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Review Article

Theme: Translational Application of Nano Delivery Systems: Emerging Cancer Therapy
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The Practicality of Mesoporous Silica Nanoparticles as Drug Delivery Devices and Progress Toward This Goal

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Abstract. Mesoporous silica nanoparticles (MSNs) have been proposed as drug delivery devices for approximately 15 years. The history of *in vitro* studies has been promising, demonstrating that MSNs have the capability for stimulus-responsive controlled release, good cellular uptake, cell specific targeting, and the ability to carry a variety of cargoes from hydrophobic drug molecules to imaging agents. However, the translation of the *in vitro* findings to *in vivo* conditions has been slow. Herein, we review the current state-of-the-art in the use of MSN for systemic drug delivery *in vivo* and provide critical insight into the future of MSNs as systemic drug delivery devices and directions that should be undertaken to improve their practicality.

KEY WORDS: drug delivery; mesoporous silica; nanoparticles.

INTRODUCTION

History

Mesoporous silica structures have been known to materials scientists for over 40 years when the term was first coined to describe zeolite-silica gel mixtures with a well-defined and uniform porosity (1). It was not until 1992, following the near-simultaneous discovery of organic-templated mesoporous silicas by two groups of scientists (2, 3) that researchers outside the field of materials engineering and petrochemicals began to take notice of these unique materials. The idea that mesoporous silica nanoparticles (MSNs) could be used as drug delivery devices would have to wait another 6 years until 1998, when a patent was filed by Muller, Reck, and Roser (4) stating that mesoporous silicates might contain pharmacologically active substances and again speculated upon by Schuth and colleagues (5) in 1999. The first account of MSNs with the ability to release a drug molecule was published in 2001 by Balkus and colleagues (6) using the material known as Dallas Amorphous Material-1 (DAM-1). This newly shown property of DAM-1 combined with the discovery that a modified Stöber process (7) could produce mesoporous silica particles of uniform size and morphology, spurred the development of MSNs toward the drug delivery platforms that proliferate in the literature today.

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Chemistry—Synthesis and Surface Chemistry

MSNs are an extraordinarily diverse family of materials which are synthesized primarily from one of two types of inorganic precursors, namely tetraalkoxysilanes and sodium silicate solutions (Fig. 1). The pH of aqueous solutions used in MSN synthesis enables control of hydrolysis and condensation reaction rates needed to form an ordered silicon dioxide matrix (Scheme 1). The extent and rate of alkoxysilane hydrolysis plays a major role in oligomerization of the silica (8, 9) which determines the stability and morphology of the MSN. The silica matrix is non-crystalline and contains abundant surface silanol groups, which allow further post-synthetic transformation of the silica surface. Alternatively, it is also possible to incorporate organic functionality onto the surface of MSNs by performing the initial hydrolysis/condensation reaction with a trialkoxyorganosilane added to the mixture. These techniques allow access to more diverse functionalities on a single carrier than many competing polymer drug delivery systems. The ability to control the formation of particles with low polydispersity value in different pH also permits the use of many different types of templating agents including ionic surfactants (10), pluronic surfactants (11), and neutral block copolymers (12). Using different templating molecules helps to control pore size, pore ordering and particle size and morphology.

The ability to tune surface characteristics and chemistry is an important attribute which has been utilized to load such diverse cargoes as small molecule drugs, short peptides, and large proteins (e.g., enzymes) (14) while retaining pharmacological and enzymatic activity. The diverse surface chemistry also enables functionalization of the outer surfaces of these particles. Surface functionalization strategies allow for the encapsulated drug molecules to be released in response to

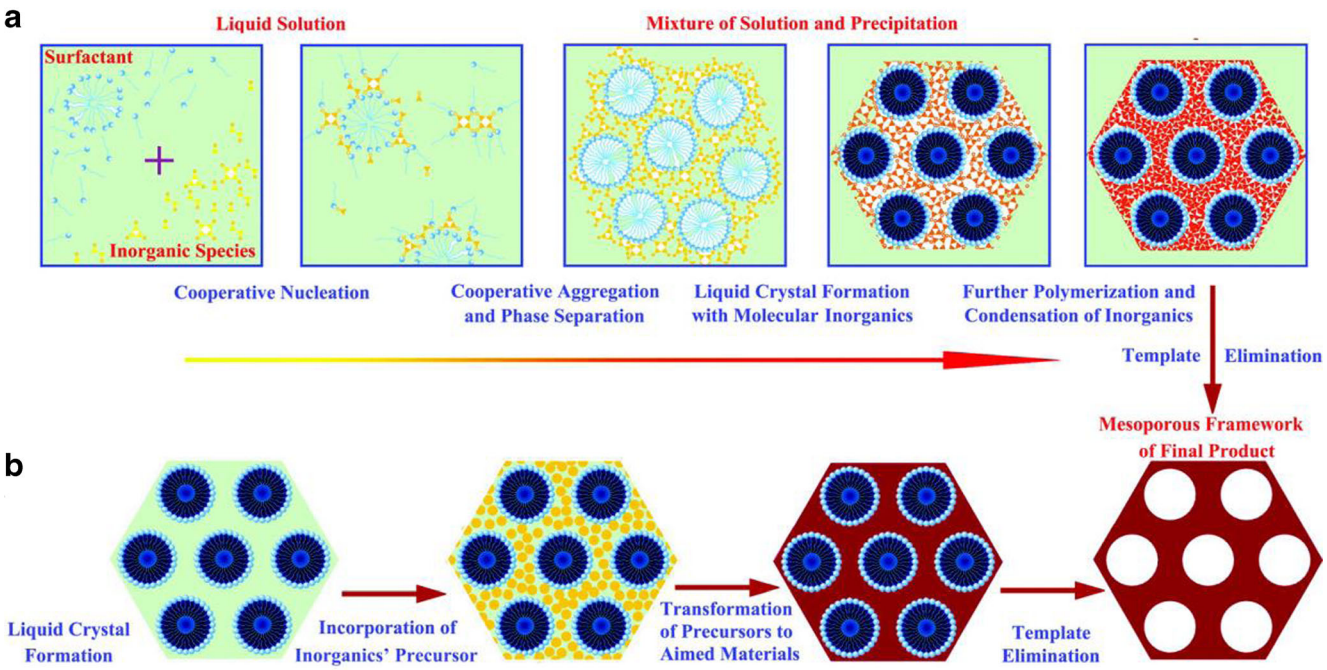
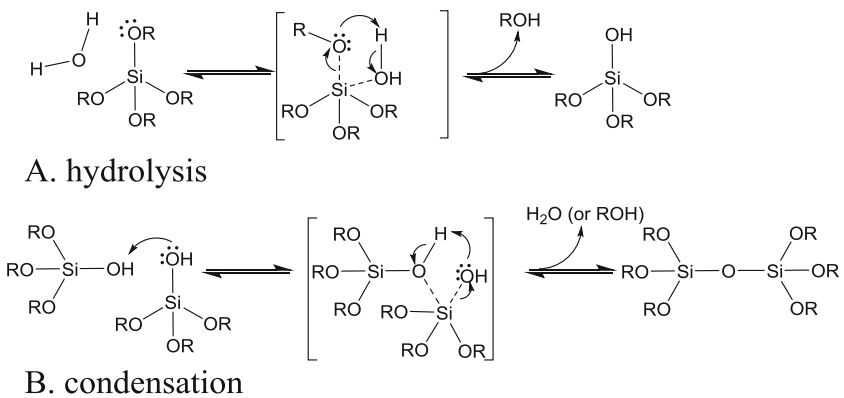


Fig. 1. The synthesis of MSNs in aqueous media is accomplished through two main strategies. In strategy **a** a solution of silica precursor and a surfactant are allowed to co-assemble, at which point the hydrolysis and condensation of precursor results in the mesoporous-ordered product. Strategy **b** involves the pre-formation of a liquid crystal template. When the silica precursor is added it orders around the liquid crystal template where hydrolysis and condensation of the silica precursor again results in the structured product. An excellent review by Wan and Zhao (13) fully explains these processes and outlines the various precursors and templating agents utilized to obtain MSNs. Reprinted with permission from Wan, Y; Zhao, D.; Chem. Rev.; 2007, 107, 2821–2860. Copyright 2013 American Chemical Society

specific stimuli and for particles to be targeted to specific cell types (15–17).

An important aspect that affects the behavior of MSNs as drug delivery devices are attributes such as large surface area (~1,000 m^2g^{-1} for MCM-41 type particles) and large pore volumes (~1 cm^3g^{-1}). These attributes allow encapsulation of large amounts of active agents in MSNs. In addition, the particles can also be viewed as having two different and chemically accessible surfaces areas, the area within the pore and the outer surface area of the particle. By carefully selecting the chemistry by which functional groups are applied and when and how templating agents are removed, it is possible to add two different functional groups to the different surfaces of the particles (18). For example, the pore surface is commonly modified with functionalities which help to control drug loading and the rate of drug release (19). The outer surface is most often used for modification with moieties that aid in increasing colloidal stability, improving biocompatibility (20–22), and achieving targeting of the particles (21, 23, 24). Importantly, particle shape (morphology) can be altered without changing the overall pore structure. Spherical and rod-shaped MSNs of different diameters and aspect ratios can be prepared by altering reaction conditions, using different surfactant or additives and by the addition of trialkoxyorganosilanes during synthesis (25–31).



Scheme 1. Proposed mechanism of an alkoxysilane hydrolysis in neutral aqueous solution. Subsequent hydrolysis reactions will also occur, resulting in a molecular formula of $Si(OR)_{4-n}(OH)_n$

Challenges for MSN Use in Drug Delivery

The ability to broadly alter properties of MSNs has led to the proliferation of reports on the use of mesoporous silicates as drug delivery devices. This is clearly borne out in literature searches using the terms "mesoporous silica" and "drug delivery". A simple SciFinder search utilizing these terms, excluding reviews and conference proceedings, results in nearly 1,200 hits (Fig. 2). If MSNs are such effective drug delivery devices, however, then why are there comparatively so few studies carried out *in vivo* and showing improvements in drug delivery? Thus, the main goal of this review article is to discuss current understanding of the *in vivo* behavior and properties of MSN. For overview of *in vitro* properties of MSN, the reader is referred to other recent articles (19, 31–36).

One issue faced with translating *in vitro* findings to *in vivo* conditions is due to the number of different synthetic routes and lack of standard assays to test MSN performance (37). For example, even within research groups where synthetic methods are conserved, conflicting results have been obtained regarding the interactions between red blood cells and MSNs (38, 39). MSNs retain an active surface chemistry, which can interfere with determining biological properties unless great care is taken in performing control experiments. For example, toxicity studies using the MTT assay in conjunction with silicon particles was reported to give falsely positive results (40, 41). Further difficulty in translating MSNs from *in vitro* to animal models may be encountered if the materials are not monodisperse in size or of similar morphologies. When MSNs with broad particle size polydispersity are compared side-by-side, inconsistencies can arise in the results at given mass-doses, which rely on particle mass, rather than the absolute particle count (42). Particles with different morphologies present another hurdle to evaluating biological interactions of MSNs. Work by Trewyn and colleagues shows that spherical and rod-shaped MSNs exhibit differences in cytotoxicity and in rates of endocytosis (43). A study by Huang and colleagues (44, 45) takes this work one step further and attempts to quantify the ways in which different morphologies of MSNs affect cellular processes and *in vivo* clearance. These studies by Huang and colleagues, which will be discussed in detail further, represent one of the few examples of direct translation by a single group attempting to correlate findings with MSN in cell culture with *in vivo* results.

IN VIVO DRUG DELIVERY USING MSNS

In Vivo Pharmacokinetics and Biodistribution of MSNs

There is a good understanding of the correlations between the physicochemical properties of MSNs and their toxicity, mechanism and rate of cell uptake, and drug delivery efficacy. However, the study of the *in vivo* pharmacokinetics (PK) of MSNs is still in its infancy, an observation shared by other authors (46). Encouragingly, an increasing number of studies published since 2010 have been adding quantitative data to our knowledge of how these nanoparticles behave in complex *in vivo* environment of animal models.

Two main sets of methods are used for tracking the biodistribution of MSNs and determining their PK: (i) labeling the particles with a fluorescent dye or a radioisotope and (ii) use of inductively coupled plasma mass spectrometry (ICP-MS) or inductively coupled plasma optical emission spectrometry (ICP-OES) to directly quantify the amount of silicon. Both sets of methods have limitations. In the former, photobleaching, difficult quantification of fluorescent signal in tissues, and separation of the label from the particles can bring about misleading results. The latter methods that directly quantify silicon are negatively

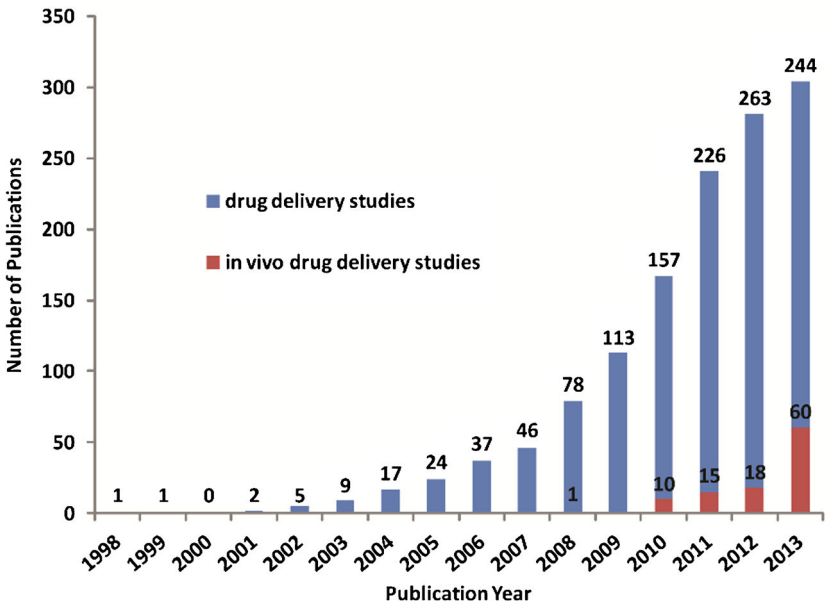


Fig. 2. Number of publications on drug delivery with MSN. Results of a SciFinder search (as of October 31, 2013) for the terms "mesoporous silica" and "drug delivery" (*blue*) and "mesoporous silica" and "*in vivo*" (*red*) (excludes conference proceedings, reviews, manuscripts not published in English, and manuscripts that included the term "*in vivo*" but had no actual data from animal studies)

affected by varying background silicon levels in different tissues. The need to digest the particles by a strong base or hydrofluoric acid further complicates the ability to distinguish intact particles from their degradation products.

Ghandehari and colleagues (47) performed a comprehensive comparative biodistribution study between I^{125}-labeled spherical and rod-shaped MSNs with different surface chemistries and porosity. As expected, following intravenous injection in mice, all the types of nanoparticles exhibited significant accumulation in the liver, spleen, and lung (~150% dose/g tissue=~15% dose/lung) (Fig. 3a). Regardless of their shape, the particles were cleared within 24 h post-injection. Interestingly, surface modification of MSNs with amine groups greatly reduced lung deposition of the spherical, but not rod-shaped particles (Fig. 3). Nonporous silica nanoparticles showed negligible accumulation in the liver as compared to porous nanoparticles.

Surface chemistry and porosity of the nanoparticles appear to be more important determinants of biodistribution than particle geometry. Similar to the Ghandehari study, Huang and colleagues (45) investigated the effect of shape and PEGylation on biodistribution of fluorescently-labeled MSN with low (NSR) and high (NLR) aspect ratios of 1.5 and 5, respectively. Confocal microscopy of tissue sections found the particles mostly in the liver, spleen, and lung as early as 2 h post-injection. Quantification with ICP-OES showed that the liver, spleen, and lung accumulation accounted for over 80% of the injected dose at 2 h (Fig. 4a).

Preferential uptake of the particles with low aspect ratio in the liver and those with high aspect ratio in the spleen was observed (Fig. 4). It is significant to note that the concentration of NSR-PEG observed in tissue samples remained constant over the 7-day experiment. NSR-PEG concentrations remained high in the blood and kidney indicating a prolonged plasma half-life and renal particle clearance (Fig. 4b). Somewhat surprisingly, however, the PEGylated particles showed higher accumulation in the lungs when compared with the control particles without PEG. This is in clear contradiction with a report by He and colleagues (48) which found that PEGylation decreases lung accumulation of MSN. Partially agreeing with the Ghandehari study, the Huang study reported that although surface properties did influence biodistribution of the particles, particle morphology also could play a role.

In conclusion, the current reports show that, just like most other types of nanoparticles, MSNs accumulate mainly in the liver and the spleen, with initial lung accumulation when particles are functionalized by PEG. Most of the available evidence implicates surface properties as the dominant factor governing the biodistribution of MSNs. PK and biodistribution behavior is the result of a complex interplay of factors like surface charge, surface functionalization, particle size and shape. Because of the limited scope of *in vivo* studies, diversity of synthetic procedures and physicochemical properties of MSNs, few generalizations can be made about MSNs behavior *in vivo* at this time. Even though PEGylation has been used to greatly extend plasma circulation half-life of many types of nanoparticles, plasma half-lives

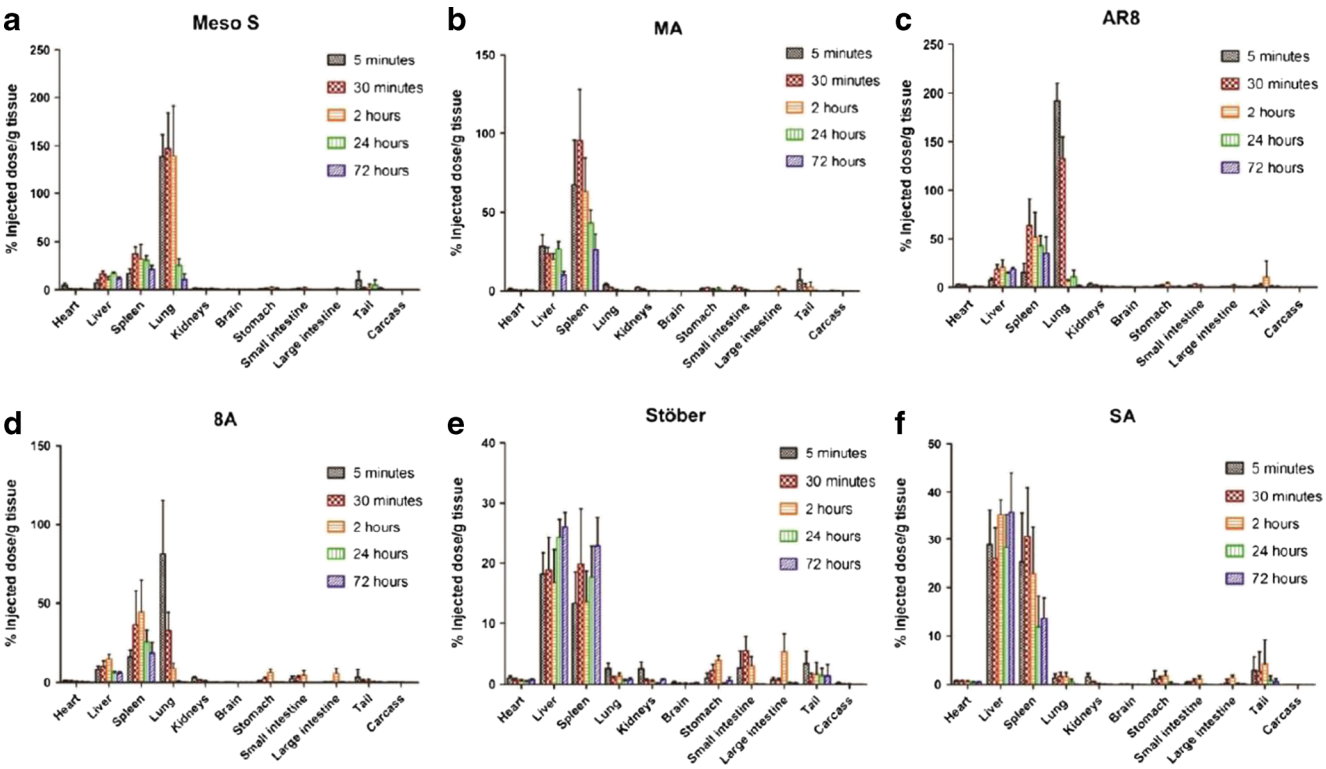


Fig. 3. Biodistribution of MSNs quantified by I^{125} radioactivity and expressed as a percentage of the injected dose/g tissue. Meso S, refers to spherical mesoporous particles **a** MA, amine functionalized mesoporous spheres **b** AR8 rod-shaped mesoporous silica particles **c** 8A, amine functionalized, rod-shaped mesoporous silica **d** Stöber, nonporous spherical nanoparticles **e** and SA, amine functionalized, nonporous spherical nanoparticles **f** in healthy mice post bolus tail vein injection at a dose of 20 mg/kg. Organ accumulation is expressed as percent of injected dose per gram of tissue post euthanasia at 5 min, 30 min, 2 h, 24 h, and 72 h. Data are presented as mean ± standard deviation (n=5) Reprinted with permission from Yu, T; *et al.*; J. Con. Rel.; 2012, 163, 46-54. Copyright 2013 Elsevier

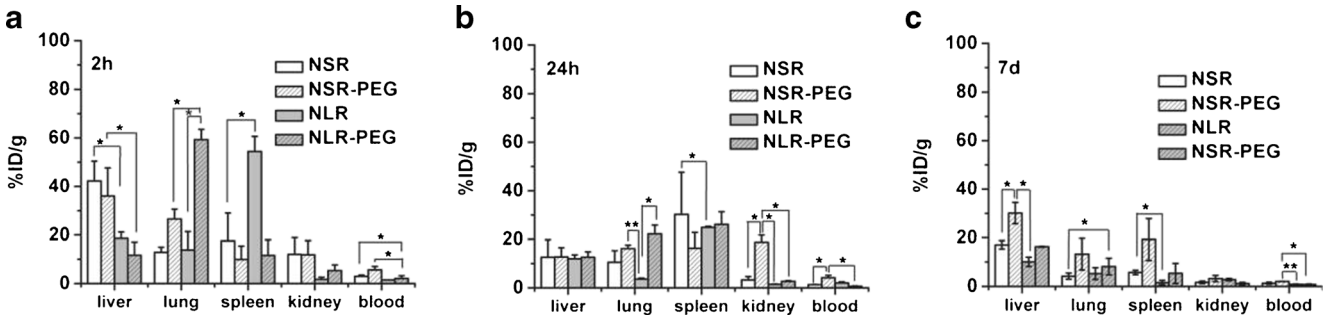


Fig. 4. Biodistibution of spherical (NSR), PEGylated spherical (NSR-PEG), rod (NLR) and PEGylated rod (NSR-PEG) MSNs at 2 h **a**, 24 h **b**, and 7 days **c**. Silicon content was quantified by digestion of the particles followed ICP-OES measurements. Reprinted (adapted) with permission from Huang *et al.*; ACS Nano; 2011, 5, 5390–5399. Copyright 2013 American Chemical Society

for all MSNs including PEG functionalized materials are low. Significantly improved plasma circulation of MSNs will be required for many drug delivery applications (i.e., delivery to solid tumors).

Elimination of MSNs *In Vivo*

Excretion of MSNs is strongly dependent on degradation of silica. The body can absorb dissolved silica or excrete it through the urine in the form of silicic acid or oligomeric silica species (49). MSNs hydrolyze under physiological conditions when concentrations are below the saturation level of silica (50–52). For MSNs injected into the body, the rapid dilution and distribution means that these particles can be expected to dissolve under *in vivo* conditions (49). For example, somewhat counter-intuitively, studies suggest that larger MSN dissolve faster than smaller MSN as indicated by faster excretion of silica in the urine, following intravenous injection in mice (48). PEGylation reduces that rate of excretion of the MSNs. Urinary excretion could reach up to 45% of the injected dose but the initial 30 min after injection accounted for major excretion through urine. After 1 month of monitoring, it was found that only 54% of the initial dose of MSN (360 nm diameter) was excreted through the urine–only a 9% increase over the initial 30 min. However, the study could not distinguish between renal and hepatobiliary clearance.

Souris and colleagues (53, 54) investigated the effect of MSN surface charge on hepatobiliary excretion following intravenous injection. The results showed accumulation of MSNs in the liver and rapid transport into gastrointestinal tract and subsequent fecal elimination. Negatively charged particles also showed high uptake and retention in the liver. Differences in the hepatic behavior of particles with different charge were reported also by Cheng *et al.* who showed that positively charged nanoparticles accumulate in hepatocytes in parenchyma due to binding by apolipoprotein E and IgA (55). In contrast, the negatively charged nanoparticles were taken up by Kupffer cells. The authors suggested that because of the MSN uptake by hepatocytes, the positively charged particles may be eliminated via the hepatobiliary excretion while the negatively charged particles would accumulate in the Kupffer cells, portending hepatotoxicity due to no apparent elimination pathway. Fluorescence imaging and ICP-MS indicated that most positively charged particles indeed pass through the hepatobiliary transport and are excreted into feces with no detectable signal in urine (56). It is worth noting that in this study, the background Si levels in tissues were determined, a control often missing in ICP analyses of MSN.

Huang and colleagues (45) studied the excretion of long and short rod-shaped nanoparticles by collecting the urine and feces samples at different time points after injection and determining silicon content by ICP-OES. At 2 h post-injection, Si was detected in urine for all nanoparticles. However excreted Si content was significantly lower for long rods than short rods. This result corresponds to the observed early biodistribution to the kidney. However, at 7 days, all the particles exhibited excretion through feces, indicating hepatic processing and biliary excretion. The

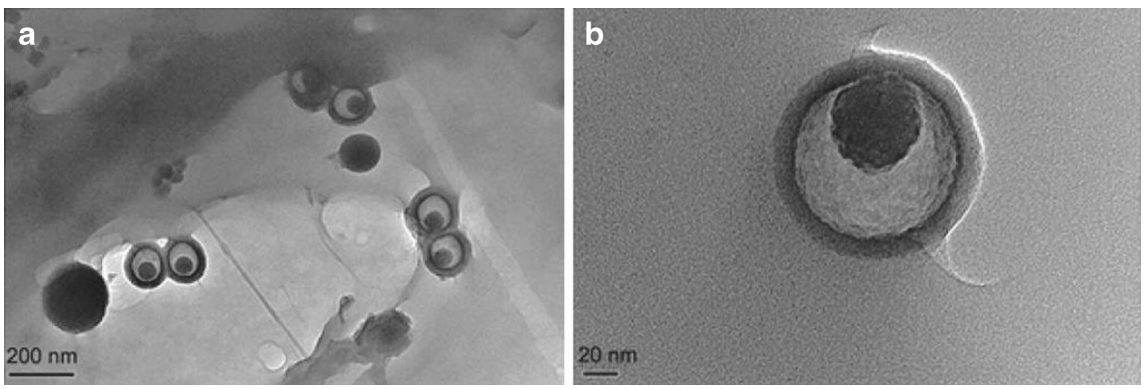


Fig. 5. TEM micrographs of intact 150 nm diameter core/shell MSNs found in the feces **a** and urine **b** of mice, 24 h post-injection. Reprinted with permission from Fu, C; *et al.*; Biomaterials; 2013, 34, 2565–2575. Copyright 2013 Elsevier

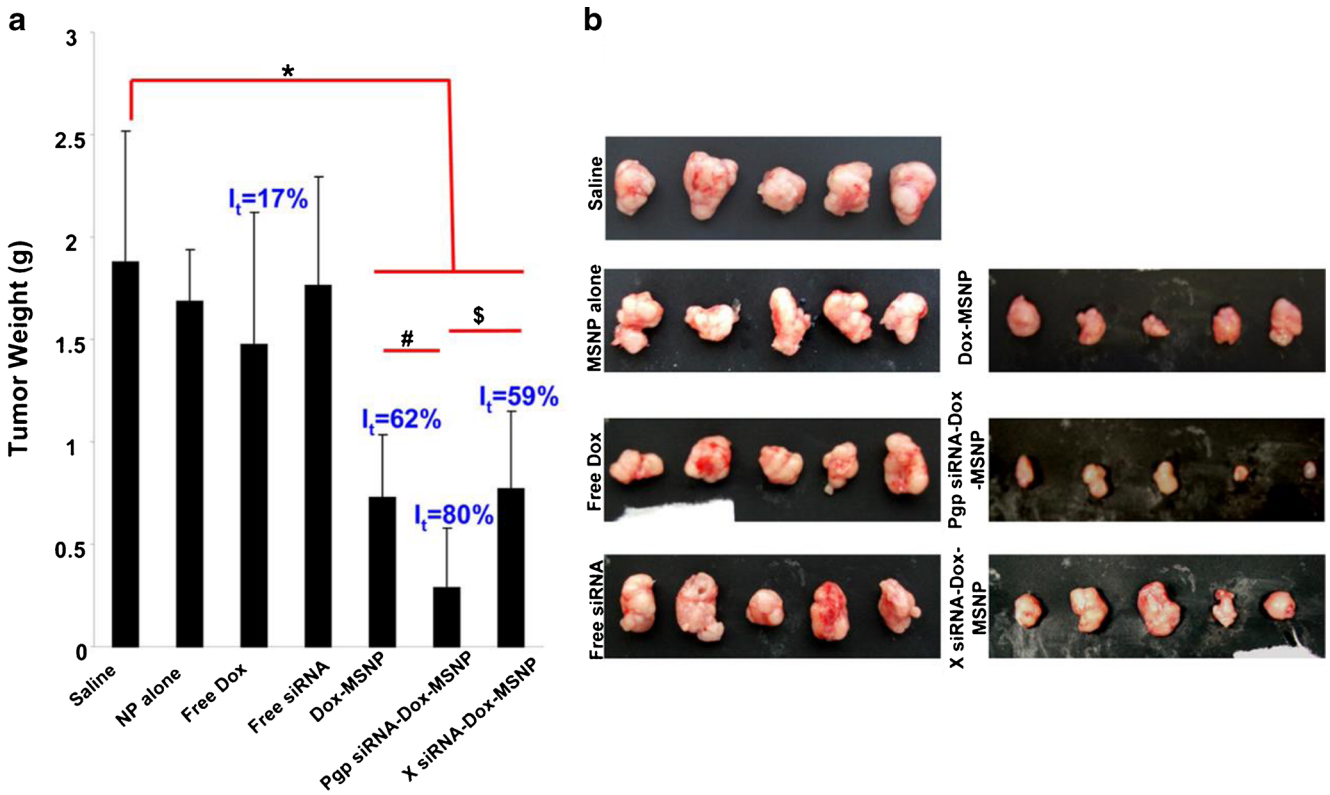


Fig. 6. **a** Comparison of the tumor growth inhibition effect of DOX-loaded MSNs containing Pgp siRNA *versus* other treatment groups: saline, MSN, free DOX, free siRNA, DOX-loaded MSN, and DOX-loaded MSN with scrambled siRNA. Following sacrifice of the animals, tumor tissues were collected and weighed to determine the tumor inhibition rate (It). (/) $p<0.05$, compared to saline; (#) $p<0.05$, compared to Dox-loaded MSNP without siRNA; ($) $p<0.05$, compared to Dox-loaded MSNP with scramble (X) siRNA. **b** Photographs of excised tumors from each of the treatment groups. Reprinted (adapted) with permission from Meng *et al.*; ACS Nano; 2013, 7, 994–1005. Copyright 2013 American Chemical Society

presence of intact particles in urine and feces was also confirmed by TEM. This observation was agreed upon by Fu and colleagues (57) who performed TEM of urine and feces collected after injection and found intact particles (Fig. 5). The reported renal clearance of MSNs represents an interesting finding since it is widely accepted that the maximum particle size that can be eliminated through glomerular filtration is ~5 nm (58). Further studies are needed to confirm that this phenomenon is due

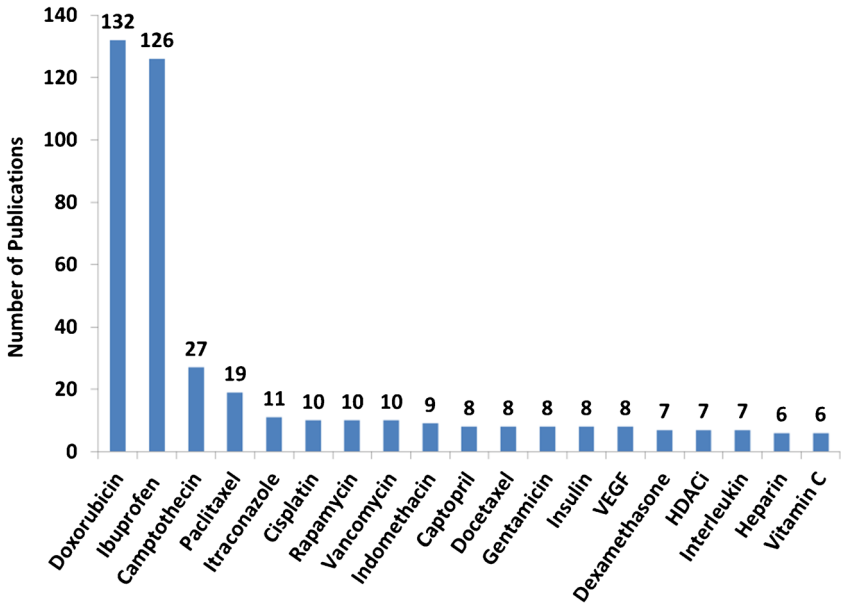


Fig. 7. Top drugs used in studies on MSN drug delivery. Results of a SciFinder search as of Oct-31, 2013–only drugs with >5 publications shown

to particle elimination, rather than elimination of low-molecular-weight silica degradation species (45).

Systemic Drug Delivery by MSNs

A common hypothesis in using MSN for drug delivery is that drugs loaded into MSNs would show increased oral bioavailability, prolonged plasma circulation times, limited biodistribution, and improved targeting to minimize side effects. The reports of drug delivery using MSNs *in vivo* run the gamut from proof-of-concept experiments which demonstrate MSN potential to highly detailed studies that may form early basis for clinical translation of MSN. In addition to drug delivery, several studies demonstrate the ability of MSNs to act as a theranostic platform. In this review, we focused mainly on the use of MSN for parenteral administration of drugs. Readers interested in MSN application in oral drug delivery are referred to a recent review by Qian and Bogner (59).

Stimulus-controlled release of drugs from MSN has often been demonstrated *in vitro*. Growing number of studies confirm translatability of such methods to *in vivo* conditions (16, 60–63). MSNs with drug release triggered by the action of matrix metalloproteinases showed the ability to release doxorubicin in fibrosarcoma mouse model (64). Alternative approach in which doxorubicin is released in response to acidification during endo-lysosomal trafficking of the particles was used by He and colleagues. In both of these studies, fluorescence microscopy of tumor sections excised from mice treated with these particles showed successful delivery of doxorubicin to cell nuclei (65).

The abundant surface functional groups on MSNs allows for the inclusion of different moieties to enhance the utility of the particles. A study that demonstrates the ability of MSN to deliver multiple types of therapeutics was carried out by Meng and colleagues (66). Using a combination of doxorubicin and siRNA against the P-glycoprotein drug transporter in a single MSN formulation, the combined treatment showed over 60% higher efficiency in treating drug resistant breast cancer xenograft than free DOX alone (Fig. 6). Furthermore, the combination MSN treatment showed decreased toxicity as indicated by unchanged liver enzyme levels in the plasma.

Modularity of the MSN design has been demonstrated by results of successful tumor targeting *in vivo* (46). Folate-targeted MSN were used to deliver camptothecin in mice xenograft models of pancreatic cancer (PANC-1 and MiaPaca-2). The targeted MSNs performed exceedingly well in this study as tumor volumes were 10 times smaller in animals treated with the targeted particles as compared to the control groups. Experiments involving the MiaPaca-2 xenografts showed that folate-targeted MSNs were able to shrink tumor size approximately sixfold, from ≈140 to ≈25 mm^3. Mice that received saline injection or MSN was seen an increase in tumor size during the 25-day experiment. All subjects maintained body mass during this experiment except those receiving only MSN.

CONCLUSION

Over the course of the last four years, the number of *in vivo* studies involving MSNs has steadily increased. Many properties, such as stimulus-responsive controlled release, cellular targeting, and multi-molecule cargoes, which were speculated upon from *in vitro* MSN studies have been demonstrated *in vivo*, albeit in limited capacity. Despite the promising developments, however, there are still serious concerns regarding the future of MSNs in systemic therapeutic or diagnostic applications. Not the least of these concerns is the pharmacokinetic profiles of different MSNs. While several authors have tackled the subjects of pharmacokinetics and biodistribution, the body of literature is too limited to fully understand the mechanism by which these nanoparticles arrive at their destinations. Excretion of MSNs poses its own set of unanswered questions related to the safety of these particles, as the methodologies to quantify excreted silica have not yet convincingly showed whether hydrolysis of particles to silicic acids or excretion of the whole particle are the main elimination mechanisms. The reports of large, seemingly intact particles in urine and the overall lack of toxicological data are of particular concern. With regards to drug delivery, a main problem remains a narrow focus on very small number of drugs. In fact, the vast majority of existing studies with MSN involves either doxorubicin or ibuprofen (Fig. 7). While sometimes justified by "proof-of-principle" nature of the studies, the focus on well-established drugs that have already been used with many competing drug delivery technologies decreases the likelihood that MSNs will have a significant clinical impact on the treatment of human diseases. The strong dependence of drug delivery behavior (i.e., loading, release) by MSNs on the physicochemical properties of the encapsulated drug further undermines the "proof-of-principle" argument. The outlook for MSNs is not necessarily dim. However, methodological consensus and increased focus on systematic *in vivo* studies will be needed to fully understand biodistribution, excretion, and the toxicology of the particles. Direct head-to-head comparisons will have to be conducted *in vivo* not only with the free parent drugs but also with competing (clinical or experimental) delivery technologies to prove the merits of MSNs.

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