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Drug Delivery

Mesoporous-Silica-Functionalized Nanoparticles for Drug Delivery

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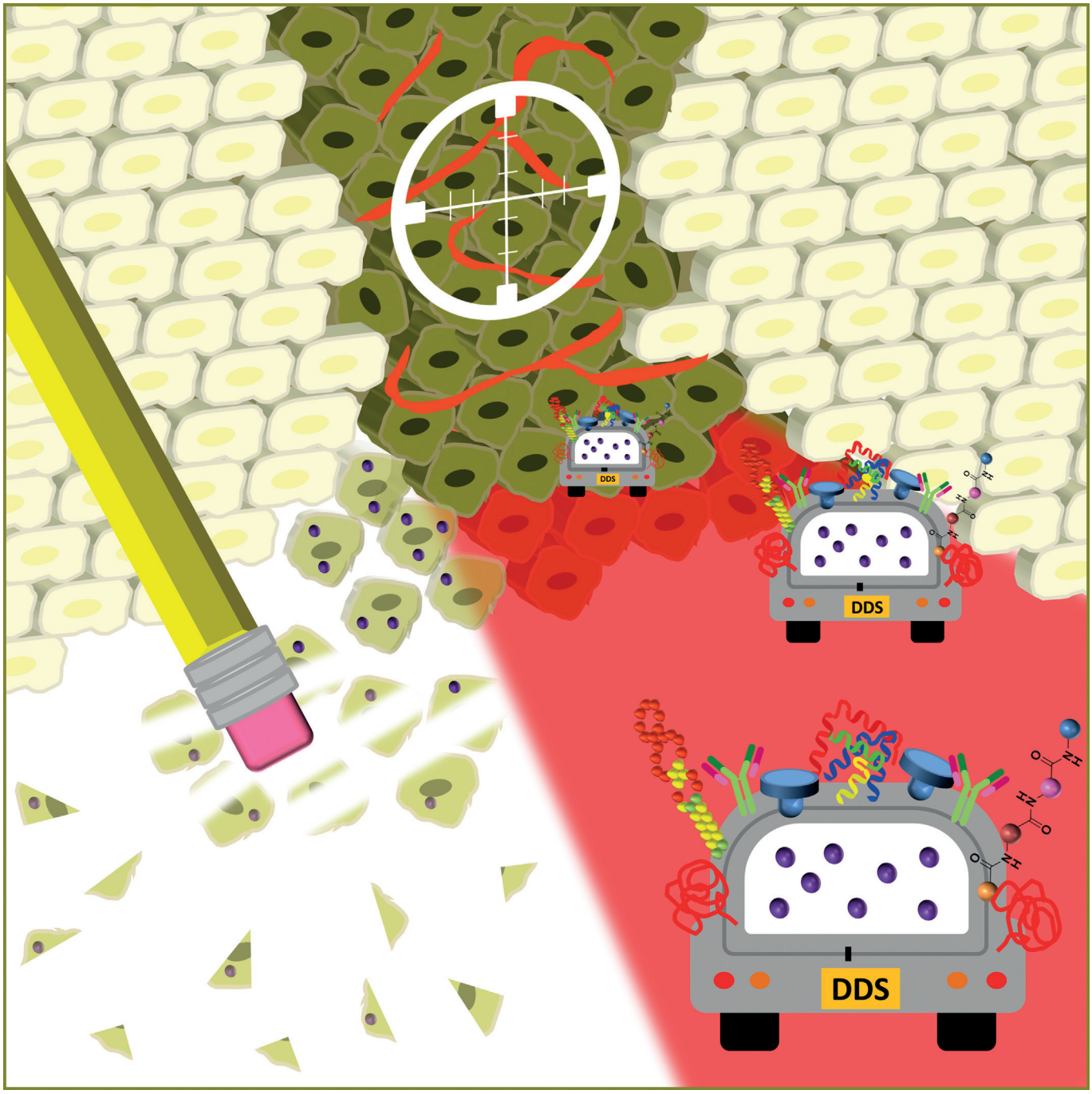


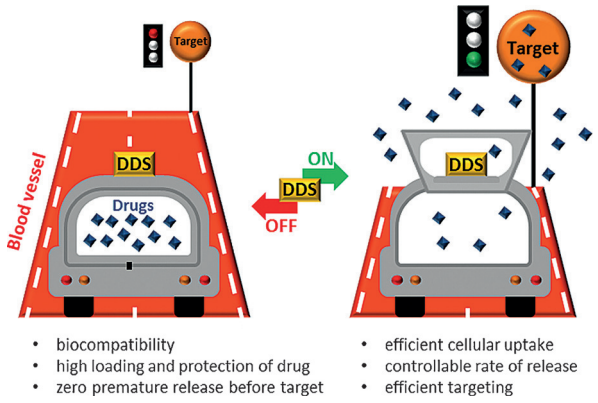
Abstract: The ever-growing interest for finding efficient and reliable methods for treatment of diseases has set a precedent for the design and synthesis of new functional hybrid materials, namely porous nanoparticles, for controlled drug delivery. Mesoporous silica nanoparticles (MSNPs) represent one of the most promising nanocarriers for drug delivery as they possess interesting chemical and physical properties, thermal and mechanical stabilities, and are biocompatibile. In particular, their easily functionalizable surface allows a large number of property modifications further improving their efficiency in this field. This Concept article deals with the advances on the novel methods of functionalizing MSNPs, inside or outside the pores, as well as within the walls, to produce efficient and smart drug carriers for therapy.

Drugs and Drug Delivery Systems

In pharmacology, a drug is a chemical substance that is used in treatment, cure, prevention, or diagnosis of diseases as well as to enhance physical or mental well-being. Drug therapy is an important part of the medical field and there is a wide range of medications that all share the same three following parameters: 1) the prescribed doses, 2) the time interval between shots and 3) the treatment duration.

Pharmaceutical drugs may be used for a limited period or on a regular basis for chronic disorders. Any increase in the treatment may cause an overdose and conversely an inadequate dose can result in incomplete treatment. Some drugs can lead to addiction and habituation and all of them have more or less severe side effects. Indeed, to reach the target, the drug must first enter the bloodstream and throughout the circulation biotransformation and/or elimination of the drugs can occur resulting in a variation of concentration. However, to achieve the therapeutic effect a minimum effective concentration in the plasma should be maintained without reaching toxicity levels. This is often difficult to achieve because of the large amount of drugs needed due to their low bioavailability and problems in crossing biological barriers.

The development of new treatments is leading to the evolution of therapeutic agents and also to the administration mechanism. Indeed, the controlled delivery is an essential tool to improve the current therapies by manipulating the biological profiles, such as pharmacokinetics, biodistribution, tissue uptake, and so forth. The design of site-specific and stimuli-responsive controlled drug delivery systems (DDSs) is of major interest for researchers worldwide. Basically a DDS can be described as a formulation that controls the rate and period of drug delivery and targets specific areas in the body. The key challenge of such DDSs is to have the ability to carry an effective amount of drugs with none or significantly decreased side effects than those of current therapy methods (Scheme 1). For that, several prerequisites for DDSs are necessary: 1) biocompatibility, 2) high loading and protection of the drug, 3) zero premature release before the target, 4) efficient cellular uptake and endosome escape, 5) controllable rate of release, and 6) efficient targeting.



Scheme 1. Schematic representation of an efficient DDS.

Nanotechnologies have great potential in this area. In the past decades, several DDSs were developed to meet these criteria. For instance several nanocarriers based on liposomes,[1] polymeric micelles,[2] dendrimers,[3] carbon nanotubes,[4] inorganic nanoparticles,[5] silicon[6]- and silica-based[7] materials have been investigated as promising candidates for drug delivery.

This concept article focuses on up-to-date strategies for functionalizing mesoporous silica nanoparticles (MSNPs) and then on the introduction of several different properties to produce very efficient drug delivery carriers. Firstly we describe how and why MSNPs became promising candidates as drug delivery carriers. Then we present the different methods to include linkers either on the pores surface and/or the outer surface or directly in the wall of the nanoparticles. Finally, we show how further functionalization can affect all stages of nanoparticles life. Indeed, by choosing appropriate functions, the loading of drugs, the circulation in blood, the targeting of cells, the internalization in cells, and the release of drugs can be influenced or even controlled.

Silica Nanoparticles as Drug Delivery Systems

Development of mesoporous silica nanoparticles for drug delivery

Following Vallet-Regi's work, who first reported the use of mesoporous silica as DDSs,[8] significant improvements have been made to develop MSNPs for drug delivery and which can chronologically be divided into three stages resulting in three generations of DDSs (Scheme 2).

MCM-41[9] or SBA-15[10] mesoporous silica type were the first-generation of material used, after loading with various cargo

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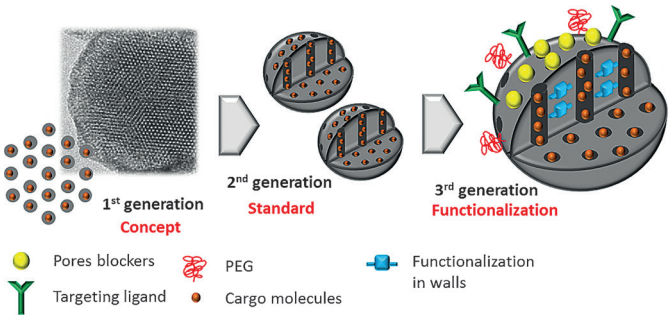


Scheme 2. Development of three generations of mesoporous silica materials for DDSs.

molecules, for in vitro evaluation of delivery performance. Using these systems, the authors were able to validate the concept of MSNPs as DDSs, but unfortunately the large particles size, irregular morphologies, and aggregation hindered in vivo applications.

Due to the progress of nano-synthetic chemistry by tuning the hydrolysis and condensation rates of silicon alkoxides under acidic or alkaline conditions in the presence of various surfactants, all the previous problems were overcome to provide MSNPs, the second generation of mesoporous silica-based DDSs. Such nanoparticles exhibit uniform size and morphology, tunable pores and compositions, and enhanced drug-loading capacity, ideal for standard in vitro and also in vivo evaluations.

Then the abundant surface chemistry of MSNPs allowed the elaboration of the third-generation of DDSs with diverse functionalities further improving the properties and efficiency of the carriers as described hereafter.

Benefits

MSNPs have received growing attention as drug delivery carriers since they possess the following unique features

1) Tunable particles sizes (in the range 50 to 300 nm) and morphology (spheres, rods).
2) Uniform and tunable pore sizes (2–6 nm).
3) High surface area (700–1000 $m^2 g^{-1}$) and large pore volume (0.6–1 $cm^3 g^{-1}$) for efficient encapsulation and high loading capacity.
4) High thermal/chemical stability compared to other polymer-based DDSs.
5) Two tunable functional surfaces: an inner surface in the pore channels and the outer surface of the particle allowing a selective functionalization.
6) Unique porous structures without any connections allow for a perfect "capping" essential for zero premature release.
7) Endocytosed in short times by numerous mammalian cells.
8) Good in vivo biocompatibility[11] (well tolerated up to 200 mg kg^{-1}) and hemocompatibility.[12]

The adopted amount of silica carriers can then be significantly reduced and the corresponding biosafety can be improved. Due to their stable and rigid framework under extreme conditions compared to organic DDSs (liposome or emulsion), silica carriers do not suffer from uncontrollable drug release owing to degradation in an explosive manner in a physiological environment, but release the drugs in a sustained way when suitably functionalized. In addition, the abundant surface silane chemistry facilitates the easy chemical modifications of MSNPs to improve their properties. Furthermore, silica carriers can be synthesized in various shapes (nanospheres, nanorods, etc.).

Biocompatibility and toxicity

As therapy, the compatibility and safety of MSNPs are required, as when they interact with the body (organs and tissues) a variety of responses may occur, for example, alterations of immune system or interactions with blood, depending significantly on their composition. Because of the chemical inertness of silica, MSNPs with optimized structural features and at suitable dosages show great biocompatibility in many biological systems, as demonstrated by several groups.[11] However several factors can affect the nanoparticles toxicity and pharmacokinetics like cell lines, concentrations, and physiochemical properties, such as size, shape, surface charge, and modification.

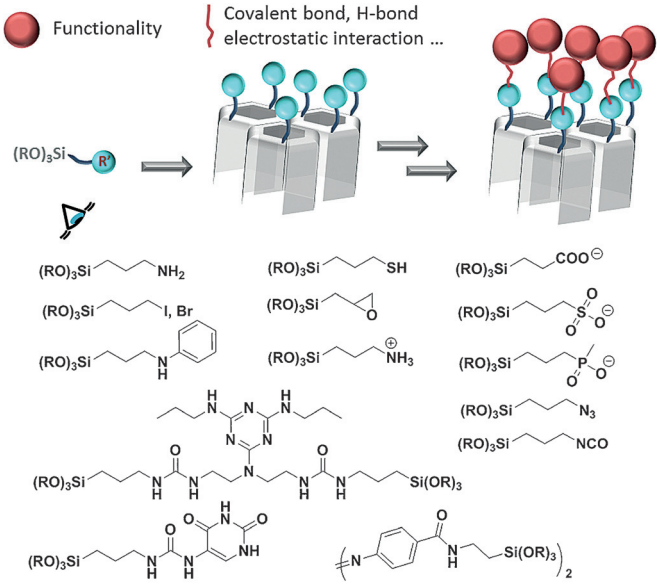
Due to the huge variation of characteristics in this class of materials, it is actually illusive to draw general conclusions for their toxicity and for this reason nanoparticles have to be evaluated individually to characterize their absorption, distribution, metabolism, excretion, and toxicity properties.

Finding the ideal treatment concentration for an efficient drug delivery and a minimal toxicity will definitively allow obtaining optimal clinical results with pronounced decrease of side effects. However, the relevance of toxicity studies may be questionable, firstly because we know that coating nanoparticles with polymers, lipid bilayers, or proteins effectively eliminate toxicity as demonstrated in vivo[13] and secondly because, when considering the high drug loading capacity of MSNPs which reduces needed dosages, appropriate concentrations to study toxicity are less than 100 $\mu g\,mL^{-1}$, an amount for which actually most studies have shown insignificant toxicity.

Methods for modification of the MSNP surface

MSNP functionality can be introduced by modifying chemically accessible silanols, which can easily react with functional alkoxysilane, introducing a desired organic unit through a covalent bond. Moreover this last functional group can be used to attach other molecules for further post-functionalization or to modify surface properties. Most of the alkoxysilane precursors used are now commercially available and some of them being more complex, for specific applications, can be synthesized (Scheme 3).

Two main approaches of surface modification exist, namely, post-functionalization methods or direct sol–gel hydrolysis–condensation routes (Scheme 4).



Scheme 3. Various alkoxysilanes to introduce functionality or modify surface properties.

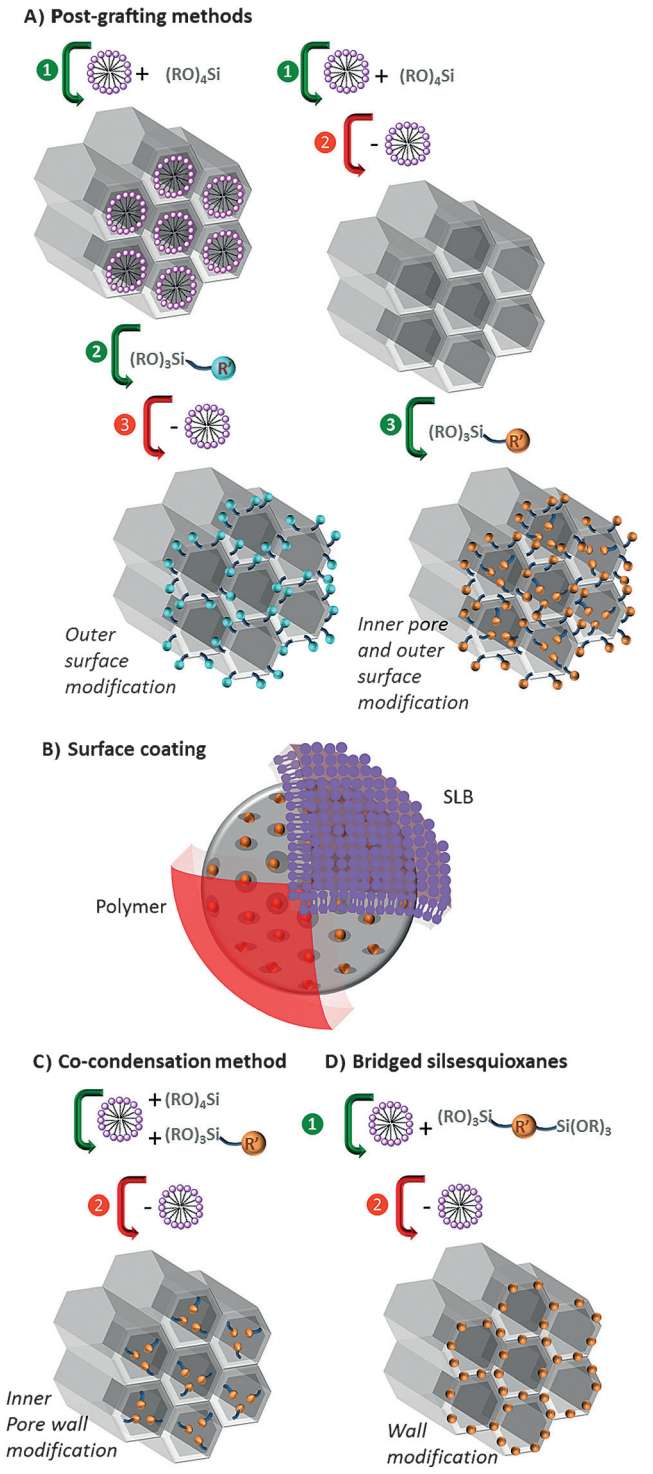
Post-functionalization methods

Through the post-grafting strategy, MSNPs can be modified by reacting accessible surface silanol groups both within the mesoporous network and on the outer surface with functional organosilanes (Scheme 4 A). Here it is possible to restrict a first-step functionalization on the outer surface prior to surfactant removal and perform a second-step functionalization after removing the latter. In this case the grafting of chemically more delicate organic functionalities prone to hydrolysis and elimination reactions is possible. However, the distribution of functional groups may not be uniform if the blocking of pores occurs.

Exploiting electrostatic interactions on the outer surface represents another way to post-modify MSNPs. Indeed, at neutral pH, the deprotonation of surface silanols occurs resulting in a negatively charged silica surface. Consequently, the surface can be functionalized electrostatically with positively charged moieties to form an adsorbed coating through noncovalent interactions (Scheme 4 B). In almost all cases polymers[14] are commonly employed on MSNPs. In addition MSNPs can be enveloped by supported lipid bilayers (SLBs).[15]

Sol–gel routes

The co-condensation method consists in coupling hydrolyzed alkoxysilanes with organoalkoxysilanes ($R'_xSi(OR)_{4-x}$), in which R′ is an added functionality that induces the modification on the surface inside the pores (Scheme 4 C). In this one-pot co-condensation process, organosilanes are added directly together with a silica source (tetramethoxysilane (TMOS) or tetraethoxysilane (TEOS)) into the gel solution with a surfactant. As organosilane is amphiphilic, it may act as co-surfactant incorporated into the surfactant micelles. When condensation occurs, the organic moieties are then anchored on the pore walls. Then, the surfactant molecules are removed by ion exchange with a solution of ammonium nitrate or HCl in ethanol. The advantages of this method are the following: a simple operation, uniformity in distribution of functionalization, and achievable high loading of organic functions. However, the simultaneous



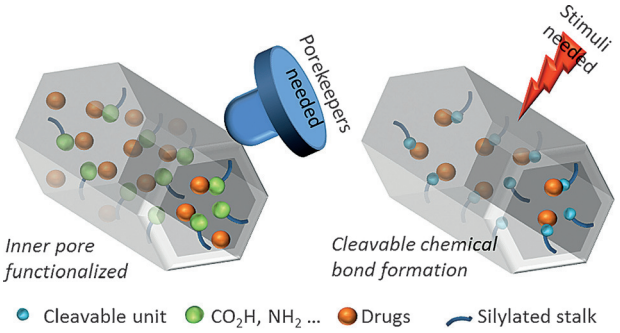
Scheme 4. Methods for MSNP modification: A) post-grafting, B) surface coating, C) co-condensation and D) bridged silsesquioxanes.

addition of functional molecules may affect the structural features of the resulting MSNPs, namely their pore structures.

In order to obtain a homogeneous distribution of organic groups inside the framework, a high loading of organic groups and a narrow pore size distribution, the sol–gel process can be performed with organo-bridged silsesquioxane (BS) precursors,[16] a single molecular organosilane with the organic fragment connected to at least two trialkoxysilyl groups, in the presence of organic soft template and without any silica source to produce periodic mesoporous organosilicas (PMO)[17] (Scheme 4D). To date, very few reports deal with the preparation of pure PMO-based nanoparticles due to the difficulty of precisely controlling the growth of the nanoparticles during the hydrolysis–condensation of the activated organosilanes, the bulkiness and chemical features of bridging groups greatly affecting the sol-.gel reaction and surface properties. In fact, most often in such MSNP synthesis, the BS precursor still forms as gel with TEOS.

Drug Loading and Release Rate

Drugs can be introduced into silica by using essentially two different strategies (Scheme 5).



Scheme 5. Strategies for drug loading.

The most commonly used method, due to several advantages, is the physical trapping of drugs inside the pores of MSNPs, the silanol groups serving as adsorption sites. This method does not require any chemical modification of the drug to form chemical bonds and can be easily applied for various drugs. In addition, it allows a high loading percent up to 30wt% due to the high surface area and pore volume of MSNPs. The adsorption can be favored when the pore surface is modified with functionalities, such as weak acids or bases, like carboxylic acids or amines, to provide additional adsorbate/adsorbent interactions, like strong hydrogen bonding, and then optimize the interactions between the drug and silica support. These modifications can also directly affect the release rate of the drug[18] by increasing its diffusion resistance. In addition, the mobility of the drugs, and consequently the release efficiency (amount of drug released/total uptaken amount) of MSNPs, is also affected by their electrostatic interactions with their surroundings. For instance, the release efficiency is higher when the silica surface is modified with positively charged amine groups—the charge expulsion between the positively charged drugs and the particle surface enables them to move efficiently out of the pores.[19]

However in most cases, the interactions are not strong enough to prevent the release of the housed compound before reaching the target site. If a nontoxic and well-tolerated prodrug,[20] for which an activating enzyme is not present and has to be co-administrated for its activation, is loaded the necessity to avoid the premature release is not as important as in the case of transporting a conventional cytotoxic drug. Indeed, for the latter avoiding this release during the blood circulation should reduce side effects and can be done by using a stimuli-responsive pore-keeper which will be outlined later below.

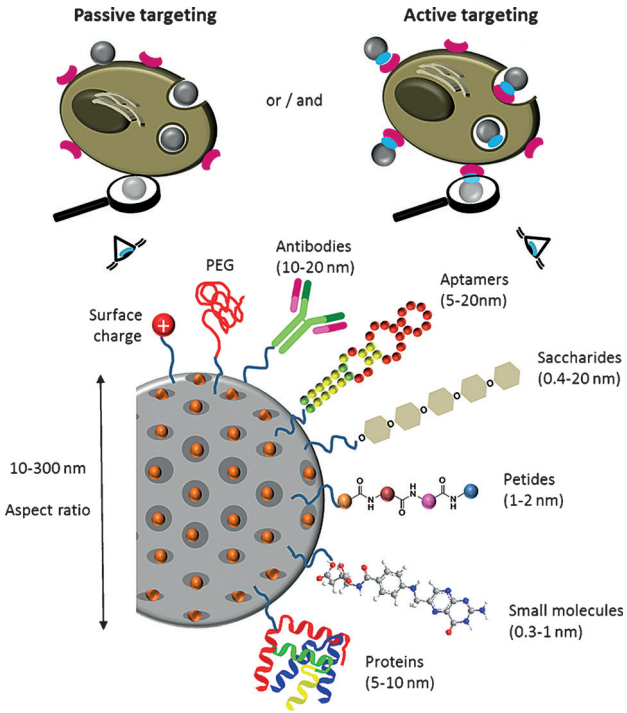
The second strategy to incorporate the drug consists in covalently linking it to silica using a stimuli-responsive cleavable bond which will be also detailed later.

Targeting

As already mentioned, one of the major disadvantages of currently used drugs is their lack of target selectivity between healthy and diseased cells which leads to significant side effects and to a reduced therapeutic efficiency. MSNPs as DDSs can provide a solution to improve the transport of drugs using, among others, their surface properties for targeting passively or/and actively[21] a specific area in the body (Scheme 6).

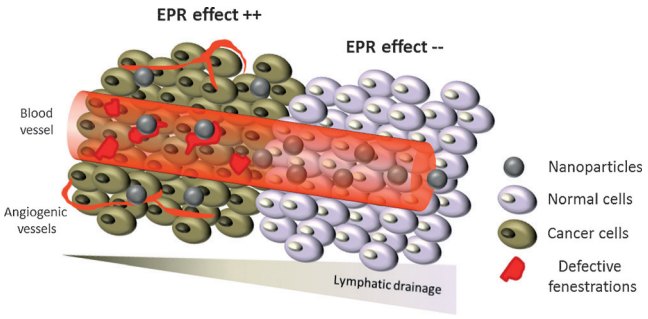
Passive targeting

Effective passive targeting is favored by the "enhanced permeability and retention" (EPR) effect, discovered by Matsumura



Scheme 6. Passive and active targeting possibilities on MSNPs.

and Maeda in 1986,[22] which causes the accumulation of nano-objects or macromolecules in tumors. The rapid angiogenesis in solid tumors, which generates anomalies in tumor blood vessels (permeability), and the poor lymphatic drainage in the tumor area (retention) lead to a preferentially delivery of nano-objects in tumors with a concentration that is 70 times higher than in normal cells. Indeed, irregular blood vessels are rapidly formed in the solid tumors to provide the nutrient and oxygen supply for cells proliferation. They thus exhibit discontinuous epithelium with wide defective fenestrations from 200 to 2000 nm depending on the location and tumor type.[23] Consequently, when the nanoparticles reach these vessels, they escape through fenestrations to the tumor interstitium during extravasation. Furthermore as the lymphatic drainage is defective in tumors, unlike normal tissues in which the extracellular fluid is constantly drained to the lymphatic vessels, nanoparticles are trapped in the tumor interstitium and hence resulting in an accumulation in the tumor tissues (Scheme 7).



Scheme 7. Enhanced permeability and retention effect.

To avail the EPR effect and obtain effective passive targeting, nanoparticles should meet some criteria for size, shape and especially surface properties.

The optimal diameter size range of nanoparticles for long circulation time, increased accumulation in the tumor and efficient cellular uptake is 50–300 nm.[24] In this range, nanoparticles will avoid renal clearance[25] and diffuse in sufficient quantities through the tumor area for a therapeutic effect.

The DDS shape plays also an important role in biological effect; however, since opposing observations have been reported, it is really difficult to take the shape as a single variable and establish the relationship between particle shape and performance for drug delivery. Recently, Huang et al[26] evaluated the capability of internalization by tumors cells through the non-specific cellular uptake of MSNPs with similar particle diameter, chemical composition, and surface charge, but with different shapes (AR: aspect ratio length/width). Their in vitro attempts showed that the rod particles (bigger AR) were internalized faster and in larger amounts than spherical ones (AR of 1). This result reminds us that MSNPs with large AR and suitable diameter may have longer circulation times than the spherical ones, which may enhance significantly the therapeutic efficacy of the nanoparticulate DDSs.[27]

The interactions between biological environment and MSNP surfaces are the main parameters to be considered to limit effects that reduce the blood circulation time of nanoparticles. The surface properties of MSNPs can be modified with functionality to prolong as long as possible their circulation in the bloodstream by decreasing the nonspecific binding of nanoparticles to plasma proteins (opsonins) causing their rapid removal by macrophages.

The combination of silica nanoparticles with hydrophilic and neutral polymers, such as polyethyleneglycol (PEG), on external surfaces has been described as "stealth" nanocarriers[28] with reduced opsonization and better stability in biological fluids due to the hindered and repulsive PEG chains. The PEGylation methods can be achieved through covalent grafting or physical adsorption of PEG chains. Compared with the PEG physical adsorption, the covalently PEGylated nanoparticles can keep higher accessibility to PEG chains and thus possess longer blood circulation half-life times. The PEG molecular weight and conformation directly affect their hydrophilicity and flexibility and consequently the steric repulsion against blood proteins and macrophages. PEG10k-silanes were reported as optimal precursors to reduce phagocytosis.[28b]

To maximize the cellular uptake of nanoparticles, their surface characteristics are also essential and, more particularly here, the charge on the surface. Some studies have shown that a highly positive-charged surface of MSNPs enhances the uptake into cells with specific endocytosis pathways. The surface modification of MSNPs to introduce cationic charges typically involves grafting with amine groups (quaternary ammonium)[29] or coating with a cationic polymer (polyethyleneimine (PEI))[14] through either covalent or electrostatic associations. However, it is important to note that the charge effect of cell-uptake is dependent on the cell type.

Active targeting

As has been seen previously, MSNP surface can be chemically modified to further include functionality, such as ligands, to promote active targeting. These ligands selectively bind molecules (antigens) or receptors overexpressed on surface or in the nuclei of the diseased target, such as mannose, galactose, asialoglycoprotein, transferrin (TfR), human epidermal growth factor (HER or EGFR), $\alpha v\beta 3$ integrins, importin α/β and folate (FR) receptors or CD20 and 44 antigens, which have been proved to be potential cellular targets for applications in nanomedecine. Therefore, several targeting ligands (Scheme 6) that compliment these receptors can be employed to conjugate on the MSNP surfaces

1) Antibodies, grafted onto PEG or other hydrophilic polymers for dispersibility and cellular uptake, to target specific antigens but with possibly immune response by the host.
2) Proteins, such as transferrin (Tf), since TfR can be overexpressed in pancreatic, breast, or cervical carcinoma.
3) Aptamers (nucleic acids) owing to their small size, non-immunogenic nature, facile synthesis and modification, and high specificity and affinity for their target.

4) Peptides (< 50 amino acids), which are more advantageous to use than proteins or antibodies, with an improved stability, easy synthesis, and no immune response.
5) Saccharides to bind lectins, carbohydrate receptors overexpressed on certain tumors.
6) Small molecules, such as folic acid which is one of the most widely used, can be conjugated on MSNPs in larger amounts than with voluminous compounds, and are less expensive and with low immunogenicity.

Table 1 shows some concrete examples of these ligands grafted on MSNPs, the corresponding targeted cells line, and cell membrane receptors.

In cancer therapy, active and passive targeting are complementary, but the targeting efficiency is not only related to the abundance of the receptor on the target, but also to the density of the ligands on nanoparticles. Indeed, as the abundance of the receptors overexpressed on membrane cell is variable, the grafted ligand density should be optimized to obtain the best targeting efficiency.

The surface grafting with ligands can then be achieved by using several methods (Scheme 8), but always in such a way that the ligand is easily accessible by the membrane cell. Different strategies based on coupling reactions have been developed: carbodiimide-mediated coupling, maleimide/thiol coupling, disulfide bond formation, epoxy opening with amines, and diethyl squarate mediated coupling. Other grafting methods were also achieved by using non-covalent interactions: electrostatic, hydrophobic, and host–guest interactions.

Table 1. Examples of ligands grafted on MSNPs.

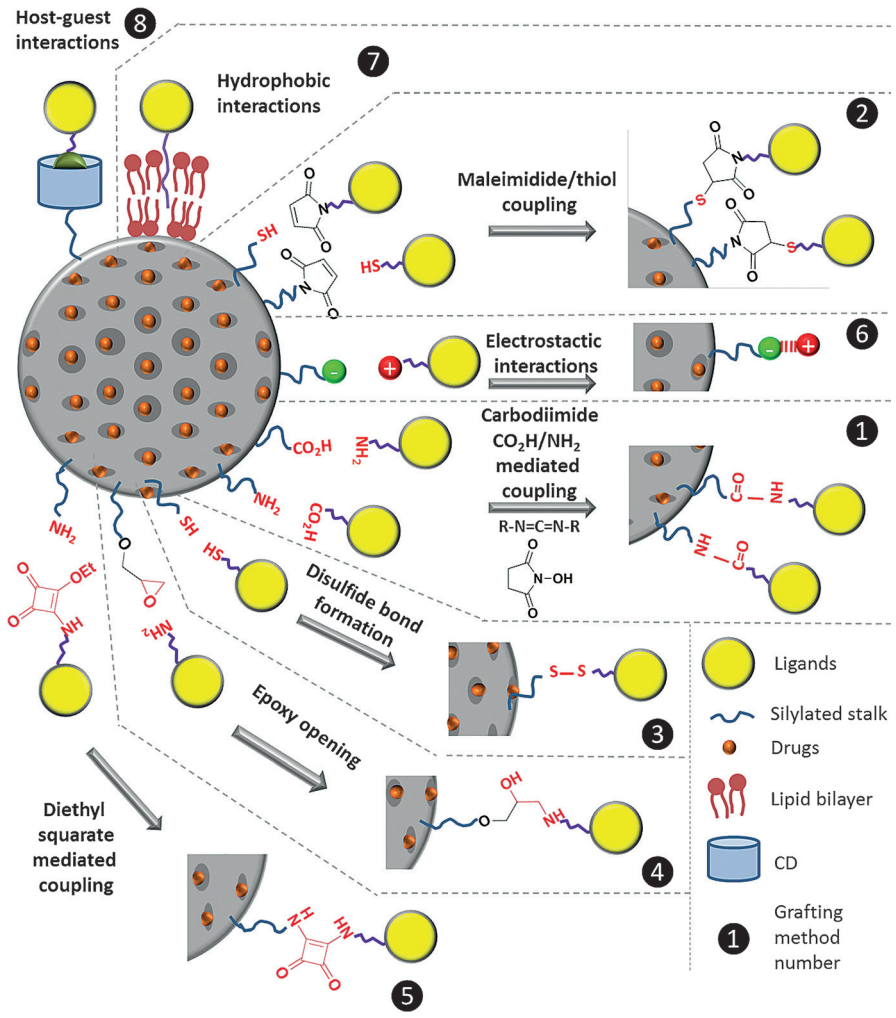
Ligand	Targeted cell line (cell membrane receptor)[a]	G.M.[b]
antibodies		
anti-ErbB 2 (Ab2428)[30]	MCF-7 (ErbB2)	6
anti-HER2/neu[31]	BT474 (HER2/neu)	2
anti-herceptin[32]	SK-BR3 (HER2)	1
anti-ME1[33]	MM (mesothelin)	1
anti-TRC105[34]	HUVECs (CD105/endoglin)	2
aptamers		
aptamer AS 1411[35]	MCF-7; MDA-MB-231 (nucleolin)	2
$TBAA_{15}C_{18}$[36]	HeLa (thrombin)	7
peptides		
c(RGDyK)[37]	U87-MG ($\alpha v\beta 3$ integrins)	2
cRGD[38]	MDA-MB 435 ($\alpha v\beta 3$ integrins)	3
IL-13 peptide[39]	U251 (IL13Rα2)	2
KALA peptide[40]	A549	3
K_7RGD; c-RGDFK[41]	HeLa ($\alpha v\beta 3$ integrins)	1
$K_8(RGD)_2$[42]	U87-MG ($\alpha v\beta 3$ integrins)	6
N_3GPLGRGRGDK-Ad[43]	SCC-7; HT-29 ($\alpha v\beta 3$ integrins)	8
N_3RGDFFFFC[44]	U-87 MG ($\alpha v\beta 3$ integrins)	3
SP94 peptide[45]	Hep3B	2
TAT peptides[46]	HeLa; MCF-7/ADR (importing α/β)	1
thiolated-RGD[47]	A375; HepG2; MCF-7; Neuro-2a ($\alpha v\beta 3$ integrins)	2
proteins		
EGF[48]	HuH-7 (EGFR)	2
Tf[38,49]	PANC-1; BT-549; HeLa (TfR)	4 or 1
saccharides		
galactose[50]	HCT-116; Capan-1; MDA-MB-231 (galactose receptor)	5
hyaluronic acid[51]	HTC-116; MDA-MB-231 (CD44)	1
lactobionic acid[52]	HepG2 (asiaglycoprotein receptor)	1
mannose[53]	MDA-MB-231 (mannose receptor)	5
small molecules		
anisamide[54]	ASPC-1 (sigma receptor)	1
folic acid[55]	HeLa; PANC; U2Os; MDA-MB-231; SK-BR-3; MiaPaca-2 (FR)	1
methotrexate[56]	HeLa (FR)	1
phenylboronic acid[57]	HepG2 (sialic acid)	1

[a] Targeted cells lines - Human: Breast cancer : MCF-7; BT474; SK-BR3; MDA-MB-435; MCF-7/ADR; BT-549; SK-BR-3; MDA-MB-231(metastatic). Multiple myeloma: MM. Umbilical vein: HUVEC. Epithelial cervical carcinoma: HeLa. Primary glioblastoma: U87-MG. Lung carcinoma: A549; H1299. Osteosarcoma: U20S. Hepatoblastoma-derived: HepG2. Squamous carcinoma: SCC-7. Intestinal epithelial: HT-29. Hepatoma: Hep3B; HuH-7. Amelanotic melanoma: A375. Pancreatic cancer: PANC-1, Capan-1; ASPC-1; MiaPaca-2. Colon carcinoma: HCT-116 - Mouse neuroblastoma: Neuro-2a. [b] G.M.: Grafting method number—see Scheme 8.

Triggered Release

MSNPs possess a unique parallel-pore network without any connections between them; however, developing DDSs with drugs simply adsorbed into these pores may present major drawbacks. Indeed, they will lead to the immediate release of the cargo molecules after the administration, then to the decomposition/denaturing of the drugs and also to the nonspecific uptake of drugs by healthy cells before reaching the target diseased cells causing, similarly to classical therapy, severe side-effects.

As already mentioned above, an ideal drug carrier should show zero premature release of the housed drugs prior to the target. This is made possible by placing different organic or inorganic moieties acting as pore-blockers or gatekeepers on the pore outlets. These blockers should be able to respond by a chemical or physical change to different stimuli allowing to close and open the pores on demand. In this case, the drugs cannot leak out from the silica carriers unless the system is exposed to an internal or an external stimulus that induces the removal of caps, thus allowing the release of the entrapped drugs. These MSNP-based stimuli-responsive systems were originally developed by Lin's group,[58]



Scheme 8. Grafting methods for functionalization of MSNPs.

and resulted in a marked increase of the efficiency of treatments.

In the following we will describe in detail different strategies of functionalization to introduce diverse gatekeepers, either directly with their silylated derivatives or using silylated linkers, which will respond to stimuli such as enzyme, pH, redox, temperature, light, and key molecules (Scheme 9).

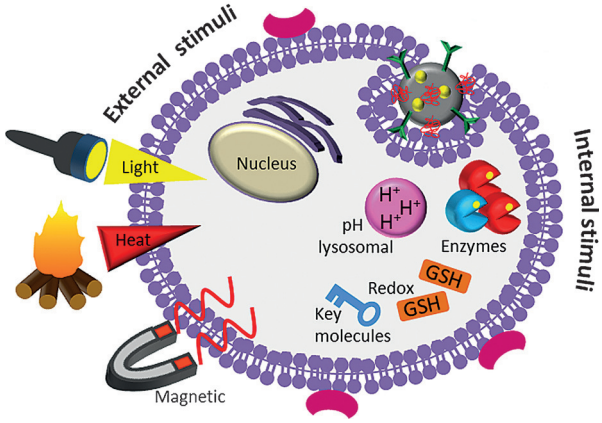
Enzyme-triggered release

Dysregulation of enzymatic activity and anomalous increase of enzymatic presence has been observed in a number of diseased states that make enzymes interesting stimuli to trigger drug release by using their biocatalytic actions.[59] Hydrolases (including proteases, lipases and glycosidases) are the most widely used enzymes for drug delivery probably due to the facile design involving the attachment of moieties to carrier through enzyme cleavable units. Recently several strategies using innovative approaches for enzyme-triggered release of entrapped drugs have been proposed with functionalized MSNPs.

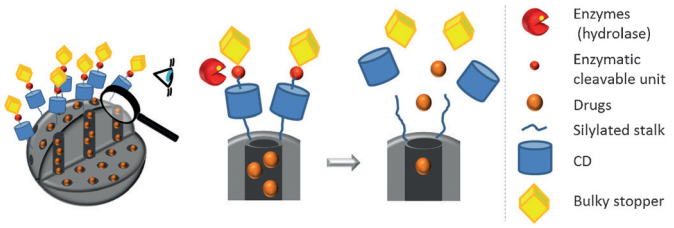
The first enzyme-sensitive gate on MSNPs was described by Stoddart and co-workers,[60] who functionalized the nanoparticle surface with stalks encircled by cyclodextrins (CD) and incorporated an enzyme cleavable site, generally an ester function, with a bulky stopper. In the presence of esterase the responsive bond is cleaved, the molecular gate removed, and the drug released (Scheme 10).

An enzyme-sensitive system was also obtained by using biotin to functionalize MSNP surface. The biotin functions can form a complex with the protein avidin[61] through strong interactions, resulting in the closure of the pores. The hydrolysis of the avidin cap by the protease trypsin opens the pores and allows the release of cargo molecules (Scheme 11).

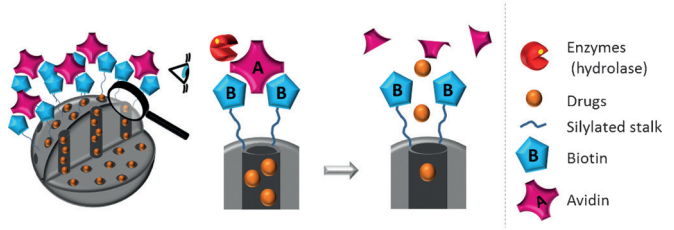
Another strategy consists in attaching enzymatic-sensitive caps to the surface to hamper the drug diffusion until the MSNPs meet enzymes capable of decomposing them and releasing the access of the pores. Polysaccharides,[62] polypeptides,[63] hyaluronic acid (HA),[51b] polyesters,[64] or CD,[65] can act as capping agents after grafting them to the entrance of the pores of MSNPs (Scheme 12), where they remain until they face β-galactosidase, amidase, esterase, protease, hyaluronidase or metallo-proteinases.



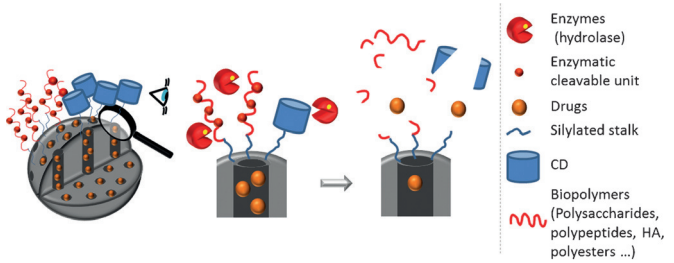
Scheme 9. External and internal stimuli used for triggered release.



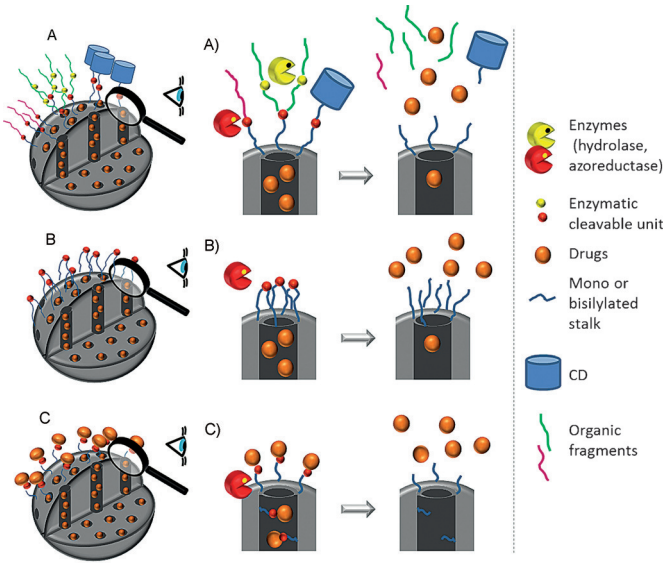
Scheme 10. Enzyme-mechanized caps.



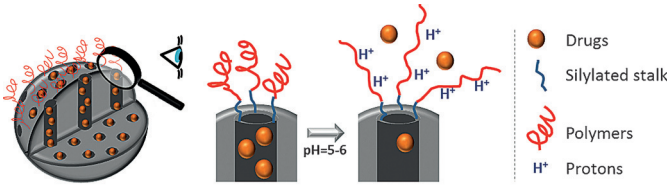
Scheme 11. Avidin–biotin caps.



Scheme 12. Decomposable caps.



Scheme 13. A) Mono and B) bi-anchored caps and C) anchored drugs.



Scheme 14. Anchored polymer caps with basic properties.

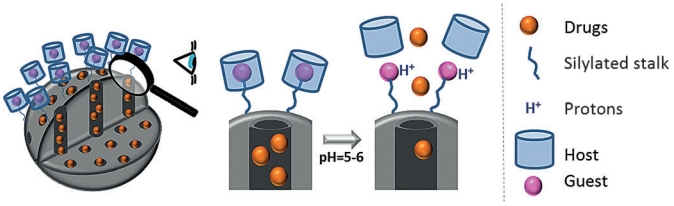
Finally the last way proposed in the literature consists in directly anchoring the cap (Scheme 13 A and B) or the drug (or prodrugs; Scheme 13C) on the silica surface by using mono- or bisilylated enzyme-sensitive linkers. CD,[65] ester–glycol groups,[66] bulky organic moieties,[67] bridged silsesquioxane[68] or sulfasalazine (prodrugs of 5-aminosalicilic acid)[69] were linked to MSNPs bearing enzyme-cleavable functions, such as esters, ureas, amides, and peptides that are responsive to hydrolases or azo bonds degraded by azo-reductases.

pH-responsive systems

pH-sensitive DDSs are often employed, since the human body exhibits variations in pH at organ, tissue and cellular levels. Indeed, pH variations are observed along the gastrointestinal tract from the stomach (1.0–3.0), to the small intestine (6.5–7.0) and to the colon (7.0–8.0). Moreover, different pathologies such as cancer or inflammation present pH gradients. For instance, the extracellular pH of tumor tissues (6.5–7.0) or the pH of inflamed tissues and wounds (5.4–7.2) are more acidic than the pH of blood and normal tissues (7.4). In addition, when nanoparticles are internalized inside cells, they can be exposed to different pH depending on the cell compartments. Indeed, pH values in cytosol (7.4), Golgi apparatus (6.4), endosomes (5.5–6.0) and lysosomes (5.0) are considerably different. Thus, by functionalizing the MSNP surface with appropriate functions, pH-sensitive stoppers can be used as pore-blockers to control the drug release in response to these pH changes.[70]

One strategy consists in the grafting of polymer chains bearing functional groups with basic properties that change their conformation in response to an external pH (Scheme 14). Diverse pH-sensitive polymers, such as poly(4-vinylpyridine),[71] poly(2-(diethylamino)ethylmethacrylate),[72] chitosan,[73] starch,[74] or poly(styrene sulfonate),[75] have been attached to MSNP surfaces. At neutral pH (7.4), the polymer chains are in a neutral state with no charge and then interact with themselves by adopting a collapsed conformation on the MSNP surface, blocking the pores and inhibiting the drug release. Under mild acidic conditions, such as in the lysosome compartment (pH ca. 5), the polymer chains are protonated and positively charged, resulting in movement to an extended conformation allowing the cargo molecules to leak out of the particles. In contrast, a neutral medium induces the pore opening of MSNPs functionalized with polyamines.[76]

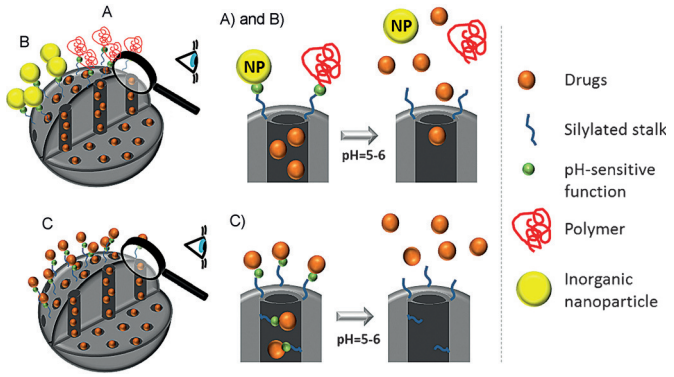
Another way to cap the pores is based on pH-sensitive host–guest interactions using mobile polymacrocyclic molecules, such as CD[77] or cucurbit[6]uril,[78] which are able to form inclusion complexes with different immobilized organic molecules covalently attached to MSNP external surface, and that



Scheme 15. Supramolecular nanovalves.

can dissociate upon exposure to acidic lysosomal pH (Scheme 15).

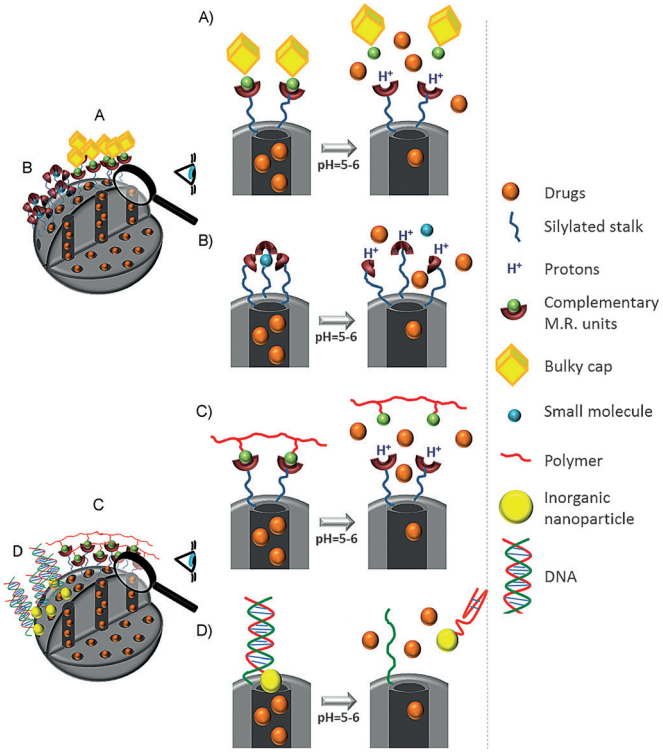
MSNP surfaces can also be functionalized with stalks containing pH-sensitive functions, such as boronates, acetals, hydrazones, imines, esters and so forth, and bearing as caps inorganic nanoparticles, such as gold,[79] iron oxide,[80] cerium oxide,[81] or polymers, such as polyacrilic acid (PAA)[82] or PEG hosting CD.[83] Under mild acidic condition the linker breaks allowing the drug to leave the pores (Scheme 16 A, B). Drugs, such as Doxorubicin (DOX)[84] or cis-platin,[85] can also be directly grafted on the surface using similar acid-sensitive functions (Scheme 16 C).



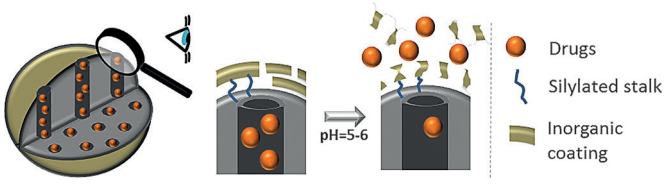
Scheme 16. Anchored A),B) caps and C) drugs.

MSNPs can also be grafted with silylated stalks bearing molecular recognition (MR) units able to form, at neutral pH, complexes through hydrogen bonding with complementary entities to cap the pores and which can dissociate at acidic pH to deliver the drug (Scheme 17). Such MR units can be a nucleic base, a DNA strand or a melamine derivative that are able to complex polynucleotides,[86] DNA strands linked to Au nanoparticles[87] or thymine–mercury–thymine pairs,[88] CD,[89] cyanuric acid, or 5-FU derivatives,[90] respectively, bearing the complementary pattern and acting as the stopper. Under the lysosomal pH (ca. 5), an acceptor site of the MR unit is protonated, cleaving the hydrogen bonds and dissociating the complex allowing cargo molecules to come out of the pores.

Finally the last approach relies on functionalizing MSNP surfaces with a pH-decomposable inorganic coating that acts as a gatekeeper either by using a covalent silylated linker (ZnO quantum dots nanolids,[91] hydroxyapatite[92]) or by electrostatic interactions (layered double hydroxide nanosheets,[93] calcium



Scheme 17. Various caps with molecular recognition units.



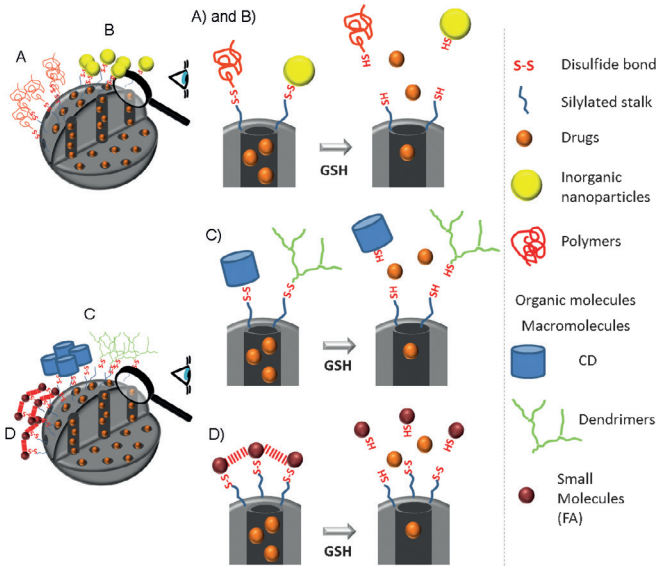
Scheme 18. Inorganic acid decomposable coating caps.

phosphate (CaP)[94]). Upon exposure to acidic pH, the coating starts to dissolve uncapping the mesopores (Scheme 18).

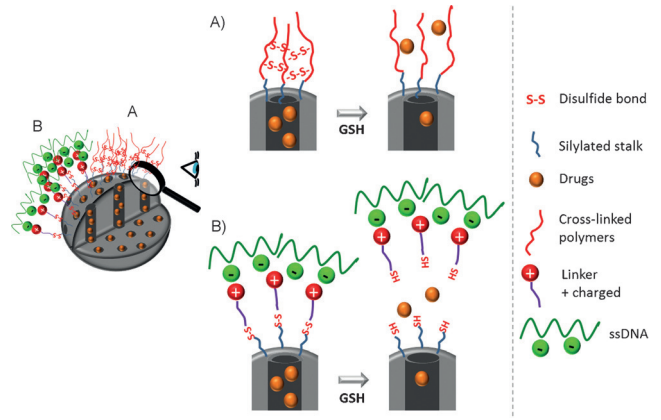
Redox-responsive systems

Glutathione (GSH), a tripeptide containing a thiol group, is a reducing agent that breaks disulfide groups to give two SH functions. As glutathione is more (1000 times) concentrated inside than outside cells and in tumor tissues rather than in healthy ones, it can be used as stimulus to release drugs[95] from MSNPs functionalized with a disulfide (S–S) linkage, which would be stable in blood and in normal cells and be scissored in cancer cells.

MSNP surfaces can be functionalized with silylated stalks containing disulfide bonds and bearing a pore-keeper that can be of a different nature: an inorganic entity, such as CdS,[58] Fe_2O_3[96] or Au nanoparticles,[97] a polymer, such as collagen[52] or PEG[98] (Scheme 19 A, B), or an organic molecule, such as CD,[99] dendrimers,[100] peptides[101] or folic acid[102] (Scheme 19 C, D).



Scheme 19. Anchored A) polymeric, B) inorganic and C),D) organic caps.

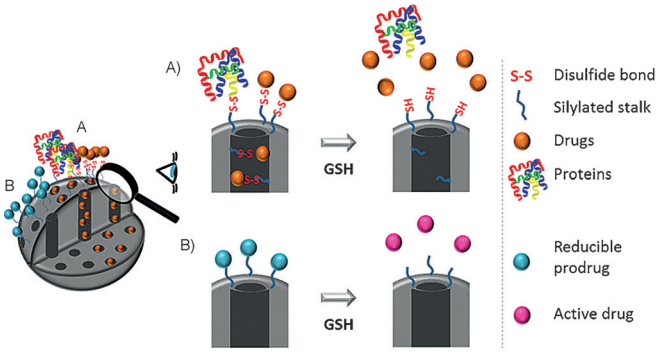


Scheme 20. A) Cross-linked polymers and B) ssDNA coating caps.

Polymers that can cross-link with disulfide bonds on the outer surface of MSNPs[103] can form a shell around the nanoparticles which through a redox stimulus will dissociate allowing the drug release to occur (Scheme 20 A).

Moreover, silylated stalks with disulfide bonds can also be endowed with a charged organic moiety (NH^{3+}) to electrostatically interact with an oppositely charged coating ($ssDNA^{-}$) acting as cap (Scheme 20 B).[104]

Active cargo molecules can also be attached to MSNPs by means of a redox-sensitive linker without losing their activity once released. Thus, anticancer drugs (paclitaxel, PTX)[105] or enzymes (carbonic anhydrase, cytochrome c)[106] have been grafted by using a silylated stalk with disulfide bond (Scheme 21 A). Furthermore reducible inactive prodrugs, such as cisplatin,[107] can also be linked on nanoparticle surfaces and be released and activated in the GSH-rich reductive environment of cancer cells (Scheme 21 B).

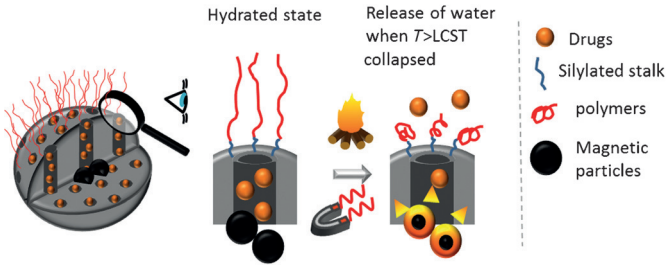


Scheme 21. Anchored A) active compounds or B) reducible prodrugs.

Magnetic and thermo-responsive systems

Hyperthermia (or thermotherapy) is a cancer treatment method in which body tissue is exposed to slightly higher temperatures (up to 45 °C) to kill cancer cells or to make cancer cells more sensitive to radiation effects and/or to certain anticancer drugs. It can be artificially induced by using injections of heated fluids or magnetic field. Consequently functionalizing MSNP surfaces with thermo-responsive agents acting as caps would provide an effective method to control drug release. In the case of magnetic field, the temperature is generated by magnetic particles encapsulated in the silica matrix. The most widely employed magnetic particles are super-paramagnetic iron oxide nanoparticles (SPION).[108]

Thermo-sensitive polymers that exhibit a hydrated state at temperatures below their lower critical solution temperature (LCST) may be used, after grafting on MSNP surfaces, as a barrier for the cargo molecules. For a temperature above the LCST they release water and then collapse causing the pores to open and the drugs to be released (Scheme 22). For example,

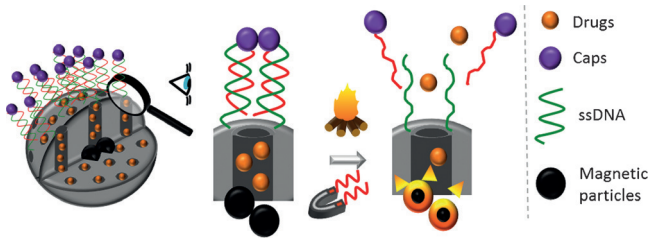


Scheme 22. Thermo-sensitive polymers with lower critical solution temperature (LCST) as a cap.

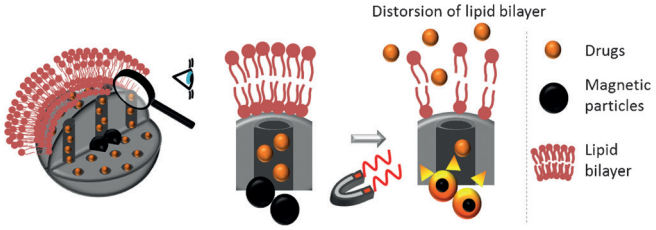
polymers such as poly-*N*-isopropylacrylamine (PNIPAM)[109] or poly-*N*-vinyl-caprolactam[110] have been used as caps. However, it was also demonstrated that, depending on the synthesis conditions, PNIPAM can also act as stoppers for a temperature above its LCST.[111] Here, PNIPAM and MSNPs are preformed and the authors explain this different behavior by the significant grafting of the former essentially at the pore surface and not within the pores like in the previous case.

MSNPs can also functionalized with a thermosensitive single-strand DNA (ssDNA) linker, which on hybridization with a complementary strand bearing a cap (iron oxide nanoparticle[112] or avidin-biotin[113]) causes the pore closure. The opening of the pore is achieved during the progressive double-strand melting by increasing the temperature allowing their dissociation (Scheme 23).

As already mentioned a lipid bilayer can create a coating on MSNPs that closes the pores.[114] On heating, through the introduction of a magnetic field, the bilayer can be distorted to release the drugs (Scheme 24)



Scheme 23. Hybridization/dehybridization by melting a DNA linker as a gatekeeping mechanism.



Scheme 24. Lipid bilayer as a cap.

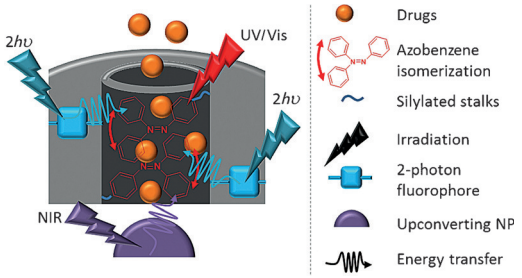
Finally, mechanized MSNPs with nanovalves have also been described as DDSs that are responsive to heat activation.[115] Indeed, a nanovalve that is non-self-opening in biological systems and which exhibits thermal stability at room temperature can be attached to the MSNP surface. An increase in temperature leads to the disassembly of the molecular machine resulting in the opening of the valve, allowing the contained cargo molecules to diffuse out.

Light-responsive systems

Light-activated drug release allows a better control, since light can be easily focused in small areas reducing the potential side effects for the neighboring regions. Different sources can be used to trigger the release: UV/Vis light—but with limited applications since it can damage the cells and does not penetrate deep inside living tissues—or NIR radiation, especially two-photon excitation (TPE), which provides deeper and safer penetration (down to 2 cm), lowers scattering losses and gives good 3D spatial resolution of the excitation at the focal point of the laser.

External light manipulations, such as changing irradiation wavelength, intensity, and time, can regulate the release of the drug precisely. Recent and striking reports on functionalized MSNPs with light-sensitive entities are described below.

A first example makes use of the anchorage of azobenzene units. The pore channels of MSNPs can be decorated with silylated azobenzene derivatives (Scheme 25). The azobenzene



Scheme 25. Various nanoimpellers.

unit isomerizes from the *cis* to the *trans* conformation under UV/Vis irradiation. Without light activation, it acts as a pore-keeper in its *trans* conformation and, under continuous UV/Vis illumination, it acts as a nanoimpeller, owing to a constant *cis*–*trans* photoisomerization of the N=N bond that causes a dynamic wagging motion and propels the drugs out of the pores.[116]

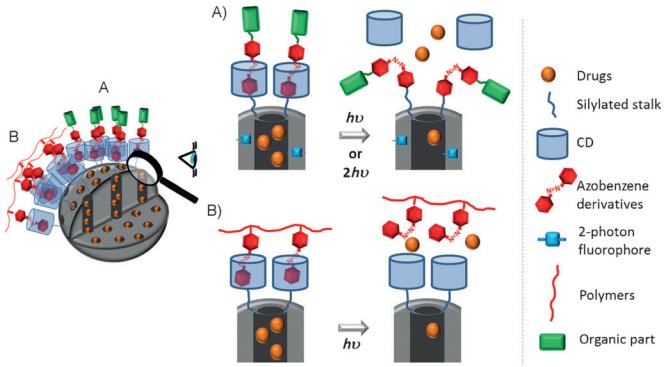
By introducing up-converting nanoparticles (NaYF4:TmYb) as core in MSNPs,[117] NIR light can also be used, since these materials are able to absorb it and emit photons in the UV/Vis region, which in turn can be absorbed immediately by the photo-responsive azo molecules. An additional way is to functionalize the walls with a bisilylated two-photon fluorophore,[118] which on light-activation is suitable to transfer energy by the Forster resonance energy transfer (FRET) to photoisomerize the azobenzene in the NIR region.

MSNP surfaces can also be grafted with stalks containing azobenzene derivatives capable of reversibly binding CD caps, again due to the photoisomerization.[119] Moreover, a silylated two-photon fluorophore[120] can also be incorporated in the walls to use NIR irradiation (Scheme 26 A). The azobenzene/CD nanovalve is then activated by FRET transfer from the two-photon excited *para*-cyclophane fluorophore delivering a drug for efficient cancerous cell killing.

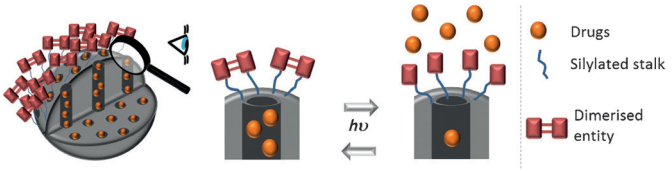
The host–guest assembly[121] can also be achieved between CD anchorage and azobenzene polymers (Scheme 26 B).

Organic moieties, which under UV/Vis suffer from reversible photodimerization, such as thymine or coumarin,[122] can also be incorporated as stoppers on MSNP surfaces (Scheme 27).

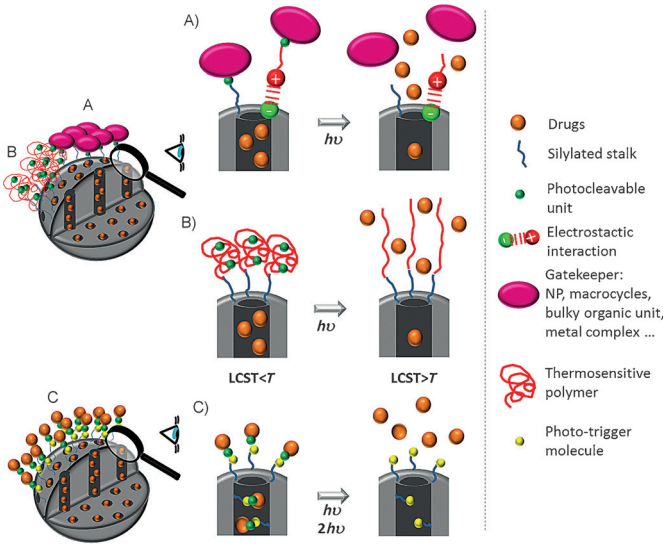
Another strategy consists in grafting gatekeepers bearing a light-sensitive linker, either covalently with a silylated stalk or using electrostatic interactions. The pore-blockers can be nanoparticles (CdS,[123] Au[124]), macrocycles (CD[125]), bulky organic units,[126] or metal complexes[127] and the photo-cleavable linker can be *o*-nitrobenzylester or carbamate, *o*-methylbenzylamine, or a coordination bond (Ru–S) (Scheme 28 A).



Scheme 26. Reversible host–guest inclusion as capping agents.



Scheme 27. Photodimerizable caps.



Scheme 28. Anchored A),B) caps or C) drugs bearing photo-cleavable linkers.

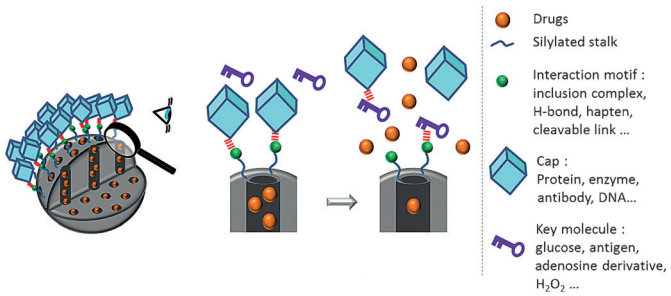
Moreover, thermo-sensitive polymers containing light-sensitive groups can also be grafted on MSNP surfaces as valves.[128] With a LCST below 37°, the polymer collapses blocking the pores. Upon UV irradiation, the photolysis of light-sensitive groups occurs that leads to an increase in the LCST of the resulting polymers higher than 37 °C. Thus the polymer changes its phase state and the loaded molecules are released from the hybrid nanoparticles (Scheme 28 B).

Drugs can also be loaded covalently in MSNPs through a silylated stalk with a photo-trigger molecule and a cleavable link. For example, a coumarin derivative modified with anticancer chlorambucil[129] has been grafted onto the surface of MSNPs. Upon the irradiation of two-photon excitation, the coumarin derivative chromophore, which has a sufficiently high two-photon absorption cross section, acts as a photo-trigger to uncage anticancer drug chlorambucil (Scheme 28 C).

Gold nanoparticles (AuNPs) possess intense adsorption bands in the NIR range and upon exposure to a NIR laser beam their adsorbed photo-energy is converted into heat with high efficiency. Consequently functionalizing MSNPs that possess a gold core with thermo-responsive pore-blockers is another way to control the drug release. For example, the photothermal conversion in AuNPs can be combined with temperature-dependent assembly properties of a CD host–guest[130] or DNA.[131] Plasmonic heating of the gold core raises the local temperature, which consequently decreases the ring–stalk binding constant or induces the DNA dehybridization, thereby unblocking the pores and releasing the cargo molecules that were preloaded inside.

Key molecules

As in the case of enzymes, some diseases accumulate or produce an abnormal amount of certain chemical species that can be used as key molecules; such molecules should possess molecular recognition and responsive properties to open pore-blockers and trigger drug release[132] (Scheme 29).



Scheme 29. Key-molecule-responsive caps.

In diabetic treatment, glucose can be used to open glucose-sensitive gatekeepers. For this MSNPs can be functionalized with proteins or enzymes (Gox, G-ins) acting as caps and the uncapping process is triggered either by the product obtained by the activity of the enzyme on the target substrate or by the target substrate itself due to a competitive reaction or a higher affinity.[133] For instance, CD-modified glucose oxidase forming an inclusion complex with propylbenzimidazole and grafted on MSNPs is split (pore opening) in the presence of glucose, which is converted by GOx into gluconic acid producing a pH drop that induces the protonation of benzimidazole.[133c]

Besides proteins, antibodies are also used as pore-blockers, binding with haptens grafted on MSNP surfaces and the uncapping being induced by the presence of an antigen with higher affinity for the antibody.[134] Such competitive binding is

also observed between aptamer- or DNA-functionalized MSNPs and adenosine derivatives.[135]

For Alzheimer's disease, H_2O_2 responsive MSNPs have also been designed by grafting aryl boronic acid on the surface which can bind immunoglobin acting as caps through boronic ester bonds. These bonds are cleaved when H_2O_2 is added, releasing the loaded molecules.[136]

Summary and Outlook

MSNPs represent promising and powerful candidates for efficient DDSs due to their excellent properties as evidenced by the numerous recent publications describing the design of new materials and the increasing number of reviews[7] devoted to them. As described in this concept article, functionalization of MSNPs has allowed the engineering of tumor-targeted and stimuli-responsive DDSs and their performance in vitro has been demonstrated successfully and is no longer in doubt.

Such MSNPs are expected to play an important role in this field although clinical applications may not emerge overnight. The next stage is to facilitate the transition from in vitro to in vivo. Indeed, when the nanocarrier is injected in blood, it will be rapidly covered by proteins that can affect its stability, the gatekeeping mechanism, or targeting capacity. Therefore more experiments are needed to guarantee that its behavior will be maintained in living tissues. In addition we need evidence to prove that the active targeting will efficiently improve their in vivo accumulation and is really advantageous compared to the passive one. Indeed, most of the targeting ligands tested for active targeting have also great absorption in the liver and spleen, which may induce side effects to normal tissues and organs.

Moreover, to increase the therapy efficiency early diagnosis is crucial for patient survival. Then, producing multifunctional MSNPs, with several organic functions required to direct specific targeted roles such as imaging and therapy, represents another challenging task in nanomedecine to provide a universal platform for theranostics. In this direction, novel nanohybrid silicas, namely nano-PMO (illustrated in Scheme 4 D), represent an emerging family of silica nanoparticles that allow multiple functionalities on a single system (functionalized inner and outer pore surface as well as pore-walls) and may thus help in conceiving and constructing new smart MSNPs with several operating functions (targeting, trigger, pore-blocking and opening, etc.) although the development of these MSNPs is still in its infancy.

Acknowledgements

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Keywords: drug delivery · mesoporous silica · nanoparticles · surface functionalization · targeting

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