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Review Article

Mesoporous Silica Nanoparticles as Theranostic Platform for Smart Drug Delivery: A Review

Dhanashri Devendra Borawake[1*], Vishal Vijay Pande[1], Mahendra Ashok Giri[2]

[1]Department of Pharmaceutics, Sanjivani College of Pharmaceutical Education and Research, Maharashtra, India

[2]Department of Pharmacology, Sanjivani College of Pharmaceutical Education and Research, Maharashtra, India

[*]**Corresponding author:** Dhanashri Devendra Borawake, Department of Pharmaceutics, Sanjivani College of Pharmaceutical Education and Research, Kopargaon, Ahmadnagar, Maharashtra, India. Tel: +919067569905; Email: dhanuborawake77@gmail.com

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Abstract

Mesoporous silica nanoparticles are backbone of nanotechnology; having very appealing properties such as large surface area, high loading capacity, large pore volume, biocompatibility. Hybrid MSNs obtain when it combines with other organic/inorganic nanomaterials demonstrate unique synergies and even greater versatility. In this review, we will focus on Hybrid Mesoporous Silica Nanoparticles (hMSNs) that having (theranostic) functionalities i.e., combine therapeutic and diagnostic function, which create a smart nanocarrier for controlled release of corgo. Now a day's theranostic application of mesoporous silica nanoparticles is one of the emerging part of drug delivery system to improve the therapeutic activities and to minimize the associated side effects.

Abbreviations

DDS	:	Drug Delivery System,
MSNs	:	Mesoporous Silica Nanoparticles,
hMSNs	:	Hybrid Mesoporous Silica Nanoparticles
SBA-15	:	Santa Barbara Amorphous
GSH	:	Glutathione
NPs	:	Nanoparticles

Keywords: Mes¬oporous Silica Nanoparticles; Stimuli Responsive Drug Delivery; Targeted Delivery; Theranostic Nanoparticles

Introduction

One of the emerging field of science is a nanotechnology, which includes synthesis and development of various nanomaterials. The objects ranging in size from 1 to 100 nm is called as nanoparticles [1]. Nanotechnology changed the landscape of pharma industry. Targeting process and drug delivery is revolutionized by era of nanotechnology. Size range of nanoparticles affects the bioavailability and bio-distribution of particles, and hence it is useful as a drug carrier [2]. Nanoparticles offer great potential for delivering drug to targeted cell or organ. From the nanoparticles which are in development liposomes, albumin nanoparticles, ceramic nanoparticles, silica nanoparticles have been widely studied [3]. Because of the poor water solubility of many drugs they show low bioavailability. In some cases, during the development process resulting drug candidate being rejected. Mesoporous material based drug delivery system has been investigated to enhance solubility and thus improved bioavailability [4,5]. (Figure 1) Shows ideal characteristics of carrier for drug delivery.

Figure 1: Ideal Characteristics of Carrier for Drug Delivery.

Mes¬oporous silica nanoparticles have been explored as effective drug delivery systems for a variety of therapeutic agents to fight against various kinds of diseases including bone/tendon tissue engineering, diabetes, inflammation, and cancer [6]. MSNs are used in controlled drug release systems, improve drug efficacy and reduce drug side effects. dye-doped imaging and detection, and intelligent anticorrosion coating, due to the performance characteristics of MSNs [7,8]. Mesoporous silica material discovered in 1992 in the labs of Mobil Oil Corporation [9,10] (Table 1 and 2).

Sr no	Advantages of mesoporous silica nanoparticles
1	Large surface area
2	High loading capacity
3	Large pore volume
4	High degree of tunability
5	Biocompatible
6	Biodegradable
7	Ease of synthesis
8	Surface functionality

Table 1: Advantage of MSNs [11-19].

Sr no	Type	Internal structure	Pore diameter (nm)
1	MCM-41	2D hexagonal	1.5-3.5
2	MCM-41	Hexagonal structure with uni-directional pore structure	3.70
3	SBA-15	2D hexagonal	6.0-10.0
4	SBA-15	2D hexagonal	7.80
5	SBA-15	3D cubic cage like	4.0-9.0
6	MCM-48	3D cubic	2.5-3.0
MCM- Mobile Crystalline Material, SBA- Santa Barbara Amorphous, 2D-Two-Dimensional, 3D-Three Dimensional			

Table 2: Various Types of Mesoporous Silica Nanoparticles with their Internal Structure and Pore Diameter [2].

Shawky SM et al developed a novel method for loading drugs into spherical mesoporous silicate nanoparticles and modified loaded MSNs to produce smart DDS. Rotary evaporation used as a novel method for preparation and loading of MSNs. loading efficiency compared with conventional impregnation loading method. It was found that loading efficiency of novel method was high as compare with conventional method [15].

Theranostic Approach Nanoparticles

Characteristics of ideal vehicle for smart delivery system are:

- Vehicle should be traceable.
- Should accommodate large drug loads.
- Should be feature targeting.
- Delivery of cargo on-demand at the desired location due to smart release control mechanisms.

If drug is efficiently delivered in needed location only at exact timely manner and the exact dosage, a large increase in the efficiency of a drug is observe; because of this associated side effects is also decrease [20]. For obtaining both therapeutic and diagnostic function from single molecular entity, development of theranostic nanoparticles have increased continuously during the last couple of years term "Theranostic" [21]. The hexagonal nanochannels/pores, silica framework, and particle exterior are the three topologically distinct regions of MSNs that can be independently functionalized and are particularly well suited for the theranostic applications with separate domains available for;

- Contrast agents, for traceable imaging of diagnostic targeting.
- Drug payloads, for therapeutic intervention.
- Biomolecular ligands, for highly targeted delivery of both platform and conveyed cargo [22,23].
- Over traditional molecular agents, nanoparticulate agents will have include the following characteristics;
- Nanoparticles provide a fluorescent nanoplatform on which targeting agents (small molecules, antibodies, peptides) can be substituted or added.
- For multimodality imaging such as (optical, magnetic resonance, and radionuclide).
- For both imaging and therapeutic abilities ("theranostic" nanoparticles) they can be functionalized.
- For providing salutary benefits related to pharmacokinetics by exclusive renal excretion they can be designed.
- They have sufficient size to permit multivalency and, therefore, the potential for higher affinity binding than standard agents.

- They enable imaging from the single cell level to the entire, intact organism in vivo [24].

In recent decades, new bioactive molecules are discovered due to the development of new techniques and synthetic strategies, the researchers have tried to extend their knowledge on developing new drug delivery nanocarriers. From these vehicles, "Nanoinorganic" systems have been studied both for therapeutic and diagnostic purposes [25] (Figure 2).

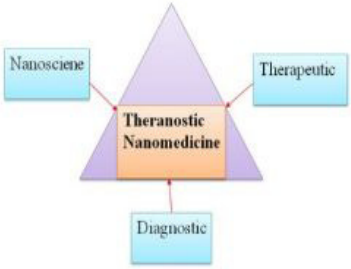

Figure 2: Shows scheme describing the combination of both therapeutic and diagnostic functions into theranostic nanomedicine.

Drug delivery system along with therapeutic agent would thereby be delivered to interior of given cell, these drug delivery systems will not only have important therapeutic and pharmacological action but also be of great interest for medical imaging and diagnosis [26]. For more specific and personalized disease management the multifunctional nanosystems such as theranostic nanoparticles are prepared by combining diagnostic and therapeutic capabilities into one single biocompatible and biodegradable nanoparticle.

Ideal theranostic nanoparticles must contain following characteristics;

- Should be safe.
- Selectively and rapidly accumulate in target(s) of interest.
- Without damaging healthy organs, efficiently deliver a sufficient amount of drug(s) on demand.
- Report biochemical and morphological characteristics of disease.
- It should be cleared from body within hours or biodegraded into nontoxic by products [27,28].

was coined to define ongoing efforts in clinics to develop more individualized, specific therapies for various diseases [29]. By surface chemical modification, nanoparticles can be coated, functionalized, and integrated with a variety of bioconjugated moieties for selective detection and treatment [30-33] (Figure 3).

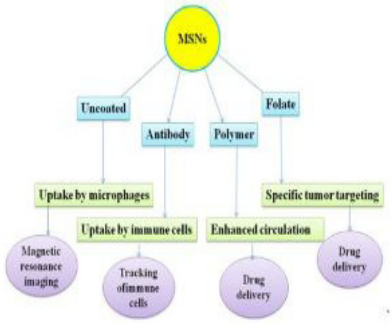

Figure 3: Bio-distribution and Biocompatibility of Mesoporous Silica Nanoparticles.

Hybrid Mesoporous Silica Nanoparticles for Cancer

Cancer may be defined as clinical stage where a mutant group of cells divides in an uncontrolled manner and invades neighboring tissues that finally destroy the whole cellular system [34]. Second cause of death in the United States is cancer which is responsible for 595,690 deaths in 2016. Due to clinical limitations of traditional approaches such as surgery, radiotherapy, and chemotherapy the diagnosis and treatment of this deadly disease are challenging. Some of the major issues related to the treatment of cancer are overcome by utilization of hybrid nano-materials. Multi drug resistance, detrimental side effects, and metastasis are the greatest challenges in cancer treatment today [35-36] (Figure 4). Hybrid nanostructures with multifunctionality are the state-of-art of nano-biomedicine, wherein the majority of interest is associated with beneficial employment of multiple materials within a single system [37-39].

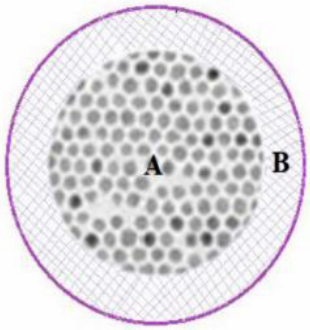

Figure 4: Shows Hybrid Mesoporous Silica Nanoparticles with A. Silica Core B. Organic Shell.

hMSNs possesses more advantages because the versatility with which the silica scaffold can be functionalized, offering the possibility of independently modifying the internal pore structure and the external particle surface (Figure 5).

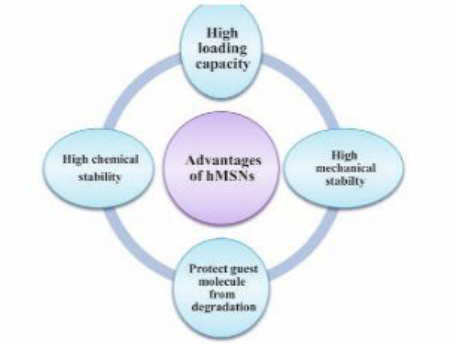

Figure 5: Advantages of hMSNs.

For the modulatation of the interactions with the cargo, internal pore functionalization is carried out and allows control over the stability, diffusional transport, and delivery kinetics of the therapeutic agents. Again, the formation of metastable crystalline forms or even prevent drug crystallization, increasing the molecular mobility and bioavailability of drugs with low water solubility is occur due to the confining effects of the (nanometer size) particle pores on drugs [20]. Yanzhuo Zhang et al developed MSNs loaded with a poorly water-soluble drug, intended to be orally administered, able to improve the dissolution rate and enhance the drug loading capacity. Spherical MSNs were synthesized using organic template method in an oil/water phase, and large pore diameter MSNs were functionalized with aminopropyl group through post synthesis. MSNs as well as functionalized MSNs were investigated as matrices for loading and release of model drug. The release rate of drug from MSNs with diameter 12.9nm was found to be effectively increased and release rate of drug from functionalized MSNs was effectively controlled compared with that from the unmodified MSNs [40].

Surface Functionalization of MSNs:

A wide variety of ligands have been incorporated onto nanoparticle surfaces, allowing them to be used in sensing of biomolecules and cells, diagnosis of diseases, and intracellular delivery [40]. MSNs contain high density of surface silanol groups. These groups can be modified with a wide range of organic functional groups. In biomedical applications of MSNs surface functional groups play several roles:

- For controlling the surface charge of MSNs.
- To chemically link with functional molecules inside or outside the pores.
- To control the size of pore entrance for entrapping molecules in the nanopores.

Surface functionalization of MSNs carried out by three methods: surfactant displacement methods, co-condensation, and post-synthesis grafting [23,42]. Amit Dubey et al. developed the mild acidic nanocatalyst, ordered mesoporous silica, chloroacetic acid functionalized SBA -15 via post synthetic grafting technique useful for acidic conversions such as Knoveneganel condensation, Mannich reaction and Biginelli synthesis. very high activity and selectivity was observed for all the conversions under milder reaction conditions [43]. Shattering of mesoporous silica by sonication, resulting in an improved intramesoporous structure. With sonication-shattered mesoporous silica, a much higher protein loading density can be achieved, which may allow more sustained protein drug release [44]. Guilan Qual et al. emphasized that, targeting property of lactose was integrated with the excellent drug delivery and endocytotic behaviors of MSNs to build a novel drug delivery system. Docetaxel was selected as a model drug, and fluorescein isothiocyante was used as a dye for the tracking to determine where the corgo will released. It is observed that the corgo loaded in MSNs with surface functionalization with lactose (hMSNs) show sustained drug release over a long period of time as compare with corgo loaded in MSNs without surface functionalization [45].

Stimuli Responsive Drug Release by hMSNs

Stimuli-responsive mechanism is a vital part of a DDS, which determines whether the DDS is endowed with controlled release functions. Relevant stimuli signals and release mechanisms are the part on which accurate design of a controlled release behavior should be based. DDS which respond to pH [46,47], temperature [48-50], light [51,52], redox state [53-57], magnetic field [58], biomolecules [59-61] or a combination of them is developed and confirmed. These stimuli signals are mainly divided into two main types: internal stimuli and external stimuli. Heterogeneities in pH value, redox state, types and amounts of biomolecules are seen due to the tremendous intracellular environment differences between tumor tissues and normal tissues. However, external stimuli are equally important, they play very significant role by applying extra stimuli at the disease location [62]. Maximum therapeutic efficacy can be realized by using stimuli-responsive targeted DDS that can effectively reach specific target sites without drug leakage on the way [63,64].

Following are the characteristics of ideal stimuli responsive Nano systems:

- Recognize tumor microenvironment in high selective manner.
- Allow for precise release in response to exogenous or endogenous stimulus [65].

In Recent year extensive attention is received by the stimuli-responsive nanomaterials for cancer treatment, and now a day this becomes a principal field in medical research. In case of cancer therapy, for achieving the complete eradication of tumors; the anticancer drugs must be administered systematically in high doses

for insurance of sufficient and sustained therapy. Sustained drug delivery systems will cause severe side-effects due to the nonspecific uptake of anticancer drugs by healthy tissues/organs such as bone marrow, liver, kidney, and heart before reaching the targeted organs or tissues. Therefore, to solve this problem, it is highly desirable to design stimuli-responsive controlled drug delivery systems [66]. Recently more attention has drawn by stimuli responsive DDS based on mesoporous silica nanoparticles (MSNs) because of some unique properties of MSNs such as extremely large surface area and pore volume which could accommodate drug molecules within the pore channels with a high payload, and the easily modified surface facilitate the attachment of different kinds of "gate-keeper" on the outlets of pore to control the release of drug [67,68]. Stimuli-responsive molecules, polymers, nanoparticles and proteins are used for the functionalization of surface of mesoporous silica nanoparticles which acting as caps and gatekeepers for such a controlled release of various cargos (Figure 6) (Table 3).

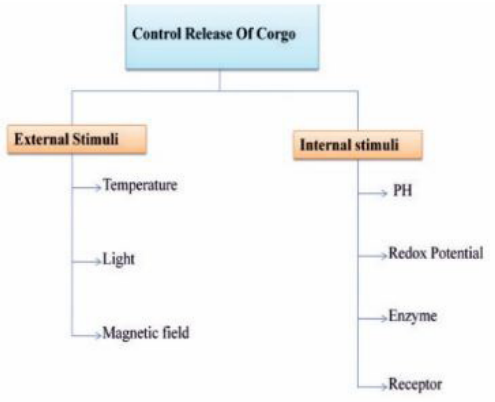

Figure 6: Stimuli Responsive Drug Release Mechanism Form Silica Nanoparticles.

Sr no	Stimuli	Principle
1	pH	It is based on more acidic pH of tumor and inflammatory tissues than that in blood and normal tissue.
2	Redox	It is based on redox con¬centrations of tumors and normal tissues are differ.
3	Temperature	Based on thermo-responsive material coated surface, drug release was closely dependent on the variation of the surrounding temperature. dilation of vessel and increase penetrability of corgo.
4	Enzyme	Upregulated expression profile of specific enzymes in pathological conditions such as cancer or inflammation.
5	Light	Non-invasiveness property and the possibility of remote spatiotemporal control.
6	Magnetic	Dependent on the temperature, magnetic nanoparticles-embedded MSNs is capable of generating thermal energy under an external magnetic field.
7	Ultrasound	The sensitive polymer changes its hydrophobicity and conformation toward coil-like gate-opening and cargo-releasing, after ultrasound irradiation

Table 3: Stimuli Responsive Drug Release from MSNs with Mechanism [71].

Effective protection from undesired degradation in harsh environments, such as the stomach and intestines is required for the delivery of antitumor drugs and other pharmaceutical cargos such as enzymes or oligonucleotides requires [69]. In the past decade Stimuli-responsive MSNs have been developed to achieve controlled drug delivery, however, in most cases MSNs were used as rigid building blocks to load drug molecules [70]. Marina Martinez-Carmona explained that, to prevent the premature release of the cargo entrapped in the mesoporous, it is feasible to cap the pore entrances using stimuli-responsive nanogates. Because of this upon exposure to external or internal stimuli, the pore opening takes place and the release of the entrapped cargo occurs. and also describe the cargo release in a needed location only due to targeting therapy by hMSNs. In another case if this type of therapy is not used, then the corgo will reaches to all circulation within body [11].

pH

For effective delivery of anticancer drugs pH-sensitive Nano systems are expected to store and stabilize the drug at physiological pH, rapidly release the drug when the pH trigger point is reached, and ensure that the intracellular drug concentration reaches the therapeutic dose [72]. In case of healthy tissues and tumors, intracellular pH is same; however extracellular pH of tumors is less when compared to healthy tissue. Generally, the average extracellular tumor pH is 6.0-7.0, in case of healthy tissue pH are 7.4.

pH sensitive nanocarriers are classified into three types;

- Polymeric nanocarriers such as (polymer-drug conjugates, nanogels, micelles and core-shell polymeric nanoparticles)
- Liposomes
- Inorganic nanoparticles

Various types of anionic and cationic polymers are used in pH sensitive drug release such as Poly (aspartic acid) (PASP), Poly(acrylic acid)(PAA), Poly(ethyl acrylic acid) (PEAA) and Poly(methacrylic acid)(PMAA), 3- methylglutarylated poly (glycidol), Poly(β-amino ester), poly(L-histidine) [73].

Redox

Intracellular microenvironment of tumor tissue is differing

than as normal tissue, such as over expressed GSH (2-10 mM). This biological feature can be used to design redox sensitive nanoparticles. mostly drug or gene delivery have received increasing interest over the past years. Cellular reductive microenvironment is regulated by tripeptide GSH. The level of GSH in intracellular compartments is 2-10 mM, which are generally 100-1000 times higher than that in human and blood. However, the cytosolic GSH level in some tumor cells has been found to be at least four times higher than in normal cells. Possibility of designing GSH sensitive NPs is developed by sharp differences in GSH levels between tumor and normal cells. After cellular uptake by disulfide cleavage NPs with GSH sensitive mechanisms can promote intracellular drug or gene delivery, and this then regulate the intracellular fates of delivered drugs and genes [74,75].

Temperature

Due to Tumors, inflammation, or infection processes moderate temperature increases up to 4-5°C. A temperature-responsive controlled release system is design by grafting temperature-sensitive Nano-switch on the surface of MSNs. Commonly used temperature-sensitive polymers are based on Poly-N-Isopropylacrylamide (PNIPAM) and its derivatives, these polymers exhibit a hydrophilic extended state below lower critical solution temperature which creates a diffusion bottleneck that hampers the drug release. Water is excluded from these polymers when the temperature is higher than the lower critical solution temperature, which collapse to release the loaded drug. The internal surface of the MSNs as modified through atom transfer radical polymerization by Lopez and coworkers, who confirmed that the PNIPAM-functionalized MSNs can release drugs at a high temperature (50oC), and inhibit the release of drugs at a low temperature (25oC). On the basis of this phenomenon, the team constructed a temperature-responsive controlled release system [8,76].

Enzyme

The design of nanomaterials is a developing arena in stimuli-responsive "smart" nanomaterials, whose chemical structures and/or physical properties are responsive to the biocatalytic action of an enzyme. In all the biological and metabolic processes enzymes play critical roles and the pathology of many diseases is underpins by dysregulation of enzyme expression and activity. In case of the therapeutics, dysregulated enzymes are promising biological triggers. When we use exploiting enzymes as a trigger these enzyme shows a number of advantages because most enzymes catalyze chemical reactions under mild conditions (low temperature, neutral pH, and buffered aqueous poly-N-isopropylacrylamide solutions, where many conventional chemical reactions fail. Enzymes can also possess exceptional selectivity for their substrates, allowing for specific, sophisticated, biologically inspired chemical reactions [77].

Following are some unique properties of enzyme;

- Isoelectric pH
- Exquisite substrate specificity
- Greater expression in particular organs and in sub-cellular organelles
- Large changes in concentration, in inflammation and disease states

In intracellular delivery proteases plays critical role and matrix metalloproteinases is specific for the cancer microenvironment. In inflammation stage concentration of elastase is increased and while in case of pancreatic cancer phospholipases are overexpressed and can be used for antibiotic delivery. Oxidoreductases also are taken advantage of oxidase-responsive DDS. By using these different enzymes MSNs can be tailored by changing the linkers and capping agents on their functionalized surface [49].

Ultrasound

Spatiotemporal control of the drug release at the desired site is achieved by Ultrasounds (US), ultrasound having following characteristics;

- Non-invasiveness
- Absence of ionizing radiations
- Cost effectiveness
- Easy regulation of tissue penetration depth by tuning the frequency cycles and exposure time

This high-frequency ultrasound allows local therapy and can penetrate deep into the body with focused beams due to this, adverse side effects to healthy tissues is avoided. Ultrasound stimulus enhances nanoparticles extravasation through blood capillaries and induce immune response against tumors and also increase cell membrane permeation [78-80].

Magnetic

In magnetic resonance imaging and magnetic targeting, magnetic mesoporous silica nanoparticles used to deliver photosensitizer to the target site using the magnetic targeting technology. This used to trace and guide drug delivery in vivo. However, combined with the advantages of mesoporous materials, including large pore size, large specific surface area, stable structure and modifiable inner surface; Magnetic mesoporous silica nanoparticle exert good drug-loading capacity and biocompatibility as reported [81-83]. It is believed that the combination of magnetic mesoporous silica nanocomposites with stimuli-responsive component in a single nanovesicle can potentially construct a delivery system with the ability to control the location, time, and amount of drug released [84]. Magnetic hyperthermia treatment is a cancer therapy that relies on the heat produced by magnetic nanoparticles under

an alternating current magnetic field and this has the potential to realize a scar less, local, and economical treatment with minimum side effects [85-88].

Stability of MSNs

Particle size and particle size distribution, morphology and orientation of the porous structure, surface area, pore diameters and chemical purity are the properties of porous silica micro or nanoparticles that need to be immediately checked after their synthesis. These parameters play a crucial role in determining the hydrothermal, colloidal, suspension and dispersion stability of the particles. Surface properties affects the total charges, particle-particle interactions, suspension stability and thermal properties of the porous particles [86]. Nanoparticles drug loading capacity, colloidal stability, and interactions with loaded drugs are related to their physico-chemical properties and are important for a functional drug delivery device. Overestimation of the silica nanoparticles responsible for the aggregation of particles [90]. Rahul Bagwe et al studied the effect of surface functionalization on MSNs for reduction of aggregation. For Preparation of uniform fluorescent dye-doped silica nanoparticles of the desired size and surface, a water-in-oil microemulsion-based surface modification method has been used. Colloid stability studies, based on the zeta potential and particle size indicate that the addition of proper ratios of inert functional groups (e.g. methyl phosphonate) to active functional groups (e.g. amino groups) to the surface of silica nanoparticles results in a highly negative zeta potential, this is necessary to keep the particles well disperse [91]. Younwoo Nam et al. developed phosphate-modified mesoporous silica nanoparticles with large pores over 10nm were synthesized successfully and the phosphate- modified mesoporous silica nanoparticles were observed to be very effective in disrupting F127 block copolymer aggregates induced by Mn2+ [92].

Applications of MSNs

As a Drug Delivery System

Immediate Drug Delivery Systems Based on Msns: Many hydrophobic drugs have poor water solubility and limited applications which results in poor absorption in the gastrointestinal tract after oral dosing [93]. As compared with other types of carriers, immediate drug delivery system based MSNs have unique features. Drugs are encapsulated with a high payload due to large surface area and high pore volume. The mesoporous channels keep drugs in the amorphous or non-crystalline state within the pores, which facilitates drug dissolution. However, the marked chemical stability and inert behavior allow for better control of drug loading and release.

Sustained Drug Delivery Systems Based on MsnsL: In case of immediate drug delivery systems frequent administration is necessary and it cannot provide long-term drug release. Therefore, there is a significant advantage of dosage form offering sustained release because sustained release is able to maintain a steady blood concentration for a prolonged period of time. For sustained drug delivery several MSNs used have been categorized into two groups: unmodified and modified silica materials [94].

MSN-Based Targeted Drug Delivery Systems: For targeted drug delivery systems MSNs have emerged as appealing candidates. By the Enhanced Permeation and Retention (EPR) effect MSNs with a particle size in the nanoscale range can accumulate in tumor tissues [95]. However specific drug delivery can be achieved via active targeting by decorating MSNs with targeting ligands such as folate [96,97]. MSNs acting as homing devices by conjugating the peptides, antibodies and magnetic materials on surface [98-101]. In the targeting process, the surface modification of MSNs and particle size critically influence particle pharmacokinetics and biodistribution [102].

MSN-Based Stimuli-Responsive Controlled Drug Delivery Systems: Chemical design and synthesis of stimuli-responsive drug carriers are the promising approach to mitigate the systemic toxicity and enhance the therapeutic outcome of therapeutic agents [103]. stimuli-responsive MSNs are developed by applying controls such as 'gatekeepers' over the pore entrance. Until the drug-loading system is exposed to external stimuli, such as pH, redox potential, temperature, photo irradiation, or enzyme; the drug cannot leak out from silica carriers. These stimuli remove the gatekeepers [94]. Due to the pH gradients that are present in different tissues and subcellular compartments pH-responsive controlled drug delivery systems have been widely investigated, among the various stimuli-responsive drug delivery systems [104].

Another Application of MSNs (Figure 7)

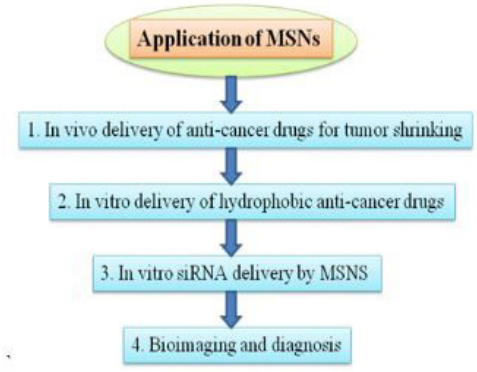

Figure 7: Describe Application of MSNs.

Conclusion

The mesoporous silica nanoparticles are the emerging field for smart drug delivery. Theranostic approach of hybrid mesoporous silica nanoparticles used for combine diagnostic and treatment.

Its various features such as stability, uniform pore structure, high surface area, tunable pore size and well-defined surface properties make it ideal carrier for therapy. Stimuli response is achieving for localization of corgo to a particular approach towards the effective and specific drug cancer cells. Targeting therapy is possible by using hybrid mesoporous silica nanoparticles.

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