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Stimuli-responsive Mesoporous silica nanoparticles for on-demand drug release

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Abstract

Mesoporous silica nanoparticles (MSN) are receiving considerably regard by the scientific society for their innovative potential in nanomedicine. The development and design of tumor-targeted MSN with stimuli-sensitive drug release ability aiming to enhance the efficacy and reduce the side effects of anti-tumor drugs for cancer therapy. MSN can be designed for responding to a diversity of internal cues afforded by tumor microenvironment like overexpressed enzymes, low pH, redox potential as well as to the application of external stimuli as magnetic field light or ultrasound (US) have been developed and expanded to trigger the drugs release at a specific site. This review will summarize and illustrate the designs strategies of the main accomplishments in the area of stimuli-sensitive mesoporous silica nanoparticles for sustained drug release.

Keywords: mesoporous silica, inclusion complex, drug release, exogenous stimulus, endogenous stimulus, active targeting.

1. Introduction

Cancer is amongst the dreadful causes of death and morbidity worldwide in recent years (Murugan et al. 2016; Silva 2017; Mollazadeh, Afshari, and Hosseinzadeh 2017). The latest statistics point to an approximately 14.1 million new cases and 8.2 million cancer-related deaths every year (Silva 2017; Peer et al. 2007).Chemotherapy remains one of the widely used for cancer treatment. However, the chemotherapeutic drugs are cytotoxic and they can cause damage to both tumor and normal cells, resulting in several side effects in the organism. Furthermore, chemotherapy drugs may not kill all cancer cells and the surviving cancer cells may become multidrug resistance (de Oliveira et al. 2016).

The modern advances in nanotechnology have revolutionized the targeting process for drug delivery and offered many solutions to problems in the area of cancer therapy. Thenanomedicines have greatly improved targeting and bioavailability compared with traditional chemotherapy drugs(Bharti et al. 2015; Zhao et al. 2017).Though surface functionalization methodologies, nanomedicines can possess the ability to control their pharmacokinetics and biodistribution as well as improve the therapeutic effect. For example, the PEGylation induces steric repulsion of between nanomedicines and blood opsonins-molecules and endows the nanomedicines with long-circulation and enhanced permeability and retention (EPR) effect for

passive target to tumor tissue in vivo. Furthermore, after modified with biologically-active ligands or antibody, nanomedicines can facilitate the target to specific cells and enhance phagocytosis via interaction between ligands and receptors or antibody and antigen (Suk et al. 2016; Zhu et al. 2011).

For preventing drug release before reaching the target as well as reducing side effect, on-demand drug release is becoming practical via the design of stimuli-sensitive systems that can recognize their microenvironment in the lesion, respond and react dynamically, and mimic the responsiveness of living organisms. Nanoscale stimuli-sensitive systems may respond to specific internal stimuli such as ATP, pH, glutathione (GSH), reactive oxygen species (ROS) and specific enzymes such as matrix metalloproteinases, HArase (Mura, Nicolas, and Couvreur 2013). Meanwhile, many external stimuli, including light, ultrasound, heat, magnetic field, radio waves and electric current et al, can also be applied to trigger the drug release in the lesion. The advantage of stimuli-sensitive nanocarriers is significant especially when the stimuli are individual to disease pathology, which allows the nanomedicines to respond accurately to the pathological “triggers”. Such environmental stimuli can be utilized for delivery both of chemotherapeutics and biological medicine for oncotherapy (Mo, Jiang, and Gu 2014).

Among the nanomedicines, mesoporous silica nanoparticles (MSN) have become one of the most promising drug delivery systems due to their noticeable properties such as surface areas, highly ordered channels and pore volumes, tunable size and morphology, facile functionalization, high physicochemical biochemical stability and excellent biocompatibility, etc.(He, Ma, et al. 2012; Kwon et al. 2017).(Chai et al. 2017; Fu et al. 2015; He, Ma, et al. 2012).

The capability to control the drug release profile and deliver to a specific location of cell or tissue still one of the essential gauntlets for developing nano-sized carriers for cancer treatment. To accomplish such objectives, stimuli-sensitive nanocarriers are presently being developed. These systems allow cargo to be released in response to an interior or exterior stimulus, such as heat, enzymatic, pH, near-infrared (NIR) radiation, ATP, redox potential, ultrasound and electromagnetic field. This approach reduces drug interactions with healthy tissues during its circulation in the human body, thus contributing to the reduction of chemotherapy side effects. Therefore, great attempts have been done for developing MSN based systems capable of attaining a controlled and sustained delivery of bioactive molecules. The drug encapsulated MSN are comprised of their pores and the blocking of this structures with stimuli-sensitive nanosystems will prevent the premature drug release and subsequently undesired drug interactions. The breaking or conformational modification of the pore blocking agent or the use of labile/cleavable bonds that are cleaved upon stimulus exposition (Moreira, Dias, and Correia 2016). In this review, we will summarize and illustrate the designs strategies of the main accomplishments in the field of stimuli-responsive mesoporous silica nanoparticles for on-demand releasing drug and treatment of cancer.

1. Internal stimuli-responsive MSN

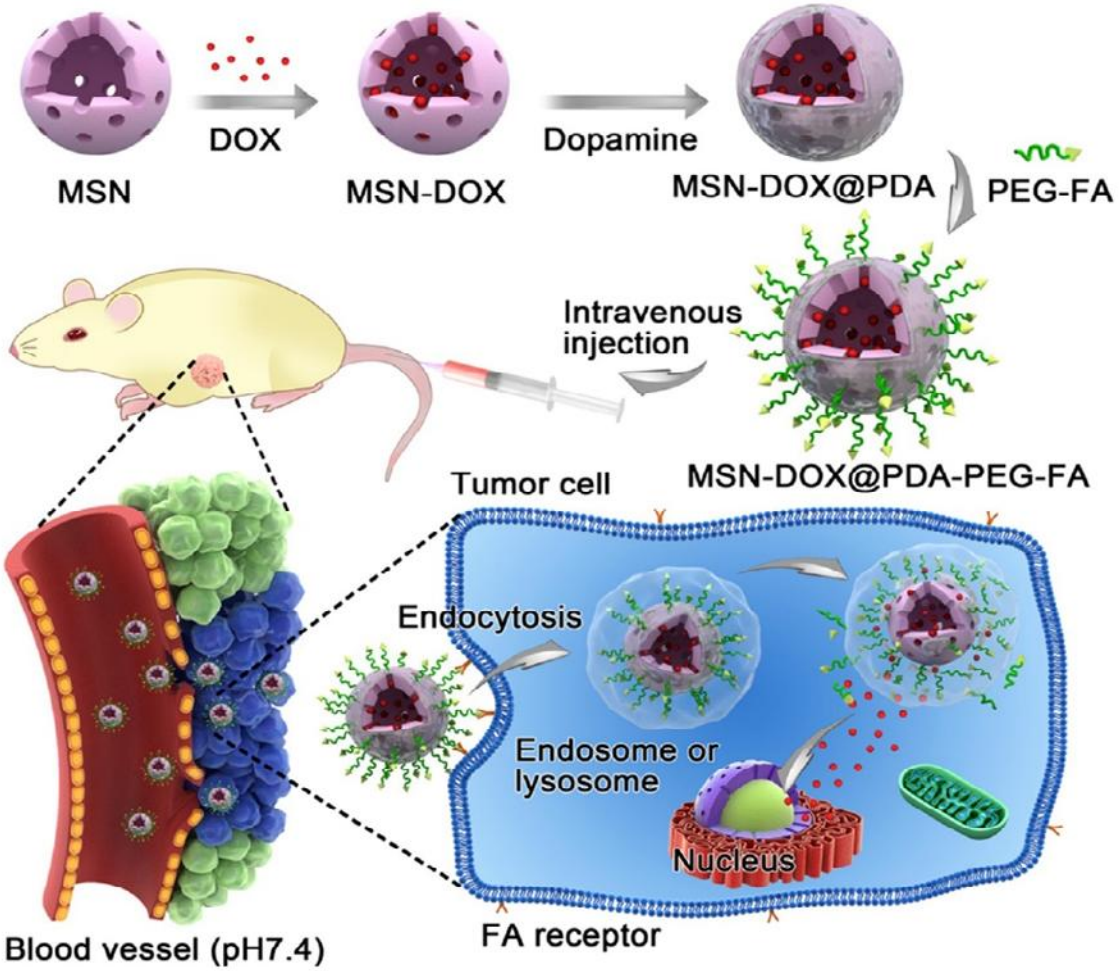
Internal stimuli-responsive preparation of MSNs take advantage of variations sensitive to specific conditions, such as a higher glutathione concentration, lowered interstitial pH or an elevated level of particular enzymes such as matrix metalloproteinases (Blum et al. 2015) (Mura, Nicolas, and Couvreur 2013)

1.1 pH-responsive MSN

When the levels of oxygen are normal or abnormal, cancer cells could take up to 12-fold glucose and have elevated aerobic glycolysis but utilize a lesser fraction of glucose for mitochondria oxidative phosphorylation, therefore producing less ATP and more lactate. This phenomenon is known as the Warburg effect. In addition to the glycolysis, lactic acid is released from cells by the H^+-monocarboxylate co-transporter, leading to an elevated amount of protons in the cancer microenvironment. Following lactic acid, considerable amounts of CO_2 which is generated by cancer cells by oxidative metabolism is another main source of the acidity of cancer extracellular. However, referred to poor lymphaticdrainage and elevated interstitial pressure of cancers, lactate and CO_2 (metabolic acids) exported from the tumor cells within the interstitial fluid unable to be exported to the blood rapidly. Resulting from the elevated proton production and poor proton clearance, extracellular pH (pH_e) demonstrated a low range of about 6–7 (He et al. 2013; Webb et al. 2011).Upon entrance into the cell through endocytosis delivery systems system face a challenge of pH variation first in the early endosome with a pH of about 5-6 then in late lysosomes with a lesser pH value of about 4-5 this change in the pH of

endosome and its posterior fusion with lysosomes can also be utilized For effective intracellular delivery (Fleige, Quadir, and Haag 2012) (Kyriakides et al. 2002). pH variations utilized to deliver pH-responsive drug delivery systems, orally-active prodrugs and for on-demand drug delivery in the gastrointestinal (G.I.) system where the pH fluctuates from highly acidic (pH 2) to basic (pH 8), along with the G.I. tract. This feature exploited to achieve the active targeting of many therapeutic agents and pharmaceuticals due to the difference in pH of the healthy tissue from diseased tissue in the body. The pH at pathological of tumors tissues, inflammation or infection is lower than that of the healthy tissues. The physiological pH in healthy tissues is around 7.4 while in the tumor tissues ranges from 6 to 7. The majority of the work reported on pH-sensitive systems was focused on designing nanocarriers with pH-responsive components which destabilize the surface-functionalized stimuli-responsive of MSN at low pH and release the drug loaded after destabilizing the nanocarrier capping. (Jhaveri, Deshpande, and Torchilin 2014).

Cheng et al functionalized poly (ethylene glycol)-folic acid (PEG-FA) onto the surface of polydopamine (PDA)-modified MSN (PDA@MSN) for drug delivery to fabricate an active targeting system, MSN@PDA-PEG-FA(scheme1). Furthermore, PEG-based polymers could facilitate the nanoparticles to escape from phagocytosis and improve their long-term blood circulation. (Scheme1) (Cheng et al. 2017).After entering into the acidic endosome/lysosome, the cap of PDA-PEG-FA would be detachable from the surface of MSN@PDA-PEG-FA, leading to accelerate DOX release. Sustained drug release achieved by this system and showed pH-dependent that could enhance the therapeutic anticancer effect and minimize potential damage to healthy cells due to the acidic microenvironment of the tumor.



Scheme1. Illustration of MSN-DOX@PDA−PEG−FA formation, endocytosis and bio-distribution (Cheng et al. 2017), © 2017 American Chemical Society

The capability of controllable drug release of the nanoparticles and their pH dependency were investigated at 37 °C in pH 7.4, 5.6, and 2.0 PBS. This system showed biphasic release pattern, a burst release of DOX in the first day then a sustained drug release up to 190 h. Under all pH values, the uncapped MSN (MSN-DOX) exhibited a higher DOX release rate than that of MSN-DOX@PDA and MSN-DOX@PDA-PEG-FA (Figure1a).The significance values of the release profile suggested that the PDA coating successfully blocked the pores of the MSN and efficiently suppressed drug release.

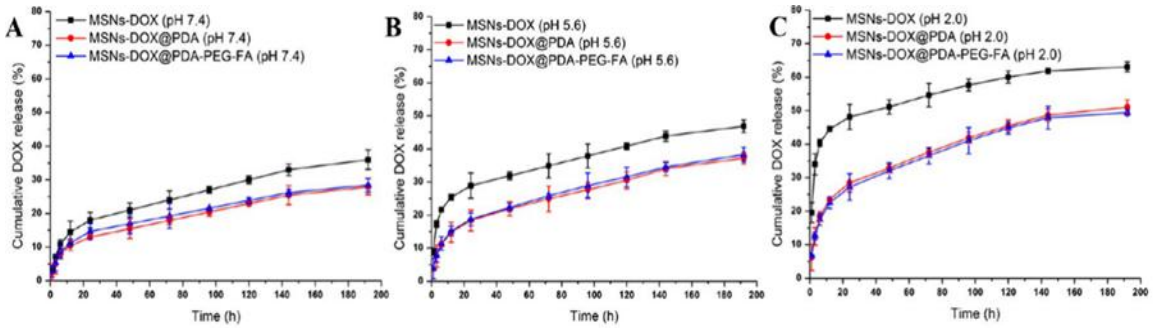
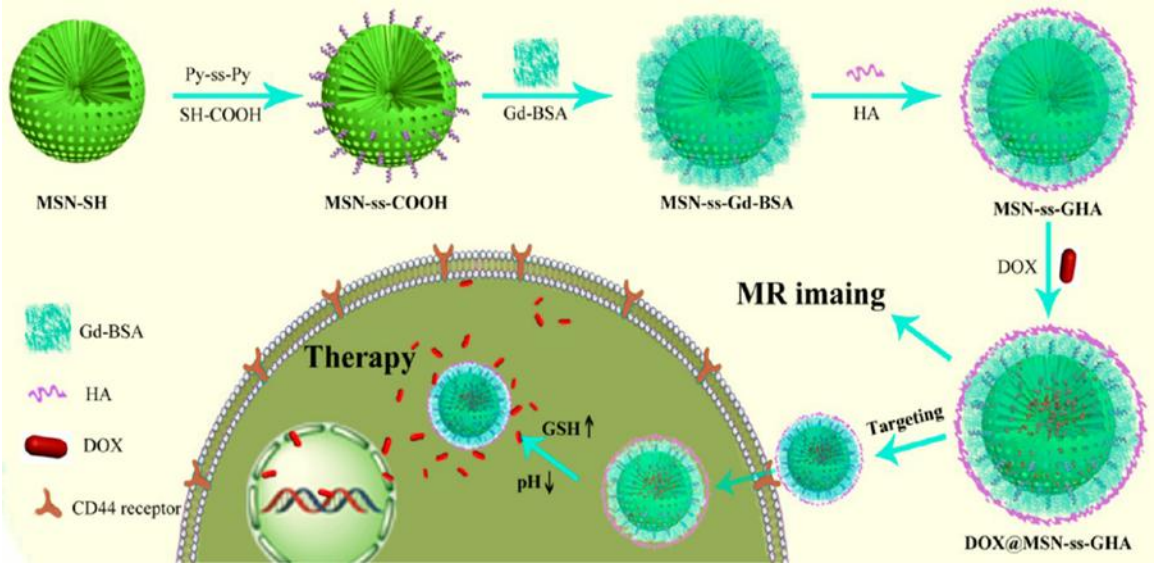


Figure 1. In vitro drug release profile of MSNs-DOX, MSNs-DOX@PDA, and MSNs-DOX@PDA−PEG−FA in media with different pH values: (A) pH 7.4, (B) pH 5.6, and (C) pH 2.0. (Cheng et al. 2017)

While the drug release rate increases as the acidity of the solution increase for both MSN-DOX@PDA and MSN-DOX@PDA-PEG-FA. At pH 7.4, the cumulative release of DOX from MSN-DOX@PDA and MSN-DOX@PDA-PEG-FA was 27.9% and 28.5%, respectively, within the 190 h. Meanwhile, the DOX-MSN@PDA exhibited a higher release of 37.2% at pH 5.6 and up to 51.1% at pH 2.0. While 38.3% and 49.5% at pHs 5.6 and 2.0 for MSN-DOX@PDA-PEG-FA, respectively (Figure 1). These results revealed that at physiological pH, the blocking agent could preserve the encapsulated drug and provided slow drug diffusion over a long period compared with PDA-modified MSN were dispersed in acidic conditions, the loaded-DOX was rapidly released due to breakage of the PDA coating, which unlocked the channels of the MSN. For the non-PDA-coated MSN (MSN-DOX), however, it found that DOX release rate increased proportionally with the acidity increasing. Due to the acidic microenvironments of tumors, this pH-dependent release behavior can enhance the therapeutic anticancer effect as well as minimize potential damage to healthy cells. This could be demonstrated by the acidity induced dissolution of DOX in aqueous environments. Acidic conditions could promote the solubility of DOX, resulting in a faster drug release.

1.2. Redox-responsive MSN

Another internal stimulus can be exploited as a trigger event is the concentration imbalance between the reductive species such as glutathione (GSH) outside and inside the cells, and between cancer and normal tissues. Sustained survival and growth of most tumor cells depend on a metabolic rewiring, distinguished by a stimulated using of glutamine through reductive carboxylation and an enhanced glycolytic flux. Mitochondrial dysfunction (for example Complex I reduced activity) ease to the insurgence of tumor metabolic rewiring. $NADP^+$/NADPH and NAD^+/NADH are involved in various reactions of the tumor metabolic rewiring pathway. The amount of reduced GSH inside the cell is higher 1000 times than in the extracellular media. When disulfide (S-S) bond breaks, a pore-blocking agent which attached to the MSN surface will be cleaved in higher level after the nanocarrier reaches the stimulus location (Baeza, Colilla, and Vallet-Regí 2015; Zhao et al. 2014)(Alberghina and Gaglio 2014).



Scheme 2: illustration of the Synthetic Process of MSN for Redox-Responsive Targeting Drug Delivery and MRI(Chen et al. 2016), © 2017 American Chemical Society

Chen et al utilized the reductive-cleavable disulfide bond for capping the DOX-loaded MSN by gadolinium-based bovine serum albumin complex (BSA-Gd) and hyaluronic acid (HA) which used as the targeted molecule and denoted as MSN-ss-GHA which improved the specificity of this system toward cancer cells (scheme 2). Meanwhile, the BSA-Gd component acted a contrast agent for magnetic resonance imaging (MRI) as well as to the act as a gatekeeper.

The release manner of DOX from MSN-ss-GHA was monitored at different conditions. Only 11.77% of DOX was released during the first 4 h, and only 5% leaked out during 60h, -suggesting the good capping ability of the gate (figure 2). By contrast, adding 10 mM of reducing agent, GSH, induced the released amount of DOX up to 51.11% at the first 12 h, demonstrating that the disulfide bond in MSN-ss-GHA could be cleaved when exposed to a high concentration of GSH within the cancer cellular environment, causing the fast releasing of DOX. Grafting of BSA-Gd complex onto the MSN surface via a disulfide linkage could render the carrier with dual-responsive drug delivery capability, which is evidenced by the elevated amount of releasing DOX at pH 5.0, which increased from 53.02 in the absence of GSH to 67.12% under 10 mM GSH, More than redox-responsiveness. The pH-dependent release profile was observed because the DOX was diffused much quicker at pH 5.0 than pH 7.4 under the same conditions. The faster release rate under the acidic condition was attributed to the improved solubility of DOX and electrostatic interaction which enhanced the therapeutic efficacy of nanocarriers.

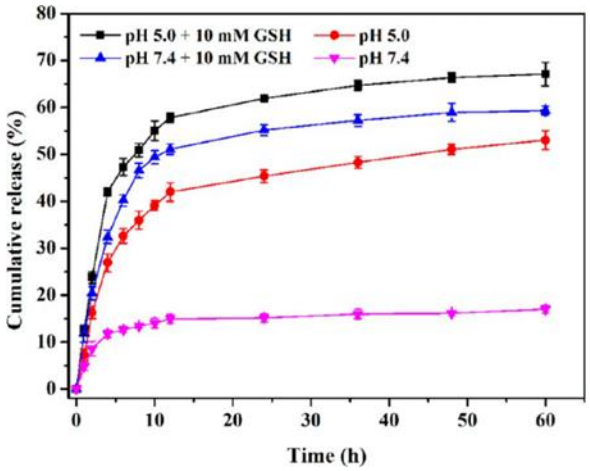
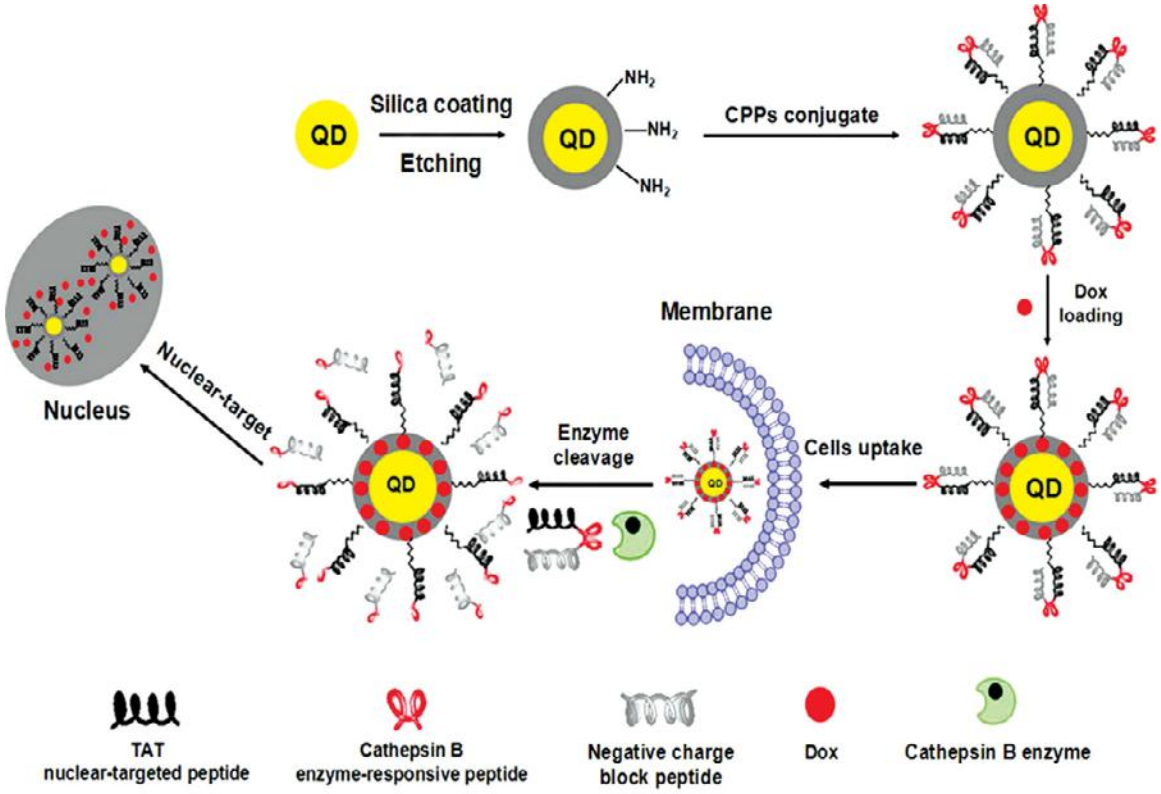


Figure 2. *In vitro* cumulative release of DOX at different conditions.(Chen et al. 2016)

1.3. Enzyme-responsive MSN

Epigenetic and genetic changes in tumor cells are inadequate to induce primary tumor progression. Either through the structure and function-based mechanisms, including ECM remodeling, release of cytokines, metabolic alterations and growth factors, or activation of stromal components and microenvironment allow tumor cells to attain an aggressive phenotype. The development of a more offensive phenotype is also promoted by MMPs secretion. MMPs can be utilized as biomarkers for disease diagnosis and prognosis, in addition, can be exploited for delivery of pharmaceuticals via an enzyme-triggered mechanism. Several components that are responsive to MMPs have been tailored for the delivery of drugs and imaging agents. Upregulation of proteases in tumors are another set of enzymes that can also be exploited to develop the enzyme-responsiveness. For example, conjugates comprised of cholesterol, polyacrylic acid, and peptide were cleaved by a tumor-associated protease (urokinase) and increased rapid drug release in an *in vitro* model(Torchilin 2014).These molecules are recognized to be metastatic and pro-angiogenic due to the digestion of the ECM by proteases as MMPs allow the entry of cancerous cells into the host tissue and passing of cancer cells via the host tissue's barrier and migrating of endothelial cells to the matrix that leads in neovascularization. In the process of decomposition, the MMPs also cause growth factors releasing that elevate the processing of tumor growth and invasion (Weber and Kuo 2012).



Scheme 3. Illustration of the enzyme-sensitive CPP-QDs@MSN nanoparticles for nucleus-targeted controlled release of drug and intracellular distribution. (Li et al. 2014), © 2014 WILEY-VCH Verlag GmbH & Co. KGaA, Weinheim.

Cathepsin B (EC 3.4.22.1), a lysosomal cysteine protease, is one of 11 human cysteine cathepsins (B, C, F, H, L, K, O, S, V, W, X/Z) (Ruan et al. 2015). Overexpression of cathepsin B has been noticed in various malignancies breast, including lung, prostate, brain, and colorectal cancer (Gondi and Rao 2013).
(de la Torre et al. 2014) designed new capped MSN for intracellular controlled drug release within cathepsin B expressing cells.

Li et al presented a rational system of antitumor drug nanocarrier by the functionalizing of an enzyme-activatable cell penetrating peptide (CPP) sequence containing a nuclear-targeted oligocationic TAT peptide onto $mSiO_2$-coated quantum dots (QDs) surface, which led to the controlled release of the encapsulated DOX into the nucleoplasm of tumor cells and allowed the nuclear-targeted delivery (scheme 3). This enzyme-cleavable sequence and an anionic-inhibitory domain sequence could neutralize the positive charges of the whole peptide structure. This system (CPP-QDs@$mSiO_2$) could respond to specific tumor protease cathepsin B. Generally; the CPP-QDs@$mSiO_2$was inactive and stable in the cells not expressing cathepsin B.

Upon internalization into the tumor cells expressing cathepsin B, the enzyme responsive linker would specifically cleave the peptide in the whole sequence and remove the anionic sequence from CPP-QDs@$mSiO_2$ surface. The improved nucleus-targeted DOX in tumor cells via utilization of the CPPs would selectively deliver DOX into the cell nucleus. The enzyme-sensitive controlled release of drug from DOX-loaded CPP-QDs@$mSiO_2$ was investigated via analysis the fluorescence of DOX with and without a stimulus (cathepsin B enzyme) under different pH conditions (7.4 and 5.5). There was minor drug release from DOX-loaded CPP-QDs@$mSiO_2$ in the absence of cathepsin B enzyme at pH of 5.5 and 7.4 (figure 3). While, in the presence of cathepsin B enzyme, apparent DOX released from the surface of the nanoparticles could be observed under prolonged enzyme treatment. There was more significant DOX release detected under pH of 5.5 than that of neutral pH conditions, which was mostly attributed to the higher activity of cathepsin B enzyme under acidic environment. As a control, in the presence of enzyme pretreated with antipain hydrochloride (protease inhibitor), there was less DOX release under both acidic and neutral pH conditions, indicating that the DOX-loaded CPP-QDs@$mSiO_2$ could respond to specific enzyme under acidic conditions and thus lead to the active drug release from the surface of nanoparticles.

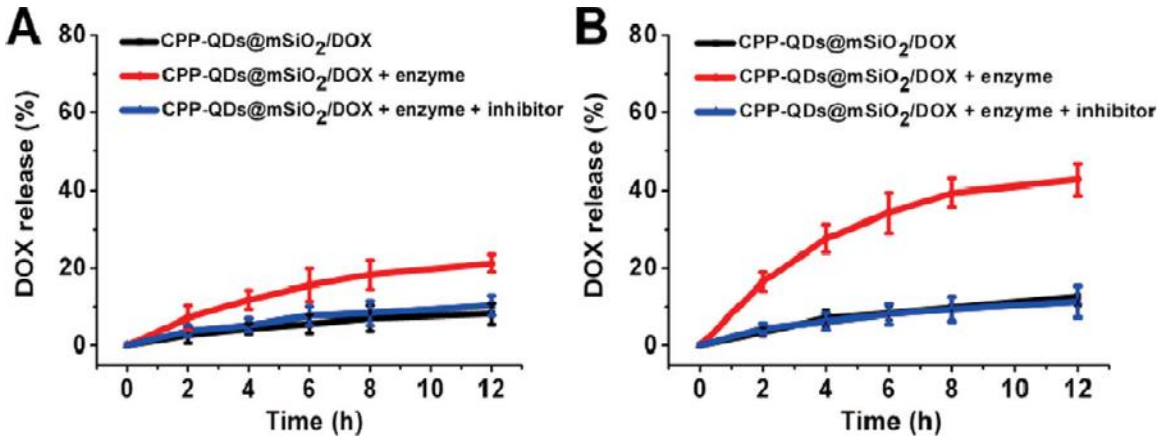


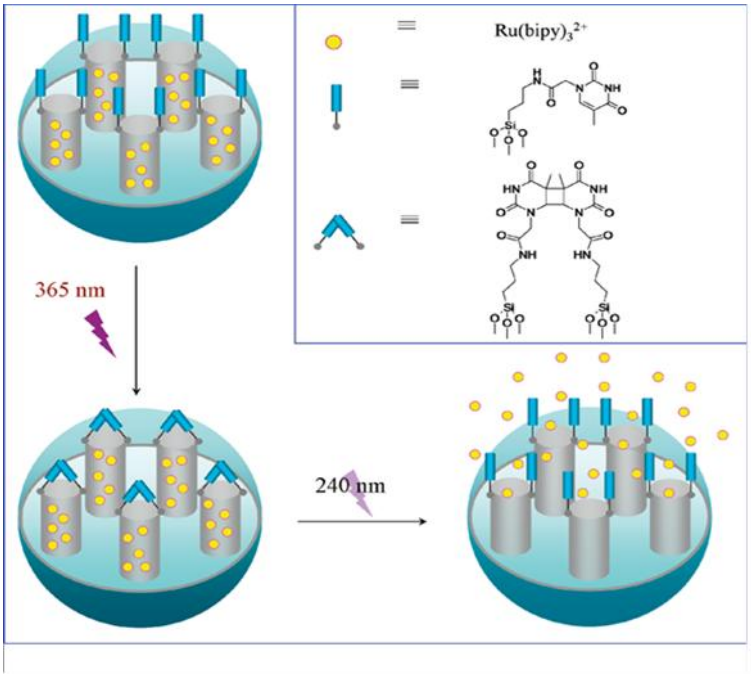
Figure 3. DOX release from the nanocarrier enzyme dependent treatment at different pH values in PBS. A) pH 7.4, B) pH 5.5. The concentration of cathepsin B was 50 $X10^{-9}$ M and the concentration of cathepsin B inhibitor was $50X10^{-6}$ M. (Li et al. 2014; Colilla, Gonza, Gonz14; Vallet-Rego 2013).

2. External stimuli-responsive MSN

Unlike internal stimuli, external stimuli are carried out via an external physical treatment. External stimuli-responsive drug delivery systems might be more favorable due to the different physiological conditions of the human population. In this section, drug delivery triggered application of external stimuli, involving temperature variations, magnetic fields, US, and light and electric fields, are discussed (Zhu and Torchilin 2013).

2.1. Light responsive MSN

Light irritation by the modulation of parameters, such as intensity, wavelength, and duration of the pulse is a promising way for many biomedical applications. Although visible, ultraviolet and near-infrared (NIR) light have been widely used in clinics, only NIR light could penetrate deeper into tissues and therefore, is more favorable for targeting of the tumor. Photodynamic therapy (PDT) is a promising light-sensitive strategy for targeting of tumors which involves the utilization of a photosensitizer (PS) such as chlorins, porphyrin derivatives, porphycenes, and phthalocyanines. Light-mediated irradiation of PS results in the generation of radical oxygen species (ROS) which collaborate to kill the targeted tumor cells(Zhu and Torchilin 2013).



Scheme 4. Representation of the light-sensitive system. The release mechanism of the system is based on the photodimerization and photocleavage of thymine based-MSN(He, He, et al. 2012), © 2012 American Chemical Society.

He et al constructed a reversible light-responsive gated system of thymine-based Ru(bipy)$_3^{2+}$-loaded MSN derivatives(TA-MSN). Thymine derivatives are well-known by their biocompatibility and hydrophilicity coated on the pores of MSN. The closing/opening mechanism and drug release are related to a photodimerization−cleavage cycle of thymine upon irradiation adjustment (scheme 4).Furthermore, thymine bases photodimerize via irradiation above 270 nm and revert to monomeric thymine again via irradiation below 270 nm. Pore blocking results by the dimerization of thymine monomer to cyclobutene via the irradiation of TA-MSN with 365 nm wavelength UV for 24 h light which leads to inhibit the drug diffusion. Luminescence spectroscopy utilized for monitoring the efficiency of loading and light-triggering release of the dye. In the dark, the emission intensity of Ru(bipy)$_3^{2+}$ in the supernatant was substantially constant, indicating good capping efficiency (Figure 4). Meanwhile, irradiating with UV light at 240 nm (~0.2 W/cm^2) the emission intensities of Ru(bipy)$_3^{2+}$ in supernatant gradually increased, affirming that the light application triggered the opening of the gate and allowed the entrapped Ru(bipy)$_3^{2+}$ to be released.

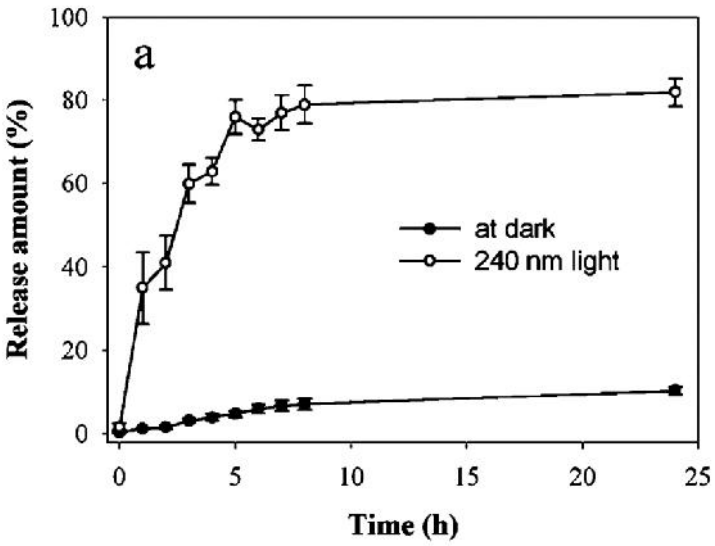
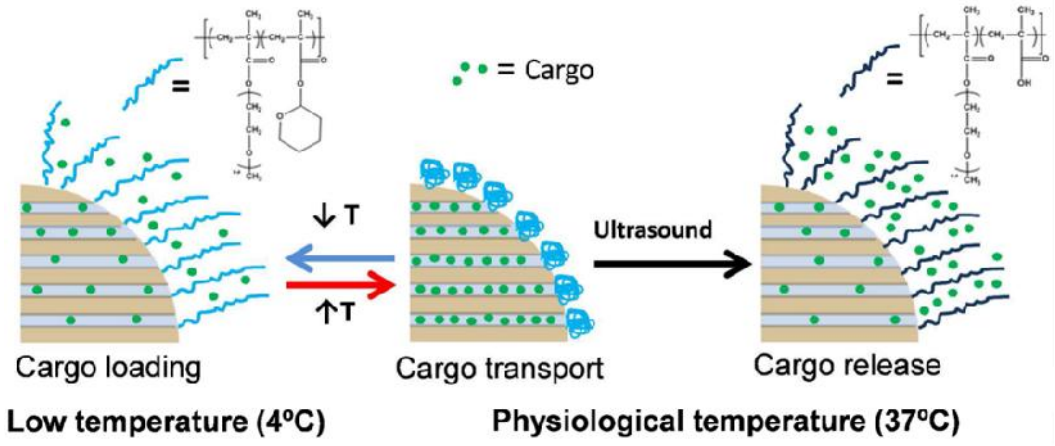


Figure 4. Release profile of the M1 in the dark and with UV light irradiation around 240 nm in PBS buffer. Luminescence spectroscopy was used to monitor [$Ru(bipy)_3^{2+}$] release into the solution(He, He, et al. 2012), © 2012 American Chemical Society.

2.2. Ultrasound responsive MSN

Ultrasound (US) is an excellent tool for achieving spatial tumor targeting and releasing drug without causing any damage to the normal tissues, which it is noninvasive and easy to use. The drug release and tumor penetration can be controlled by modifying the frequency, some cycles, and exposure duration time. The US can induce the drug release from different carriers through a process known as cavitation. The cavitation can be gained by low US frequencies. Cavitation spurs the destabilization of MSN for drug release while increasing vessel permeability to induce the influx of prepared MSN at the cellular level. US-mediated chemotherapies with microbubbles (MBs) have exhibited a tremendous potential for cancer treatment (Jang et al. 2016).Paris et al (Paris et al. 2015)developed an US-sensitive system based on MSN. US waves can increase thermal and mechanical effects that can trigger the drug release.MSN have been functionalized with a copolymer capable of opening and closing the gates of the carrier pores through a nanogate. Copolymer p(MEO2MA)-co-THPMA an US-sensitive hydrophobic tetrahydropyranyl moieties, presents a lower critical solution temperature (LCST) below the physiological temperature (scheme 5).



Scheme 5. Schematic illustration of the drug release behavior of the US-sensitive system(Paris et al. 2015), Copyright © American Chemical Society.

At 4°C, the polymer is in its coil-like conformation, which allows the drug to be loaded into MSN pores. While the temperature is elevated to physiological temperature, the copolymer converts to a collapsed state (insoluble) and the nanogates are closed detaining the loaded-drug into the MSN pores.

Upon applying the US waves, the hydrophobic form of tetrahydropyranyl moieties will be detached, leading to the hydrophilicity of the polymer to be induced and, therefore, an elevating of the LCST over physiological temperature. This change will lead to convert the conformation of the polymer to coil-like, opening the nanogates of the MSN mesopores and allowing the encapsulated drug to be released. To evaluate the US-sensitivity of the copolymer-grafted MSN, fluorescein was utilized as a model molecule. Hybrid-MSN were distributed into a solution of 20 mg/mL of the fluorescein dissolved in PBS at 4°C for 24 h. 4°C is lower than the LCST, so the copolymer p(MEO_2MA-co-THPMA) exhibits a hydrophilic behavior with a confirmation of coil-like, which allows the fluorescein dye to be introduced into the MSN pores. Afterward, the temperature elevated up to 37°C (higher than the LCST), so the copolymer exhibits a hydrophobic behavior with a collapsed state, which blocks the outlets of the MSN pores and inhibits the fluorescein release. TO confirm that the US-irradiated hybrid-MSN is behaving with totally-opened gates, the release pattern was very similar to MSN with no polymeric gates (Figure 5).

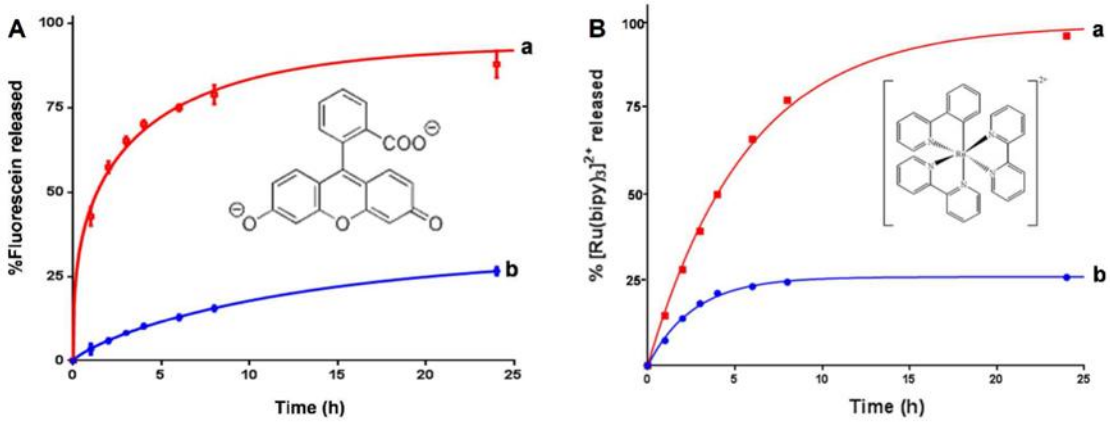
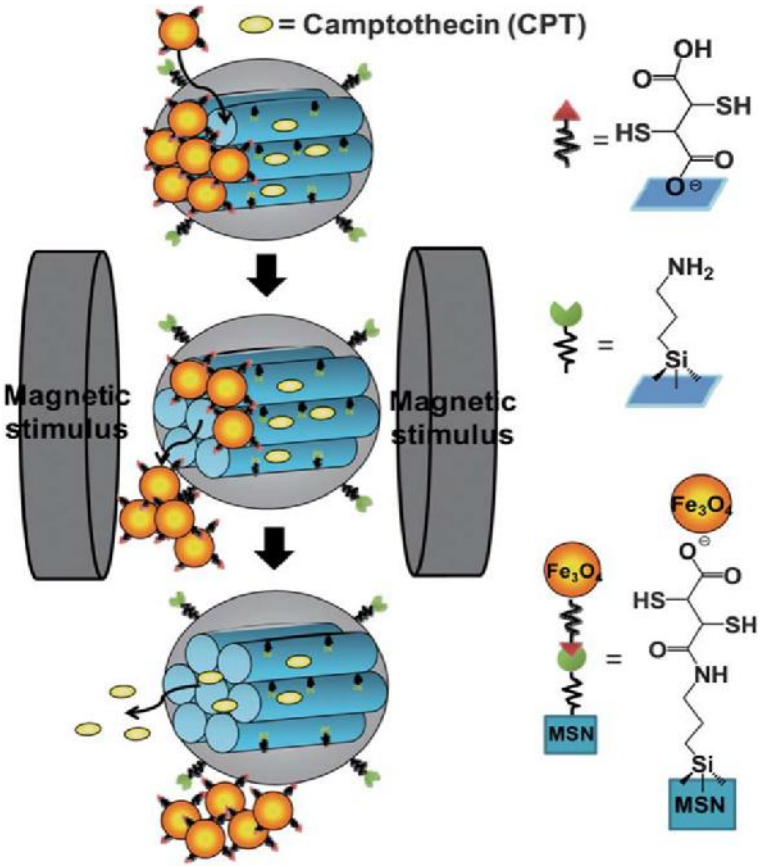


Figure 5. Drug release behavior A) release of fluorescein from hybrid-MSNs in PBS solution versus time with US exposure (10 min and 1.3 MHz, 100 W) (a) and without US (b). B) release of $[Ru(bipy)_3]^{2+}$ from hybrid-MSNs in PBS solution versus time with US exposure (10 min and 1.3 MHz, 100 W) (a) and without US (b), (Paris et al. 2015).

2.3. Magnetic responsive MSN

Magnetic nanoparticles (mNPs) are an essential class of nanomaterials that consist of typical magnetic elements, such as iron, nickel, cobalt, chromium, gadolinium, and manganese, as well as their derivatives. Furthermore, mNPs with a controllable particle size in the nanometer range and have high values of magnetic susceptibility and saturation magnetization, are applicable in biotechnology(Colilla, González, and Vallet-Regí 2013). Application magnetic fields can be utilized to control drug release from such nanoparticles (Fleige, Quadir, and Haag 2012). The High-frequency magnetic field (HFMF) accelerates the rotation of mNPs encapsulated in the MSN matrix and generates heat energy and then enlarges the porous channels that cause the drug to be released easily (Hu et al. 2008).Chen et al(Chen et al. 2011), constructed (MSN@Fe_3O_4) by chemical bond capping MSN with monodispersed Fe_3O_4 nanoparticles. The chemical bonding provides adhesion, which permits the mNPs as nanogates, to efficiently cover the MSN pores and be firmly bonded to the surface (scheme 6).The incorporation of mNPs on the MSN surface synergizes the efficacy of the nanosystem for fluorescence imaging, magnetic resonance imaging (MRI), inhibiting the premature release of drugs, and controlling the drug release upon external magnetic field irradiation.



Scheme 6. Schematic illustration of the cargo release behavior of the Fe_3O_4 nanoparticles-capped mesoporous silica drug nanocarriers upon remote controlled magnetic field application(Chen et al. 2011), © The Royal Society of Chemistry.

The camptothecin (CPT) was encapsulated into the pores of the amine-functionalized MSN in DMSO for 48 h and dried under vacuum for 24h. The mesopores of the MSN-loaded drug was covalently capped via amidation of the 3-aminopropyltrimethoxy silane bound at the pore surface with meso-2,3-dimercaptosuccinic acid functionalized superparamagnetic iron oxide nanoparticles (DMSA-Fe_3O_4 nanoparticles).

To confirm the successful immobilization of the functionalized DMSA-Fe_3O_4 nanoparticles on the MSN surface, there were no signs of cleavage from the surface upon vigorous stirring in distilled water via spectroscopic analysis after capping Fe_3O_4 nanoparticles formed a uniform and dense layer tightly bound to the surface of MSN. The drug release experiment proves that both systems showed sustained-release behavior, but the release rates were significantly different. The amount of CPT released from the MSN up to 95% within 48 h, while only 2.6% was released from the MSN@Fe_3O_4. These results revealed that most of the drug molecules were well-anchored within the mesopores of the MSN without leakage. The difference in drug release rate is attributed to the efficient capping of Fe_3O_4 nanoparticles for the surface of MSN which prevented the CPT leakage. Meanwhile, the concentration gradient led the CPT to be diffused from the MSN without Fe_3O_4 capping(Figure 6a). Under the magnetic stimulus, the CPT released from the MSN@Fe_3O_4 nanocarrier increased from 0.2% to about 21.9% over a 5 min stimulus (Figure 6b). After 24 h, the cumulative drug release raised from 21.9% to 45.9%. When consecutive magnetic stimuli of 1 min and 3 min duration applied, the release rates of CPT showed different profiles before and after themagnetic stimulus. In spite of some of the Fe_3O_4 nanoparticles were removed from the surface of the MSN upon magnetic stimulus then CPT burst from the MSN matrix in 10 min, a slow release over a time span of 24 h was observed right after the stimulus was removed. Noteworthy, increasing stimulus duration caused a steady increase of CPT release and a linear profile against the magnetic stimulus duration was obtained.

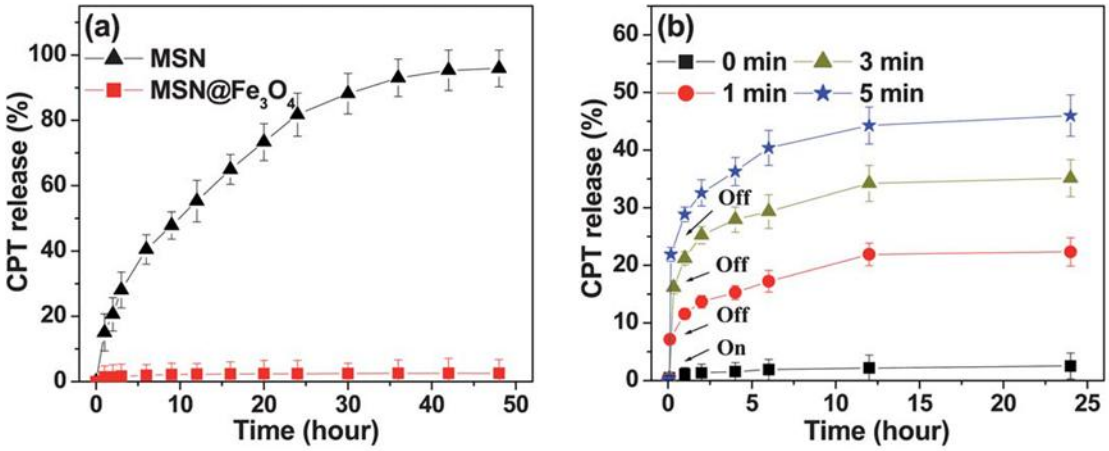


Fig 6. a) Cumulative drug-release of MSN and MSN@Fe_3O_4 nanocarriers. The MSN@Fe_3O_4 nanocarriers showed no drug leakage compared to MSN nanoparticles. (b) Cumulative drug release profiles of CPT from MSN@Fe_3O_4 nanocarriers triggered by magnetic stimulus for 1imulus (Chen et al. 2011).

3. Conclusion

In summary, as a drug delivery system, mesoporous silica nanoparticles have shown the most promising properties such as very high drug loading, favored biocompatibility and enormous surface area and pore volume. We have highlighted the mesoporous silica nanoparticles (MSN) ability to be utilized as a stimuli-responsive nanocarrier for cancer therapy by evaluating the capping efficiency of MSN comparing with and without applying stimulus.

The increasing number of researches and the diversity of the efforts deployed it's difficult to predict which expansion of this field must be reckoned with. MSN have the most promising advantages in aspects such as their delivery properties which make the system more suitable for active compound release and transport of pharmaceuticals. Particularly promising is the work of the drug delivery systems that react to an external stimulus by releasing active compounds. In addition to the traditional clinically approved anticancer drugs, other emergent drugs could be also delivered via MSN to reduce the side effects of drugs and improve the bioavailability.

It is difficult to determine which stimuli-sensitive nanocarriers have the best opportunities for reaching the clinic. The medical applications of most of the systems that we have discussed in this Review correspond to either therapeutic niches, or to orphan diseases that are resistant to already available treatments or for which no therapeutic alternative exists. We can expect many more levels of sophistication in their design and in the diversity of their payload.

Conflict of interest: None

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