Application of mesoporous silica nanoparticles as drug delivery carriers for chemotherapeutic agents

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Recently, remarkable efforts have focused on research towards enhancing and delivering efficacious and advanced therapeutic agents. Even though this involves significant challenges, innovative techniques and materials have been explored to overcome these. The advantageous properties of mesoporous silica nanoparticles (MSNs), such as unique morphologies and geometries, makes then favorable for use for various drug delivery targeting purposes, particularly in cancer therapy. As we discuss here, MSNs have been utilized over the past few decades to improve the efficiency of anticancer drugs by enhancing their solubility to render them suitable for application, reducing adverse effects, and improving their anticancer cytotoxic efficiency.

Introduction

Over recent years, various different studies have focused on the application of mesoporous silica-based platforms as effective nanocarriers in chemotherapy [1]. Mesoporous silica has favorable properties for use as a nanocarrier, such as large pore volume, large surface area, and adjustable pore morphological structures [2,3].

The characteristics of inorganic silica (e.g., size, surface, and topology) can be altered to generate distinct interactions with different types of biological system. Thus, mesoporous silica, amorphous silica, microporous crystalline titanosilicates, and zeolites have been widely used in biomedical applications [4]. The desirable features of mesoporous inorganic materials, more specifically MSNs, are easily tailored to incorporate and interact effectively with an array of poorly soluble drugs and biomolecules. thus, it is clear to see why there is a growing interest in this field [5,6]. Ordered MSNs are characterized by particle size (50–200 nm), pore sizes of 2–6 nm, bulk pore volume of 0.6–1 cm^3/g and a large surface area of 700–1000 m^2/g. Moreover, MSNs have the ability to bind to various kinds of functional groups of active pharmaceutical ingredients (APIs) to allow targeted delivery to the required site of action. These explicit characteristics render MSNs as promising nanocarriers that have revolutionized different drug delivery approaches [7], such as controlled [8], targeted [9,10], sustained [11], and responsive systems [12–14]. The characteristics of MSNs have been studied in depth with respect to their pharmacokinetic and immunological properties, which are major challenges to overcome to realize their potential in the clinic [15]. In this review, we discuss the different characteristics of MSNs and emphasize their involvement in recent advances in different drug delivery systems

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(DDSs), with a specific focus on their potential biomedical use in chemotherapy and cancer treatment.

MSNs as a targeting delivery system for anticancer drugs

Recent research has resulted in the applications of several targeting tools for use in drug discovery. Smart nanostructured vehicles have been utilized to improve the efficacy of anticancer drugs while reducing their nonselective adverse effects on nontarget tissues [16–19]. Different surface modification procedures have been used to achieve targeted localized delivery of anticancer agents to improve their efficiency in reducing tumor progression and their adverse effects [19]. MSNs have been used to successfully deliver different types of chemotherapeutic drug, including doxorubicin

TABLE 1

Applications of MSNs in cancer therapy

Cancer type	Drug name	Targeted cell type	Functionalized mesoporous carrier	Pore size	Notes	Refs
Liver	ATO	SC-7721	LPMSNs	7 nm	*In vitro* assays showed huge cytotoxicity and significant induction of apoptosis	[57]
	Sorafenib	HCC	Gold nanoshell MSNs	Not stated	Improved cancer suppression activity because of higher accumulation of SO in hepatic tumor cells	[58]
Prostate	DOX	LNCaP-AI	$CaCO_3$ capped MSNs	Not stated	Enhanced antitumor activity and premature release stimulated under pH 7.4 and fast drug release under cancerous acidic environment (pH 6.5 and 5.0).	[62]
	DOX	LNCaP-AI	PMSA surface-modified MSN	4 nm	Improved cell internalization (~ 25%) observed in simulated physiological medium	[63]
Breast	Paclitaxel and curcumin	Canine breast cancer cell line	Lipid bilayer-coated MSNs	2.754 nm	Bilipid layer improved loading of drugs by enhancing their solubility, exhibited prolonged release and high cytotoxic activity against breast cancer	[21]
	ATZ	MCF-7	Chitosan folate-capped MSN-41 type MSNs	3.36 nm	pH-responsive targeting; *in vitro* drug release profile exhibited controlled pH-responsive and enhanced drug release rate; cytotoxic against breast cancerous cells	[59]
	DOX	MCF-7 cell line	MSN-coated gold nanorods	Not stated	Synergistic effect; chemotherapeutic effect of DOX loaded in mesoporous shell; photothermal effect of gold core; resulted in significant damage to cancer cells	[29]
Lung	Cisplatin and DOX	BCL2 and MRP1	PEG-modified MSNs	Not stated	Enhanced cytotoxicity and induction of selective apoptosis resulting from co-delivery of cisplatin and DOX simultaneously with BCL2 and MRP1 siRNAs. *In vivo* assays showed MSNs were inhaled through lungs, avoiding their uptake by systemic circulation	[64]
	Bortezomib	A549 cells (p53 wild-type) and H1299 cells (p53 mutant)	HMSNs	4.1 nm	Synergetic effect of bortezomib and HMSNs demonstrated improved tumor apoptosis	[65]
Colon	DOX	Human mesenchymal stem cells	PAA-functionalized SBA-15-type MSNs	7.8 nm	*In vitro* studies confirmed high loading drug capacity (~785.7 mg/g), excellent compatibility, and good pH-triggered response	[66]
	5-FU	HT-29 adenocarcinoma cell line	Guar gum-capped MCM-41-type MSNs	2.9 nm	Guar gum capping used as effective *in vivo* enzyme-responsive carrier	[67]
Brain	DOX	U-87 MG-luc2 cells	Tf-modified MSNs	3.6 nm	Tf-magnetic field resulted in high drug delivery capacity with enhanced cytotoxicity and release profile against cancerous cells compared with normal cells	[69]
		U87 glioma cells	Functionalized MSNs with arginylglycylaspartic acid peptide	Not stated	Tailoring particle size and functionalization of MSNs achieved improved efficacy and targeting against glioma cell lines	[70]
Bone		MC3T3-E1 preosteoblastic cell line	PAA-capped MSNs	2.4 nm	PAA acted as gatekeeper, reducing premature release of drug and resulting in pH-responsive release in tumor target site; ligand-selective binding to cancer cells overexpressing glycans (e.g., sialic acids)	[14]
Detection of ovarian tumors	N/A	ES-2	WMSNs	Not stated	A new approach to using MSNs in detection of early-stage ovarian cancer using nanostructured formulations	[13]

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(DOX) [20] and paclitaxel [21], which resulted in inhibitory effects on tumors. Table 1 highlights the range of MSN applications in cancer therapy.

Three distinct approaches have been developed when utilizing MSNs: passive targeting, active (cell-selective) targeting, and controlled stimulus-responsive release targeting [22]. Several studies have shown the defective structure of blood vessels in tumors tissues, which allows different vascular permeability in cancer cells. Therefore, most solid tumors are characterized by a degree of vascular permeability, which provides a suitable supply of oxygen and nutrients that enable the fast growth of cancerous tissues. This is known as the enhanced permeability and retention (EPR) effect [23]. As a result of this effect, any macromolecules (>40 kDa) can selectively escape from cancerous blood vessels and accumulate in cancerous tissues [24]. By contrast, the EPR effect does not occur in normal tissues. Thus, in solid tumor tissues, the EPR effect can be a target for chemotherapeutic agents and is increasingly emerging in drug delivery science as a promising clinical treatment [23].

Passive targeting

To accomplish effective targeting delivery of NPs, it is crucial to extend their circulation time through the mononuclear phagocytic system (MPS) and decrease their rate of renal clearance. Therefore, it is essential for nanoparticles to be 10 nm diameter and 100–200 nm size [25] to penetrate the tumor tissues via passive diffusion and to avoid the MPS [26,27]. Meng *et al*. reported effective passive targeting using polyethyleneimine-polyethylene glycol (PEG)-functionalized MSNs with a particle size of 50 nm [28]. The results indicated an improvement in DOX delivery through passive diffusion to cancerous cells. This system not only achieved the EPR effect, but also improved DOX cellular uptake by tumor cells by using a nanostructured particulate system. Therefore, it preferably induced cellular apoptosis and tumor size reduction alongside avoiding severe DOX cytotoxic effects [28]. Another study demonstrated that mesoporous silica-coated gold nanorods showed an efficient passive targeting effect [29]. This unique nanodevice exerted two synergistic therapeutic effects; the chemotherapeutic effect of DOX loaded in the mesoporous shell and the photothermal effect of the gold core. This nanosystem achieved exceptional results compared with pure DOX, including targeting tumor tissues, inducing damage to Ehrlich ascites carcinoma *in vivo*, causing significant cytotoxicity to a breast cancer cell line (MCF-7), and decreasing cytotoxic effects on normal tissues [29].

Active targeting

Active targeting can be used to improve the therapeutic efficiency of a drug by overcoming the challenges associated with passive targeting systems, such as the lack of the ability to control entrapped API release and reduced tumor specificity. In active targeting, specific ligands are conjugated to MSNs via surface modification. Ligand-modified MSNs tend to recognize receptors that are selectively expressed on the membrane of cancerous cells via ligand–receptor interactions, therefore improving the antitumor selectivity [26,27]. The ligands could be peptides [30], aptamers [31], antibodies [32], proteins [33], saccharides [34], and folic acid [35]. Active targeting offers a pathway for selective localized delivery of anticancer drugs to tumor cells, causing efficient cellular endocytosis [6]. Bioactive molecules, such as folic acid, have been used extensively to deliver several anticancer therapeutics to different kinds of tumor (i.e., those that overexpress folate receptors on their surfaces) including lung, ovarian, breast, kidney, endometrial, colon, and brain cancers [36]. A recent study developed a smart device compromising functionalized hyaluronic acid (HA) MCM-41-type MSNs to achieve active targeting utilizing two different molecular weights of HA (6.4 and 200 kDa). The study demonstrated that optimizing different parameters, including the method of loading and molecular weight of HA, resulted in the enhanced stability and dispersity of MSNs in biological fluids. It indicated that high-molecular-weight HA-functionalized MSNs demonstrated high biocompatibility, low cytotoxicity, and favorable targeted binding to HA receptors (CD44) that are overexpressed in many cancerous cells. These results suggest that HA-functionalized MSNs are a promising platform for cancer-targeting therapy [10].

Responsive targeting systems

Stimuli-responsive systems are an advanced strategy that provides on-demand release of therapeutic molecules in response to external or internal stimuli [22]. The on-demand release of APIs inside specific intracellular compartments can be only achieved as a response to explicit endogenous or exogenous changes in the microenvironment of the cells [37]. These changes can be triggered by external stimuli (e.g., electricity, temperature, ultrasound, light, and magnetism) and internal stimuli (e.g., enzymes, reactive oxygen species, redox potential, pH, and ionic strength). Nevertheless, on-demand release (which is triggered by intracellular stimuli) is a more suitable pathway for clinical applications [38]. Here, MSNs are utilized to protect cargo molecules from premature release and only allow their release upon exposure to stimuli that are selectively present in the tumor tissues [39], such as acidic pH [13] and enzymes [20,40]. Many studies have used this responsive release strategy to improve the treatment outcomes of chemotherapy, including its safety and efficacy [6]. Three essential routes can be utilized to achieve on-demand release: modifying the surface of MSNs via a responsive polymer coating [41], attaching certain ligands (gatekeeper) to their mesopores [42], or anchoring the anticancer agent to MSNs via responsive cleavable linkers [43].

The flexibility of MSN synthesis techniques has enabled their layer-by-layer construction to result in mate4rial of an accurate thickness, which results in advantages including permeability properties and elasticity [44,45]. The delivery of their cargo depends on interactions between molecular charges. When the pH is neutral, charges are electrostatically stable and the layers stay locked, which maintains the cargo within the layers and avoids its premature release. Once the pH shifts, the molecular charges react, destroying the multilayered assemble to release the cargo for targeted delivery [46].

Protein regulation and metabolism result in acidic cancerous tissues, with a pH range of 4–6.5 [47]. The difference in pH between normal and cancerous cells can be useful in targeting drug delivery [39]. The flexible MSN structure allows different molecules to attach to their surface for specific targeting [48]. Functionalized MSNs can be modified chemically via degradation or charge conversion as a response to pH changes. These drug carriers tend

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to be stable in a neutral pH environment (pH 7.4) and degrade upon exposure to an acidic pH environment (e.g., tumor tissues) [47]. Thus, MSNs have been exploited using this approach to increase cellular uptake and to reduce the adverse effects of chemotherapy. For example, an effective nanocarrier was developed using conjugated MSNs to target bone cancer by exploiting their pH-responsive properties [14]. A novel device of DOX-loaded MSNs was formed that was coated with a polymeric shell (polyacrylic acid; PAA) via acid degradable linkage. PAA acted as a gatekeeper to reduce the premature release of DOX but to allow its release in response to changes in pH in the tumor site. A synergist active targeting effect was provided by grafting lectin concanavalin A into MSNs. This targeting ligand selectivity binds to glycan (e.g., sialic acids)-overexpressing cancer cells. *In vitro* studies showed that this novel DOX-loaded MSNs increased the anticancer efficacy of DOX up to eightfold compared with free drug [14].

MSNs are not only used for cancer therapy, but are also being explored as a promising diagnostic approach to assist clinicians in detecting tumors at earlier stages of disease. A recent study demonstrated wormhole-shaped mesoporous silica nanoparticles (WMSNs) for the diagnosis and detection of ovarian cancer owing to their ability to target tumor tissues. With a diameter of 27 nm, these MSNs were produced by sol-gel process and were loaded with imaging probes for diagnosis purpose. WMSNs were functionalized with chitosan and a V7 pHLIP peptide to achieve the pH-responsive release of the imaging probes only inside the acidic environment of ovarian tumors, preventing their off-target premature release. Intravenous injection of this complex in mice allowed the early detection of primary-stage ovarian tumor. Thus, the study highlighted how nanostructured formulations can be explored to discover tumors using constantly evolving imaging technology [13].

MSN applications in chemotherapy

Cancer is a significant cause of morbidity in humans. Although chemotherapy is considered to be the most potent anticancer treatment, it does not destroy cancer tissues specifically, but instead also affects noncancerous tissues [49]. To overcome this issue, researchers have developed cargo delivery systems to increase the drug concentration in tumor tissues and to improve the delivery of the drug molecules to the target area [6,15].

The most crucial aspect of chemotherapy is the use of different chemical entities to induce cellular apoptosis. However, the systemic administration of cytotoxic therapeutic agents results in cellular death in both cancerous and healthy tissue [1]. Given the deficiency of selectivity of chemotherapeutic agents, severe adverse effects [e.g., hair loss, myelosuppression, cardiotoxicity, immunosuppression, mucositis (gastrointestinal tract inflammation) and neurotoxicity] can be induced [50], resulting in decreased patient compliance. For example, the use of the anticancer drugs paclitaxel and docetaxel (derived from natural sources and used for the treatment of solid tumors [51]) has been restricted because of their cardiotoxicity effects and poor aqueous solubility [22,52]. As a result, there have been various attempts to enhance the therapeutic profiles of these cytotoxic compounds and increase their applicability. In addition to toxicity, conventional chemotherapy also suffers from the poor solubility of hydrophobic drugs, fast systemic elimination, and multidrug resistance (MDR) [49]. MDR is defined by the ability of drug-resistant tumors to express resistance simultaneously against several functional and structural unrelated anticancer compounds [53]. Therefore, research has focused extensively on developing nanostructured chemotherapeutics carriers that are capable of achieving anticancer on-site delivery to address MDR [1,54], resulting in various biomedical applications [22]. Among different inorganic nanomaterials, MSNs have attracted significant interest as effective vehicles in anticancer drug delivery because of their flexible *in vivo* and *in vitro* properties [42]. The discovery of silica-based nanoparticles was an important milestone in cancer therapy owing to their favorable characteristics, such as biocompatibility, chemical and thermal stability, tunable pore size, high pore volume, and ease of surface area alteration [36]. In addition, most antitumor drugs demonstrate poor water solubility, poor permeability across biological membranes, and inadequate bioavailability that restricts their administration by intravenous or oral routes. Thus, MSNs have been used to improve their solubility and enhance their permeability [55], resulting in a better accumulation of anticancer drugs at the tumor site, improving their efficiency [12,16,46,55].

Moreover, the structures of MSNs can be modified via diverse stimuli-responsive gatekeepers to enhance drug release. In addition, ordered MSNs are able to carry a high payload, thus ensuring controlled delivery for chemotherapeutics to cancerous tissues. Their nanosize enables the EPR effect and their surface-grafted ligands allow active targeting of specific molecular structures on the surface of the cancer cells [22].

MSNs in liver cancer

Despite significant advances in treatments, mortality resulting from liver cancer remains high worldwide [56]. There has been much interest in the use of nanocarriers as a DDS to improve the treatment of hepatic cancer. For example, arsenic trioxide (ATO), an antileukemia drug, has been approved by the FDA as a chemotherapeutic agent for solid tumors. Chi *et al*. encapsulated ATO prodrugs into the pores of large-pore MSNs (LPMSNs) to treat hepatocellular carcinoma (HCC). The authors reported real-time monitoring using magnetic resonance imaging by inserting magnetic iron oxide NPs into the MSN pores [57]. Stimuli-responsive targeting was achieved by modification of the silica surface using folic acid ligand (M-LPMSN-NiAsOx-FA). *In vitro* assays demonstrated improved cytotoxicity efficacy compared with free ATO because of a significant induction of apoptosis in SC-7721 cells. Furthermore, *in vivo* showed a controlled release delivery system through the imaging ability of M-LPMSN-NiAsOx-FA. Thus, this work highlights the versatility of MSN-based platforms [57].

Another report indicated a potential candidate for HCC treatment and tumor apoptosis via a combined chemo/photothermal line therapy based on a MSN platform. A novel design of sorafenib (SO), an antitumor agent and first-line HCC therapy, was developed in this study. SO-Au-MSNs were obtained with a gold (Au) nanoshell for photothermal conversion. The authors reported improved cancer suppression activity as a result of the higher accumulation of SO in hepatic tumor cells. In response to near-infrared radiation, the synergistic chemo/photothermal effect resulted in a higher drug absorption rate and enhanced cytotoxicity of SO [58].

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Thus, multifunctional designated MSNs have resulted in increased tumor death with respect to HCC, reducing the adverse effects of the API while achieving its controlled release.

MSNs in breast cancer

MSNs have been explored to enhance the solubility of therapeutic agents for use against breast cancer [52]. Given the obstacles of administrating antitumor agents (including solubility and stability), new tools have emerged to overcome these difficulties. For example, some researchers used lipid bilayer-coated MSNs to co-deliver two anticancer drugs (paclitaxel and curcumin) intravenously to breast tumors with the aim of enhancing their bioavailability and reducing adverse effects. Both drugs exhibit low aqueous solubility and permeability, which results in their poor bioavailability and adverse effects, limiting their therapeutic use. Loading these agents into lipid bilayer-coated MSNs improved their solubility, achieving a sustained release and enhancing their cytotoxicity against breast cancer. The excellent dispersibility and high surface area of the lipid bilayer-coated MSNs also allowed the intravenous injection of the hydrophobic anticancer drugs [21].

In addition, pH-responsive MSNs have been developed for the delivery of anastrozole (ATZ) to overcome traditional problems associating with chemotherapeutic drugs. The synthesis of MSNs was accomplished to attain the carboxylic functional group CH. For this purpose, ATZ was loaded into the pores of the MSNs, which were capped with a chitosan-folate conjugate (MSN-ATZ-CH-FA) (Fig. 1a). The *in vitro* drug release study demonstrated a controlled pH-responsive and improved drug release profile, while being selectively more cytotoxic to breast cancer cell lines. The study also highlighted the usefulness of MSN engineered-based systems as effective *in vivo* pH-responsive carriers that can restrict cancer metastasis [59].

Surface modification of MSNs resulted in significantly improved cargo bioavailability and cytotoxicity of the encapsulated drugs against breast cancer with a sustained release profile. Thus, MSN-based DDSs are considered to be promising carriers for breast tumor therapies.

MSNs in prostate cancer

Prostate cancer is one of the most frequent tumors affecting men. The treatment of prostate cancer has improved over the past few years, leading to an increase in survival rates. However, it remains a serious cause of death in several regions [60]. Owing to the beneficial properties of MSNs as DDSs, hydrophobic cargo mole-

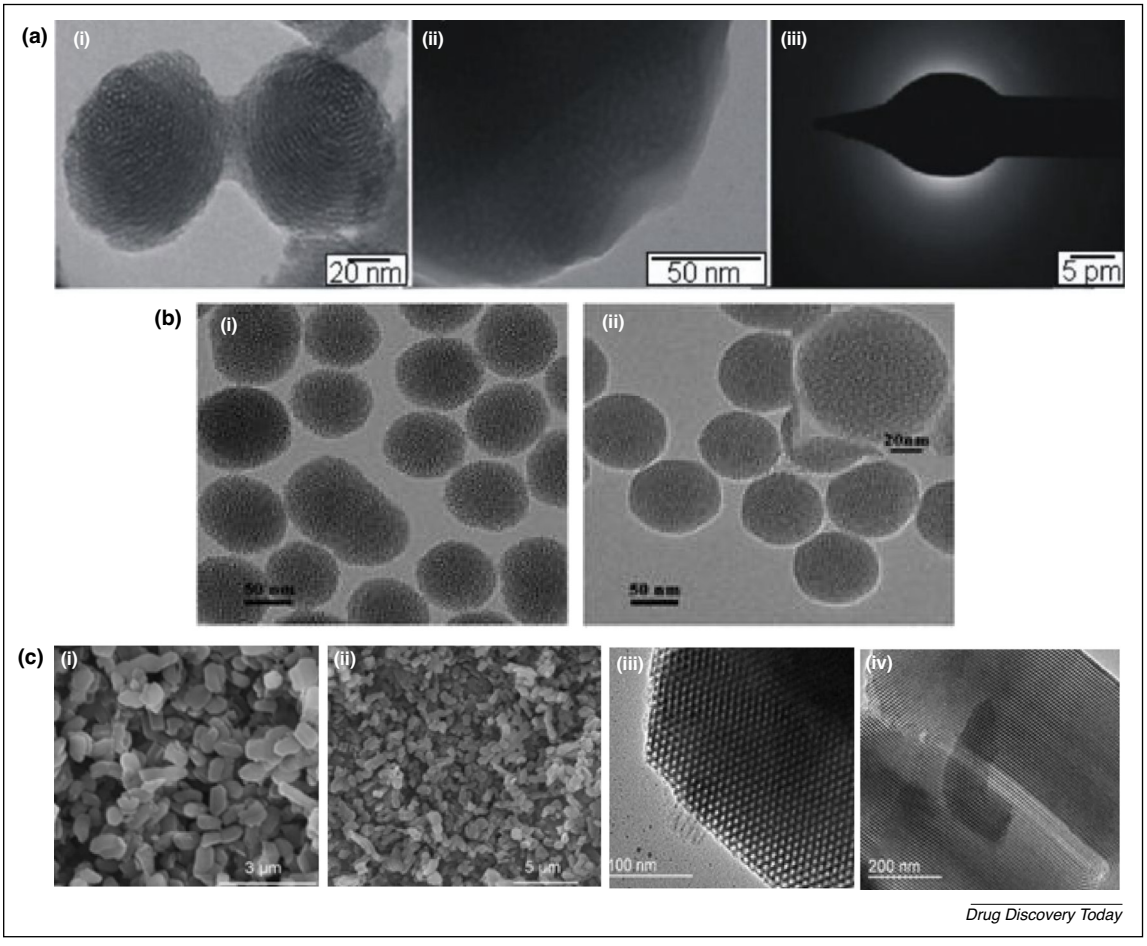

FIGURE 1

Examples of mesoporous silica nanoparticles (MSNs) in chemotherapy. (a) Transmission electron microscopy (TEM) images of MSNs (i), MSN-anastrozole (ATZ)-chitosan (CH)-folate (FA) (ii); selected area (electron) diffraction (SAED) image of MSNs (iii) [56]. **(b)** TEM of MSN (i) and doxorubicin (DOX)/MSN@$CaCO_3$ (ii) [59]. **(c)** Scanning electron microscopy (SEM) images (i,ii) and TEM images (iii,iv) of SBA-15 [63].

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cules can be attached to their pores for targeted delivery. To this end, different studies have applied conjugated antibody/NP systems to treat prostate cancer. Despite the evolution of DDSs, there have been no published reports of the use of MSNs as targeted therapy against prostate tumors. However, research has been reported on the administration of particular antibodies by MSNs [61].

For example, Liu *et al*. successfully synthesized a biocompatible encapsulated core/shell designed NP to promote tumor apoptosis in prostate cancer cells (LNCaP-AI). In this study, DOX/MSNs@$CaCO_3$ was covered with an outer layer of cancerous cell membrane (CM) to enable the MSNs to enter and accumulate at high levels within, the tumor site. The surface modification of MSN@$CACO_3$ was introduced as a detachable pH-sensitive stimulus for controlling DOX release without affecting the morphology of the NP (Fig. 1b). Premature release was stimulated under pH 7.4 and fast DOX release under cancerous acidic environment (pH 6.5 and 5.0), showing better anticancer activity compared with free DOX [62].

Another innovative drug delivery system was developed by Rivero-Buceta *et al*., who reported a stable conjugated ligand of DOX with an antiprostate-specific membrane antigen (PSMA) molecule (anti-FOLH1 monoclonal antibody, clone C803 N) in MSNs against LNCaP-AI cells. These MSNs demonstrated better cell internalization (~25%) in a simulated physiological medium. Moreover, the cytotoxicity of DOX increased twofold compared with untargeted NPs and free DOX. By contrast, nonbearing-PSMA and PC3 cell lines showed a lack of targeting efficiency. Therefore, this study highlights the potential use of MSNs against non-metastatic prostate cancer [63].

MSNs in lung cancer

Annually, almost 220 000 people are found to have lung cancer in the USA. There are two different kinds of lung cancer; non-small cell lung cancer (NSCLC) and small cell lung cancer (SCLC). Significant progress has been made in this field using MSNs, which can be administrated via the inhalation route to deliver drugs to lungs to achieve local targeted action.

For example, the delivery of cisplatin and DOX simultaneously with BCL2 and MRP1 small interfering (si)RNAs to lungs has been accomplished using MSNs. This co-delivery system is administered via inhalation to target lung carcinoma. Additionally, a targeting peptide (LHRH) was attached to the MSN surface using PEG as a linker. This unique combination inhibited both pump and nonpump-resistance mechanisms, enhancing the cytotoxicity of the loaded anticancer drugs and inducing selective apoptosis of NSCLC. *In vivo* administration of MSNs through inhalation achieved a local preferential targeting action in murine lungs and avoided their escape to the systemic circulation. This was evidenced by accumulation of 73% of MSNs in the lungs and their absence or minor presence in other tissues (spleen, heart, kidney, and liver). By contrast, intravenous administration of MSNs caused serious accumulation of the NPs in liver (73%), with only 5% being found in lungs [64].

Another study established a nanocarrier delivery system including the encapsulation of bortezomib (a proteasome inhibitor) and *p35* into hollow MSNs (HMSNs) for the treatment of NSCLC. The study enhanced the efficacy of the encapsulated drug and prompted p35 signal pathways. Given the synergetic effect of bortezomib and HMSNs, tumor apoptosis was clearly achieved. p35 exhibited slow release under normal physiological conditions and very fast under acidic conditions (lysosomes and endosomes) [65].

Thus, advances in DDSs based on MSN nanocarriers have resulted in local targeted delivery via inhalation, improved accumulation of anticancer drugs in the target area, and successful gene delivery to tumor sites, achieving tumor suppression.

MSNs in colon cancer

The application of capped MSNs has achieved successful treatment of colon cancer using the oral route because of their ability to enhance the solubility of hydrophobic anticancer drugs targeting colon carcinomas, preventing premature drug release [66]. For example, a pH-triggered nanodevice was developed based on PAA-functionalized SBA-15 type MSNs (Fig. 1c). PAA acted as a gatekeeper to retain DOX molecules within SBA-15 mesopores during their transportation to the target site. Under gastric conditions (pH 2.0), DOX was protected from premature leakage whereas, under colonic conditions (pH 7.6), DOX demonstrated immediate release. *In vitro* studies showed a high loading drug capacity (~785.7 mg/g), excellent compatibility, and a good pH-triggered response. Furthermore, this study indicated the improved solubility of DOX molecules in the colonic environment [66].

Kumar *et al*. investigated a colon cancer treatment using MCM-41-type MSNs to increase the effectiveness of 5-flurouracil (5-FU) using an enzyme-responsive system. They functionalized MSNs with a natural polymer (guar gum) to retain the drug inside mesoporous channels under physiological conditions. 5-FU release was activated through the degradation of the guar gum cap in response to colonic enzymatic activity. The release of the anticancer agent was around zero when the enzymes were absent in different gastrointestinal tract conditions. thus, the study highlights another significant form of MSN engineered-based systems using guar gum capping as an effective *in vivo* enzyme-responsive carrier [67].

MSNs in brain cancer

Although there has been great progress in the detection of different cancers, many challenges remain associated with brain cancers. A major form of brain cancer is a high-grade malignant glioma, glioblastoma multiforme (GBM), which is defined by the successive growth and immediate damage of brain parenchyma. Given its strong resistance to chemotherapy, fast cell damage, intense frequency of relapse, and poor survival rates, GBM is classified as a life-threatening tumor [68]. Step-by-step exploration of mesoporous silica materials has enabled the development of an innovative drug delivery platform for use against GBM [36].

A study reported improved anticancer drug delivery to GBM by using protein-grafted MSNs. Transferrin (Tf), a biological blood glycoprotein, was added to the external surface of the MSNs with conjugated magnetic silica poly(d,l-lactic-co-glycolic acid) NPs (MNP-MSN-PLGA-Tf NPs). In these NPs, Tf is considered as both the gatekeeper and the targeting agent to achieve the better therapeutic efficiency of DOX The abundant presence of the Tf-magnetic field resulted in DOX being delivered with higher cyto-

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toxicity and enhanced release rate compared with free DOX. Thus, Tf-modified MSNs are a potential carrier system that can suppress tumor growth, resulting in a selective cytotoxic effect against GBM and reducing systemic adverse effects [69].

Mo *et al*. tailored the size of MSNs to successfully cross the blood–brain barrier to target GBM. The authors fabricated different-sized MSNs (20,40, and 80 nm) with capped arginylglycylaspartic acid peptide cRGD-conjugated DOX. This allowed the MSNs to selectively attach to U87 cells with a large $\alpha\nu\beta3$ integrin and improved cellular uptake using a particle size of 40 nm. Thus, amending the particle size and functionalization of MSNs could be an effective approach to target GBM via a sequentially enhanced cancer-targeting effect [70].

Concluding remarks and perspectives

Despite significant research on MSNs and their potential as a cancer therapeutic, there remains a lack of MSNs in clinic practice owing to the their inability to be successfully delivered to and accepted by living organisms hence hindering the process to clinical trials [71]. Nevertheless, they have shown great progress in their use as imaging systems and theranostics, specifically in aiding the diagnosis of ovarian cancers [13].

Various technologies are involved in the engineering of these carriers. Conventional methods, such as solvent impregnation, are common fabrication methods that have successfully yielded MSNs [5,32]. More recent emerging engineering technologies, such as electrohydrodynamic atomization (EHDA), have started to be exploited to develop MSNs in a simple one-step, cost-,effective method [72,73]. By utilizing ever-evolving technologies, these beneficial carriers can be continuously fabricated in a cost-effective, easily adaptable, and modified way that can be altered to fit specific requirements or criteria, rendering them attractive for personalized drug delivery and therapy.

This review focused on recent applications of MSNs from a chemotherapy prospective. In addition, it highlighted the relevant characteristics of MSNs, such as adjustable pore size, high surface area, bioactivity, and release properties, and the different types of technique used, to deliver safe and compatible anticancer APIs. Despite the challenges associated with delivering a drug, significant progress has been made in the biomedical field, particularly with MSNs. Moreover, numerous methods can be used to aid MSN-surface modifications to enhance the responsive release of drugs and control drug delivery. MSNs can be also used in optical imaging to in diagnose tumors at early stages of disease. Thus, effective MSN-based platforms could in the future overcome the disadvantages associated with current stand-of-care chemotherapy.

Conflict of Interest

The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

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