Review Article

Surface Decorated Mesoporous Silica Nanoparticles: A Promising and Emerging Tool for Cancer Targeting

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ABSTRACT

Background: In nanotechnology, the most promising inorganic materials for cancer targeting are Mesoporous silica nanoparticles (MSNs). This review gives a state of the art description of current status and applications of surface functionalized MSNs in the field of cancer theranostics. It also gives a detailed description of surface decorated MSNs researched upon so far in various types of cancer and the benefits associated with these. **Applications:** Ease of surface functionalization also offers additional functionalities like cell recognition, absorption of specific biomolecules, improving cell interaction and cellular uptake that significantly modifies the *in vitro* and *in vivo* behavior of the drug. Therefore, they have proved to be effective in gene delivery and multi drug resistance cancer treatment. Though, their biocompatibility still remains debatable. Biodegradation of MSNs is quite simple and it is safely excreted through kidneys via silanoic acid formation. Moreover, the USFDA has already approved the silica under the 'GRAS' category which has further made MSNs a thrust area for research in cancer theranostics. **Summary:** This review summarizes the journey of multifunctional MSNs beginning with its origin, mechanism of formation of mesoporous structure with surface functionalization to till date and recent advances in the arena of cancer targeting.

Key words: Mesoporous silica nanoparticles, Cancer targeting, Surface modification, Theranostics, Biomedical Application, Biodegradation.

INTRODUCTION

Cancer is second leading causes of death amongst all the lethal diseases prevalent. It is estimated globally that nearly 1 in 6 deaths is because of cancer.[1] Which puts a tremendous pressure on the researchers to find a cure for the same. Every day new advances are being made towards cancer treatment, by synthesizing new moieties or by researching new molecular mechanisms. Current drug molecules available for cancer treatment include peptides, steroid molecules and oligonucleotides. Most of them are hydrophobic in nature and hence, possessing low solubility and bioavailability. Therefore, the desired therapeutic dose will not reach to the target and requires a higher dose for therapeutic effectiveness. This may damage healthy cells and tissues, leading to severe side effects like, severe hair falls resulting in baldness, acute vomiting and nausea, low blood cell counts making patients more susceptible towards developing infection or anaemia.[2]

Since last couple of decades, research breakthroughs have been made in outlining pharmaceutical medications for different disorders. This has significantly propelled the learning of physico-chemical properties and cellular uptake mechanisms and thereby generating effective therapeutic strategies. In chemotherapy, the present treatment strategies basically rely on the utilization of ordinary cytotoxic medications which have adverse effects and restricted efficacy. Numerous studies ascribe this to the inefficiency of anti-cancer drugs in reaching the target site. To tame this obstacle, a target specific nano drug delivery system is employed

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for effective delivery of drug to the targeted area, thus minimizing its adverse effects. Furthermore, nano sized drug delivery system can passively targeted to cancer cells by Enhanced permeability and retention (EPR) effect.[3,4]An ideal drug delivery system should encourage the intracellular accumulation of drug in the targeted cells and maintain drug concentration to its effective level. This is possible by two ways viz., (a) by designing a formulation that gives controlled or sustained release or (b) by concentrating the drug to its target i.e. tumor cell. The research thrust these days is on designing a targeted drug delivery system that will deliver a therapeutic dose to the cancerous cell and ultimately reduce its reach to healthy cells thereby decreasing their side effects.[5] Targeting concept is now in focus and vast researches are involved to formulate a nano system, including liposomes,[6-8] solid lipid nanoparticles,[9] Self-micro emulsifying drug delivery system (SMEDDS).[10] Mesoporous silica nanoparticle (MSNs) is one of the nano carriers, which are in focus for targeting the tumor cells.[10,11]

MSNs based targeted delivery offers a promising tool for increasing the intra tumoral concentration of anticancer drugs and limiting its toxic effects to normal cells as they bind to cell membrane receptors which are over expressed in cancer cells only. This has led to a great research interest towards targeting the drug loaded MSNs into tumor cells. The Unique properties of MSNs like flexible surface, porosity, shape, size, surface functionalization etc collectively decide mechanism of action, their interaction with living body components such as cells, tissues and biomolecules and release pattern of formulation in biological systems, with considerable increment in therapeutic ability. Together, all these have a direct impact on safety, biodistribution and theranostic potential.[12] Moreover, theranostic application of MSNs is also in the limelight where, the name theranostic itself suggests dual application of MSNs in therapeutic and diagnosis filed. This dual characteristic is solely attributed to its flexible surface that can easily be modified to achieve the desired objective.[13] MSNs with particle size ranging from 50-200 nm have been studied as nanocarriers for the delivery of small drug molecules and antigen and it has been proved that MSNs are having high drug loading capacity.[14-18] Furthermore, tumor targeting has been specifically accomplished either by functionalization of nano-carriers having selective and specific interaction with tumor-over expressed receptors[19-21] or by designing stimuli-responsive nano therapeutics or combination of both.[22,23] It has been proven that tumor cells are more acidic as compared to healthy cells and this concept can be utilized for targeting of MSNs by coating their surface with different pH responsive material. E.g. pH responsive microspheres having a core of Fe_3O_4 nanoparticle, a bilayer of mesoporous silica and a shell of crosslinked poly methacrylic acid (PMAA), were successfully synthesized via distillation precipitation polymerization.[24] The temperature difference between normal and cancerous cell is also an another approach used for targeting.[25] Redox,[26] light[27] and enzyme[28] are some of the emerging strategies for the same. Moreover, MSNs also possess unique features like biocompatibility, high drug loading and entrapment efficiency, stability on storage, cell specificity and site directing ability.[5,29] Despite of all these applications, they are yet to be explored and commercialized. A general review of the recent advances in cancer targeting using MSNs is presented here.

Mesoporous Silica Nanoparticles

Mesoporous materials are in the limelight due to their potential applications in catalysis, adsorption, ecology, nanotechnology, chemical and biological separation, chromatography, photonic and electronic device preparation and medical uses. Since last decade mesoporous silica has shown tremendous potential in drug delivery applications.[30] MSNs possess unique features like large surface areas, pore volume and pore size. Different types of carriers available are shown in Table 1.[31-33] Amongst various nano drug delivery systems, MSNs are emerging as a promising drug carrier, which can perform all the aforementioned functions at the same time. After the discovery of highly ordered mesoporous silica material MCM-41 (Mobil crystalline of materials) by the mobile corporation in 1992, noteworthy research efforts have been in progress to accomplish control over the characteristics of mesoporous silica especially pore size and morphology. Lately, various types of mesoporous materials have been discovered e.g. MSU, SBA, HMS, OMS, TUD and MCF were developed with typical pore size and particle shapes.[34,35]

The unique identities possessed by MSNs as mentioned earlier helps in encapsulating a variety of therapeutic agents and also in targeting them to cancerous cells. Notably, the fabrication of MSNs is simple, scalable, cost-effective and controllable.[36] MSNs have also been widely used as a controlled drug release and delivery carriers,[37-39] biosensors,[40] bio-markers,[41] enzyme supporters,[42,43] etc. Usually, MSNs are utilized as a drug delivery system because of their unique 2D hexagonal framework, uniform molecular sizes, controllable molecular morphology with the tendency of modifying inner and outer surface.[44] Apart from having such unique qualities, MSNs have a couple of additional advantages like high thermal and chemical stability. Also, the ease of

functionalization makes them perfect for use as a support for adsorption and catalysis.[45] Conclusively, it could be said that MSNs are nanomaterials having characteristics of both silica as well as mesoporous materials and can be functionalize MSNs surface by silica chemistry and also integrate the desired material within the silica matrix.[46]

Design and Preparation of MSNs

Principle Behind Formation of MSNs

The general mechanism of MSNs synthesis includes condensation of silica precursors governed by self-assembled liquid-crystal arrays of surfactants. Thorough studies state two proposed mechanisms for the formation of MSNs. The first synthesis procedure was proposed by Mobile corporation scientists in 1992 named as a Liquid crystal templating (LCT) mechanism.[47] As per this proposed mechanism surfactants have a structure directing property which encourages the formation of the mesophase. Hence, the mesoporous structure formation depends on the hydrocarbon chain length of the surfactant tail group and it has been proved that the increment in the surfactant concentration may initiate aggregation of spherical into cylindrical or rod-like micelles. In other words, this mechanism involves a condensation of silicate ions around the preformed hexagonal surfactant array (Sol-gel formation). The final step involves exclusion of surfactant to get a highly ordered hexagonal pattern as shown in Figure 1.[48] However, according to another strategy, surfactant will form a micellar structure which interacts with silica and bi to tri-layered silica will form surrounding the micellar assembly. Spontaneously these species will self-organize to form a well-ordered hexagonal structure.[49]

Various Elements Influencing Drug Loading

Application of mesoporous material as a drug carrier is being comprehensively studied in pharmaceutical field to develop targeted drug delivery systems. Loading of the drug in MSNs is the most critical and key portion contributing to success of formulation which ultimately depends on the selection of an appropriate loading condition. There are several factors that affect the encapsulation of the drug in the MSNs like loading method, pore size, pore volume, surface area, surface chemistry, effect of solvent, temperature and time of stirring, etc as described further.[30,50]

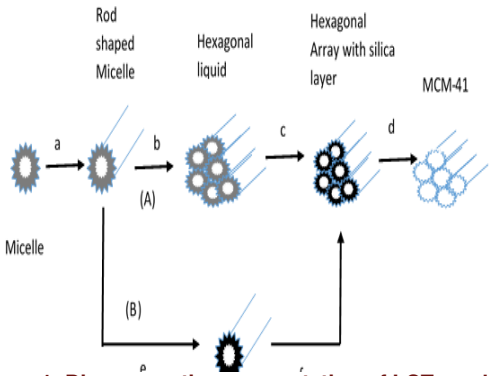

Figure 1: Diagrammatic representation of LCT mechanism of MSNs formation with two possible pathway; (A) a: growth of micelle; b: aggregation; c: hexagonal assembly with outer silica layer; d: calcination (B) e: Outer silica layer on rod shaped micelle; f: packing to form hexagonal structure [49].

Loading methodology plays a vital role in drug encapsulation within nanoparticles. The type of loading method used, affects the extent of drug being loaded into the mesopores, their fitting into the pores and distribution in the carrier. The various methods used for drug loading in MSNs are an *immersion method* in which the MSNs are immersed in concentrated drug solution. The drug molecules fill the pore of nanoparticles through capillary action followed by drug diffusion in MSNs and adsorption on the pore wall. The drug loaded nanoparticles are collected by filtration. Ibuprofen loaded MCM-41 was obtained by ensuing this method.[51] In *Incipient wetness impregnation method* a highly concentrated drug solution is used for loading of the drug whose concentration is close to its solubility. Once the solvent gets evaporated, the chances of recrystallization of residual drug become high in this method. This approach has been applied for encapsulation of various drugs such as Aceclofenac,[52] Carvedilol,[53] Ezetimibe,[54] Fenofibrate,[55] Indomethacin.[56,57] Melt method is a loading method where a physical mixture of MSNs carrier and drug is prepared and ignited above the melting point of the drug. However, there is a high chance of degradation of drug as the mixture is heated above the melting point.[50] In *Rotavapor method* instead of using normal or vacuum filtration procedure, rota evaporator is used for removal of the solvent. A concentrated drug solution is prepared, followed by addition of carrier and stirring for a predefined time at a particular stirring speed, subjected to evaporation in rota evaporator. Indomethacin drug has been successfully loaded by this method.[56] The same approach has been applied to Atazanivir.[58] In a *Fluidized bed method*, the solvent is evaporated by spraying and heating the suspension using the fluidized bed machine. Indomethacin has been prepared by this method using MCM-41 as a carrier. It was concluded that degree of loading was higher in rotavapor and fluidized bed method compared to the conventional impregnation method.[56] Apart from the loading method, the type of solvent, degree of stirring, temperature of stirring can also affect the drug loading inside the pores. However, from the various factors affecting drug loading, type

of loading method employed is a key factor having an active impact on the degree of success of drug loading.

Surface Functionalization of MSNs

Surface Functionalization of MSNs Through Mussel-Inspired Chemistry

Mussel chemistry is a very important tool useful in surface functionalization of nanocomposites. The facileness and versatility of mussle inspired chemistry make it an attractive concept to follow.[59,60] Mussel adhere strongly in wet conditions to wood and are underwater specialist due to different mussel foot proteins containing 3,4-dihydroxy-L-phenylalanine (DOPA) and lysine amino acids secreted during adhesive formation in the adhesive plaque of mussel byssus.[61] Mussel inspired polydopamine coating has garnered a significant attention due to simplicity, material independency in deposition, favorable cell interaction and strong reactivity for secondary functionalization.[62] Since PDA contain both catechol and amine groups it is used as a one-step facile method for surface coating in nanoparticles useful in material science, biomedical, biology and environmental fields.[60,63-65] PDA is an emerging soft matter and a crucial component of mussel inspired chemistry.[66] Wei *et al.* synthesized novel fluorescent organic nanoprobes for biological imaging applications based on self-polymerization of dopamine and polyethyleneimine.[67] A similar principle is applied to inorganic silica nanoparticles.

Biosilification between PDA and silicic acid is utilized. PDA blocks are selectively incorporated into silica framework by controlled addition of Dopamine. The PDA-MSN hybrid nanocomposites have proved to be advantageous exhibiting a high drug loading, sustained drug release and enhanced anticancer efficacy.[68] They can also serve as useful nanocatalyst and antimicrobial agent.[69] PDA-MSNs are responsive to pH stimulus and hence can act as an effective anticancer agent. The PDA coating works as an effective gatekeeper for time bound pH sensitive controlled release of drug.[69] Polydopamine and peptide decorated MSN has been researched upon as potential targeted drug delivery system for bladder cancer therapy.[70]

Pore Gating

This system involves unifying of bulky molecular moieties like proteins and peptides or incorporation of metals like iron (Superparamagnetic iron oxide nanoparticles; Fe-NP) and gold (A gold nanoparticle; Au-NP). Giri S, *et al.* formulated the mesoporous silica nanorods with iron oxide (Fe-NP) cap, possessing a redox responsive cleavable disulphide linker which upon cleavage releases the cargo.[71] One more pore gating MSNs has been designed by researchers A Schlossbauer, *et al.* which deals with the strategy of melting of DNA linkers by MSNs decorated with temperature programmable molecular valve system comprising avidin caps.[72]

External surface modification of MSNs

Outer layer of MSNs carrier is feasible for surface modification and provides an opportunity to prepare tunable MSNs. This external surface decoration may affect the release profile and may possess targeting efficiency.[73]

Two basic mechanisms exist for grafting of functional groups on the surface of carrier viz., physical and chemical. These also depend on the solubility of the drug. Physical adsorption is commonly seen in external grafting of MSNs. Hydrogen bonding, electrostatic and hydrophobic interactions are the representative forms of the physical adsorption. In case of non-functionalized MSNs, where plenty of OH groups are available on the surface, hydrogen bond becomes a representative of physical adsorption, but once the surface is functionalized latter two types of interaction will represent physical adsorption.[50]

Two main strategies are applied for surface modification viz., co-condensation and post-synthetic grafting method. In the former technique, functionalizing ligand is administered during the synthesis of bare MSNs, whereas in the latter case, functionalizing moiety is incorporated once the unmodified MSNs carrier is synthesized.[74]

Co-condensation process

The process of co-condensation involves direct functionalization of MSNs' outer surfaces during synthesis only. This strategy modifies mesoporous silicate surface by sol-gel chemistry between tetra-alkoxysilane and one or more organo-alkoxysilanes with Si-C bonds and this will synthesize hybrid inorganic-organic mesoporous silicates. This method is also applicable for synthesis of MSNs for imaging purposes. E.g. use of co-condensation method for incorporation of two different Gd^{3+} complexes at very high loading (15.5%–28.8 %w/w) and this synthesized, MCM-41 carrier was successfully characterized by SEM, TEM, TGA, PXRD, DCP. General steps involved in synthesis of MSNs (Addition of silica source i.e. TEOS, surfactant, water etc., autoclaving and calcination) are displayed in Figure 2.[75,76]

Post synthesis strategy

This process involves the surface modification after synthesis, i.e. post synthesis functionalization method. It involves modification of the surface of MSNs usually after removal of surfactant. Here, the Si-OH group

which is present on the surface of MSNs acts as an anchoring moiety for functionalization. It is mostly carried out by silylation process. Grafting can be done on internal as well as external surface. The detailed pictorial diagram is depicted in Figure 3.[76]

The co-condensation method is preferred as found in most of the literature due to more uniformity. e.g. Surface of MCM-41 was functionalized by vinyl group using both the above-mentioned techniques. Lim and Stein have compared the relative distribution of surface groups based on powder X-ray diffraction (XRD), X-ray photoelectron spectroscopy (XPS) and bromination kinetics data. Results showed a wider distribution of vinyl groups on the surface of MCM-41 prepared by direct co-condensation method, whereas for those prepared by the post grafting method, the results showed a lack of uniformity with a large proportion of vinyl groups on the external surface of the crystallites or inside channels but lesser number near the channel openings.[77] In products obtained from a direct co-condensation reaction, the vinyl groups appeared to be more uniformly distributed throughout the channels. A number of functional groups have been trying to set the functionalized MSNs which could be used as drug carriers. E.g. Outer decoration of MSNs with disulphide linked polymer to achieve the redox responsive release of drug has been done by author Liu R, *et al.*[78] A variety of functional group or moieties can be attached on the surface of MSNs by either of the above mentioned techniques as listed in the Table 2.[11,79-90]

Backfilling strategy is another approach used for MSNs fabrication. It is a simple approach to introduce active molecules into the empty pores of mesostructured silica wherein, these empty pores are exposed to the solution or vapour of active molecules and are allowed to diffuse. However, this strategy does not involve chemical modification of the material and hence is a less widely used method.[5]

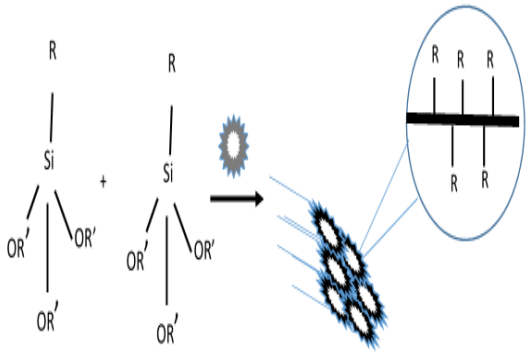

Figure 2: Basic steps involved in MSNs synthesis.[64,65]

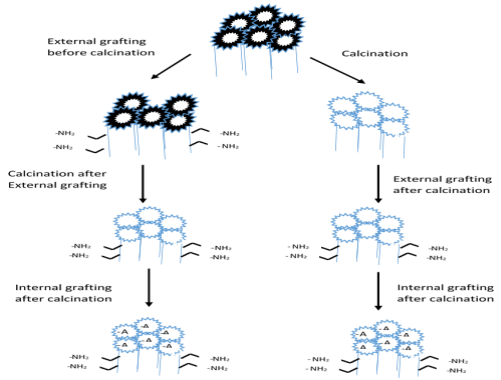

Figure 3: Two different strategy for functionalization of carrier.[65]

Tunable Mesoporous Silica Nanoparticles

Surface functionalization results in the alteration of MSNs feature like pore size, pore diameter, pore volume, surface area, etc. The pore structure can be modified prior to the surface modification by thermally annealing in an inert nitrogen atmosphere. This treatment reduces the overall pore volume, since it causes pore coalescence, which may melt pores together. Particle size and particle shape are unique properties of MSNs and solely represent the release profile of the drug.

Particle Size

Mesoporous silica microspheres

Mesoporous silica has size ranging from nano to micro size, i.e. mesoporous silica nanomaterials and mesoporous silica micromaterials respectively. Well established method for synthesis of monodisperse non-porous silica particles are Stober method. This method involves the use of TEOS (A silica source), alkyltrialkoxysilane (Porosity generating molecule), ethanol (Co-solvent), water and aqueous ammonia (Catalyst).[91] Unger and Stucky are the first group to synthesize micrometer sized mesoporous silica spheres.[92,93] It was concluded that by controlling the ratio of water, ammonia, ethanol and other reagents one can get micron to submicron sized mesoporous silica sphere with varying porosity and surface area.

Mesoporous silica nanospheres

A well-known mesoporous silica nanocarrier is MCM-41, which usually involves the use of TEOS as a silica source. Often fumed silica is used as a silica source, cationic surfactant CTAB or CTAC is added as a structure directing agent and water is the used as a solvent. These are a very commonly used ingredients for mesoporous silica nanosphere synthesis by various researchers. But the proportions of these materials are varied depend-

ing upon the synthesis scheme which ultimately makes a difference in surface area, pore diameter and pore volume, even though utilizing the same ingredients (Tuning of surface area and pore volume). The MSNs are exposed to facile endocytosis in both plant and animal cell without exhibiting much cytotoxicity, this is attributed to their tunable particle size ranging from 50 to 300 nm. A typical MSNs have an average particle diameter, surface area, pore size and pore volume around 100 nm, >900 m^2/g, 2 nm and >0.9 cm^3/g respectively with the hexagonal structure. This can be altered by modifying the time required for hydrothermal treatment, molar composition of ingredients used and duration of calcination.[38]

Particle Shape

MSNs can have various shapes like spheres, rod, tube etc. This again depends on ratio and type of ingredient taken during synthesis. E.g. incorporation of double concentration of TEOS, NaOH and CTAB gives tubular MSNs rather regular spherical MSNs with the same pore size and structure. By increasing the APTMS/TEOS ratio from 1.28% to 12.8mol%, shape simultaneously changes from kidney bean rod to sphere.[94] Replacing APTMS with AAPTMS and AEPTMS gives twisted columns and micrometer size mesoporous silica spheres. Using 1-octadecyl-3-methylimidazolium as a surfactant template leads to the generation of a helical structure instead of parallel channels.[95]

Recent Development of AIE-Active Materials for Biomedical Applications

Synthesis of Fluorescent polymeric nanoparticles (FPNs) with AIE emission has been widely researched upon. An effective and facile method for their synthesis is microwave-assisted Kabachnik–Fields method which gives AIE active FPNs possessing high water dispersity, intensive fluorescence and low cytotoxicity which enhances their applicability in biomedical field apart from being a facile, fast and atom economical strategy.[96] The AIE phenomenon was first reported in 2001 by Tang and co-workers.[97,98] FPNs based on conventional organic dyes suffer from Aggregation caused quenching (ACQ) and effect and hence exhibit reduced fluorescence intensity. Whereas organic dyes with AIE characteristics show a weak fluorescence in dilute solution and strong one in aggregated state. This can easily conquer the drawbacks of ACQ effects. Also, majority of organic dyes suffer from biocompatibility and stability issues which needs to be addressed. Certain strategies useful in achieving this are non-covalent self-assembly, covalent conjugation, controlled living polymerization, formation of dynamic bonds and anhydride ring opening polymerization.[99-102] Other synthesis procedures are catalyst free azide-alkyne click reaction,[103] thionyl click reaction,[104] dynamic phenyl borate bond formation,[105] multicomponent reaction (One-pot strategy).[106,107] Most prominent applications of AIE induced FPNs is in bioimaging[96,108] with certain modifications proving to be a boon like salicylic acid-poly-PEG-co-vinyl aniline which provide fluorescent nanoparticles having excellent biocompatibility, enhanced cellular uptake and superior photo bleaching resistance behaviour.[109] Similar advances have been made in preparation of luminescent MSNs as discussed further.

Fabrication of Luminescent MSNs

Intrinsic/label-free Luminescent mesoporous silica nanoparticles (L-MSNs) have proved to be highly useful in biomedical field and have various applications in drug delivery. MRI contrast agent, cell sorting and cell labelling.[110] Uniform pore size, multi functionality and low cytotoxicity are the major reasons for popularity of MSNs over other nanocarriers in biomedical applications. However, synthesis of luminescent or magnetic MSNs need to be properly monitored and optimized since irregular pore structures lead to diminished efficacy in biological systems. Label-free approach has garnered lot of attention and is a facile way of Luminescent-MSN synthesis. Jin *et al.*[111] found that calcination of MSNs at 400ºC gave mesoporous organosilicon NPs with strong fluorescence of ultimate photo and chemical stability. It was reported that the origin of luminescence were carbon dots generated from calcination and not due to the silica matrix defects as contrary to the traditional belief. Furthermore, it was also observed that the calcination did not affect the drug loading and biomolecule conjugating properties of the MSNs. The novel calcination induced fluorescence could contribute to MSNs synthesis for use in drug delivery, nanoparticle coating and immunofluorescence imaging. Other methods include labelling of silica particles with a fluorophore like Organic dye molecule loaded by chemical conjugation or physical adsorption or a NP fluorophore like Quantum dot (QDs)[112] or up conversion NPs.[113,114] However, there are several drawbacks of this methods when compared with label-free technique; like time consuming, expensive, high toxicity, increased particle size and dye leakage.[115,116] Another approach of bottom up self-assembly followed by post calcination was used in synthesizing oxygen deficient luminescent MSNs for drug loading/delivering and cell imaging. Triethoxy silane was employed as a silicon source to create oxygen vacancies by dehydrogenation between terminal groups

during post-calcination. Electrochemical etching of silicon wafer in HF based electrolyte solutions followed by ultrasonic fabrication or mechanical milling and subsequent centrifugation or filtration causes poor size and morphology control on MSN pores along with low yield due to unwanted micro particles also obtained.[117,118] Jain and group[119] also synthesized highly stable L-MSNs by optimizing APTS and TES ratio (Stober process followed by calcination) and concluded that formation of carbon dots was responsible for Luminescence as confirmed by fluorescence anisotropy measurements. Another example of L-MSN synthesis includes their application in photodynamic therapy. A photosensitizer zinc pthalocyanine was incorporated into MSN and excited by NIR laser through which activated nanocrystals could convert NIR light to visible light which in turn activated photosensitizer to release reactive singlet oxygen species to kill cancer cells.[114]

Biomedical Applications of MSNs

MSNs serve as a magic bullet for theragnostic medicine and in biomedical applications.[74] Mechanized MSNs functionalized with nanomachines proffer enumerable advantages as nanotheranostic agents. Some of them include possessing a higher surface area to volume ratio which leads to ease of surface functionalization to fit any desired need related to targeting and theranostics. Thus, ease of surface functionalization makes it easier to attach various targeting moieties using a simple surface functionalization process. This ease of surface decoration or ligand attachment is not prevalent on large scale in case of other nanocarriers and polymeric micelles. Polymeric luminescent nanomaterials also possess multifunctional ability and good photostability.[120] However, MSNs apart from all these aspects also possess zero premature leakage. A major issue associated with Fluorescent inorganic nanoparticles (FINs) is the problem of *in vivo* biodegradability associated with them attributed to their accumulation in reticuloendothelial system. On the other hand, Silica comes under the category of GRAS (Generally regarded as safe) for human use and also used as an additive in tablet manufacturing. Inside body also it is converted to a non-toxic silicic acid and excreted mostly through urine. Although, a new class of Fluorescent organic nanoparticles (FONs) provide excellent biocompatibility and good dispersibility. FONs with aggregation induced emissions hold a good potential in various bio-imaging applications.[121,122] A broader excitation wavelength is desirable for biomedical applications.[100] Although, Various organic dyes possess rapid labelling, non-toxicity and easier clearance, they are vulnerable in biological environments and exhibit aggregation caused quenching (ACQ).[123] Fluorescent silica nanoparticles offer advantages like higher quantum yield and better fluorescence stability as compared to small organic fluorescent molecules.[124] PhE-PEG FONs were reported to possess excellent biocompatibility, water dispersibility and fluorescence.[125] Semiconductor quantum dots and metal clusters possess several disadvantages like intrinsic cytotoxicity and difficulty in surface functionalization.[126] In both the aforementioned aspects MSNs hold an upper hand. Nanodiamonds are another form of delivery system widely being investigated upon. Te cyclodextrin based nanocomposites possess greater water dispersibility, high drug loading and controlled drug release.[105] However, comparatively MSNs also offer tunable pore size which can easily control site and time of cargo release; apart from possessing high payload capacity.

Targeting by MSNs

MSNs can be altered by providing good end capping, precise targeting and stimuli triggered drug release to fulfil the aim of efficient drug loading with minimum side effects. Previously, organic molecules,[10] inorganic nanoparticles[127] and molecular switches[128] *etc,* were employed to block the mesopores of MSNs for preventing drug leakage. MSNs can be targeted to cancer cells implementing receptor-based targeting approach or stimuli responsive targeting strategy. Various receptor binding ligand used so far involved lactose,[129] folic acid,[128] DNA aptamer,[27] peptides[130] and phenylboronic acid[131] that follows the former approach of targeting. Whereas, letter strategy requires an efficient stimulus to trigger drug release inside the tumor cells. An external stimuli can be divided into physical stimuli like light,[27] magnetic field[132] *etc* and biological stimuli in the tumor microenvironment like redox[128] pH[111] enzyme[133,134] *etc.* Details of both the approach are summarized below.

Stimuli responsive MSNs targeting

MSNs have been explored in depth for stimuli-based cargo delivery. Various stimuli like pH, redox, enzyme, magnetic field and temperature are widely used to stimulate MSNs prepared. This strategy is highly useful in addressing the issue related to off target toxicity in cancer therapy.[135] The controlled release is obtained at three levels (1) using gatekeepers by pore sealing with particle or molecular gates, (2) surface coating of particle and (3) coupling of cargo onto the internal walls of pores.[136] They further depend on two types of responses first is a conformational change of the pore sealing agent and the second is exposure to stimuli which can lead to the cleaving of bonds. Frequent method used in latter case

is cleavage of disulphide bond as a part of redox stimuli-based cargo delivery system. A summary of recent stimuli responsive mesoporous systems having an application in cancer is enumerated in Table 3.[137-146]

pH

The pH responsive behaviour is most researched upon and accepted worldwide as a tumor specific drug delivery of anticancer drugs. The basic fundamental involved here is the fact that tumor micro-environment has an acidic pH than normal tissues. Thus, designing a delivery system which can release drug at an acidic pH can be highly beneficial for targeted delivery of anticancer drugs. The difference in pH can be credited to the high proliferative rate of cancer cells, leading to an increased lactic acid production and enhanced efflux of protons present within the cell.[147] Recently Nasab *et al.*[148] have synthesized a pH based mesoporous drug delivery system for curcumin using natural polymer chitosan for capping. There was an appreciable increase in the solubility of curcumin and remarkable improvement in its therapeutic efficacy as tested against U87MG glioblastoma cancer cell line. There was also encouraging results when IC_{50} values of free curcumin and capped MSNs were calculated with almost three times enhancement in cytotoxicity at same IC_{50} dose. Similarly, Kienzle and co-workers designed a pH stimuli responsive dendritic mesoporous network for TNF-Alpha. The stimuli system consisted of a block copolymer gate system synced with charged hyper branched polyethylenimine and nonionic hydrophilic PEG for TNF-Alpha encapsulation and delivery into various cancer cell lines and dendritic cells. There was a reduction in EC_{50} for prepared MSNs by more than two times and showed stability in the media up to five days.[149] Further, MSNs have also been employed in lymphoma treatment. E.g. Zhou *et al.* have developed an intracellular pH responsive conjugated MSN system for rituximab targeted delivery to lymphoma B cells. Avidin-biodin bridging approach was undertaken and the results showed little premature release at physiological pH and enhance release in microtumor environment leading to enhanced therapeutic value and diminished off-target toxicity.[150]

Redox

The fundamental involved here is that in the human body, glutathione-GSH/ GSH disulphide is one of the major redox couplets which play a pivotal role in minimizing the damage caused due to Reactive oxygen species (ROS).[151] The most important fact to consider here is that in tumor cells, the GSH concentration is elevated 100 to 1000 times more and this is exploited in designing of redox stimuli based delivery system.[26,151] GSH acts as an effective, reducing agent for the cleavage of disulphide bonds. Chen *et al.*[152] have reported the synthesis of transferrin gated MSNs for Redox based Doxorubicin (DOX) release. The idea was successful as there was a burst release when exposed to GSH, due to the cleavage of disulphide bonds in MSNs. Transferrin served a dual purpose of both capping and targeting agents. Site specific delivery was achieved with this biocompatible carrier. A major breakthrough was achieved by Zhao and group when they synthesized MSNs for co delivery of Si-RNA and DOX through MSNs. Where, Si-RNA was joined to the core via disulphide linkage and interestingly played a gatekeeper role. There was an enhanced accumulation of DOX in the cancer cells and prepared MSNs could knock down expression of target proteins. Thus, they exhibited a wide tumor targeting potential.[109]

Magnetic field

Magnetic MSNs have been widely explored for diagnosis and treatment of cancer. Although, a strong magnetic field may not always be an economically feasible option, still they are being researched upon due to the positive results and encouraging outcomes they have so far given in cancer theranostics.[153] They require minimum one exogenous stimulus for responding to magnetic field. MSNs as MRI contrast agents have been more intensively studied. They are also in the limelight due to their proved biocompatibility.[154] Li *et al.* designed a magnetic MSN system for co delivering of DOX and VEGF Si RNA for MR imaging and cervical cancer targeting. This included a Magnetic mucus penetrating nanoparticles (MMPP) by employing the ultrasound emulsification method and Superparamagnetic iron oxide nanoparticles (SPIONS) encapsulated into a blend of PLGA and PLGA-PEG polymers. Under magnetic field explosion the penetration speed of prepared NPs was found to be increased three fold than in the absence of magnetic field.[155]

It is widely known that the therapeutic efficacy of Photodynamic therapy (PDT) is limited by hypoxia associated with cancer due to the fact that PDT is an oxygen concentration dependent process. Kim *et al.*[156] designed a biocompatible manganese ferrite anchored MSNs to overcome hypoxia thereby enhancing the therapy of PDT. This can be attributed to the continuous oxygen evolving property of Mn-Fe_2O_4 nanoparticles via Fenton reaction. Additionally, modified MSNs also exhibited a T2 contrast effect in MRI imaging having a benefit of *in vivo* tracing of administered MSNs. Thus, they exhibited a huge potential in theranostic therapy

of cancer. Tian and group synthesised magnetic MSNs coated with a thermoresponsive polymer *i.e.* P(NIPAM-co-MAA). The magnetic supermagnetic nanoparticles were loaded with DOX and exhibited both pH and temperature responsive behaviour. They had higher efficacy in killing cancerous HeLa cells. It was also proved that magnetic MSNs are capable of higher internalization in cancer cells.[157]

Enzyme

Enzyme responsive cargo delivery system has been developed in the mesoporous silica framework. The MSNs have been employed as theranostic agents for cancer therapy. Hu *et al.* had developed an enzyme Matrix metallo proteinase II (MMP-II) based MSNs for tumor targeted drug delivery and imaging. MMP-II activated fluorescent imaging peptides served as diagnostic probes as well nanovalves which blocked the pores based on enzyme responsiveness. MMP-2 overexpression in tumor tissue also triggered the drug release effectively.[158] Recently Chunlin *et al.* employed a mussel mimetic enzyme responsive coating on MSN. They reported a facile strategy for polylysine-dopamine film coating via self-polymerization of dopamine derivative dopamine-lysine under basic conditions. Once the formulation reaches cancer cell, DOX was released via enzyme responsive degradation of peptide bonds.[151] Tukappa and co-workers reported polyglutamic acid gated enzyme based drug delivery in metastatic breast cancer treatment.[159] This system was developed for efficient co-delivery of Rhodamine and DOX. The cargo delivery occurred in pronase triggered manner. More than 90 percent of SK-BR-3 cancer cells was killed in the 100-ppm concentration and the developed NPs were proved to be non-toxic as well.

Light

Light is another stimuli used to trigger a selectively controlled release in cancer cells. Lu J *et al.* has engineered a camptothecin loaded and light activated MSNs having azobenzene impellers, which were photoactivated at specific wavelengths to trigger the impellers and lead to liberation of drug under light excitation.[160]

Temperature

Temperature is also applied as external stimuli to direct cargo release inside the cancer cells. It is mainly achieved by attaching thermosensitive poly (N-isopropyl acrylamide) derivative.[25,161] Whereas, another research group has utilized octadecyltrimethoxysilane and paraffins to prepare thermo sensitive MSN where an increase in temperature above the melting point of paraffin resulted in cargo release.[162]

Dual stimuli

Dual or multiple stimuli responsive MSNs have also been developed and tested successfully for effectiveness and biocompatibility. As the name suggests here more than one stimuli are at work for cargo release, mostly employed for theranostic purposes. Recently, Wang *et al.* fluorescent carbon-dot gated multifunctional MSNs for redox and enzyme (Dual) responsive for the purpose of achieving controlled drug delivery and real time bioimaging.[163] Furthermore, Zhu and group have prepared dual thermo and magnetic responsive nanoparticles.[164]

Receptor Based MSN Targeting

Various receptors have been explored so far to study targeting efficiency of MSNs. E.g. Khosravian and coworkers have engineered a docetaxel loaded folic acid or methionine functionalized MSNs. From the *in vitro* cell line, *in vivo* biodistribution study and *ex vivo* fluorescence imaging data, it was concluded that folate capped MSNs displayed significant tumor targeting efficiency with respect to methionine modified MSNs. As cancer cell displayed an overgrowth of folate receptor, a folate capped MSNs displayed relatively high affinity toward tumor cells.[165] Similarly, Yu *et al.* had synthesised doxorubicin incorporated and hyaluronic acid modified MSN to target CD44 receptors overexpressed tumor cells. The success of drug concentration inside the tumor cells was confirmed by performing cellular uptake studies by confocal microscopic experiment and flow cytometric analysis.[89] Goel S. *et al.* had formulated Vascular endothelial growth factor receptor (VEGFR) targeted MSNs with the goal of treating VEGF overexpressed tumor cells. Herein, the researcher had prepared NOTA-MSN-$VEGF_{121}$ nanoparticle using PEG linkers. Where, $VEGF_{121}$ was used as a VEGFR binding ligand. The *in vitro*, *in vivo* and *ex vivo* finding supported a successful synthesis of tumor targeted nanoparticles.[166]

Toxicity, Biocompatibility and Biodegradation of MSNs

Although having a tremendous application in the pharmaceutical world, the biocompatibility of MSNs is still debatable and it is essential to discuss about their biocompatibility and safety profile. Numerous parameters have direct influence on the safety profile of MSN which covers surface properties, particle size, charge, shape etc. At cellular level, MSNs can interact with the biological system through many of the mechanisms like mitochondrial dysfunction, glutathione depletion, membrane peroxidation and DNA damage etc. Research also says that the pristine MSNs are having less hemocompatibility as compared to surface deco-

rated MSNs. Furthermore, apart from having targeting properties, the surface decoration exhibits reduced undesirable interaction with the internal organelles.[167] Moreover, Lu *et al.* concluded 50nm particle size is the optimal size for the drug delivery by MSNs with respect to 30nm or even 200nm.[168] Whereas, He *et al.* demonstrated that as the size of MSNs increases, the excretion from urine also increases correspondingly. Further, they also claimed that smaller size MSNs i.e. 190nm and 420nm size MSNs are more cytotoxic with respect to bigger sized MSNs i.e. 1220nm.[169] Further the smaller nanoparticles are having more haemolytic effect as compared to bigger sized nanoparticles.[170] Overall, there are dual thoughts for biocompatible nature of MSNs and it further requires an in depth exploration. Their biodegradation is debatable. Chen *et al.* have demonstrated a detailed degradation of MSNs in human embryo kidney 293T cells by measuring the silica content in culture medium and performing depth TEM analysis. They claimed, upon degradation of MSNs into the cells, the size and dispersibility of cells were unchanged and hence the toxicity due to accumulation of silica aggregates in the tissues would be reduced.[171] Further, Zhai *et al.* inferred that the degradation of MSNs took place in cytoplasm initially followed by in lysosomes later on. Moreover, the culture of MSNs with human endothelial cells experiments revealed higher accumulation of MSNs in the culture media *i.e.* outside the cell supports the claim that MSNs are not having cell toxicity.[172] Additionally, research also says that the MSNs are converted into silanoic acid inside the body, which is excreted through kidney majorly. Further, the study also says that the silica particles mainly converts into its bioavailable form *i.e.* monomeric orthosilicic acid, which is essential for bone and connective tissue hemostasis.[167]

Current Application of MSNs in Cancer Treatment

MSNs are being explored for wide disease categories till now. Applications of MSNs in varied cancers are reported by many research groups. Few of them are explained briefly here.

Breast Cancer

(A) MY Hanafi-Bojd and group have synthesized an epirubicin loaded and MUC1 aptamer conjugated MSNs. The formulated nanoparticles were characterized thoroughly and were investigated for *in vitro* cellular uptake study on human breast carcinoma cells i.e. MCF-7 cells. Cytotoxicity results displayed significant breast targeted efficiency for aptamer attached MSNs with respect to unmodified MSNs and thus the formulation could improve the efficacy and possessed least adverse effect.[173]

(B) Ma'mani L, *et al.* has synthesized curcumin loaded and guanidine functionalized pegylated MSNs for breast cancer therapy. The surface of MSNs was modified by the isocyanate group with the aid of 3-(triethoxysilyl) propyl isocyanate (TESPIC) reagent under appropriate conditions. This surface modified MSNs were pegylated using PEG (MW 600Da) and finally with guanidine. To this multifunctionalized MSNs, curcumin was successfully loaded. Surface diameter was decreased from 834.61 (bare MSNs) to 234.6 (Curcumin loaded guidine+PEG coated MSNs) m^2/g with a particle size range of 60-70 nm. The success of this functionalization was confirmed by various analytical techniques like DSC, FT-IR, BET, *etc. In vitro* release study showed higher and tailor-made drug release in acidic pH (5.4 pH) compared to neutral pH (7.4). The results themselves depicts that curcumin showed pH responsive controlled release *i.e.* more release in an acidic environment (Tumor cells). The cell internalization study was successfully done by using the human breast carcinoma MCF-7 cell line. This showed a successful targeted delivery of curcumin to breast cancer cell.[174]

(C) A Second strategy of targeting involves enzyme responsive MSNs preparation. Briefly, it involves synthesis of MSNs as per the literature method available. Synthesised MSNs have been functionalized with carboxylic group and peptide sequence and finally with human serum albumin (HSA) having particle size of 80 nm. To this functionalized carrier *i.e.* HSA labelled MSNs, DOX was successfully loaded. Cell apoptotic assay on HepG2 cells displayed a promising curative effect in breast targeted enzyme responsive delivery by MSNs.[28]

(D) Song H, *et al.* has synthesized folic acid-chitosan conjugated nanoparticles for improving tumor targeted drug delivery. Synthesized MSNs showed average particle size of 38±2 nm having positive zeta potential values. Further, this MSNs showed a biphasic release pattern of DOX from folate-chitosan coated MSNs compared to chitosan coated MSNs. Fluorescent images showed higher internalization of folate modified MSNs by folate receptor positive SMMC-7221 cell line compared with folate receptor negative MCF-7 cell line and this can be used as a promising tool for targeting a nanoparticles to cancerous cell.[175]

Lung cancer

It is the highest cause of death in patients suffering from cancer. It has been proven from the literature available that MSNs can also be used successfully for lung cancer targeting.

(A) Wang *et al.* have formulated paclitaxel loaded core-shell MSNs as a lung targeted nanoparticles. To investigate the targeted efficiency of synthesised nanoparticles,

time dependent cellular uptake study and the apoptosis study were carried out on human A549 cells and results demonstrated the targeting potential poorly soluble drug for treatment of lung cancer.[176]

(B) Gao Y, *et al.* has synthesized albumin coated MSNs for the purpose of lung targeted controlled release of paclitaxel. *In vitro* cytotoxicity study was performed on lung cancer cell line A549 for formulated MSNs and results showed a significant anti-proliferative activity of albumin coated MSNs in lung cancer treatment.[177]

(C) Sundarraj S, *et al.* has synthesized EGFR antibody conjugated MSNs nanoparticles for lung targeted delivery. The mechanism involved here was receptor mediated endocytosis of antibody coated MSNs. Ligand receptor mediated recognition of EGFRab-SN pyrrolidine-2 nanoparticles attributed to higher cellular internalization through lung tumor cells, which was confirmed using human lung epithelial cell line L-132.[178]

Prostate Cancer

After lung cancer the second highest cause of cancer mortality in male is prostate cancer. Mannose 6 phosphate receptor is the main target of drug binding to prostate cancer. A carboxyl analogue (Mannose 6 carboxylate) of mannose 6 phosphate has been synthesized and this synthesized mannose 6 carboxylate was coated on MSNs following amination. TEM data revealed pore diameter of 15-25 nm. Further characterization was done by zeta potential and XRD analysis. *In vitro* cell line cytotoxicity study was performed on LNCaP prostate specific cell and results showed significant accumulation of MSNs inside the prostate cells.[179]

Colorectal Cancer

(A) Xie *et al.* has synthesized an aptamer coated and DOX encapsulated MSNs for treatment of epithelial cell adhesion molecule (EpCAM) overexpressed colon cancer. The targeting efficiency was performed on EpCAM over-expressing SW620 colon cancer cells and the aptamer coated MSNs exhibited significant inhibiting effect on the overexpressed EpCAM SW620 cells.[180]

(B) Here the strategy involves the development of eudragit fabricated hollow MSNs for targeted delivery. In the pharma field eudragit is widely used in enteric coated formulation, especially for pH responsive release *i.e.* to release a drug above pH 7. Eudragit was fabricated during synthesis of carrier (MCM-41) i.e. co-condensation method of surface functionalization having a particle size of 120 nm. 5-flouro uracil has been loaded successfully into this carrier. *In vitro*, *in vivo* and cell cytotoxicity studies revealed a colon targeted release of 5-FU from the formulation. MSNs exhibited high drug loading with sustained and targeted drug delivery to the colon.[181]

(C) Tan L, *et al.* has developed glucose and pH responsive MSNs which selectively release the drug in an acidic environment. MSNs that are fabricated with Poly acrylic acid (PAA) brush on the surface with the aid of t-butyl acrylate. This PAA layer was again modified with glucosamine to obtain P(AA-AGA) and finally it was modified by adding 4,4-(ethylenedicarbamoyl)-phenylboronic acid (EPBA), showing the particle size of about 100 nm. This will form boronate esters which will be dissociated in the presence of glucose and in an acidic environment. Here, the rate of release can be altered by changing pH or concentration of glucose in the surrounding environment. This combination showed a higher possibility of release of drug in mild acidic environment *i.e.* pH 6.0.[182]

Hepatic Cancer

(A) Wang Z. *et al.* had formulated lactose mediated MSNs for delivery of platinum to liver cells by active targeting approach. The *in vitro* cell viability and cellular uptake study along with *in vivo* biodistribution study revealed prominence liver cell targeting efficiency of lactose coated MSNs. Further, the designed formulations displayed enhanced circulation time along with selective concentration inside the liver cells.[183]

(B) Quan G, *et al.* has synthesised lactosaminated mesoporous silica nanomaterials for asialoglycoprotein receptor (ASGPR) targeted delivery of docetaxel to hepatoma cells. MSNs carrier was synthesised as per Zink's report. Synthesised nanoparticles were functionalized with amino group by aminopropyltriethoxysilane reagent (APTES) and finally an attachment of lactose group was carried out with the aid of sodium cyanoborohydride solution. The calculated surface area was 1012 m^2/g with the average pore size was 3.7 nm from the BET result with an approximate diameter of 100 nm. It was found that Lactosaminated MSNs (Lac-MSNs) selectively bind with ASGPR in hepatic cells and showed a high hepatic targeting efficiency. Lac-MSNs were selectively endocytosed by ASGPR-positive hepatoma cell line, HepG2 and SMMC7721 cell line compare to ASGPR-negative NIH 3T3 cells. This was further confirmed by flow cytometry and confocal microscopic studies.[11]

Pancreatic cancer

One of the challenging category of cancer to treat is pancreatic cancer. Liu X, *et al.* have synthesized irinotecan loaded lipid bilayer coated MSNs having a particle size of 75-80 nm, which lowered premature drug release with enhanced stability of formulating MSNs. The effectiveness of the formulation toward pancreatic tumor cells was studied on tumor specific orthotopic Kras-derived pancreatic ductal adenocarcinoma model

and the engineered formulation was compared with liposomes.[184]

Ovarian Cancer

The Ovarian Cancer Cell has also Been Targeted Successfully using MSNs

(A) Guo and co-worker have formulated MSNs for active targeting of ovarian cancer. The research group has synthesized hollow MSNs loaded with DOX and NVP an inhibitor of insulin like growth factor receptor (IGF-1R). An IGF pathway was selected herein as a target as it is associated with the progression of ovarian cancer. The results displayed an active targeting of HMSN-COOH-DOX fluorescence NVP along with blocking the IGF pathway by NVP. Thus, the prepared MSNs were selectively targeted ovarian cancer cells.[140]

(B) Tumor endothelial marker 1 (TEM1)/endosialin (Ab-/scFv)-conjugated nanoparticles were synthesized by Zhang Y, *et al.* Cellular uptake study and intracellular distribution of bevacizumab loaded and antibody conjugated MSNs showed promising results in human ovarian cancer cells *i.e.* OVCAR-5 cells. Thus, the significant accumulation of nanoparticles within the cells concluded the successful formation of ovary targeted nanoparticles.[185]

Apart from having a vital application in targeted nano technology, MSNs are having other multiple applications. E.g. A novel use of MSNs to overcome multidrug resistance (MDR) is now in the limelight. MDR is the major obstacle to be encountered during treatment of cancer. Co-administration of the MDR reversal agent along with disease treatment moiety improves the behaviour of MSNs toward MDR. For an instance, Lejiao jia, have formulated a multifunctional MSNs to overcome MDR of MCF-7/ADR cells by co-administering paclitaxel with tetrandrine, a MDR reversal agent to solve above problem regarding MDR.[186] Likewise, Huan Meng *et al.* has formulated multifunctional MSN having the drug and the Si RNA combination to overcome MDR especially observed in breast cancer. The aim was to target the p-glycoprotein drug exporter following high throughput screening in MCF-/MDR.[187] Moreover, MSNs are also recently been utilized for diagnostic purposes. MSNs are widely being researched upon for theranostic applications. Theranostic also termed as "theragnostic" is a term describing both therapeutic and diagnostic applications. MSNs are widely being researched upon for theranostic applications. Theranostic also termed as "theragnostic" is a term describing both therapeutic and diagnostic applications. Cheng *et al.*[188] employed novel tri-functionalized MSNs for imaging, targeting and therapy of cancer. This all in one approach was found to be very effective, with this theranostic platform exhibiting minimal collateral damage, high therapeutic effect and maximum targeting specificity. The MSNs were sequentially functionalized with contrast agents that enable traceable imaging of particle targeting, drug payload and biomolecular ligands for therapeutic effect and targeted delivery of particle respectively. The entire system consisted of palladium-porphyrin based photosensitizer for PDT therapy and cRGDyK peptides for targeting of $\alpha_v\beta_3$ integrins overexpressed in cancer cells. Each and every aspect of theranostic application was optimized successfully for imaging/targeting//therapy purposes. The latest theragnostic MSNs synthesized and their applications are summarized in Table 4.[86,179,189-197] A schematic diagram of multifunctional MSNs is portrayed in Figure 4.

Present Scenario

Being a firm platform for satisfying multi purposes, still the field of MSNs has remained untouched and require to be explored. Cornell dots (C-dots form of MSNs) a USFDA approved product is in stage clinical trial. It is engineered for fluorescence imaging purpose and utilized for lymph node mapping in cancer. It includes cyclic RGD peptides as a targeting moiety, a polymer layer and NIR fluorescent dye labelled internal silica core. Silica has already obtained a tag of Generally regarded as safe (GRAS) but the same question arises for MSNs and it is to be answered. A first trial in human in 5 patients indicated a favourable pharmacokinetics and safety profile, creating opportunities for further trials in future. Silica listed under the GRAS category by USFDA. So far, it is already in use for human consumption as an excipient for tablets and food additive. Presently, silica nanoparticles are already in use in available commercial products like Nanoceuticals™ chocolate slim shake and Lancome® Renergie microlift, a cosmetic product.[198] However, a major breakthrough

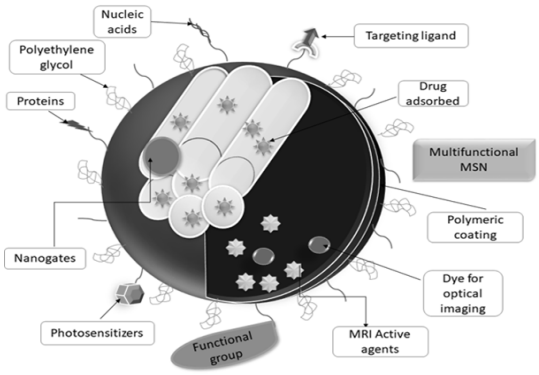

Figure 4: Multifunctional MSNs.

was achieved when USFDA approved for the first time human trials for Cornell dots, a fluorescent core shell silica nanoparticles to be used as biological markers for diagnosis in metastatic melanoma patients.[199]

CONCLUSION

Of all the drug delivery platforms available MSNs do hold a special position due to the various advantages associated with them. Some of them being ease of surface functionalization, zero premature leakage and tunable pore size. The targeting efficiency of MSNs has been widely researched upon with numerous positive outcomes reported. In spite of the special attributes of MSNs a wide research needs to be done to determine their biosafety in human clinical trials. Luminescent MSNs and theranostic applications are the recent advances and relatively newer trends still in naive stage. However, they serve as the most suitable candidates for potential biomedical applications. They provide an ideal platform for drug and diagnostic agent delivery and are a valuable asset in bright future of biomedicine and nano delivery systems.

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CONFLICT OF INTEREST

The authors declare no conflict of interests.

ABBREVIATIONS

5-FU: 5-Flouro Uracil; **AAPTMS:** N-(2-Aminoethyl)-3-Aminopropyltrimethoxysilane; **AEPTMS:** 3-[2-(2-Aminoethylamino)Ethylamino]Propyltrimethoxy-Silane; **APTES:** Aminopropyltriethoxysilane; **APTES:** 3-Aminopropyl Triethoxysilane; **ASGPR:** Asialoglycoprotein Receptor; **CPTES:** 3-Cyanopropyltriethoxysilane; **CTAB:** Cetyltrimethylammonium Bromide; **CTAC:** Cetyltrimethylammonium Chloride; **DOX:** Doxorubicin; **EGFR:** Epidermal Growth Factor Receptor; **EPBA:** 4,4-(Ethylenedicarbaamoyl)-Phenylboronic Acid; **EpCAM:** Epithelial Cell Adhesion Molecule; **EPR:** Enhanced Permeability And Retention; **GRAS:** Generally Regarded As Safe; **HAS:** Human Serum Albumin; **IGF-1R:** Insulin Like Growth Factor Receptor; **LCT:** Liquid Crystal Templating; **MCM:** Mobile Composition Of Matter; **MDR:** Multidrug Resistance; **MMP-II:** Metallo Proteinase II; **MMPP:** Magnetic Mucus Penetrating Nanoparticles; **MPS:** Mononuclear Phagocytic System; **MRI:** Magnetic Resonance Imaging; **MSNs:** Mesoporous Silica Nanoparticles; **MSU:** Michigan State University; **MTD:** Maximum Tolerated Dose; **PAA:** Poly Acrylic Acid; **PDT:** Photodynamic Therapy; **PEG:** Polyethylene Glycol; **PMAA:** Poly Methacrylic Acid; **PXRD:** Powder X-Ray Diffraction; **ROS:** Reactive Oxygen Species; **SBA:** University Of California At Santa Barbara; **SEM:** Scanning Electron Microscopy; **Si-RNA:** Small Interfering Ribonucleic Acid; **SMEDDS:** Self-Micro Emulsifying Drug Delivery System; **SPIONS:** Superparamagnetic Iron Oxide Nanoparticles; **TEM:** Transmission Electron Microscopy; **TEM1:** Tumor Endothelial Marker 1; **TESPIC:** 3-(Triethoxysilyl) Propyl Isocyanate; **TGA:** Thermo Gravimetric Analysis; **TUD:** Technischeuniversiteit Delf; **USFDA:** United State Food And Drug Administration; **VEGFR:** Vascular Endothelial Growth Factor Receptor; **XPS:** X-Ray Photoelectron Spectroscopy; **XPS:** X-Ray Photoelectron Spectroscopy; **XRD:** X-Ray Diffraction.

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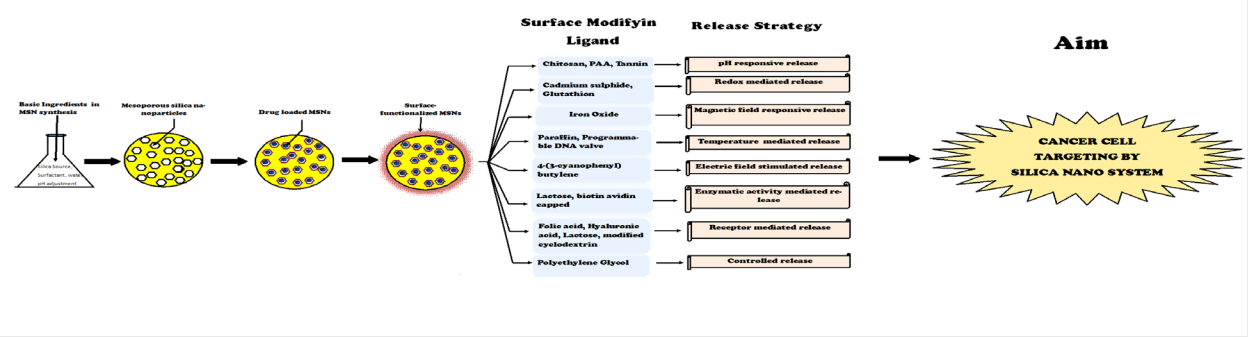
PICTORIAL ABSTRACT



SUMMARY

In this review, we have emphasized on the utility of novel approaches of multifunctional mesoporous silica nanoparticles. Property of cell specificity helps in targeting the MSNs to tumor cells by modifying the silanol group presented on external surface. A tailor-made approach of MSNs gives an option of tuning the particle size and particle shape as per the user requirement. Biocompatibility investigation of MSNs has demonstrated its safe nature. Despite of having numerous advantages, an in-depth research is still needed to be done on MSNs to make the pharmaceutical world more familiar with MSNs applications.

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