Materials Research Express

TOPOCAL REVIEW

Role of mesoporous silica nanoparticles for the drug delivery applications

Baranya Murugan, Suresh Sagadevan, Anita Lett J, Is Fatimah, Kamrun Nahar Fatema, Won-Chun Oh, Faruq Mohammad and Mohd Rafie Johan

1 Centre for Nanotechnology & Advanced Biomaterials, School of Chemical & Biotechnology, SASTRA University, Thanjavur 613 401, Tamil Nadu, India
2 Nanotechnology & Catalysis Research Centre, University of Malaya, 50603 Kuala Lumpur, Malaysia
3 Department of Physics, Sathyabama Institute of Science and Technology, Chennai-600119, India
4 Chemistry Department, Universitas Islam Indonesia, Kampus Terpadu UII, Jl. Kaliurang Km 14, Sleman, Yogyakarta 55584, Indonesia
5 Department of Advanced Materials Science and Engineering, Hanseo University, Seosan-si, Chungnam 356-706, Korea
6 Surfactant Research Chair, Department of Chemistry, College of Science, King Saud University, PO Box 2455, Riyadh 11451, Saudi Arabia

E-mail: drsureshnano@gmail.com and isfatimah@uii.ac.id

Keywords: mesoporous silica nanoparticles, nanomedicine, drug delivery system, biomedical application

Abstract

The mesoporous silica nanoparticles (MSNs), because of the synthesis, ease of surface functionalization, tunable pore size, large surface area, and biocompatibility, are being useful in many of the biomedical applications like drug delivery, theranostics, stem cell research, etc. It has been a potent nanocarrier for many different therapeutic agents, i.e., the surface functionalization of silica nanoparticles (SNs) with chemical agents, polymers, and supramolecular moieties enable the efficient delivery of therapeutic agents in a highly controlled manner. Also, the toxicity, biosafety, and in vivo efficiency involving biodistribution, pharmacokinetics, biodegradation, and excretion of MSNs play an important role in their involvement in the clinical applications. A coherence between chemistry and biological sciences extends its opportunities to a wide range in the field of nanomedicine such as smart drug delivery systems, functionalization and gating approach, controlled drug delivery systems, diagnostic and targeted theragnostic approach etc. Thus, taking advantage of the inbuilt properties of the MSNs applicable to the biomedical sector, the present review describes a panorama on the SNs which are presently used for the development of theragnostic probes and advanced drug delivery platforms.

1. Introduction

In recent years, the mesoporous silica nanoparticles (MSNs) have been developed to serve as the theranostic probes and versatile drug delivery systems (DDS) because of their inbuilt properties like stability, tunable porosity, mesoporous nature, biocompatibility, ease of functionalization, non-toxicity, and biocompatibility [1–3]. For both of the applications, the MSNs formed by the chemical modification technique are suitable for imparting target-oriented internalization [3], stimuli-responsive release [4], enhanced circulation time, and as contrast imaging agents [1]. For example, the folate-conjugated MSNs have been demonstrated for the specific internalization into the cancer cells and the efficiency of cellular localization is very high as compared to that of normal cells [5]. For such internalization of mesoporous particles, the extent of chemical functionality incorporated at the surface significantly influences the extent of their cellular uptake due to enhanced interaction with that of cells. Also, in a different study, the mobile composition of matter-41 (MCM-41) MSNs are being modified chemically with three different ligands, namely, amine functionalization, hyaluronic acid (HA) conjugation, and chitosan incorporation. Although the formed three MCM-41-type particles exhibit good cytocompatibility with fibroblast cells, they all found to have a significant variation in their cell internalization, i.e., the decreased order of internalization is HA-MCM-41 > amine-MCM-41 > chitosan-MCM-41. The
observation of such variation in the internalization was attributed to the relative aggregation tendency of nanoparticles (NPs) and the extent of their surface interaction with that of cell membrane components [6]. In a similar study, the Si NPs were functionalized with either of neutral poly(ethylene glycol) (PEG), cationic amine, or anionic carboxylic acid groups; on testing, the cationic amine-bound Si NPs found to maintain enhanced interactions with that of macrophages cell membrane along with high inflammatory responses, while the other two modifications did not exert any noticeable toxic effects [7]. Further, in the case of stimuli-responsive mesoporous systems, the sensitivity or responsiveness of the probe is controlled by the nature of the responsive element and its mode of attachment at the surface [8].

Another property that significantly influences the efficiency of MSNs in the drug delivery sector is the particles size, i.e., the cells cannot accommodate the micron-sized particles because of their larger size, restricting the entry into cells by means of both active and passive transport phenomenon. Since the micro-capillaries of cells having the dimensions in the order of 200 nm and it becomes difficult to pass the micron-sized particles and so the nanosized particles in the range of 10–1000 nm are mostly preferred for the applications of drug delivery [9]. By making use of two different major pathways (active and passive mechanism), the particles can internalize into the cells. Within the active mechanism, the particles up to 200 nm size undergo clathrin-mediated endocytosis, and 200–500 nm size range particles follow caveolae-mediated endocytosis, while the micron dimension particles follow passive mechanisms such as macroinocytosis and phagocytosis for the internalization [10]. Although many different mechanisms are available for the internalization of particles with varied sizes, the nano-dimensional particles having the size >300 nm still finds their way to be difficult to internalize into the cells. In a study for example, the amine functionalized Fe3O4-MSNs formed in three different sizes (200, 450, and 650 nm) and surface positive charges to support better cell membrane interaction when tested on HeLa cancer cells, the maximum uptake was noted for the lowest sized particles (200 nm), followed by the 450 and 650 nm [11]. In a similar study, the calcium oxalate monohydrate and dihydrate crystals when formed in three different sizes (50, 100, and 1000 nm), the highest cell internalization followed by clathrin-mediated endocytosis was recorded for the smallest sized particles. This localization has contributed to a great loss to the viability of Vero cells, while only limited toxicity effects were observed in the larger sized particles treated cells because of poor internalization occurred through the microinocytosis mediated pathway [12].

Also, the heterogeneous core–shell type Si NPs on testing with different cell types, it was found that the activity is significantly influenced because of the size variations and associated changes in the cell–particle interaction [13]. However, the homogenous core–shell type of the same Si material, i.e., solid silica core with mesoporous silica shell formed in different sizes of 50–140 nm and on testing, the 90 nm sized particles exhibited the highest cell internalization. The observation of such an enhanced activity by the ultrafine particles was attributed to their low adhesion energy and the tendency to aggregate in serum proteins which has an effect towards the cellular uptake [14]. Moreover, it was found that the particles having sizes <50 nm can internalize effectively in some type of cells, but their drug encapsulation capacity is very limited and so the ideal size selected for the drug delivery applications includes the 100–200 nm. Further, to get a better idea about the MSNs and their inbuilt properties applicable in the biomedical sector, the present review is aimed to cover various aspects starting from the chemistry, recently introduced synthesis methods, followed by the functionalization approaches. In addition, the development of MSNs-based smart delivery platforms that make use of both internal (pH, redox, and enzyme) and external (temperature, ultrasound, and light) stimuli are reviewed. Finally, the MSNs involved biomedical applications like therapeutic/diagnostic confronts, photodynamic, tomography, bioimaging, antimicrobial, and gene therapy applications are also covered, in addition to the discussion of biodegradation, biocompatibility, and toxicity of MSNs.

2. Origin and chemistry of MSNs

In the 1970s, the mobile research and development corporation initiated the synthesis of MSNs from aluminosilicate gels through a liquid-crystal template mechanism. In the year 1992, IUPAC described the MCM-41 with a pore size ranging from 2–50 nm and an ordered arrangement in the pore structure. The pore sizes can be tuned based on the choice of the surfactants and the generated MCM-41 with its hexagonal moiety widely suitable for the development of DDS [15]. Also, the synthesis of other mesoporous structured materials with varying pore sizes can be produced by simply tuning the precursors and reaction conditions. The other types of mesoporous materials such as MCM-48 look like a cubical arrangement and MCM-50 as a lamella like an arrangement [16]. Besides, depending upon the symmetry of mesoporous structure and triblock polymers, the non-ionic triblock copolymeric surfactants like alkyl poly(ethylene oxide) (PEO) oligomers, and poly (alkylene oxide) block copolymers are widely used as a template for the synthesis of SBA-11 (cubic), SBA-12 (3-d hexagonal), SBA-15 (hexagonal), and SBA-16 (cubic cage-structured). For achieving the required orientation and symmetry of mesoporous materials, the concentration of ethylene oxide to propylene oxide is greatly
differed. The SBA-15, a highly ordered mesoporous structured material has been widely used for biomedical applications following its synthesis for the first time by the University of California, Santa Barbara, and so it was named as Santa Barbara Amorphous type material (SBA) and it has a varied pore size than that of MCM, i.e., SBA has larger pores of 4.6–30 nm and thicker silica walls. Taking advantage of the varied pore sizes, the SBA-15 and MCM-50 are best suitable for the adsorbent and catalysis related applications. In a similar way, the FSM-16 in the form of a folded sheet of mesoporous material was synthesized to be applicable in the catalysis and pharmaceutical sector and for that, the template of quaternary ammonium surfactant and layered polysilicate Kane mite was used. Further, the noteworthy mesoporous materials with the change of size and shape in the area of MSNs include, TUD-1 (Technical Delft University-1), HMM-33 (Hiroshima Mesoporous Material-33), and COK-12 (Centre for Research Chemistry and Catalysis-12) [17].

3. Advances in synthesis methods

Stober method is the most used and well-oriented approach for the formation of micron size silica particles with spherical morphology and monodispersity and this method was the beginner in developing a chemical reaction for MSNs [18]. These methods can be well versed in acidic, basic, and neutral conditions and by simply changing the reaction parameters, this synthesis approach results in the formation of MSNs with different shapes and sizes. Grun et al first introduced a cationic surfactant-based template for the development of spherical MCM-41, and the schematic representation of the mechanism of the formation of MCM-41 is illustrated in (figure 1). The researchers were successful in developing a spherical MCM-41 with the same properties compared to that of other methods [19], where the formed MSNs serves as the potent nanocarriers for drug delivery applications. Also, this approach allows for the tuning of various physical and chemical properties of MSNs as per the requirement, i.e., the particle size, shape, pore-volume, and total surface area are generally changed to enhance the drug loading capacity of the particles. To control these physical characteristics of the formed MSNs, the commonly controlled parameters in the synthesis process include the reaction pH, temperature, type and amount of surfactant, a silica source, etc. For example, the MSNs formed by liquid crystal template method is a way of producing the particles at the surface of surfactant micelles by means of hydrolysis and condensation of silica which further transforms the liquid silica into solid form via the silica precursor tetraethyl orthosilicate [20]. Also, some of the earlier reports described that the MSNs can be formed through the liquid crystalline template mechanism of non-ionic surfactants. Also, the researchers say that the hydrolyzed silica get adsorbed on the surface of the micelles or in SBA-15 type mesoporous, the surfactant molecule and silica act together at the initial phase to generate core–shell type materials [21].
4. Functionalization and gating approach

One of the main steps during the development of stimuli-responsive DDS involves the inclusion of gating molecules at the pore surface and this gating can be done through the surface functionalization, capping agents, linkers to the internal pore, and by molecular pore gating. The molecular pore gating can be done by blocking the pores with molecules such as iron oxide NPs, gold NPs, proteins, etc., which are known as the ‘molecular pore gating’ agents [22]. The supra macromolecular structures are conjugated with a gating molecule called the linkers, which are attached to the surface of NPs and these linkers are disintegrated on exposure to the stimulus causing the release of blocking moiety [23]. Certain parameters to be tuned such as the length of linker, size of blocking molecules, and density of surface coating molecules [24]. The other gating concept includes the polymer chains and lipid bilayers used for closing the pores and thereby preventing the premature release. These gating moieties disassembled on exposure to stimulus trigger the release of cargo because of the competitive displacement [25]. The last approach of the gating concept includes the functionalization of pores using a capping molecule that encapsulates the drug molecule inside the silica network. These capping molecules lysed using the lysing agents such as glutathione and mercaptoethanol, stimulates the drug release [26]. The following (figure 2) represents the gating strategies that have been explored in mesoporous systems and the functionalization of NPs can be done easily by the presence of silanol groups present in the MSNs [27]. The surface modification in general used to enrich the physicochemical properties, decrease hydrophobicity, improve semiconducting, stimuli responsiveness, and luminescent properties of the material [28].

Organically modified silica is the most important type of MSNs that enriches the organic molecules, which covalently bonded to the inorganic network of Si NPs [29]. For example in a study, the poly(N-isopropyl acrylamide) (PNIPAM)-capped core–shell type MSNs were first formed by ATRP (atom transfer radical polymerization) on the surface of silica [30] and further, these polymer capped core–shell type NPs entrapped with FITC (fluorescein isothiocyanate) for imaging applications in the breast cancer cells [31]. Also, there were some other mechanisms also described for the grafting of PNIPAM chains to the surface of MSNs. At first, the surface of MSNs was modified using tri(methoxysilyl)propyl methacrylate and in the following step, a monomer was grafted through radical polymerization mechanism. Finally, the system was conjugated with PEG onto the mesoporous silica followed by the loading of Doxorubicin anticancer drugs to act against the ovarian cancer cells [32].

The surface modification process can be done through the post-synthesis method or co-condensation method; the post-synthesis method is the most familiar method, in which the organic moiety is grafted covalently onto the surface of MSNs [33]. Herein, the hydroxyl group available in the MSNs be exploited as a
connecting group for the surface functionalization, and these hydroxyl groups are converted to silanol or geminal silanol groups (–Si–OH) and thereby participating in a surface functionalization process which ultimately alters the surface density [34]. In a similar way, the co-condensation method makes use of the sol-gel process involving tetra alkoxysilane and organo alkoxysilanes for the functionalization process [35]. In this, the amino silane functionalities are introduced into mesoporous silica through cationic surfactants such as cetyltrimethylammonium bromide (CTAB), which slows down the functionalization process through electrostatic repulsive forces. Also, the challenges in the post-synthesis grafting method include the alteration of amino silane functionalities and controlling of the aggregation kinetics. The most commonly used surface-active agents for the surface modification of amino silane functionalities include vinyltriethoxysilane (VTS), 3-glycidoxypropyltrimethoxysilane (GPTS), methacryloxypropyltriethoxysilane (MPTS), 3-aminopropyltrimethoxysilane (APTS), chloropropyltriethoxysilane (CPTS), and 3-mercaptopropyltriethoxysilane (McPTS) [36].

5. Development of smart MSNs for drug delivery

5.1. Internal stimuli-involved DDS

In this part, we describe the advances in internal stimuli-based DDS. The various internal stimuli have been used as a stimulus to trigger the release of loaded drug molecules towards cancer therapy and the most commonly stimuli includes, pH stimuli responsiveness, redox stimuli responsiveness, and enzyme stimuli responsiveness.

5.1.1. pH stimuli responsiveness

The pH stimuli-responsive DDS are investigated to serve as an ideal candidate for biomedical applications. For example, Junghwan et al developed an MSNs and was surface-functionalized with capping agents like tetrathio-maleimide (TTM) via a ‘host-guest’ complexation mechanism. The outer surface was modified with melamine behaves as ‘host’ and TTM as ‘guests’. Through the melamine capped functional groups on the MSNs covalently immobilized on the cargo and loaded into the mesopore channels. The TTM units on the outer surface act as a gatekeeper to prevent the premature drug release and this system controls the drug release upon exposure to the pH of releasing medium [37]. Similarly, the ZnO quantum dots (QDs) have been used to obstruct the pores of MSNs and thereby preventing the premature drug leakage. Once it enters the cells, the ZnO QDs lid dissolves in an acidic environment and therefore it releases the drug in the cytosol which is a potent candidate for pH stimuli-responsive DDS [38]. In another study, a group of researchers has worked on the targeted pH responsive DDS where the MSNs were capped with that of an ultra pH-sensitive gatekeeper, and to enhance the dispersity, it is grafted with PEG and poly(2-(pentamethyleneimino)ethyl methacrylate) (PPEMA) to make as a pH-sensitive drug delivery. Thus, the formed system has controlled drug release properties under open and closed (hydrophilic to hydrophobic) charge transformations [39]. In (figure 3), the researchers have made many attempts for the development of novel pH-responsive strategies involving hollow MSNs (HMSNs); the systems were assembled using 3-(3,4-dihydroxy phenyl)propionic acid (DHPA) functionalized with that of β-cyclodextrin (β-CD) and were capped onto the surfaces of HMSNs via boronic acid-catechol ester bonds. To this HMSNs-β-CD nanocarrier, the PEG conjugated adamantane (Ada) was tied up via host-guest interaction, and this system was expected to permeate into the tumor through the enhanced permeability and retention (EPR) effect. The developed system containing the PEG and Ada groups and having the benzoic-imine bonds gets lysed inside the tumor microenvironment as it has the weak acid pH of 6.8, while the disintegrated PEG protective layer leads to the cellular uptake of HMSNs system. Consecutively, the hydrolysis of the boronic acid-catechol ester bond linkers under low endosomal pH conditions (4.5–6.5) facilitates the intracellular drug delivery, and finally attributed to the efficient apoptosis mechanism in the cells [40].

5.1.2. Redox stimuli responsiveness

Murugan et al developed a novel MSNs containing the MCM-41 that was functionalized with organosilane group 3-mercapto propyltrimethoxysilane (SH group) and these SH groups spontaneously oxidized to form the disulfide bonds. The disulfide bonds formed were get lysed on exposure to the thiol reducing agent, causing the drug release towards the breast cancer cells [41]. Hu et al developed a multifunctional nanocarrier constructed by the tagging of transferrin onto the surface of HMSNs via a disulfide bond and these disulfide bonds get lysed by the addition of glutathione. Here, transferrin acted as the gatekeeper to mediate the controlled drug release, and to enhance the accumulation of drug-loaded particles at the specific tumor site concurrently. Based on the analysis, the transferrin mediated multifunctional nanocarrier would be an ideal candidate for the redox stimuli-responsive DDS [42]. Also, the researchers have studied redox stimuli-responsive DDS using collagen latched on the Si NPs through a disulfide bond, and lactobionic acid (LA), cell-specific targeting moiety, which causes the cleavage of disulfide linker and resulted in cell-specific intracellular drug delivery and enhanced the endocytosis
with a model drug FITC [43]. In (figure 4) Zhang et al developed a GSH (glutathione S-transferase) responsive MSNs functionalized 3-mercaptop propyl trimethoxysilane and capped with RGD containing peptide and were further loaded with doxorubicin anti-cancer drug (DOX@MSN-S-S-RGD). Once the DOX@MSN-S-S-RGD system enters the cells, the accumulation within the tumor cells gets enhanced by the receptor-mediated endocytosis and gets cleaved on exposure to the intracellular GSH which triggers the drug release and finally destroys the tumor cells [44].

5.1.3. Enzyme stimuli responsiveness

Cai et al developed a biocompatible and controlled drug delivery system using MSNs and it makes use of the tumor microenvironment enzymes for the release of loaded drugs. The enzyme-based system was constructed by grafting the phenylboronic acid coupled human serum albumin (PBA-HSA) onto the surface of MSNs as a closing agent, through a functional and polycation cell-penetrating peptide (CPP) polyarginine, and matrix
metalloproteinase 2 substrate peptide. Doxorubicin was used as an anticancer agent that got loaded inside the nanocarrier. The in vitro and in vivo experiments proved that these systems could efficiently destroy the cancer cells and prevent tumor growth with adverse effects \[45\]. Also, the researchers have attached TPP (triplopolyphosphate) for mitochondrial targeting purposes at the surface of the MSNs and further functionalized with HA. The presence of HA enhances the CD44 receptor-mediated cancer cell targeting and acts as a gatekeeper to block the pores and prevents premature leakage. The HA available at the surface of MSAs gets degraded by hyaluronidase (HAase) in the acidic microenvironment maintained inside the tumor tissues, while no degradation inside the normal tissues due to the neutral pHs. On testing, the in vitro and in vivo experiments proved that the TPP–DTX@FA-chol-BSA NPs have demonstrated for a significant antitumor effect because of the accumulation of particles inside the mitochondria \[46\].

5.2. External stimuli-based DDS

5.2.1. Temperature stimuli responsiveness

Shun et al developed a DDS for the smart delivery of pesticides that can reduce the side effects of agricultural chemicals and for that, a formulation that works on the temperature stimuli-responsive release was prepared by involving the hollow mesoporous silica (HMS) as the core, thermoresponsive copolymer, poly(N-isopropyl acrylamide-co-methacrylic acid) (P(NIPAM-MAA)) as an outer shell, and the loaded insecticide having a type of positive temperature coefficient includes Thiamethoxam (THI) pesticide to ultimately generate THI@HMS@P(NIPAM-MAA). The release rate was based upon the temperature of induction, i.e., at lower temperature conditions, the release rate was less and with an increase of temperature, a trigger that supported a faster drug release. Based on the temperature dependence release, the formed system would be an ideal candidate for the controlled and sustainable pesticide release \[48\]. Similarly, another temperature-sensitive PEG/PCL multiblock copolymer used as a gatekeeper was modified on the surface of MSNs. This system triggers the drug release on response to heat shock stimuli on the detachment of polymer from the surface of Si NPs \[49\]. Also, the iron oxide capped thermoresponsive MSNs grafted with poly(N-isopropyl acrylamide-co-3-(methacryloxypropyl) trimethoxysilane) (P(NIPAM-co-MPS) on the surface generated MMSNP-P(NIPAM-co-MPS) that can be able to release the drug below 25 °C and above 40 °C at lower critical solution temperature (LCST). The results obtained described that the thermoresponsive copolymer acted as a gatekeeper and thus the developed formulation serves as a promising strategy towards the thermoresponsive DDS \[50\]. In a different study, the researchers have developed a microwave thermal responsive DDS based on the thermosensitive peptide coated core–shell MSNs, where the core–shell type NPs are made of mesoporous silica shell for drug loading and doped with ZnO@Fe3O4 core for enhancing the heat generation. The Fe3O4 tagged ZnO provides accelerated thermal properties that could generate heating for the blocking and opening of the pores which can disintegrate the peptide from the surface. This system can act as an excellent thermal triggering for the smart DDS \[51\].
5.2.2. Ultrasound stimuli responsiveness
In researchers developed an ultrasound responsive MSNs-based DDS through blocking the pore entrances with a copolymer and this copolymer has the labile acetal group which could lyse via ultrasound stimuli. The acetal group removal causes a change in the hydrophobicity of the polymer and the transformation from hydrophobic to hydrophilic results in a shift on the polymer conformation that can trigger the drug release [52]. Maria et al developed an ultrasound-based mesoporous silica DDS where the surface of Si NPs capped with a specifically designed copolymer that can act as a gatekeeper for the pores. The NPs can load the drugs at low temperatures (4 °C) and 37 °C, the copolymer tends to collapse causing the pore entrance blockage and leave the NPs to hold the drugs at physiological temperatures by preventing the premature release. On exposure to ultrasound irradiation, the copolymer changes its transition state from hydrophobicity to hydrophilicity, leading to the opening of gates and cargo release from the pores of silica [53]. In a similar study, the researchers have developed MRgHIFU (magnetic resonance-guided high-intensity focused ultrasound), which is a powerful technology and used for cancer targeted therapy triggering within a physiological temperature. These MRgHIFU used to minimize the thermal damage to neighboring tissues. In this, mesoporous silica was capped with PEG to cover the surface of pores, HIFU stimulates the drug release, with no change in the temperature (~4 °C). Also, the gadolinium-based contrast agent, (gadopentetate dimeglumine (Gd (DTPA))2−) was encapsulated to measure the triggered release in situ through magnetic resonance imaging (MRI). The release of Gd (DTPA)2− was managed by HIFU stimulation times and power levels. This temperature-controlled ultrasound-mediated DDS would be an ideal platform for imaging and targeted release [54].

5.2.3. Light stimuli responsiveness
Luisa De Cola and colleagues developed a light cleavable MSNs capped with bis–alkoxysilane and loaded with provitamin D3, and this system upon exposure to light irradiation, the biologically important provitamin D3 molecule is thoroughly degraded from the pores of silica. Based on this system, light stimuli have gained much importance in material science [55]. Also, the researchers have developed, demonstrates a light-responsive mesoporous silica DDS using near-infrared (NIR) light, due to its potential advantages in cancer therapy such as deep tissue penetration, reduced auto-fluorescence, tissue scattering, and biosafety. The mesoporous silica is functionalized with inorganic NIR responsive, lanthanide-doped up conversion NPs (UCNPs) which can transfer energy from NIR light to UV/vis radiation. The NIR thermal converting NPs used are NIR plasma resonance and carbon–based materials [56].

A light-responsive DDS was also achieved by modulating the surface state of the superhydrophobic/superhydrophilic nature of MSNs and for that, the surface of silica was modified with octadecyl trichlorosilane (OTS) with superhydrophobic nature that prevented the encapsulated drug release from the MSNs. Upon exposure to a high-pressure mercury lamp of 400 W at different time intervals, decaying of OTS results in the changing from ‘closed’ to ‘open’ state led to the release of encapsulated drug from the pores [57].

5.2.4. Dual and multiple stimuli responsiveness
A group of researchers worked on novel glutathione and pH dual-responsive DDS by fabricating with CS, carbon dots (CDs), and HA functionalized on the surface of MSNs to generate MSN-CS@HA–CDs system that showed a better enhancement towards the controlled release and targeted delivery, which is a promising platform for cancer therapy [58]. Also, researchers from other groups have studied and developed a tri stimuli-responsive DDS to overcome the premature leakage and the instability of drug delivery. In (figure 6), the mesoporous silica was attached by multiwalled carbon nanotubes (MWCNTs) and grafted with poly(N-isopropylacrylamide–block–poly(2-(4-formylbenzoyloxy) ethyl methacrylate) through disulfide bonds to generate MWCNTs@MSN-s-s-g-PNIPAM-b-PFPEMA. These multifunctional materials encapsulated with anticancer drug Doxorubicin and attributed the pH, temperature, and reduction induced tri multi stimuli responsiveness to enhance the dynamics of drug release towards the cancer treatment [59].

The researchers have also developed a combination of redox and enzyme dual-stimuli responsive delivery system (MSN-SS-HA) using MSNs for targeted and controlled delivery of loaded drugs. The HA was attached on the surface of silica pores through disulfide linkages as HA has numerous advantages such as acting and targeting ligand, possess prolonged blood circulation, and enhancing the biocompatibility of mesoporous silica. The drug release was triggered using HA and GSH and overexpression of CD44 receptor to HCT 116 cancer cells [60].

6. Advances in biomedical applications

6.1. Therapeutic/diagnostic confront
Theragnostic is a new area of medicine which involves the combined application of disease diagnosis as well as therapy and this theragnostic paradigm makes use of principles from nanoscience and nanotechnology to unite a
radioactive agent for the diagnosis and a therapeutic drug within a single system [61]. This technology makes use of various therapeutic approaches like chemotherapy, nucleic acid delivery, hyperthermia, photodynamic, and radiation therapy joined by one of the other imaging moieties for both \textit{in vitro} and \textit{in vivo} studies. In this, the peculiar imaging probes include the MRI contrasting agents, nuclear imaging agents, and fluorescent markers widely loaded with that of other therapeutic agents to aid for their imaging and check the involving pathways, therapeutic efficacy, and mathematical kinetics models [62]. Nanomedicine is currently in an initial stage of clinical trials and development and the one pharmaceutical industry called Cristal Therapeutics is under Phase I trial for combined therapeutic agent (docetaxel) and imaging agent for positron emission tomography (PET) imaging (Zirconium-89) is known as CriPec®. This is to estimate the biodistribution and accumulation of tumors in solid tumors and for developing a best-targeted therapy [63]. Also, NBTXR3® combination of hafnium oxide NPs as a radio-enhancer to destruct the tumor employing radiation-stimulated technology is under Phase I/II trials at Nanobiotix company [64].

6.2. Photodynamic therapy (Figure 7), explains the manganese ferrite nanoparticles (MFNs) are Fenton catalysts, which are surface functionalized on mesoporous silica and loaded chlorin e6 and further capped with PEG to inhibit nonspecific protein binding and enhances the passive targeting through EPR mechanism. The hydrogen peroxide is an ample metabolite produced in a hypoxic microenvironment in the presence of MFN can counteract the oxygen loss by producing \( \text{O}_2 \) [65]. The researchers also worked on chemo responsive NPs by using MSNs surface-functionalized with 3-mercapto propyl tri methoxy silane, which spontaneously oxidized to form the disulfide linkages. On exposure to red laser irradiation and the GSH, causing the lysis of the disulfide bond and leading to drug release [66]. The chemosensitive MSNs also used for two-photon therapy applications.

6.3. Gene therapy applications
The gene therapy was introduced as an alternative to the conventional therapy to minimize the side effects and improve the stability of the drug and premature leakage where this therapy model makes use of the developed MSNs [67]. In this, the nanocarriers play an important role in any cancer therapy, and there are two different
strategies for gene delivery systems such as viral delivery and non-viral delivery systems. The viral delivery is more efficient in terms of safety concerns, immunogenicity, gene recombination, and non-specificity [68], while the non-viral delivery systems involve the cationic compounds, recombinant proteins, polymeric and inorganic NPs [69]. In recent years, the liposomes are widely used for gene transfection with the disadvantage of instability [70] and the inorganic NPs are mostly used due to the advantages like biocompatibility, surface functionalization, easy synthesis, and stability. Also, the MSNs played a greater role in gene therapy as a nanocarrier, because of its potential advantages such as tunable pore volume, surface area, ease of surface functionalization, and serving as an effective nanocarrier for gene transfection and intracellular uptake [71].

6.4. Bioimaging applications

Due to the potent advantages of MSNs, it has played a greater role in bioimaging applications since the MSNs possess a hydrophilic surface and can be very well dispersed in an aqueous solution [72]. The other main advantage is the optical transparency of MSNs supported by their smaller particle size. There are so many reports on medical imaging applications and with that concern on MSNs, the widely used imaging agents and dyes are listed as, fluorescent dyes to measure the live-cell imaging, intracellular pH values in the cytosol, and the mitochondrial trafficking [73]. The FITC and Rhodamine B isothiocyanate (RITC) is widely used imaging dyes along with mesoporous silica [74]. The upconverting NPs and QDs also play a major role in achieving the bioimaging approach [75].

6.5. PET applications

PET is a highly quantitative technique used for screening the entire body by imaging, for clinical diagnosis and pre-clinical research. The most commonly used radionucleotide is the Titanium-45 with half lifetime approximately 3.08 h [76]. For example, in a study, the $^{45}$Ti labeled to MSNs (mesoporous silica nanocarrier is an ideal platform for DDS) applied for an in vivo tumor passively targeted imaging [77].

6.6. Antimicrobial activity

Many bacterial infections are occurred by antibiotic-resistant strains and persistent biofilms, which are structured communities of bacterial cells immersed in a self-produced matrix and added to a variety of chronic infections. The decoration of NPs for antibacterial treatments and diagnosis is a potential platform to get the better of and improve the challenges of bacterial infections [78]. In that view, the silver nanoclusters are one of the most efficient antibacterial agents and because of their size, shape, and surface charges they can hinder the silver oxidization and finally end up in the particle aggregation and prevent this, they are conjugated with that of mesoporous silica [79]. In a study, for example, Liu et al developed a silver nanocluster capped with MSNs proved to be efficient in sustained release of silver ions and further, the developed nanoclusters are served to be an ideal platform for microbial infections [80].

7. Biodegradation, biocompatibility, and toxicity of MSNs

MSNs have many advantages in the drug delivery platform and to empower these materials for other biomedical applications and to inhibit the long-term bioaccumulation, the biodegradability of Si NPs can be fine-tuned by
modulating the physicochemical parameters [81]. The toxicity and safety of MSNs is a major issue and is due to the high surface to volume ratio compared to other counteracts. The biocompatibility of any nanocarrier is the most important property to be checked in the pharmaceutical industry and to make sure that this product does not assemble in the human body for longer duration causing severe biological effects [82]. Like that, liposomes have found to be used as a nanocarrier with an efficient loading of both hydrophobic and hydrophilic drugs, and similar to that, any nanocarrier should be safe and biocompatible. The other FDA approved polymer used for DDS is poly (lactic-co-glycolic acid) (PLGA) and is one of the renewed based carriers. Although these polymer experiments proved to be for human use and still, there are few disadvantageous to move forward such as controlled drug release, stability, and difficulty to cross through a few of the barriers as a nanocarrier [83].

8. Conclusions and future perspectives

In this review, we have covered some important aspects of MSNs and their suitability as sustainable materials for the development of smart DDS. From the analysis, we observed that the MSNs, because of their fully tunable surface properties, pore size and volume, high loading capacity, and high surface area are making them a potential candidate for DDS. By playing with the molar composition of reactants and reaction conditions, the mesoporous silica with different particle sizes, shape, and pore volume can be formed. Also, by fine-tuning the surface area, pore size, and pore volume, one can control the total loading capacity and drug release. The MSNs have many biological applications such as drug delivery for cancer treatment, bioimaging, biosensors, catalysis, and photodynamic therapy. By anchoring the Si NPs with linker moiety, the surface functionalization can be used to deliver the cargo to the tissue-specific tumor regarding the internal and external stimuli. This type of nanocarrier prevents premature release leakage and the biodistribution depends upon the route of administration. The significance of this nanocarrier is the long-term usage and is mere unanswered and because of this lacuna, the MSNs serve as a versatile nanocarrier to stay back without stepping into the clinical side.

There are many issues to overcome in this concern like the amount of drug release from the nanocarrier, the bioactivity of drug-loaded mesopores, unspecific protein adsorption in the circulation. Also, the administration of insulin through oral is a major challenge to overcome for decades and so the future MSNs should aim to overcome this issue. The size of the nanocarrier is also a major reason for preventing the penetration of the cell membrane. The oral absorption of macromolecules, proteins, peptides is entirely based on the surface functionalization of Si NPs to absorb in the gastrointestinal tract and to deliver in the targeted location. Therefore, the future advancements in MSNs in nanomedicine is still had few hindrances due to its pore size as it plays a major role in the biological applications. Hence there is a strong need to develop simple synthesis procedures to produce monodispersed spherical small NPs (2–3 nm) with larger pores (>5 nm) that can be of special interest in the biomedical sector. In the case of macromolecules, proteins, peptides, and nucleic acids, the prerequisite is to have larger pores to deliver efficiently for the gene delivery applications. The other factors which are in major concern are clinical development about the relationship between in vitro and in vivo studies. In that way, the laboratory in vitro results should be transformed in to in vivo biodistribution studies, closely related to patient requirements. Finally, enough scientific work to be explored to achieve the major challenges and to successfully transform into a new drug delivery platform in clinical practice and at last towards hitting the market as the healthcare products.

Acknowledgments

The authors would like to acknowledge the financial support provided by a Research University grant from University of Malaya (RU001-2020).

Competing interests

The authors declare no conflict of interest.

ORCID iDs

Suresh Sagadevan https://orcid.org/0000-0003-0393-7344
Anita Lett J https://orcid.org/0000-0003-2917-4277
Is Fatimah https://orcid.org/0000-0001-5551-6563
References

[1] Agmon C and Yoshitake S 2017 Thermosensitive block copolymer ([PNIPAM]−b−[Glycine]) thin film as protective layer for drug loaded mesoporous silica nanoparticles Mater. Res. Exp. 4 105306

[2] Kankaala R K et al 2020 Nanoarchitectured structure and surface biofunctionality of mesoporous silica nanoparticles Adv. Mater. 32 1907035

[3] Li Z, Zhang Y and Feng N 2019 Mesoporous silica nanoparticles: synthesis, classification, drug loading, pharmacokinetics, biocompatibility, and application in drug delivery Expert Opin. Drug Deliv. 16 219–37

[4] Cho B 2019 Preparation of hollow porous silica nanospheres and their potential for glucagon-like peptide-1 delivery Mater. Res. Exp. 6 045016

[5] Silva C R P, Ferreira F R, Welber G D, Silva A O S, Abreu F C and Fonseca R J S 2017 Encapsulation of mangiferin in ordered mesoporous silica type SBA-15: synthesis and characterization Mater. Res. Exp. 4 065402

[6] Al F, Zhao G, Lv W and Lin J 2020 Facile synthesis of cetyltrimethylammonium bromide-loaded mesoporous silica nanoparticles for efficient inhibition of hepatocellular carcinoma cell proliferation Mater. Exp. 7 085008

[7] Gustafsson H H, Holt-Casper D, Gränder D W and Chandhedi H 2015 Nanoparticle uptake: the phagocyte problem Nano Today 10 487–510

[8] Albayrak S H M and Deveci P 2019 pH and GSH dual responsive smart silica nanocarrier for doxorubicin delivery Mater. Exp. 6 065705

[9] Hoshyar N, Gray S, Han H and Bao G 2016 The effect of nanoparticle size on in vivo pharmacokinetics and cellular interaction Nanomod. (Lond.) 11 673–92

[10] Foroozandeh P and Aziz A A 2018 Insight into cellular uptake and intracellular trafficking of nanoparticles Nanoscale Res. Lett. 13 339

[11] Shang L, Nienhaus K and Nienhaus G U 2014 Engineered nanoparticles interacting with cells: size matters J. Nanobiotechnology 12 5

[12] Behzadi S, Serpooshan V, Tao W, Hamaly M A, Alkawareek M Y, Dreaden E C, Brown D, Alkilany A M, Farokhzad O C and Mahmoudi M 2017 Cellular intake of nanoparticles: journey inside the cell Chem. Soc. Rev. 46 4218–44

[13] Lin J T, Wang C, Zhao Y and Wan G H 2014 Mesoporous silica nanoparticles with controlled loading of cationic dendrimer for gene delivery Mater. Res. Exp. 1 035403

[14] Halamoda-Kenzoufi B, Ceridono M, Colpo P, Valseia A, Urban P, Ojeda-Jiménez I, Gloria S, Gilliland D, Rossi F and Kinsner-Ovsakainen A 2015 Dispersion behaviour of silica nanoparticles in biological media and its influence on cellular uptake PLoS One 10 e0141593

[15] Colilla M, Manzano M and Vallet-Regi M 2008 Recent advances in ceramic implants as drug delivery systems for biomedical applications Int. J. Nanomedicine 3 403–14

[16] Chaudhury V and Sharma S 2017 An overview of ordered mesoporous material SBA-15: synthesis, functionalization and application in oxidation reactions J. Funct. Mater. 24 741–9

[17] Carafa M and Marianucci C 2019 Smart Nanovesicles for Drug Targeting and Delivery (Basel: MDPI Publisher) 147 MDPI AG978-3-03897-895-4 3–03897–895–4Smart Nanovesicles for Drug Targeting and Delivery Pharmaceuticals978-3-03897–895–4

[18] Borenbard M A, Oben D T, Durand G G, Taylor P G, Bruce J J, Bassindale A R and Taylor A 2018 Influence of the initial chemical conditions on the rational design of silica particles J. Sol-Gel Sci. Technol. 88 430–41

[19] Bhattacharyya S, Selog S and Saboungi M-L 2006 Recent progress in the synthesis and selected applications of MCM-41: a short review J. Exp. Nanosci. 1 375–95

[20] Seo J W, Lee W J, Nam S, Ryu H, Kim J N and Ko C H 2015 Mesoporous structure control of silica in room-temperature synthesis under basic conditions J. Nanomater. 2015 149634

[21] Fujimoto Y, Shimojima A and Kuroda K 2006 Surfactant-free synthesis of lamellar and wormhole-like silica mesostructures by using 1-alklynyltrimethoxysilanes J. Mater. Chem. 16 986–94

[22] Li Z, Barnes J C, Bosoy A, Stoddart J F and Zink J I 2012 Mesoporous silica nanoparticles in biomedical applications Chem. Soc. Rev. 41 2590–605

[23] Alberti S, Soler-Illia G J A and Azzaroni O 2015 Gated supramolecular chemistry in hybrid mesoporous silica nanoarchitectures: controlled delivery and molecular transport in response to chemical, physical and biological stimuli Chem. Commun. (Camb.) 51 6030–73

[24] Heinz H et al 2017 Nanoparticle decoration with surfactants: molecular interactions, assembly, and applications Surf. Sci. Rep. 72 1–58

[25] Quinn J F, Whittaker M R and Davis T P 2017 Glutathione responsive polymers and their application in drug delivery systems Polym. Chem. 8 97–126

[26] Wen J, Yang K, Liu F, Li H, Xu Y and Sun S 2017 Diverse gatekeepers for mesoporous silica nanoparticle based drug delivery systems Chem. Soc. Rev. 46 6024–45

[27] Natarajan S K and Selvaraj S 2014 Mesoporous silica nanoparticles: importance of surface modifications and its role in drug delivery RSC Adv. 4 14328–34

[28] Su H, Price C A, H, Jing L, Tian Q, Liu J and Qian K 2019 Janus particles: design, preparation, and biomedical applications Mater. Today 24 100033

[29] Barandeh F, Nguyen P-L, Kumar R, Iacobucci G J, Kuznicki M L, Kosterman A, Bergey E J, Prasad P N and Gunawardena S 2012 Organically modified silica nanoparticles are biocompatible and can be targeted to neurons in vivo PLoS One 7 1–5

[30] Taran E, Demirci S and Caykara T 2010 Synthesis of thermo-responsive poly(N-isopropylacrylamide) brush on silicon wafer surface via atomic transfer radical polymerization Thin Solid Films 518 5890–4

[31] Chowdhury P, Nagesh P K B, Khan S, Hafeez B B, Chauhan S C, Jaggi M and Yallapu M M 2018 Development of polyvinylpyrrolidone / polyacrylic acid self-assemblies for breast cancer Acta Pharm. Sin. B 8 602–14

[32] Ali I, Afshehal M, Scotti L, Tullius Scotti M, Tsal S-T, Yu R-S, Hsieh M F and Chen J-C 2020 Progress in polymeric nano-medicines for therapeutic cancer treatment Polymers (Basel) 12 1–32

[33] Zaharudin N S, I, F D M, Ahmad H R, Abdul M B and Jumbri K 2020 Functionalized mesoporous silica nanoparticles templated by pyridinium ionic liquid for hydrophilic and hydrophobic drug release application J. Saudi Chem. Soc. 24 289–302

[34] Musso G E, Bottiniel E, Celli L, Magnacca G and Berlier G 2015 Influence of surface functionalization on the hydrophilic character of mesoporous silica nanoparticles Phys. Chem. Chem. Phys. 17 13882–94

[35] Merhari I 2009 Hybrid Nanocomposites for Nanotechnology: Electronic, Optical, Magnetic and Biomedical Applications (US: Springer)

[36] Wu S-H, Mou C-Y and Lin H-P 2013 Synthesis of mesoporous silica nanoparticles Chem. Soc. Rev. 42 3862–75

[37] Santhi Moothy M, Bharathi Raj S, Manivasagam P, Lee K D and Oh J 2017 Synthesis of surface capped mesoporous silica nanoparticles for pH-stimuli responsive drug delivery applications Med. Chem. Commun. 8 1797–805
[38] Muhammad F, Guo M, Qi W, Sun F, Wang A, Gao Y and Zhu G 2011 pH-triggered controlled drug release from mesoporous silica nanoparticles via intracellular dissolution of ZnO nanorods J. Am. Chem. Soc. 133 8778–81

[39] Chen T, Wu W, Xiao H, Chen Y, Chen M and Li J 2016 Intelligent drug delivery system based on mesoporous silica nanoparticles coated with an ultra-pH-sensitive gatekeeper and poly(ethylene glycol) ACS Macro Lett. 5 55–8

[40] Liu J, Luo Z, Zhang J, Luo T, Zhou J, Zhao X and Cai T 2016 Hollow mesoporous silica nanoparticles facilitated drug delivery via cascade pH stimuli in tumor microenvironment for tumor therapy Biomaterials 83 51–63

[41] Murugan B, Narashimhan Ramana L, Gandhi S, Sethuraman S and Krishnan U M 2013 Engineered chemoswitchable mesoporous silica for tumor-specific cytotoxicity J. Mater. Chem. B 1 3494–9

[42] Chen X, Sun H, Hu J, Han X, Liu H and Hu Y 2017 Transferrin gated mesoporous silica nanoparticles for redox-responsive and targeted drug delivery Colloids Surf. B. Biointerfaces 152 77–84

[43] Zhong L, Kaiyong C, Yan H, Li Z, Peng L, Lin D and WeiHu Y Mesoporous silica nanoparticles end-capped with collagen: redox-responsive nanoperoxo sorbers for targeted drug delivery Angew. Chemie Int. Ed. 50 640–3

[44] Li Z-Y, Hu J-J, Xu Q, Chen S, Jia H-Z, Sun Y-X, Zhao R-X and Zhang X-Z 2015 A redox-responsive drug delivery system based on RGD containing peptide-capped mesoporous silica nanoparticles J. Mater. Chem. B 3 39–44

[45] Liu Y, Ding X, Li L, Luo Z, Hu Y, Liu J, Dai L, Zhou J, Hou C and Cai K 2015 Enzyme responsive drug delivery system based on mesoporous silica nanoparticles for tumor therapy in vivo Nanotechnology 26 145102

[46] Naz S, Wang M, Han Y, Hu B, Teng L, Zhou J, Zhang H and Chen J 2019 Enzyme-responsive mesoporous silica nanoparticles for tumor cells and mitochondria multistage-targeted drug delivery Int. J. Nanomedicine 14 2533–42

[47] Cai D, Han C, Liu C, Ma X, Qian J, Zhou Z, Li Y, Sun Y, Zhang C and Zhu W 2020 Chitosan-capped enzyme-responsive hollow mesoporous silica nanoplatforms for colon-specific drug delivery Nanoscale Res. Lett. 15 123

[48] Gao Y, Xiao Y, Mao K, Qin X, Zhang Y, Li D, Zhang Y, Li J, Wan H and He S 2020 Thermoresponsive polymer-encapsulated hollow mesoporous silica nanoparticles and their application in insecticide delivery Chem. Eng. J. 383 123169

[49] Cho I-H, Shim M K, Jung B, Jang E H, Park M-J, Kang H C and Kim J-H 2017 Heat shock responsive drug delivery system based on mesoporous silica nanoparticles coated with temperature sensitive gatekeeper Microporous Mesoporous Mater. 253 96–101

[50] Peralta M E, Jadhav S A, Magnacca G, Scaralone D, Márteř D O, Parolo M E and Carlos L 2019 Synthesis and in vitro testing of thermoresponsive polymer-grafted core–shell magnetic mesoporous silica nanoparticles for efficient controlled and targeted drug delivery J. Colloid Interface Sci. 544 198–205

[51] Shi Z, Yang C, Li R and Ruan L 2020 Microwave thermal-triggered drug delivery using thermosensitive peptide-coated core–shell mesoporous silica nanoparticles J. Mater. Chem. B 5 6118–29

[52] Manzano M and Vallet-Regí M 2019 Ultrasonic responsive mesoporous silica nanoparticles for biomedical applications Chem. Commun. 55 2731–40

[53] Vallet-Regí M, Coilla M, Iquieiro-Barba I and Manzano M 2017 Mesoporous silica nanoparticles for drug delivery: current insights Molecules 23 1–22

[54] Cheng C-A, Chen W, Zhang L, Wu H H and Zink J 2019 A responsive mesoporous silica platform for magnetic resonance imaging-guided high-intensity focused ultrasound-stimulated cargo delivery with controllable location, time, and dose J. Am. Chem. Soc. 141 17670–84

[55] Picchetti P, DiMarco B N, Travaglini L, Zhang Y, Ortega-Liebana M C and De Cola L 2020 Breaking with light: stimuli-responsive mesoporous organosilica particles Chem. Mater. 32 592–9

[56] Zhao T, Chen L, Li Q and Li X 2018 Near-infrared light triggered drug release from mesoporous silica nanoparticles J. Mater. Chem. B 6 7112–21

[57] Khammohamadi Chenab K, Sohrabi B and Rahmanzadeh A 2019 Superhydrophobicity: advanced biological and biomedical applications Biomater. Sci. 7 3110–37

[58] Chen Y, Wang Y-F, He L, Wang Z, Shen Y-Q, Cong H-L and Yu B 2019 Redox and pH double stimulus-responsive mesoporous silica nanoparticles for drug delivery Ferroelectrics 549 1–11

[59] Zhang R-Q, Liu Z-Q, Luo Y-L, Xu F and Chen Y-S 2019 Tri-stimuli responsive carbon nanotubes covered by mesoporous silica graft copolymer multifunctional materials for intracerebral drug delivery J. Ind. Eng. Chem. 80 431–43

[60] Zhao Q, Liu J, Zhu W, Sun C, Di D, Zhang Y, Wang F, Wang Z and Wang S 2015 Dual-stimuli responsive hyaluronic acid-conjugated mesoporous silica for targeted delivery to CD44-overexpressing cancer cells Acta Biomater. 23 147–56

[61] Pene F, Courtois E, Cazin A and Mira J-P 2009 Toward theragnostics II. Curr. Med. Chem. 16 3501–8

[62] Farkas E and Ryadnov M 2012 Amino Acids, Peptides and Proteins 37 (London: Royal Society of Chemistry) 122–90978-1-84973-585-8

[63] van der Meel R, Sulheim E, Shi Y, Kiessling F, Mulder W J M and Lammers T 2019 Smart cancer nanomedicine Nat. Nanotechnol. 14 1007–17

[64] Pottier A, Borghi E and Levy L 2014 New use of metals as nanosized radioenhancers Anticancer Res. 34 443–53

[65] Kim J, Cho H R, Jeon H, Kim D, Song C, Lee N, Choi S H and Hyeon T 2017 Continuous O2-evolving MnFe2O4 nanoparticle-anchored mesoporous silica nanoparticles for efficient photodynamic therapy in hypoxic cancer J. Am. Chem. Soc. 139 10992–5

[66] Croissant J G et al 2015 Synthesis of dsf-fulfide-based biodegradable bridged silsesquioxane nanoparticles for two-photon imaging and therapy of cancer cells Chem. Commun. (Camb.) 51 12324–7

[67] Zarei H, Oskuee R K, Hanafi-Boid M Y, Gholami L, Ansari L and Malaekh-Nikouei B 2019 Enhanced gene delivery by polyethyleneimine coated mesoporous silica nanoparticles Pharm. Dev. Technol. 24 127–32

[68] Sung Y K and Kim S W 2019 Recent advances in the development of gene delivery systems Biomater. Res. 23 8

[69] Rai R, Alwani S and Badae I 2019 Polymeric nanoparticles in gene therapy: new avenues of design and optimization for delivery applications Polymers (Basel) 11 1–33

[70] Safarri M, Moghimi H R and Dass C R 2016 Barriers to liposomal gene delivery: from application site to the target Iran. J. Pharm. Res. 15 3–17

[71] Kesse S et al 2019 Mesoporous silica nanomaterials: versatile nanocarriers for cancer theranostics and drug and gene delivery Pharmaceutics 11 1–26

[72] Bonelli B, Freyra F S, Rosetti I and Sethi R 2020 Nanomaterials for the Detection and Removal of Wastewater Pollutants; Micro and Nano Technologies (Amsterdam: Elsevier Science) 3 47–69978-0-12-818489-9

[73] Flak D, Przysecka L, Nowaczyk G, Scheibe B, Kościński M, Jesionowski T and Jurga S 2018 GQDs-MSNs nanocomposite nanoparticles for simultaneous intracellular drug delivery and fluorescent imaging J. Nanoparticle Res. an Interdiscip. Forum Nanoscale Sci. Technol. 20 306

[74] Grumezescu A and Holban A M 2019 Materials for Biomedical Engineering: Bioactive Materials for Antimicrobial, Anticancer, and Gene Therapy (Amsterdam: Elsevier Science) 1-6 12119780128184363
[75] Yao J, Huang C, Liu C and Yang M 2020 Upconversion luminescence nanomaterials: a versatile platform for imaging, sensing, and therapy Talanta 208 120157
[76] Chaple I, Thiele K, Thach D, Koller A, Boros E and Lapi S 2020 Development of titanium-45 for PET imaging of PSMA+ prostate cancer J. Nucl. Med. 61 1111
[77] Chen F, Valdivinos H F, Hernandez R, Goel S, Barnhart T E and Cai W 2017 Intrinsic radiolabeling of Titanium-45 using mesoporous silica nanoparticles Acta Pharmacol. Sin. 38 907–13
[78] Vallet-Regí M, González B and Izquierdo-Barba I 2019 Nanomaterials as promising alternative in the infection treatment Int. J. Mol. Sci. 20 1–28
[79] Shaikh S, Nazam N, Rizvi S M D, Ahmad K, Baig M H, Lee E J and Choi I 2019 Mechanistic insights into the antimicrobial actions of metallic nanoparticles and their implications for multidrug resistance Int. J. Mol. Sci. 20 1–15
[80] Liu J, Li S, Fang Y and Zhu Z 2019 Boosting antibacterial activity with mesoporous silica nanoparticles supported silver nanoclusters J. Colloid Interface Sci. 555 470–9
[81] Fu C, Liu T, Li L, Liu H, Chen D and Tang F 2013 The absorption, distribution, excretion and toxicity of mesoporous silica nanoparticles in mice following different exposure routes Biomaterials 34 2565–75
[82] Li X, Wang L, Fan Y, Feng Q and Cui F 2012 Biocompatibility and toxicity of nanoparticles and nanotubes J. Nanomater. 2012 548389
[83] Elmowafy E M, Tiboni M and Soliman M E 2019 Biocompatibility, biodegradation and biomedical applications of poly(lactic acid)/poly(lactic-co-glycolic acid) micro and nanoparticles J. Pharm. Investig. 49 547–80