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Review

Therapeutic Potential of Polymer-Coated Mesoporous Silica Nanoparticles

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Abstract: Mesoporous silica nanoparticles (MSNs) find tremendous applications in drug delivery due to several advantages such as their easy fabrication process, high drug loading, biodegradability, biocompatibility, and so forth. Nevertheless, despite several advantages, the use of this striking drug delivery carrier is restricted due to premature drug release owing to the porous structure. Coating of the pores using polymers has emerged as a great solution to this problem. Polymer coatings, which act as gatekeepers, avoid the premature release of loaded content from MSNs and offers the opportunity for controlled and targeted drug delivery. Therefore, in this review, we have compiled the polymer-based coating approaches used in recent years for improving the drug delivery capability of MSNs. This manuscript provides an insight into the research about the potential of polymer-coated MSNs, allowing the selection of right polymer for coating purposes according to the desired application.

Keywords: polymer coating; mesoporous silica nanoparticles; targeted drug delivery; stimuli responsive drug delivery

1. Introduction

With the advent of nanotechnology in biomedical sciences, the application of different materials has increased exponentially to offer solutions for drug delivery and diagnostic challenges [1,2]. Mesoporous silica nanoparticles (MSNs) are an example of such a material that has been widely used for the development of modern nanoparticulate drug delivery systems targeting various diseases, ranging from cancer to neurodegenerative disorders as well as metabolic disorders such as diabetes.

Although discovered in the early 1990s [3], mesoporous silica found their way into the biomedical sciences in 2001 when an mobil composition of matter-41 (MCM-41) material was used for drug loading and the release of ibuprofen [4]. A few years later, mesoporous silica saw a significant boost in this area when the preparation of this material in a nanoparticulate form (i.e., MSNs) began to be reported on. One of the foremost advantages of MSNs are their large surface area and pore volume, which lead to exceptionally high drug loading capacity, but, in turn, may also result in the premature release of the drugs [5,6]. Premature drug release before reaching the target site hampers the utility of MSNs in targeted therapy. However, the tunable surface chemistry of MSNs allows surface polymer coating,

thus providing sustainable and controlled release functions to be integrated by polymers acting as gatekeepers [6,7]. The optimal biodistribution, biodegradation, and biocompatibility of polymer coated MSNs favour them as a potential type of drug delivery system. Just like any nanocarrier, MSNs absorption and distribution mainly depend on the administration route. For instance, MSNs with a 110-nm size were delivered via intravenous (i.v.), hypodermic, intramuscular, and oral routes in mice to compare absorption and distribution. After oral administration, MSNs were absorbed after 24 h through the intestine followed by transpose to the liver. Delivery via hypodermic and intramuscular route demonstrated poor absorption whereas after i.v. injection, MSNs were mainly deposited in liver and spleen. However, particle size also played an important role in determining the fate of MSNs in vivo [8]. In a recent study, a decrease in particle size from 142 to 32 nm of MSNs, increased bioavailability regardless of the administration route; intravenous (i.v.), or intraperitoneal with accumulation in the liver and spleen. The surface chemistry of MSNs played a significant role in excretion, where a positive charge with shielded surface amines demonstrated a higher excretion rate and thus displayed lower liver accumulation compared to cationic and neutral MSNs [9]. The excretion of MSNs was monitored through urine and faeces with no change in kidney structure, suggesting the low toxicity of these nanocarriers [8]. The adsorption, distribution, metabolism, excretion (ADME), and safety of MSNs have been reviewed multiple times in the literature [10–13]. Since the physical and chemical properties of MSNs can be easily modulated by organic functionalization, the majority of future work is focused on polymer coated MSNs to optimize the properties of these multifunctional hybrid nanocarriers. Though there is a long way to go for MSNs to appear in clinics, some of the parent silica particles have appeared in clinical trials and are presented in Table 1.

Table 1. Clinical trials on silica nanoparticles.

S. No	Title	Submission Date	Identifier	Recruitment Status
1	Plasmonic Photothermal Therapy of Flow-Limiting Atherosclerotic Lesions with Silica-Gold Nanoparticles: a First-in-Man Study	30 December 2010	NCT01270139	Completed
2	Targeted Silica Nanoparticles for Real-Time Image-Guided Intraoperative Mapping of Nodal Metastases	3 April 2014	NCT02106598	Recruiting
3	Molecular Phenotyping and Image-Guided Surgical Treatment of Prostate Cancer Using Ultra small Silica Nanoparticles	18 November 2019	NCT04167969	Recruiting

Numerous published reports discuss the applications of MSNs in the biomedical field [14,15], but literature presenting the significance of polymer coating on MSNs is still somewhat lacking and, therefore, this review will shed light on various polymers utilized for the synthesis of polymer coated MSNs for effective management of their properties under biological conditions (Table 2). Coating of the polymer onto MSN and drug loading are usually performed via two different approaches. In the first approach, pristine MSNs are coated with polymer followed by drug loading, whereas in the second approach, drug loaded MSNs are prepared first, followed by the polymer coating (Figure 1). The selection of the right approach for drug loading depends largely on the physicochemical properties of the drug molecule, as well as the polymer characteristics and coating procedure.

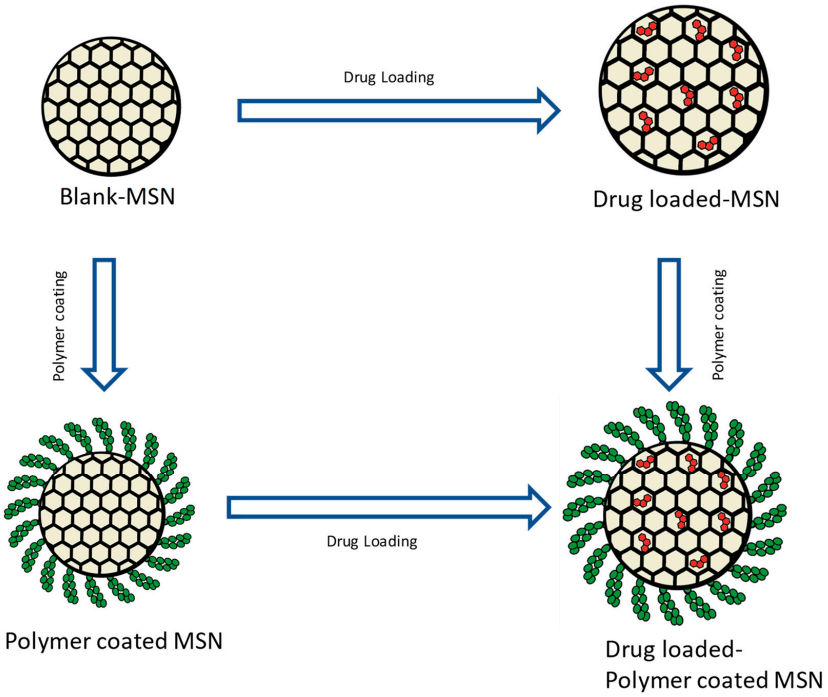

Figure 1. Graphical representation of the approaches used to prepare drug loaded MSNs coated with polymer.

Natural polymers such as chitosan and poly(dopamine), as well as chemically synthesised artificial polymers such as poly(ethyleneimine) (PEI) and poly(ethyleneglycol) (PEG), have been widely utilized for coating purposes (Figure 2). The selection of a polymer for coating is mostly based on the predefined properties required for the desired outcome, such as sustained release, biocompatibility, targeting, or stimuli responsive release of cargo from MSNs [16]. The stimuli-responsive drug release characteristic in MSNs could be of great benefit, which allows the release of the loaded drug only at the target site and thus enhances the therapeutic response and minimizes the side effects. The stimuli-responsive trigger can be either exogenous (external stimuli such as magnet, light, temperature) or endogenous (internal stimuli such as pH, redox, enzyme). However, a combination of more than one stimuli-responsive character to generate multiresponsive systems are reported to be superior to single systems. Specifically, the endogenous stimuli responses are highly variable in different patients due to changes in the pathophysiology of disease in each individual. Thus, a dual or triple responsive carrier system with a combination of endogenous and/or exogenous characteristics is capable of releasing the drug more precisely at target sites [17,18].

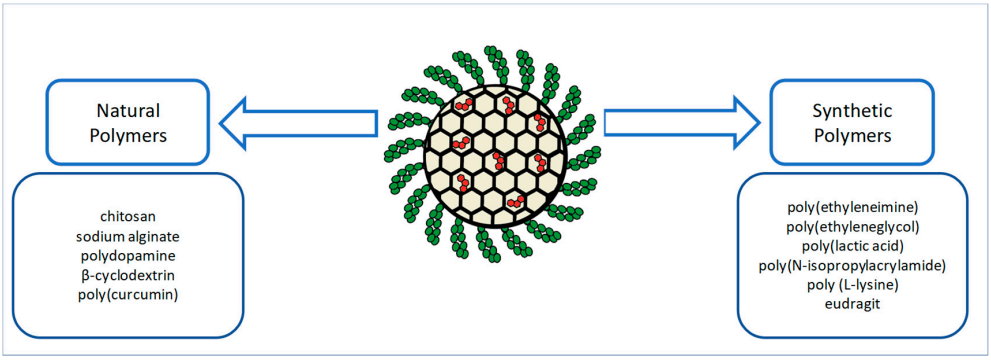

Figure 2. Polymers of natural and synthetic origin that have been used as coating agent for MSN for providing control over drug release.

The pathophysiological condition of the targeted disease forms the basis of properties required to design a polymer coated MSN, and effective treatments of numerous diseases through polymer coated MSNs have already been explored (Figure 3). Therefore, in this review, the polymer coated MSNs have been categorized based on the disease conditions, and the associated advantages are discussed in detail.

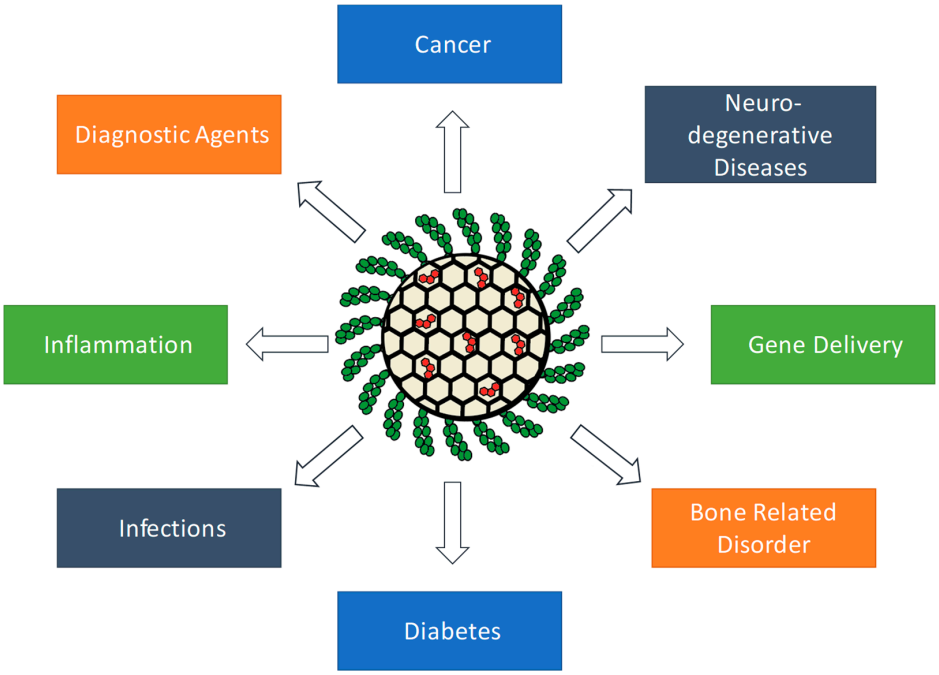

Figure 3. Biological disorders that have been targeted using polymer coated mesoporous silica nanoparticles.

2. Polymer Coated MSNs for Cancer

Nanocarriers find enormous application potential in the diagnosis and treatment of cancer due to their capability of providing controlled release and targeted therapy. MSNs, due to their high surface area, tunable pore size, and flexible surface modification possibilities, along with good biocompatibility, have been prominently employed in cancer treatment research. In addition, the surface coating of MSNs offers the opportunity of achieving stimuli-responsive drug release at target sites, thus decreasing the systemic toxic effect of antineoplastic drugs [19]. Internal as well as external stimuli are widely explored for the selective release of drugs at tumor sites. Several polymers have been utilized to coat the MSNs in order to increase their potential in this respect and are discussed below.

Li et al. prepared polydopamine (PDA) coated MSNs for dual stimuli-responsive drug delivery of doxorubicin (DOX). A simple stirring of bare MSNs and dopamine in Tris buffer allowed the coating of PDA over the MSN surface. The developed MSNs were responsive to ultrasound and pH. The accelerated release of DOX was observed at low pH owing to the high solubility of DOX and degradation of PDA under acidic conditions. In addition, a unique "On-Off" release of DOX was observed in the presence of HIFU (high-intensity focused ultrasound) irradiation due to the mechanical changes in the structure (Figure 4) [20]. Similarly, Rahoui et al. developed gold modified PDA-coated DOX-loaded MSNs for synergistic chemo-photo therapy. High DOX release was observed at low pH from MSNs with an average diameter of 60 ± 5 nm due to the presence of PDA coating and a reduction in electrostatic interaction between MSN and DOX. On the other hand, less than 10% release was observed at physiological pH, advocating the advantage of PDA coating to avoid premature drug release. In addition, the irradiation of NIR light (808 nm) upsurged DOX release at low pH (pH—5.0) with the possibility of an on-off mechanism. It was proposed that NIR light increases the solution temperature due to the presence of gold particles and thus promote DOX diffusion from MSN [21].

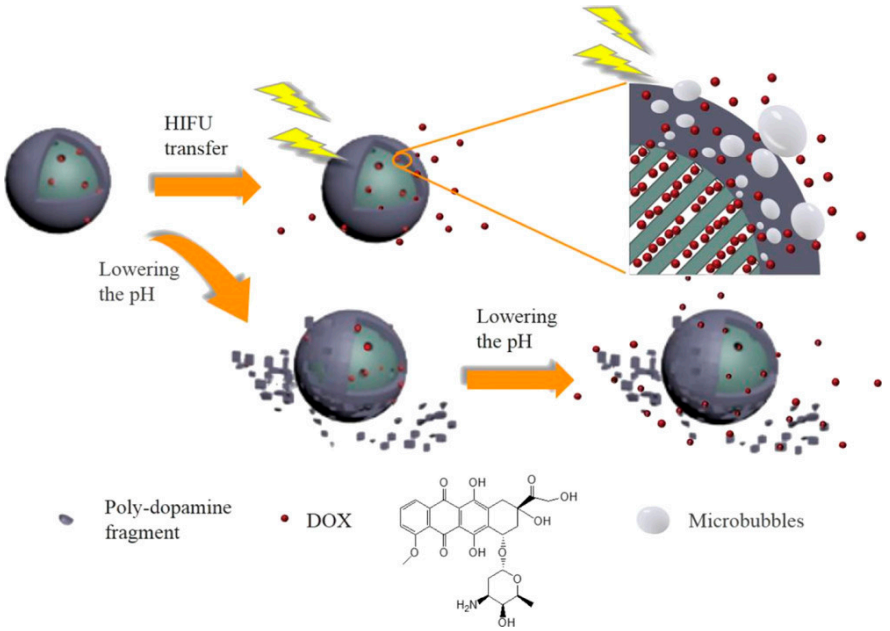

Figure 4. Pictorial presentation of pH/HIFU dual-responsive release characteristic of DOX loaded MSN–PDA. Reproduced with permission from reference [20].

In another example, PDA was used to coat MSN to facilitate pH sensitive drug release. Polyethylene glycol conjugated with epithelial cell adhesion molecule (EpCAM) aptamer was later attached to the MSNs to prepare a targeted drug delivery system for the treatment of colorectal cancer. DM-1, a cytotoxic agent, loaded MSNs demonstrate an increase in cytotoxicity to SW 480 cell lines by up to 50% after 48 h incubation compared to the free drug [22]. Recently, PDA coated MSNs were employed by us to further evaluate the effect of MSN shape on intracellular uptake and drug release rate. We demonstrated that rod-shaped MSNs exhibited delayed intracellular drug release with higher uptake compared to spherical MSNs [23] thus suggesting that polymer surface coating in combination with other design aspects can be utilized to fine-tune the drug delivery properties of the system [24]. This was a follow-up study to another one where we showed that on one hand, high drug loading (>30 wt% for water soluble compounds DOX and calcein) can be achieved owing to the π–π stacking interactions between the abundant aromatic rings of PDA and the aromatic backbones of drug compounds, and on the other hand catechol–metal–drug coordination systems can easily be constructed based on the coordination bonding between catechols in PDA and transition metal ions (Fe^{3+}, Zn^{2+}) as well as that between metal ions and anthracycline drugs such as DOX, resulting in an acid-triggered drug release (Figure 5) [25].

PDA coated metal dichalcogenides ($MoSe_2$) sheets were also employed to cap MSNs to develop a modified nanocarrier for chemo-photothermal therapy in cancer treatment (Figure 6). These ~300 nm particles loaded with DOX (427 mg/g) demonstrated accelerated drug release in response to low pH and exposure of NIR laser (808 nm). A superior antitumor efficacy with high safety was observed in vivo for these nanoparticles in combination with laser exposure compared to free DOX and other tested monotherapies [26].

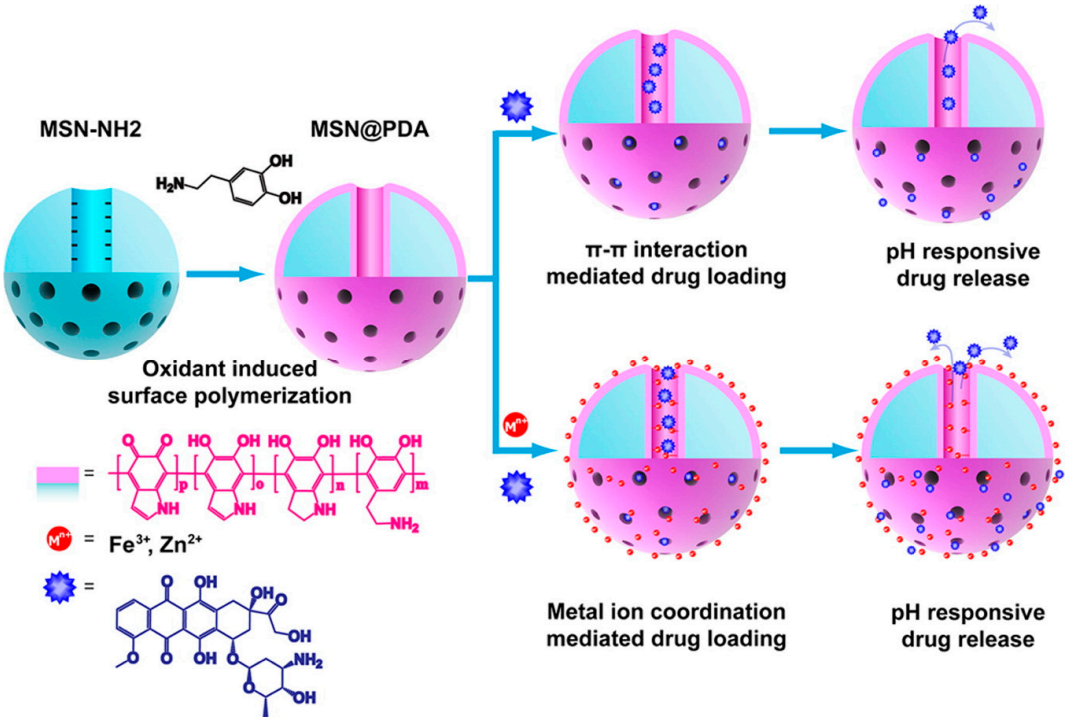

Figure 5. Schematic illustration of the progress in constructing polydopamine-coated MSN particles for drug loading and release. Adapted with permission from [25], copyright (2015) American Chemical Society.

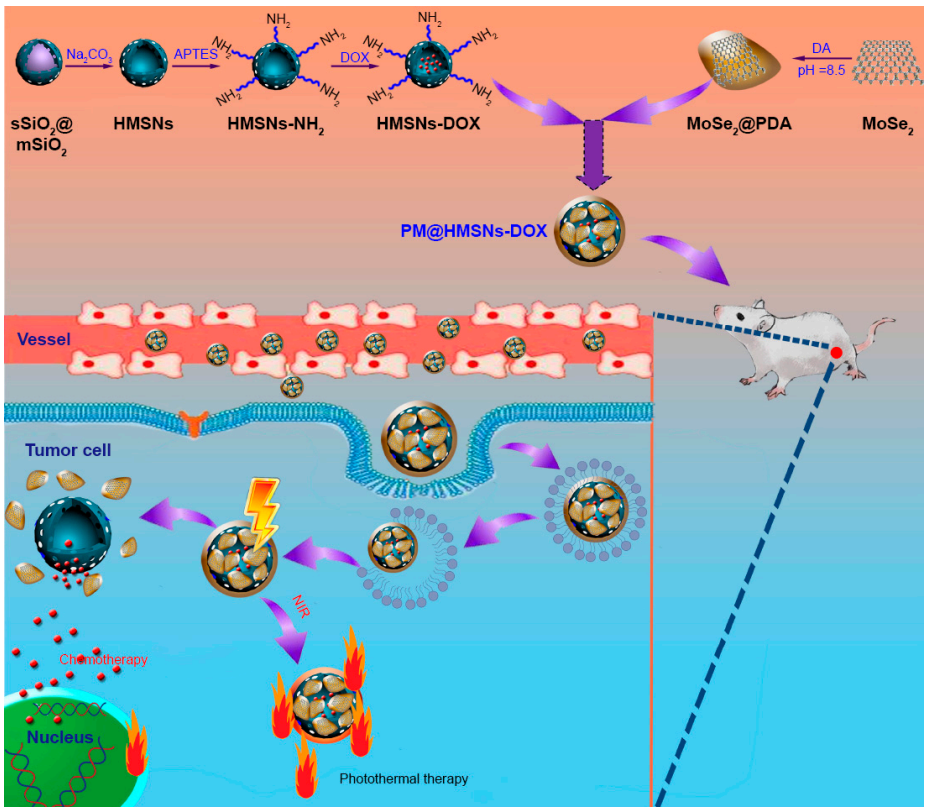

Figure 6. Graphical representation of the preparation of dual sensitive MSNs for pH/NIR-responsive chemo-photothermal therapy [26].

Alpha-tocopheryl polyethylene glycol 1000 succinate (TPGS) functionalized polydopamine-coated MSNs were also investigated for the treatment of multidrug-resistant lung cancer. An additional coating of TPGS is supposed to suppress P-glycoprotein (P-gp) meditated resistance in cancer cells. The TPGS conjugated MSNs enhanced cellular uptake in drug resistant A549 cells, thus suggesting the possibility of drug resistance reversal [27].

A polyelectrolyte complex approach was utilized by Szegedi et al. to prepare polymer coated MSNs for the controlled delivery of curcumin. Curcumin loaded amine terminated MSNs were coated using the "layer-by-layer" technique by depositing oppositely charged polyelectrolytes. Further, κ-carrageenan and chitosan were used as polyelectrolyte polymers due to the presence of opposite charges. Four alternating layers of coating were deposited around the particles, starting with carrageenan followed by chitosan. The loss of anti-neoplastic activity of the drug was not observed after polymer coating, but the coating aided the sustained release of curcumin over a 24-h period [28]. Chitosan coated MSNs modified with dual targeting ligands, i.e., folic acid and hyaluronic acid, for the active targeting of DOX to tumor cells was developed by Hu et al. for effective cancer therapy [29]. Chitosan coated MSNs were also employed to sustain the release of gallic acid [30].

A pH-sensitive MSN coated with poly(L-histidine) (PLH) and poly(ethylene glycol) (PEG) were synthesized by Mu et al. for tumor specific release of sarafenib [31]. PLH exhibit solubility alteration based on the surrounding pH and thus, the coating provided an "on-off" mechanism of drug release (Figure 7). The PLH was grafted through a Michael addition reaction from thiol functionalized MSNs followed by the grafting of PEG as a hydrophilic coating. Coated MSNs with a size of 160 nm and with 20-nm thick coating were capable to trigger the release of drugs in lysosomes after the uptake of nanoparticles, due to the low lysosomal pH as evidenced by confocal microscopy in HepG2 cells. Further, nanoparticles showed negligible haemolysis activity and no visible tissue toxicity along with good anti-proliferative and tumour growth regression in vivo [31].

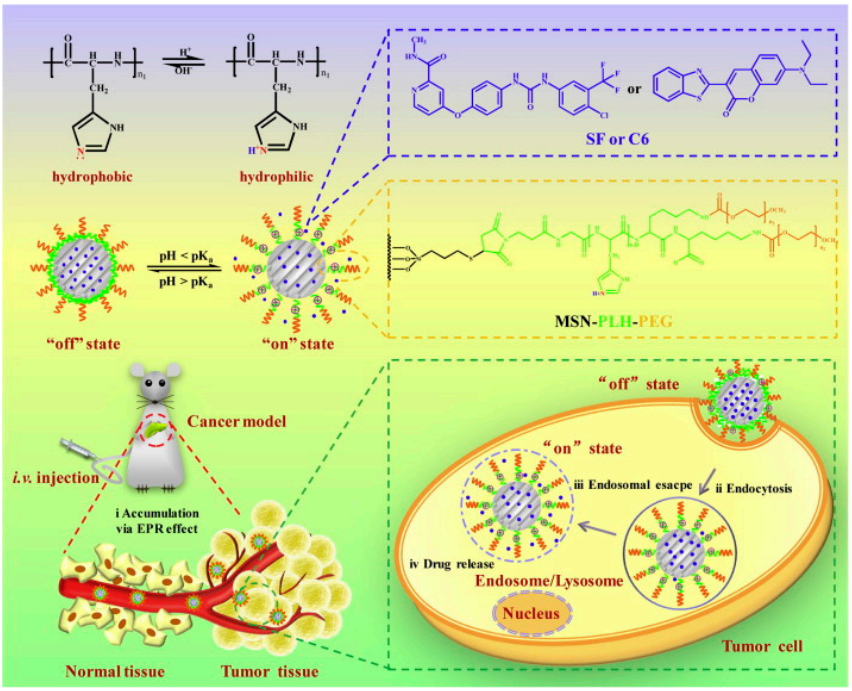

Figure 7. Schematic presentation of pH responsive drug release with the aid of poly(L-histidine) (PLH) coated MSNs. Reproduced with permission from reference [31].

In another example, PEGylated lipid bilayer coated MSNs were utilized for the co-delivery of paclitaxel and curcumin. A film hydration method was used for MSN coating with 1:1.1 MSN/lipid ratio, which provided a 13–15 nm uniform coating of the surface. An in vitro drug release assay demonstrated

the sustained release of drugs with improved aqueous solubility, which persistently promoted the cytotoxic effect against breast cancer cells (7364 cells) [32]. A "dendritic" structured mesoporous silica nanoparticle with large pores, coated with a PEI–PEG copolymer was also explored for the controlled delivery of highly toxic tumour necrosis factor-alpha (TNF-α). The PEI–PEG coated MSN led to the pH dependent sustained release of TNF-α, reduced its systemic toxicity, and demonstrated the efficient regression of 3D melanoma spheroids in a time and dose-dependent manner [33].

PEG coated MSNs were also utilized for chemo-photodynamic therapy using chlorin-e6 as a photosensitizer. As such, (3-aminopropyl) triethyoxysilane (APTES) conjugated with chlorine-e6 was employed to prepare MSNs and DOX was loaded into the pores. PEG was later conjugated onto MSNs surface via oxygen sensitive bis(alkylthio)alkene linker to control the drug release by light irradiation. On irradiation of red light (660 nm), chlorin-e6 generates killer ROS, which along with initiating cell apoptosis, also cleaved the oxygen sensitive linker leading to PEG de-shielding and allowing the accelerated release of DOX for chemotherapy. The superior anticancer effect of MSNs was further demonstrated in vivo, in which a significant anticancer effect was observed in mice treated with modified MSNs when irradiated with a red light. In addition, the photodynamically triggered endosomal escape of the carrier by light irradiation owing to the presence of chlorin-e6 was successfully confirmed in vitro [34].

A triple responsive drug delivery system was fabricated by applying a thermo-responsive polymer poly(*N*-isopropylacrylamide) (PNIPAAm) coating to MSN via disulfide linkage. In addition to the temperature and redox responsiveness, iron oxide nanoparticles were incorporated inside MSNs to make them triple responsive (i.e., magnetic field). DOX was encapsulated as an anticancer agent and its release was controlled via a magnetic field, temperature, and the presence of a reductive environment (Figure 8) [35].

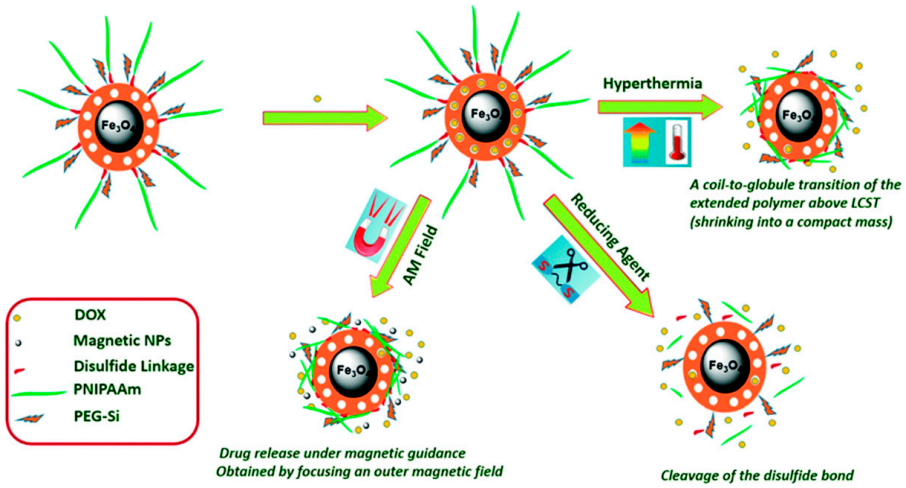

Figure 8. Schematic representation of a triple responsive release mechanism of drug from PNIPAAm coated magnetic MSNs. Reproduced with permission from reference [35].

Dual responsive MSNs were also utilized to co-deliver evodiamine and berberine (herbal anticancer drugs) by Feng et al. Poly(NIPAM-co-MA) was used as a dual sensitive polymer to seal the pores, which imparted pH and thermo-responsive drug release characteristics. MSNs were further coated with DSPE-PEG_{2000}-modified lipid bilayer to enhance the biocompatibility of the nanoparticles. An accelerated release of drugs was observed at pH 5.0 and at high temperature (41 °C). The dual drug loaded nanoparticles having a 1:6 ratio of evodiamine:berberine led to an increase in apoptosis rate and was found to be almost similar to taxol to inhibit tumor growth in vivo, but with fewer side effects [36].

Synergistic cancer starvation and chemotherapy was attempted by Du et al. using a poly (L-lysine) and hyaluronic acid (HA) coated MSN for the co-delivery of glucose oxidase and paclitaxel (PTX) (Figure 9). Poly (L-lysine) was attached to the MSN surface via a pH-sensitive benzoic-imine bond to

prevent drug leakage and to facilitate endosomal escape. An additional coating of HA was performed to avoid the toxic effect of poly (L-lysine) due to the presence of amine groups, consequently increasing biocompatibility and simultaneously HA is acting as a targeting ligand. It was observed that the surface coating of HA enhanced the cellular uptake of nanoparticles via CD44 receptor-dependent mechanism in HepG2 cells. A significant reduction in tumor growth was observed in vivo with modified MSNs compared to PTX alone. It was suggested that the glucose oxidase elevated the toxic H_2O_2 level by oxidizing intratumoral glucose (which block the energy supply to tumor cells) and thus demonstrated remarkable anticancer activity along with PTX [37].

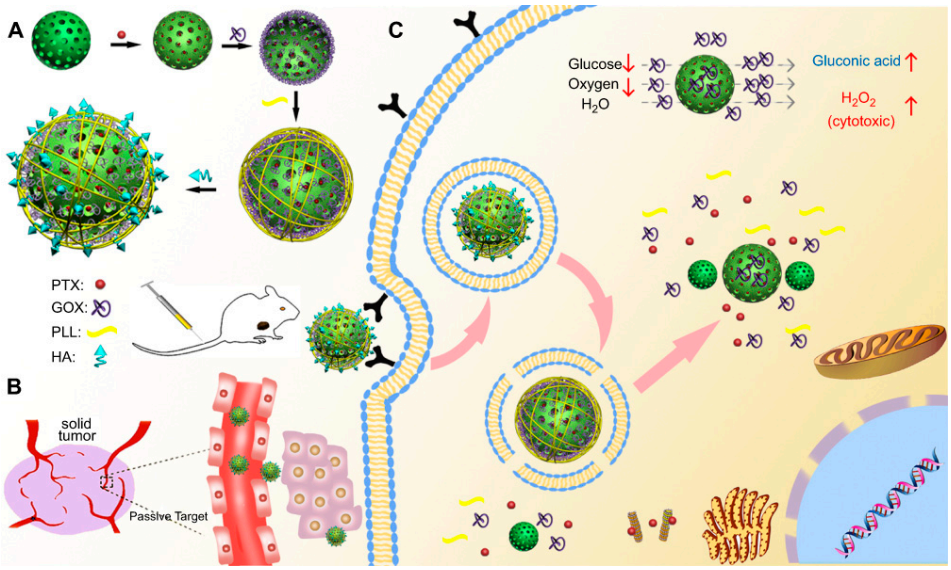

Figure 9. Schematic presentation of coated MSNs for synergistic tumor-targeted therapy [37].

Sodium alginate coated MSNs was developed for dual responsive controlled release of DOX. Sodium alginate was attached to MSNs via disulphide linkage to add reduction sensitive property, whereas alginate itself exhibit pH responsive characteristics. A higher DOX release (more than 60%) was observed at pH 5.0 in the presence of glutathione (10 mM) whereas less than 20% drug was released in the absence of stimuli. The biocompatibility of blank nanocarrier was ascertained by MTT assay using HeLa cells (above 90% survivability) while DOX loaded MSNs killed 54% of the cells [38].

Iron oxide core@shell MSNs coated with pH-responsive poly(ethyleneimine) (PEI) and folic acid was fabricated for the effective delivery of erlotinib. The iron oxide core aided in tumor-targeted magnetic resonance imaging, whereas PEI was integrated to support the controlled release of the drug. Folic acid was attached to PEI by a DCC coupling reaction before coating the surface of MSNs. The resulting nanoparticles demonstrated higher toxicity in HeLa cell lines at 62.5 μg mL^{-1} concentration of drug compared to free erlotinib [39]. A 30% boost in drug release was observed at pH 5.5 when compared to physiological pH for the PEI-coated MSN, compared to the non-coated MSNs for which the release behaviour under different pH conditions was not pronounced. The authors attributed this to the lower attraction between the silica surface and PEI at a lower pH, through which the silanols become less deprotonated (i.e., loses some negative charge) and any loaded drug molecules can escape through the polymer coating. We note that, in this study, the drug release behaviour was correctly compared between coated and non-coated MSNs. Thereby, especially with regard to DOX release studies, often only the release for the final MSN design is shown, this being a very frequently encountered misconception upon which "pH-responsive release" is claimed, even though the observed release differences are solely due to the pH-dependent solubility of DOX. We also note that, given most drug molecules are weak acids or bases, when using pH-sensitive polymer coatings such as polyamines (in essence, any polyacid or polybase) one needs to take into account the pH-induced changes a coating may impart on any loaded agents [40], thus altering their physicochemical properties.

β-cyclodextrin coating was employed by Liu et al. to control the release of indocyanine green from mesoporous silica coated gold nanorods. Adamantane decorated dual-functional RLA peptide was then attached to modified MSNs via host–guest interaction for membrane penetration and mitochondrial targeting. Later, to impart biocompatibility and stability, a charge-switchable and anti-fouling polymer (2,3-dimethylmaleic anhydride modified chitosan oligosaccharide-b-poly(ethylene glycol)) was coated through electrostatic interaction. It was proposed that at an acidic pH of the tumor microenvironment, an electrostatic interaction between the anti-fouling polymer and RLA peptide weaken, leading the exposer of RLA for enhanced cellular internalization and mitochondrial accumulation. A combined photodynamic and photothermal therapy was demonstrated upon NIR exposure, due to the presence of indocyanine green and gold rods, leading to the excessive generation of killer ROS and subsequently resulting in tumor cell apoptosis in vitro and in vivo [41].

Poly(acrylic acid) (PAA) coated MSNs loaded with arsenic trioxide were prepared by Tao et al. for targeted and pH triggered release in glioma. The MSNs were further encapsulated within liposomes coated with angioprep-2 as a targeting ligand to prepare a hybrid nanocarrier for targeted therapy (Figure 10). The amine functionalized MSNs were reacted with poly(acrylic acid) to achieve surface coating and pH sensitive properties. These 140-nm particles with negative zeta potential (−13 mV) showed improved cellular uptake in HBMEC cells and blood brain barrier (BBB) permeation in an in vitro model, ascribed to the presence of the targeting peptide. A remarkable antitumor activity was observed in C6 glioblastoma orthotopic rats when treated with ligand targeted hybrid carrier (tumor volume = 27.43 ± 11.92 mm^3) compared to free arsenic trioxide (80.91 ± 13.45 mm^3) or with polymer coated MSNs (52.82 ± 10.82 mm^3) [42].

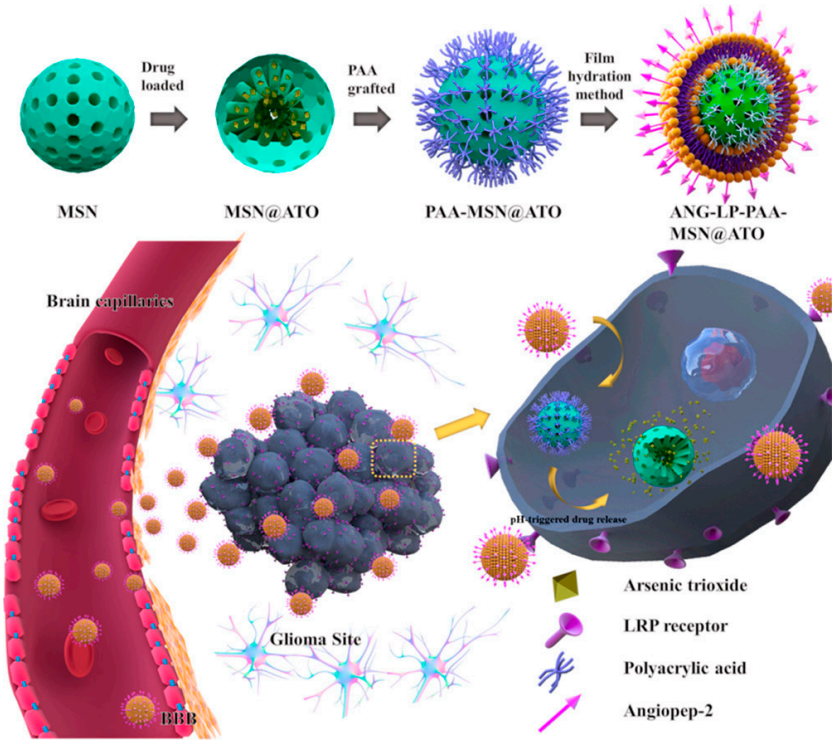

Figure 10. Graphical representation of the synthesis of PAA coated MSNs and their encapsulation in liposomes for glioma therapy [42].

Table 2. Tabular presentation of different coating materials used for MSNs along with their investigated applications.

Sr No	Investigators	Silica Core	Polymer Used	Drug	Application
1	Li et al. [20]	MSNs	Polydopamine	DOX	Cancer
2	Rahoui et al. [21]	Gold modified MSNs	Polydopamine	DOX	Cancer
3	Yang et al. [22]	MSNs	Polydopamine, PEG and EpCAM aptamer	DM-1	Colorectal cancer
4	Chai et al. [26]	MoSe2 wrapped MSNs	Polydopamine	DOX	Cancer
5	Cheng et al. [27]	MSNs	Alpha-tocopheryl polyethylene glycol 1000 succinate functionalized polydopamine	DOX	Cancer
6	Szegedi et al. [28]	KIL-2 and KIT-6	k-Carrageenan and Chitosan	Curcumin	Cancer
7	Hu et al. [29]	MSNs	Folic acid modified Chitosan and Hyaluronic acid	DOX	Cancer
8	Iraji et al. [30]	MSNs	Chitosan	Gallic acid	Cancer
9	Mu et al. [31]	MSNs	Poly-(L-Histidine) and PEG	Sorafenib	Cancer
10	Hegazy et al. [35]	Core-shell magnetic MSNs	Poly(N-isopropylacrylamide) (PNIPAAm)	DOX	Cancer
11	Feng et al. [36]	MSNs	Poly(N-Isopropylacrylamide-co-methacrylic acid) and DSPE-PEG_{2000}	Evodiamine and Berberine	Cancer
12	Du et al. [37]	MSNs	Poly(L-lysine) and Hyaluronic acid	Glucose Oxidase and Paclitaxel	Cancer
13	Yuan et al. [38]	MSNs	Sodium Alginate	DOX	Cancer
14	Avedian et al. [39]	Fe_3O_4 core MSNs	Polyethyleneimine and Folic acid	Erlotinib	Cancer
15	Moreira et al. [43]	Gold core MSNs	Poly-2-ethyl-2-oxazoline	DOX	Cancer
16	Yu et al. [44]	MSNs	4-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)benzyl acrylate polymer	DOX	Cancer
17	Liu et al. [45]	MSNs	Lipid Galactosyl-Ceramide	Hydroxy-campothecine	Cancer
18	Ma et al. [46]	MSNs encapsulated in liposomes	Calcium Phosphate	DOX and Zinc Phthalocyanine	Cancer
19	Liu et al. [41]	Gold Nanorods coated with Mesoporous silica	β-cyclodextrin and (2,3-dimethylmaleic anhydride modified chitosan oligosaccharide-b-poly(ethylene glycol))	Indocyanine Green dye	Cancer
20	Lin et al. [32]	Highly ordered MSNs	PEGylated Lipid bilayer	Paclitaxel and Curcumin	Cancer
21	Kienzle et al. [33]	Dendritic MSNs	Polyethylene imine and Poly ethylene glycol	TNF-α	Cancer
22	Lee et al. [34]	Chlorin-e6 loaded MSNs	PEG	DOX	Cancer

Table 2. *Cont.*

Sr No	Investigators	Silica Core	Polymer Used	Drug	Application
23	Tao et al. [42]	MSNs encapsulated in liposomes	Poly(acrylic acid)	Arsenic trioxide	Glioma
24	Tzankov et al. [47]	MCM-41	Chitosan and Sodium alginate	Pramipexole	Neuroblastoma
25	Shen et al. [48]	MSNs	Poly(lactic acid)	Resveratrol	Parkinson's disease
26	Cheng et al. [49]	MSNs	plasmid RhoG-DsRed	Curcumin	Oxidative stress
27	Mandic et al. [50]	MSNs	PEG	Quercetin, myricetin and myricitrin	Oxidative stress
28	Peralta et al. [51]	MSNs	Poly(N-isopropylacrylamide-co-3-(methacryloxypropyl) trimethoxysilane)	Ibuprofen	Inflammation
29	Gulin-Sarfaz et al. [52]	MSNs	PEI and PEG	Dexamethasone	Pulmonary Inflammation
30	Popova et al. [53]	SBA-15 and MCM- 41	Eudragit S and Eudragit RL	Sulfasalazine	inflammatory bowel disease
31	Liu et al. [54]	Gold nanorods coated mesoporous silica	PEG	Indocyanine green	Light-induced imaging-guided cancer therapy
32	Tran et al. [55]	FITC-MSNs	Polydopamine and Graphene oxide	Cisplatin	Theranostic Cancer therapy
33	Xu et al. [56]	MSNs	Poly Curcumin	DOX	Theranostic Cancer therapy
34	Song et al. [57]	SBA-15	Polydopamine	Silver	Antibacterial therapy
35	Lehi et al. [58]	SBA-15 nanowishkers	Tannic acid	Metronidazole	Trichomonasis
36	Tamanna et al. [59]	MSNs	Nafion Polymer	Gentamicin	Immunoassay
37	Zhang et al. [60]	Lithium Doped Silica Nanospheres	Polydopamine	Polyetherether ketone implant	Bone regeneration
38	Sun et al. [61]	MSNs	Distearoyl phosphatidylcholine	Rhodamine- B	Osteoarthritis
39	Ngamcherdtrakul et al. [62]	MSNs	PEI and PEG	siRNA	Gene Delivery
40	Zarei et al. [63]	Phosphonate modified MSNs	PEI	Plasmid DNA and chlooquine	Gene delivery
41	Zhang et al. [64]	Lanthanide doped upconversion Silica nanoparticles	PEG	siRNA and hypocrellin A	Gene delivery
42	Esmaeli et al. [65]	MCM-41	PAMAM dendrimer and chitosan-gelatine scaffold	Insulin and cinnamaldeyde	Diabetes

Likewise, gold core@shell MSNs have also been investigated in cancer chemo-photothermal therapy. These MSNs (nanorods) were coated with poly-2-ethyl-2-oxazoline in order to increase the biocompatibility and blood circulation time. Polymer coated MSNs were able to load more DOX compared to bare MSNs and provide a slow and controlled release of drug. It was observed that polymer coating leads to the improvement of the performance of gold core MSNs for multifunctional combinatorial cervical cancer therapy [43].

Yu et al. used a temperature and ROS dual responsive polymer, 4-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)benzyl acrylate, to coat MSNs for the stimuli sensitive delivery of DOX. The drug was loaded at low temperature (4° C) and the pores were then blocked by raising the temperature (37° C). A zero burst release was observed under physiological conditions, whereas a rapid release of cargo was observed in the presence of H_2O_2 due to the phase transition of coated polymer from hydrophobic to hydrophilic [44].

Liu et al. developed MSNs coated with lipid galactosylceramide for the sustained delivery of hydroxycamptothecine. The MSNs were prepared by a modified Stöber method and the lipid membrane was coated on the MSN surface using a lipid film hydration method. These nanoparticles showed that up to 30% of drug loading and approx. 48% of the drug was released in a simulated tumor environment in a sustained manner. The cell viability studies using these nanoparticles suggested that drug loaded nanoparticles had up to three times more stronger inhibitory effects on hepatocellular carcinoma cells compared to free hydroxycamptothecine [45].

Ma et al. prepared DOX loaded MSNs coated with pH sensitive calcium phosphate for chemo-photodynamic therapy. To impart photosensitivity, these MSNs were encapsulated in PEGylated liposomes containing zinc phthalocyanine as a photosensitizer. The liposomes were passively targeted and showed outstanding tumour accumulation, which was investigated by confocal laser scanning microscopy [46].

3. Polymer Coated MSNs for Neurodegenerative Diseases

The treatment of neurodegenerative diseases, such as Parkinson's, Alzheimer's, and so forth, represent a great challenge due to the existence of the BBB. However, MSNs demonstrate their potential to cross the BBB and it has been reported that polymer coated MSNs could perform better than their uncoated counterparts in terms of BBB penetration [66,67].

Negatively charged MSNs loaded with pramipexole were coated with chitosan and sodium alginate via electrostatic interaction for the treatment of oxidative stress associated with Parkinson's disease. The polymer coated MSNs showed sustained drug release and minimized initial burst release at acidic and neutral pH. Cytotoxicity assay results suggested that the toxicity of the free drug was greatly reduced upon encapsulation in coated MSNs, and the designed drug delivery system showed promising potential in preventing H_2O_2-induced oxidative damage in human neuroblastoma SH-SY5Y cells [47]. The same group later demonstrated the ability of chitosan and sodium alginate coated hollow MSNs for the delivery of dopamine-receptor agonist pramipexole [68].

Polylactic acid (PLA)-coated MSNs, attached with low-density lipoprotein receptor (LDLR) as a ligand were evaluated for brain targeting. These targeted particles were capable to cross the BBB to deliver resveratrol in CNS. In this study, PLA was explored as a stimuli-responsive gatekeeper. It was demonstrated that PLA significantly hinders the release of drug in PBS, but in the presence of superoxide (ROS), drug release increased owing to the accelerated degradation of PLA [48].

In an interesting study, a plasmid RhoG-DsRed was used to coat the MSNs to control the release rate of loaded curcumin and simultaneously for promoting neurite outgrowth in treating oxidative stress. Negatively charged plasmid was adsorbed on the surface of positively charged MSN via electrostatic interaction. Further, to promote cellular uptake, RhoG was mixed with cell penetrating peptide TAT, which subsequently showed higher cellular uptake in N2a cells compared to TAT unmodified MSNs. Curcumin loaded engineered MSNs significantly reduced paraquat (superoxide anion radical generator) induced signals in N2a cells [49].

PEG coated MSNs were explored to deliver flavonoids (quercetin, myricetin and myricitrin) with strong antioxidant properties in order to improve their aqueous solubility, release characteristics, and stability. High drug loading was observed for the flavonoids (up to 27 weight %) and the loaded flavonoids were capable of suppressing H_2O_2-induced changes in model lipid membrane's elasticity and morphological properties. The results suggested that flavonoid loaded MSNs showed neuroprotective activity, and that atomic force microscopy could be a valuable technique for monitoring the drug-induced effects at the membrane level, which may be extended to the cellular level [50].

4. Polymer Coated MSNs for Inflammation

Ibuprofen was the first drug molecule to be loaded and released from mesoporous silica in 2001 and has been vastly employed as a model drug in the context of mesoporous silica ever since. Also, stimuli-responsive systems have been designed based on ibuprofen release. For instance, MSNs grafted with thermo-responsive polymer poly(N-isopropylacrylamide-co-3-(methacryloxypropyl) trimethoxysilane) (PNIPAM-co-MPS, LCST—40 °C) were developed by Peralta et al. (Figure 11). The MSNs were magnetised by encapsulating iron oxide nanoparticles using the solvothermal method. The author's observed low loading efficiency of the drug in polymer coated MSNs (6.2 wt%) compared to uncoated MSNs (24 wt%), and this was attributed to the poor diffusion of drug through the polymer chains during the loading process. A temperature dependent release behaviour was observed from hybrid MSNs, where only 20% release was observed at 20 °C in 16 h but complete drug release at 40° C was observed within 24 h due to the coil-to-globule transition of the LCST polymer [51].

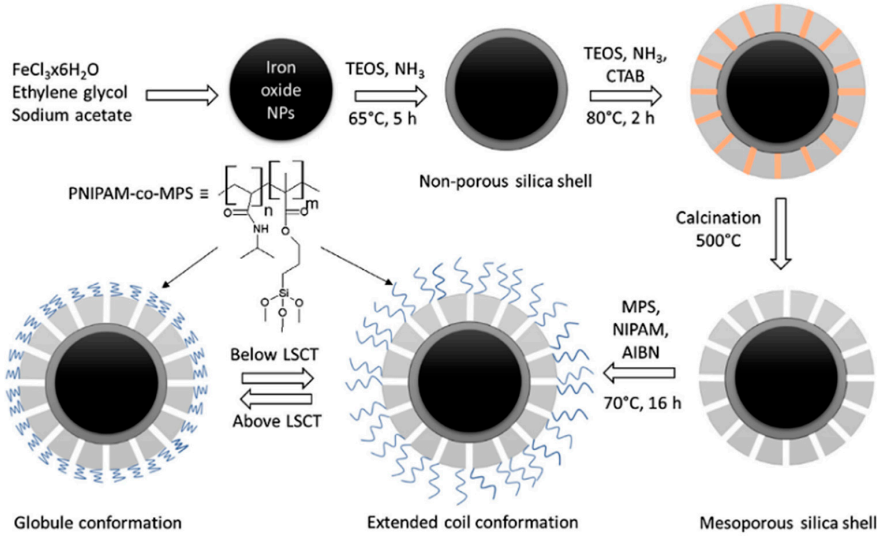

Figure 11. Preparation of polymer coated magnetic MSNs for delivery of Ibuprofen. Reproduced with permission from reference [51].

PEI-b-PEG coated MSNs loaded with dexamethasone was reported by Gulin-Sarfraz et al. for the treatment of airway inflammation. PEG–PEI coating improved the dispersibility of drug-loaded particles and suppressed unfavorable interactions within the airways. The coating was performed by electrostatically adsorbing PEI-b-PEG onto silica particles loaded with the drug. The aerosol formulation prepared using MSNs were administered in vivo via a nebulizer in two different mice groups with pulmonary inflammation induced by either melphalan or lipopolysaccharide. The obtained results suggested that drug loaded MSNs were as effective as free drug for treating the inflammation induced by melphalan. However, surprisingly, it was found that the blank particles were also capable of reducing inflammation in a lipopolysaccharide induced animal model [52].

Eudragit coated santa barbara amorphous-15 (SBA-15) and MCM-41 silica nanoparticles were developed with the aim to enhance the efficiency of sulfasalazine through the oral route. Amine

terminated MSNs were prepared using 3-aminopropyltriethoxysilane (APTES) and loaded with drug followed by coating with pH sensitive Eudragit S and Eudragit RL to control the drug release. The polymer coating restrained the drug release at pH 1.2 but accelerated the release at target pH, i.e., 6.2, as expected [53].

5. Polymer Coated MSNs for Infectious Diseases

Growing antibiotic resistance and persistent biofilms are the major reasons for the failure of potent antibiotics to combat infections. Nanomedicine, particularly MSNs, have recently demonstrated their capability in the treatment of bacterial infections owing to enhanced penetration through biological barriers [69].

SBA-15-type MSNs coated with PDA containing silver as an antibacterial agent were prepared by Song et al. to prolong the inhibition of bacterial growth via in situ formed silver nanoparticles. PDA coated MSNs control the release of silver particles and a prolonged inhibitory effect was observed with *E. coli* (60 h) and *S. aureus* (36 h) bacterial strains [57]. Similarly, whisker-like SBA-15 particles coated with 10% tannic acid were utilized as a carrier system for metronidazole for the treatment of trichomoniasis. The coating of tannic acid over the surface of nanoparticles was assisted by glutaraldehyde. The presence of tannic acid allowed pH sensitive drug release and improved the drug loading capacity of metronidazole by 7%. The coated MSNs demonstrate 100% protozoal growth inhibition for 180 min in vitro, which was superior to metronidazole solution [58].

In one of our own studies, the antibacterial properties of the naturally derived polymer chitosan were used as a coating on silver-doped MSNs to introduce multimodal antibacterial properties [70]. Also, in this case, a clear shape-dependent effect was observed especially on *E. coli.* when administered concomitantly with the antibiotic drug kanamycin, an enhanced antibacterial effect against *Vibrio cholerae* (*V. cholerae*) was achieved. Since MSNs are especially suitable for modular design, great promise can be envisaged in producing multifunctional MSNs including several antibacterial constructs in one system, prospectively making them more efficient in combating antibacterial resistance than drugs alone.

Tamanna et al. reported the preparation of gentamicin loaded MSNs, coated with Nafion polymer as a thin film on a slide (Figure 12). Nafion polymer provides stability to the film along with pH responsive release behaviour. Prepared films of MSNs were found stable for up to 90 days at pH 7.4 and release the loaded drug sustainably over up to 38 h in a mildly acidic solution, whereas up to 56 days at physiological pH. The utilization of this novel thin film system to protect against bacterial infections was proposed for implantable medical devices [59].

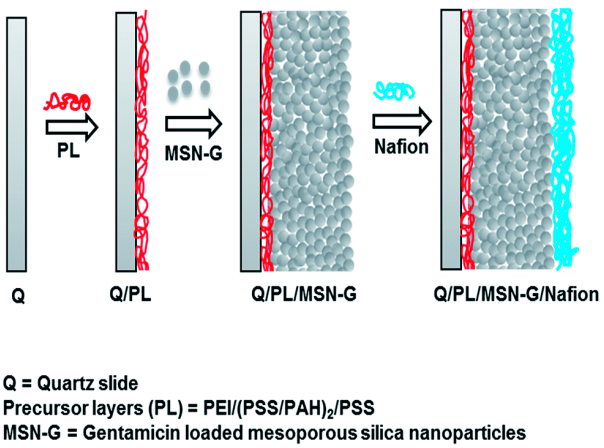

Figure 12. Pictorial presentation of thin film preparation of MSNs coated with Nafion. Reproduced with permission from reference [59].

6. Polymer Coated MSNs for Bone Related Disorders

MSNs also find applications in treating bone related diseases. Recently, lithium doped silica nanospheres coated with PDA was prepared by Zhang et al. to improve the bioactivity and osseointegration ability of polyetheretherketone (PK) orthopaedic implant. Nanospheres were coated on PK surface by direct immersion and coated PK demonstrate excellent cell proliferation suggesting bone tissue formation and enhanced osseointegration in vivo. The improvement in PK performance after nanosphere coating was attributed to the change in the surface characteristics and release of Si and Li ions, which supported the osteogenic activity of osteoblasts [60].

In another study, Sun et al. developed phospholipid coated MSNs to provide additional lubricating effects during treatment of osteoarthritis via nanoparticles injected directly to joint capsules. Tribiological test results suggested that coated MSNs provide effective lubrication via hydration lubrication mechanism owing to the amphiphilic nature of phospholipids. The release kinetics of nanoparticles were studied using rhodamine B as a model compound and a sustained release was observed from lipid coated MSNs compared to uncoated particles. Cytotoxicity assay on MC3T3-E1 cells suggests the low toxic behaviour of coated MSNs, advocating the use of developed particles in biomedical applications [61].

7. Polymer Coated MSNs for Gene Delivery

Cationic particles are mostly investigated for gene delivery due to nucleic acids being highly negatively charged, thus allowing complexation and, ultimately, better transfection efficiency. PEI is therefore, the most employed and efficient in vitro gene transfection vector, but due to its cytotoxicity, it is not suitable for therapeutic applications. Nevertheless, when derivatized, or used as a construct in drug delivery system design, the cytotoxicity of plain PEI can be significantly suppressed [40]. Therefore, MSNs ~100 nm in size coated with PEI and PEG polymers were utilized by Ngamcherdtrakul et al. to deliver siRNA to $HER2^+$ breast cancer cells. PEI coating was performed followed by cross-linking (by bio-reducible cross linker), to promote the endosomal escape of particles via the alleged proton sponge effect, whereas PEG coating protected the siRNA from degradation and avoid aggregation and adverse immune response from the cationic nanoparticles. Trastuzumab was used as a ligand for the selective uptake of nanoparticles by cancerous cells. These nano-constructs were selectively taken up by $HER2^+$ cells via the antibody–receptor interaction and successfully silenced HER2 expression, as evident from in vitro and in vivo experiments [62]. Furthermore, similar nanoparticles were used to deliver Polo-like kinase 1 siRNA (PLK1) for the treatment of triple negative breast cancer. The treatment was able to bring down the onset of death in mice and improved the overall survival in a TNBC mice model. The authors also claimed that these modified MSNs are capable to scavenge intracellular ROS and modulate NOX4 activity, which results in the inhibition of cellular invasion and migration in breast cancer cells in vitro [71].

PEI coated phosphonated MSNs were also evaluated for the delivery of plasmid DNA by Zarei et al. The coating was performed by electrostatic complexation between cationic PEI on anionic phosphonate modified MSNs, which also lead to a reduction in PEI toxicity. The transfection of particles was tested on Neuro-2A cells and found that transfection efficiency of MSN-PEI modified with 10 and 25 KDa respectively at C/P of 0.5 was significantly higher than PEI 10 and 25 kDa polymer. The authors also demonstrated that the loading of chloroquine, a lysosomotropic compound, does not always enhance the transfection efficiency [63].

PEI is not only useful for enhancing the transfection efficiency, but also for complexing/loading the negatively charged nucleic acids. Therefore, in one of our own studies, we functionalized MSNs with surface-hyperbranched PEI for the efficient loading of siRNA, which was covalently attached to the MSNs tethered via redox-cleavable linkers. The hyperbranched structure of surface-grown PEI provided a high surface concentration of attachment sites for the siRNA, yielding loading degrees of 120 $mg \cdot g^{-1}$. To ensure efficient cellular uptake, a second layer of short (low MW) PEI was attached to the surface of MSNs, yielding an overall positive surface charge. Triggered by the intracellular redox

conditions, the siRNA was sustainably released inside the cells over a period of several days. These hybrid nanocarriers prospectively allow for more efficient and long-term siRNA delivery, suitable also for therapeutic gene silencing in RNA interference (RNAi) therapy [72] while yielding an overall positive net surface charge for efficient intracellular uptake.

In another study, MSNs loaded with lanthanide-doped upconversion nanoparticles (UCNPs) covered with PEG or PEG-folic acid was employed for effective delivery of siRNA. PEG was coated via a photocleavable linker to introduce a photoresponsive characteristic, which controls the release of loaded siRNA. The irradiation of 980 nm light cleaves the linker and eradicates PEG from the MSN surface to release siRNA at the target site. However, the presence of PEG hindered the endosomal escape of siRNA, and thus a photosensitizer, hypocrellin A, was also loaded into the MSNs which, upon light irradiation, generate ROS to disrupt the endosomal membrane and facilitate siRNA release into the cytoplasm as well as promote cell apoptosis (Figure 13). Photo-controlled gene therapy was efficiently demonstrated in vitro and in vivo for the treatment of cancer [64].

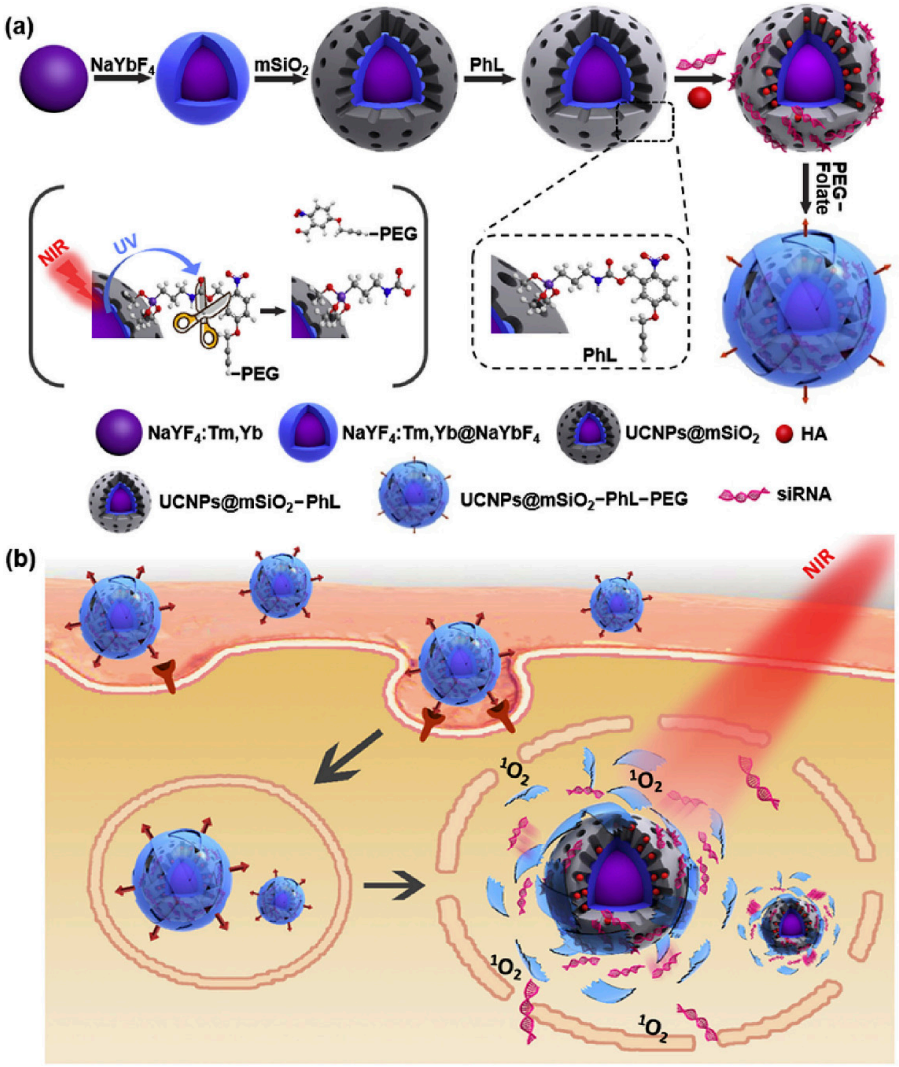

Figure 13. Graphical representation of (**a**) synthesis of nanoparticles, and (**b**) receptor-mediated endocytosis and NIR controlled intracellular delivery of siRNA. Reproduced with permission from reference [64].

8. Polymer Coated MSNs for Diabetes

The oral delivery of insulin is always attractive for the treatment of diabetes, but, at the same time, challenging due to the degradation of insulin in the physiological environment. To overcome this issue, Esmaeli et al. prepared poly(amidoamine) (PAMAM) dendrimer coated MSNs and investigated their capability to deliver insulin via oral route. The MSNs were loaded with insulin and coated with PAMAM dendrimer through urea linkage to provide better control over drug release. Cinnamaldehyde was loaded within the PAMAM structure to provide synergistic effects, and these nanoparticles were suspended in a chitosan-gelatine scaffold to further control the release rate of drugs. In vivo studies suggested that the prepared insulin loaded MSNs were able to decrease the blood glucose level for up to 10 h in streptozotocin-induced diabetic rat [65].

9. Polymer Coated MSNs for Imaging

The synthesis of mesoporous silica not only allows for the precise control of pore size and structure, as well as particle size and shape, but is also suitable for constructing core@shell composites by coating other nanoparticles with porous silica shells. For imaging purposes, inorganic materials are frequently used as core materials due to their inherent detectability by several (bio)medical imaging techniques, e.g., iron oxide cores for MRI as exemplified above. Amorphous silica itself is optically transparent, so in lieu of a detectable core material, MSNs can be loaded or conjugated to molecular imaging probes for introducing traceability in the physiological environment [73]. Simultaneously, a silica layer does not interfere with the imaging signal of optically active core material and provides better dispersibility to the otherwise most often hydrophobic inorganic cores [74]. Consequently, these core@shell constructs are fully composed of inorganic materials and usually require polymer coatings as well to render them more functional or responsive to the physiological environment, as outlined above for plain MSNs. In one example, fluorescent nanodiamonds (ND) were used as an optically active core material, which were coated with porous silica shells to introduce drug delivery ability to the system. Coating with silica yielded more uniform particles as compared to the irregularly shaped and sized ND cores, and the porous shells could be amply loaded with cargo molecules instead of adsorption to the ND surface, which is otherwise a customary strategy for ND drug delivery [75].

In an example, gold nanorods coated with mesoporous silica (Au@MSNs) were fabricated by Liu et al. as a theranostic agent for NIR imaging and photothermal cancer therapy. PEG was used to cover the silica pores and to introduce stealth property. PEG was also used as a linker for attaching targeting ligand polypeptide (tLyp-1). This indocyanine green (tracker dye) loaded nano-system offered a promising theranostic system for near-infrared (NIR) light-induced imaging-guided photothermal cancer therapy [54].

In another study, cisplatin loaded MSNs were prepared using starting material (3-aminopropyl)-trimethoxysilane (APTMS) labelled with fluorescein isothiocyanate (FITC) for theranostic application in cancer therapy. MSNs were further coated with PDA and graphene oxide (GO) to control the release of drug and for better dispensability of the particles. The thin layer of PDA over the MSN surface was created by oxidative self-polymerization, and later, coated MSNs were double wrapped with GO sheets via electrostatic interaction, followed by the conjugation of epidermal growth factor receptor (EGFR) peptide as a targeting ligand (Figure 14). In addition to pH responsive drug release, NIR light responsive accelerated drug release was also observed due to the higher NIR absorbance of the GO/PDA coating, which in turn produced an excellent photothermal effect. Confocal microscopy demonstrated the localisation of FITC-MSNs in the cytoplasm and the results also suggest that GO promotes the internalization of MSNs in H-SY5H cells through clathrin-mediated endocytosis. As expected, EGFR functionalized MSNs demonstrate more pronounced cytotoxicity due to specific targeting via receptor mediated endocytosis [55].

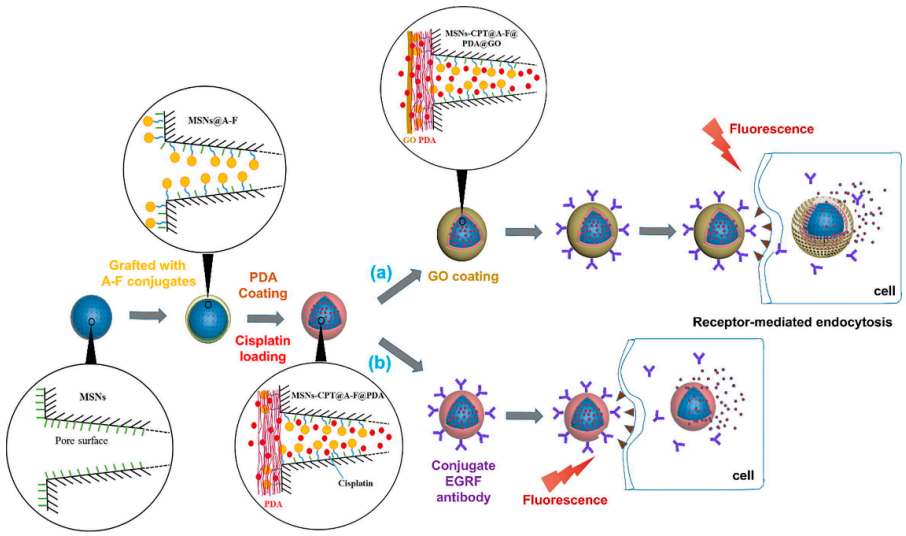

Figure 14. Illustration of preparation of theranostic MSNs (**a**) graphene oxide coated and (**b**) EGRF antibody conjugated without graphene oxide coating, for targeted delivery and imaging in cancer cells. Reproduced with permission from reference [55].

In an interesting study, curcumin polymer was prepared and used as a multifunctional material, which provides MSNs with a coating, acts as fluorescent probe and offers stimuli-sensitive drug release. Curcumin polymer was prepared from bis-acrylated curcumin derivative and later coupled to MSNs via thiol-ene coupling reaction in the presence of 3-mercaptopropyltrimethoxysilane (MPTMS) and dithiothreitol (DTT) to impart a reduction sensitive property. The accelerated release of loaded DOX was observed in the presence of glutathione owing to the degradation of curcumin polymer, and the polymer also demonstrated fluorescence imaging capability as evidenced by confocal microscopy [56].

10. Toxicity Aspects of Polymers

One of the major parameters in selecting the polymer for coating purposes of MSNs is its inherent toxicity. Although in most cases polymers are known to reduce the toxicity of the wrapped material, e.g., PEG coatings, in other cases, the polymer might induce the overall toxicity. As discussed in this paper, many studies have utilized poly(dopamine) as a polymer for MSN coating. In one study, polydopamine coating was used to attenuate the in vivo toxicity of two well-known low toxic materials, i.e., quantum dots and poly(lactic acid) while in contact with blood or tissues, suggesting the highly biocompatible behavior of poly(dopamine) [76]. Another natural polymer used considerably for coating is chitosan, which is also known to be a biocompatible material and its toxicity is mainly based on the surface charge [77]. Hyaluronic acid and poly(L-histidine) are usually considered as safe materials [78,79] whereas high molecular weight poly (L-lysine) (>30 kDa) with LD_{50} of 15 mg/kg is capable to produce undesired immunogenic responses [80].

Being a cationic molecule, PEI poses cytotoxicity issues where high molecular weight branched PEI has been found to be more toxic than the linear or low molecular weight counterparts [81,82]. However, the toxicity of PEI is concentration dependent and can be reduced by masking the polymer's cationic charge via derivatization, e.g., additional polymer coating. Although monomer NIPAM is toxic, poly(NIPAM) has been found to be less toxic in vitro and in vivo within working concentration ranges. The biodegradability of poly(NIPAM) can be tuned by making its copolymers, which also move the toxicity window of the copolymer to a higher concentration [83,84]. All the other polymers reported in this article usually demonstrate concentration and time dependent toxicity, whereas the reported concentrations in the literature were well below the toxic level.

11. Conclusions

Polymer coatings provide tremendous advantages in introducing functionality and responsiveness to MSNs in the biological/physiological environment, as well as facilitating the multifunctionality of MSNs in theranostic applications. With the aid of a polymer coating, MSNs biocompatibility, blood circulation time, and colloidal stability can be improved. Further, drug release in a spatially and temporally controlled manner, e.g., using targeting ligands and stimuli-responsive release, is possible by applying polymer coatings, thus providing innovative concepts in drug delivery research using MSNs. However, despite being comprehensively explored for the treatment of numerous diseases, the translation of this carrier system in clinics is still hampered. The major problems could be connected to reproducibility, scale-up, and in vivo fate in the human body. The more complex the design, the more complex these aspects are to realize and explore. MSNs as a drug carrier and reservoir with a polymer coating and a loaded drug, could already go a long way. Therefore, future research should be more focused on the translational aspects of this remarkable carrier system, so that patients and subsequently the wider society will benefit from the research.

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