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MULTIFUNCTIONAL MESOPOROUS SILICA NANOPARTICLES FOR BIOMEDICAL APPLICATIONS

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ABSTRACT

In the recent developments on the biomedical application of (Mesoporous Silica Nanoparticles) MSNs are summarized. We mainly focus on the designing of MSNs based smart drug delivery system, respond to endogenous tumor microenvironment (acidic pH, hypoxia, and up regulated enzyme, etc.) or the physical exogenous stimuli like light, magnet, ultrasound, and X-ray.

KEYWORDS: Bio-distribution, Evaporation induced self assembly, silica precursors, surface functionalization, Target Drug delivery.

1. INTRODUCTION

In the last two decades, he world has witnessed and novel industry and break thoughts on the synthesis and application of a wide variety of Nanoparticles, such as quantum dots, carbon nanotubes, polymers, and inorganic (metal oxides, silicas with high surface areas, tunable pore sizes, large pore volumes and rich morphology.[4-5]

Modern nanotechnology has evolved as the boon to the medicine and diagnostic sector.[6] The structure of Mesoporous Silica resembles that of the Honeycomb and can be visualized through Transmission Electron Microscopy. Conventional MSNs have the capacity to load a dose of active pharmaceutical moiety up to 200-300 mg which can be extended up to 600 mg/1g of MSNs. However, hollow MSNs with hollow core-mesoporous shell structures are able to achieve a super-high drug loading capacity because these provide more space to load drugs due to the hollow cores, typically > 1 g drug/1 g of silica. The biocompatibility of mesoporous silica depends upon the shape, size, surface charge and porosity. The MSN materials having a size in between 100-200 nm are considered safe and biocompatible. Spherical MSNs are internalized faster by Chinese Hamster Ovarian (CHO) and normal

human fibroblast cells than the rod-shaped nanoparticles, possibly due to the lower tendency of the former to form aggregates. MSNs with fewer silanol groups on their cell-contact surfaces are considered to trigger the haemolysis of RBCs lesser than their nonporous silica counterparts containing a higher density of cell contactable surface silanol groups.[13-15] MCM-41, MCM-48 and SBA-15 are the most common mesoporous silica materials with the pore size ranging from 2-10 nm and 2D-hexagonal and 3D- cubic structural characteristics.[16] In contrast to solid silica nanoparticles, structurally ordered mesoporous silica materials, such as MCM-46 and SBA-type mesoporous silicas, offer many advantageous features, such as high surface area, narrow pore size distribution, and high chemical and physical stability. These materials attracted much attention worldwide due to their potential application in catalysis, chromatography, controlled release delivery, sensor design, and new semiconducting nanostructures.[17-29] In this review article, we discuss research towards general morphology, functionality, methods of synthesis and applications of mesoporous silica nanoparticles. Taking advantage of rich silane chemistry, many multi functional MSNs have been created and applied, and the MSN material is now one of the most widely studied nanomaterials in the field of nano-biomedicine.

2. The present review especially emphasizes on following applications

1. Biosensing Applications
2. Targeted and controlled Drug Delivery
3. Solubility Enhancement
4. Gene Delivery
5. Wound Healing

1. BIOSENSING APPLICATIONS

The surface to volume ratio of NPs is quite high which allows the incorporation of abundant functional ligands, and also enables multivalency on NP surface which increases the interactions with targets. Capping and gating of MSN derivatives are frequently done to exploit their applications in Controlled-release System (CRS). Different detection technologies have been coupled with the CRS to develop diverse biosensors. Zhonghui Chen and its colleagues developed a simple, low cost and highly sensitive Cocaine Biosensor based on Chemiluminescence (CL) system of luminol/H2O2. Controlled release mesoporous silica had been coupled with a chemiluminescent detection technique to develop a sensitive biosensor for the target which does not cause an effect on the CL system itself. Initially,

MSNs are loaded with glucose, then positively charged MSN reacts with the aptamer cocaine which is negative in charge and closes the mesoporous of MSNs. In the presence of the target, cocaine binds with its aptamer with high affinity; the flexible linear aptamer structure undergoes non- Watson & Crick interaction and gets converted to branched stems which lead to the release of glucose into the solution. The released glucose reacts with the dissolved oxygen to produce gluconic acid and H2O2 in the presence of Glucose Oxidase (GOx), which further enhances the CL of luminol in the NaOH solution. The increased chemiluminescence intensity is directly related to cocaine concentration. The present method successfully detected cocaine in serum with high selectivity. Zhu and coworkers developed an ATP biosensor that used aptamer modified Au nanoparticles and closed the pores of MSN, these pores opened in the presence of adenosine triphosphate (ATP) through the comptetitive binding and cargo was released. This study demonstrated that the aptamer- target interaction could be used as a stimuli- responsive mechanism in controlled release systems. As a broad range of targets have exploited to obtain the aptamers including have an equally broad spectrum of applications. Zhang Xueao and other Co-workers, in 2009, developed a biosensor based on acetylcholinesterase immobilized on mesoporous silica thin films. The sensors properties of the biosensor were investigated by using acetylcholine iodide as the substrate and Cyt c as the electron transfer mediator. The inhibition versus the logarithm of concentration was found to be linear to organophosphorus pesticide dichlovos.

Targeted and Controlled Drug Delivery

- **Mesoporous Silica Nanoparticles (MSNs):** MSNs are nanoscale particles with a honeycomb- like mesoporous structure. They possess several advantageous properties:
- Large surface area: This allows for efficient drug loading.
- Tunable pore size: MSNs can be tailored to accommodate different drug molecules.
- Biocompatibility: Silica is well-tolerated by the body.
- Stability: MSNs maintain their structural intergity.

These properties make MSNs ideal candidates for drug delivery systems

1. Drug loading and Controlled Release

MSNs can encapsulate drugs within their pores.

The controlled release of drugs from MSNs can be achieved through various mechanisms: pH-responsive release: MSNs release drugs in response to changes in pH (e.g., acidic tumor microenvironments).

2. Stimuli-responsive release: External triggers (such as light, heat, or magnetic fields) can activate drug release.

3. Gradual diffusion: MSNs allow for sustained drug release over time. By tailoring the pore size and surface properties, researches can precisely control drug release kinetics.

4. Targeted Drug Delivery

MSNs can be functionalized with targeting ligands (such as antibodies or peptides). These ligands recognize specific receptors on the surface of target cells (e.g., cancer cells). Upon reaching the target site, MSNs release the drug payload, minimizing off-target effects. Targeted drug delivery enhances therapeutic efficacy while reducing side effects.

5. In Vivo Investigations

Researches have studied MSNs loaded with drugs (such as docetaxel) in animal models. These studies demonstarte enhanced bioavailability and controlled release. For instance, doctaxel nanosuspensions in MSNs showed higher bioavailability compared to microsuspensions.

6. Future Directions

Ongoing research aims to optimize MSNs for clinical translation. Smart nanocarries that repond to specific stimuli hold promise for personalized medicine. Collaborations between scientists, clinicians, and industry parters are crucial for advancing MSNs-based drug delivery.[34]

Chen and other scientists, in 2018, developed a self-targeting and controllable drug delivery system by fabricating chitosan film formed over doxorubicin-loaded MSNs and functionalized with folic acid having multi stimuli responsive drug release for cancer treatment. They formed a layer of chitosan crosslinked by disulfide bond on drug-loaded mesoporous silica which was susceptible to pH and GSH stimulated drug release. Moreover, folic acid conjugation targeted the platform to cancer cells. *Invitro* study on HepG-2 cancer cell line showed folerateреceptor mediated endocytosis to occur successfully. It increased the cellular intake of the nanoparticle and showed antitumor activity toward malignant cells and provided safe controlled release and targeted delivery of the anticancer drug.[35]

Fig. (1) shows the multidisciplinary nature of MSNs.

Fig. (2) depicts the porous nature of mesoporous silica and its capacity to load the drug.

3 SOLUBILITY ENCHANCEMENT

Fig. (4). depicts the ability of MSNs to load the crystalline drug into pores and convert it to amorphous in order to enhance the solubility of the drug.

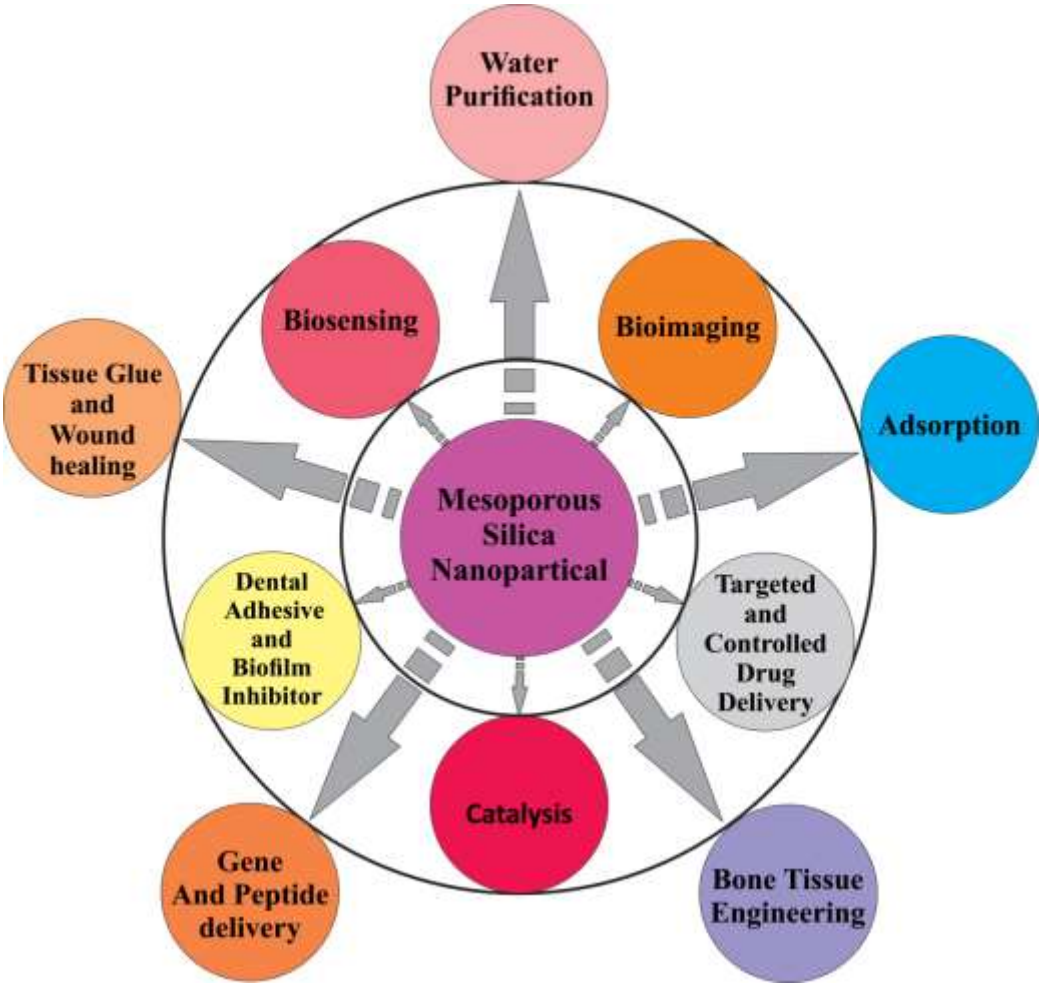

Fig. 1: Different Applications of Mesoporous Nanoparticles.

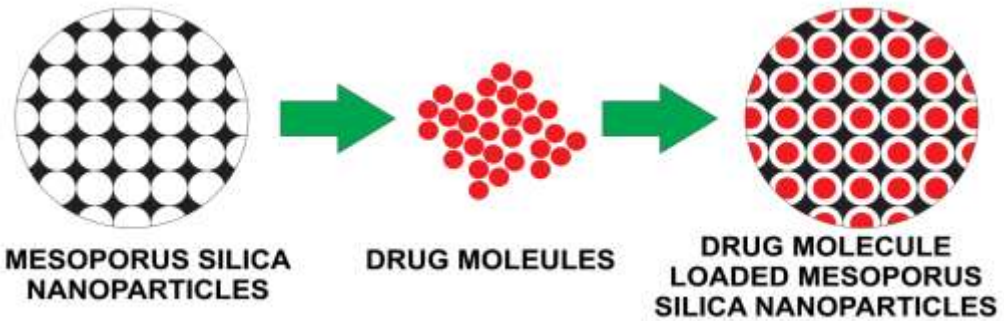

Fig. 2: Drug Loaded Mesoporous Silica Nanoparticles for Different Applicants.

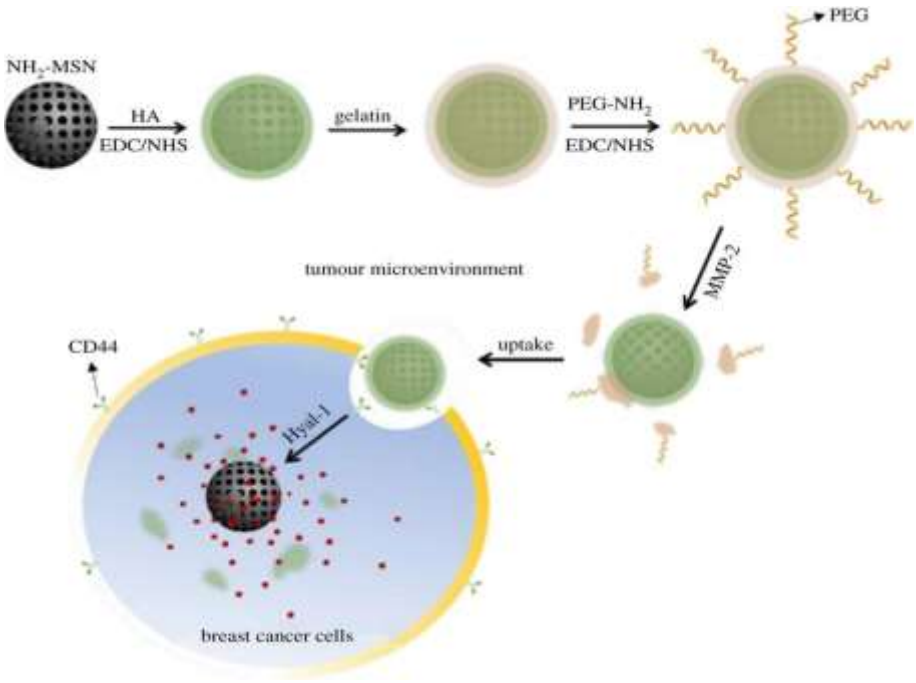

Fig. 3: Targeted Tissue and Drug Delivery System.

Table 1: Drug Loading Capacity and release profile of different MSN Templates.

Sr. No.	MSN Template	Model Drug	Loading Capacity	Drug Release	Reference
1.	MCM-41 HMSNs	Ibuprofen	35.9 74.5	Complete release in 10 h followed by 100% Release in 3 days	[80-82]
2.	MCM - 41 SBA-15 SBA-15(C8) SBA-15(C18)	Erythromycin	29 34 13 18	60% release within 5 h Total release within 14h Complete release in 10h 25% in the 24 h, sustained beyond 80 h	[83-86]
3.	SBA-15	Gemcitabine hydrochloride	76%	47.3% in 10h	[16]
4.	SBA-15	palperidone	62.44%	95% in 120 min.	[30]
5.	SBA-15	Gemcitabine	60%	49.3%in 10 h	[87]

Fig. 4: Application of wound healing by Mesoporous Silica.

Mesoporous silica has proved to be advantageous for poorly soluble drugs in increasing its solubility.[36-38] MSNs have a high specific surface area, high pore volume and appropriate pore sizes in the molecular range, ordered pore structures and silanol groups on their surfaces that can interact with a variety of drug molecules.[39] The solubility of the drugs markedly increase due to the confinement of the drugs into the tiny pores of MSNs having a size of 3-50 nm range.[40] The entrapment of the drug in MSNs is done by the solvent impregnation method.[41-42] Not only the drug solubility increases due to entrapment but also the drug can be protected from different destructive environment.

Mesoporous silica has proved to be advantageous.[43-45] MSNs have a high specific surface area, high pore volume and appropriate pore sizes in the molecular range, ordered pore structures and silanol groups on their surfaces that can interact with a variety of drug molecules.[46] The solubility of the drugs markedly increase due to the confinement of the drugs into the tiny pores of MSNs having a size of 3-50 nm range.[47] The entrapment of the drug in MSNs is done by the solvent impregnation method.[48-49] Not only the drug solubility increases due to entrapment but also the drug can be protected from different destructive environments.[50] This nature of the MSNs has proven to be an excellent solubility enhancer and bioavailability enhancer as well. The solubility enhancement mechanism of the mesopoorous silica is clearly associated with the conversion of unstable crystalline form to stable amorphous form Katarina Bukarawhile working with her co-workers in 2016 developed a proof of concept of solubility enhancement in humans using ordered Mesoporous Silica Nanoparticles and Fenofibrate as a model drug. The study was performed as an open-label, randomized, two-way cross-over study, in which 12 healthy human volunteers were made to fast overnight. Fenofibrate formulated with ordered mesoporous silica or a marketed product based on micronized fenofibrate was given as a single dose. Plasma concentrations of fenofibric acid (pharmacologically active metabolite of fenofibrate) were monitored up to 96 h post-dose. The rate (Cmax/dose increased by 77%; tmax reduced by 0.75 h) and extent of absorption (AUC0-24h/dose increased by 54% of fenofibrate significantly enhanced following administration of the ordered mesoporous silica-based formulation. This proof of concept developed a novel formulation strategy for the delivery of poorly water-soluble drug valsartan using functinalized Mesoporous Silica Nanoparticles. During the study, he developed amine-functionalized mesoporous silica loaded Valasartan [VAL] and coated it with pH-sensitive polymer eudragit L100-55 for pH-dependent sustained release of aniconic VAL. During the animal study, he found out that there was a 1.82-fold in bioavialability as

compared to the marketed tablet. The blood pressure of rats was under control for 840 minutes as compared to the marketed tablet which lasted for about 360 minutes. From this study, he concluded that the marked increase in solubility and bioavalibility was observed due to the amine-functionalized MSNs. Vishal Pande and his colleagues, in 2018, studied the solubility and dissolution enhancement of poorly water-soluble drug Palperidone using MSNs. They synthesized amine-functionalized MSNs and loaded the drug Palperidone with the help of the wet impregnation method. The in-vitro and in-vivo drug releases were studied which were found to be significally enhanced. The in-vitro drug release in 120 min for MSN loaded drug was 96% while that of the plain drug was 30%. The in-vivo study also confirmed the enhancement of solubility and dissolution of Palperidone.[50]

4. GENE DELIVERY

The drug delivery applications are most common and have already been reviewed earlier. Various development have taken place in this context using different functionalizations, different gates, different trigger mechanisms, etc. The study of specific molecules like gene, proteins and peptide is noteworthy. The size of mesoporous silica nanoparticles varies from template to template. Moreover, the pore size can be increased by agents like Trimethyl Benzene [TMB]. the size ranges from 2-40nm. The size of protein molecules entrapped upto 100 kDa. The target specific delivery of the genes to the selected cells is the most important challenge in gene delivery. In general, gene delivery vectors can be classified into two categories: viral vectors and non-viral vectors; each of them has been widely reported for gene delivery. Though viral and non-viral vector systems are available for gene delivery, there are amny problems associated with them like biocompatibilty, immunogenecity, etc. But as mesoporous silica is an approved biocompatible and biodegradable carrier by the FDA (US), it is suitable for targeted gene delivery. It is important to note that Mesoporous silica has those three major properties which are required to deliver the gene successfully.

1. While there exist nucleases in the bloodstream and intracellular matrices, MSNs can protect the gene from degradation.
2. MSNs have the capacity to pass the gene through the plasma membrane, endosome and/or nuclear pore complexes.
3. MSNs are non toxic in nature.

Flow cytometer study was employed to evaluate the cellular transfection efficiency of hollow MSNs which suggests that a two-fold increase in transfection efficiency was observed due to

MSNs. MSNs have been proven as an excellent gene carrier because of their ability to achieve a positive charge on their surface. The positive charge has the capability to interact with nucleic acids which are negatively charged to form the delivery complex. The rest of the positive charges of the complex are favourable for cell entry. These groups include amine group and cationic polymers like PEI[51], PLL[52], PDEAEMA[53], PAMAM.[54]

Small amino-functionalized MSNs are far better for the delivery of gene as compared to the cationic polymer grafted MSNs. They have some of the disadvanteges like reduced pore volume, abundant positive charges nucleic acids may hinder the release of gene make them a strong alternative and future source for gene delivery. It can be strongly mentioned that efficient, reliable and exact gene delivery can be achieved by MSNs.

6 WOUND HELAING

Fig. 5: Demonstrates the nano bridging and tissue gluing effect.

Current available options for fast gluing of tissues are fibrin glue, cyanocrylate adhesives, etc. The problem associated with the cyanocrylate adhesives is the immunogenic reaction of severe heat produced at the point of application and damage of tissue may take place at this site. Also, these may liberate formaldehyde which is severly toxic. Moreover, the surgical stitches and staples are also available but the after marks remain in case of stitches so these are also not acceptable. There should be a platform that may glue the tissues and serve as liquid stitches. Mesoporous silica has found its application in this field as well. Nanoparticles have the ability to glue together the tissues by nanobridging effect. Nanobridging requires a paricle size less than 100nm while the clotting of blood depends on the porosity and the paticle size of MSNs.

Various metal oxide nanoparticles have already been proven as effective tissue adhesives but it is worthy to know the ability of Mesoporous silica combined with metal oxide nanoparticles to be an effective tissue adhesive and antibacterial platform for wound gluing and healing. As the mesoporous silica is biocampatible, it does not have any toxic effect post application. It is biodegradable hence it will get degraded to a maximum extent. Meng-meng Lu and Co-investigators, in 2018, designed a silver nanoparticle decorated biodegradable mesoporous silica for rapid wound closure. They studied the platform for its wound healing ability in the Wistar rats. They concluded that the wound closed in 30 seconds while it healed in 5 days. Biodegradability was also confirmed which took place completely in 96 hours. It showed excellent antibacterial activity against Ecoli and the S.aureus which are major wound

infecting organisms. MSNs proved to be an excellent nano adhesive and aesthetic wound healer as well. Wu and other associates, in 2017, developed a ceria nonocrystal decorated mesoporous silica nanoparticles as a tissue glue for wound healing. They immobilized the ultra samll Ceria nanocrystals on the surface of the MSNs. It not only healed the wound but also significantly inhibited ROS exaberation mediated deleterious effects, which potentially accelerated the wound healing process. Also, it did not allow to form any scar. Moreover, the platform can be much useful where wound healing and ROS Scavenging activity will be required simultaneously. It may be interesting to note the haemostatic efficacy of MSN. It could significantly promote the blood clot. There is a direct relationship between pore size and clotting efficiency, while the particle size of MSN has a little influence on the blood clot. The accessibility amd diffusion of clotting- promoting proteins to and from the interior surfaces of MSN may be associated with each other as pore size gets directly impacted, and pores on the MSN surface get removed due the curvature difference caused by the particle size. The ability of MSN to promote cell viability was proved in biocampatibility analysis of MSN where larger pore size resulted in better biocampatibility, but particle size had a negative influence on the cell viability. Rapid haemostasis of MSN in rabbit femoral artery injury testified the superb haemostatic efficiency of MSN. So, we can conclude that MSN has a haemostatic effect and it can be successfully implemented in wound healing; furthermore, it will enhance its effect and braoden its applicability. Moreover, the nano bridging effect of the MSNs could prove itself as a liquid stitches formulation for rapid wound closure.

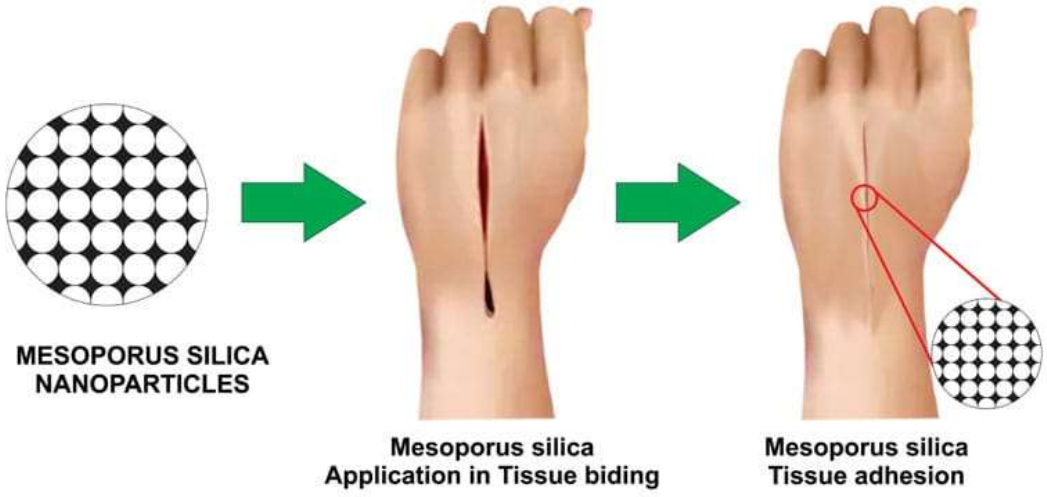

Fig. 5: Application of wound healing by Mesoporous Silica.

Synthesis of Mesoporous Silica Nanoparticles (MSN)

Initially, the groups of Cia[69], Mann[70] and Ostian[71] successfully synthesized and reported mesoporous silica nanoparticles. After that the term "MSNs" became familiar when Victor Lin introduces mesoporous silica nano spheres.[28] In last, few years mesoporous silica nanoparticles have been synthesized with multiple adjustments in synthesis conditions like pH change, using different surfactants or co-polymers, and with different concentrations and sources of silica. In the synthesis of an ideal MSNs the characteristics like well suspended stable solution, controlled and uniform particle size, controlled pore size and large pore volume must be considered.[13] Furthermore, two conditions need to be satisfied during synthesis of MSNs (a) Well controlled nucleation and growth rate of MSNs (b) Non-sticky nature of MSNs.[72] Various synthesis methods of MSNs are discussed below.

Growth-quench appraoch

To quench the silica condensation reaction, Mann et al[70] firstly used dilution anf pH change method to prepare sub-100 nm MSNs, he particle size of MSNs may vary from 23-100 nm by using in different time-delays between dilution and neutralization steps.[72] Triethanolamine[73] and alcohol co-solvents[74] are used as reaction slowing agent due to their silicon- chelating capability. Recently, Suteewong et al.[75] reported MSNs with cubic pore structure having high laminated functionality, are synthesized in which to quench the growth of MSNs ethyl acetate is used.

Limitations: From pH quench approach, less ordered and less stable MSNs materials are resulted due to poor condensation of silica. Similarly, in dilution quench approach scaling up may occur.[72] Considerable time and energy is required to collect MSNs from highly diluted solution.[13]

Separation of nucleation and growth

Mou et al introduce a process to prepare mono-disoerse MSNs in a dilute alkaline solution in two steps i.e. by separating the nuclei formation and particle growth.[76] LaMer diagram clearly explains nucleation , a transparent solution of micelle/silicate clusters containing nuclei are formed by adding the whole quantity of surfactant (CTAB) and small quantity of TEOS. In second step to initiate the growth process, a large quantity of TEOS is added. Uniform inite size of particles is obtained due to the exhaustion of material in growth acceleration process, he resultant MSNs possesses ideal structure order and showing 4 XRD peaks for 100 nm size of MSNs. No aggregation of MSNs occurs when it shows hexagonal

facets. Small particle size can be achieved at low pH[77], and by decreasing the amount of ammonia use (i.e., 280 nm to 300 nm). his method is considered to be size- focusing[78] as it gives very sharp size and shape distribution. Lin et al. Obtain regular hexagons having 2D photonic crystal like structure.[79]

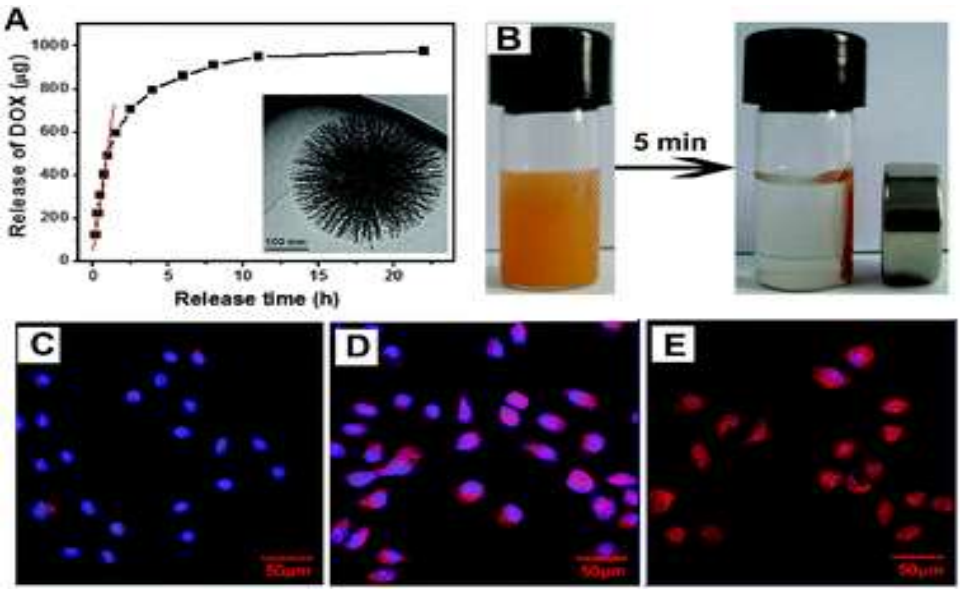

Fig. 6: Illustration of Drug-release profile of DOX-Fe3O4/FMSMs in PBS buffer in TEM image. (B) By using magnet separation process of Fe3O4 / FMSMs. Images of incubated HeLa cell with DOX-Fe3O4/FMSMs ([DOX]=2 mM) for 10 min using Confocal laser scanning microscopy (CLSM) (C), 60 minutes (D), and 6 hours (E) at 37 degree C, blue colour being dyed by Hoechst 33324=the merged images of both the nuclei of cells and red=DOX fluorescence in cells.

Stober method and its modifications

Stober et al. Discovered "Stober method" which is used to synthesis monodispersed silica particles. By using this method silica and non silica particles can be synthesized. He particles having diameter from tens of nanometers to a few microns can be obtained. In this method hydrolysis of tetraalkyl silicates in a mixture of alcohol and water is involved using ammonia as a catalyst.[80-82]

Grun et al. Redesign stober method by changing the composition of stober synthetic method. Hey obtained sub micrometer sized MCM-41 spherical paractical by using cationic surfactant in the reaction mixture.[83] Likewise, uniform MSNs with diferent pore sizes and pore structure are obtained by using mixture of alcohol water and ammonia.[84]

In later studies, it was discovered that at the initial stage of synthesis, the sudden aggregation of small clusters leads to the synthesis of MSNs. And then residual silica precursors react with the surface silanols on MSNs particles.[85]

Nooney et al. prepared mesoporous silica nanoparticles with the size ranging from 65to740nm by using diferent ratio of tetraethyl orthosilicate (TEOS) surfactant under dilute conditions. He also used netural(n-dodecylamine) and cationic (CTAB) surfactants as templates in their experiment.[71]

Quio et al, found that decrease in pH from 10.0 to 6.0 lead to increase the size of MSNs from 30nm to 85 nm due to decrease condensation rate.[86] Furthermore, chiang et al. Studies all the particles size of MSNs and concluded that pH value played a key role in controlling the size of MSNs as shown in figure 7.[87]

Moreover, Lin et al. demonstrated that the MCM-48-type MSNs dismeter ranging from 70-500nm can be obtained by adding diferent amounts of pluronic F127.hey also used CTAB, pluronic F127, NH40H and TEOS to synthesis MCM-48-type MSNs.[88]

Hollow silica nanoparticles synthesis

Soft templating method: hollow silica nanoparticles, is a sub-class of mesoporous silica nanoparticles and is denoted by HSNs. Because of the important MSNs applications in drug release and bio-sensing, hollow MSNs.[89] Sot templating method for the preparation of mesoporous silica nanoparticles(MSMs) includes:

* Single micelle- templating.
* Vesicle- templating.
* Micro- emulsion- templating.

Single micelle- templating: yang et al. synthesized small hollow organosilica nanotubes and nano- spheres by using sufficient amount of organosilica as a precursor and pluronic triblock copolymer with the different hydrophobicity.[90,91] Mandal and kruk produced HSNs of varying size by using pluronic F127 block copolymer template synthesis of ethylene- bridged organosilicas in the presence of swelling agent.[92] Cationic block coploymer micelle used under.

Vesicle- templating: Vesicle templating methodis used to further increase the size of HSNs. As a source of silica, mixture of silanes and silicates are used as well as cationic surfactant

and anionic co-surfactants are involved to lower the curvanture as meso- structural templates.[94] Co-codensation process is used to synthesis uniform MNMs with the size of 25-105 nm. his processs invovles the co-codensation of tetraethylothosilicate (TEOS)and oraganotriethoxysilanes in an alkaline aqueous solution containing trithanolamine and cationic surfactant cetyltrimethylammonium chloride (CTACl).[95]

Another important method to prepare mesoporous silica nanorods and hollow spheres are to use a mixture of single tailed anionic and cationic surfsctants. heses surfactants lead to the formation of a variety of meso- structures like cylindrical micelles, spherical miscelle and vesicles. These micelles have various remarkeble morphologies and act as organic templates or the synthesis of desired forms of mesoporous silica nanoparticles. hen, at a pH where templates and silica species have matching interactions, condensates around the curved surface produce silica nanoparticles with organic structures.[96]

Micro-emulsion- templating: for the preparation of hollow
Mesoporous silica nanoparticles, a stable micro-emulsion of oil- inwater (o/w) is used. His emulsion is prepared by mixing oil, water, surfactant and small amount of alkaline solution. These hollow silica nanospheres are prepared by controlling condensation of silica shell thickness.[97]

Mou et al, introduced another method in which they used waterin-oil (w/o) emulsion consisting of water, hydrocarbons and cationic surfactants, and prepared thermally stable nanoparticles.[98,99]

Hollow silica nanospheres with relatively large mesopores on its outer surface are synthesized by Hao et al. In this method 1, 3, 5 trimethylbenzene (TMB) act as a swelling agent and triblock copolymer pluronic F127 act as a template in the presence of an inorganic salt i.e., potassium chloride.[100]

Hard templating method: In biomedical ield, both discrete
And mono- dispersed MSNs plays a key role in providing enough stability in physiological environment and its nano-size provides effective distribution of a drug in the body. Because of their hollow interior, MSNs have large capacity to load biomedicines, enzymes, or nanoparticles and ligands.

In mono-dispersed MSNs, products polymer lattices, metal oxides and silica colloids are used

in hard template method. High- idelity inorganic silica replica of hard template method requires 3 basic measures;

Saturation of silica at the surface of organic template is a fast process as compare to self condensation of silica species in bulk solution. For this silicate surface must have a suitable functional group for its recognition under appropriate reaction conditions.

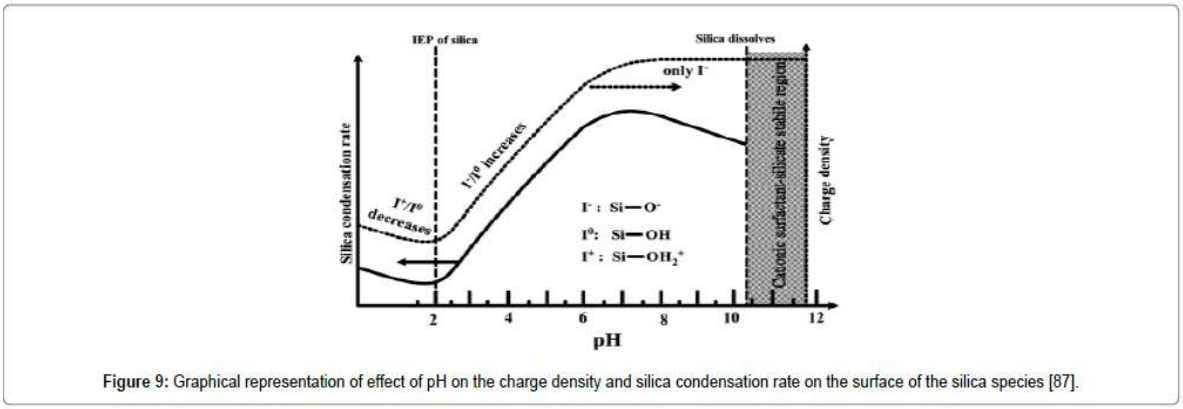

Figure 9: Graphical representation of effect of pH on the charge density and silica condensation rate on the surface of the silica species [87].

Fig. 7: Graphical representation of effect of pH on the change density and silica condensation rate on the surface.

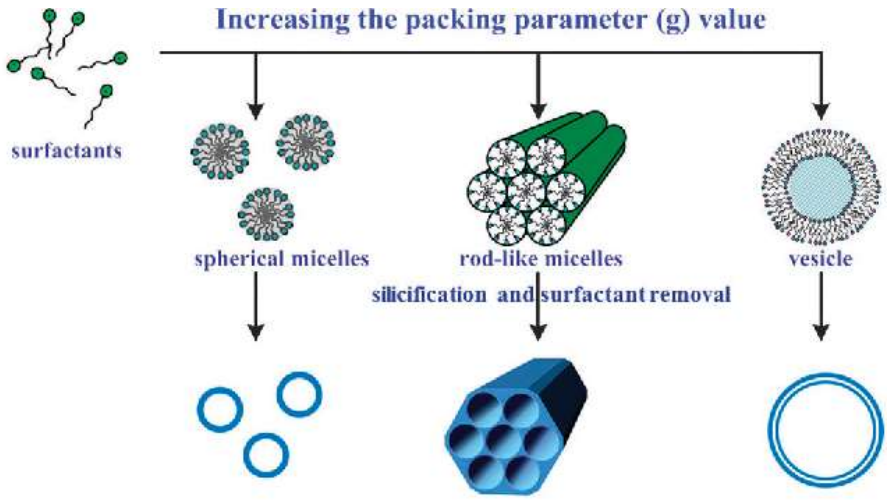

Fig. 8: Soft Surfactant templating approaches to synthesize mesoporous silica.

- In the whole process of silicate deposition and condensation, stability of organic template is essential. He stronger interaction of any of the components of surface activated template with silicates may lead to the failure of silica casting. Due to this, the original organic template leaches out and gathered at the surface of silicates rather than the organic template surface.

- The sacrificial template approach is used to remove template without breaking inorganic silica cast. In this approach, dissolvable or combustible internal part can be removed after solvent extraction, acid- dissolution and calcination under mild conditions.[13]

Hard templating method for the preparation of mesoporous silica nanoparticles (MSNs) includes:

- Polymer latexes- templating.
- Metal or metal oxide nanoparticles.

Polymer latexes- templating: On the surface of polymer latex, silication occurs through surface activation by using suitable functional group. A layer-by-layer deposition technique via electrostatic attractive interaction is used to introduce functional group for silica gelation, as surface activation method.[101]

To avoid the leaching of capping agents during the process of silica deposition, the strong interaction between functional group and polymer latex is needed. However, polymer latex templating method is avoided because it is a complex procedure for surface modification.

By controlling the pH values, we can achieve high integrity of MSNs. Meso- structure and pore size of silica shell depend on type of surfactant used. Likewise, mesoporous silica replicas can be synthesized by using appropriate ratio of surfactant or polymer / latex. Along with hollow MSNs broken mesoporous silica particulates are formed at both lower and higher ratio.[13]

Metal or metal oxide nanoparticles: discrete and mono-dispersed single Fe3O4 nanocrystals mesoporous silica are prepared by Kim et al. For this purpose cetyltrimethylammonium bromide (CTAB) is used as stabilizer and mesostructural directing agents.[102] In another similar study, Liong et al. Proposed a method to synthesis MSNs in which mesoporous silica surround the iron nanoparticles, pores contain the hydrophobic anti-cancer ligand, whereas, folic acid and phosphate are used for surface modification.[59] The thickness of mesoporous silica shells can be controlled by adjusting the ratio of surfactant and amount of silica source.[13]

Furthermore, a mixture of anionic and zwitter ionic surfactant is used to form vesicles in order to encapsulate the MSNs. He protoned amino-silica is added into the silica source to match the interaction with negatively charge surface. Different yolk-like silica shell structures

synthesized after hydrolysis and condensation. Hese yolks can be Fe203 nano-spindle or silica beads.[103]

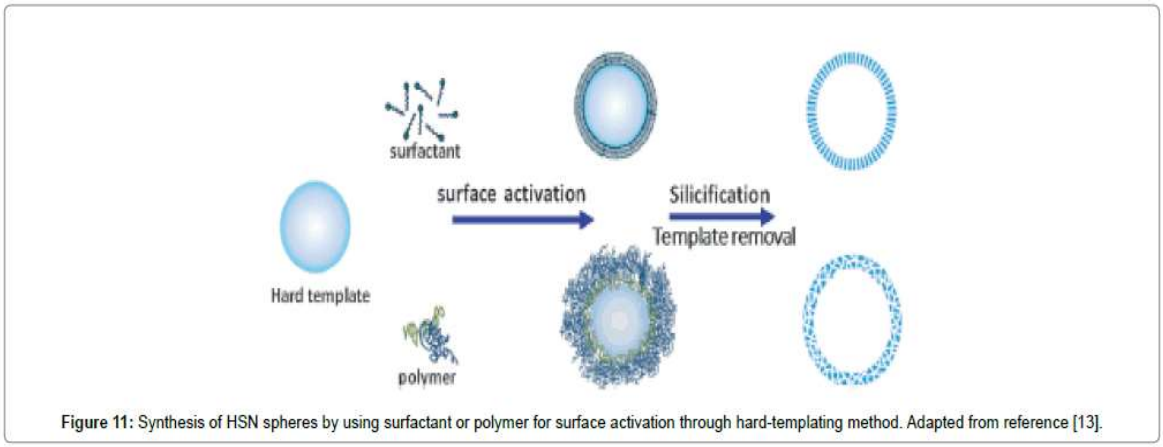

Figure 11: Synthesis of HSN spheres by using surfactant or polymer for surface activation through hard-templating method. Adapted from reference [13].

Synthesis Procedure

Surfactant: 0.78 g Cetyltrimethylammonium bromide (CTAB) in Round Bottom Flask (RBF).

↓

21.6 ml nanopure water + 3.42 ml EtOH + 41.02 microlitres Diethanolamine.

↓

STIR FOR 30 MIN IN OIL BATH, 60 degree C (SOLUTION IS CLEAR)

↓

AFTER 30 MIN. STIIRRING
TMOS IS ADDED (SLOWLY)
(COLOUR CHANGE OCCURS)

↓

2.19 ml Tetramethyl orthosilicate (TMOS)
Added slowly- over 6 minutes.

↓

SOLUTION STIRS FOR 2 HRS, THEN….

PART 2: WASH OUT CTAB

THE MESOPOROUS TEMPLATE TAKES SHAPE.

20 ml of MSN-CTAB in MeOH solution

……previously washed with EtOH (2-3x)

HCL IS ADDED AND STIR 6-8 HRS

IN OIL BATH, 60 DEGREE C

1.44 ml HCL

Assists in CTAB removal

THE MSN IS WASHED AND DRIED…

NOW… THE FINAL PRODUCT

NANOPARTICLES!!!

Application of Mesoporous Silica Nanoparticles

Mesoporous silica nanoparticles (MSNs) have a number of potential applications depending upon the nature of pore, size, shape and connectivity of mesoporous silica particles as we discussed earlier in detail.[41] In catalyst, the short channels of mesoporous silica nanoparticles based catalysts can manufactured by inserting different functional group as well as different metal oxides and metal complexes.[104-105] mesoporous silica nanoparticles contain small channels as compare to mesoporous silica bulk material which improves transport of large molecules for example, biomolecule and biodiesis. That's why reactant and product molecule use nano-channels and do not attain long route.[13] he biological application of mesoporous silica nanoparticles includes imaging and diagnostic agents, specificity, dispersibility and capability to load and deliver of high concentration of different molecules.[106]

Imaging and diagnostic agents

Mesoporous silica nanoparticles are used for quantitative imaging for a longer time period, when use in small dosage and it has ability to eliminate from the body when the imaging

process is complete. For this purpose, silica based imaging nano-probes are extensively used for optical resonance imaging and Magnetic Resonance Imaging (MRI) or a combination of both.[107] Bio-distribution, cancer cell targeting efficiency, cytotoxicity, internalization pathway and the progress of the therapy is observed well by direct method of imaging of mesoporous silica nanoparticles. He core material can be illed with therapeutic agents, quantum dots and fluorescent dyes like Fluorescein isothiocyanate (FITC) and rhodamine B isothiocyanate (RITC). The most commonly used Near-IR dyes for imaging includes AlexaFluor 700 and DyLight 680. He Fluorescent mesoporous silica nanoparticles that qare resulted have the ability to generate high resolution, provide quantitative data and multichannel images.

Target Specificity

Mesoporous silica nanoparticles can be used on the intended areas to reduce non-specific binding and to increase specific binding to target cell or tissue. Both passive and active targeting specificity plays a major role in increasing bioavailability.[106] Target specificity of mesoporous silica nanoparticles decreases the dosage of drug and eliminates the harmful toxic effects of drugs after administration.[108]

Passive targeting increases permeability of tumor blood vessels and allow the accumulation of nanocarriers at tumor site. But decrease therapeutic efficacy, drug expulsion and multiple drug resistance occurs due to the lack cell specificity.[109] Binding and internalization of nanocarrier can be increase by selective targeting I.e., specific interaction of drugs with receptor site.[110] His could only be happen when cancer cells or tumor cells are highly exposed with receptors (104-105 copies/cell) as compare to normal healthy cell.[106] Xia et al. Manifested that if mesoporous silica nanoparticles coated.

With cationic polymer (PEI), it will increase the uptake of MSN.[111] Meng et al. Proved that increase EPR effect can be achieved on xenograt model by both controlling the size and addition of PEI/PEG copolymers as a coating material.[112]

In active targeting surface modification of MSN with cancer specific targeting drugs increase the specificity of drug to the cancer cells as compare to normal healthy cells.[113] For this purpose biologically active drug like folate RGD peptide and transferrin are used.[114] For instance, folic acid as folate receptors are extensively use in many types of human cancers includes endometrial breast colorectal. Lungs and ovarian.[113,115] More efficient drug delivery

requires high specificity and binding affinity which can be achieved through high concentration of surface conjugated drug molecule that ultimately enhances multivalent binding effects.[111]

Capability to load and deliver of high concentration of different molecules

The loading of high concentration of various classes and multiple cargos is achieved by large surface area and through controlling the surface chemistry of MSNs, and it enter into the cell through the process of endocytosis and macropinocytosis.[116-118] Initially, drugs having low solubility in water like ibuprofen and aspirin were used for drug delivery through MSNs.[10] Lu and Liong et al. Latterly worked on mesoporous silica nanoparticles for the delivery of hydrophobic chemotherapeutic agent, camptothecin, into cancer cells.[119] He mesoporous silica nanoparticles have large surface area and pore volume which permit hydrophobic ligands to enter into the pores, from non-aqueous environment and retained in aqueous environment. But in case of hydrophilic drugs further changes of MSNs is required. Such as, Meng and Liong et al. Enables loading and reaction of positively charge hydrophilic drug, doxorubicin (DOX) by using negatively charge group on the surface of MSNs.[120]

The capacity of doxorubicin in MSNs is 1000 times greater than FDA approved Doxil because of its attractive electrostatic interaction and high surface area.[117]

Dispersibility

For biomedical application MSN must remain dispersed for its stability and its aggregation must be avoided because due to this cell internalization suffers, its distribution in body become difficult to control and enlarge particle size causes high toxicity.[106] By chemical modification of the surface of MSNs,[119] coating with proteins and polymers[112] and lipid bilayer coating particle aggregation can be decreased.[117,118,121] By using these methods stearic hindrance and electrostatic repulsion is achieved , as a result stable saline dispersion of MSNs is formed.[106]

Other applications include bio-sensing and cell tracing, use in optoelectronic devices, CdS nanoparticle capped MSNs use for delivery of drug molecules/ neurotransmitters.

Bio sensing and cell tracing

The versatile surface chemistry and small particle size of MSNs work as a sensor system for the detection of target within individual cell both in vivo and in vitro.[122] Nanoparticles have

the ability to avoid fluorescence, self-quenching and other diffusion related issues. His capability of mesoporous silica nanoparticles to functionalize its surface with greater amount of cell recognizing agents or other site directing compounds make MSNs an excellent cell tracing agent.[123]

Use in optoelectronic devices

A transparent silica- polymer, having high mechanical strength and low thermal expansion, can be synthesis by accurate surface modification of MSNs.[124] These high transparency MSNs- polymers are used in optoelectronic devices like optical fibers LED or solar cell covers, and light guide films.[13]

CdS nanoparticle- capped MSNs

Lin et al. Explained the stimuli- responsive controlled release system in MSNs.[28] he CdS nanocrystals with mercaptoacetic acid coating were and encapsulated drugs/ neurotransmitters. With the help of various di-sulphide reducing agents, the di-sulphide linkage between MSNs and CdS caps were cleaved and the entrapped contents released from the channel.[13]

CONCLUSION

Mesoporous Silica possesses tremendous desirable properties. The exploitation of all these properties can lead to benefits and gains in numerous applications. The pore size and loading capacity facilitate the controlled release of the drug; moreover different functionalizations of MSNs can be used to target drugs at specific sites. The release of these drugs can be monitored by ultrasonic waves, light, pH, magnetic properties, etc. The crystalline drugs are converted to amorphous by entrapment into MSNs which provide enhanced solubility and dissolution rate. The nanobridging effect associated with MSNs is utilised by combining with drug or metal nanoparticles, which has proved to be a significant tissue adhesive and an excellent wound healer. Maximun porosity and the adsorption capacity of MSNs make their use feasible in the loading of drugs, NPs, etc. And in drug therapy. MSNs can also be used as a bioimaging tool by combining them with an MRI active agent.

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