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Review

Silica-based organic-inorganic hybrid nanoparticles and nanoconjugates for improved anticancer drug delivery

After the introduction of first generation MSNs for drug delivery with some challenges such as large particle sizes, irregular morphologies and aggregations, second generation provided uniform spherical morphologies, tunable pore/particle sizes and compositions. Henceforth, organic-inorganic hybrid mesoporous silica nanosystems have grown rapidly and utilized for active and passive targeting of tumorigenic cells especially conjugated with organic polymers followed by third generation counterparts with improved functionalities for cancer therapy. The aim of this review article is to focus on the advancements in mesoporous silica based organic-inorganic hybrid nanoparticles developed as drug carriers targeting cancer cells. Brief introduction to the state-of-the-art in passive and active targeting methods is presented. Specifically, therapeutic, diagnostic and theranostic applications are discussed with emphases on triggered and ligand conjugated organic-inorganic hybrid mesoporous silica nanomaterials. Although mesoporous silica nanoparticles perform well in preclinical tests, clinical translation progresses slowly as appropriate doses needs to be evaluated for human use along with biocompatibility and efficiency depending on surface modifications.

Keywords: Active targeting / Anticancer drug delivery / Diagnostic / Mesoporous silica nanoparticles / Theranostic

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1 Introduction

The inorganic nanoparticles such as quantum dots (QDs), gold nanoparticles (GNPs), magnetite (Fe_3O_4) nanomaterials have many advantageous features such as luminescent properties with a controllable wavelength, unique surface plasmon resonance properties or high magnetization in the presence of an external magnetic field. Another class of inorganic nanoparticles are silica-based nanomaterials that can be investigated in two major groups: solid lipid nanoparticles (SNPs) and mesoporous silica nanoparticles (MSNs) [1]. Mesoporous silica nanoparticles are widely explored silica based nanomaterials due to large surface areas and specific pore volumes owing to ordered pore structures, which enable drug loading. Furthermore, drug release rates can be regulated by editing the size of mesopores [2, 3]. MSNs, such as 2D hexagonal MCM-41 (Mobile Crystalline Material) and 3D cubic SBA-15 (Santa Barbara Amorphous) are silica-based porous materials with hundreds of empty channels, so called mesopores with a narrow size distribution in the range of 2–50 nm. Mesopores are appropriate supports for drug delivery and biomedical applications due to their high chemical and thermal stability [4]. Their drug adsorption and release rates mainly depend on the textural and structural properties of the host-matrix [5] and can be regulated to maximize cellular uptake [6]. The approximate drug loading dose of conventional MSNs is about 200–300 mg which accounts for 600 mg drug/g silica [7].

First drug loaded into mesopores was isoprofen packed in MCM-41 exhibiting a sustained drug release performance with improved loading ratio [8]. Thereafter, biomedical studies on MSNs have grown rapidly and their development as a drug carrier has engendered in three generations [9, 10]. The first generation was introduced for the sustained release with many

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Abbreviations: DOX, Doxorubicin; **GNPs**, Gold nanoparticles; **GNRs**, Gold nanorods; **GSH**, Glutathione; **ICG**, Indocyanine green; **MDR**, multidrug resistance; **$mSiO_2$**, Mesoporous silica structures; **MSNs**, Mesoporous silica nanoparticles; **NIR**, Near-Infrared; **PEG**, poly(ethylene glycol); **PEI**, polyethyleneimine; **P-gp**, P-glycoprotein; **p(NIPAm)**, poly(N-isopropylacrylamide); **PVP**, Polyvinylpyrrolidone

challenges such as large particle sizes, irregular morphologies, several aggregations, cell level evaluations and *in vivo* applications. In conjunction with the fast development of synthetic chemistry, the second generation MSNs were constituted nanosized and uniform spherical morphology, tunable pore/particle sizes and compositions. Generation II MSNs have been constructed with various structures and morphologies such as hollow nanostructures, janus MSNs, yolk shell nanorattles (a special kind of core-shell nanostructure) and organic–inorganic hybrid mesoporous silica. In addition, MSNs integrated with comprehensive functionalities have been presented as generation III, which were designed and fabricated in a more complex manner in regards to surface chemistry and synthesis approaches. The surface modifications are based on the silanol groups (Si-OH) on the outer or inner mesoporous surfaces with various types of functional groups. The functional groups can be biological recognition ligands, peptides, aptamers, antibodies, nanovalves to control release profiles (e.g., stimuli responsive release, on-demand release), genes for synergistically overcoming multidrug resistance (MDR) of cancer cells, biocompatible functional polymers/materials for improving blood circulation time and fluorescent agents for bioimaging. Consequently, the latest generation MSNs explore a wide variety of synthetic strategies for functionalization of inorganic nanoparticles with organic molecules and macromolecules.

Although, inorganic nanoparticles are highly stable and multifunctional, their biodegradability and biocompatibility have been disputed. Furthermore, burst release of active ingredients from the matrix is one of the major disadvantages of MSN limiting their use in clinical applications where controlled release is required. On the other hand, organic carriers are known for their high biocompatibility and biodegradability, but low stability and single functionality. The advancements in material science and drug delivery systems catalysed the fabrication of organic-inorganic hybrid nanoparticles which combine desirable properties of organic and inorganic materials to overcome the weaknesses of MSNs [11–14]. Hybridization of organic and inorganic components can lead to multi-functionality and enhanced material properties [15]. The hybrid nanoparticles have significant properties of both inorganic and organic moieties and in addition they can be modified through the combination of functional elements. Also surface modification with the targeting moieties provides specific targeted imaging and therapeutic properties [1]. Hybridized mesoporous nanoparticles can be synthesized via hydrolysis and condensation of organic and inorganic precursors under acidic or basic conditions resulting in monodisperse nanoparticles and tailored for internalization of various drugs [16, 17]. These particles may have various morphologies such as stellate [18], ellipsoidal, spherical [19], octopus [20] and walnut kernel-like [21]. It would have been interesting to investigate the effects of these morphologies on drug loading efficiency, release kinetics, cellular uptake, subcellular localization, and cytotoxicity. Hybrid mesoporous materials are reported to act as host matrices for a wide range of drugs via weak interactions [8]. The internal surfaces of mesopores can be functionalized to improve drug and carrier interaction. For instance, trimethylsilyl groups were incorporated inside the pore surfaces to enhance loading of hydrophobic drug molecules on to MSNs [18, 22].

This review article focuses on the advancements in mesoporous silica based organic-inorganic hybrid nanoparticles developed as drug carriers targeting cancer cells. Brief introduction to the state-of-the-art in both passive and active targeting methods are presented. Particularly, therapeutic, diagnostic and theranostic applications are discussed critically with emphases on triggered and ligand conjugated organic-inorganic hybrid mesoporous silica nanomaterials.

2 Drug targeting to cancer cells

2.1 Passive targeting

Passive targeting is a kind of drug delivery strategy facilitated by nanoparticle fabrication techniques. The change in size, shape, charge and stiffness of the materials to enhance tissue accumulation, adhesion, cellular uptake of nanoparticles and drugs are part of the strategy [23]. The polymeric drug carrier particles have more advantages than administration of free drugs like increased circulation time in the body because free drugs can be detected by the reticuloendothelial system (RES) and eliminated. Some anticancer drugs like camptothecin and doxorubicin (DOX) are effective in chemotherapy but the applications in humans were limited due to the poor water solubility of the drug. Therefore, a suitable solution for hydrophobic drug molecules is of prime importance [24]. For instance, silicone oxide-deposited DOX-loaded stearic acid-grafted-chitosan nanoparticles were compared with stearic acid-g-chitosan polymeric micelles. The results showed that the nanoparticles have a more rapid drug release rate *in vitro* than the micelles and they could easily penetrate into the cells due to higher specific surface area obtained by their mesoporous structure [25] which, not only serve as unique drug reservoirs but also have a part in multiphasic release systems. In another study, drug delivery system using DOX loaded mesoporous silica nanoparticle composite nanofibers was fabricated which can release anti-tumor drugs in two phases (burst release in the early stage and sustained release at a later stage) to reduce local recurrence of breast-conserving therapy [26]. The drug entrapped within MSNs must first be released at a solution state, then from polymeric fibers to the surrounding medium.

Polymeric particles may also be prone to delay or prevent recognition properties due to RES [24]. Many types of generation II MSNs were synthesized with various structures and surface morphologies that could be used for targeted drug carrier systems passively through surface modifications with functional polymers. For example, poly(ethylene glycol) (PEG) can significantly enhance the circulation time due to its excellent protein repellent properties [27]. The polyethyleneimine-polyethylene glycol (PEI-PEG) decoration on the surface of the nanoparticles was reported to decrease RES uptake and resulted in the retention of about 8% of the administered particle dose at tumor site [28]. Polyvinylpyrrolidone (PVP) is another type of polymer for functionalization of nanocarriers. In one of the studies, PVP was used as a protecting polymer adsorbed on the surface of silica microspheres and NaOH was employed as an etching agent. Mesopores were created in the silica microspheres owing

Table 1. Passively targeted drug delivery or fluorescent imaging with organic-inorganic hybrid silica nanosystems

Treated cells/ animals	Drug molecules or imaging agent	Structure/hybrid type	Ref.
Hep-G2 mice	Docetaxel	PEGylated mesoporous silica nanorattle	[27]
MCF-7/MDR mice	DOX and siRNA	Mesoporous silica nanoparticles were functionalized by PEI-PEG copolymer	[28]
A549	DOX	Stearic acid-grafted chitosan (CS-SA) core and SiO_2 shell	[25]
HeLa	DOX and fluorescein	Fluorescent and cross-linked organic–inorganic hybrid mesoporous poly-(cyclotriphosphazene-*co*-fluorescein) 'PCTPF' nanoshells	[36]
HeLa	Ibuprofen	Fluorescent poly(p-phenylenevinylene) (PPV)	[34]
MDA-MB-231 mice	DOX	PLLA-(MSN/DOX)-DOX composite electrospun nanofibers	[26]
A549	Rhodamine B	Combined a fluorescent inorganic silica core with a biocompatible polymer shell	[24]
HeLa	DOX	Luminescent $YVO_4:Eu^{3+}$ nanocrystals integrated mesoporous silica nanoparticles	[29]

to the protective nature of PVP and inhomogeneous etching [29]. The surface modifications of recent organic-inorganic silica hybrids with polymers are mostly based on PEG [27], PEI [28], PVP [29], chitosan [25] and poly-L-lactic acid (PLLA) [26] for drug targeting to cancer cell (Table 1).

Meng and co-worker [28] prepared MSNs functionalized with PEI-PEG copolymer carrier to overcome DOX resistance in the MDR human breast cancer xenograft by co-delivering DOX and siRNA that targets the P-glycoproteins (P-gp) drug exporter. MDR is one of the main obstacles in effective chemotherapeutic treatment of cancer, where pump and non-pump drug resistances are reported as two major mechanisms. P-gp and MRP-1 (MDR-associated protein-1) are pump-related gene products existing at the cellular and the nuclear membranes and pumps anticancer drugs to the extracellular matrix while drug-induced expression of Bcl-2 protein is responsible for the activation of anti-apoptotic cellular defence as major mechanism in nonpump resistance [30, 31]. Many studies have shown that co-delivery of Bcl-2 siRNA with chemotherapeutic drugs by functionalised MSNs downregulates the Bcl-2 protein expression, which in turn could induce remarkable cell apoptosis [32, 33].

Co-delivery of DOX and siRNA by the PEI-PEG copolymer functionalised MSN nanocarriers resulted in synergistic inhibition of tumor growth in a MDR tumor xenograft model *in vivo* compared with free DOX and the carrier loaded with either drug or siRNA alone [28]. Another approach for functionalization of mesoporous silica nanoparticles is the formation of core-shell structure. An example for this approach is poly(p-phenylenevinylene) (PPV) functionalized MSNs which were further coated with a layer of mesoporous silica shell to form the core-shell structure. The PPV serve as a fluorescent polymer and the developed fluorescence MSNs with or without core-shell structures were reported to improve the capabilities of drug loading, sustained drug release and cancer cell bioimaging [34].

2.2 Active targeting

During the last decade, surface-functionalized, end-capped MSNs have been designed for controlled anticancer drug delivery due to their low toxicity, high surface area and large accessible pore volumes which are suitable for loading drug molecules [35, 36]. These systems have the capability of releasing the cargo only at the desired location by responding to certain external stimuli or specific ligand matching which was referred as active targeting [23, 37]. Among stimuli response properties, pH changes represent an effective strategy especially for cancer therapy since the extracellular pH in tumour tissue is slightly lower than in normal tissue [35]. Consequently, active targeting can not only be achieved by stimuli responsive mesoporous silica nanoparticles that can respond to changes in pH [38–41], temperature [42, 43], magnetism [44, 45], chemicals [46], enzymes [47], redox [48] or light [38, 49–52], but also associated with receptor recognition reactions. We discussed these active targeting strategies based on the organic-inorganic hybrid mesoporous silica nanocarriers for the therapeutic and diagnostic approaches in the next sections.

2.2.1 *Therapeutic or diagnostic approach*

2.2.1.1 Stimuli responsive organic-inorganic hybrid silica nanomaterials. Stimuli responsive organic-inorganic hybrid silica nanocarriers doped with chemotherapeutic drugs or imaging agents for therapeutic or bioimaging purposes are provided in Table 2. The pH sensing functions are of prime importance in MSN-based triggered-release nanocarriers. In one of the studies, fluorescent organic/inorganic hybrid MSNs were prepared with controllable redox-responsive release of rhodamine B as a model drug [53]. Indeed, many of hybrid materials prepared for controlled drug release on tumor location were often based on pH or glutathione (GSH) level changes because of acidic pH (5.0)

Table 2. Stimuli responsive or ligand conjugated organic-inorganic hybrid silicas for therapeutic or diagnostic purposes

Target cell/animal	Therapy or imaging agent		Nanoparticle/bioconjugate type and triggering factors	Ref.
Stimuli responsive organic-inorganic hybrid silicas				
A549	DOX	–	Organic-inorganic hybrid mesoporous nanoparticles with pH- and GSH-responsiveness	[55]
–		Rhodamine B	Fluorescent pH-sensing organic/inorganic hybrid mesoporous silica nanoparticles	[53]
–		Rhodamine 6G	Mesoporous SiO_2 films, functionalized with high quantities of azochromophores as photodriven nanoimpellers	[52]
KB-V1	DOX and siRNA	–	PEI coated mesoporous silica nanoparticles	[30]
Ligand conjugated organic-inorganic hybrid silica nanomaterials				
U87 MG HEK 293	DOX		GNPs@RGD peptide-capped MSNs	[59]
HCT116 mice	5-Fluorouracil	-	MSN-P(OEGMA[a])-co- RGD peptide	[89]
HeLa HEK 293	DiI[b] and DiO[c] as model drugs	-	Folic acid-conjugated and PEI-functionalized MSNs	[90]
HeLa MCF-7	Camptothecin		Tumor homing and penetrating peptide (tLyP-1) functionalized MSNs	[91]

[a] poly(oligo(ethylene glycol)monomethyl ether methacrylate).
[b] 1,1'-dioctadecyl-3,3,3',3'-tetramethindocarbocyanine perchlorate.
[c] 3,3-dioctadecyloxacarbocyanine perchlorate.

and high GSH concentration levels (2−10 mM) on tumour intracellular environment compared with normal tissues [54]. In another study, DOX hydrochloride was released by responding to acidic tumour intracellular environment [55]. A dynamic cross-linked supramolecular network of poly(glycidyl methacrylate)s (PGMAs) derivative chains was constructed on mesoporous silica nanoparticles via disulfide bond and ion-dipole interactions between cucurbiturils and protonated diamines in the polymer chains, where this network was employed as a pH and GSH dual stimuli-responsive nanovalve. Disulfide bonds between PGMA chains and MSNs endowed the hybrid material GSH responsiveness.

Another approach to deliver drugs to specific locations is to control the drug release by light due to its non-invasive nature. Mesoporous silica nanoparticles have large hollow interiors that serve as large reservoirs for enhanced drug-loading capacity and demonstrate special structure–property relationships for nanomedicine [56]. The first organic–inorganic hybrid hollow mesoporous organosilica-based nanovehicles (HMOVs) were synthesised as nanocarriers. HMOVs with phenylene-bridged silsesquioxane frameworks have been employed as excellent nano co-delivery platforms for efficient intracellular transport of gene-silencing agent namely the P-gp and anticancer drugs. The co-delivery of P-gp associated short hairpin RNA and DOX enhanced chemotherapeutic efficiency due to higher intracellular DOX concentration [57]. Not only the hollow structure of HMOVs was found to be responsible for the high cargo-loading capacity, but also its phenylene-bridged framework acted as pH-responsive drug release.

2.2.1.2 Ligand conjugated organic-inorganic hybrid silica nanomaterials. Despite the notable success of external and internal stimuli responsive organic-inorganic hybrid silica nanoparticles, more specific applications were required in cancer therapy such as ligand conjugating strategy as active targeting in order to improve the specificity of nanoparticles towards tumor cells. For instance, traditional MSN drug release systems were not able to distinguish inflammatory tissues, resulting in damage of both inflammatory and healthy tissues [58]. Thus, researchers searched for alternatives to improve the delivery efficiency and cancer specific recognition and focused on active targeting ligands, peptides and antibodies that recognize particular receptors in target cells with subsequent uptake through receptor-mediated endocytosis. An example is functionalized MSNs showing sensitivity to pH by α-amide-β-carboxyl unsaturated bond and further end-capped with functional RGD peptide-coated gold nanoparticles (GNPs). Hereby, bioactive surface of the GNPs-peptide-capped MSNs facilitated the binding to $\alpha_v\beta_3$ integrin overexpressed U87 MG cancer cells. On the contrary, limited internalization was observed in $\alpha_v\beta_3$ integrin negative HEK 293 cells [59]. As majority of the publications related to ligand conjugated organic-inorganic hybrid silica nanomaterials are designed for both therapeutic and imaging purposes, these will be discussed in the following section.

2.2.2 *Theranostic approach*

Theranostics describes the co-delivery of therapeutic and imaging agents in a single formulation [60] where drug delivery can all be integrated into one functionalized nanoparticle [61]. There have been many platforms that combine imaging and therapy for optimization of efficacy and safety of therapeutics such as nanocarriers related to light, magnetism, and sound [62].

Ligand-conjugated organic-inorganic hybrid silica nanoparticles with triggered mechanisms and stimuli responsive counterparts for theranostic purposes are summarised in Tables 3 and 4, respectively. Various ligands that can specifically bind to receptors overexpressed in cancer cells were utilized for the

Table 3. Organic-inorganic hybrid silicas with target-ligand interactions for theranostic purposes

Target cell/ animal	Chemo-therapy agents	Imaging agents	Triggering event	Other therapy responsible agents	Targeting ligand	Target receptor	Nanoparticle/Bioconjugate type	Ref.
Human squamous carcinoma cell spheroids (MCS)	DOX	–	NIR and enzyme dual responsive	Gold nanobipyramids (AuNBs) as a photothermal converter	Azobenzene and α-cyclodextrin functionalized hyaluronic acid (HA)	CD44 is a major receptor for HA overexpressed in many solid tumor cells	HA(shell)-MSNs-AuNBs(core) triple-layer core-shell nanocomposites switchable system	[85]
AsPC-1 mice	–	Iron oxide as MR contrast agent	NIR light	ICG fluorescent dye as a PTT agent, The gold nanoshells enhance the fluorescence of ICG	antibody (AntiNGAL)	Neutrophil gelatinase-associated lipocalin (NGAL)	Encapsulated with iron oxide and ICG and then AntiNGAL-conjugated theranostic triple-layer-gold nanoshells (TGNS)	[81]
U251/Normal human astrocytes, 1800	DOX	–	pH sensitive and NIR stimulative	Graphene nanosheet as a PTT agent	IP peptide	Receptor chain 2 of interleukin 13 (IL-13Rα2)	A targeting peptide (IP)-modified mesoporous silica-coated graphene nanosheet (GSPI)	[76]
A549 mice	DOX	–	NIR light	GNRs as a PTT agents	RGD peptide	$\alpha_v\beta_3$ integrin receptor	Conjugated RGD peptides on the terminal groups of PEG on mesoporous silica-encapsulated GNRs	[86]
PC-3 HDFs	–	–	NIR light	Gold shell as a PTT agent	EphrinA1 ligand	EphA2 receptor	Gold-coated silica nanoshells conjugated to ephrinA1 ligand via PEG linker	[82]
SK-BR-3 HDF	–	–	NIR light	Gold shell as a PTT agent	Human epidermal growth factor (HER)	HER2 receptor	Gold-coated silica nanoshells conjugated to HER via PEG linker	[64]
HeLa MCF-7	Campto-thecin	Fluorescein isothiocyanate (FITC)	NIR light	Au nanorod core as a PTT agent	tLyP1 tumor-homing peptide	neuropilin-1 (NRP1) receptor	tLyP1—Conjugated Mesoporous silica-coated Au nanorod, (AuNR@SiO_2) nanoshell	[84]
SK-BR-3 MCF-10A	DOX	–	pH and NIR responsive	Mesoporous carbon cores serve as a drug carrier and PTT agent	SP13 ligand	HER2 receptor	SP13 peptide-conjugated graphitic carbon (core) @ mesoporous silica nanospheres/(MMPSD)	[77]
SK-BR-3 MCF-10A mice	DOX	FITC	pH and NIR responsive	semi-graphitized carbon (sGC) on the inner wall can effectively convert NIR light into heat	DNA aptamer (HB5)	HER2 receptor	PEGylated mesoporous silica-carbon nanoparticles (MSCN) with HB5 aptamer	[63]
NCL positive MCF-7 cancer cells	DOX	Cy5.5 fluorescence	NIR light	Graphene oxide (GO) gatekeeper converted NIR light into heat	Cy5.5 labelled AS1411 aptamer	Nucleolin receptor	Cy5.5-AS1411 aptamer conjugate graphene oxide nanosheet coated mesoporous silica nanoparticles (MSN@GO)	[73]
MCF-7 HEK-293	DOX Curcumin	–	NIR light	$Cu_{1.8}S$	Aptamer-modified GC-rich DNA helix as gatekeepers and targeting ligand	Nucleolin receptor	DNA-hybrid-gated nanocarrier based on mesoporous silica-coated $Cu_{1.8}S$ nanoparticles	[92]

Table 4. Stimuli responsive organic-inorganic hybrid multifunctional silicas for theranostic purposes

Target cell/animal	Chemo-therapy agents	Imaging agents	Triggering event	Other stimuli-responsive agents	Nanoparticle/Bioconjugate type	Ref.
SKOV3	Indomethacin	Gd^{3+} ions as a T_1-MR contrast agent	Temperature changes	p(NIPAm-co-AAm) was responsive to pH/temperature changes	Luminescent rattle-type hollow mesoporous silica microspheres with a thermosensitive hydrogel via p(NIPAm-co-AAm conjugation	[93]
HeLa	DOX	Blue-emitting AIE luminogen	pH responsive	-	AIE luminogen-functionalized hollow mesoporous silica nanospheres (FHMSNs) with pH- responsiveness	[94]
A549 mouse	DOX	Y_2O_3:Yb,Er core	pH/temperature and NIR light	$Au_{25}(SR)_{18}$ clusters were photodynamic (PDT) and photothermal therapy (PTT) agents.	Core/shell structured Y_2O_3:Yb,Er(core) @Y_2O_3:Yb(shell)@mSiO_2-Au25-P(NIPAm-MAA) (YSAP) up-conversion nanoparticles	[95]
MCF-7	DOX	Gadolinium(III)-chelated complexes as MRI contrast agents	NIR laser irradiation	ICG as photothermal agent	Gadolinium(III)-chelated silica nanospheres loaded with DOX and ICG and then coated PDC (poly(diallyldimethylammonium chloride) (PDC)	[96]
HeLa	DOX	Cu_{2-x}Se	pH and NIR light	Copper selenide (Cu_{2-x}Se) as a PTT agent	Cu_{2-x}Se nanoparticles core combined with DOX-loaded MSN shell and then PEGylated	[80]
HeLa	DOX	CuS	pH and NIR light	CuS nanocrystal cores as PTT agents	CuS crystals @mSiO_2-PEG core–shell nanoparticles	[79]
HepG2 Chang liver cells	DOX	CuS	NIR laser irradiation	CuS as an efficient PTT agents	PEG-modified DOX-loaded/MSN@CuS nanohybrids	[78]
MCF-7 mice	DOX	GNRs	pH and NIR light	GNRs as an PTT agents	DOX loaded mesoporous silica-coated gold nanorods (GNRs@mSiO_2-DOX)	[74]
HeLa	DOX	GNRs	pH/temperature and NIR light	GNRs as an PTT agents and poly(N-isopropylacrylamide)-based N-butyl imidazolium responsible for thermosensitivity	DOX loaded mesoporous silica shell-coated GNRs	[97]

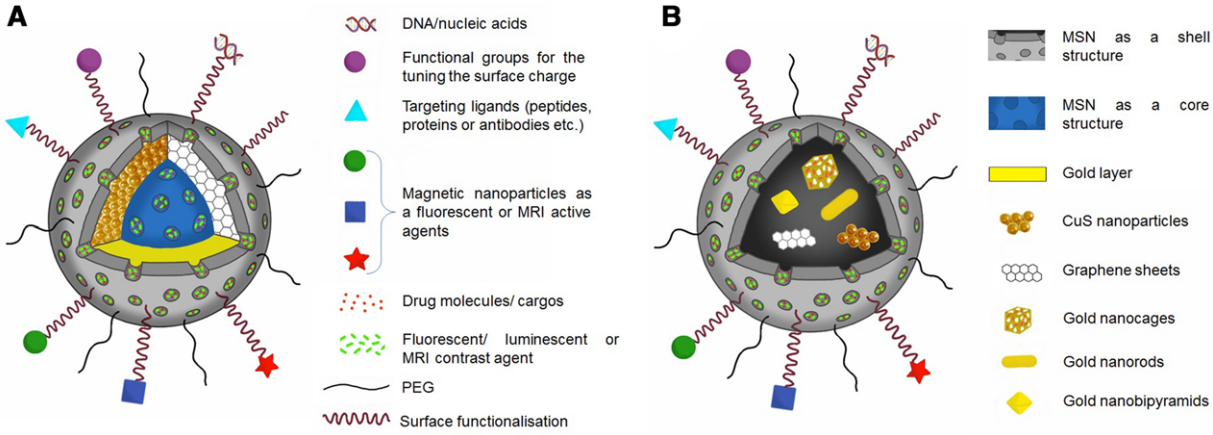

Figure 1. Two types of NIR-triggered core-shell type nanoshells; mesoporous silica core encapsulated with drug, fluorescent agent or photothermal therapy agent covered with an NIR responsive shell and an additional outer mesoporous silica shell functionalized for targeted delivery (A), NIR responsive core such as copper, graphene nanosheets and gold derivatives coated with mesoporous silica shell as a drug reservoir and functionalized surface (B).

design of targeted drug delivery systems [63]. The differential expressions of receptor proteins, residing in cytosol, organelles or membrane are used as molecular markers. An example is the human epidermal growth factor receptor HER2 which is overexpressed in ~30 % of breast cancers and used as a marker to target breast cancer cells [64]. Overexpressed or specifically expressed receptors in various cancer tissues and cells are reported in literature [65–70]. As receptor-ligand interactions are highly specific, this mechanism is applied for active targeting of nanocarriers or nanoconjugates [71].

As for stimuli responsive systems, especially Near-Infrared (NIR) triggered multifunctional organic-inorganic hybrid silica nanoparticles are commonly used as cancer theranostics. NIR-triggered organic-inorganic hybrid silica drug carriers include mainly two components; NIR absorption agents and a drug-containing silica (mostly mesoporous) moiety, which can enable a synergistic treatment for cancer cells via dual effects of photothermal ablation and chemotherapy [72]. Photothermal therapy (PTT) employs near-infrared (NIR) laser photo-absorbers to generate heat upon NIR laser irradiation. Indocyanine green (ICG) is one of the fluorescent dyes used for PTT, which absorbs NIR and converts light to heat in order to form localized hyperthermia in the cancerous tissue. Although ultraviolet (UV) and visible (Vis) lights have been used as exogenous stimuli to trigger drug release, concerns about high toxicity to healthy tissues and low penetration depth (~10 mm) due to strong scattering ability of skin and soft tissues have limited their applications. NIR light triggered drug delivery systems offered some advantages such as deeper penetration, lower scattering and minimal damage [73]. Gold nanorods (GNRs) as cores of nanoshells [74], gold layers in core-shell nanoplatforms, gold nanocages [75], graphene nanosheets [76], graphitic [77] / semi-graphitic carbon cores [63] and CuS nanoparticles [78, 79] and some other copper compounds [80] are the mostly studied NIR-absorbing agents in NIR-triggered hybrid silica nanocarriers.

In an attempt to discuss NIR-triggered silica nanocarriers in more details, core-shell structure is regarded as a common denominator and these nanoconjugates are reviewed in two groups. One of the groups is represented with a mesoporous silica core and NIR-responsive shell (Fig. 1A) is generally required as an additional outer mesoporous silica shell [81] encapsulated with drug, fluorescent agent or photothermal therapy agent. It is worth to mention that surface PEGylation might be required for higher stability and ligand conjugation [64, 82]. An example to the first group of nanoconjugates is gold nanoshells (AuNS) with a dielectric core such as silica and a metallic gold layer which shows ~1 million-fold greater absorption than conventional NIR dye, ICG [83].

The other group has a metal core and mesoporous silica shell structure (Fig. 1B) demonstrating many advantages in comparison to carbon derivative or single metal particles [76, 84–86]. As an example for single metal particles, GNRs with nonporous structures exhibit low loading capacities and limited elasticity, restricting their applications in drug delivery [86]. But they are still in use due to single- and two-photon induced luminescence and longitudinal plasmonic resonance that can be tuned to near infrared wavelengths [87]. Hence, the drug-loaded mesoporous silica coating on the surface of this type of NIR-converting agents improved biocompatibility, drug loading and post modification [77]. A mesoporous silica-coated graphene nanosheet (GS) was conjugated with a peptide for glioma targeting. The results showed that peptide conjugation enhanced cellular uptake in human glioma cell line, whereas normal astrocyte cells were not affected, indicating a selective therapeutic effect [76].

Another study focused on mesoporous silica coated graphitic carbon nanospheres conjugated with HER2 receptor specific SP13 peptide for DOX delivery with photothermal effect of NIR responsive graphitic carbon core on the SK-BR-3 breast carcinoma cells. The combined effect of nanocarrier system with NIR was remarkable with significantly lower IC_{50} of DOX (10.05 μg/mL) compared to that of free DOX (124.5 μg/mL) [77]. A similar combined chemo-photothermal therapy was attempted by the design of mesoporous silica encapsulated gold nanorods. A549 human lung adenocarcinoma epithelial cells

were incubated with the nanocarrier loaded with DOX and a synergistic effect was reported with lower systematic toxicity [86]. The multifunctional hybrid nanocarriers can enhance cancer therapy by providing chemo- and photothermal therapies while allowing fluorescence imaging for diagnostic purposes.

3 Concluding remarks

In the mid to late 1970s, the concept of polymer-drug conjugates or "nano-therapeutics" have initiated targeted or site-controlled drug delivery systems in nanoscopic era. The discovery of three key technologies, PEGylation, active targeting to specific cells by ligands or other molecules conjugated to the drug delivery system and passive targeting to solid tumors via the EPR effect stimulated the development of polymeric and nano-sized carriers as practical clinical applications from late 1980s to the present [88]. Although MSNs perform well in preclinical tests, few clinical trials are performed and there are some comprehensible and essential hurdles regarding scale up of its synthesis to required dosage for acceptable pharmacokinetic and pharmacodynamic profiles [2]. Herein, just a few of many topics were scrutinized related to silica based mesoporous organic-inorganic hybrid nanocarrier systems in order to present latest developments in passive and active targeted drug delivery for cancer therapy. As our knowledge of material and biological sciences advances, so our ability to design more complex and multifunctional nano-structures will continue to grow and MSNs have a promising future for innovative cancer treatments.

Practical application

This review highlights the most recent advances in the use of silica based organic-inorganic hybrid drug carriers based on cancer therapy with different therapeutic, diagnostic and theranostic applications. Also their novel advantages through drug loading abilities, shape/size modifications and sophisticated functionalization processes were critically discussed in the light of technological developments. Multifunctionalisation techniques such as coating, grafting or capping allow specific responsiveness and homing properties to these nanocarriers. Not only passive or active targeting offer key technologies to tumor homing and penetrating but also photothermal therapy serves as an interesting tool for selective targeting of cancerous tissues.

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