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A Review on Mesoporous Silica Nanoparticles as Efficient Drug Delivery Carrier

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ABSTRACT

Mesoporous silica material is continuously gaining attention as an efficient drug carrier due to their unique structural properties like tunable pore structure, large pore volume, easily facilitate the drug/ gene loading, chemically and thermally stable nanoparticles. Drug loaded mesoporous silica formulations of poorly water-soluble drugs enhance their dissolution and permeation behavior has been achieved in the pharmaceutical research area. As the carrier with various physicochemical properties can promote absorption from the gastrointestinal tract to the systemic circulation. This review highlights the different methods which are used to synthesize silica materials. Meanwhile, the functionalization of mesoporous silica nanoparticles is provided by using a co-condensation and grafting method. This review article also deals with the most important features of nanostructured silica drug carriers, such as pore size, particle size, particle morphology, surface functionalization, surface area, pore-volume, the effect of solvent. In prospects, mesoporous silica drug delivery is considered as an alternative strategy for the enhancement of drug solubility.

INTRODUCTION

The low solubility of any drug is an increasing problem to formulate any dosage form. Oral drug delivery is a convenient method for drug administration than any other method (1). But in oral administration, for drugs to achieve it is systemic absorption and bioavailable in the body it needs to be present in solution form in the gastrointestinal tract and permeate across the intestinal wall. This drug is classified according to BCS classification system BCS-II drug and BCS-IV drug whose bioavailability is said to be dissolution rate-limited (3). In the early 1990s, mesoporous silica materials have attracted special attention as carriers in drug delivery system. In the field of nanomaterial and nanomedicine, multifunctionalised MSN is widely studied (6). Silica nanoparticle with mesopores referred to as mesoporous silica nanoparticle (MSNs) has gained wide popularity and attraction over recent years. Porous silicon is a mesoporous material that has been successfully applied in the delivery of poorly soluble drugs. Mesoporous silica nanoparticles appear as a promising drug carrier, and drug loading into MSNs has been considered as a possible formulation strategy to overcome several problems such as failure of target drug delivery, reduced control over the drug release rate, and drug degradation in the GI tract. Typically, in comparison with traditional drug delivery formulations, the inorganic silica material provides greater stability of active compound to temperature variation, acidic conditions (in the GI tract). Also, several excellent features of MSNs, such as large pore volume, tunable pore size, high surface to volume ratio, efficient and simple functionalization stipulate great possibility to transport active compounds into tissues and organs (10).

1. Silica materials

1.1. Silica:

A wide range of silicon dioxide (Silica) material is available for oral drug delivery amorphous hydrophilic silica has been used. Silica can be classified into two categories porous silica and nonporous silica.

Much colloidal silicon dioxide is available in commercial varieties. Colloidal silica has been used as a glidant in the tableting process in pharmaceutical industry from many years (3).

1.2. Mesoporous silica:

The silica materials have smaller holes in their structures are called porous materials.

The porous material is ordered or disordered in nature. The porous material is classified into 3 different categories.

Porous material

Microporous- pore diameter <2 nm

Mesoporous- pore diameter 2-50 nm

Macroporous – pore diameter >50nm

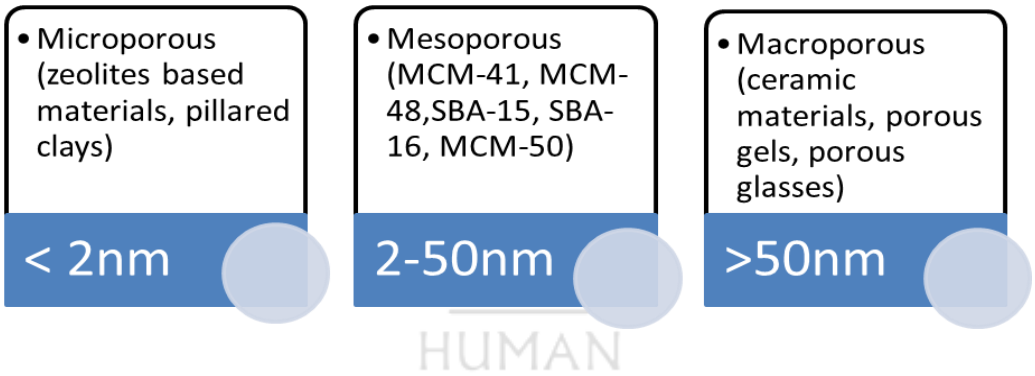

Figure No. 1: Different pore sizes of materials

Mesoporous silica (pore size of 2-50 nm) has been shown to improve the dissolution rate of poorly water-soluble drugs. (3)

1.3. History of MSN:

MSN was 1st discovered in 1990 by scientists in Japan. In 1992, MSN is synthesized in Mobile Corporation Laboratories name it molecule 41 sieves (M41S). MCM-41, MCM-48, and MCM-50 are more popular mesoporous silica material in the M41S family. This mesoporous silica is highly ordered, large surface area and uniform mesoporous structure. MCM-41 is in the hexagonal packed rod-shaped micelle structure, whereas MCM-48 is in cubic structure, MCM-50 is in lamellar structure shown in fig.2.(15).

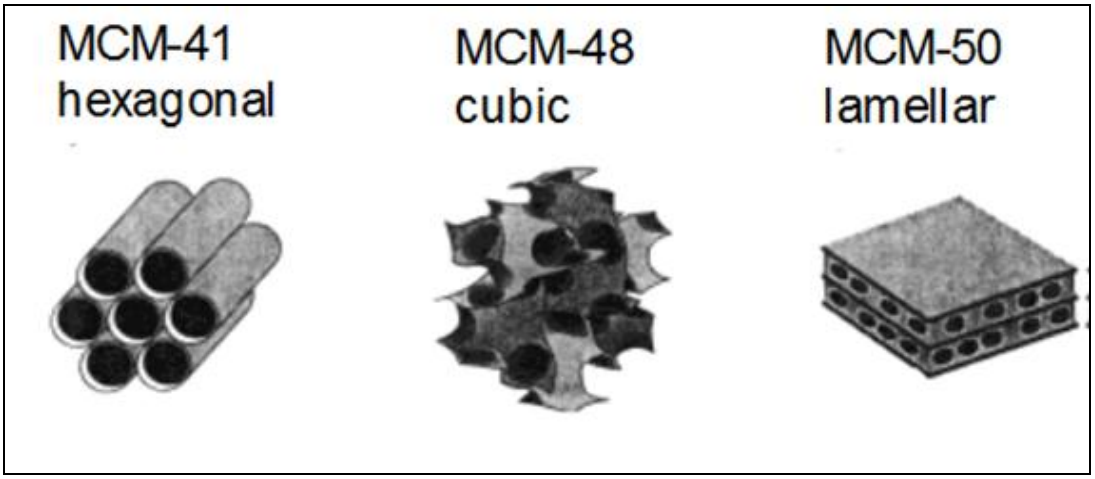

Figure No. 2: Structures of mesoporous M41S materials

In 1995, New research on mesoporous silica material have been started to produces new MSN material namely as Santa Barbara Amorphopus No.15 (SBA-15). Another type of mesoporous silica nanoparticle was synthesized such as SBA-16, FDU (Fudan University material (FDU), and Korea Institute of Technology (KIT).

1.4. Properties of MSNs:

Researchers have synthesized both non–ordered and ordered mesoporous silicas.

-ordered mesoporous silica material have uniformity in pore shape, size, and volume.

-They have long-range ordered porous structure.

-Their pore size can be varied from 2nm to 30 nm by changing the composition of synthesis materials.

-They have a large surface area.

-Different structures of MSN can be obtained such as rods sheets and 3D structure by using a different surfactant.

-They have high thermal stability and hydrothermal stability.

-They have tunable pore size, easily realized by varying the surfactants or varying its concentration.

-They have a low mass density.

-They have non-toxic.

-They have easily modified surface properties.

-They have good biocompatibility, because of all these properties of MSNs, they consider as important carriers in sensors, catalysts biomedicine, and in environmental applications (3, 22).

2. Synthesis of MSN

Stober was the pioneer in developed new chemical reactions for the synthesis of spherical monodisperse micron size silica. This method called "Stober synthesis" (11). After that, many modifications have been made to Stober's synthesis to synthesized ordered nanosized silica particles (10). Stober's method of synthesis was modified by Grun *et al.*, where they used a cationic surfactant as a template to synthesis a spherical rather than a hexagonal MCM-41 structure. Further, many more variation is carried out in synthesis conditions and methods to yield stable MSNs (12).

2.1 Mesoporous silica can be synthesis by different techniques such as:

- Sol-Gel techniques
- Template assisted technique
- Microwave-assisted technique
- Chemical etching technique
- Sol-Gel techniques:

In this method, sol-gel process, at starting a colloidal suspension is prepared for the growth of the inorganic network and then gelation process of sol is carried out to form a network in a continuous liquid phase (i.e. called gel).

The reaction involved in the sol-gel method was based on the hydrolysis following by the condensation of metal alkoxides (16, 17).

For the synthesis of mesoporous material by the sol-gel process, different templates can be used as structure-directing agents such as cation surfactants, triblock copolymers organic small molecule (18).

- Template assisted technique:

In this method, a template is used to synthesize MSN.

Two types of template: hard matter template and soft matter template.

A porous solid is used as a template in a hard matter template called "exotemplate" and surfactant used as a template in a soft matter template called end template.

- Microwave-assisted technique:

In this technique, self-assembly of organosilane precursors and block copolymer and subsequent hydrothermal treatment was carried out under the microwave irradiation (19).

- Chemical etching technique:

In this method, an appropriate etching agent is used then selective etching takes place at interior while the outer shell remains intact. By using an appropriate etchant, tunable and uniform size and shell thickness can be well controlled (20, 21).

3. Mechanism of formation of MSNs:

3.1 Silica Preparation:

Silica prepared from a dilute solution of surfactants (13). Hydrolyzed silica get adsorbed around the micelles. Surfactants and silica get to interact at the initial stage and form a core shell-like structure (14). It was observed that during the early hydrolysis of silica precursor TMOS (tetramethyl orthosilicate), the silicate ions tend to adsorb around the surfactant micelles during the growth phase. As charge around the surfactant reduces due to initial hydrolysis and condensation of the silica precursor, the intermicellar repulsion reduces, after that small aggregates of silica formed.

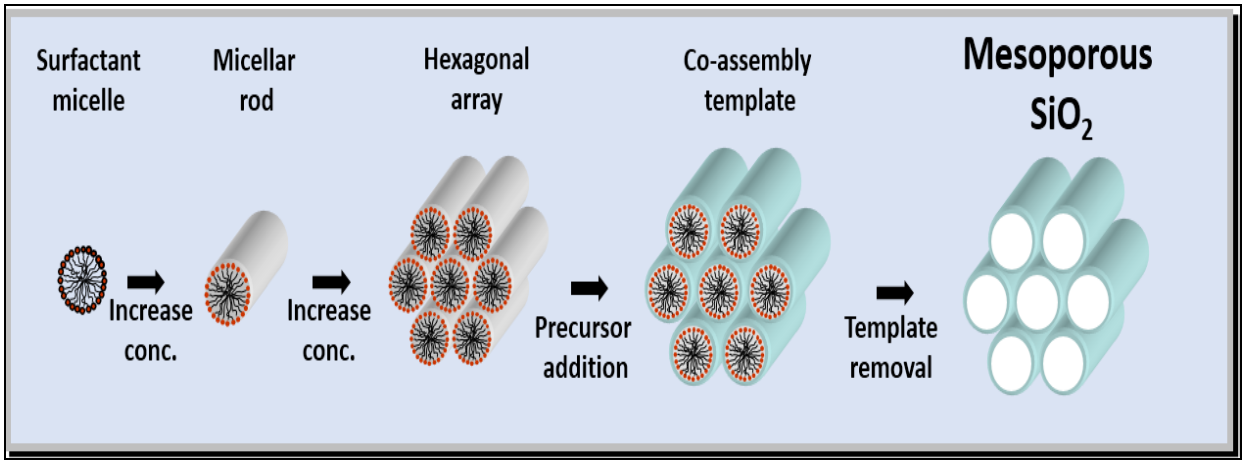

Figure No. 3: Schematic representation of MSNs synthesis

3.2 Surface functionalization of MSNs:

Functionalization aims to increase the attraction between drugs and silica. There are different methods for functionalized mesoporous silica including co-condensation (one-pot synthesis), grafting (post-synthesis modification), an imprint coating method. Most of the literature said that the grafting method is better than the co-condensation method (4). A controlled release formulation can be easily formulated using functionalization. In surface functionalization, hydrophobic moiety is attached to MSN, the drug–surface interactions are not necessarily increased, but the aqueous medium does not easily penetrate the functionalized silica particle and this slow down the drug release rate. Mesoporous silica had been modified by silylation to produce controlled-release formulations. Increased drug surface interaction is the most useful method to control drug release. To achieve this, modification with chemical groups on the surface of MSNs is done which links the drug molecule through ionic bonds/ ester groups. One of the most reported methods is amino-functionalization. Mesoporous silica materials with luminescence and/ or magnetism functionalization provide targeted drug delivery applications. Mostly this system of drug delivery useful in cancer therapy drugs because of their toxic effects. A smart combination of different functional materials can lead to the development of multifunctional mesoporous silica nanoparticles which provides targeted delivery, fast diagnosis, and efficient therapy.

4. Factor affecting:

- **Pore Size:**

The pore size is an important factor during drug loading into a mesoporous channel. Generally, the ratio of pore diameter/drug molecule size should be >1 will be approachable for the loading of drugs into pores of MSN.

If this ratio is greater than 3 then there is full utilization of surface area and therefore consider as high drug loading (1). Horeajada *et al.* (2004) synthesis MCM-41 with different pore sizes and studied the effect of pore size on drug loading. It showed that drug loading is more in pore size 3.6nm than pore size 2.5nm (2).

The pore size of MSNs depends on the type and concentration of templating surfactant to be used in synthesis. Tetraalkyl ammonium salts (CTAB/CTAC) are the most widely used surfactant to prepared ordered MSNs.

Pluronic surfactants, poly (ethylene oxide)- poly (propylene oxide)-poly (ethylene oxide)(PEO-PPO-PEO) blocks polymers are also excellent surfactant to be used for the preparation of mesoporous silica (23).

- **Particle size:**

Nano-sized mesoporous silica materials have benefits including good dispersibility and fast mass transport (24, 25). Hydrolysis rate of silane and siloxane bond condensation both depend on the pH, it is a critical factor in the control particle size of Mesoporous Silica material (26, 27). By quickly increasing pH from 2 to the range of 6-9, Fast condensation of silica with strong electrostatic attractions between silica and cationic surfactant may increase the silica/surfactant Nuclei.

TEA (Triethanolamine) mostly used in the synthesis of Mesoporous silica materials. TEA act not only as a base for accelerating silica hydrolysis but also acts as a complexing agent for silicate to prevent aggregation of particles. Another crucial parameter is reaction temperature which can affect the particle size of MSNs (28, 29, 30).

The stirring rate of the reaction mixture is also important to factor in the synthesis of Mesoporous silica materials (31).

- **Particle Morphology:**

Mesoporous silica materials can be synthesized with different shapes like spherical, rod, cubic, film, platelet, ellipsoid (32). It has been studied that small changes in acidity and molar ratios of the reaction mixture can affect the shape of Mesoporous silica materials (33).

The aspect ratio of Mesoporous silica materials is controlled by surfactant and base concentration. Surfactant–assisted self–assembly is used for the preparation of Mesoporous silica materials with specific morphology. Although, it is difficult to prepare with one template (34,35). To overcome these problems nowadays, used dual-surfactant systems such as CTAB/dodecanol (35), CTAB/acrylic acid (36). Highly porous silica was prepared by dual templating technique. One template act as a pore-forming agent and another one acts as a void forming agent or even without a void forming agent (37).

- **Surface functionalization:**

The surface properties of mesoporous silica can be altered by using surface functionalization. Generally, grafting and co-condensation methods are used for the surface functionalization. Retaining the mesoporosity of parent silica after grafting of the functional groups is the main advantage of functionalization (23). The functionalization with organic groups affects drug absorption and drug release. Increased drug surface interaction is also a useful technique to control drug release. Another most useful method to target drug delivery is magnetic nanoparticles, which providing the target location to the Mesoporous silica nanoparticles particle (7).

- **Surface Area:**

The surface area is directly proportional to the amount of drug adsorbed. For controlling the amount of incorporated drug in the Mesoporous silica nanoparticles achieved by decreasing or increasing the surface area (8,9).

- **Pore volume:**

The amount of drug adsorbed can be determined by pore volume. The pore volume can affect drug loading capacity.

- **Solvent:**

The polarity of the solvent can play a vital role in influencing drug loading. The highly polar solvent causes a low degree of drug loading. Non-polar solvent favors the adsorption of drug molecules rather than solvent with high polarity (1).

CONCLUSION

In our review, different approaches are discussed for synthesizing mesoporous silica nanoparticles. Commercial production of such materials will be the major challenge for pharmaceutical industries due to their highly specific characteristic nature, uniformity, and reproducibility. Mesoporous silica drug delivery has remarkable attention from the last decades. Mesoporous silica materials have potential carriers for the improvement of drug solubility or oral bioavailability of poorly water-soluble drugs. MSNs are considered biocompatible and biodegradable and ample of their reactive groups allow for sufficient functionalization which is may be used to enhance loading capacity, targeting ability, and colloidal stability. Furthermore as a technical concern, with mesoporous silica nanocarriers are related to the ability to scale-up their development process, the amount of material required to achieve a therapeutic effect, cost of formulation, and shelf-life of drug-loaded materials must be thoroughly evaluated for potential commercial uses. Our efforts should also focus on the improvement of the targeting ability of orally administrated MSNs by their increased penetration through different barriers.

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