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Mesoporous Silica Nanoparticles as Versatile carrier platforms in therapeutic applications

Z.Jafari[a], S.Honarmand[a], F.Rahimi[a], A.Akbari[a,b], S.Akbari [a,b*]

[a] *NanoSciTec GmbH, Rosamunden Str.9, Munich, 81827, Germany*
[b] *GreenNanoTech Kft, Király Utca 80, Budapest, 1068, Hungary*

Abstract

The utilization of nanotechnology is one of the fast-growing scientific discoveries that significantly affect our daily lives, especially its application in nanomedicine and targeted gene/drug delivery. The pharmaceutical researchers aim to design new carrier platforms to decrease the unwanted side effects of common medicines and the desired control over therapeutic agent distribution in the targeted part of the body. The new systems must have some advantages over the traditional medicines, such as improving the stability, uptake, therapeutic concentration, and long-term release of the drug into the target tissue. Among the extended material list used as nanocarriers for drug delivery purposes, mesoporous silica nanoparticles (MSNs) have attracted considerable attention in this regard. The high porosity of mesoporous silica materials allows different sizes of biologically active molecules (BAM) to settle in their cavities. As a result, a wide range of BAM, such as small molecules, proteins, deoxyribonucleic acids (DNAs), and ribonucleic acids (RNAs), are loaded into the MSNs cavities for therapeutic purposes. Here, we review recent researches on MSNs applications in gene/ drug delivery in various diseases.

Keywords: Mesoporous Silica Nanoparticles, Drug Delivery, Gene Delivery, Cancer, Therapeutic Agents

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*Corresponding author: S. Akbari. Tel.: +49-151-664-32106 *E-mail address*: somayeh.akbari@nanoscitec.com

1. Introduction

Cancer therapy methods are currently at risk of damaging normal tissues or incomplete eradication of the cancerous cells. These methods including surgery, irradiation, and chemotherapy have many severe side effects that can affect normal human life. Therefore, functionalized materials have been designed to overcome these unwanted problems and enhance therapeutic efficiency. For example, gene delivery uses foreign nucleic acids into the target cells for therapeutic purposes. Viral and non-viral carriers are utilized in gene delivery methods. Non-viral vectors compared to viral vectors are cost-effective with more excellent reproducibility that does not eliminate the genes to convey and gene delivery cargoes [1]. Nanoparticles (NPs) entitled non-viral vectors have been introduced as favorable gene carriers with the ability to encapsulate and quickly circulate in the bloodstream [2]. They are attractive for pharmaceutical applications since their pharmacokinetics can be tuned without affecting the genes' activity [3]. Various therapeutic materials, including plasmid DNAs (pDNAs), small interfering RNAs (siRNAs), and drugs could be transferred into the target cells via MSNs to treat certain diseases, shown in Figure 1.

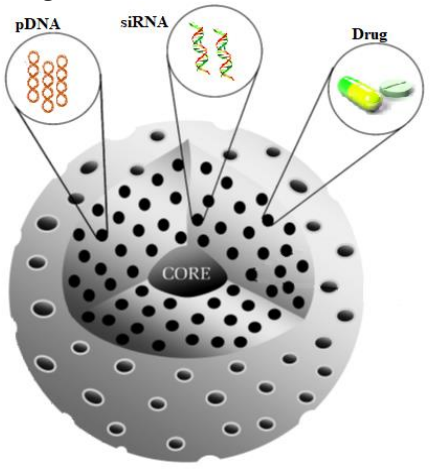

Figure 1. The general features of MSNs for nucleic acid and drug delivery. [4]

Inorganic nanoparticles are good candidates for gene delivery purposes. Properties of inorganic nanoparticles, such as easy preparation, suitable tailoring of their functionality, potential capability for targeted delivery, good biocompatibility, and storage stability, introduced them as a versatile cellular delivery components. Different inorganic nanoparticles used for gene delivery from gold nano particles to quantum dots. Among the inorganic nanoparticles, Mesoporous silica nanoparticles (MSN) with sizes about 10-20 nm are one of the outstanding candidates for various biomedical applications, especially in gene deliveries due to their interesting properties, such as high porosity, easy preparation methods, remarkable biocompatibility, large surface area (up to 1000 m^2/g), and suitable pore volume (from 5 to 13 nm). Furthermore, MSNs could be internalized into living cells without any cytotoxicity [5, 6]. The first report of MSN synthesis was in 1992 by Beck et.al; and was the initiation for some synthesis methods using silica sources [7]. MCM-41, a subtype of MSNs, can be synthesized through a simple procedure using only four ingredients: a silicate source, a template molecule, an acid, and water. Although sodium silicate and tetraethylorthosilicate (TEOS) are two important silicate sources in MSN synthesis, some natural sources like wheat stem ash are used and mesoporous MCM-41 has been produced with micrometer-scaled rope morphology [8]. Synthesis of MSNs carried out by using cationic surfactant micelle templates that act as surface directing agents and polymerizing silica components due to electrostatic interactions as shown in Figure 2. The silica type in wheat stem ash is suitable for the synthesis of MCM-41 because it could easily dissolve in sodium hydroxide and forms sodium silicate. The template molecule could be selected among various surfactants such as cetyltrimethylammonium bromide (CTAB), and sodium dodecyl sulfate (SDS). Stucky et al, investigated the influence of surfactant on the structure of the obtained MSNs [9].

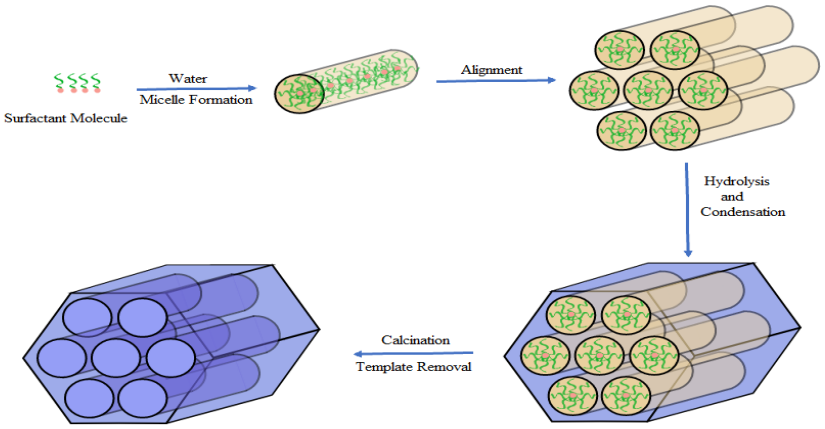

Figure 2. Schematic representation of the formation mechanism of MCM-41.

The addition of acid is essential to make progression in the synthesis of mesoporous silica materials. Acetic acid, sulphuric acid, and hydrochloric acid are exapmles of the common acids used in MSN preparation. After preparing the organic template molecule, the surfactant molecule could be removed from the silicate lattice by one of the two major pathways, calcination and washing. In the calcination, the organic template burnt out without integrity of silicate structure. The high temperature could cause a significant shrinkage in the mesoporous silica lattice, and to avoid this unwanted effect, washing could be used for template removal. Boiling HCl/ethanol mixtures is one of the best mixtures used in template washing and it caused less lattice shrinkage than the calcination method. The size and morphology of MSNs are influenced by several factors including the rate of hydrolysis, condensation of silica source, and level of interaction between assembled template and silica polymer. In addition, based on reports, the stirring rate has a key role in the particle size in the way that the slow rate led to the production of long fibers, whereas the fine powder formed by fast stirring [10]. Furthermore, the MSNs pore sizes are controlled by the amount of silica source, surfactant, and packing capacity of surfactant [11]. The surface area has also influenced the gene/drug delivery capability of MSNs and is closely related to the maximum loading of the cargo [12]. The first report for applying mesoporous silica material in drug delivery was in 2001, in which MCM-41 has been used as a carrier platform [13]. MSNs with specific textural properties that enhanced drug loading inside the pore and channels attracted attention in this area [14]. The ability of MSNs in cargo adsorption and release could be modified through superficial organic groups. MSNs have enormous silanol groups on their surface, and they could interact with organic groups to make grafting organic silanes. These functional groups can link to the gene/drug molecules through ionic bonds or ester groups [15]. In order to increase silica affinity towards nucleic acid agents such as DNA, short amine silane moieties have been used extensively [16].

2. Synthesis of Mesoporous Silica Nanoparticle

Several methods have been used for synthesis of mesoporous silica nanoparticles. The first step to obtain MSNs is generating silica by a sol-gel process followed by applying a surfactant to direct the final structure to the MSNs and finally modifying the reaction condition to achieve spherical nanoparticles. Sol-gel is one of the most favorite methods that is wildly used for producing MSNs from silicon precursors through hydrolyses and condensation in presence of an acidic or a basic catalysis. In this method, surfactant molecules act as a template for the final structure. The condensation of these templates led to preparation of a colloidal solution (sol) and after manipulation of the reaction condition, the gel gradually forms from discrete particles. Templating method is used to produce hollow porous MSNs in which a structure-directing agent (template) has been used for obtaining a hollow porous structure. Two kinds of materials could be used in this procedure including soft and hard matter templating named endotemplate and exotemplate, respectively. A surfactant is used in soft matter templating without application of any hard template solid while in exotemplate method, a porous solid is used as a template, and the hollow spaces are filled using an inorganic precursor, which is then transformed under proper pH and temperature [17]. Mobil Composition of Matter No. 41 (MCM-41) is one of the highly porous silica based materials, which can be synthesized through the microwave-assisted method

in a short time and using C-TAB as a template directing material. The application of organo-silica-surfactant material led to preparation of hexagonal mesostructure with short-range symmetry and nano materials with abput 30 nm in diameter that have uniform morphology [18]. Hollow type mesoporous silica nanoparticles (HMSNs) are another type of MSNs that can be synthesized without any template reagents. The heterogeneous hollow type MSNs containing different inorganic nanocrystals such as Au and Fe_3O_4 nanoparticles as the core and mesoporous silica as the shell could be prepared with this method [19]. Therefore, the characteristic of HMSNs are a hollow core-mesoporous shell structure. HMSNs are excellent platforms for active agents for the therapeutic applications owing to the extraordinary drug loading capacity (> 1 g drug/1 g silica) and easy surface functionalization and since they can efficiently enter into cancer cells, they can overcome the failure of conventional therapeutic agents [20]. HMSN have been prepared by tetraethyl orthosilicate (TEOS) as silica source hexadecyl trimethyl ammonium chloride (CTAC) as templating agent for co-delivery of Sorafenib and CRISPR/Cas9 for cancer treatment by gene−chemo-combination therapy [21]. The difference between MSNs and HMSNs is that the HMSNs possess large hollow interiors that can storage of more cargos, therefore they can present highly promising potentials as a delivery platform. HMSNs modified with poly (2-(diethylamino) ethyl methacrylate) as a pH-sensitive cap have been synthesized in which protonated polymer chains would adopt extended conformation, allowing the opening of mesopores for the cargo release [22]. Generally, tunability of MSNs causes their extended use in gene delivery and gene silencing and investigation of the influence of the carrier properties on the gene-silencing efficacy. Three-dimensional dendritic mesoporous silica nanospheres are kind of novel uniform monodispersed MSNs that have been synthesized using oil−water biphase stratification approach by Zhao et al. [23]. The benefit of this synthesis procedure is the average pore size of each generation for the 3D-dendritic MSNSs can be tuned independently by changing hydrophobic solvents as well as changing the concentration of silica source in the upper oil phase. The average pore size can be adjusted from 2.8 to 13 nm and the thickness of each generation can be tuned from ∼5 to 180 nm depend open the reaction time and amount of silica source as well. In this approach the reaction, take place in the water and oil interface so the control of the assembly is convenient due to the changing or adding reactants in each phase without disturbing the interface. Tetraethyl orthosilicate (TEOS) solution in a hydrophobic organic solvent forms the upper oil phase while the lower aqueous phase is an aqueous solution combined by cationic cetyltrimethylammonium chloride (CTAC) as a template and organic base triethanolamine (TEA) as a catalyst as shown in Figure 3. The 3D-dendritic MSNs could be biodegraded in the simulated body fluid very fast and the biodegradation process completed entirely in 24 h that is very rapid in comparison with other MSNs. Furthermore, the degradation of 3D dendritic MSNs undergoes a two-stage process in the way that the first stage is rapid degradation for the outside second-generation shells. The nanoparticles lost their silica shells and seemly returns to the first generation in about 12 h and then the rest nanocarriers show a slow degradation rate. The results show that the hierarchical mesostructure have a multistage hierarchical degradation behavior due to their unique structure.

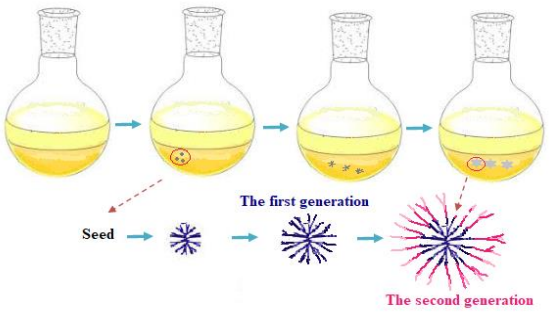

Figure 3. Nucleation process and formation of the second generation of the 3D-dendritic MSNSs. [6]

The synthesis of orderly curled silica nanosheets (OCSNs) with macromolecular loading pores and its use as a carrier platform have been reported by Lu et al. [24]. Hierarchically silica nanomaterials with large superficial channels can concurrently house large guest molecules like siRNA and chemotherapeutic drugs. The hydrophobic organic solvents form oil@water micelles in a solution with high concentrations of CTAB and alkali that act as mesoscaled templates to generate silica nanomaterials with large pores. OCSNs with an orderly curled sheet-like morphology, a uniform diameter of ∼42 nm, and large pores (∼13.4 nm) are like a small “spitball” with orderly connected channels. The synthesis mechanism of OCSNs is based on the oil/water bi-phase reaction system like the method of synthesis of 3D-dendritic MSNSs. As it has shown in Figure 4, by adding the mixture of cyclohexane and TEOS into the aqueous phase, a curled lamellar was formed and then a “frizzy-paper” intermediate

continued to grow to become a "crumpled paper" with more wrinkles and pores. After a while, the "paper" further folded into a structure with size expansion and more crumpled channels, and finally formed OCSNs. Furthermore, OCSNs have good biocompatibility due to the reduction of Si−OH groups in the special curled structure. It is worth to mention that the degradation of silica in aqueous media take place in three steps including hydration, hydrolysis, and ion-exchange [25]. In the first step, water molecules are absorbed into the Si-O-Si framework and then this network hydrolysis to form Si-OH moieties which is removed by OH^- nucleophilic attack in the form of $Si(OH)_4$. The final products of biodegradation of MSNs are nontoxic and can diffuse into the blood stream or the immune system to be eliminated out through urine. The different structures based of MSNs have been applied in gene delivery systems in order to enhance the treatment ability and due to their biodegradability. Here, we focused on the application of MSNs in treatment of different disease in different part of the human body and how the MSNs based therapeutic agents work in gene delivery.

3. Application of MSNs in eye disease therapy

Anatomically, the eye can broadly divide into two segments including anterior and posterior. The anterior segment consists of the cornea, iris, ciliary body, and lens, and the posterior segment of the eye includes the vitreous humor, retina, choroid, and optic nerve. As a result of the unique anatomy and physiology of the eye as well as the various barriers protecting the eye ocular drug delivery is a challenging issue [26, 27]. Topical administration is utilized to treat anterior segment diseases. In the preocular space, due to tearing clearance and blinking the bioavailability of topical ophthalmic drugs is highly limited [27, 28]. Sustained release of drug, which extends the period of drug release duration, can be an effective strategy to enhance drug delivery efficacy to the eye. The hollow structure of MSNs provides a high surface area and high pore volume to absorb and encapsulate relatively large amounts of the drug. Therefore, being loaded in the mesopores, the drugs could be released in a sustained manner.

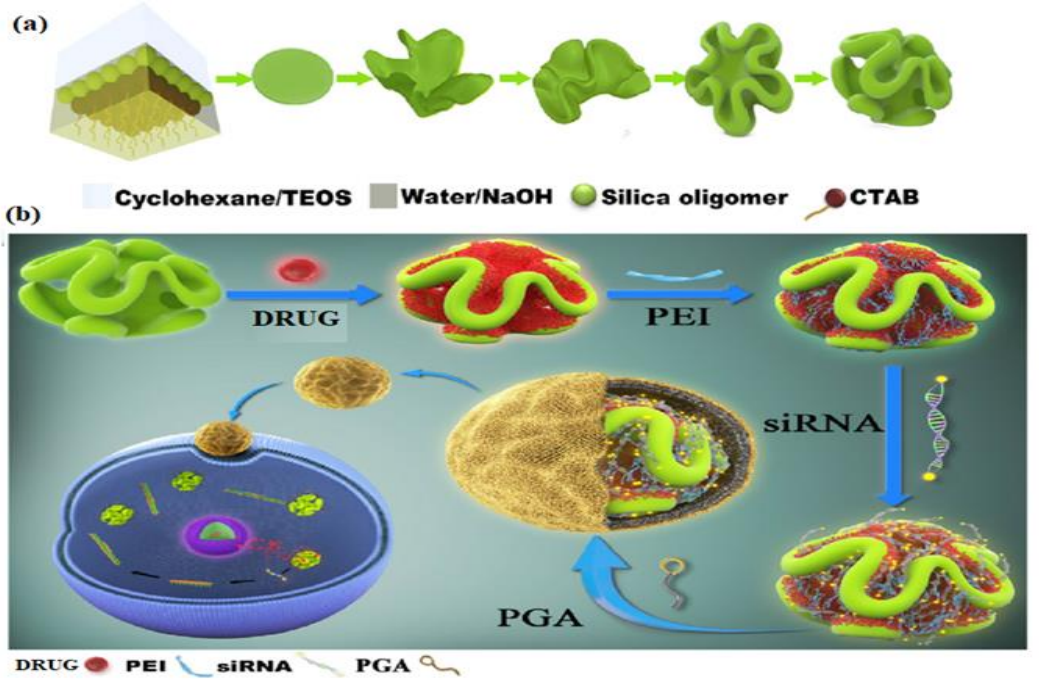

Figure 4. (a) Schematic illustration of the silica formation from a lamellar at the initial stage to the final structure of the orderly curled nanosheets. (b) the targeted delivery of siRNA and drug using OCSNs to kill the drug-resistant cancer cells, including the orderly ligation of drug, PEI, siRNA, and PGA to the surface of the silica, and the killing effects of these OCSNs on drug resistant cancer cells. [24]

On the other hand, applying ophthalmic drugs in conjunction with a mucoadhesive nanocarrier is another way to solve the problem of low drug delivery efficacy in preocular space. Functionalized mesoporous silica nanoparticles with organic capping agents or functional groups like amine can be used as delivery carriers to extend the drug release duration [29-31]. An amino-functionalized and gelatin-functionalized mesoporous silica (MS) was used for topical delivery of brimonidine and pilocarpine -the glaucoma drugs- respectively, to the eye. The presence of amino and hydroxyl groups on the surface of these carriers allows them to form an ionic complex and hydrogen bonds with the mucin, respectively. This mucoadhesive property prolongs drug residence time at the preocular region and improves the ocular bioavailability of drugs. Both mentioned research works reported that the ocular bioavailability of drugs was successfully increased and the intraocular pressure (IOP) which is abnormally elevated in glaucoma, reduced [30, 31] (Figure 5).

Therefore, a large proportion of atoms are available to attach with surrounding chemical or biological molecules, which increases surface reactivity and toxic effects of the nanoparticle. In the other words, the large surface of MSNs is a double-edged sword that may lead to both toxic effects and strong absorption capability on the surface of nanoparticles [34]. Chen et al. assessed the toxicity of large-surface-area featured MSNs and its synergistic adverse effect with Ag^+ on the ocular surface. Since MSNs with a large surface area have a high ability to absorb hazardous substances, they choose Ag^+ as an attached hazardous substance widely used in daily life to simulate MSNs exposure in real environments. The in vitro study exhibited that MSNP-Ag^+ at a safe dose show more cytotoxicity than MSNs. Following the toxicity evaluation, they also suggested the mechanism of MSNs and MSNs-Ag^+ toxicity in human corneal endothelial cells (hCECs). MSNs-Ag^+ through MAPK pathway and mRNA surveillance signaling pathway can cause oxidative stress, DNA damage, and apoptosis.

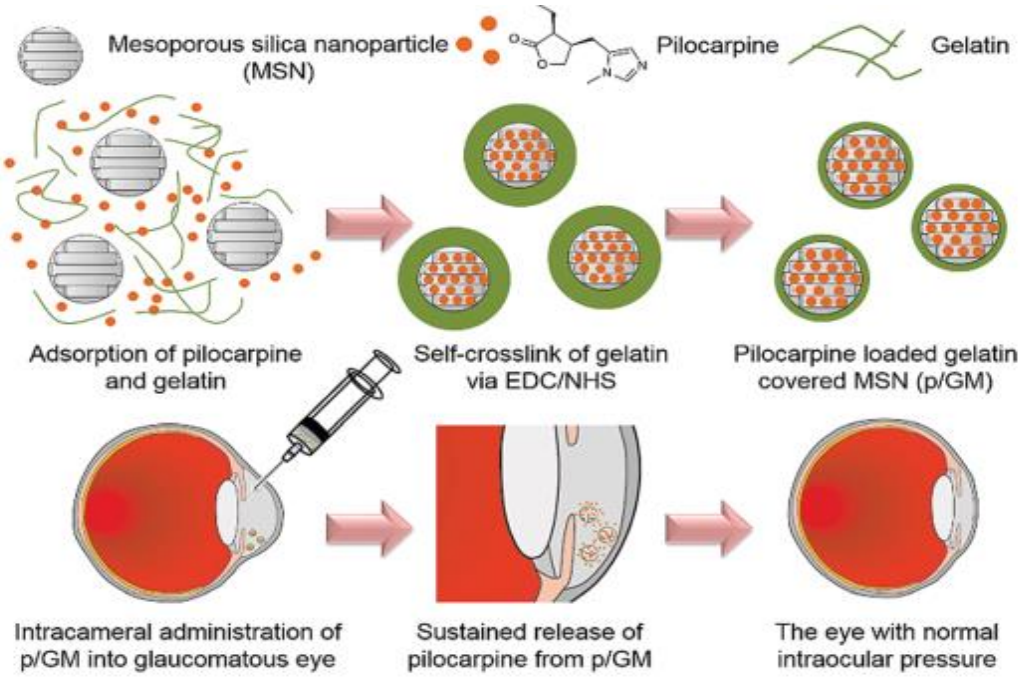

Figure 5. Schematic representation of pilocarpine-MSNs covered with gelatin as a drug delivery system into the anterior chamber of the eye. [31]

It is also showed that the repeated short-term exposure of both MSNs and MSNs-Ag^+ to rats could cause central corneal damage. However, the eye injuries caused by MSNP-Ag^+ in rat models were severer than non-mesoporous and mesoporous silica nanoparticles [35]. In addition, they proposed a therapeutic approach for MSNs induced corneal disease based on a protein corona shield. It is reported that a surface modification of nanoparticles with protein corona can decrease their toxicity by blocking their surface-active groups. MSNs can simply bind with proteins such as fetal bovine serum (FBS) and hemoglobin to form a protein corona shield around the nanoparticles. Hence, they treated rats with %100 FBS after every exposure to MSNs and MSNs-Ag^+. It is shown that FBS can considerably relieve corneal injuries [35]. However, the architecture of porous plays generally a key role in nanocarriers toxicity [36]. As a superior advantage, the nano-scaled pores of MSNs are tunable. A recent study on sol-gel MS commercial microparticles, investigating their intravitreal safety profiles in the vitreous of a living eye, pointed out that microparticles with small pores (10nm) are safe for intravitreal injection as drug delivery vehicles [37].

4. Application of MSNs in skin disease therapy

The skin, one of the crucial body organs which constitute the largest mechanical barrier against microorganism, is composed of three layers including the epidermis, the dermis, and subcutaneous tissue [38]. Cutaneous delivery of therapeutics can be a promising approach to treat a variety of skin diseases with minimum systemic effects and high bioavailability. Almost, all experiments that have yet been carried out using MSNs in drug delivery and gene delivery to the skin pursued this goal. Herein, we pointed out these experiments and discussed their results. There are two categories of skin cancer including melanoma and non-melanoma. Squamous-cell skin cancer (SCC) and basal-cell skin cancer belong to later ones [39]. In respect of cancer treatment, a commonly used chemotherapeutic agent is methotrexate (MTX). Generally, the most common administration of MTX is systemic via intravenous, intramuscular, and oral routes even in skin diseases. However, in skin cancer and some other skin disorders treating by MTX, the topical administration of MTX via cutaneous route may be able to restrain its side effects and toxicity for normal cells. The efficacy of MTX topical delivery in the treatment of skin diseases was investigated by Sapino et al. synthetized an inclusion complex of MTX and MCM-41-like nanoparticles with high biocompatibility. This study showed that the epidermal accumulation of MTX-loaded MSNs is enhanced compared with free MTX and also this complex could reach the deeper layers of the epidermis. Besides, the skin absorption of the MTX/MSNP complex was considerably increased by the addition of shea butter which functions as a penetration enhancer [40]. In addition to chemotherapy or radiotherapy, an alternative method for the treatment of cancers is photodynamic therapy (PTD). It is a non-invasive treatment strategy based on the administration of a photosensitizer. The process of PDT requires three elements, namely photosensitizers, oxygen, and light. Once the photosensitizers accumulate in cancer cells, they produce cytotoxic reactive oxygen species (ROS) using the energy of a specific wavelength of light in the cells which results in inducing apoptosis. However, because of hydrophobicity, poor stability within the PDT environment, and low cell permeability, the clinical application of conventional organic photosensitizers is limited [41, 42]. Hence, applying a carrier for efficient delivery of organic photosensitizers is an appropriate way to expand their utilization. Considering this subject, a multifunctional hollow MSNs as a delivery vehicle of 5-aminolevulinic acid (5-ALA) aiming at PDT against skin cancer was fabricated by Ma et al. 5-ALA is widely used in PTD because of its nontoxic effect and fine excretion rate from biological systems. 5-ALA is a precursor for the heme synthesis pathway through which it is converted to a strong photosensitizer, protoporphyrin IX (PphIX), to achieve the functions of PDT (Figure 6).

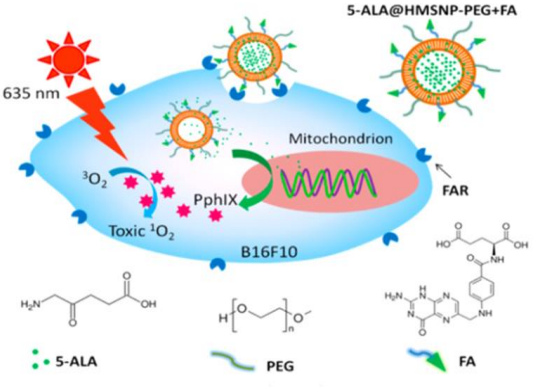

Figure 6. Schematic sketch of multifunctional hollow MSNP based 5-ALA Delivery for Targeted PDT in skin cancer treatment. When 5-ALA loaded MNSPs enter the cancer cells through endocytosis, 5-ALA is converted to PphIX in the mitochondrion and subsequently produce cytotoxic reactive oxygen species (ROS) using the energy of a specific wavelength of light which results in inducing apoptosis. [43]

They designed perpendicular nanochannels connecting to the internal core of MSNs which facilitate drug loading and releasing. Polyethylene glycol (PEG) and folic acid conjugated MSNs could enhance the cellular uptake of 5-ALA through receptor-mediated endocytosis. Therefore, an efficient cancer cell killing effect for 5-ALA loaded MSNs was reported [43]. In a similar study, to enhance drug release and skin permeation of lidocaine, MCM41, and amine- functionalized derivative were employed as a delivery system. Lidocaine (Lido) is a local anesthetic with poor water solubility and low tissue uptake which restricts its bioavailability in the skin. The data demonstrated that rather than Lido/MCM41, the functionalized complex excel at drug release and skin absorption which can be associated with the electrostatic interaction between the positive surface charge of MCM41-NH_2 and the negatively-charged skin pores. Positive surface charge of factionalized MSNs could provide efficient skin permeation and drug release in cutaneous delivery [44]. Taking the advantage of cationic nanoparticles for delivering therapeutic agents to the skin tumors, recently a noninvasive transdermal delivery system for oligonucleotides based on MSNs was introduced. The complex was designed as the oligonucleotides be loaded into pores of MSNs and then be coated with a layer of poly-L-lysine. In this research, cell experiments were conducted with a molecular beacon, a hairpin-shaped oligonucleotide containing an internally quenched fluorophore whose fluorescence is restored as hybridizing to the target nucleotide sequence. This experiment indicated that although the cationic coated MSNs improved cellular internalization, they could not sustain siRNA release and the release was abrupt. Afterward, the system was tested on topically deliver siRNA targeting TGFβR-1 (Transforming growth factor-beta receptor I) to the skin squamous cell carcinoma (SCC) in a mouse xenograft model. TGFβR-1 is overexpressed in 80.3% of patients with skin SCC and anti-tumor effects of its inhibitors have been proven in many cancers. The results exhibited a 2-fold suppression of TGFβR-1 with TGFβR-1 siRNA-loaded MSNs [45]. In another attempt to exploit the unique features of MSNs, they were used integrated with microneedles patches. Microneedles (MNs) are promising tools for transdermal drug delivery containing an array of microscale tapered tips which can penetrate the epidermis layer. In this study, after the modification of MSNs with 4-(imidazole carbamate) phenylboronic acid pinacol ester (ICBE), Insulin, and a glucose-responsive factor, Glucose oxidase was encapsulated into MSNs' pores. Then a host-guest complexation between the phenylboronic ester functional moieties of ICBE and α-cyclodextrin (α-CD) was formed. The mechanism of drug release in this delivery system was based on glucose mediating and H_2O_2-response. Once glucose oxidase in MSNs converts glucose to gluconic acid and produces H_2O_2 the phenylboronic esters on the surface of MSNs could be oxidized and destroy the host-guest complexation which causes the drug-loaded MSNs to disassemble and subsequently the insulin is released (Figure 7).

The transdermal administration of these microneedles to the diabetic rats showed an effective hypoglycemic effect than that of subcutaneous injection [46]. These days there are many attempts to formulate enriched skincare products with natural compounds to add valuable benefits to them. One group of these natural products is flavonoids with various health benefits and beauty such as anti-inflammatory, antioxidant, and sun protection properties.

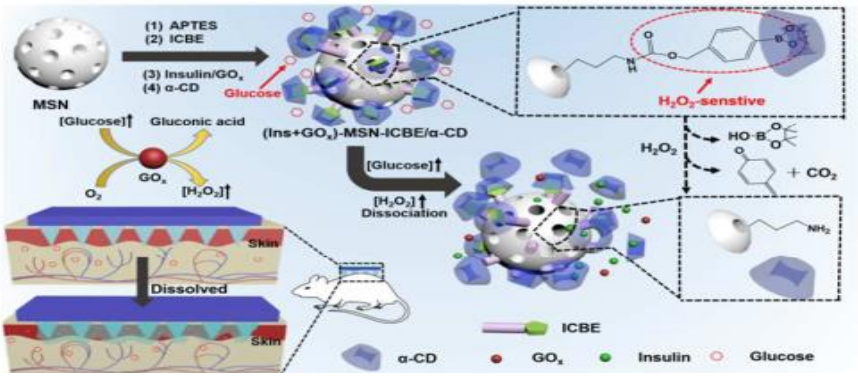

Figure 7. The mechanism of drug release in the $H2O_2$-responsive MSNPs integrated with MNs Patches. Once glucose oxidase in MSNPs converts glucose to gluconic acid and produces H_2O_2 the phenylboronic ester on the surface of MSNPs is oxidized in the presence of H_2O_2 and that result in the destructive of host-guest complexation and subsequently the drug loaded MSNPs to disassemble and subsequently the insulin is released. [46]

Nonetheless, there is a limitation on the cutaneous application of flavonoids because of their poor solubility, poor stability, and low release after application. Stabilization of antioxidants in product formulation is a key task for pharmacists. By designing proper nanoparticles, antioxidants can be preserved from being inactive before reaching the target and last long enough in tissue to exert the effects. In 2016, a stimuli-responsive system based on MSNs was designed and fabricated to control the dermal release of quercetin. Quercetin is categorized as a flavonol from the flavonoid group. MSNs were functionalized with a thermoresponsive copolymer of Poly (N-isopropyl acrylamide) (NIPAM), a well-known temperature-sensitive polymer [47]. NIPAM is water-soluble at temperatures below its lower critical solution temperature (LCST) of almost 33 °C. However, above this temperature NIPAM displays a coil-to-globule transition due to the hydrophobicity enhancement. This temperature change behavior of NIPAM is a helpful property in controlling the delivery of bioactive molecules [48].

This nanocarrier, prepared in two different pore sizes (3 nm and 5 nm) demonstrated better thermoresponsive properties in the case of larger pores. Also, it was shown that the accumulation of quercetin loaded in copolymer-grafted MSNs with big pores was higher than quercetin/MSNs complex with the same pore size in porcine skin [47]. Sunscreens currently use TiO_2 and ZnO nanoparticles to protect the skin from the UV radiation that there are concerns about their environmental impact. Therefore, it is necessary to use safer alternatives and eco-friendly materials [49]. Several studies have pointed out the importance of silica-based nanoparticles in protecting the skin from UV irradiation [50-52].

5. Application of MSNs in brain disease therapy

The human brain is the most sensitive and complex organ in the body and is protected by a highly efficient barrier called the Blood-Brain Barrier (BBB). This barrier is well able to defend brain cells against the contents of the blood and its toxic compounds. But the same barrier also restricts the entry of drugs into the brain [53-55]. Intrathecal injections can be used to deliver drugs to the brain tissue, which is limited to certain areas of the brain and is an invasive procedure. For this reason, more research has moved towards non-invasive methods such as the use of prodrugs and Nanoparticles [56, 57]. By increasing the lipophilicity of small drug molecules, the possibility of their transfer into the brain increases. Prodrugs are often produced with the same properties. Increasing lipophilicity of all drugs is not effective and possible because sometimes with these changes, drugs lose their therapeutic effect. In addition, not all prodrugs can break down in the brain. In such cases, nanoparticles can be used for drug delivery [58, 59]. Several nanoparticles (carbon nanotubes, liposomes, inorganic nanoparticles, polymeric micelles, and dendrimers) have been reported for targeted drug delivery for neurodegenerative diseases [60-62]. But MSNs are suitable for the treatment of neurodegenerative disorders and brain diseases due to their unique properties such as high porosity, high load capacity, low toxicity, and acceptable biocompatibility [63]. Baghirov et al. investigated the effect of functionalized rod and spherical MSNs on BBB. They used PEG–PEI copolymers to functionalize the nanocarrier. The results showed that this polymer coating increased the uptake of MSNs, especially rod-shaped, by brain cells without damage to the BBB or having a toxic effect [64]. There have been numerous reports of MSNs that effectively target receptors on the endothelial cell membrane of the brain such as transferring (Tf), low-density lipoprotein, lactoferrin (Lf), mannose, folic acid (FA), RGD (arginine–glycine–aspartic acid) and insulin [65-69]. Peptide RGD interacts with αVβ3 receptors, which are highly expressed on the surface of cancer cells. It has been used to functionalize nanocarriers to target cancer cells [70]. One of the most widely expressed receptors is the transferrin receptor. Song et al. functionalized MSNs with Lf, which induced targeted drug delivery to brain cells via Lf-mediated transcytosis. They also used PEG to cover the surface of the nanocarrier to prevent it from being cleaned by the reticuloendothelial system. They observed the displacement of NPs based on the size in brain cells with maximum transport efficiency for 25 nm nanoparticles. Thus, Lf functionalized MSNs that are transported across the BBB by receptor-mediated transcytosis can be useful for drug delivery to the brain [71]. Bouchoucha et al. demonstrated uptake and drug delivery of antibody-functionalized MSNs by brain endothelial cells. This nanoparticle showed a high affinity for neuronal and endothelial cells of the brain and their endocytosis into these cells is mediated by transferrin receptors [72]. Studies have also shown that the presence of glucose and glucose-PEG-amino (glucose-poly (ethylene glycol) methyl ether amine) on the surface of MSNs increases their uptake by neurons. The adsorption mechanism of these NPs is a combination of receptor-mediated endocytosis and transcytosis using low-density lipoproteins (LDL), apolipoprotein E (apoE), and glucose transporter (GLUT) [73].

5.1 Glioblastoma (GB)

Glioma is one of the primary tumors of the central nervous system that occurs in the spinal cord or brain. The tumor originates from glial cells and the most common site of glioma tumor is the brain [74]. Approximately 80% of malignant brain tumors are gliomas. There are several treatment strategies for the tumor, such as surgery, chemotherapy, and radiotherapy. However, due to the high recurrence rate, the resistance of the precursor cells to chemotherapy and radiotherapy, the hiding of the tumor in inaccessible areas that make surgery impossible, and the inability of many drugs to pass through the BBB, the effectiveness of these treatment methods are greatly reduced [75-77]. Therefore, it is necessary to use nano drugs that easily pass through the BBB and target gliomas. To destroy glioblastoma tumors, Mo et al. designed MSNs loaded with the anti-cancer drug doxorubicin (DOX) and functionalized with PEI-cRGD. Their results showed that MSNs with a size of 40 nm have the highest antitumor effect and the highest rate of cell uptake (Figure 8) [78]. You et al. synthesized MSNs functionalized with RGD peptide to deliver organic selenium compound as an anti-cancer drug. This nanocarrier easily passed through the BBB and was absorbed by tumor cells which show high expression of integrin. It can activate MAPKs and p53 pathways and inhibit tumor cell growth [79]. In another experiment to monitor MSNs-RGD cellular uptake, nanocarriers were conjugated to fluorescent ruthenium polypyridyl complexes (RuPOP). The presence of RGD peptides increased the cellular uptake of MSNs in target cells through endocytosis. These NPs had a high toxicity effect on cancer cells expressing αVβ3 receptors [80]. One of the drugs that are widely used in the treatment of a large number of cancers is the platinum group, that the leader of it is cisplatin (CisPt). This drug combines with the DNA of cells to stop mitosis. It is more effective in cells with high proliferative capacities, such as many cancer cells, and several normal tissue cells in the body with high proliferative power [80, 81]. Ortiz-Islas et al. Synthesized MSNs -loaded with CisPt and functionalized with folic acid to target glioblastoma cells. MSNs- CisPt- FA was biocompatible and the cytotoxic effect of the drug increased, so it may have an important role in the treatment of GB cancer [83]. The transferrin receptor is probably expressed in all cells, but its expression level is very high in rapidly dividing cells such as malignant cells. Sheykhzadeh et al. developed Tf-conjugated MSN and investigated its effect on inhibiting GB migration using a microfluidic chip. These particles exhibited an inhibitory effect on GB cell migration and reduction in cancer recurrence [84]. Cheng et al. reported that neural stem cells have the potential to migrate to tumor cells and can be used to targeted deliver drugs to these cells. They designed 80 nm DOX-MSNs and treated them with trimethylammonium to increase surface charge and their absorption. Then they used a neural cell line to deliver these NPs. The results showed that DOX-MSNs- stem cells have a significant cytotoxicity effect on glioma cells and cause their apoptosis [85]. In another study, a Fe-MSN nanoparticle was designed consisting of an iron oxide core to pass through the BBB cells and deliver drugs to glioma cells. They used fibronectin ligands to target the delivery of NPs to the endothelium of glioma cells. When Fe-MSN is exposed to the radiofrequency fields, it releases the drug from silica pores [86]. Today, medicinal plants and their compounds are widely used for various therapeutic purposes. Thymoquinone (TQ) is bioactive in some herbs which significantly inhibits the migration of cancer cells. Fahmy et al. studied free and encapsulated TQ in mesoposrous silica nanocarriers. They showed that TQ-MSNs have higher permeability to brain areas such as midbrain, hypothalamus, cortex, and thalamus compared to Free TQ [87]. Shahein et al designed TQ- MSNs consist of two types of polymer layers as a shell. Drug release was done by changing the pH. TQ-MSNs showed high drug release at pH 7.4 while TQ-MSNs with whey protein and gum Arabic shell and TQ- MSNs with chitosan and stearic acid shell released TQ at pH 5.5 and 6.8, respectively; therefore, the effective release of the drug takes place in the acidic environment of the tumor. Also, the anticancer mechanism of these NPs was higher than free TQ and had the less cytotoxic effect [88].

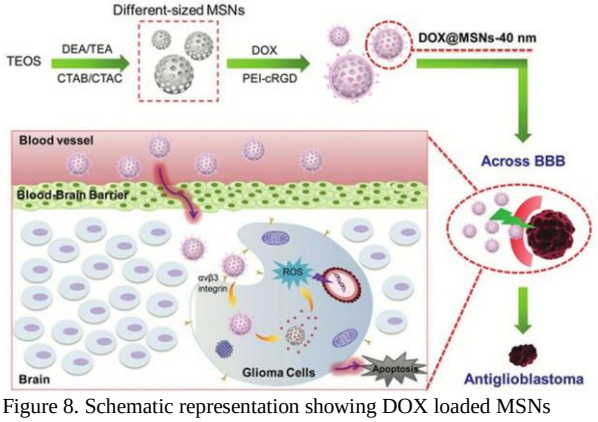

Figure 8. Schematic representation showing DOX loaded MSNs targeting BBB for the treatment of glioblastoma. [78]

5.2 Alzheimer's disease

Alzheimer's disease is the most common cause of dementia and is associated with symptoms such as progressive, gradual, and irreversible loss of memory. In the brain of infected individuals, an extracellular protein called amyloid plaques deposits between the nerve cells which causes communication disorders between nerve cells as well as nerve cell damage in addition to plaques, the formation of hyperphosphorylated tau protein in damaged cells forms neurofibrillary tangles that initiate subsequent damage and neuronal death [89]. The study of the interaction of amyloid beta-peptide with metals and their chelation shows that metals such as $Cu2^{+}$, Zn^{2+} and, Fe^{2+}, which are abundant in cerebral synapses, play a role in beta-amyloid deposition and oxidation. In other words, the presence of these metal ions destroys the folding of the protein [90]. Therefore, some metal chelators, such as 8-hydroxyquinoline derivative (PBT2) and clioquinol (CQ), have been introduced to treat this disease [91]. But these chelators cannot easily cross the BBB and are unable to distinguish between normal metal ions and those involved in plaque formation, so they can have many adverse side effects. Therefore, the development of drug-carrying NPs that target only metal ions causing AD will be effective. MSNs have been noted for their high surface area, large pore volume, controllable pore size, and high drug loading capacity for treating Alzheimer's disease [92]. Oxidative stress indicates an imbalance between the production and emergence of oxygen free radicals and the ability of the biological system to detoxify or repair their destructive effects. Research has shown that in Alzheimer's disease amyloid beta-Cu complex reacts with O_2 and produces H_2O_2, which causes oxidative stress. To deal with oxidative stress, Geng et al. designed MSNs loaded with a metal chelator and functionalized with arylboronic acids and IgG as a nanoscopic cap. In the presence of H_2O_2, a redox reaction occurs, so with the oxidation of the arylboronic esters, the antibody cap is removed and the metal chelates are delivered (Figure 9) [90]. In another study, MSNs with ultra-large porous were designed. These NPs were functionalized with scFvs that adsorb Aβ monomers and prevent them from aggregation. Anti-Aβ scFvs show a high affinity for Aβ peptides and increase cell viability by reducing Aβ agglomerations (Figure 10) [93]. clioquinol as an antiprotozoal and antifungal drug has been effective in the treatment of Alzheimer's disease by interfering with the metabolism of brain metals [94]. clioquinol loaded Au-MSN were synthesized to target Aβ plaques. Metal chelator is released in the presence of high H_2O_2 in plaques environment and prevents the aggregation of Aβ caused by Cu^{2+}. The presence of gold in the nanoparticle is more effective in reducing Aβ accumulation than clioquinol-MSN and reduces oxidative stress and ROS -induced apoptosis [95]. rivastigmine hydrogen tartrate (RHT) is a butyrylcholinesterase (BChE) and acetylcholinesterase (AChE) inhibitor so it can prevent the hydrolysis of acetylcholine. Increasing the level of acetylcholine facilitates the transmission of nerve impulses and can be useful in the treatment of Alzheimer's and Parkinson's disease [96]. However, delivering RHT to the brain is very challenging because of its hydrophilic nature; its entry into the brain is limited and repeated doses can also cause harmful side effects [97]. To use nanoparticles for RHT delivery in SY5Y cells, MSNs were designed that functioned separately with succinic anhydride (S-MSNs) and 3-aminopropyltriethoxysilane (APTES). Comparison of these nanoparticles showed that APTES-MSNs have a higher loading capacity and the rate of release of functionalized RHT -MSNs is higher than non-functionalized ones [98].

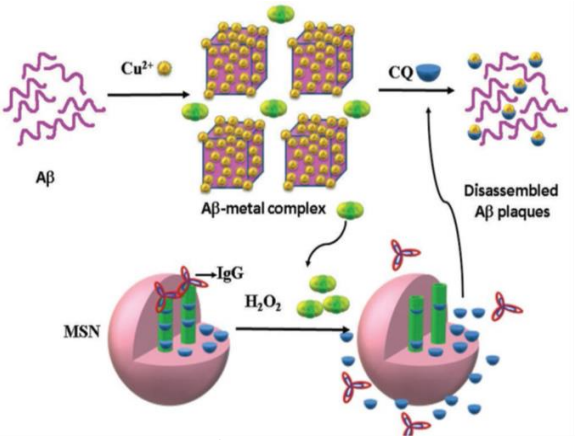

Figure 9. Design MSNs functionalized with arylboronic acids and capped with IgG and sensitive to H_2O_2 for drug release. [90]

6. Application of MSNs in cancer therapy

The enhanced permeability and retention (EPR) effect is a phenomenon by which tumor tissue allows materials in nanoscale to accumulate inside the tissue due to hypervascularization [99]. Although it is a controversial subject, the application of nanoparticles in cancer therapy was initiated by observations on the EPR effect [100]. Specific delivery of therapeutic agents treating cancer diseases is based on two strategies including passive targeting and active targeting. Passive targeting exploits the EPR effect while active targeting is associated with a specific

ligand binding with the corresponding receptor. These receptors may be localized on the cell surface or in the cytoplasm [101]. Among various nanocarriers used for drug or gene delivery applications in cancer cells, mesoporous silica nanoparticles (MSNs) have attracted a great deal of attention due to their exclusive physicochemical features. These features include tunable pore size (2–50 nm), ordered porous structure, high drug-loading capability due to their large surface area and pore volume, and easy surface modification [102, 103]. MSNs were developed in the early 1990s [104] and have recently obtained FDA investigational approval for their human use in clinical trials [105, 106]. This subject can declare that MSNP is a delivery platform of some significance.

7. The application of MSNs in drug delivery for cancer therapy

Minimizing the systemic toxicity of drugs [107], enhancing low stability and low solubility of drugs [108], improving their biological half-life [109], overcoming drug resistance [103, 110], and controlling drug release [111, 112] are numbers of the rationales in using the delivery systems based on nanoparticles for targeted delivery of anticancer drugs. MSNs are a promising delivery platform used to further improve the anticancer effect of many chemotherapeutics like doxorubicin in the treatment of different cancers [109, 113, 114]. They also have a dual function of chemotherapy drug delivery carrier and immunopotentiator [114]. The dual drug delivery or combined delivery is a therapeutic approach using to exert a synergic anticancer effect, as well as overcome the occurrence of multidrug resistance (MDR), a major factor in the failure of many chemotherapeutics. MDR is an intrinsic mechanism of cancer cells through which ABC transporters family are overexpressed on the cells and efflux drugs out of the cell against a concentration gradient by energy derived from ATP hydrolysis [115]. In a recent experiment in this respect, paclitaxel and quercetin co-loaded functional MSNs were fabricated by Liu et al to conquer multidrug resistance in breast cancer. It is reported that quercetin in the combination of doxorubicin and paclitaxel could reverse MDR [110]. Ali et al. also recently developed lactoferrin-targeted MSNs for dual delivery of pemetrexed and ellagic acid in the treatment of breast cancer which showed a sustained release of drugs [116]. Another significant characteristic of MSNs which makes them a promising vehicle delivery for cancer therapy is their ability to encapsulate various types of drugs in high amounts in their pores. In addition, the convenient surface modification of MSNs with polymer shells provides improved biocompatibility and stability for them by reducing the interaction of silanol functional groups with biomolecules [112, 113]. These interactions can cause hemolysis [112] or aggregation of silica nanoparticles [117]. A study using an unmodified MSNP as a dual drug delivery system in breast cancer showed low stability in solution over time [118]. Moreover, it is reported that a core-shell structure of MSNs can considerably improve drug solubility in water for two reasons. The drug particle size can be reduced by the spatial confinement effect of MSNs while the specific surface area of the drug particles increased and as a result, it will increase the dissolution rate of drugs. Secondly, due to their physicochemical properties such as regular shape, low density, and good flow ability, the core-shell structure of MSNs would increase the water solubility of drugs [108]. To achieve efficient delivery of anticancer drugs, the pore size of MSNs plays a crucial role. One study, in this case, illustrated that doxorubicin-loaded MSNs with a small pore size (2.3 nm) had minimum drug loading capacity compared with the large (8.2 nm) and medium (5.4 nm) ones. Also, the doxorubicin-loaded MSNs with medium pore size could release the drug quickly and completely [102]. In addition to pore size, a uniform size structure of MSNs could provide a high drug-loading efficiency [118]. The controlled release of the drug could increase the treatment modality in cancer. In this respect, one approach to having precise control over drug release is blocking the drug-loaded pores of MSNs with stimuli-responsive substances. For example, a pH-responsive MSNP for breast cancer targeted delivery of anastrozole was designed and fabricated. In this design, a layer of chitosan-folate conjugation (CH-FA) capped the surface of drug-loaded MSNs. In a low pH media, a hallmark of malignant solid tumors, the CH-FA cap is destroyed and the drug release [111]. Regarding pH behavior of MSNs, at neutral pH (7.4) MSNs modified with positively charged functional groups (amine groups) show burst release of drug while the one which is modified with negatively charged groups (phosphonate groups) display slower release kinetics. However, both surface-modified MSNs at lower pH (5.5) show a significant control over drug release. This study was conducted for resveratrol, a natural polyphenol, delivery to prostate cancer cells [111]. A comparison study between MSNs and mesoporous silica nanorods (MSNR) illustrated that MS with different shapes and morphology have different drug loading capacity and control of the drug release. This study

served both MSNP and MSNR as a nanocarrier to deliver DOX into the cancer cells. The results indicated that although both carriers are very efficient in cytotoxicity at very low concentrations, the behavior of these two delivery vehicles is different in cancer cells, as the rod-shaped MS showed a sustained release of DOX as well as high drug loading capacity compared to the MS with spheroidal morphology. Moreover, with a high aspect ratio (length/width) than MNSPs, rod-shaped MS have a greater surface area to interact with the cell surface that provides better and faster cellular uptake [119]. Cancer cells are more sensitive to the treatment of hyperthermia than normal cells due to their rapid growth and metabolism. In general, there are several methods of transferring energy to the body to warm the body tissues, including the use of the electric field, microwave radiation, electromagnetic pulses, ultrasound, and infrared light. Using these methods for heat therapy, the energy distribution is not the same in all parts of the tumor and the healthy tissue around the tumor is also damaged. The use of nanostructures as agents that can only accumulate specifically in tumor cells and act as energy converters has received considerable attention in recent years (nanoparticles can convert radiated energy into heat in tumor cells). Gold nanostructures absorb light in the visible and infrared region and also produce heat rapidly (in picoseconds or less) so they are a great tool for treating cancer hyperthermia. In addition, gold nanostructures as a contrast agent are a good tool for detecting cancer through scattering and photoluminescence properties 3D body imaging techniques [120]. These NPs are normally coated to prevent them from clumping and rapidly excreted by the immune system. In addition, cells that contain nanoparticles, if exposed to laser radiation, quickly convert the absorbed light into heat that kills cancer cells [121]. Agabeigi et al. investigated the effect of folic acid and methotrexate loaded on silica-coated gold nanoparticles (Au-SiO_2) in combination with Low-level laser therapy as a safe and FDA-approved treatment for breast cancer. Au-SiO_2 nanoparticles were prepared in spherical shapes with a diameter of about 25 nm and a surface charge of -19.7 mV. The size and surface charge of these NPs was also acceptable for biological distribution in the human body. The successful targeting of these NPs was evaluated by comparing the uptake rates of MDA-MB-231 and MCF-7 as two breast cancer lines with different expressions of folate receptors. MTT test, DAPI staining, and cell cycle studies indicate that combination chemotherapy-photothermal therapy increases cell mortality and apoptotic effect in both MDA-MB-231 and MCF-7 cell lines, especially in the MDA-MB-231 cells. These NPs did not show any toxicity, so using a combination of chemotherapy and Low-level laser therapy could be useful for cancer treatment programs [122].

Recently a bioreducible and traceable nanoprodrug for efficient and safe non-small cell lung cancer (NSCLS) therapy has been developed. This multifunctional nanodrug was synthesized by integrating a multifunctional fusion protein-incorporated liposome with ruthenium (III) prodrug-loaded mesoporous silica nanoparticle. The multifunctional fusion protein consisted of the H1299.2-targeting peptide, green fluorescent protein, and mechanosensitive channel protein. As the ruthenium (III) prodrugs were reduced into highly active ruthenium(II) drugs in response to a high level of glutathione in the cells, tumor apoptosis was induced through DNA intercalation of ruthenium(II) that blocked DNA replication [123].

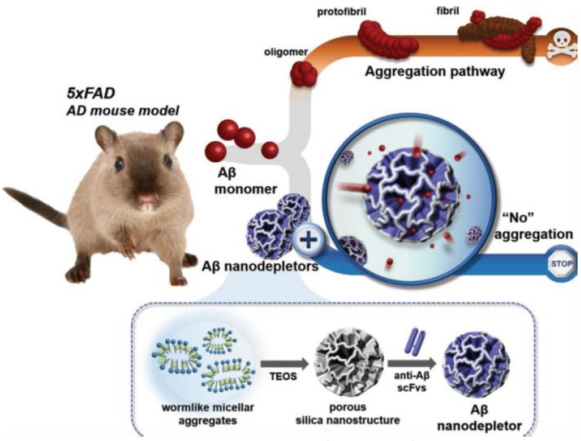

Figure 10. Schematic illustration of MSNs functionalized with anti-Aβ scFvs. [93]

8. The application of MSNs in gene delivery for cancer therapy

There are many clinical trials in gene therapy for the treatment of diseases, including cancer. [124, 125]. Scientists mainly follow three strategies in gene delivery by employing MSNs as the delivery vehicle. One strategy includes the surface modification of MSNs with positively charged functional groups. The presence of positively charged functional groups enhances electrostatic interactions between anionic nucleotide sequences and cationic surface-functionalized MSNs and resulting in electrostatic adsorption of nucleotide sequence onto nanoparticles. Amine modification, the most common method for nucleic acid delivery by surface-functionalized MSNs, can carry out by applying (3-Aminopropyl) triethoxysilane (APTES). Using this strategy, wang et al. recently developed multifunctional tumor-

penetrating MSNs for dual delivery of a siRNA and a miRNA. The loaded MSNs were coated with a layer of peptide-modified lipid to stabilize. This peptide named iRGD was a tumor penetrating peptide which interacts with integrins and neuropilin-1 receptors. Incorporation of the iRGD peptide into an RNA delivery system likely increases their efficacy for cancer therapy. In this study also a photosensitizer indocyanine green was encapsulated to MSNS to facilitate endosomal escape. It is reported that applying a photochemical component in RNA delivery systems can improve cytoplasmic delivery of small RNAs by rupturing endosomal membranes in response to light-activated production of reactive oxygen species (ROS). This multifunctional nanocarrier was synthesized to deliver Polo-like kinase 1 siRNA and miR-200c. Polo-like kinase 1 is a mitotic regulator of the cell cycle, which is overexpressed in many tumor tissues. Silencing of this protein can induce apoptosis by preventing cell proliferation. MiR-200c is a short non-coding RNA that shows a tumor suppressor effect through inhibition of epithelial-to-mesenchymal transition (EMT). EMT is a process by which the epithelial cancer cells obtain the migratory and invasive characteristics of mesenchymal cancer cells. Accordingly, this combination of therapeutic RNAs showed proper inhibition of tumor growth and antimetastatic activity [126]. In another research, by Ahir et al., amine-functionalized MSNs loaded with a combination of two miRNA coated with a triblock copolymer containing hyaluronic acid, polyethylene glycol, and Poly (D, L-lactide-co-glycolide) (PLGA). They showed that polymer coating of RNA-loaded MSNs can stabilize the MNSPs themselves and the release of RNA inside the cell and also protect RNA from the nuclease. They delivered Anti-miR-10b and miRNA-34a into triple-negative breast cancer cells by targeting CD-44 receptors to improve the efficacy of chemotherapy. MiR-34a is a tumor suppressor microRNA whose expression is reduced in metastatic breast cancer cells and human primary breast tumors with a lymph node. MiR-10b is another microRNA that their critical role of starting tumor attack was shown in breast cancer. In vitro and in vivo studies demonstrated that the combined delivery of miR-34a and miR-10b have an efficient effect on tumor growth inhibition and retardation of metastasis [127]. Another group using for surface functionalization of MSNs is L-histidine (His). A study compared the gene transfection of His-functionalized MSNs with the amine-functionalized one. This experiment demonstrated an improvement in the transfection efficiency with MSNP-His/pDNA compared to MSNP-NH_2/pDNA, which resulted in a better internalization of MSN-His [128]. The second strategy of nucleic acid delivery by using the MSNs is done by polycation coating. This strategy also employs a positively charged modification, except that it uses cationic polymers such as polyethyleneimine (PEI) [129], poly-L-argenine [130], and dendrimers [131]. In one study of gene delivery on ovarian cancer, therapeutic siRNA was complexed by electrostatic interactions with PEI-coated MSNs. Hyaluronic-acid conjugated MSNs carried TWIST siRNA into the target. TWIST is a protein that plays a crucial role in tumor metastasis by its upregulating. This delivery system led to tumor burden reduction and enhanced sensitivity to cisplatin in ovarian cancer cells [132]. Other polycations were employed to absorb nucleic acids on MSNs are poly(2(dimethylamino)ethylmethacrylate) (PDMAEMA) and poly (2-(diethylamino) ethylmethacrylate) (PDEAEMA) [133, 134]. One study investigated the effect of the shape and size of polycation functionalized MSNs declares that the morphology of silica nanoparticles has a significant role in gene transfection, especially in the case of a low amount of polycation. It is also shown that the morphology of silica nanoparticles could have a great impact on their interaction with cells. Regarding gene transfection efficiency, hollow nanosphere-based carriers are more effective than solid counterparts [134]. As the third strategy, the nucleotide sequences can be integrated into the mesopores. In this approach, it is required that the pore size be large enough to enable MSNs to capture nucleic acid molecules and facilitate their release [135].

9. The application of MSNs in gene and drug co-delivery for cancer therapy

The Simultaneous delivery of a therapeutic gene and anticancer drug using a nanocarrier would be an efficient approach in cancer therapy mainly because of exploiting the synergistic effects of the gene in sensitizing the drug-resistant cancer cells to chemotherapeutics. Many studies proved that gene and drug co-delivery in comparison to monotherapy provides a more efficient therapeutic outcome [136]. Regarding the effectiveness of co-delivery, a recent study exploited folic acid conjugated MSNs to carry multidrug resistance protein (MRP-1) siRNA combined with myricetin, a flavonoid compound, to lung cancer cells. The results showed further improvement in the tumor-suppressive effects of myricetin on non-small cell lung cancer in comparison with free myricetin [137]. MSNs have a suitable capacity to be used in the co-delivery method because according to what mentioned in the previous

part when MSNs are loaded with nucleic acids by functionalization or polycation coating, the two more common methods for gene loading, the inner space of mesopores remain available to be loaded with drugs molecules [138]. The amount of small molecule loading depends on the pore structure and with high surface area higher oligos could be load to the particle [139, 140]. However, these open pores may lead drug molecules to leak. For example, multiple studies have reported doxorubicin (DOX) leakage during the delivery process which decreases the delivery efficacy of MSNs [141, 142]. Accordingly, employing a gatekeeper for mesopores to block cargo leakage is required. Many substances with different nature have been employed as a gatekeeper to anchor to MSNs. For example, Zhuang et al. recently designed a co-delivery system based on MSNs that covalently bind to two types of nucleic acid as a gatekeeper containing a DNA aptamer (AS1411) and a siRNA targeting TIE2 (siTIE2). AS1411 aptamer also served as a cancer-targeting ligand. TIE2 is a tyrosine kinase receptor for angiopoietin-1 and -2 and its expression is reportedly associated with the metastasis of breast cancer. The attachment of these nucleotide sequences was via disulfide bonds which could simply reduce in the environment of the cells by glutathione. These redox-responsive MSNs by co-delivering of siTIE2 and DOX into breast cancer cells showed a synergic suppression effect in cancer cell metastasis [143]. In another study, PEGylated MSNs with abundant pristine amino groups were prepared and demonstrated high efficiency in drug and siRNA loading and pH-sensitive drug release. This delivery system was used to deliver DOX in conjunction with a siRNA targeting T-type Ca^{+2} channel into the drug-resistant breast cancer cells [144].

It is reported that MSNs can efficiently enhance the cytotoxicity effect of anticancer platinum drugs [145]. Taking advantage of this, a co-delivery of cisplatin and HNF4α-encoding plasmid was conducted using PEI-modified MSNs by Tsai et al. Hepatocyte nuclear factor 4 α (HNF4α) is a transcription factor which plays a part in the maintenance of the differentiated state and functional activity of hepatocytes and its low expression is associated with metastatic features in hepatocellular carcinoma. The co-delivery of HNF4α-encoding plasmid and cisplatin exhibited inhibition in the S-phase of the cell cycle and which resulted in cell apoptosis. It also could inhibit the capability of pluripotency and tumorigenesis. As mentioned earlier MNSR possesses a higher drug loading capacity than MSNs with spheroidal morphology. Taking this advantage, a new co-delivery platform based on MSNR was designed and constructed to deliver camptothecin, a topoisomerase I inhibitor, and survivin shRNA-expressing plasmid to clone cancer cells. The prepared camptothecin-iSurDNA MNSR were PEGylated and tagged with AS1411 DNA to facilitate the drug uptake through the interaction with nucleolin, a protein that is highly expressed in the cytoplasm and surface of numerous cancer cells. Nanocarriers with the positively charged surface are more likely to interact he negatively charged protein in the physiological environment which causes the protein corona effect and toxicity. This issue could be addressed with some chemical modifications. For instant, Sanchez-Salcedo et al. designed and fabricated multifunctional MSNs with a zwitterionic surface and a core-shell structure. In fact, due to the presence of a PEI-shell with positive charge coating MSNs they served 2-methacryloyloxyethyl phosphorylcholine (MPC), a Zwitterionic material, to prevent this effect. This delivery system was prepared to carry anti-TWIST siRNA and daunorubicin. TWIST is a transcription factor that its reactivation is associated with angiogenesis, metastasis, and drug resistance. The release of the drug was in response to an external magnetic field. The nanoparticles with core-shell structure generate a local heating as a respond of oscillating magnetic fields that is affected the drug delivery properties [146]. Preserving nucleotide fragments from nuclease degradation at the circulatory system is another consideration in nano-carrier designing that should be taken into account. In a nano- carrier design, hyaluronic acid (HA), an anionic glycosaminoglycan assembled on top of gene and drug-loaded MSNs, acting like a protective layer. The results suggested that the HA layer provides effective control on the drug release and MSNs internalization. This study was conducted aiming at co-delivery of MTH1 inhibitor (TH287) and MDR1 siRNA in oral squamous cell carcinoma. The protein MutT homolog 1(MTH1) is responsible for the hydrolyzing of oxidized purine nucleoside triphosphates to prevents misincorporation of these impair nucleotides into DNA. Down-regulation of MTH1 can effectively decrease tumor cell survival and replication. The multidrug resistance (MDR) protein 1 (MDR1) is a cell membrane protein that pumps foreign substances, including chemotherapeutics, out of cells. Therefore, in addition to preventing the MDR1 function, HA-siTMSN also increases the cell-killing effect of TH287 in the cancer tissues [115].

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