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MESOPOROUS SILICA NANOPARTICLES AND ITS SYNTHESIS: A REVIEW

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ABSTRACT

In the past decade, non-invasive and biocompatible mesoporous silica materials as efficient drug delivery system have attracted special attention. Great progress in structure control and functionalization of mesoporous silica nanoparticles for its biomedical application has been achieved. Application of mesoporous silica nanoparticles as fillers in the preparation of nanocomposite of polymers has drawn much attention, due to the increased demand for new materials with improved thermal, mechanical, physical and chemical properties. This paper is written by emphasizing on the synthesis of silica nanoparticles, surface modification for preparation of homogeneous nanocomposites.

KEYWORDS: Mesoporous silica nanoparticles, MCM-48, SBA-15, Ostwald ripening, 3-aminopropyltrimethoxysilane.

1. INTRODUCTION

In the current century modern nanotechnology has evolved as the principal component of science. In many developments of nanoparticles have been explored as drug carriers, diagnostic sensors. Silica nanoparticles with mesopores –referred to as mesoporous silica nanoparticles (MSNs) have gained wide popularity over the recent years. Mesoporous silica nanoparticles whose attributes include uniform mesopores, easy functionalization, significant biocompatibility, have gained much recent attention for biomedical applications. The most well known and common mesoporous silica materials include MCM-41, MCM-48 and SBA-15 which present different structural pore sizes (2-50nm) and different structural characteristics (2D hexagonal and 3D cubic). SBA-15 is much more difficult to reduce to nano size due to its acidic synthetic condition. Due to pore components and large surface area it is useful for building a multifunctional theronastic agent.

Mesoporous silica nanoparticles with three distinct domains that can be functionalized

a) silica framework b) nano channel pores c) nanoparticles outermost surface Mesoporous silica nanoparticles are specially well suited to the task of incorporating the essential capabilities of a theronastic platform in a single particle, with separate domains for

1) The contrast agent that enables traceable imaging of theronastic target
2) The drug payload for therapeutic intervention
3) The biomolecular ligand for highly targeted delivery
4) In vivo biocompatibility
5) Straight forward surface functionalization

Interior pores can protect a high loading of organic molecules such as fluorescent, MRT contrast agent. External surface can be functionalized to give site-specific targeting ability. Pores can be containers for drugs, DNA or RNA. Mesoporous silica nanoparticles (MSNs) possess well defined structure and high density of surface silanol groups which can be modified with a wide range of organic functional groups.[2]

Functional group play role in biomedical application of mesoporous silica nanoparticles (MSNs)

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

An overview of the synthesis and theory behind formation of MSNs is provided to discuss the factors affecting the shape and size of MSNs. Some important characteristics of mesoporous materials are:

1) They have long range ordered porous structure.
2) Their pore size distribution is usually quite narrow and the pore size can be varied from 2 nm to 30 nm by changing the composition of the synthesis mixture or surfactants;
3) They have large surface areas, enable them for sorption processes.

4) Different structure of these materials such as rods, sheets and 3D structures can be obtained by using different surfactants.
5) High thermal stability and hydrothermal stability can be obtained after modification

2. Synthesis of MSNs

Stober was the first pioneer in developing a system of chemical reactions for the synthesis of spherical monodisperse micron size silica particles. Hence, the method is known as Stober synthesis. To get desired nanosized, monodisperse, ordered silica particles many modifications can be done on Stober's synthesis. This method was first modified by Grun et al. by using cationic surfactant as a template he gave spherical shape rather than hexagonal MCM-41 structure. For getting a good results the particle size needs to be uniform; pore volume has to be large to enhance loading capacity.

Mesoporous material can be synthesized by following methods

a) Sol-gel method
b) Template assisted method
c) Chemical etching method
d) Microwave assisted method

Table 1: List of commonly used chemicals in the synthesis of MSNs.

Chemical Constituents	**Function**
Cetyltrimethylammonium bromide(CTAB)	Structure directing agent/template
Cetyltrimethylammonium chloride(CTAB)	Structure directing agent/template
Pluronic F123,F127	Surfactant template
Brij-76	Surfactant template
Triton X-100	Surfactant
Tween 20,40,60,80	surfactant
Tetramethyl orthosilicate(TEOS)	Inorganic silica source
Tetramethoxy silane(TMOS)	Inorganic silica source
Tetrakis(2-hydroxyethyl)orthosilicate(THEOS)	Inorganic silica source
Trimethoxyvinylsilane(TMVS)	Inorganic silica source
Sodium silicate	Inorganic silica source
Ethanol	Cosolvent to solubilize TEOS
Sodium hydroxide(NaOH)	Base catalyst
Ammonium hydroxide(NH_4OH)	Base catalyst
Triethanolamine(TEA)	Base catalyst, complexing agent and growth inhibitor
Diethanolamine (DEA)	Base catalyst
Disodium hydrogen phosphate-sodium	Reaction medium
Trisopropylbenzene(TIPB)	Pore-expanding agent
Tetrapropoxysilane(TPOS)	Pore-expanding agent
Pluronic polymer P103	Pore-expanding agent

2.1. Sol-gel method

It is a wet chemical technique, another name is used for this process is chemical solution deposition method. In this sol-gel method, the condensation process proceeds by first maximizing the number of Si-O-Si bond and resulting in number of terminal hydroxyl groups being minimized by internal condensation. This condensation includes rapid ring formation into which monomer is binded and form 3D small particles. These formed particles are compact and have-OH groups only on the particle surface. Particle growth and Ostwald ripening follows. Ostwald ripening is helpful for further growth of particles resulting in size growth. Both pH and temperature have an effect on the progress of particle growth. Particles aggregate into branched chains and networks leading to the forming of a gel.

The sol-gel process can be described by three equilibrium reactions.
Where R is an alkyl group
Hydrolysis

$$\equiv Si-OR + H_2O \rightleftharpoons \equiv Si-OH + ROH \qquad \text{(eq. 1)}$$

Esterification
Alcohol condensation

$$\equiv Si-OR + HO-Si\equiv \rightleftharpoons \equiv Si-O-Si\equiv + ROH \qquad \text{(eq. 2)}$$

Alcolysis
Water condensation

$$\equiv Si-OH + HO-Si \rightleftharpoons \equiv Si-O-Si\equiv + H_2O \qquad \text{(eq. 3)}$$

Hydrolysis

Silicon alkoxide is used as the starting material as a silica precursor. The starting material is processed to form a dispersible oxide and forms a solution in contact with water or dilute acid. Remove the liquid it gives gel; the particle size and shape are controlled by sol/gel transition. Calcination of gel produces oxides. In acidic conditions the hydrolysis rate will decrease with each subsequent hydrolysis and condensation step but increase under basic conditions due to electron withdrawing capabilities of –OH compared to –OR group. Hence, for decay this method is widely used for production of silica, glass and ceramic materials due to its ability to form pure and homogenous products at mild conditions.[1]

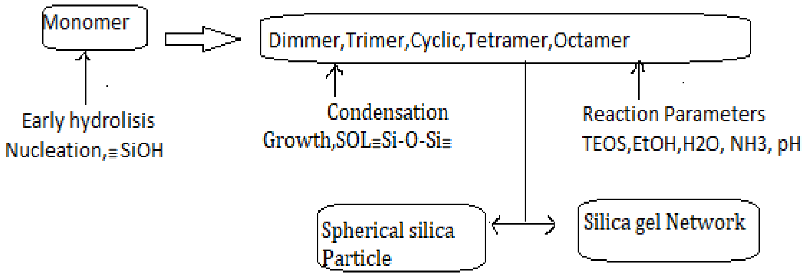

Fig.1.Schematic silica formation by sol-gel process

2.2. Template Assisted Technique

Template assisted technique is a well known and cheaper technique to synthesize ordered mesoporous silica materials. In this process, template is helpful for synthesizing mesoporous materials. There are two types of template assisted method one is exoemplate and another is endotemplate.

2.2.1. Exotemplate

In this method porous solid is used as template hence, it is called as hard matter templating. Inorganic precursor is used for filling the hallow spaces that provide exotemplate framework, pore system is formed on which drug material can be loaded.

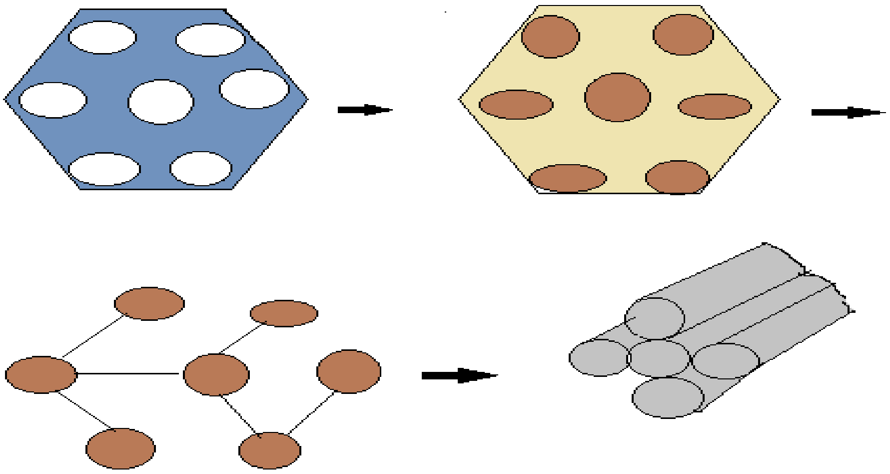

Fig2.Exotemplate (hard matter templating approach)

2.2.2. Endotemplate

In this method surfactant a Structure Directing Agent is used as template for the synthesis of ordered mesoporous silica material. In endotemplate method no hard template i.e. solid is used therefore it is also called soft matter templating method.

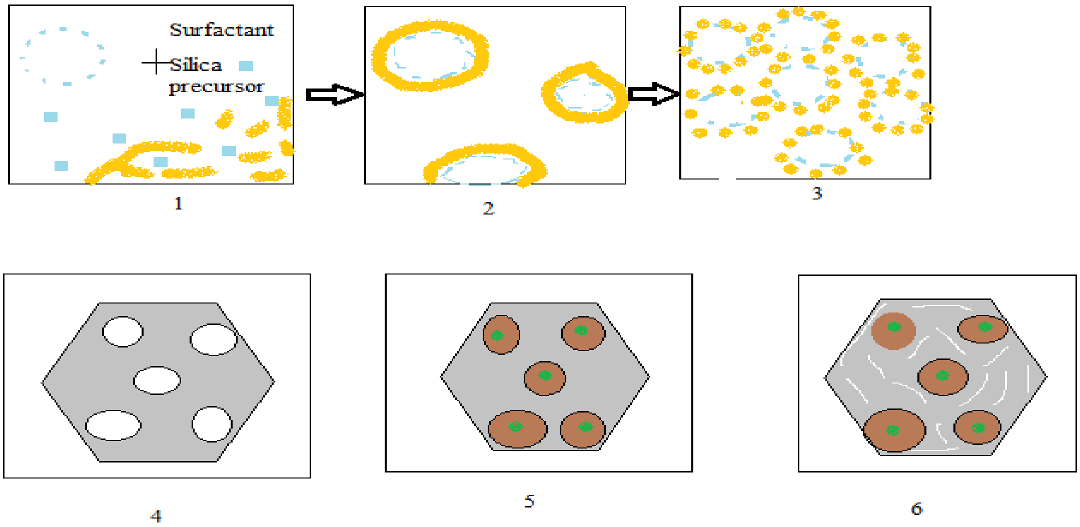

Fig.3.Endotemplate (soft matter templating) method for porous materials

Recently, ordered mesoporous silica materials can be synthesized by using template assisted self assembly method of silica species with surfactant structures. During this synthesis, mesophase can be formed by attractive interaction between the head group of structure directing agent and silica precursor through electrostatic, counter-ion mediation or hydrogen bonding interactions.

If synthesis takes place under acidic alkaline conditions and cationic quarternary ammonium surfactant (QAS) are used as structure directing agent, silicate species are present as anions and this pathway is termed **$S^+ I^-$**. If synthesis takes place under acidic condition and cationic QAS are used as SDA, silicate species are present as cations and mediator ion is needed to create interactions between those species and the surfactant head group is termed as **$S^+ X^- I^+$**. If alkaline condition, anionic surfactant as SDA the silicate species are, present as anion and mediator is again needed. This is termed as **$S^- M^+ I^-$**. In acidic condition there is no mediator ions can be required and is termed as **$S^- I^+$**.

Chiral mesoporous silica nanoparticles is also synthesized by using co-operative self assembly method. Mesoporous silica with various ordered mesostructured can be generated by the co-operative self-assembly of amphiphiles and silicates, incorporate this into chiral templating process has favored the formation of inorganic chiral materials with highly ordered mesostructures.

Formation of Chiral mesoporous silica

Chiral mesoporous silica synthesized by co-operative self assembly of chiral or achiral amphiphiles and silica precursors, based on electrostatic interactions between the head groups of amphiphiles inorganic reagents. For, cationic amphiphiles positively charged hydrophilic group interact with negatively charged silicates in alkaline solution. OR indirectly interact with positively charged silicates, mediated by counter ions, in strong acidic conditions. For anionic amphiphiles Co-structure Directing Agent such as 3- aminopropyltrimethoxysilane (APS), N-trimethoxysilylpropyl, N,N,N-trimethylammonium chloride(TMAPS). These are positively charged interact with negatively charged head group of anionic amphiphile through neutralization or double decomposition reaction. Alkoxysilane sites of APS or TMPAS are polymerized with silica precursor to form silica framework. Such co-operative interaction between amphiphiles and silica precursors drive organization of silicates around micellar superstructure of amphiphiles.

2.3. Microwave Assisted Technique

The microwave assisted method used for making molecular sieves is relatively new technique in the field of research’s technology. This method is useful for synthesizing numerous ceramic oxides, hydroxylated phases, porous materials and metal powders. This method has many advantages as compared to conventional process such as rapid heating to crystallization temperature faster supersaturation by rapid dissolution of precipitated gels and shorter crystallization time as compared to conventional autoclave heating.[8] It was reported that, MCM-41 mesoporous materials can be obtained via microwave heating using Cetyl Trimethyl Ammonium Bromide (CTAB) as the template.

2.4. Chemical Etching technique

This method is very useful for the synthesis of hollow type mesoporous silica structure to create hollow interiors. Hollow mesoporous silica with controllable pore size can be synthesized which sows high drug loading capacity. It is helpful to prepare different kinds of heterogeneous hollow type nanostructures with inorganic nanocrystals, such as Au, Fe_2O_3 and Fe_3O_4

nanoparticles as the core and mesoporous silica as the shell.

In chemical etching technique, a homogeneous templating route, namely, "structural difference based selective etching" is applied to fabricate porous structure and create unique core/shell structure. Tiantian Li. et.al synthesized Kaolin based mesoporous silica, with improved specific surface area (604 m^2/g) and large pore size (4.41nm) at the maximum probability via successive treatment of natural kaolin by a calcination alkali activation and acid etching.[9]

3. Method for Template Removal

Template molecules are removed after the silica framework has reached a sufficient degree of condensation to open the porous structure. This process is very important for material preparation. The template can be removed by: 1. Calcination 2. Plasma extraction 3. Supercritical fluid extraction 4. Solvent extraction 5. Ozone treatment.

In calcination process the as-synthesized dried materials are heated in air and by applying heating rates of 1K/min upto at least 823K followed by extended period usually 4-8hr of heating at a temperature plateau. Due to heat treatment there is contraction of the silica structure, which is, result of an increased degree of condensation of silica network and remove the template.

The template removal by solvent extraction is depend on synthesis employed. The extraction process for materials those prepared in basic conditions involve extraction in acidic ethanol or ethanolic solution of ammonium nitrate.

4. The Chemistry of Silica Surface

Silanol and siloxane these are mainly two functional groups present on intrinsic-silica surface on the amount of hydroxyl, or silanol (Si-OH) and siloxane (Si-O-Si) groups the degree of hydrophilic and hydrophobic properties of silica surface is depend. As a silanol is hydroxyl group then higher the number of silanol groups present on silica surface more is the hydrophilic nature of silica surface. By doing protonation and deprotonation of the surface silanol groups the charge on intrinsic silica nanoparticle can be changed and the extent of the repulsive energy keeping the particles dispersed in solution.

Thermal treatment of the material leads to condensation of silanol groups (Si-OH) into siloxane(Si-O-Si) bridges. Thermal treatment removes water and makes the silica surface network denser and increases its hydrolytic stability in aqueous solution.

5. Functionalization of the Silica surface

The possibilities for functionalization of silica surface are many and often based on the use of functional silanes Mesoporous silica nanoparticles contain three distinct domains that can be functionalized i.e.-the silica framework, nanochannels or pores and exterior part of particle. The silica framework provides structural order as well as thermal, mechanical stability. Surface functionalization of silica can be carried out by using various methods such as covalent binding, chemisorption, electrostatic or hydrophobic interaction.

Functionalization of amorphous silica can be done by co-condensation, by imprint coating, by post-grafting or by surface polymerization that includes "grafting to" or "grafting from" methods.[13]

6. Drug Loading

The unique feature of MSNs which makes it a widely exploited carrier for drug delivery is its high drug loading capacity due to its large pore volume and surface engineering properties. Adsorptive properties of MSNs is helpful for drug loading. Both hydrophilic and hydrophobic cargos can be incorporated into the pores of MSNs. Due to the large pore volume MSNs possess greater loading capacity as compared to other carriers. For enhancing the loading capacity to other carriers. For enhancing the loading capacity MSNs many extensive work can be carried out. She et.al. attempted to increase the loading of 5-flurouracil (5-FU) into hollow MSNs by functionalizing the surface silanol groups with different silanes viz. octadecyltrimethoxysilane(OTMS), 3-(aminopropyl) triethoxysilane (APTES), 3-cyanopropyltriethoxysilane(CPTES). An improved loading of 28.89% was observed for amine functionalized HMSNs compared to plain HMSNs with 18.34%.[10]

Comparing MSNs with HMSNs, HMSNs proved to be better carrier in terms of loading capacity due to their hollow cavities. Pore expansion can be done by using different pore swelling agent such as alkanes/ethanol, triisopropyl benzene (TIPB), trioctylamine (TOA), decane etc. Following Table3. gives comparison of drug loading capacity of various MSNs.

Table 2: Comparison of loading in MSNs.

Drug	Carrier	Loading (wt%)
Ibuprofen	MCM-41 HMSNs	35.9 74.5
Doxorubicin	MCM-41 HMSNs	48.16 112.12
Lysozyme	MSN-C0 MSN-C10	34 42

7. Applications

1. MSNs have been widely used for a variety of purposes ranging from biomedical application to the waste water treatment, base catalysis, enzyme immobilization, post-synthesis functionalization. Fig.4. shows versatility of MSN carrier.

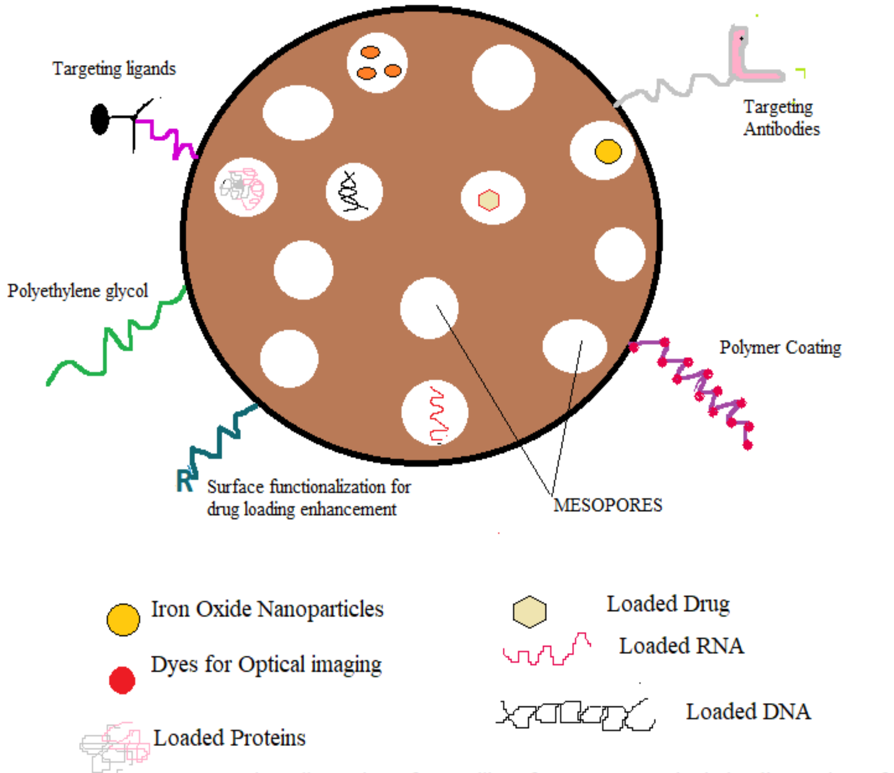

Fig.4.Illustration of versatility of MSN as a carrier in loading variety of

2. MCM-41 and SBA-15 these are the widely used silica drug carriers. Ibuprofen was loaded onto multimodal pore channels and the effect on its release was studied other similar studies were carried out on the aspirin[11] and Indomethacin[12] by using MSNs with high drug loading and slow release profile.

3. By doing different surface functionalization of MSN the site-specific drug delivery and avoidance of side effect can be enhanced. The given Table: 3 shows few of ligands which have been explored for cancer drug delivery using MSNs.

Table 3: List of functionalized MSNs explored for tumour targeting.

Drugs	Targeting ligand	Receptor	Application
5-fluorouracil	Hyaluronic acid	CD44	Colorectal cancer
5-fluorouracil	Epidermal Growth Factor(EGF)	EGF	Colorectal cancer
Curcumin	Chondroitin sulphate	CD44	Cervical cancer
Docetaxel	Lactose	Asialogylcoprotein	Hepatoma

4. pH is widely explored stimuli to trigger the drug release as the body has a wide range of pH. The release of curcumin improved when moving from pH 7.4 to pH 5.5. Cell uptake studies in U87MG glioblastoma cancer cell-line showed a decrease in the half maximal inhibitory concentration (IC50) values indicating an improved accumulation of curcumin in cancer cells when encapsulated within chitosan loaded MSNs.[14]

5. Thermoresponsive MSNs have also been widely been studied as a possible means of controlling drug release. In this context, PEO-b-poly(N-isopropylacrylamide) based copolymeric micelles as structure directing agents for the synthesis of functionalized MSNs was developed by Bathfield et.al.[15]

6. Various stimuli can also be used for drug delivery through MSNs. The release of drugs from MSNs can also be triggered via magnetic attraction. Baeza et.al.reported the synthesis of a hybrid polymer which responded to both thermal and magnetic stimuli. They incorporated superparamagnetic iron-oxide nanocrystals into the mesoporous which was capable of providing a sufficient heating capacity for hypothermia cancer therapy.[16]

7. MSNs can be widely used for optical imaging, magnetic resonance imaging (MRI), positron emission tomography (PET). Optical imaging is a technique wherein the specific probes are excited by incident light usually in the visible or near infrared regions, thus emitting light at a lower energy. MRI is a powerful in vivo imaging technique which gives a three dimensional anatomical picture of the region of interest with a high resolution.

CONCLUSION

Mesoporous silica nanoparticles pay attention as a drug carriers owing to their distinctive features over the others. Due to their tunable pore size, pore volume, high loading capacity it's widely exploited as nanocarriers. In this review we have to focused on its synthesis by using different types of reactant, changing the molar composition of the reactants and applying different reaction condition, MSNs of different pore volume and particle shape, size can be obtained. The surface and pore functionalization is major research which is useful for the treatment of cancer.

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