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Publication Date

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Development of mesoporous silica-based nanoparticles with controlled release capability for cancer therapy☆

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Abstract

Nanoparticles that respond to internal and external stimuli to carry out controlled release of anticancer drugs have been developed. In this review, we focus on the development of mesoporous silica based nanoparticles, as this type of materials provides a relatively stable material that is amenable to various chemical modifications. We first provide an overview of various designs employed to construct MSN-based controlled release systems. These systems respond to internal stimuli such as pH, redox state and the presence of biomolecules as well as to external stimuli such as light and magnetic field. They are at a different stage of development; depending on the system, their operation has been demonstrated in aqueous solution, in cancer cells or in animal models. Efforts to develop MSNs with multi-functionality will be discussed. Safety and biodegradation of MSNs, issues that need to be overcome for clinical development of MSNs, will be discussed. Advances in the synthesis of mechanized theranostic nanoparticles open up the possibility to start envisioning future needs for medical equipment.

Keywords

Controlled release; Targeting; Mesoporous silica nanoparticles; Nanovalve; Nanoimpeller; Two photon excitation; Oscillating magnetic field

1. Introduction: nanoparticles and controlled release

Recent advance in nanotechnology is having a major impact on cancer therapy and diagnosis [1,2]. At the center of this development is a variety of nanoparticles. These particles with a diameter in the range of 50–400 nm can accomplish targeted delivery of anticancer drugs [3]. A variety of nanoparticles have been developed and some of these are shown in Fig. 1. Liposomes are lipid based vesicles and are widely used as drug delivery vehicles. Some are already used in clinics. Polymer micelles are another type of nanoparticles that have been widely used and are evaluated in clinical trials. Dendrimers are formed by hyperbranched polymers. In addition, inorganic nanoparticles such as mesoporous silica nanoparticles, nanodiamonds and gold nanoparticles are used for drug delivery. Finally, engineered natural

products that include engineered virus particles and vault nanoparticles have been developed.

Because of their small size, these nanoparticles can take advantage of a leaky vasculature and accumulate in the tumor. This so-called EPR (enhanced permeability retention) effect [4] appears to be particularly effective with tumor that has extensive vasculature. In addition to this passive targeting, positive targeting can be achieved by adding a targeting moiety on the surface of nanoparticles. Ligands or antibodies for receptors overexpressed on the surface of cancer cells can be used to accomplish positive targeting. These include folate, transferrin and RGD [5–7].

Another important feature of nanodelivery is that it is possible to design nanoparticles that can accomplish controlled release of anticancer drugs. For cancer therapy, an ideal type of nanodelivery system is the one that keeps anticancer drugs inside the nanoparticles until they reach tumor and the cargo is released only when a signal to release is provided. This "zero release until nanoparticles reach tumor" is an important feature of nanoparticles used for cancer therapy. A variety of stimuli have been employed to accomplish this type of controlled (on-command) release. The stimuli employed include internal conditions such as pH, redox state as well as external cues such as light and magnetic field. In addition, it is increasingly becoming apparent that multiple functionalities can be built onto nanoparticles. In addition to carrying out delivery of anticancer drugs, they can carry compounds such as fluorescent dye so that imaging can be accomplished; imaging and drug delivery can be carried out simultaneously leading to the operation of theranostics [8]. It is expected that multifunctional nanoparticles will be widely used for cancer therapy in the future.

2. Mesoporous silica nanoparticles and their features

Mesoporous silica nanoparticles are synthesized by a sol–gel method to produce homogeneous size nanoparticles. Addition of surfactant during the synthesis results in the generation of a structure with many small pores (mesoporous structure). Fig. 2A shows an example of MSNs that have a diameter of 130 nm with approximately 1400 pores per particle (pore diameter is 2–3 nm). The idea of surfactant templating to produce mesoporous materials was initially reported in 1988 by Dr. Kazuyuki Kuroda and others [9,10]. A similar method was published by the Mobile Corporation in 1992 [11]. Since then, a variety of mesoporous silica nanoparticles have been synthesized that include organosilica and periodic mesoporous organosilica materials that incorporate organic material [12].

Mesoporous silica nanoparticles (MSNs) possess a number of features that are advantageous for developing controlled release systems. First, their relative stability enables one to chemically modify the nanoparticles. A variety of chemical modifications have been made on their surface as well as on pore interiors. Second, extensive surface area enables various modifications to be carried out. Third, the pores in the nanoparticles provide storage space for anticancer drugs resulting in high loading of anticancer drugs. Finally, it should be pointed out that the ease of MSN synthesis allows one to scale up the synthesis thus enabling large scale synthesis of this nanomaterial.

3. Mesoporous silica nanoparticle (MSN)-based controlled release systems

3.1. Overview of MSN-based controlled drug release systems

Mainly two approaches have been taken to design and equip MSN with controlled release capabilities. One approach is a so-called "capping" or "gating" approach. This involves attaching organic molecules at the pore opening thus preventing release of the cargo stored in the pore. As shown in Fig. 2B, "nanovalves" can be attached to the pore openings to provide open and close function for the cargo stored in the pores. The anticancer drugs stored in the pores will remain inside nanoparticles by closing the nanovalve. Opening the nanovalve allows the release of stored anticancer drugs. One type of organic molecules used for the nanovalve is rotaxanes and pseudorotaxanes and this approach was pioneered by Dr. Fraser Stoddart and Dr. Jeffrey Zink [13]. Various other materials have been developed for capping (gating). Polymers have also been used to cover pore openings. The other approach to equip MSN with controlled release feature is to attach drugs to the surface of MSNs via stimuli-responsive linkages.

Tables 1 and 2 summarize some of the MSNs that have been developed. There are two kinds of stimuli that can be employed. First, intracellular or intratumoral conditions such as low pH [14–24], reducing conditions [25–34] as well as enzymes and biomolecules [35–40] have been utilized so that MSNs respond to these conditions and release drugs. This can be called autonomous release of anticancer drugs (Table 1). Second, MSNs that respond to external stimuli such as light [41–52], and magnetic field [53–59] have been developed. Use of ultrasound to trigger drug release has also been explored [60]. These are external stimuli-responsive anticancer drug release mechanisms (Table 2). These provide on-command feature with more precise control. Operation of these nanomachines on MSNs has been evaluated first using aqueous solutions, then in cancer cells and then in animal models. They are at different stages of development and this situation is described in Tables 1 and 2. Although mesoporous silica nanoparticles without nanovalves have been shown to be useful for delivering chemotherapeutic drugs [61], it is important to confer specific controllable capability so that any premature release can be prevented. For more detailed information on chemical features of these and other nanoparticles, please refer to a review by Song and Yang [62].

3.2. Systems that respond to low pH conditions

Among a number of different controllable release designs, pH-sensitive activation is of particular interest, as delivery can be autonomously activated in vitro and in vivo. When the nanoparticles are taken up into cells, they enter cells by endocytosis and will encounter endosomal/lysosomal environments where low pH condition is prevalent. In addition, tumor interior has low pH environment due to hypoxic conditions. This feature provides an advantage that the drug release is more restricted to cancer. Various designs for the controlled release mechanism that respond to low pH conditions have been pursued. Some examples are listed in Table 1. In the first case, drugs (doxorubicin) are conjugated to the inner walls of the MSN pores [15] providing protection to the drug. The conjugation involved hydrazone bonds that are labile and can be cleaved by acidic conditions (protonation). The operation of this system was demonstrated in aqueous solution as well as

in cells. Biodistribution in mice was also examined. The second case involves capping pore openings using low pH-sensitive cap (gate). Various materials are used for capping the pore openings. One material used is pseudorotaxane type molecules. Anilin based stalk with α-cyclodextrin was used in one approach [6], while N-methylbenzimidazole (MBI) stalk and β-cyclodextrin as the cap were used in another approach [19]. In yet another example, polyethyleneimine (PEI) was used as a stalk and α-cyclodextrin as a cap [18]. In another approach, boronate modified Fe_3O_4 nanoparticles were anchored at the pore openings [16]. This capping is labile to low pH, as the hydrolysis of the boroester bond takes place at low pH conditions. A similar gate-like function of boronate modified gold nanoparticles as a cap for mesoporous silica material has been reported [17]. In the third case, a pH-responsive system based on the coordination bonding of metal ions was developed [21]. In this system, a gate is formed at pore openings by forming metal-aminopropyl group bonding. Guest molecule is added to close the gate. Finally, in the fourth case which is using a different principle, chitosan is used to block drug release, as chitosan molecules are orderly aggregated [22,23]. Similarly, pH-sensitive lipid can be used to cover pore openings [24].

Fig. 3 shows an example of a pseudorotaxane based pH responsive system [19]. This nanovalve consists of an aromatic amine containing stalk that is attached to the opening of pores. β-cyclodextrin is then added as a cap that encircles the stalk. This non-covalent interaction blocks the release of anticancer drugs from MSN. Protonation of the aromatic amines results in the release of the β-cyclodextrin cap leading to the release of the cargo. As shown, this nanovalve is completely closed at pH 7.0 but can release cargo at lower pH as demonstrated by the release of doxorubicin. In cell experiments, the release of doxorubicin led to killing of cancer cells and this was dependent on low pH, as the addition of NH_4Cl blocked this effect.

One of the issues that is of practical importance concerns attachment of dual features such as controlled release and targeting. Hwang et al. [6] addressed this issue by developing mesoporous nanoparticles that have cancer-targeting capacity (trasferrrin as a targeting moiety) as well as pH-sensitive nanovalves. In vitro studies showed the autonomous activation and function of the nanovalves in the system under biological conditions depending on lower pH. To demonstrate that the release of dyes and anticancer drugs is dependent on low pH of endosomes/lysosomes, Bafilomycin A, a chemical that increases pH of these organelles, was used. Pretreatment of cells with Bafilomycin A resulted in the inhibition of the release of dyes and drugs. Animal experiments using SCID mice with human cancer xenograft successfully demonstrated that these pH-nanovalve-MSN systems are fully functional to effectively deliver anticancer drugs and suppress tumor growth in animals, providing the first proof of concept of nanovalve functionality in animals. Importantly, release of doxorubicin in the tumor was observed by its fluorescence inside tumor.

Theron et al. [63] designed a cap that employed stable multi-H-bonded and base-pairing systems. After the loading with drug molecules, the nanoparticles were capped through hydrogen bonds with complementary nucleic acids, prepared with covalently coupling a uracil or an adenine unit to the bulky β-cyclodextrin. These nanomachines were stable at neutral pH, but a controlled release was observed immediately when exposed to weak acidic

media. This system is based on a pH-sensitive bridged silsesquioxane in which the silica-anchored melamine fragments hold cyanuric acid molecules through hydrogen bonds. These H-bonds can be cleaved under mild acidic conditions. Cell experiments with human cancer cells showed a quick release of anticancer drugs inside cancer cells and a decrease in cell viability similar to that of the drug alone, suggesting effective pH-responsive release of loaded anticancer drugs [63]. Nanomachines activated by a pH change can also be combined with polymer coatings on mesoporous silica nanoparticles to produce a new generation of nanoparticles that can increase the cellular uptake, avoid the reticuloendothelial uptake, enhance tumor accumulation of nanoparticles, and respond to acidic microenvironment in the tumor. Experiments carried out with these pH-nanovalve-polymer systems showed optimal controlled release of loaded molecules, producing enhanced biological properties and multi-task drug delivery ability [64].

3.3. Redox and biomolecule-activated systems

Another type of internal stimuli is redox condition. Glutathione concentration is 2 μM in the blood stream but is increased to 10 mM inside the cell. This suggests that a nanovalve that contains a disulfide bond will be closed while traveling in the bloodstream but will open once nanoparticles enter the cell. Various materials that contain disulfide bonds have been developed and they are listed in Table 1. This includes the use of disulfide containing rotaxane nanovalves as a cap [34] as well as linking nanoparticle cap to the pore opening [25,26]. Also, cyclodextrin is attached to the pore opening via disulfide linker [29,30]. In addition, collagen and polymers are attached via disulfide linkage [31,33].

Incorporating an enzyme cleavable linkage into a nanovalve is another way of developing a system that responds to internal stimuli. When a nanoparticle encounters an enzyme inside the cell, nanovalve is opened and the content is released. In one example, saccharides are attached to the pore openings [39]. Uncapping of the pores through selective hydrolysis of the 1–4 glycosidic bond in the starch chains was demonstrated by the use of pancreatin (mixture of amylase, lipase and proteases) [39]. Protease cleavable peptides are also used to produce an enzyme sensitive cap [40]. Instead of enzymes, biomolecules can be used. In one case, ATP was used to change conformation of ATP-aptamer cap resulting in the opening of the cap [37]. Also, antibody molecules have been used to cap the pore which can be opened with an antigen addition [35].

3.4. Systems that respond to light

Compared with the above-mentioned internal stimuli-activated nanovalves for anticancer drug delivery, a more precise and easily controllable nanodelivery system can been developed by using external stimuli. We have pioneered in the use of azobenzene. This design takes advantage of photoactivated material azobenzene to achieve light-induced drug delivery under external light control at a specific time and location (Fig. 4A). Photoactivated moving parts based on the photoisomerization of azobenzene derivatives have been incorporated into the pores of mesoporous silica nanoparticles (Fig. 4A) [44]. The dynamic back and forth wagging motion of azobenzene that alternates between the cis and trans configurations upon light exposure has been used to regulate loading and releasing of drug molecules through pores. The ability to deliver and release anticancer drugs into living cells

upon external light irradiation has been tested using an anticancer drug camptothecin (CPT). CPT was released inside of cancer cells that are illuminated at the specific wavelengths that activate the impellers. The quantity of molecules released was dependent on the light intensity and the irradiation time. The release of CPT resulted in the induction of apoptosis as demonstrated by the appearance of chromosome condensation. Since the light used in this study is not harmful to human body, this provides a method that is advantageous, as it can potentially make the drug delivery system more biologically compatible and more effective. Instead of pore interior, azobenzene can be added to nanovalve [41,65]. This system used a supra-molecular system that involves a cyclodextrin threaded onto an azobenzene-based molecule grafted onto the surface of MSNs that functions as a nanocarrier and is activated using ultraviolet (UV) light. Other azobenzene containing systems include the one using azobenzene containing nucleic acid as a cap [42].

However, the systems described above require UV–Vis light which limits their applications due to its limited tissue penetration. Thus, this system has limited applicability for internal drug delivery. The optimal wavelengths for tissue penetration are within the biological spectral window (typically 800–1100 nm). Therefore, a new generation of light-activated nanoimpellers using near-IR wavelengths has been developed in collaboration with Dr. Jean-Olivier Durand and others (Fig. 4B) [66]. This system uses a two-photon fluorophore which absorbs energy from two-photon light and transfer to azobenzene promoting drug release. Two-Photon Excitation (TPE) in the near-infrared region is a promising alternative to UV–Vis light due to the many advantages TPE provides including precise controls (three dimensional spatial resolution), lower scattering losses, and deeper penetration into tissues. The two-photon light responsive MSNs shown in Fig. 4B takes advantage of the two-photon activated photo-transducer N^1-(4-((1E,3E)-4-(4-(dipropylamino)phenyl)buta-1,3-dien-1-yl)phenyl)-N^1-propylethane-1,2-diamine (2PNT). Dye release in the solution as well as release of camptothecin in human cancer cells has been accomplished. A similar two-photon responsive MSNs by using azobenzene containing nanovalves has been developed (Fig. 4C) [67]. Operation of these two-photon responsive MSNs was demonstrated in solution as well as in human cancer cells. It is also worth pointing out that the fluorescence of the two-photon fluorophore provides a reagent to enhance imaging of these nanoparticles.

Instead of azobenzene, photolabile coumarin derivatives have been used [45,47]. In one example developed by Guardado-Alvarez et al. [45], stoppers (caps) were assembled by binding photolabile coumarin-based molecules to the nanoparticle surface which are followed by noncovalently conjugating with bulky β-cyclodextrin (CD) molecules. The cap blocks the pores and prevents the leaking of anticancer drugs. Two-photon excitation at 800 nm cleaves the bond holding the coumarin to the nanopore, releasing both the CD and the drug molecules. This nanovalve has been shown to be effective for the delivery of dye molecule inside cancer cells. No premature release of anticancer drugs in cells was observed without light activation. Release of dye from the MSN was observed when irradiated with TPE beam for a short period of time.

A different principle for light activated systems is to use light to increase temperature resulting in the release of anticancer drugs from MSN. One example is the use of copper sulfide nanoparticles attached to MSN by two complementary oligonucleotides which act as

a cap (gate) to prevent release of Doxorubicin (DOX) from MSN [52]. NIR irradiation causes temperature increase resulting in the release of DOX [52]. Another example is the use of NIR-light-absorbing plasmonic nanomaterials. In one case, gold nanoshell is used to coat MSN [49]. NIR laser irradiation results in temperature increase and this hyperthermia effect is toxic to cells. In another example, Pd/Ag nanoplate was used as a core for MSN [50]. NIR light exposure converts light to heat resulting in the increase of nanoparticle temperature. This temperature increase destabilizes the bond that is used to attach Doxorubicin.

3.5. MSN-based drug release systems that respond to magnetic field

Using magnetic field as external stimuli for controlled release has an advantage, as it has much better tissue penetration than light. To carry this out, it is necessary to use a special type of nanoparticle that contains iron oxide magnetic core [5]. Preparation of this material was accomplished by first synthesizing iron oxide crystal of 2–5 nm. Then, mesoporous silica coating was added to make a particle of about 100 nm (Fig. 5). The magnetic core confers a number of new properties to the nanoparticle. First, because of superparamagnetic property of iron oxide core, the nanoparticles can be heated up by the exposure to oscillating magnetic field. Second, the magnetic property can be used to recover nanoparticles or to collect them to a desired site. Third, iron oxide has a property to enhance MRI imaging by T1 property as demonstrated by a darker image of cells that have taken up magnetic nanoparticles.

Exposure of iron oxide core MSNs to oscillating magnetic field results in heat generation due to superparamagnetic property of iron oxide. This temperature increase can be used to allow opening of a nanovalve. To accomplish this, a special type of nanovalve consisting of a stalk and cucurbit[6]uril was synthesized so that the heat generated by the exposure to oscillating magnetic field can be used to open the valve (Fig. 5). Thomas et al. [59] exposed breast cancer cells that have taken up magnetic core MSNs containing Doxorubicin to oscillating magnetic field generated by magnetic coil with 500 kHz and current amplitude of 37.4 kAm^{-1}. 5 min exposure resulted in the release of Doxorubicin inside the cell. In addition, cell killing due to the drug release was observed demonstrating the feasibility of this approach. One of the keys to successfully achieve the above magnetic field activated drug release is to heat up iron oxide core so that the temperature increase is just enough to open the nanovalve. In this sense, this approach is quite distinct from hyperthermia approach which uses heat to kill cells. Dong et al. developed nanothermometer [68] which allows monitoring of nanoparticle temperature. In this case, a crystal of $NaYF_4Yb^{3+}Er^{3+}$ was added to MSNs with iron oxide core. This crystal will generate luminescence that reports the temperature of MSNs. In one experiment, it was found that the MSNs can be heated up to 42° while maintaining the surrounding temperature of 19°.

Thermodegradable polymers have been used as a shell for iron oxide core MSN. One example of the polymer was made of polyethylene glycol functionalized with azo bonds that break with an elevation of temperature [53]. Another example is polyethyleneimine-*b*-poly(N-isopropylacrylamide) which acts as a thermosensitive gatekeeper [58]. Instead of

using iron oxide as a core, the magnetic nanoparticle can be used as a cap to prevent the release of drugs [54].

4. Adding multi-functionality to MSN-based drug release systems

Because of relative stability of the material, MSNs are suitable for developing multifunctional nanoparticles. For example, MSNs can co-deliver anticancer drugs and siRNA. We as well as others have shown that MSNs can be surface coated to carry and deliver siRNA to shut down gene expression [69]. For this purpose, low molecular weight PEI (polyethylene imine) can be used to coat MSN surface, and the positive charge of PEI attracts negatively charged siRNA resulting in stable association of siRNA. In fact, loading of siRNA to MSN led to protection of siRNA from RNase attacks. Using this method, knockdown of the expression of AKT as well as downregulation of the RAS/RAF/MEK signaling was accomplished in human cancer cells. More recently, siRNA against TWIST, one of the key regulators of epithelial–mesenchymal transition (EMT) was shut down in a mouse tumor model [70]. We can envision multifunctional MSNs that can have siRNA delivery capability together with controlled release of anticancer drugs.

Efforts have been made to introduce imaging capability to MSNs to accomplish theranostics. For example, iron oxide core MSNs can also function as an agent to enhance MRI signal. Fluorescent dye can be incorporated into nanoparticles. A general idea for designing multifunctional and multimodal nanoparticle can have the following points. An iron oxide core is arranged in the center of a mesoporous silica nanoparticle for MRI enhancement, and oscillating magnetic field responsive nanovalves are intended for on-command drug delivery from inside of mesoporous structures. The surface of nanoparticles can be coated by polyetherimide (PEI) in order to allow siRNA delivery, and targeting moiety can be attached further. This type of MSNs should enable proper targeting and combined use of multifunctional and multimodal technologies, and an advanced medical treatment can be expected.

Progress on the development of theranostic nanoparticles can be coupled with the advancement in imaging studies; molecular imaging techniques enable one to achieve new physiological and pathological findings with high diagnostic accuracy. When considering the movement of targeted tissues, improving the spatial resolution of the imaging device to the cellular level is difficult. In the case of molecular imaging using a probe that is bound to specific molecules or cells, it is possible to image the location of molecular targeting of the cancer cells. The X-ray computed tomography (X-CT) and magnetic resonance imaging (MRI) have a feature of being able to capture the morphological information of living tissues due to high spatial resolution as a fine image. Double imaging that combines MRI and fluorescence as well as X-CT and ultrasonography with specially designed nanoparticles has been developed [71–74]. Moreover, triple imaging that combined MRI, fluorescence and positron emission tomography (PET) has also been developed [75]. Another important advance concerns multimodal imaging utilizing characteristics of several measurement methods. Currently, PET and MRI are measured by independent equipment in almost medical facilities. A practical development of PET/CT equipment where two imaging techniques are united was initiated.

5. Biocompatibility, safety and biodegradability

Biocompatibility and safety is one of the major issues that needs to be addressed for clinical development of MSN based drug delivery systems. Various studies have addressed this issue [76–79]. In one study, a systematic characterization to examine safety of the material was carried out using mouse model systems [76]. Long term and short term safety was examined with MSN surface modified by phosphonate administered twice a week at 50 mg/kg on body weight. No significant adverse effects were observed with kidney, lung functions and hematologic profiles. Similar biocompatibility in a mouse model system was observed recently with MSNs equipped with pH-sensitive nanovalve [6]. However, a systematic characterization is needed, as various modifications on MSNs will affect their in vivo behaviors. It has been reported that biodistribution and pharmacokinetics of silica nanoparticles depend on geometry, porosity and surface characteristics [80,81]. Thus, characteristics of each nanoparticle need to be taken into consideration when safety of MSN materials is considered.

It has been reported that MSNs are excreted in urine and feces [76, 79,82]. In one experiment with phosphonate modified MSN [76,82], a majority of silica material was recovered in urine and feces four days after injection into mice as determined by ICP-MS. In another study, MSNs with highly positive charge were found to be excreted from the liver into the gastrointestinal tract ending up in feces [83]. Clearance of MSNs through urinary system of mice due to their in vivo degradation has been reported [84].

There are reports that MSNs are degradable, as silica can undergo hydrolysis to form silicic acid (discussed in [79]). These biodegradation byproducts are non-toxic to different cell lines [85]. More recently, it was reported that theranostic MSNs biodegraded after drug delivery and ultrasound/magnetic resonance imaging of stem cells [86]. It is also worth noting that a different line of effort has begun that involves introducing biodegradability into MSN. Croissant et al. [87] reported synthesis of ethylene-bis(propyl)disulfide based periodic mesoporous organosilica nanorods and nanospheres. Degradability of these nanoparticles in a solution containing mercaptoethanol was demonstrated.

6. Impact of MSN-based controlled release systems on the design of new medical equipment

Considering rapid advance in nanotherapeutics using nanoparticles, it is possible to envision making modifications to existing medical equipments. The first example concerns endoscopy used to detect gastrointestinal cancers such as stomach cancer and colorectal cancer. As shown in Fig. 6A, an endoscope that can reach an affected part is inserted into a hollow organ, not only to observe the affected part but also to collect and treat the tissue in situ. Therefore, the endoscope is one of the effective technologies that can integrate diagnosis and therapy. In a conventional endoscope, an image similar to that observed with naked eyes of the affected area is obtained by using a charge-coupled-device (CCD) camera. If the affected area can be imaged at a wavelength with a specific narrow-band visible outside, it also becomes possible to capture an autofluorescence and a blood vessel image of cancer tissues that cannot be observed with naked eyes. Moreover, molecular imaging can

be obtained by utilizing a fluorescent probe that specifically binds to a particular molecule or a cell [88–90]. We can envision combining our two-photon light-activated MSNs with the endoscope. The MSNs can be administered so that they can accumulate in the tumor. Then, endoscopy is carried out to identify tumor. When any tumor is identified, two-photon light exposure will be carried out to release anticancer drug in the tumor. In fact, endoscopy is already used to insert a liquid solution through a catheter from outside the body. Fabrication of a yolk-in-shelled particles with a Gd_2O_3 core capable of a drug release by controlling a pH trigger [91], a ribotoxin–curcin conjugated biological gold nanoparticles [92] and nanoparticles with an iron oxide core [93,94] that have pH triggers and photothermal ablation characteristics have been reported.

Various methods using electromagnetic waves, technologies concerning ultrasonic imaging, X-CT and MRI have been developed (Fig. 6B). PET and single photon emission tomography (SPECT) for measurements of a dynamics and a biodistribution by tracer that a radioactive drug is inserted to the body (Fig. 6C) have made significant progress in recent years. By combining with a nanodelivery strategy, ultrasonic or electromagnetic waves can be used to trigger for drug releasing, and expected to enhance the effect on tissues. For example, our magnetic core MSNs can be used to enhance MRI enabling detection of tumor, and then oscillating magnetic field can be activated to release anticancer drugs in the tumor. This type of combined approach has been tried with an ultrasound diagnosis and therapy of nanoemulsion using a vaporization of perfluoropentane [95]. Moreover, other nanodelivery strategies containing a platinum (IV) core that can be photoactivated by ultraviolet (UV) [96], and a magnetic nanoparticle encapsulated poly(D,L-lactic-co-glycolic acid) nanoparticles [97] have also been proposed.

In the future, we can envision cancer therapy without watching and touching directly to the affected area. The development of remote diagnosis and therapy with viewing an image on a display and operating manipulators of the robot and the capsule endoscope is expected. A wireless capsule endoscope can be employed for this purpose. In the current state of capsule endoscopes, an image is captured while moving passively by peristaltic movement of the intestine, and a transmission of a detected position and the image is performed by communication with the outside. For expansion of application areas and multi-functionality, a miniaturization of the capsule endoscope is an important issue. One idea is to provide a therapeutic function in the wireless capsule endoscope. Releasing anticancer drug in the tumor that contains nanoparticles by exposure to light is an attractive option. This requires mounting a light source into the capsule endoscope. This and many other modifications can be explored in the future.

Acknowledgments

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therapeutic approach, accelerated by magnetic hyperthermia. Int J Nanomedicine. 2014; 9:437–459. [PubMed: 24531392]

a) Liposome **b)** Polymers **c)** Dendrimer

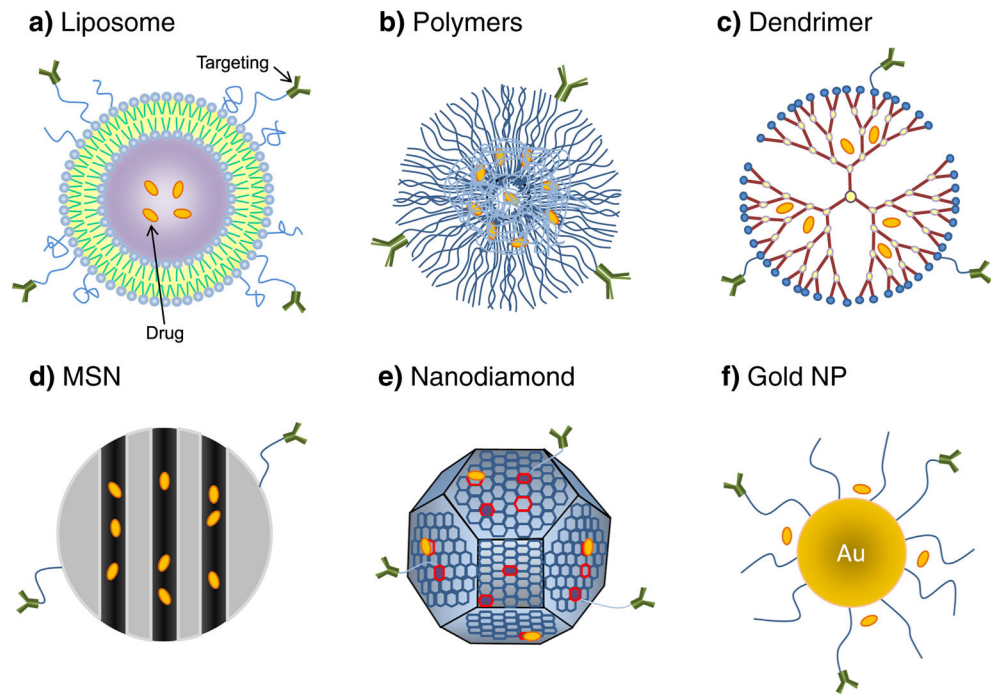**d)** MSN **e)** Nanodiamond **f)** Gold NP

Fig. 1.
Various nanoparticles used to develop drug delivery systems. Some representative nanoparticles are shown. Drugs stored in the nanoparticles as well as targeting moiety attached to nanoparticles are shown.
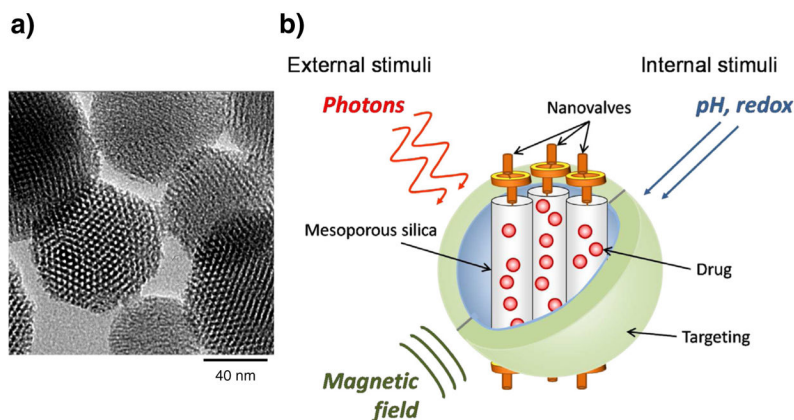
Fig. 2.

Mesoporous silica nanoparticles synthesized by the sol–gel method. A: TEM of MSNs. They are homogeneous with the diameter of approximately 130 nm and contain 1400 pores that can be used to store anticancer drugs. B: A schematic overview of mechanized nanoparticles based on MSN. Nanovalves will be attached to the opening of the pores so that open and close function can be conferred. Cargo molecules such as anticancer drugs and dyes can be stored in the pore. Surface modifications can be made to target MSNs to tumor. Nanomachines that respond to internal stimuli such as pH and redox as well as external stimuli such as light and magnetic field will be used to operate nanovalves.
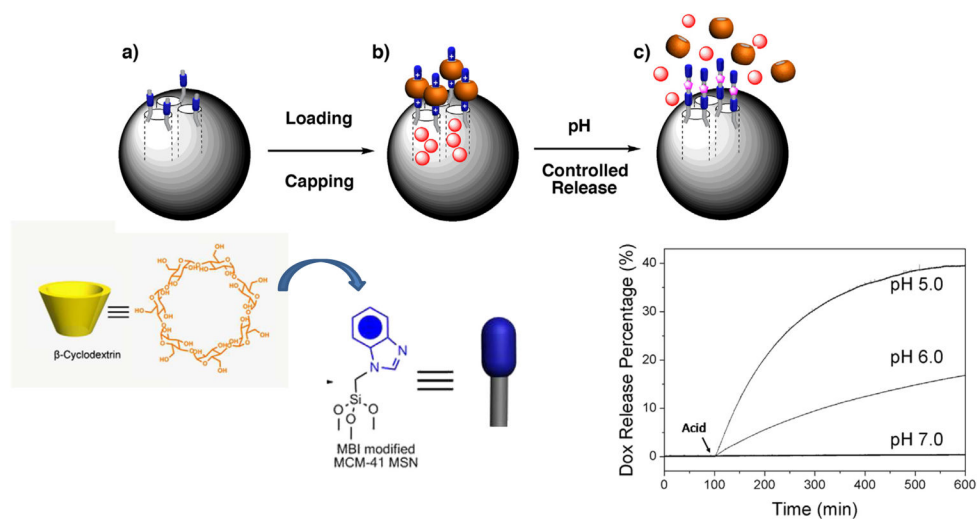
Fig. 3.
Design and operation of MSNs equipped with low pH responsive nanovale. Low pH responsive nanovalve is attached to the opening of pores in MSN. This nanovalve consists of an aromatic amine stalk that has β-cyclodextrin attached non-covalently. Protonation of the aromatic amines results in the release of β-cyclodextrin thus opening the nanovalve. Reprinted with permission from [19].
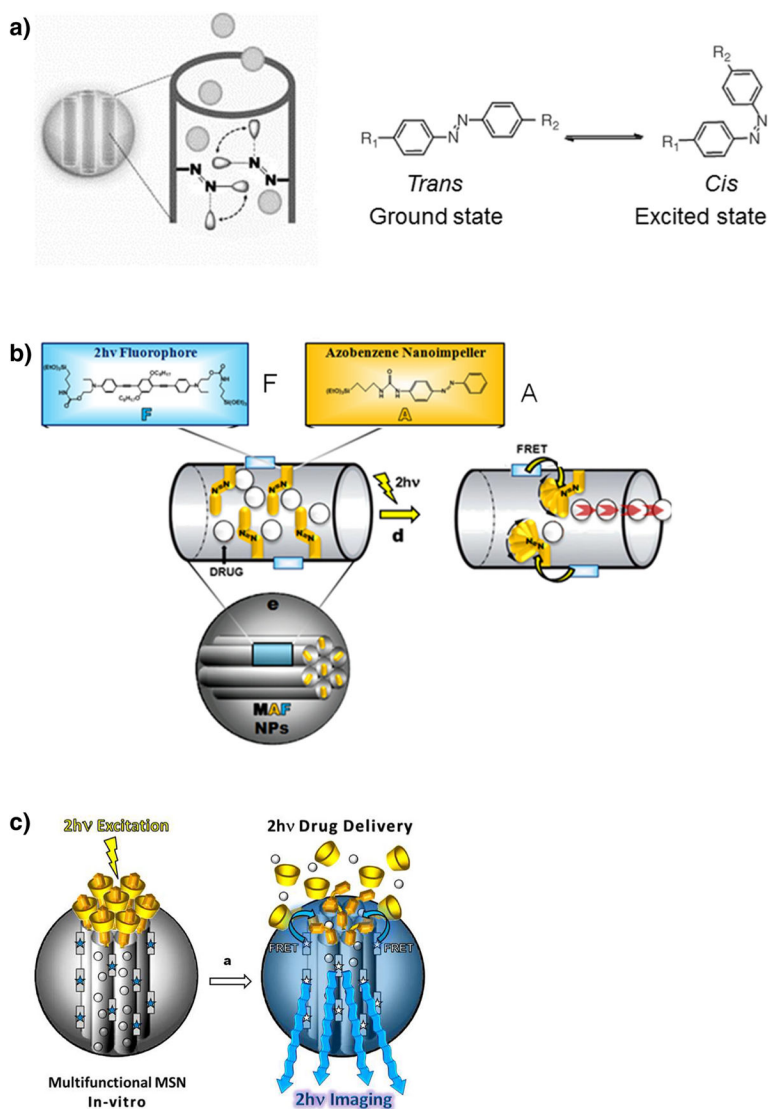
Fig. 4.
Design and operation of light responsive MSNs. A: The pore interior was modified with azobenzene that can oscillate between the trans and cis conformation upon light exposure. This provides a motion upon light exposure resulting in the release of cargos. B: Two-photon responsive MSNs. Nanoimpeller was modified by the addition of a two-photon fluorophore that absorbed two-photon energy. The energy was transferred to azobenzene resulting in the release of cargo such as dye and anticancer drugs. C: Azobenzene was incorporated into nanovalve and this MSNs were further modified by the addition of a two-photon fluorophore. Reprinted with permission from [44,66,67].
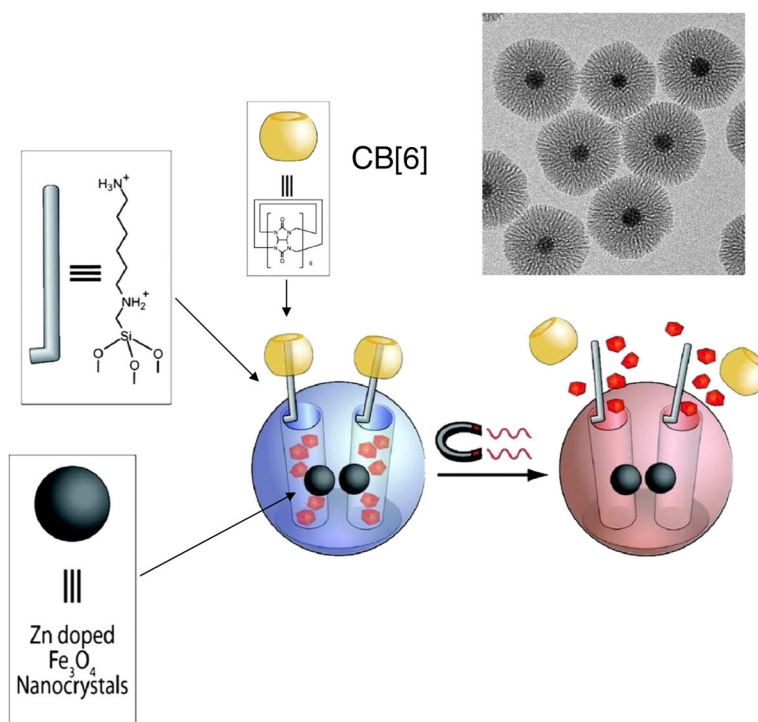
Fig. 5.
MSNs that respond to magnetic field were developed by using MSNs with iron oxide core. Zinc doped iron oxide nanocrystal was used. Super paramagnetic property of iron oxide conferred the ability to increase temperature upon exposure to oscillating magnetic field. The temperature increase causes the nanovalve to open releasing cargo molecules. Reprinted with permission from [8].
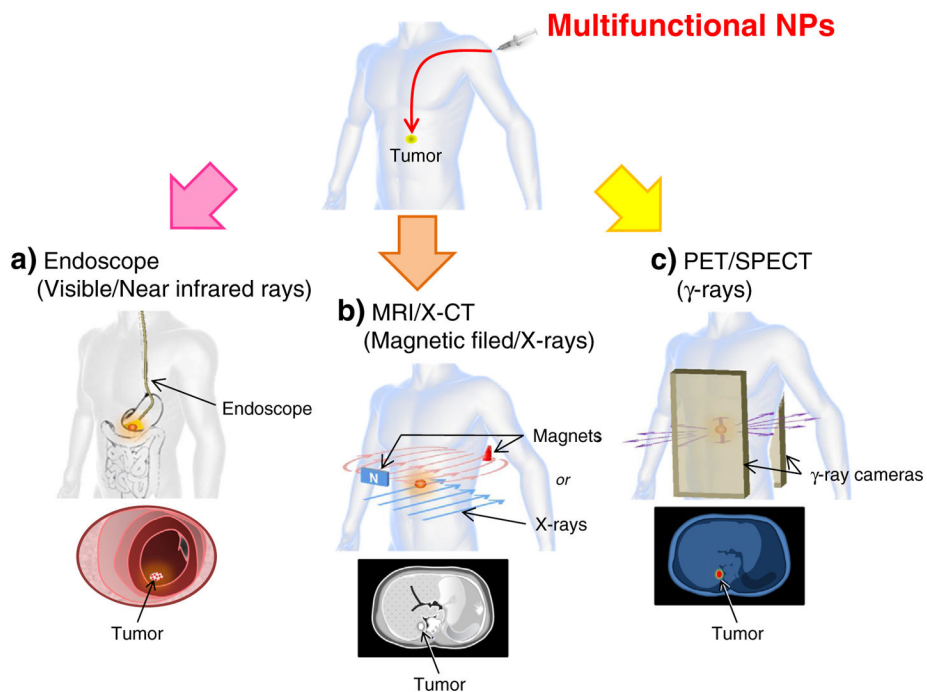
Fig. 6.
Image views of multifunctional and multimodal medical equipments for cancer therapy and diagnosis. a. MRI/X-CT/PET + robotic surgery and b. capsule endoscopy + PDT + nanodelivery equipments.

Table 1

Various designs for internal stimuli-responsive MSN-based drug delivery systems.

Category	Mechanism	Aq. exp	Cell exp	Animal exp	Ref
Low pH activated	1. Drugs conjugated to the pore walls by hydrazone bonds				15
	2. Pseudorotaxane with cyclodextrin as a cap				6, 19,20
	3. PEI/cyclodextrin cap at the pore openings				18
	4. Boronate modified Fe_3O_4 NPs as a cap				16
	5. Coordination bonding of metal ions as a cap				21
	6. Polymer and lipid coating preventing drug release				22–24
Redox activated	1. Rotaxanes containing disulfide bond as a cap				34
	2. Nanoparticles linked via disulfide bond as a cap				25,26
	3. Collagen immobilization via disulfide bond				33
	4. Polymers attached via disulfide bond to the pore openings				31
	5. Disulfide-linked PEG as a cap				28
	6. Cyclodextrin cap via disulfide linker				29,30
Biomolecule activated	1. Antibody molecule as a cap at pore openings				35
	2. Saccharide derivatives as a cap that can be cleaved with enzymes				36,39
	3. ATP-aptamer as a cap				37
	4. Protease cleavable peptides as a cap				38,40

Table 2

Various designs for external stimuli-responsive MSN-based drug delivery systems.

Category	Mechanism	Aq. exp	Cell exp	Animal exp	Ref
Light activated	1. Azobenzene in the pore and in the pseudorotaxane cap				41,43,44,66,67
	2. Azobenzene modified nucleic acid as a cap.				42
	3. Coumarin derivative incorporated within the cap				43,45,47
	4. Copper sulfide NPs attached to MSNs via two oligonucleotides as a cap				52
	5. Gold nanoshell				49
	6. Pd@Ag nanoplate core				50
Magnetic field activated	1. Iron oxide core MSN with pseudorotaxane as a cap				59
	2. Iron oxide core MSN coated with thermodegradable polymer				53,58
	3. Iron oxide nanoparticles as a cap for pores				54