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REVIEW ON PROPERTIES AND APPLICATIONS OF MESOPOROUS SILICA NANOPARTICLE

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ABSTRACT

The Mesoporous silica nanoparticles have nanoporous structure and high Surface Area with large pore volume, and pore size facilitates the better performance in loading of drug overcoming the lacking properties such as specificity and solubility of drug molecule due to which patient is required to take high doses of drug to reach the therapeutic effect for the disease treatment. In this paper, a comprehensive literature of mesoporous silica nanoparticle on the properties such as particle size, pore size, surface area, etc. and applications in drug delivery system, bioavailability enhancement, imaging and diagnostic agent, biomedical application and in food have been compiled and reviewed.

KEYWORDS: Mesoporous silica nanoparticle, nanoporous, drug delivery system, bioavailability enhancement, imaging and diagnostic agent, biomedical.

INTRODUCTION

Porous silica is a porous material which has been commonly used as a pharmaceutical excipient. The mesoporous (2-50 nm) silica materials was discovered in the 1990s, the synthesis and application of mesoporous silica received substantial importance due to their unique features such as, inert nature, high surface area, large pore volume, good compatibility and high physicochemical stability. As the mesoporous silica size ranges from 2-50nm, the confinement effect can be used as dissolution enhancers. Due to large pore and physical size it can load high amount of drug. Mesoporous silica as a drug carrier was first determined by Vallet-Regi et al. and it was also reported that MSN contains low toxicity. Adsorption onto mesoporous silica (MS) is a new emerging technology which improves the performance of

poorly water soluble drugs by improving their dissolution rate and solubility and thereby enhancing oral bioavailability. A drug solution is loaded into pores through capillary forces.

In the beginning MSNs use was limited for controlled delivery of various hydrophilic or hydrophobic active agents. Later advances in MSNs properties such as surface functionalization and PEGylation rendered them as a promising drug delivery vehicle.

Mesoporous silica nanoparticles (MSNs) have been studied and vastly developed since the first preparation of MCM-41 in 1992. A great variety of mesoporous silica materials, such as SBA, MSU and FSM, and various grades of MCM have been developed using different synthetic approaches, including fast self-assembly, soft and hard templating, modified Stöber method, dissolving reconstruction, and modified aerogel approaches.

Various types of MSNs with their internal structure and pore size.

Type	**MCM-41**	**MCM-41**	**SBA-15**	**SBA-15**	**SBA-15**	**MCM-48**
Internal structure	2D hexagonal	Hexagonal with unidirectional pore structure	2D hexagonal	2D hexagonal	3D cubic cage like	3D cubic
Pore diameter (nm)	1.5-3.5	3.70	6.0-10.0	7.80	4.0-9.0	2.5-3.0

PROPERTIES OF MESOPOROUS SILICA NANOPARTICLE

Particle size

The particle size of MSN is tunable (30-500nm) which allows a facile endocytosis by living animal without cytotoxicity (Asad et al., 2017).

The factors that controls the size and morphology of mesoporous silica nanoparticle by controlling pH, using different templates and co-solvents are.

- Rate of hydrolysis
- Interaction between drug and silica material
- Condensation of silica source

Ozin et al. (1998) studied the effect of pH on morphology of MSNs and also demonstrates the under mild acidic condition.

While synthesizing the MSN, the Stirring rate controls the particle size of MSNs, as the rate is slow long fibres are produced and upon fast stirring fine powder is formed.

Dynamic light scattering is now a days used to determine the particle size of MSNs is preffered.

Ordered Pore structure

MSNs contain long ordered porous structure without interconnection between porous channels, which allows fine control of the drug loading and release kinetics.

Pore size

The pore size can be controlled at 2-8nm by using different soft templates and thr pore structure has 2 dimensional cylindrical structure or interconnecting structure. Pore diameter behaves as as a size selector for the loading of biologically active molecules within the mesoporous cavities which can regulate the release rate.

X-ray diffraction and transmission electron microscopy (TEM) are used to evaluate the pore structure of MSNs and nitrogen sorption is used to measure the pore width. The 2D hexagonal p6m (MCM-41), the 3D cubic Ia3d (MCM-48) and the lamellar p2 (MCM-50) are the common mesophases in silicas with pore sizes between 2 and 5 nm. Similarly, 2D hexagonal p6m is reported in MSNs with large pore size 6-20 nm.

Surface area

Surface area determines the molecules loading capacity of these nanoparticles, because the higher the contact surface the greater the number of guest molecules incorporated. Surface area of MSNs is in the range of 700-1000m^2/g. The MSNs have high drug loading capability which can possibly attain localized and even promising alternatives to develop advanced nanotherapeutics.

Large Pore volume

The pore volume of MSNs is in the range of 0.6-1cm^3/g. The amount of drug contained in MSNs can be determined by pore volume. In MSNs due to the loading of drug consecutively it causes large filling of mesopores due to which drug-intermolecular interactions within pore wide is increased which indicates the pore volume and amount of drug loaded are directly proportional to each other.

Good Biocompatibility

According to the United Food and Drug Administration (USFDA), Silica is generally regarded as safe. The MSNs is degradable in an aqueous solution, and thus there is no problem related to removal of MSNs from body after administration.

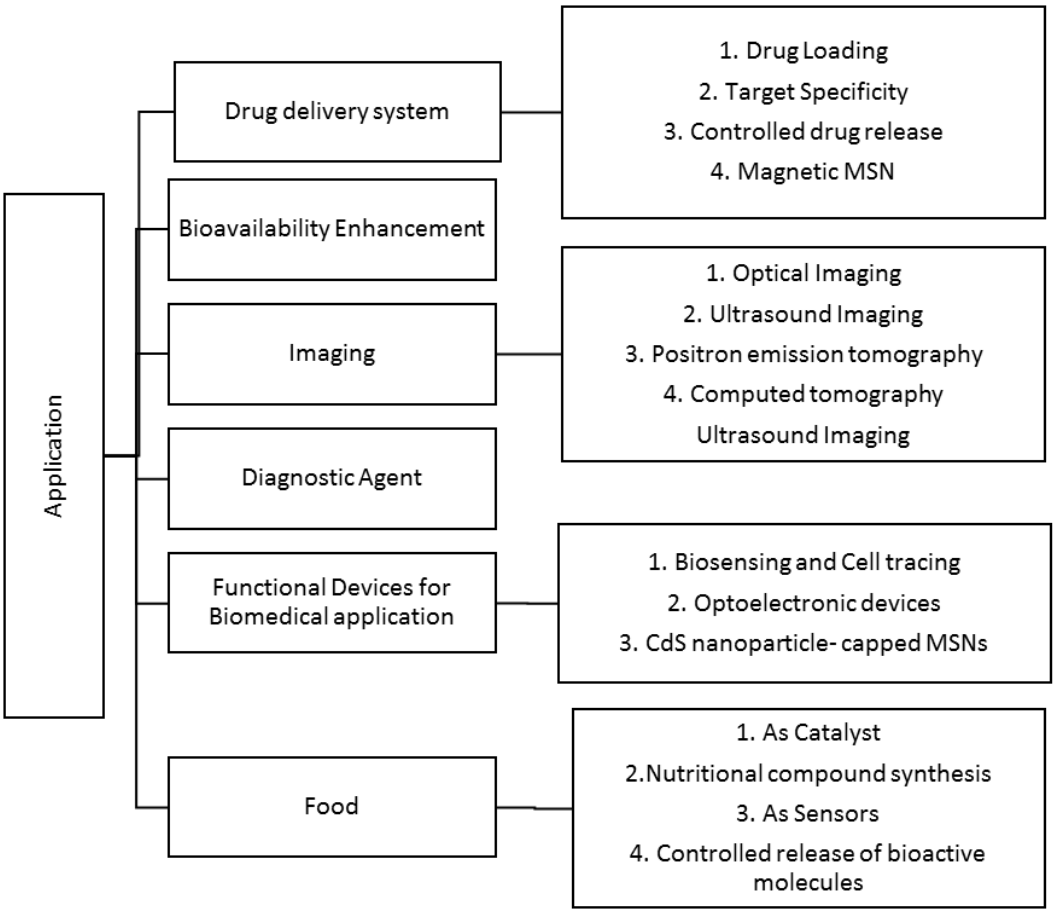
Low Toxicity

Potential suitability for delivery of various hydrophobic and hydrophilic agents such as drugs, proteins, etc.

As the MSNs contains size and shape controllable pores they can store drugs and can prevent the release and degradation before reaching the designated target. The nanoparticle size and surface grafted ligand enhanced the uptake by cancer cells, thus due to MSNs the improve in efficiency of anticancer drugs increases the accumulation in tumours. Once the MSN drug vehicles reach the cancer cells, the functionalized controlled release property responses to the biological environment and exhibited intracellular drug delivery. The biocompatible MSN drug carriers at the effective dosages with targeting properties have shown to effectively deliver anticancer drugs to tumors, and exhibit excellent tumor suppressing effects. Functionalized MSN drug carriers have achieved steady progress in these targeted drug delivery areas.

APPLICATIONS OF MESOPOROUS SILICA NANOPARTICLE

As mesoporous silica nanoparticle consist of properties such as its nature of pore, size, shape and connectivity it has number of potential applications. The application of mesoporous silica nanoparticles include.



Flowchart of Applications of Mesoporous Silica nanoparticle.

I. DRUG DELIVERY SYSTEM

Mesoporous silica materials plays an important role in delivering the drug at the site of action which includes following application.

1. Drug Loading

The loading is done by incorporating MSNs in a solution of drug to interact between the drug and the particle surface by adsorption. The interaction is due to hydrogen bonding and electrostatic attractions. The high concentration of drug can also be loaded in MSNs as it contain large surface area and by controlling the surface chemistry of MSNs, enters into cell through endocytosis and macropinocytosis process.

Drug loading is achieved by covalent attachment with the surface of particle. As MSNs contains large surface area and pore volume it permits the entry of hydrophobic ligands into the pores.

2. Target Specificity

To reduce the non-specific binding and increase specific binding to target cell or tissue, MSNs can be used which gives both passive and active targeting specificity by increasing the bioavailability. The decrease in dosage of drug and eliminating the toxic effects of drugs after administration can be achieved by target specificity of mesoporous silica nanoparticle.

2.1. Passive Targeting

The increase in permeability of tumour blood vessels is done by Passive targeting and it also allows accumulation of nanocarriers at tumour site. When the cancer cells or tumor cells are highly exposed with receptorsas compare to normal healthy cells, the binding and internalization of nanocarrier can be increase by selective targeting. Passive targeting can be enhanced through the use of a magnetic DDS such as Fe_3O_4 in MS by the application of a static magnetic field at the site which attracts and retains magnetic DDSs.

2.2. Active Targeting

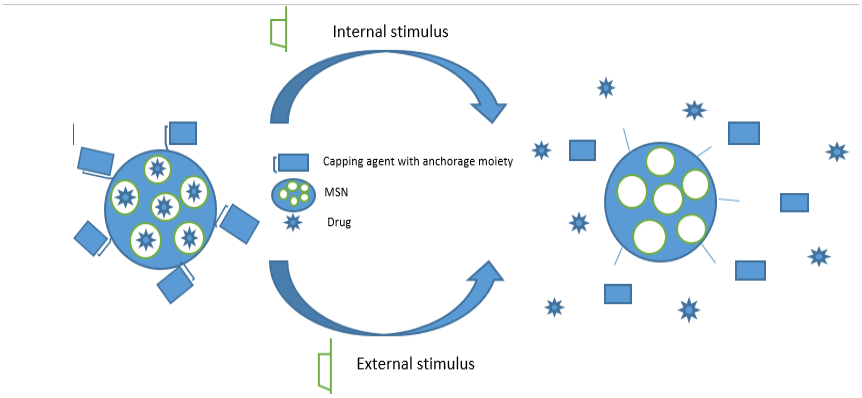
For the treatment of Drug resistant diseases, passive targeting is augmented with active targeting to achieve cellular uptake of the drug delivery system. When the modification of the DDS surface with target-specific ligands is done to tune the interaction with corresponding receptors expressed on the outer membrane of the target cells, the active targeting is achieved. Antibodies, amino acid chains, and nucleic acifds are some common targeting ligands.

3. CONTROLLED DRUG RELEASE

Variety of controlled release mechanisms can be employed to prevent premature release of the payload during the targeting process when a DDS circulates in the bloodstream. For the release pattern simply dissolution of the drug is allowed and the release method is strongly dependent on the solubility of the drug. This method is useful for the hydrophobic drug molecule that would not dissolve until it comes in contact with a non-polar environment. The pore structure has shown to influence the release kinetics. Therefore, it is possible for dissolution-mediated drug delivery to be controlled primarily through particle structure.

The incorporation of a magnetic core provides additional formats for controlled drug release via stimuli response. Stimuli responsive behavior can be accompolished by pore blocking caps throughout linkers which can be cleaved upon exposure to given stimuli. Classified as internal and external stimuli.

Internal Stimuli	External Stimuli
Ph redox potential enzymes	Magnetic fields Ultrasounds or light



3.1. Internal Stimuli-Responsive Drug delivery MSNs: It incorporates mainly a sensitive linker and/or a capping agent. The linker is able to break, degrade a conformational change in the presence of the given stimulus. The capping agents, such as inorganic nanoparticles, polymers, blocks the mesopore entrances and hinders premature cargo departure. It is possible to use coatings of organic or inorganic chemical nature as blocking caps able to degrade under the stimulus action, allowing the pore uncapping and drug release. Table summarizes the main internal stimuli-responsive MSNs recorded, specifying the endogenous stimulus, the responsive linker and capping agent.

Table: Internal stimuli-responsive strategies for Drug delivery MSNs.

Stimulus	**Responsive Linker**	**Blocking cap**
pH	Acetal linker Boronate ester Gelatin Aromatic amines Benzoic-imine bonds CaP soluble at acid pH	AuNPs Fe_3O_4NPs Gelatin coating CDs Polypseudorotaxanes CaP coating
Redox Potential	-S-S- -S-S- -S-S- -S-S-	SsDNA PEG CdS NPs PPI dendrimer
Enzymes	MMP-degradable gelatin Protease-sensitive peptide sequences	Gelatin coating PNIPAm-PEGDA shell
Small molecules	ATP aptamer	ATP aptamer

3.2. External Stimuli-Responsive Drug Deliver MSNs.

The stimuli responsive MSNs have been developed capable to respond to externally applied stimuli, such as magnetic fields, ultrasounds or light, among others.

4. MAGNETIC MESOPOROUS DRUG DELIVERY SYSTEM

Magnetic nanoparticle drug carrier are fabricated by embedment into mesoporous silica generally in two steps [Shou-Cang et.al., 2017].

1. The monodispersed magnetite was synthesized
2. Then the magnetic nanoparticles were coated with mesoporous silica using non-ionic block copolymer surfactants as structure directing agents.

For improved drug loading and controlled drug delivery, surface modification or functional polymers were conjugated with magnetic functional mesoporous materials to form mesoporous composites as drug carriers.

II. MESOPOROUS SILICA FOR POORLY SOLUBLE DRUG FORMULATION

Most of the poorly water-soluble drugs loaded onto mesoporous silica excipients were performed by Impregnation and Solvent evaporation method. With the increasing numbers of innovative new drugs in development, almost 70% of new drug candidates exhibit low aqueous solubility, ultimately resulting in poor absorption. In an attempt to overcome this solubility obstacle and to improve the oral bioavailability, a growing number of drug delivery technologies have been developed. With the excellent features including huge surface area and ordered porous interior, mesoporous silica can be used as a perfect drug delivery carrier for improving the solubility of poorly water-soluble drugs and subsequently enhancing their oral bioavailability. When water-insoluble drug molecules are contained in mesoporous silica, the spatial confinement within the mesopores can reduces the crystallization of the drug. Compared with the crystalline drug, the amorphous drug can reduce the lattice energy, subsequently resulting in improved dissolution rate and enhanced bioavailability. Moreover, the huge hydrophilic surface area of mesoporous silica facilitates the wetting and dispersion of the stored drug, resulting in fast dissolution.

III. BIO-IMAGING AND DIAGNOSTIC AGENTS.

As the MSNs contain unique features, an imaging agent supported by MSNs can be a promising system for developing targeted bio-imaging contrast agents with high structural stability and enhanced functionality that enable imaging of various modalities. The

development of functional MSNs for bio-imaging applications, including optical imaging, magnetic resonance imaging (MRI), positron emission tomography (PET), computed tomography(CT), ultrasound imaging, and multimodal imaging for early diagnosis are some recent achievements. The advantage of MSN-based imaging agents can track one single cell and specific cellular organs in vitro. And, in vivo results have confirmed the potential as diagnostic agent as well as drug delivery carriers. MSNs can be eliminated from the body after the quantitative imaging process is complete. The direct method of imaging of MSNs such as Bio-distribution, cancer cell targeting efficiency, cytotoxicity, internalization pathway and progress of the therapy is observed [Bong et.al., 2017].

The Mesoporous silica nanoparticle are also used as a diagnostic and therapeutic tool for bacterial infection.

IV. Functional devices for biomedical application

Bio sensing and cell tracing

A sensor system for the detection of target within individual cell both in vivo and in vitro work by the versatile surface chemistry and small particle size of MSNs [Liu J et.al., 2009]. The fluorescence, self-quenching and other diffusion related issues can be tackled by nanoparticles. Capability of MSNs to functionalize surface with greater amount of cell recognizing agents or other site directing compounds make MSNs an excellent cell tracing agent.

Use in optoelectronic devices

By accurate surface modification of MSNs, a transparent silica-polymer, having high mechanical strength and low thermal expansion, can be synthesized [Suzuki N et.al., 2012]. Some examples of optoelectronic devices are optical fibers LED or solar cell covers, and light guide films.

CdS nanoparticle-capped MSNs

The CdS nanocrystals with mercaptoacetic acid coating can be chemically prepared as removable caps to block MSNs and encapsulated drugs/ neurotransmitters. By using various di-sulphide reducing agents, the di-sulphide linkage between MSNs and CdS caps were cleaved and the entrapped contents can be released from the channel.

V. FOOD

The mesoporous silica material are used for the controlled release of bioactive molecules, as catalysts in the synthesis of essential nutrients, as sensors to detect unhealthy products etc., and with many applications in food technologies.

When mesoporous silica material is combined with food, the healthier products, it can improve our quality of life [Benardos et.al., 2013]. This can also develop in protecting bioactive molecules during their passage through the digestive system. This is the reason, the controlled release of bioactive molecules is a very interesting topic in the food technology. Mesoporous silica supports the use as catalysts in the synthesis of nutrients and as sensors for the detection of unhealthy products, essential in food, is in great demand industrially for the manufacture of functional foods and films for food and industrial packaging.

CONCLUSION

This review reports about the unique properties of Mesoporous silica nanoparticle which supports display characteristics that usually cannot be found in classical drug delivery system (such as dendrimers, polymers, micelles, etc.) helps in loading of drug for various applications for cargo controlled release using different stimuli, there capped materials can help in the design of new and creative ways to deliver drugs, nutrients, and bioactive molecules. MSNs are proved as a promising nanocarriers for transport of toxic drugs. It also have stimuli responsive drug release which reduces the side effect of anti cancer drugs in therapy. Mesoporous silica nanoparticle had shown various approaches in applications like drug/ biomolecules/ gene delivery, targeted drug delivery, as diagnostic and imaging agent, and many more.

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