Expert Opinion

Controlled release using mesoporous materials containing gate-like scaffoldings

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The use of gated mesoporous silica solids as suitable systems for controlled-release protocols is reviewed. These materials are based on mesoporous silica supports that can be prepared with tailor-made pores of around 2 – 10 nm and that show a very large specific surface area (up to 1200 m^2/g), thus having a large load capacity. The solids can be additionally functionalised in the external surface with gate-like systems that can be opened on command to allow cargo release. Light, redox reactions, pH, temperature, polarity and enzyme-driven protocols are shown. The possible application in drug delivery protocols is discussed.

Keywords: controlled delivery, gate-like scaffoldings, hybrid materials, mesoporous silica

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1. Introduction

Most of the functional objects that perform active tasks in living organisms are nanometric or micrometric in size and are built up from very simple molecules such as amino acids, sugars, nucleobases and certain inorganic materials. It is therefore not surprising that chemists have attempted to make use of concepts and strategies from nature to enhance 'bottom-up' approaches in order to develop complex nanometric ensembles that can mimic biological structures and functions [1,2]. Some of such structures are the so-called channels, pumps and gates. Whereas ion channels usually permit the flow of just one specific type of ion, most ion pumps transport different kinds of ion in opposite directions across cell membranes. Additionally, some channels are called gates and they can, depending on the environment, be open or closed. The operating principle of such a device usually includes two activities: coordination with the binding sites, and changes in the chemical structure of the channels after the gate is opened.

Inspired by these examples from nature, chemists have worked out how to prepare abiotic molecular gates. In fact, the design of channels and pores with stimulus-activated gating mechanisms is a research field with very promising applications. Molecular or supramolecular gates can be defined as nanoscopic supramolecular-based devices, attached to certain solid supports, in which mass transport can be triggered by a target external stimulus that can control the state of the gate (closed or open) at will [3-5]. A schematic representation of a gate-like superstructure is shown in **Figure 1**. The scheme shows how the outer surface of a mesoporous support is functionalised with suitable molecules. Upon an external stimulus, the gate opens and allows the release of previously entrapped guests (i.e., drugs) [6,7].

In recent years, we and others have reported the development of nanoscopic gated systems using preorganised nanoscopic silica mesoporous solid structures and molecular functional units attached on the outer surface of the inorganic supports in a synergic fashion. The distinctive characteristics of mesoporous silica supports such as high homogeneous porosity, inertness, thermal stability, the presence of

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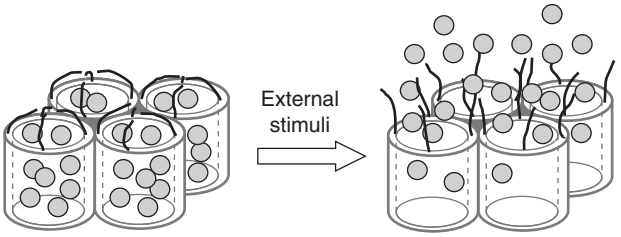

Figure 1. Schematic representation of a molecular gate prepared by the attachment of gate-like scaffoldings onto the outer surface of mesoporous material.

tunable pore sizes with a diameter of around 2 – 10 nm, homogeneous pore distribution and the possibility to easily functionalise the external (or internal) surface, makes these scaffoldings ideal for hosting functional guest molecules [8-11]. Additionally, the possibility of incorporating in the external surface functional groups able to open or close at will, or including capping molecules, provides advanced controlled-release applications.

This review article focuses on typical examples published dealing with the development of nanoscopic gated systems using mesoporous hybrid scaffoldings. The examples have been gathered in relation to the stimulus used to trigger the delivery of the cargo located inside the mesopores. As we will see below, light, redox reactions, pH, changes in polarity, temperature and the use of certain enzymes have so far been employed as external stimuli. This is a timely topic for research; an increasing interest in these systems is envisioned due to their application in many fields, including the design of smart stimuli-controlled delivery systems.

2. Nanoscopic gated systems

2.1 Light-driven

Light is a powerful tool for the control of open/closed cycles in molecular gates and the grafting in the outer of the pores of photoresponsive organic molecules is a general method for the preparation of hybrid molecular gated materials. In light-driven gated materials, the release of the cargo can be controlled spatially and temporally by fine-tuning the area and time of the light stimulus. This may allow a fine control of mass movement at nanoscopic level that would be useful for certain applications such as medical diagnostics and drug delivery. This field was first explored by Fujiwara and colleagues, who grafted photoresponsive coumarin derivatives onto the pore outlets of a mesoporous (MCM-41-type) solid [12,13]. The intermolecular photodimerisation of coumarin to the bulker cyclobutane dimer results in the blockage of the pore entrances (see **Figure 2A**). To test the hybrid material as drug delivery nanodevice, the authors filled the pore voids with cholestane and other steroid hormones. The irradiation at wavelengths > 350 nm induced the photodimerisation of the coumarin molecule, closing the pores by formation of the cyclobutane dimer and preventing the leaching of the drugs. When the molecular gate was irradiated at 250 nm, the coumarin monomer was regenerated, allowing the release of the drugs contained inside the pores of the material.

In a more recent work, the same authors prepared a multifunctional storage and release nanodevice by functionalising MCM-41 mesoporous material with 7-[(3-triethoxysilyl) propoxy]coumarin in the pore outlets and with phenylazo-*N*-(3-triethoxysilyl)benzamide inside the mesopores [14]. Then the pores were loaded with cholesterol and the release studied upon irradiation cycles alternating UV and visible light. In this nanodevice the azobenzene moieties acts as a nanomechanical stirrer under continuous UV/vis irradiation due to a reversible *trans*/*cis* isomerisation process, whereas coumarin moieties acts as molecular gates. Cholesterol is released from the mesopores when the coumarin gates are opened (with UV irradiation) and the release is greatly enhanced by the stirring action of the azobenzene moiety induced by UV/vis irradiation cycles. The authors reported that the multifunctional material was able to release 60% (after 120 min) of the entrapped cholesterol upon UV irradiation (open gate without stirring), whereas the release increased to 95% (after 120 min) when alternated UV and visible irradiation was used (open gate and active stirring). These results clearly indicated that it is possible, not only to prepare practical photocontrolled storage-release nanosystems, but also to have some control over the release rate of delivery by photoacceleration.

A similar approach was followed by Zink and co-workers, also using the well known *cis-trans* photoisomerisation of azobenzene [15]. In a first example, the authors attached a small azobenzene derivative (AzoH) to the inner mesopores of silica spherical nanoparticles via co-condensation method. Continuous excitation at 457 nm produces a dynamic wagging of the photoisomerisated moieties due to the continuous isomerisation between *cis* and *trans* forms which resulted in the expulsion of the luminiscent probe molecules, coumarin 540A and rhodamine 6G, entrapped in the pores to the exterior of the material. The second system was developed attaching, by post-synthesis modification method, a larger azobenzene derivatised with a G1 Frechet dendron (AzoG1) to the pore openings. The dynamic movement due to the continuous photoisomerisation opens the pores intermittently, allowing the release of the entrapped dyes. In a subsequent work, the same authors tested this light-controlled nanoimpeller for the release of drugs in cancer cells [16]. They carried out *in vitro* studies of the release of a fluorescent probe and the anticancer drug camptothecin on two human cancer cell lines (PANC-1 and SW480). As a result, they observed apoptosis when the nanoparticles were activated by light.

Some of us have recently reported the first two-input (photochemical and chemical) gated hybrid system operative in water based on photo-switchable molecules anchored on a mesoporous silica support [17]. The nanodevice consists of

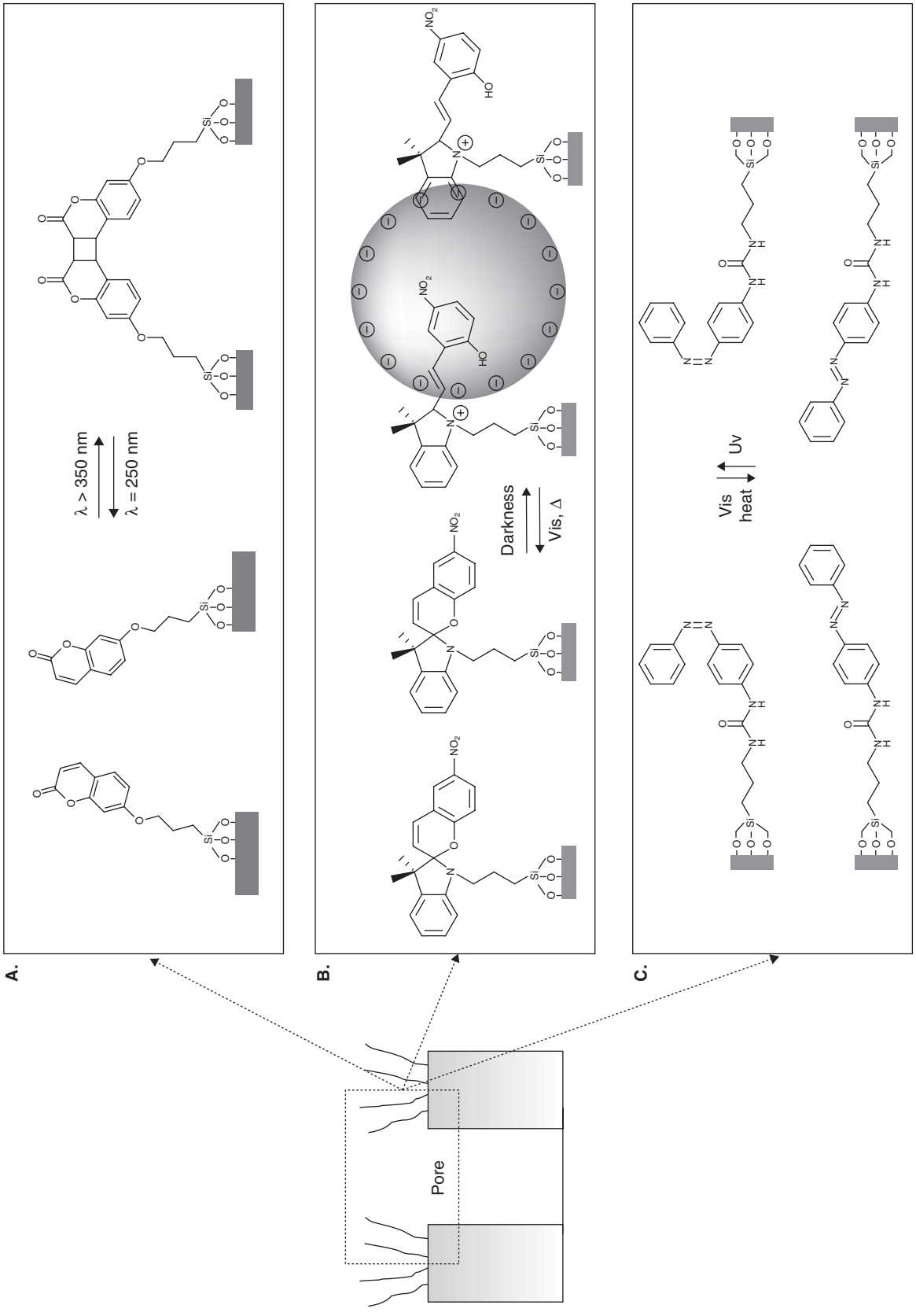

Figure 2. Examples of light-driven molecular gates. See text for detailed explanation.

spiropyran photochrome units attached to the external surface of the mesoporous MCM-41 type solid that can be transformed reversibly between the two forms, the neutral spirocyclic and the positively charged merocyanine, upon the application of an external light source (**Figure 2B**). To achieve the controlled release, negatively charged PAMAM dendrimers (G1.5) were used as molecular stoppers that electrostatically interact with the positive merocyanine. The cargo of the material was the dye $Ru(bipy)_3^{2+}$, which remained on the mesopores in the darkness due to the electrostatic interaction between the negatively charged dendrimers and the positively charged merocyanine form. When the cargo was required to be released, the material was irradiated with visible light, reverting the merocyanine molecule to their neutral spirocyclic form with no affinity for the dendrimers, thus allowing release of the entrapped molecules to the bulk solution.

Photoresponsive nanoporous membranes were also prepared by the inclusion of azobenzene ligands into the inner surface of a mesoporous by Brinker and co-workers [18]. The authors demonstrated that the effective size of the pores was controlled through light-induced changes in the molecular dimensions (about 6.8 Å) due to reversible *trans-cis* photoisomerisation of the azobenzene moieties (see **Figure 2C**). The mass transport behaviour of these nanostructures was tested with ferrocene dimethanol and ferrocene dimethanol diethylene glycol as redox probes. Thus, the photoresponsive membranes were spin-coated onto an indium tin oxide (ITO) substrate and the steady-state oxidative currents at constant potential for the reactions taking place at the electrodes were monitored. At constant potential, the increase or decay of the redox signal until steady-state conditions are reached is a measure of the accessibility of the surface and thus of the mass transport through the pores. The accessibility could be controlled many times by switching between 360 and 465 nm (change between the more compact *cis* form to the extended *trans* form).

2.2 Redox-driven

Redox reactions have also been widely used for the development of gated mesoporous hybrid materials. Some of the examples reported (see below) display gating response in pure water. Additionally, the labile redox linkages used to connect the capping molecules with the mesoporous surface are easy cleaved by certain reducing agents, suggesting that they could also be opened by certain antioxidants produced by cells.

For instance, Stoddart and Zink described a redox stimulated nanovalve by the formation of a [2]pseudorotaxane consisting of a linear 1,5-dioxylnaphthalene (DPN) containing derivative and cyclobis-(paraquat-*p*-phenylene) ($CBPQT^{4+}$) that recognises the DPN groups via non-covalent interactions (see **Figure 3A**) [19]. The nanovalve consists of a mesostructured silica thin film with cylindrical pores of ~ 2 nm diameter around which DPN derivative was covalently attached. To monitor how the system runs, the fluorophore $Ir(ppy)_3$ was introduced in the mesopores by immersion of the film in a solution of this luminiscent molecule. After that, the addition of the ring $CBPQT^{4+}$ blocked the pores via the formation of the correspondent pseudorotaxane. The nanovalve can be opened by the addition of the external reducing agent $NaCNBH_3$. The reduction of DPN starts a spontaneous dethreading of the $CBPQT^{4+}$ ring, allowing the release of the guest from inside the pores. In a further evolution, a double redox-active site system was prepared employing DPN and introducing as linker of the sites an oligoethyleneglycol chain incorporating a rigid terphenylene spacer that connects with the second active site, tetrathiafulvalene (TTF) [20] Finally, a bulky 4,4′-((4-ethylphenyl)(phenyl) methylene)bis(*tert*-butylbenzene) group acts as the outer stopper. The redox-induced movement relies on the major stabilisation energy between TTF and $CBPQT^{4+}$ (gate open), but the addition of the oxidant species $Fe(ClO_4)_3$, which induced the transformation of the TTF to the oxidised TTF^{2+}, destabilises the interaction, favouring the DPN-CBPQT^{4+} one (gate closed). Reduction of TTF^{2+} back to neutral TTF (by the addition of ascorbic acid) causes the $CBPQT^{4+}$ ring to shuttle to the TTF unit, with the subsequent opening of the nanovalves. The MCM-41 submicroparticles were loaded, by soaking, with both a neutral and a cationic compound, $Ir(ppy)_3$ and rhodamine B, in organic solvents in order to test the work of the nanomachine. The authors also tested the system through the measurement of DPN emission because the $CBPQT^{4+}$ ring quenches the DPN fluorescence when the valve is closed. In a optimisation of the work, the authors used spacers of different lengths for the [2]rotaxanes selected to control the open/close cycles of the nanovalves [21]. The [2]rotaxane gatekeepers were attached through the use of linkers with different lengths and would be located in the inner (by the use of co-condensation method in the preparation of the mesoporous nanoparticles) or in the outer (by post-synthetic grafting when the pores were filled with the surfactant molecules used as template in the synthesis) surface of the pores. The controlled release of certain fluorescent dyes (again rhodamine B, $Ir(ppy)_3$, coumarin 440 and coumarin 460) from the pore voids upon addition of ascorbic acid was studied; it was concluded that the nanovalves were more efficient when the gatekeepers were anchored deep within the pores, rather than when attached closer to the pore entrances. The length of the linker between the surface and the rotaxane molecules also played an important role in determining the effectiveness of the nanovalves.

Taking this further, the same authors constructed their DPN-$CBPQT^{4+}$ valve on MCM-41 silica beads and demonstrated that the nanovalve can be also triggered by UV light grafting near the DNP stalks the photosensitisers 9-antracenecarboxylic acid (ACA) or $Ru(bpy)_3^{2+}$ [22]. The ACA photosensitiser resulted in more efficient function. Moreover, this light-activated material needs a sacrificial reducing agent to regenerate the ACA^+ moiety to ACA again. Using this approach, the authors were able to develop a dual-control

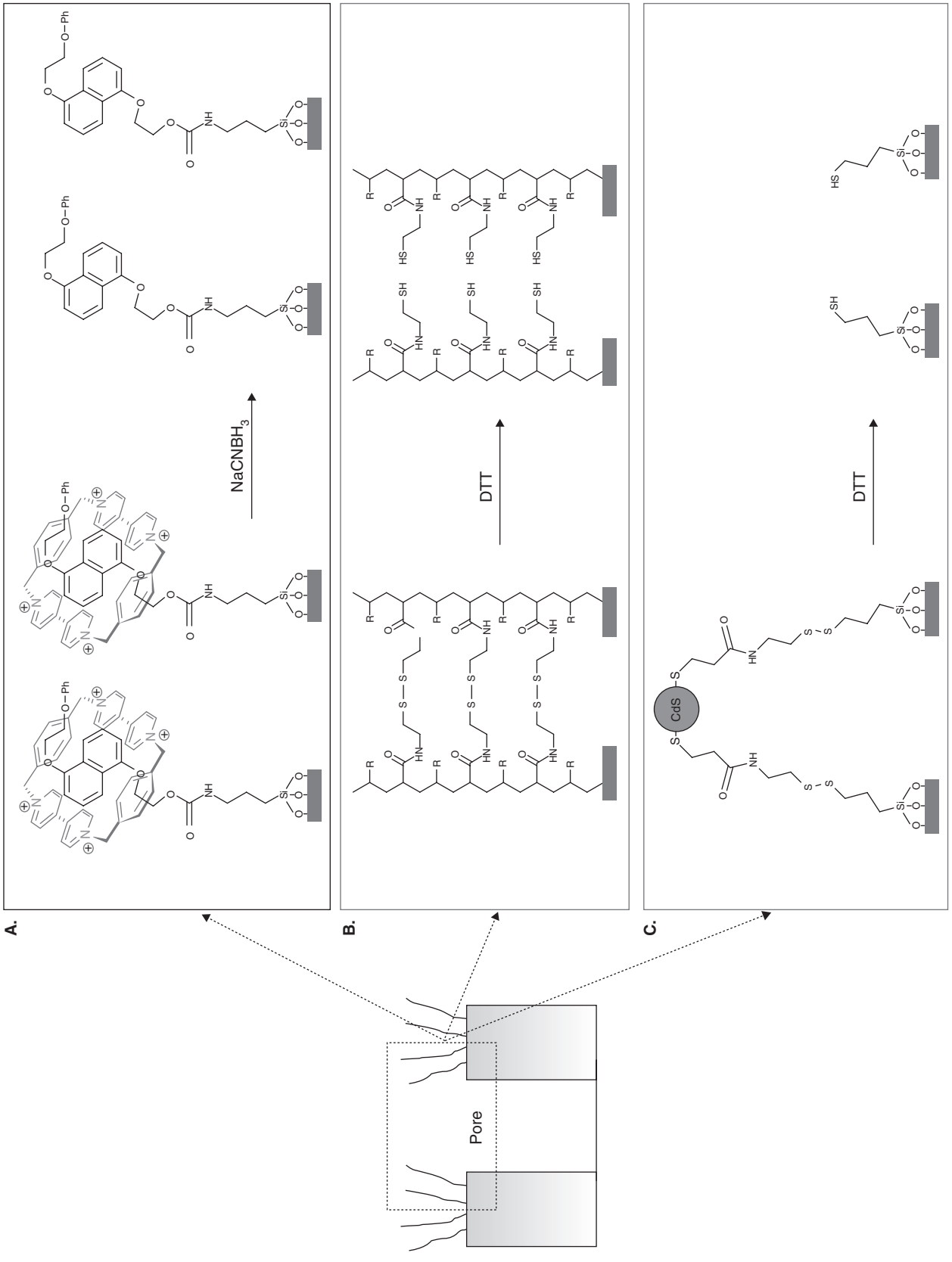

Figure 3. Examples of molecular gates controlled by redox reactions. See text for detailed explanation.

(redox and light) nanovalve with different rates of release of the entrapped guest. While redox control promotes a rapid aperture of the nanovalve, the light-activated mode provided a regional and temporal control.

Fujiwara and colleagues developed a redox-driven nanomaterial by controlling the dimerisation reaction of α-methylstyrene (AMS) [23]. In this case the authors did not study the delivery of an entrapped guest, but the access from the solution to the inner pores of AMS. The authors modified a mesoporous silica material (MCM-41 type) with Al to obtain highly acidic catalytic sites where the AMS could dimerise. The evaluation of the gate mechanism was followed by the amount of AMS dimerisation. The pore outlets of the inorganic matrix were grafted with a disilane–disulfide derivative that was cleaved by the addition of dithiothreitol (DTT, a disulfide-reducing agent), allowing the AMS to get into the pores and yielding the dimerisation products. The addition of I_2 restores the initial disulfide moiety, not permitting the AMS access to the inner pores, with the consequent inhibition of the dimerisation process.

MCM-41 particles were also used by Feng and co-workers for the development of a redox-responsive gate-like scaffolding by the anchoring of a crosslinked polymer network in the inner pores than act as gatekeeper (see **Figure 3B**) [24]. The authors grafted poly(*N*-acryloxysuccinimide) to the pore entrances of MCM-41 particles. Then the pores were loaded with rhodamine B and blocked by the addition of cystamine, a disulfide primary amine, which allows polymer chains to be crosslinked (through the formation of a disulfide linkage upon reaction between cystamine and *N*-oxysuccinimide groups located along the polymer chains). In this state, no release of rhodamine B was observed. Addition of DTT to the suspensions induced the release of the entrapped dye due to the rupture of the disulfide link. The release dye concentration is dependent on the added DTT amount, this behaviour being clearly ascribed to different degrees of disulfide cleavage. It was suggested that this hybrid gated system could be a promising material for *in vivo* site-specific drug delivery, since disulfide bonds can also be cleaved by cell-produced antioxidants such as dihydrolipoic acid or glutathione.

In the examples shown above, the open/closed state of the mesopores in the mesoporous materials are controlled through redox reactions that induced the molecular movement of certain molecules through wire-like organic scaffoldings or the rupture of a covalent bond. In the following examples of this section, the gated systems used certain types of nanoparticles as molecular caps for the blocking of the pore entrances. The nanoparticles were attached to the outer surface of the mesoporous materials through organic moieties containing a covalent linkage that can be broken by the addition of a redox agent, allowing the removal of the cap and release of the entrapped guest.

Lin and colleagues were the first investigators to use nanoparticles as capping agents to build 'zero-release' nanogates on mesoporous materials. In a first example they anchored 2.0 nm CdS nanoparticles to mesoporous silica nanospheres, with an average particle size of 200 nm and an average pore diameter of 2.3 nm, via an organic disulfide-containing link (**Figure 3C**) [25]. The mesopores of the hybrid material were filled with various pharmaceutical drug molecules and neurotransmitters such as vancomycin and ATP. The guests were released by the addition of the disulfide-reducing agents, DTT or mercaptoethanol (ME). The authors also demonstrated the efficient delivery in astrocytic neuroglial cells *in vitro* using these mesoporous gated systems. The same research group, following the use of supramolecular ensembles as stoppers, developed a gating mechanism in which poly(amidoamine) dendrimers (PAMAM) were attached to the outer surface of a mesoporous support through a disulfide-containing linker and monitored the ATP release from the pores of the nanospheres by using ATP-induced luciferase chemiluminescence imaging in real time [26]. In this work, the investigators compared both CdS-capped and PAMAM-capped systems, concluding that the dendritic cap allowed more efficient sealing of the nanopores [27].

In a further step, Lin and co-workers have used magnetic nanoparticles not only as cap but also as carrying-director agent [28]. In this study, mesoporous silica nanorods functionalised with 3-(propyldisulfanyl)propionic acid groups were used as inorganic support and were capped by reaction with 3-aminopropyltriethoxysilyl-appended superparamagnetic iron oxide nanoparticles with an average diameter of 10 nm. As the nanoparticles were larger than the aperture of the pores, they close the pores rather like the lid on a pot, fully covering the entrance. Again, the addition of a reducing agent such as dihydrolipoic acid or dithiothreitol resulted in the opening of the gate. The considerable advantage of this capped nanosupport relates to the possibility of directing the material magnetically to a site of interest where the cargo can then be released. The authors also demonstrated the performance of the fluorescein-loaded nanogate in aqueous buffer solution.

In a more recent study, Lin and colleagues developed a gold nanoparticle-capped mesoporous system capable of delivering not only chemicals entrapped in the silica channels but also genes, as coating of the mesoporous nanoparticles, into plants [29]. Gold nanoparticles, attached to the siliceous surface through covalent bonds, physically block the nanopores loaded with the GFP expression inducer β-estradiol or the imaging agent fluorescein. Further addition of the disulphide-reducing antioxidant DTT induced the rupture of a covalent sulphur–sulphur bond, with consequent release of the entrapped cargo.

2.3 pH-driven

Some examples use pH as the stimulus to develop open/close protocols in mesoporous gated materials. The grafting in the pore outlets of organic moieties containing protonable atoms or functional groups that would give protonation processes

have been used as molecular gate-like scaffoldings. Upon protonation, changes in size/shape or attraction/repulsion interaction with other charged species are responsible for modulation of the gate. Despite increasing interest in the development of conceptually new gating systems, there are few examples where solids containing gate-like structures have found practical applications in the field of advanced smart delivery systems. pH-controlled gate-like scaffoldings may show certain advantageous features. For instance, most of the examples reported are in principle reversible and display gating response in aqueous environments (see below). One possible application of pH-controlled gate-like scaffoldings is the development of orally applicable delivery systems designed to have the specific ability to protect the cargo from the acidic conditions of the stomach (acid pH, gate closed) but to release the load at the intestine (basic pH, gate open). Also, it would be feasible to fine-tune the pH at which the gate is open/closed by simply changing the pH-responsive molecular entities anchored on the external surface of the siliceous support.

Martínez-Máñez and co-workers reported the first nanoscopic molecular gate driven by pH and able to work in aqueous solution [30]. This system operates as a function of pH due to the protonation/deprotonation processes of polyamines grafted into the pore outlets of the mesoporous inorganic scaffolds (see **Figure 4A**). In this study, the mesoporous silica used was a UVM-7 material, a MCM-41-type support with a characteristic bimodal pore system of intrananoparticle mesopores (MCM-41 type, 2.6 nm diameter) and larger interparticle pores (45.2 nm diameter textural porosity). The gate open/close mechanism was related to hydrogen bonding interactions between unprotonated amines (open gate) and coulombic repulsions between protonated amino groups (closed gate). Along with the pH-controlled mechanism, fine control of the gate aperture can be achieved by using different anions at a certain pH. For instance, the authors found that the use of bulky anions such as ATP could block the entrance of the pores due to the formation of strong complexes with the polyamines; small anions such as chloride did not close the gate, allowing dye release. In fact, a fine control of the opening can be achieved via modulation of the size and charge of the anionic species present in the solution.

As a continuation of this work, and taking into account this double-control protocol, the same authors developed an ATP probe that can discriminate GMP and other inorganic anions from ATP and ADP, using the ability of the latter to selectively inhibit dye delivery from an amine-functionalised mesoporous support [31]. Later, the same authors reported a complete study of the behaviour of this pH-driven and anion-controlled nanosupramolecular gate-like ensemble [32]. In this study, they examined the remarkable anion-controllable response of the gate-like ensemble, which can be explained in terms of anion complex formation with the tethered polyamines. The experimental observations were additionally supported by computational simulations with fluoride, chloride, iodide, and dihydrogen phosphate anions. In that model, larger anions pushed the tethered polyamines toward the pore openings more efficiently, resulting in decrease of the pore aperture. Furthermore, it was found that anions showing a strong tendency to form hydrogen-bonding networks (e.g., phosphate) blocked the pores more efficiently. Finally, the selectivity of the system was discussed in terms of kinetic rates of the release of the $Ru(bipy)_3^{2+}$ dye from the amine-functionalised dye-containing material. In a further step, the same authors used the pH-controlled gate-like scaffolding as a suitable prototype for the development of delivery systems able to protect the cargo (riboflavin) from the acidic conditions of the stomach (acid pH, gate closed) and release the load at the intestine (basic pH, gate open) [33].

Whereas the pH gate-like device based in polyamines (see above) tends to be closed at acidic pH and open at neutral and basic pHs, Xiao and co-workers reported a molecular gate showing an opposite behaviour by anchoring carboxylates in porous SBA-15 silica rods [34]. The inner of the pores was then loaded with vancomycin and the pore blocked with the addition of the positively charged poly-(dimethyldiallylammonium chloride) (PDDA) to give electrostatic interactions with the negatively charged carboxylates located in the outer surface of the pores (**Figure 4B**). The release of vancomycin from the pore voids was easily controlled by changes in the pH of the medium. At acidic pH, the vancomycin was released due to protonation of the surface-attached carboxylates, resulting in a disruption of the electrostatic interactions with the positively charged polyelectrolyte.

Stoddart and Zink reported the design, synthesis and functional behaviour of a pH-controlled supramolecular gate-like scaffolding consisting of the [2]pseudorotaxane formation via the encirclement of dialkylammonium cations with the macrocyclic polyether dibenzo[24]crown-8 (DB24C8) close to the pore orifices of a mesoporous material (see **Figure 4C**) [35]. The luminiscent probe coumarin 460, loaded inside the mesopores, was used to show how the system operates via the control of its release from the pores. The 1:1 complex between the ammonium ion and the polyether can be dethreaded via deprotonation by the addition of bases with different strengths and structural dimensions, as hexamethylphosphorus triamide, *N*,*N*′-diisopropylethylamine or triethylamine. Later, in another paper, the same authors reported the activation of the delivery by competitive binding of the DB24C8 ring by fluorodialkylammonium salts via the shifting of the equilibrium between the ring and the stalks [36].

Recently, Zink and colleagues have also reported a new pH-responsive supramolecular mesoporous system that operated in water, using a ion-dipole interaction between curcubit[6] uril and bis-ammonium stalks that resulted on the formation of a [2]pseudorotaxane monolayer on the surface of mesoporous silica nanoparticles [37]. At neutral or acidic pH values, the pores are blocked by the pseudorotaxane that can be dethreaded upon addition of a base (NaOH). As a

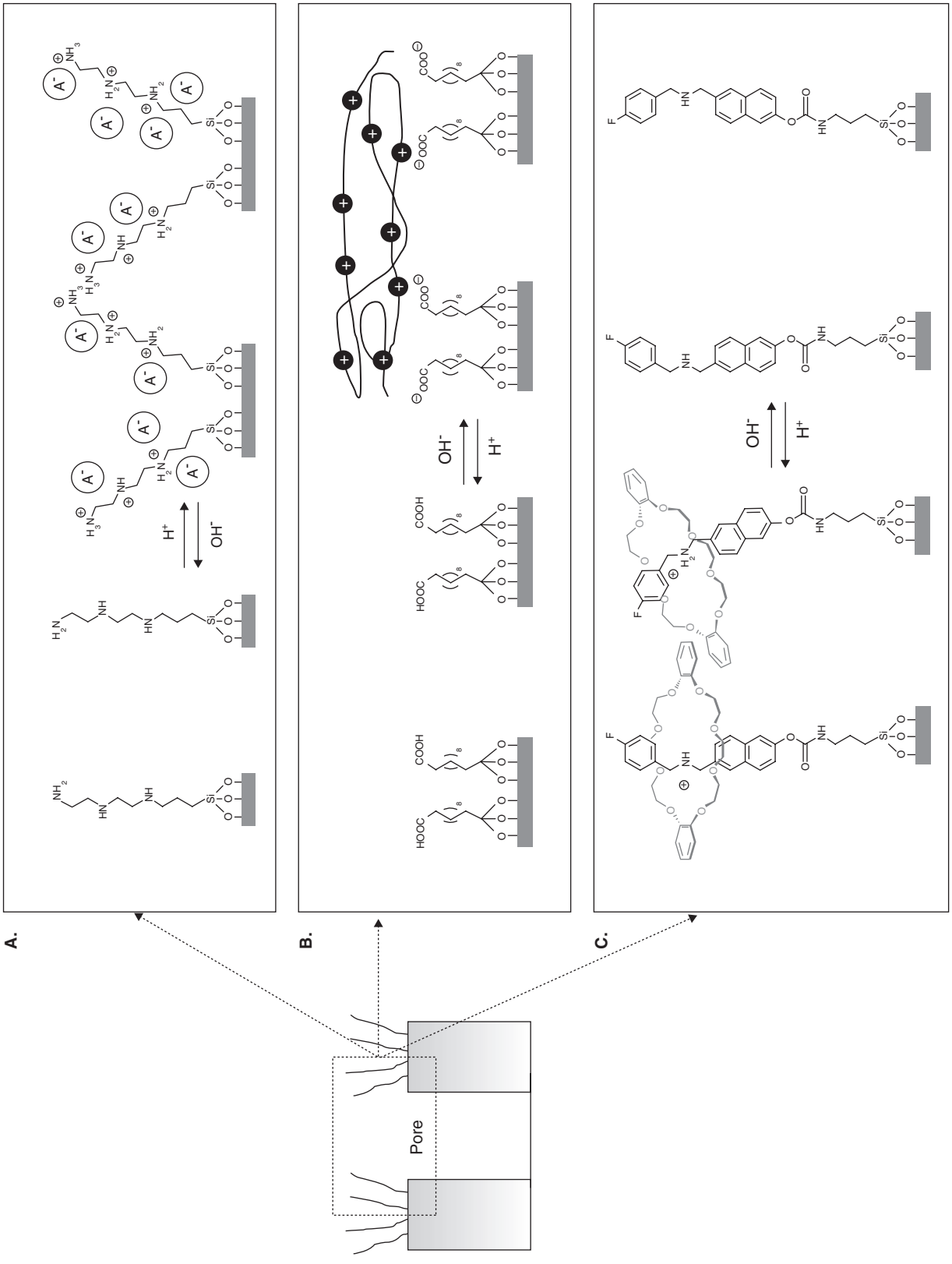

Figure 4. Molecular gates controlled by pH changes. See text for detailed explanation.

consequence, the dye rhodamine B was released from the inner of the pores. Through studies on optimising the length of the linker, the authors used a shorter linker that curtails the length of the stalk of the pseudorotaxane such that the ring is positioned about 0.2 nm closer to the surface of the silica nanoparticle, tightening the nanovalves and preventing leakage of the rhodamine B.

The preparation of pseudorotaxanes for the development of a pH-responsive delivery system has also been reported by Kim and co-workers, who functionalised the external surface of the silica particles with polyethyleneimine (PEI) and then loaded the pore with calcein. After this, the nanopores of the functionalised silica particles were closed by addition of α- and γ-cyclodextrin at pH 11.0 due to formation of a polypseudorotaxane between the grafted PEI moieties and both cyclodextrins [38]. The threading and dethreading process of α- and γ-cyclodextrin onto the PEI moieties, and the subsequent release of calcein, was controlled through pH variations: at pH 11.0 the polypseudorotaxane was formed, whereas at pH 5.5 the polypseudorotaxane is dethreaded due to amine protonation. In particular, at pH 11.0 weak calcein fluorescence was observed due to self-quenching of calcein molecules into the pores, whereas an increase in the emission intensity was observed at pH 5.5.

2.4 Miscellaneous

As we have seen above, several examples dealing with the design of light- [12-18], redox- [19-29] and pH-responsive [30-38] mesoporous materials containing functional gating groups for controlled release applications have been reported. We will detail in this section some other recent studies that explore the use of other stimuli for triggering delivery in mesoporous systems, few examples of which have so far been reported.

2.4.1 *Temperature-driven*

Temperature-reactive nanoscopic gated hybrid materials have been reported via the use of modified mesoporous silica nanoparticles by atom transfer radial polymerisation with the temperature-sensitive polymer N-isopropylacrylamide [39]. The mesoporous material was loaded with fluorescein to test how it operated. At room temperature, the polymer was hydrated, preventing dye release, while at higher temperatures the polymer was hydrophobic and collapsed within the silica pore network, allowing the diffusion of the molecules entrapped inside the mesopores.

2.4.2 *Molecular interaction-driven*

Changes in the polarity in the microenvironment around the nanopores due to molecular coordination with binding groups have also been described as a mechanism to control the release of entrapped guests. Addressing this concept, Martínez-Máñez and colleagues prepared a mesoporous support functionalised in the external surface with imidazolium groups and loaded with the dye $[Ru(bpy)_3]^{2+}$ that was used to study the delivery process in the presence of linear carboxylates (**Figure 5A**) [40]. The investigators observed that pore blockage did not obey to a gradual tendency, but to an 'on/off' behaviour, since small carboxylates from acetate to octanoate provided free dye release while longer-chain carboxylates blocked the pores completely. The observed behaviour can be explained by the interaction between the long chains of the fatty carboxylates through van der Waals forces, resulting in the formation of a hydrophobic 'cork' around the pore openings.

2.4.3 *Enzyme-driven*

The only example of a gating mesoporous system that responds to a biostimulus was reported very recently by Zink and Stoddart in 2008, using an enzyme-catalysed reaction. The wide range of available enzymes that can selectively catalyse a large number of different chemical reactions opens new perspectives of applicability for drug-delivery applications using mesoporous nanoscopic gated systems. In the example, the authors loaded mesoporous silica nanoparticles with rhodamine B and then functionalised the outer surface with a [2]rotaxane formed by the inclusion of an α-cyclodextrin molecule onto a polyethyleneglycol fragment that was additionally capped with an ester-linked adamantyl stopper (see **Figure 5B**) [41]. Water suspensions of these functionalised mesoporous nanoparticles were unable to release rhodamine B, whereas in the presence of porcine liver esterase (PLE) the fluorescent dye was delivered to the bulk solution. The synthesis and lack of response of a similar hybrid material in which the linker moiety between the adamantyl group and the [2]rotaxane was an amide, instead of an ester, confirmed that the fluorescent dye release was ascribed to the dethreading of the [2]rotaxanes due to hydrolysis reaction of the adamantyl ester induced by the PLE.

3. Conclusions

In summary, several examples based on the use of mesoporous siliceous materials containing gate-like scaffoldings for the controlled release of the cargo via the use of different stimuli have been reported recently. Most reported examples use light, redox reactions and pH modulations in order to control the delivery of the entrapped cargo. Some recent interesting examples have also been reported using temperature, modification of the polarity and the use of enzymes as stimuli. Although the development of nanoscopic mesoporous devices containing gate-like scaffoldings for controlled-release protocols is still in its infancy, we believe that gated systems based on organic/inorganic hybrid supports will be a very promising tool for the development of new and smart advanced nanodevices for controlled drug delivery in nanomedicine applications. A number of new advances in this area in the near future are anticipated.

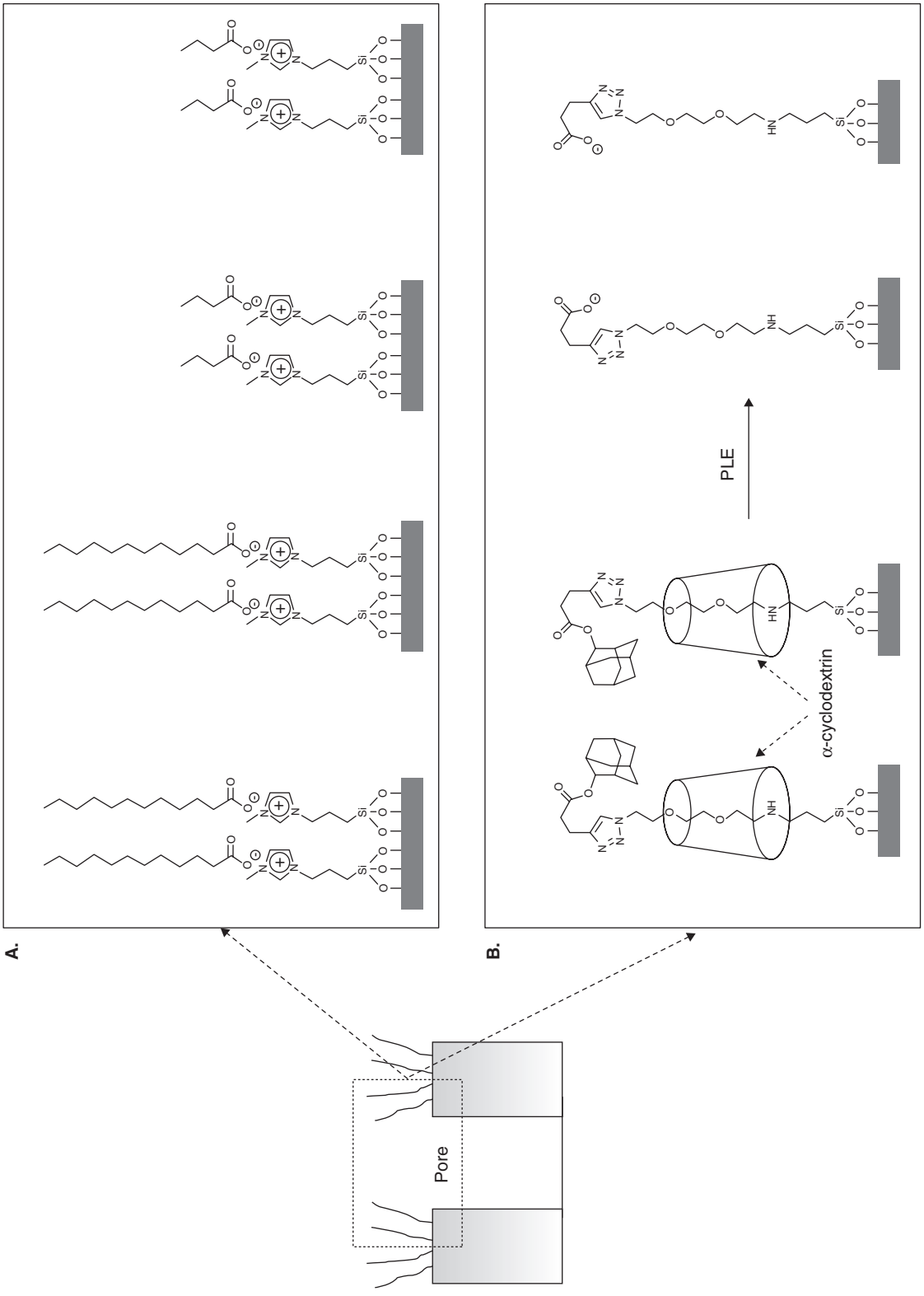

Figure 5. Molecular interaction- and enzyme-driven molecular gates. See text for detailed explanation.

4. Expert opinion

Drug therapy is a complex concept that involves many factors including mode of administration, concentration accumulated in the required tissue, possible toxicity of the drug, degradation processes, bioavailability, etc. To minimise some of these specific problems, scientists have explored various drug-delivery and drug-targeting methods that try to transport the drug intact to the target tissues or cells. Indeed, one of the technological challenges to be met in the future is the development of novel nanodelivery systems with the capability to transport the desired guest molecules to the targeted site and release that cargo in a controlled manner. It is well recognised that the way in which a drug is delivered can have an important impact on its efficacy. Drug delivery systems are based principally on polymers, mainly because these materials are relatively easy to prepare and their properties can be tailor-made by relatively well-known chemical procedures. However, release of the cargo from these polymers devices is generally diffusion-controlled or occurs via degradation of the polymer container. Despite the use of certain stimuli-sensitive delivery systems such as those relying on hydrogels, in most cases the drug is released following non-stimuli-controlled protocols. However, this could be a problem in cases where the drug is degraded in the solution or when using certain highly toxic antitumour substances.

As a possible alternative to polymer-based systems, here we have reviewed the use of mesoporous materials having gating functionalities for controlled delivery of the target guest. Mesoporous materials offer several unique features: they are stable biocompatible solid supports, can be prepared with tailor-made pores of around 2 – 10 nm; show a very large specific surface area (up to 1200 m^2/g), thus having a large load capacity; have a well-known and relatively easy functionalisation chemistry that allows control of the pore size and pore polarity; and in general, can be prepared to host molecules with various sizes, shapes and functionalities. As we have seen above, the mesoporous supports can be functionalised with stimuli-responsive systems. Finally, these mesoporous supports can also be obtained in a nanometric size, resulting in suitable materials for the design of nanodevices for on-command delivery of drugs.

Despite the promising proof-of-concept examples that have been reported, the approach of using siliceous-based mesoporous supports containing gate-like scaffoldings for the development of drug delivery systems remains at an embryonic stage. In fact, apart from some interesting examples (mostly reported by Lin and colleagues) that have demonstrated controlled delivery in cells using gated mesoporous supports, there is still a lack of studies exploring potential therapeutic applications. Also, some of the reported systems display gating effects in non-aqueous solvents or respond to external stimuli that are difficult to apply in real delivery protocols. These are not the only issues to be addressed in the future: for instance, there is a need to prepare more advanced systems that can be selectively opened in the presence of target biomolecules or using bio-friendly external stimuli such as light, magnetic or electric fields. Additionally, the possibility of easily carrying out different functionalisations at the surface of the nano mesoporous supports allows us to envision the design of advanced nanodevices that contain a gating-responsive mechanism coupled with ligands that are selectively recognised by given receptors on cells of interest.

In summary, the attractive properties of these solids and the possibility of easily functionalising the siliceous surface with one or various functional groups to include a gating-responsive mechanism but also actively targeting groups, suggest that significant progress will be made in this field over the next few years. This innovative procedure offers the potential to develop nanocarriers for effective drug delivery.

Declaration of interest

The authors state no conflicts of interest and have received no payments in the preparation of this manuscript.

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