The mesopores were then capped with a CD-modified-glucose oxidase (CD-GOx) through the formation of an inclusion complex between the cyclodextrins and the propylbenzimidazole units tethered to the mesoporous surface. The addition of glucose in the presence of GOx in the nanopore surroundings led to the local formation of gluconic acid and the concomitant protonation of the benzimidazole units, causing the dethreading of the inclusion complex and the subsequent cargo release.

Shi and coworkers[97] described the preparation of glucose-responsive nanoplatforms for controlled release of insulin based on the integration of enzyme multilayers on mesoporous silica particles (Fig. 9). The insulin was hosted in the internal mesoporous framework whereas multilayer shells constituted of glucose oxidase (GOx) and catalase (CAT) were cross-linked with glutaraldehyde on the surface of the nanoparticles. The enzyme shells act as a valve to control the release of insulin in response to the presence of glucose. The principle of operation is based on the GOx-catalyzed conversion of glucose into gluconic acid, which decreases the pH value of the local environment and propels the swelling of the enzyme multilayer shells.

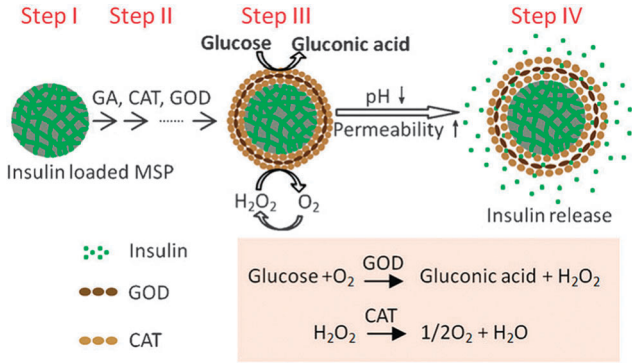


Fig. 9 Schematic representation of the construction and operation of glucose-responsive delivery nanovehicles based on mesoporous silica particles capped with glucose oxidase and catalase multilayers. Reproduced with permission from Zhao *et al.*, *Chem. Commun.*, 2011, **47**, 9459–9461. Copyright 2011 Royal Society of Chemistry.

This biochemical transformation ultimately leads to structural changes on the capping layer and the subsequent release of insulin from the porous framework. CAT is co-immobilized with GOx to decompose $H_2O_2$ into $H_2O$ and $O_2$ provided that peroxide produced during the oxidation of glucose can affect the enzymatic activity of GOx. Competitive binding of glucose to lectins has been recently proposed as a route to design gated nanodelivery vehicles.[98] Mesoporous silica nanoparticles were functionalized with mannose ligands and then capped through molecular recognition of exposed sugar sites by Concanavalin A (Con A) in order to encapsulate rhodamine 6G within the pores. In principle, low concentrations of glucose cannot trigger the cargo release because this sugar is a weak competitor in comparison with mannose. However, high concentrations of glucose can disrupt the multivalent mannose–Con A interactions on the pore outlets and trigger the release of the fluorescent dyes from the mesopores.

On the other hand, specific interactions between ions in solution and the receptor anchored on the pore outlets can trigger the release of cargo molecules. Aznar *et al.*[99] reported the functionalization of $[Ru(bipy)_3]^{2+}$-loaded mesoporous silica particles with *N*-(3-triethoxysilylpropyl) gluconamide at the pore outlets. Based on the selective reaction between the appended saccharide units and the borate anions in solution these authors developed a borate-controlled gate-like delivery vehicle. They showed that diffusion of $[Ru(bipy)_3]^{2+}$ from the mesopores into the aqueous solution is precluded in the presence of borate, as demonstrated in water at neutral pH. The formation of the corresponding boroester derivative is not affected by the presence of other ionic species in the medium. Indeed, experimental evidence conclusively confirmed that only the borate anion can act as a "molecular tap" and control the delivery of entrapped species from gluconamide-terminated mesopores. The interaction between long-chain carboxylate ions and binding sites like imidazolium, urea or thiourea surface-grafted on the pore outlets can be similarly exploited to manipulate the retention and delivery of guest molecules from mesoporous materials.[100] Oligonucleotide chemistry also provides versatile supramolecular tools to manipulate the gating properties of nanopore ensembles in the presence of specific ionic species. One remarkable example is the actuation of DNA-functionalized silica nanoparticles in the presence of mercuric ion ($Hg^{2+}$) in solution. Two DNA strands were designed by Zhang *et al.*[101] to cross-link on the surface of rhodamine 6G-loaded mesoporous silica in order to cap the pore. In the presence of traces of $Hg^{2+}$, one DNA strand with higher affinity to $Hg^{2+}$ was dehybridized from the other strand to uncap the pore, thus releasing the fluorescent dye from the pore voids. The DNA motif is very specific to $Hg^{2+}$ and rhodamine 6G release is only observed in the presence of this particular species. The generation of a measurable fluorescence signal in the presence of $Hg^{2+}$ provides the framework for the colorimetric detection of this toxic pollutant. In a rather similar way, Tang and co-workers[102] described the sensitive detection of lead ions using target-responsive cargo release from $Pb^{2+}$-specific DNAzyme-capped mesoporous silica nanoparticles. The strategy to create the $Pb^{2+}$-controlled gate-like nanopore ensemble involved the grafting of catalytic strands of $Pb^{2+}$-specific DNAzyme. Then, after loading the cargo molecules in the mesopore voids, the catalytic strand of DNAzyme was hybridized with the substrate strand. In this configuration the DNAzyme duplex formed on the pore entrance acted as a gatekeeper. In the presence of $Pb^{2+}$ ions, catalytic cleavage of the DNAzymes gave rise to the opening of the pore outlets and release of guest molecules from the pores.

In pioneering works, Martínez-Máñez and his co-workers[103,104] demonstrated how ionic interactions can control transport processes in gate-like molecular systems utilizing dye-loaded mesoporous silica nanoparticles functionalized on the pore outlets with polyamines. The interaction of protonated polyamines with bulky counterions led to a "shielding effect" controlling the access to the pores. The magnitude of this "shielding effect" was proportional to the ability of the anions to form strong ion pairs with the cationic polyamines. In a more comprehensive view, these ion-pairing interactions prompted the formation of a stopper network at the pore openings. Typically, the strongest ions pairs are formed by polyamines in the presence of large anions with low hydration energies. Bulky anions display stronger interactions with the protonated amines than small anions, leading to an ion-pairing efficiency sequence of adenosine triphosphate (ATP) > sulfate > chloride. In the presence of small anions, like $F^-$, $Cl^-$ or $Br^-$, the dye release kinetics was not affected by the presence of different counterions. However, in the presence of ATP no dye release was observed. These experimental observations demonstrate the versatility of noncovalent ionic interactions to modulate the response of gated delivery systems.

Özalp and Schäfer[105] described the construction of switchable ATP-responsive nanoensembles using fluorescein-loaded mesoporous particles which were modified on the external surface using an ATP binding aptamer sequence, *i.e.*: nucleic acids with biorecognition properties.[106] One of the remarkable aspects of aptamer sequences is that they undergo complex intramolecular structural switching upon binding the target

molecule. The conceptual framework developed by Özalp and Schäfer takes advantage of this feature to control the on–off states of the nanopores. Dimensions of the duplex DNA helix are about 2 nm in thickness whereas single-stranded DNA is of subnanometer size. Hence, DNA duplexes can operate as gatekeepers blocking the narrow pores of the mesoporous particles (~2.6 nm in diameter) and inhibit the delivery of entrapped molecules. These proof-of-principle studies demonstrated that the hairpin aptamer blocked the pores prior to addition of ATP, whereas the presence of ATP triggered the pore opening and hence release of dye probe molecules. Control experiments performed with an aptamer mutated in four nucleotides to obtain a sequence that was not responsive to ATP showed no evidence of dye release in the presence of the target molecule.

Calixarene and pillarene-based supramolecular nanovalves grafted on mesopore ensembles were chemically actuated in the presence of acetylcholine (Ach) as a competitive agent.[107] Indeed, experimental results demonstrated that not only competitive binding can turn on the supramolecular nanovalves to release the guest molecules from the pores but also weaker competitive binding of ACh towards macrocycles can prompt the cargo delivery. Pyridine-terminated mesoporous silica nanoparticles loaded with the dye rhodamine 6G (Rh6G) were capped with sulfonatocalix[4]arene (SC[4]A) or carboxylatopillar[5]arene sodium salt (CP[5]A) units. Rh6G release experiments in the absence and in the presence of different concentrations of ACh confirmed that this chemical stimulus can effectively trigger the cargo delivery with a negligible premature release due to nanovalve leakage. However, some differences between the release behavior of SC[4]A- and CP[5]A-capped systems were observed due to the differences in binding constants of inclusion complexes.

Noncovalent chemical stimulation of release processes from mesoporous silica particles has been exploited by Martínez-Máñez and his collaborators to devise and implement new strategies for the optical detection of explosives.[108,109] The core concept behind this method is that the interaction between the target analyte and the gated ensemble controls the release of a dye, which is ultimately translated into a measurable chromofluorogenic signal. In particular, mesoporous silica particles loaded with $[Ru(bipy)_3]^{2+}$ dye and capped with tetrathiafulvalene (TTF) derivatives were employed for turning-on the optical detection of nitroaromatic explosives (Fig. 10). TTF units form a dense network around the pore outlets precluding the release of $[Ru(bipy)_3]^{2+}$. In the presence of the target molecules, the strong interaction between the electron-deficient nitroaromatics and the electron-rich TTF subunits results in rupture of the TTF–TTF interactions giving rise to the gate opening with the concomitant release of the fluorescent dye. The same authors extended this approach through the replacement of TTF by bulky pyrene moieties around the pores with the aim of inhibiting the delivery of the dye.[110] In this new example the formation of pyrene–nitroaromatic complexes promoted the reorganization of the bulky caps from the pore outlets, thus triggering the delivery of the dye.

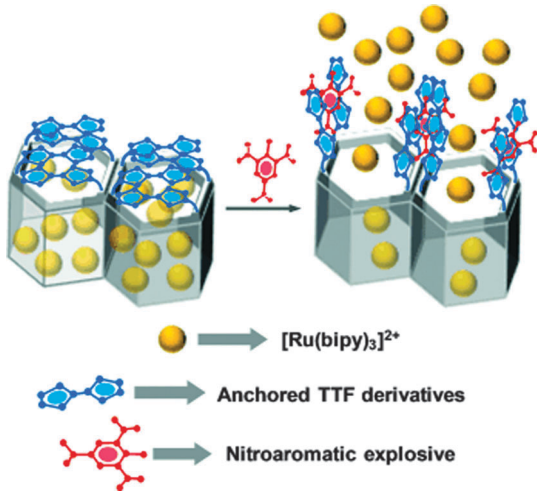


Fig. 10 Simplified scheme of the mesopore outlets capped with tetrathiafulvalene (TTF) units. Grafted TTF derivatives reorganize due to strong donor–acceptor interactions with nitroaromatic derivatives turning-on the release $[Ru(bipy)_3]^{2+}$ molecules hosted in the mesoporous framework. Reproduced with permission from Salinas *et al., Chem. – Eur. J.*, 2014, **20**, 855–866.Copyright 2014 Wiley-VCH Verlag GmbH & Co. KGaA.

## 3. Gatekeeping ensembles stimulated by physical signals

### 3.1. Thermally activated delivery systems based on mesoporous materials

The first example of mesoporous materials integrating thermoactive units with the aim of controlling their gating properties was reported by Lopez and his collaborators in 2003.[111,112] These authors based their approach on the surface-initiated atom transfer radical polymerization of poly(*N*-isopropyl acrylamide) (PNIPAM) brushes grafted from mesoporous silica particles. Uptake and release of rhodamine 6G from the mesoporous particles was monitored by flow cytometry, spectrofluorometry and confocal microscopy revealing that the presence of poly(*N*-isopropyl acrylamide) (PNIPAM) in the mesoporous material can be used to modulate the transport of aqueous solutes. PNIPAM brushes are hydrated and soluble in aqueous media below the lower critical solution temperature (LCST) of ~32 °C, but above the LCST, water is a poor solvent. This temperature-dependent solubility transition is commonly exploited to selectively switch the interfacial properties of PNIPAM-modified substrates. Below LCST, PNIPAM brushes are hydrated and extended and inhibit the transport of solutes. However, at higher temperatures the polymer collapses within the porous matrix and allows the release of the entrapped dye. Later on, Lin and co-workers[113] explored a similar concept using surface-initiated reversible addition–fragmentation chain transfer (RAFT) polymerization to finely tune the degree of polymerization on the exterior surface of the mesoporous silica nanoparticles. In a similar vein, Zink's group[114] reported the preparation of mesoporous thin films modified with [poly(*N*-isopropylacrylamide-*co*-acrylamide)] capable of acting as temperature-activated gatekeepers. Below the LCST the swollen polymer chains block

the transport through the pore openings whereas above LCST the collapsed polymer unblocks the pores, allowing the trapped molecules to escape into the solution. Within this framework it is important to note that the grafting density of the polymer chains can also play an important role on the gating characteristics of PNIPAM brushes. For instance, Oupicky *et al.*[115] showed that densely-grafted PNIPAM-modified mesoporous silica nanoparticles exhibit good uptake and release properties of fluorescein at room temperature (below LCST) and a low level of leakage above LCST. This experimental evidence suggests that fluorescein diffusion occurs readily when the polymer is in a hydrophilic extended conformation but is significantly retarded when the polymer is collapsed above LCST (Fig. 11). This mechanism of action in the hybrid mesoporous materials reported by Oupicky's group is clearly different from that reported by López and co-workers, where release was observed above LCST. According to these authors the densely grafted PNIPAM chains constitute the capping layer that prevents the uptake and release of cargo molecules when polymer brushes are collapsed on the nanopore outlets.

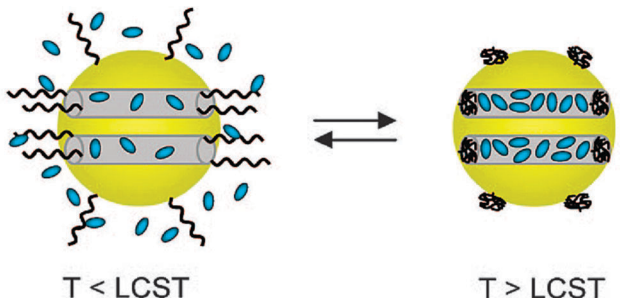


Fig. 11 Schematic representation of the principle of operation of delivery systems based on mesoporous silica particles capped with PNIPAM brushes. Reproduced with permission from You *et al.*, *Chem. Mater.*, 2008, **20**, 3354–3359. Copyright 2008 American Chemical Society.

Along these lines, Vallet-Regí and co-workers[116] described the use of mesoporous silica nanoparticles modified with poly(ethyleneimine)-*b*-poly(*N*-isopropylacrylamide) (PEI/NIPAM) presenting iron oxide nanocrystals inside the silica matrix as delivery platforms activated by magnetically-induced thermal changes. This hybrid system presents the ability to increase the temperature of the surroundings under alternating magnetic field due to the presence of trapped superparamagnetic iron oxide nanocrystals. As a consequence, conformational and polarity changes in the capping layer can be controlled by direct thermal stimulation as well as alternating magnetic fields. The magneto-thermal-induced release was demonstrated using fluorescein as a probe molecule entrapped in the mesoporous framework. Hybrid samples were exposed to an alternating magnetic field of 24 kA $m^{-1}$ and 100 kHz, in order to promote the heating of the surroundings above LCST and trigger the release of fluorescein from the mesopores.

From an alternative perspective, Martínez-Máñez and his collaborators[117] proposed the creation of customizable thermoactive nanocarries using paraffin-coated mesoporous materials. These materials were prepared using mesoporous silica nanoparticles functionalized with octadecyltrimethoxysilane and capped with paraffins, which are able to form a hydrophobic capping layer that hinders the diffusion of the cargo molecules. A temperature increase above the paraffin melting point prompts the release of the entrapped molecules. For instance, the use of paraffins exhibiting different melting points, *e.g.*: heneicosane or tetracosane, facilitates the fine tuning of the thermal trigger over a wide range of working temperatures, and presets the uncapping process at a given temperature (Fig. 12).

Biological building blocks have been used successfully for creating thermoactive nanogates in mesoporous materials.

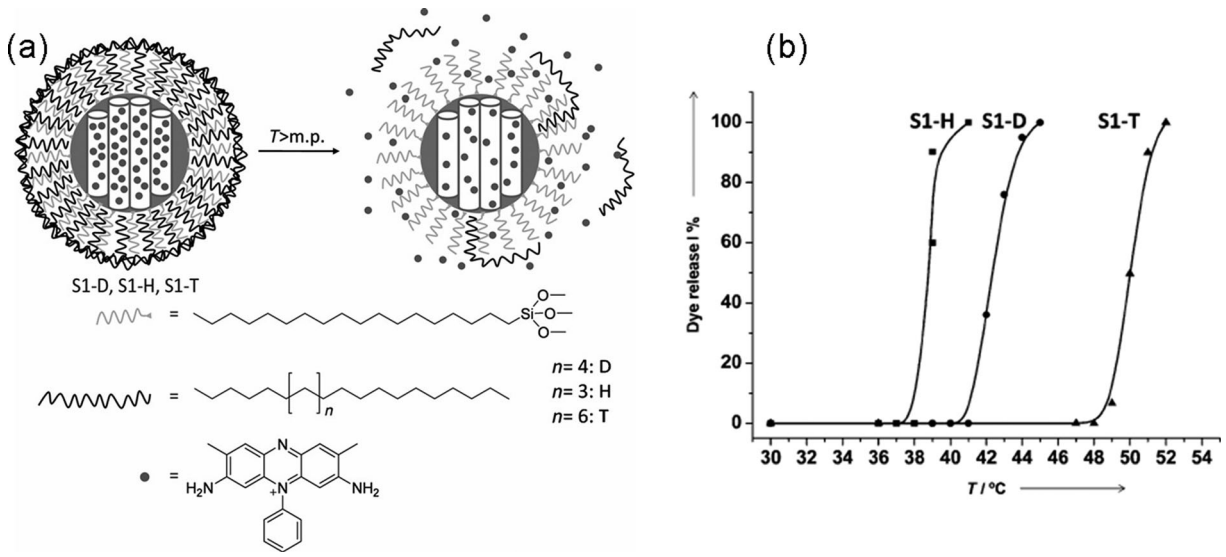


Fig. 12 (a) Principle of operation and schematic representation of the mesoporous particles functionalized with octadecyltrimethoxysilane and capped with paraffin. (b) Release profile of mesoporous particles capped with heneicosane (S1-H), docosane (S1-D) and tetracosane (S1-H) at different temperatures. The delivery of the dye safranine O is triggered when temperature rises above the paraffin melting point. Reproduced with permission from Aznar *et al.*, *Angew. Chem., Int. Ed.*, 2011, **50**, 11172–11175. Copyright 2011 Wiley-VCH Verlag GmbH & Co. KGaA.

Very recently, de la Torre *et al.*[118] reported an interesting strategy to design gated mesoporous particles in which peptides can act as thermoactive molecular gates. The mechanism of action in these hybrid materials is based on the well-known temperature controlled α-helix-to-disordered structural transformation that takes place in certain peptides. Biomacromolecular reorganization in α-helical bundles blocks the pore outlets and hinders cargo delivery, whereas a disordered conformation reduces the steric crowding around the pore entrance which permits the diffusion of the cargo molecules into the solution. As a proof of concept, these authors used mesoporous silica nanoparticles loaded with safranin O and a capping peptide sequence based on a self-aggregating 17-mer peptide anchored onto the external surface. Fluorescence measurements confirmed that no dye release occurs over the temperature range in which the peptide exhibits the α-helix conformation. However, cargo delivery was observed under thermal conditions triggering the peptide structural conformation from α-helix to a random coil.

Oligonucleotides were also used as thermoresponsive units in the construction of mesoporous delivery platforms. Bein *et al.*[119] described a molecular valve that releases entrapped fluorescein upon heating to the specific melting temperature of double-stranded DNA sequences that are attached to the pore openings of mesoporous nanoparticles. More recently, Tang and co-workers[120] reported a novel approach to construct temperature-responsive nanocarriers for controlled release based on mesoporous silica modified with reversible single-stranded DNA "valves". To achieve this goal, carboxyl-terminated single-stranded DNA units were conjugated to amino groups exposed on the surface of amino-modified mesoporous particles. Due to electrostatic interactions negatively charged DNA adsorbs on the amino-terminated surface, resulting in the "off" state of the nanogate. As temperature increases the thermal energy overcomes the electrostatic interactions between mesoporous silica and DNA strands, leading to the "on" state of the valves and the concomitant release of the cargo molecules from the mesoporous matrix. Then, upon decreasing temperature, electrostatic interactions again dominate the assembly/adsorption of DNA strands on the mesopores and the system is switched back to the original state. This process leads to the capping of the pores and inhibits the delivery of hosted molecules. The critical temperature for opening the DNA-based nanogates can be controlled by adjusting the length of the grafted oligonucleotides.

### 3.2. Light-activated gating in mesoporous materials

Light is one of the least invasive stimuli available in order to elicit responsive behavior. For this reason, light-driven chemical transformations represent an appealing strategy to attain precise external modulation of chemical changes in mesoporous materials. Indeed, light can approach materials in a noncontacting manner also, permitting various types of modulations in terms of intensity and energy, as well as multiplexed excitation or detection. First attempts to control molecular transport in mesoporous materials using photo-responsive molecular arrays were reported by Fujiwara *et al.* a decade ago.[121] These authors showed that the uptake, storage and release of organic probe molecules in MCM-41 can be regulated through the photo-controlled and reversible intermolecular dimerization of coumarin derivatives attached to the pore outlets. The photodimerization promotes the closure of the pores by formation of a cyclobutane dimer spanning the pore diameter. Then, the pore could be re-opened by light irradiation at 250 nm to regenerate the coumarin monomer by photocleavage of the dimers. More recently, coumarin-modified mesoporous materials have been used as anticancer drug release platforms regulated by either one- or two-photon processes.[122]

Azobenzene-based molecules represent another class of molecular systems compatible with the design of mesoporous materials with photoactive response. Brinker and coworkers produced photoresponsive mesoporous silica thin films modified with azobenzene ligands.[43] Size-selective photoregulated mass transport through the membrane to the electrode surface was observed for two ferrocene-based molecular probes (ferrocene dimethanol and ferrocene dimethanol diethylene glycol). This work demonstrated that the optically switchable conformation (*trans* or *cis*) of azobenzene ligands controls the effective pore size which in turn rules the transport behavior on the nanoscale.[44] Zink and co-workers prepared light-responsive mesoporous silica particles displaying azobenzene derivatives anchored on the particle surface.[123,124] Azobenzene moieties were positioned in the pore interiors with one end attached to the pore walls and the other end free to undergo photoisomerization Exposure of the mesoporous materials to 413 nm light triggers the photoisomerization of the azobenzene moieties that act as "impellers" and expel the probe molecules out of the pores. In this way, the release properties can be manipulated by varying both the light intensity and the irradiation time. The same group developed another strategy to create reusable nanovalves based on the association and light-operated dissociation of the α-CD[125] and β-CD[126] rings with the azobenzene-containing stalks on the surfaces of the MCM-41 nanoparticles.

Yuan *et al.*[127] reported the light activated gating of mesoporous materials using azobenzene-modified nucleic acids. In this system, the azobenzene-incorporated DNA double strands were immobilized at the pore mouth of mesoporous silica nanoparticles (Fig. 13). The photoisomerization of azobenzene induced dehybridization/hybridization switch of complementary DNA, causing the uncapping/capping of the pore gates. These DNA–azobenzene/mesoporous silica hybrid materials were shown to be an efficient reversible photoregulated release platform capable of delivering doxorubicin (DOX) on demand. Croissant *et al.*[128] recently reported the synthesis of nanoimpellers functionalized with a two-photon fluorophore exhibiting a high two photon absorption cross-section.[129] These molecular assemblies are suitable for Förster resonance energy transfer (FRET) to photoizomerize azobenzene moieties in the near infrared (NIR) region. The nanoimpellers grafted on the porous framework permit the physical confinement of the drug molecules, which are then released from the mesoporous matrix by two-photon-triggered photoisomerization.

Another appealing strategy relies on the use of upconverting nanoparticles (UCNPs) to active photochemical processes in a

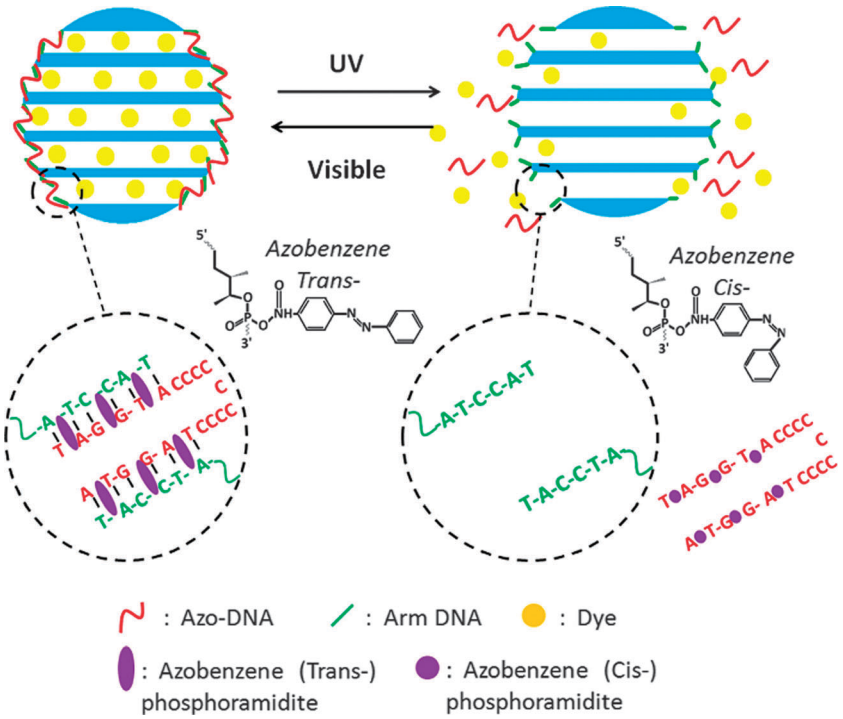


Fig. 13 Principle of operation of azobenzene-modified DNA-controlled reversible mesoporous release system. Visible light irradiation at 450 nm brings about the hybridization of the linker and the complementary DNA strand. UV irradiation at 365 nm converts azobenzene units to the cis form, leading to dehybridization and the pore opening. Reproduced with permission from Yuan *et al.*, *ACS Nano*, 2012, **6**, 6337–6344. Copyright 2012 American Chemical Society.

controlled manner. UCNPs based on lanthanide ions are able to absorb NIR light and convert it into high energy photons in a broad energy range from the UV to the NIR region. Such unique photophysical properties of UCNPs have been employed by Shi and co-workers to trigger the release of anticancer drugs using NIR light. Their strategy consisted of coating core–shell UCNPs with mesoporous silica, which is then functionalized with azobenzene groups at the mesopore entrance. Using 980 nm light Liu *et al.* showed that the amount of the released anticancer drug can be well controlled by varying the intensity and/or time duration of NIR light irradiation.[130] Stoddart and Zink and collaborators[131] described the use of supramolecular nanovalves constructed from [2]pseudorotaxanes to create light responsive gates. The [2]pseudorotaxane [BHEEENδ CBPQT]$^{4+}$ [BHEEEN ≡ 1,5-bis[2-(2-(2-hydroxyethoxy)ethoxy)ethoxy]naphthalene and CBPQT4+ ≡ cyclobis(paraquat-*p* phenylene)] is tethered on the surface of the mesoporous silica and it constitutes the supramolecular nanovalves. The mesoporous silica is also modified with built-in photosensitizers. Upon irradiation with laser light of an appropriate wavelength, the excited photosensitizers transfer electrons to the CBPQT$^{4+}$ rings, reducing them so that they dissociate away from the BHEEEN stalks on the surface of the mesoporous silica particles, thus leading to a controlled release of the luminescent probe molecules.

Knežević *et al.*[132] exploited the light induced cleavage of coordination compounds to trigger the release of cargo molecules from mesoporous materials. These authors used sulforhodamine 101 dye loaded into the mesopores of mercaptopropyl-functionalized mesoporous silica nanoparticles. These probe molecules were confined inside the mesoporous space by addition of [Ru(bpy)$_2$(PPh$_3$)Cl]Cl, a compound that forms coordination bonds with mercaptopropyl moieties from the silica surface, and prevents the release of the cargo molecules. Exposure to visible light led to the cleavage of the gatekeeper and the release of the cargo molecules into the particle suspension.

Decoration of mesoporous silica nanoparticles with singlet oxygen sensitive linkers can be a plausible strategy to manipulate the release properties of mesoporous particles. To achieve this goal, it is necessary to integrate long-wavelength light photosensitizers and singlet oxygen sensitive crosslinkers into mesoporous particles.[133] Electrostatic repulsions between the host and cargo molecules promoted by light irradiation can be a triggering factor to deliver doxorubicin (DOX) from mesoporous matrices. DOX is known for its ability to strongly attach to the silica surface, due to formation of strong hydrogen bonds and charge interaction with surface silanols. DOX was adsorbed on nitroveratryl carbamate protected aminopropyl-functionalized mesoporous silica nanoparticles. Upon exposure to UV light positively charged propylammonium moieties were formed on the nanoparticle surface, which promoted the desorption of positively charged doxorubicin molecules from the nanoparticle surface.[134]

The use of photo-cleavable molecular arrays has been also exploited by Martínez-Máñez and his co-workers[135] to attain the controlled release of cargo molecules from mesoporous systems capped with photo-cleavable *o*-methoxybenzylamine moieties.

 

The photo-cleavable group is bulky enough to preclude the release of the entrapped probe molecules. However, upon UV irradiation the photocleavage eliminates the steric hindrance and facilitates the release of the entrapped dye. In a similar way, Brunsen *et al.*[136] demonstrated that photocleavage of poly2-[(4,5-dimethoxy-2-nitrobenzoxy) carbonyl] aminoethyl methacrylate (PNVOCAMA) brushes grown atop mesoporous platforms can be exploited as macromolecular gates to trigger the perm-selective transport of charged species through the mesoporous environment.

Light-induced chemical transformations generating local pH changes have been also exploited to trigger the release of probe molecules. Malachite green carbinol base (MGCB) molecules were anchored on mesoporous substrates as a light-induced hydroxide ion generator whereas i-motif DNA assemblies were grafted on the same surface as a capping agent (Fig. 14).[137] MGCB molecules dissociate into malachite green (MG) cations and $OH^-$ ions upon irradiation with 365 nm UV light. This photochemical process induces the i-motif DNA to unfold into the single-stranded form due to the increase of the local pH. As a result of the i-motif unfolding, the pores are uncapped and the confined probe molecules are released. It is interesting to note that after the light is turned off local pH changes are reversed, *i.e.*: malachite green cations recombine with the $OH^-$, and the single-stranded DNA switches back to i-motif structure, which in turn leads to the reversible capping of the pore.

The use of supramolecular machineries of higher complexity displaying light responsiveness represents an attractive scenario to control the release of drugs from mesoporous particles. Zhao and collaborators[138] described the gating of mesopores functionalized with [2]rotaxanes in which the α-CD rings were threaded with a linear photothermal-responsive azobenzene moieties. These authors exploited the back and forth movement of α-cyclodextrin rings originating from the photothermal-induced reversible *trans–cis* isomerization of the azobenzene moieties to control the on/off gating mechanism of the pore entrance. This strategy has been successfully used for *in vivo* release of curcumin into zebrafish embryos.

Light-responsive nanocarriers based on mesoporous silica nanoparticles modified with spiropyran-containing light-responsive copolymers were reported by Xing *et al.*[139] The spiropyran-containing amphiphilic copolymer was able to shift its hydrophilic–hydrophobic balance to become hydrophilic upon UV irradiation and then break away from the mesopore surface. This UV-induced interfacial reorganization process is accompanied by the uncaging and release of the pre-loaded drugs.

Very recently, Wan and collaborators[140] described the preparation of photo-degradable, protein–polyelectrolyte complex (PPC)-coated mesoporous silica nanoparticles as versatile platforms to attain controlled co-release of proteins and model drugs in different settings. Random copolymers composed of oligo(ethylene glycol) monomethyl ether methacrylate (OEGMA), and a photolabile *o*-nitrobenzyl-containing monomer were first grafted onto the mesoporous nanoparticles and then quaternary aminated to obtain positively charged copolymers exhibiting photo-induced charge conversion characteristics. A combined assembly of the photoactive copolymer and bovine serum albumin (BSA) was utilized as the capping layer for the mesopores. Upon UV irradiation, charge conversion of copolymers led to the disruption of the capping assembly on the mesopores and the subsequent release of the trapped cargo molecules and BSA by electrostatic repulsion.

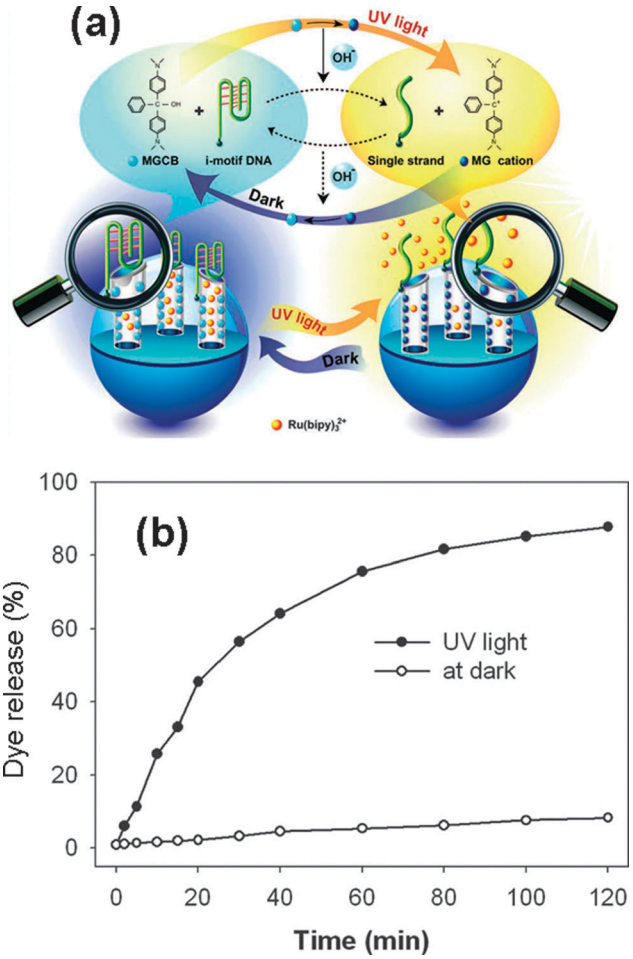


Fig. 14 (a) Light-induced release of $[Ru(bipy)_3]^{2+}$ molecules from the mesopores of silica particles capped with i-motif DNA. The conformational switch is associated with the UV light-induced formation of hydroxide groups from malachite green carbinol base (MGCB) provided that the i-motif DNA unfolds due to the increase of the local pH. (b) Release profile of $[Ru(bipy)_3]^{2+}$ molecules in the dark and with UV light. Reproduced with permission from He *et al.*, *Adv. Funct. Mater.*, 2012, **22**, 4704–4710. Copyright 2012 Wiley-VCH Verlag GmbH & Co. KGaA.

A light-responsive release system based on mesoporous particles was achieved by adjusting the wetting properties of the mesoporous surface. The mesoporous materials were modified with a mixed assembly of spiropyran moieties and fluorinated silane in such a way of attaining a mesopore surface that is protected from being wetted by water. This non-wetting surface was able to inhibit the release of fluorescein disodium (FD, a cargo probe molecule). Upon irradiation with 365 nm UV light, the conformational conversion of spiropyran from a "closed" state to an "open" state caused the surface to be wetted, leading to the release of FD from the pores.[141]

Light can be also used as an indirect driving force to trigger a secondary stimulus. Photo-thermal effects are probably the most prominent examples of this type of combined stimuli. Compared to UV light, near-infrared (NIR) light is much less damaging to biological specimens and living tissues as well as has remarkably deeper tissue penetration. In the past few years, much interest has arisen in the use of near-infrared light responsive mesoporous architectures to trigger the release of drugs in different environments. A pioneering work by Croissant and Zink[142] gave an important thrust to the molecular design of delivery platforms based on ''plasmonic heating'' of nanomaterials. By using hybrid nanoparticles consisting of gold cores inside mesoporous silica spheres they designed a light operated nanovalve capable of controlling the pore openings of mesoporous silica. The nanovalves consisted of cucurbit[6]uril rings encircling stalks that were anchored to the narrow pore openings. The mechanism of operation of the molecular machine relies on temperature-dependent noncovalent interactions between the stalk and the cucurbit[6]uril ring. Plasmonic heating of the gold core raises the local temperature and decreases the ring–stalk binding constant, thereby unblocking the pore and releasing the cargo molecules that were preloaded inside. These authors demonstrated that low-intensity illumination is sufficient to operate the valves without damaging the nanoparticle containers. Very recently, Yang *et al.*[143] reported the use of gold nanorods incorporated within a mesoporous silica particle that was surface-functionalized with aptamer DNA as a near-infrared light responsive drug delivery platform. They showed that upon application to NIR light, the photothermal effect of the gold nanorods was able to trigger a rapid rise in the local temperature (photoenergy is converted to photothermal energy). The local thermal change prompted the dehybrization of the DNA duplex to release the G-quadruplex. As a result the mesopores are spontaneously unblocked facilitating the release of the entrapped probe molecules. A rather similar concept was also employed by Zheng and collaborators to photo-stimulate the release of DOX from mesoporous silica-coated Pd@Ag nanoparticles.[144]

# 4. Bioresponsive releasing systems based on mesoporous silica particles

## 4.1. DNA-gated mesoporous materials

The use of oligonucleotides as ''bioresponsive'' capping agents on the surface of mesoporous silica particles was initially put forward in 2010 by Martínez-Máñez and his collaborators.[145] The operation principle and the preparation protocols are very simple but very effective and specific. Aminopropyltriethoxysilane-modified mesoporous particles are loaded with the guest molecules, *i.e.*, fluorescein. Under neutral pH conditions the amino groups in the periphery of the particles are partially charged and interact with negatively charged oligonucleotides, resulting in the formation of an electrostatically assembled capping layer closing the pore outlets. In the presence of the complementary oligonucleotide strand, the hybridization of both strands takes place resulting in the removal of the capping layer from the pore entrances and the concomitant release of the hosted fluorescent dye. This type of gating mechanism based on the use of oligonucleotide recognition was further extended by the same group to the highly sensitive and rapid detection of *Mycoplasma* in contaminated cell-culture media, allowing a limit of detection of 70 DNA genome copies per microliter.[146] Zhang *et al.*[147] reported the creation of multi-responsive DNA-gated mesoporous silica nanoparticles functionalized with disulfide-linked acridinamine intercalators. Native duplex DNA was tethered to calcein-loaded mesoporous particles modified with disulfide-linked acridinamine derivatives through intercalative binding. In this design procedure tethered duplex DNA play a role as a biocompatible multi-responsive gatekeeper meeting multiple requirements of stimulated release. In the presence of disulfide reducing agents, like dithiothreitol or glutathione, the disulfide bonds were cleaved, resulting in the removal of the capping DNA layer and the release of the calcein from the pores. At elevated temperatures ($\sim$50 °C) duplex DNA can be dehybridized into single-stranded DNA, resulting in opening of the pores. On the other hand, in the presence of endonucleases, like DNase I, DNA strands are cleaved giving rise to the release of guest molecules from the pores.

Aptamer–target interactions have been used to create bioresponsive controlled-release mesoporous nanovehicles.[148] The supramolecular construction of such architectures involves the integration of metal nanoparticles as capping agents and aptamers as biorecognition elements. Mesoporous silica particles were functionalized with a derivative of the ATP molecule and their pores were capped by mixing the fluorescein isothiocyanate-loaded particles with Au nanoparticles functionalized with an ATP aptamer (Au-aptamer). Stimulated delivery of fluorescein was investigated by addition of ATP molecules to a solution containing the capped mesoporous particles. In the presence of target molecules, the association between the mesoporous particle and the Au-aptamer was disrupted through a competitive displacement reaction with the concomitant release of the fluorescent dye from the particle. Aptamer-mediated release from mesoporous particles was also investigated by Martínez-Máñez and co-workers.[149] Mesoporous silica nanoparticles loaded with rhodamine B were functionalised with 3-aminopropyltriethoxysilane. Thereafter, the negatively charged thrombin-binding aptamer (TBA) was electrostatically assembled onto the amino-terminated scaffold that is partially charged under neutral conditions. The assembled TBA aptamer constitutes the capping layer of the loaded nanovehicle that is displaced from the pore outlets as a consequence of the aptamer–thrombin recognition process. Fluorescence measurements confirmed that the release of the dye was induced when the target molecule, *i.e.*: α-thrombin, was present in the solution. Duplex DNA structures that included in one of the strands the adenosine 5′-triphosphate (ATP)–aptamer sequence were used to block the pore outlets of mesoporous particles. The formation of the ATP–aptamer complex released one of the strands, thus leading to the opening of the pores and the release of the entrapped payload.[150] More recently, DNAzyme–substrate

 

complexes were used to lock the pores of the mesoporous particles and release the substrates upon the addition of the DNAzyme cofactor, *e.g.*, $Mg^{2+}$ or $Zn^{2+}$ ions.[151]

### 4.2. Enzyme-responsive mesoporous platforms

The use of enzymatic processes to control the opening of capped mesoporous materials has received increasing attention during recent years. In a first attempt Zink and Stoddart and co-workers[152] loaded mesoporous silica particles with rhodamine B as guest molecules, and functionalized the external mesoporous surface with [2]rotaxanes constituted of an inclusion complex of α-cyclodextrin and tethered polyethyleneglycol units capped with an ester-linked adamantyl stopper. These nanomaterials retained the guest molecules until the incorporation of porcine liver esterase that cleaved the adamantyl ester and induced the dethreading of the [2]rotaxane with the concomitant release of the cargo molecules.

Since then, the use of estearase to uncap nanopores through the cleavage of ester bonds in the capping layer has been employed by different groups as a general strategy to trigger the delivery of the payload. Capping layers constituted of sulfonatocalix[4]arene [2]pseudorotaxanes with ester-linked stalks,[153] polyesters bearing azobenzene derivatives[154,155] or even ester glycol derivatives[156] were able to block the delivery of guest molecules due to the steric hindrance imposed by the bulky molecular units. However, the presence of estearase enzyme gave rise to the release of the cargo molecules due to the cleavage of tethering sites in the stalk components of the supramolecular nanovalves or the progressive hydrolysis of the grafted polymeric chains.

Bein's group[157] described the controlled release of fluorescein molecules using biotin–avidin assemblies as enzyme responsive capping layers assembled on the surface of mesoporous particles. Biotinylated mesoporous particles were loaded with fluorescein and capped with avidin through the formation of very stable biotin–avidin complexes that prevented the fluorescent dye from escaping from the pore voids. Addition of protease trypsin to the mesoporous particle suspension initiated the proteolytic digestion of the capping layer, *i.e.*: avidin, enabling the release of the dye from the mesoporous framework. In parallel, Bernardos *et al.*[158] reported the preparation of lactose-capped mesoporous silica particles that were selectively uncapped using the glycoside hydrolase β-D-galactosidase through the rupture of glycosidic bonds on the pore outlets. The modification of the external surface of mesoporous silica particles with lactose derivatives precluded the release of $[Ru(bipy)_3]^{2+}$ molecules stored in the mesoporous particles due to the formation of a network of disaccharides interconnected *via* hydrogen bonding interactions around the pore outlets. The lactose derivative consisted of β-D-galactose and β-D-glucose monosaccharides linked through β1 → 4 glycosidic bonds. The addition of β-D-galactosidase led to the hydrolysis of these 1 → 4 glycosidic bonds, thus promoting the gradual degradation of the bulky gatekeeper and the subsequent release of the guest. In an example of the latter approach the same group functionalized the pore outlets of mesoporous materials with different carbohydrate derivatives which were cleaved in the presence of enzymes like pancreatin or β-D-galactosidase to release drugs like doxorubicin in a controlled fashion.[159]

By using the same conceptual framework these authors prepared safranine O-loaded mesoporous silica particles modified with *N*-(3-triethoxysilylpropyl)gluconamide. In the absence of the target enzymes, the release of the dye from the aqueous suspensions was inhibited as a result of the steric hindrance imposed by the bulky dense hydrogen-bonded network of the gluconamide derivative. However, the addition of amidase or pronase to the suspension led to the enzymatic hydrolysis of the amide bond in the anchored gluconamide derivatives with the subsequent delivery of the payload. These gluconamide-gated nanomaterials were employed to deliver cytotoxic drug camptothecin into HeLa cells. Experimental results demonstrated cell death of tumoral cells as a result of material internalization and ulterior cellular enzyme-mediated hydrolysis in the presence of lysosomal enzymes leading to the release of the camptothecin cargo.[160] In a similar way, taking advantage of the overexpression of endogenous lysosomal β-galactosidase that specifically occurs in senescent cells Martínez-Máñez and collaborators designed mesoporous silica particles capped with galacto-oligosaccharides for the targeted cargo delivery of probe molecules into these cellular systems.[161] More recently, Qu and co-workers[162] described a rather similar strategy employing mesoporous silica capped with Konjac oligosaccharide "gatekeepers" which can be degraded in the presence of β-mannanase to release the cargo molecules hosted in the porous framework.

Fluorenylmethoxycarbonyl (Fmoc) chemistry was utilized to generate bioactive peptide shells that acted as specific gatekeepers on the outer surface of mesoporous particles.[163] Confinement inside the pores was attributed to two factors: π–π interactions between adjacent Fmoc groups causing the closing of the pore and the presence of bulky Fmoc groups that physically prevent the release of cargo molecules into the solution. The principle of action of this particular setting relied on the enzymatic cleavage of the peptide sequence in the presence of thermolysin that resulted in the removal of Fmoc groups and the opening of the gate to enable the diffusion of cargo molecules from the particle core into the solution. In a similar vein, Coll *et al.*[164] demonstrated that anchoring complex peptide sequences on gatelike scaffolds can be a valuable strategy to develop nanoensembles with transport properties activated by targeted proteolytic enzymes (Fig. 15). By using the modular peptide H-GGDEVDGGDEVDGGDEVD-OH as a substrate of the proteolytic enzymes obtained from *Streptomyces griseus* these authors showed that long modular protease-sensitive peptides grafted on the pore outlets through a "click" chemistry approach can regulate the delivery of cargo molecules in the presence of very specific enzymatic stimuli.

Hanagata and co-workers[165] designed and constructed enzyme-responsive nanovehicles for codelivery of drug and gene using mesoporous particles modified with degradable multilayer assemblies. Fluorescein-loaded mesoporous silica particles were modified with layer-by-layer assemblies of positively charged poly(L-lysine) (PLL) and negatively charged cytosine-phosphodiester-guanine

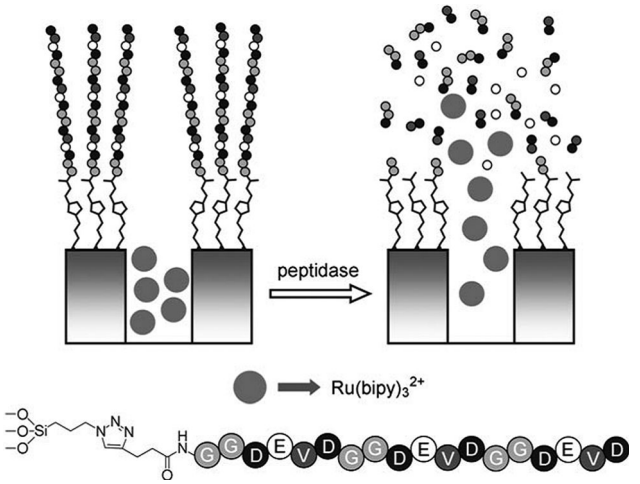


Fig. 15 Representation and principle of operation of the mesoporous silica functionalized with 3-(azidopropyl) triethoxysilane and capped with the peptide. The C-terminus amide bonds of the negatively charged amino acids contained in the peptide are cleaved in the presence of the enzyme peptidase. This enzymatic process uncap the mesopores and triggers the release of $[Ru(bipy)_3]^{2+}$ molecules from the pores. Reproduced with permission from Coll *et al., Angew. Chem., Int. Ed.*, 2011, **50**, 2138–2140. Copyright 2011 Wiley-VCH Verlag GmbH & Co. KGaA.

oligodeoxynucleotide (CpG ODN). Addition of α-chymotrypsin to a suspension of these hybrid particles promoted de enzymatic degradation of the PLL layers giving rise to the disassembly of the capping multilayer with the concomitant release of CpG ODN and fluorescein into the aqueous solution. Similarly, Mondragón *et al.*[166] has shown that ε-poly-l-lysine polymers covalently anchored onto the external surface can act as gatekeepers and deliver the entrapped guest in the presence of proteases and lysosomal enzymes. On the other hand, CpG ODN layers electrostatically assembled on fluorescein-loaded amino-functionalized mesoporous silica particles have been used as biodegradable capping layers in enzyme-triggered drug delivery systems.[167] In this case the uncapping process was triggered by the addition of deoxyribonuclease I (DNase I) that promoted the degradation of the CpG ODN layer, thus allowing the release of the cargo molecules from the mesopores. Hyaluronic acid (HA)-capped mesoporous silica particles also represents a valuable platform for the design of enzyme-responsive nanoreservoirs for efficient targeted drug delivery to cancer cells. Qu *et al.*[168] demonstrated that cargo release can be triggered by HA degradation in the presence of lysosomal enzyme hyaluronidase-1 (Hyal-1), which is the major enzyme found in the tumor microenvironment.[169]

Very recently, Willner and his collaborators[170] reported the gating of mesoporous materials through the coupling of recognition and biocatalytic effects. The principle of operation is based on the use of tailored nucleic acid as capping layers to block the pore outlets of the nanoparticles. The unlocking process is governed by analyte-induced rearrangements of the nucleic acid caps that undergo catalytic fragmentation in the presence of Exo III or a nicking enzyme. In other words, the recognition events of an analyte transform the capping element into a new functional element that undergoes biocatalytic scission to trigger the cargo release.

# 5. Closing remarks and outlook – moving forward and opening up new doors in integrative design of gated mesoporous materials

*"The noblest pleasure is the joy of understanding"*
Leonardo da Vinci

The emerging field of "gated nanochemistry" is soundly based upon the efforts of two communities that have made impressive progress in the last twenty years: mesoporous materials and soft matter. During this time, chemists and material scientists improved their collective understanding as well as developed new skills in their respective fields. In little more than a decade after the first reports in this subject were published, materials chemistry of responsive mesoporous systems became a mature discipline with high standards and challenging goals. The successful synergy between sol–gel techniques, self-assembly, polymer synthesis, surface engineering and physical chemistry in confinement represents a unique and versatile toolbox to achieve the building up of complex nanosystems with well defined physical and chemical properties at several length scales: molecular, supramolecular and mesoscopic.

The integration of switchable, stimuli-responsive units in the surface or mesopore space of these materials constitutes an important foundation for the development of gated delivery or perm-selective devices able to respond to specific chemical, physical and/or biological inputs. These advanced materials can actually behave as abiotic pores with properties akin to the pore systems found in Nature. A palette of different approaches has been developed that facilitates the production of nanosystems responsive to environmental variables (pH, redox potential, ionic strength, the concentration of a particular molecule or ion), physical stimuli (light, temperature, electric fields) and the presence of biomolecules such as DNA or enzymes. In all these cases, imparting functionality to these systems relies in the control of the whole material. We can distinguish in principle two spatial domains that are relevant, and often have to be separately designed and built in order to achieve a functional material: the outer surface, which defines the interactions with the medium, and the mesopore nanospace, which defines the payload content and the confinement-derived properties.[171] This latter concept is understood as the whole pore identity, reflected in the control of the pore wall composition, pore surface and the whole pore volume. Therefore, a major issue is the development of orthogonal chemical strategies to separately functionalize the outer surface and pore interior. This has been achieved by different routes: (a) exploiting size differences (polymer or nanoparticle capping), (b) performing outer surface functionalization while blocking the mesopores with the template (surface passivation), (c) exploiting a combination of selective reactions and diffusion (delayed reactivity),[17,18] (d) resorting to multilayer or core–shell systems with well defined regions presenting different reactivity.[27] It is important to stress that both types of surfaces (*i.e.*: outer and inner pore surfaces) constitute by themselves regions or domains that can

 

lead to enhanced properties; for example, preconcentration of molecules can be achieved through adsorption, or by partition into the new phase resulting from preferential adsorption on any specific surface. In this context, although a wealth of successful synthesis paths have been reported, the molecular engineering of surfaces is a crucial field that requires systematic research in order to fully understand the physico-chemical phenomena (*i.e.*, selective reactivity, surface self-assembly, partition phenomena) that will permit to design nanosystems with precise chemical positioning.

A second issue is the design of the functional mesoporous matrices, including the inorganic framework and the channel systems. A great number of well developed strategies have been reported for the production and functionalization of mesoporous materials maintaining tight control over the pore geometry, interconnectivity and size. In addition, essential to responsiveness is the control of surface functionality and/or chemical speciation of the surface functions. Surface charges also play a critical role in molecular transport of ionic species provided that typical dimensions of mesopores are comparable to the Debye length in solution. This leads to charge-selective transport properties associated with enhancement and depletion phenomena in confinement, in close resemblance to those typically observed in nanofluidic devices.[172–178] The actual chemical identity and properties of the surface grafted groups strongly depend on the interaction balance between the adsorbed or grafted groups and their pH-dependent chemical speciation, which is evident in the case of silanols.[179] A palette of functional engineering techniques has been developed that permit to position different functional groups within the mesopores with precise distances between them, either by exploiting selective reactivity, assembly, masking techniques, self-assembly or the use of silanes.[180–182] It is interesting to note that the field of mesoporous material synthesis and functionalization is well developed and, concomitantly, a generous toolbox is ready for specific applications. In addition, the wide palette of supramolecular approaches towards mesopore functionalization either by adsorption, capping, charge matching or brush synthesis permits to develop tailoring strategies only limited by the imagination. Again, in this area, fundamental studies are required to optimize the polymer loading and positioning, and use the forces of self-assembly and preconcentration within pores as synthetic tools. Finally, although most of the studies presented here relied on well-known silica matrices such as MCM-41 and SBA-15, which present highly reproducible synthetic protocols and have demonstrated low cytotoxicity, a wealth of non-silica oxides, phosphates, carbons and polymers is ready to enter the world of gated materials.[183] This is particularly interesting in order to impart new properties stemming from the use of transition metal oxide matrices with semiconducting or magnetic properties (*e.g.*, photoactivation, magnetism, charge localization, *etc.*).

A key point to note in gated nanomaterials is the design and optimization of the stimulus-to-signal transduction. To this end, several methods have been implemented to translate the external solicitation into a response of the system. This implies exploiting spatial and physico-chemical effects that are particular to mesoscale, and which can be summarized as ''meso-stereochemical effects''. The response is coded in the overall synergy between the molecular components, the mesopore space and the surface, and generally implies control of: (a) steric hindrance, (b) equilibrium displacement in confined systems, (c) changes in charge distribution within the Debye layer, (d) changes in local environment, (e) swelling, (f) electron transfer, (g) local heating, and so on. Possible new responses to other solicitations may be achieved by using new inorganic frameworks that present electron transfer, catalytic or photo-responsive behaviour. In addition, the use of asymmetric building blocks can bring forth the possibility of using light polarization or frequency doubling as a coding or stimulus for remote stimulation applications. The coding of chemical signals caged on the mesopore walls combined with mesopore patterning permits to envisage the upcoming of artificial synapses or other biomimetic systems.

Last, but not least, it has to be stressed that although most synthetic strategies converge into mesoporous particles for targeted drug delivery, soft chemical processing methods allow for the combination and integration of these building blocks in a variety of responsive materials such as films, gels, fibers or even micro- or nanofluidic devices. In this case, the responsive system is part of a hierarchical material that incorporates other functionalities such as tissue compatibility or controlled swelling. The design of responsive scaffolds for ''on-command'' delivery that incorporate gated mesoporous silica nanoparticles and can activate bone growth is an interesting recent example.[184] The available complexity of these systems is growing day by day, and a ''nano-building block approach'' is now feasible. It is expected that these intelligent mesosystems will have profound implications in future technologies, not only in the initially endeavored gated drug delivery and sensing/nanofluidics fields, but also in energy, food and environment technologies.

In summary, the tailored coupling of mesoporous and supramolecular building blocks permits the creation of porous networks with physical properties or (bio)chemical functions which can show noticeable changes in their properties upon exposure to environmental stimuli. Throughout the (relatively) brief history of gated mesoporous materials, one of the key drivers has been the quest for strategies to achieve a molecular-level control over the modification of the mesopore surface in order to suit specific needs. To reach this goal, mesoporous silica architectures have been modified by a number of sophisticated molecular assemblies that not only involve organic molecules and supramolecular motifs, but also nanomaterials and biomolecules. The gated nanoscopic hybrid materials discussed here not only herald a new era in integrative design of intelligent materials that can accomplish ''smart'' drug delivery or adaptive permselective transport, but also give the reader a perspective of the promising future in the development of mesoporous platforms that can control mass transport on command through the combination of flexible supramolecular pathways. The exquisite control with which nowadays material chemists manipulate morphology, loading capacity, surface chemistry and porosity of mesoporous silica, together with its intrinsic biological compatibility, have

made this type of material an ideal scaffold for the creation of gated delivery systems actuated by complex interactions or external stimuli. In addition, mesoporous silica and the molecular and polymer building blocks used in their modification are generally scalable. This encourages industrial applications, that are even more promising if we consider the high added value and implications of health, energy and environmental applications. This is an exciting new field that has just started up – the only limit is our imagination.

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