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Critical Elements to Scrutinize While Selecting Mesoporous Silica Nanoparticle: A Review

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ABSTRACT
To select a novel drug delivery system over conventional dosage forms have become the commonest approach these days, as the former leads to overcome the drawbacks of the latter in an efficient manner. Likewise, Mesoporous Silica Nanoparticles are one of the novel approaches on nanoparticle system which have got an eye by the researchers to formulate it into drug delivery. The pore size ranging from 2-50 nm with larger surface area is what makes it as an effective drug carrier system. The three main chemicals constitute the base for Mesoporous Silica Nanoparticles preparation including Silica Precursor, Structure Directing Surfactant and Catalyst particularly by Sol-Gel process which is typically a two-step procedure hydrolysis and condensation. The reason why MSNs brought into drug delivery system is because all types of drug release like immediate release, sustained release as well as targeted release systems can be designed through this approach. There are several key factors with which the delivery rate of Mesoporous Silica Nanoparticles can be regulated like controlling the pore size, regulation of particle size, pore volume and making the Mesoporous Silica Nanoparticles in ordered structure. In addition, the drug loading is achieved effectively by controlling these parameters and it can load both hydrophilic and hydrophobic drugs. The review on this topic sets tone for considerations to follow before the selection of mesoporous silica nanoparticle because more knowledge is required to fulfil this carrier as drug delivery system. This review seeks about using Silica derived mesoporous nanoparticles as a perfect system for the enhancement in solubility along with release of drug at a rate which can be controlled.

KEYWORDS: Mesoporous Silica Nanoparticles discovery, Factors, Sol-Gel Process, Uptake of MSN, Evaluation, Biosafety profile.

INTRODUCTION

As disadvantages together with side effects by simple dosage form i.e., conventional drug delivery system come against the favor, researches have been made to overcome these drawbacks leads to generation of novel drug delivery system (NDDS) which is further categorized into various branches. The example of NDDS is the nanoparticle invention in which the particles are of nano range with submicron size (<1µm). Their size in nanometer is what makes them effective to pass through any spaces and not only that the surface area of nanoparticles enables them to load drug with high capacity is also included. A comprehensive set of scholarly works are accessible and inquire about is still underway in assessing modern roads for the utilization of Mesoporous Silica Nanoparticles (MSNs) in medicate conveyance. A few audits relating to MSNs in progressing the dissolvability (1,2) of the medicate as controlled and sustained (3) sedate conveyance framework and application in biomedicine (4,5) have been dispersed.
MSNs are categorized under inorganic nanoparticles which have garnered the interest from analysts in recent years. The versatility in pore size that ranges from 2-50 nm with larger surface area and ease in functionalization makes it promising and effective drug carrier system. The term 'Mesoporous' is its pore size which is placed between microporous and macroporous is why it is a good candidate for drug delivery. Here, 'Silica' is a forerunner which is thermally stable with good biocompatibility and chemical properties.

DISCOVERY OF MSNs

The materials constructing the assessment of MSNs was already synthesized in 1970s and yet unnoticed, but then Mobil Research and Development Corporation synthesized aluminosilicate gels-mesoporous solids with the assistance of template mechanism of liquid crystal in 1992 (6–8). The foremost broadly surveyed medicate conveyance fabric for MSN arrangement is MCM-41 which is hexagonal featuring pore sizes ranging from 2.5-6 nm, where surfactants (especially of cations) as template system are utilized. The drug delivery material for MSN preparation is MCM-41 which is reviewed and used extensively. Besides that, copious other mesoporous materials are unified with the alteration in the initial pioneers and reaction order, which can result in different arrangement of structure with pore sizes (9). Not as it were that, there are also Non-ionic triblock co-polymers, for instance alkyl poly ethylene oxide (PEO) oligomeric surfactants and poly alkylene oxide block co-polymers, have also been regarded as templates. These are designated as

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SBA-11 with cubic structure, SBA-12 of 3-dimensional hexagonal, and SBA-15 having hexagonal structure, and SBA-16 showing cage structured in cubic arrangement, reflecting the usage of triblock polymers stabilizing the meso-structure symmetry (10).

METHODS FOR THE PREPARATION OF MSNs

Materials required: Generally, three fundamental raw materials contributing as a building block for MSNs synthesis that includes source of silica, template for directing the structure of MSNs i.e. surfactant and a catalyst. They are categorized into various categories according to their function that are being used during the synthesis process:

1. **Structure Directing agent:** CTAB, CTAC (11–14), Pluronic F127, F123 (10,15), Tween 20, 40, 60, 80 (16) , Brij-76 (17,18) **.**
2. **Silica Precursor:** TMOS (19,20) , TEOS (11,12), TMVS (21), Sodium silicate (22)
3. **Catalyst:** NaOH (12), NH_4OH (11), Triethanolamine (13)
4. **Other agents:** Ethanol (14), Phosphate buffer solution (23), TIPB (24,25)

Methods for the preparation

1. **Sol-gel process:** The most widely in use with its effectiveness to produce MSNs, is Sol-Gel Process (also known as Stober Method) involving firstly hydrolyzing the silica initiators such as tetraethyl orthosilicate (TEOS) often used, tetramethyl orthosilicate (TMOS), sodium silicate as alternative to TEOS. using the help of structure directing agents such as surfactants followed by condensation to form the desired referring nanoparticle structure. The removal of surfactant is necessary which is done by using various other techniques (26).

Steps involved in sol-gel method: -

a. **Preparation of sol**: a colloidal solution is formed when TEOS gets hydrolyzed in the presence of CTAB. This is the beginning of a sol-gel process.
b. **Process of gelation**: the condensation of a colloidal solution into gel like network leads to gelation and this sets the template to form mesoporous structure.
c. **Drying**: the strengthening of the formed network of gel can be done by drying it to exclude out the solvent.
d. **Solvent removal**: this is the step which is required for because surfactant is only necessary for the templating of mesoporous structure, which is done by calcination or by solvent extraction (27–29).

2. **Soft templating method**: Apart from Sol-Gel process, another effective method for preparing the MSNs is Templating technique including soft templating method (involves the use of organic molecules in templating to form the mesoporous arrangement. This is a self-assembly mechanism between silica precursor and surfactant, ultimately removing the organic template at last leads to formation of MSNs
3. **Hard templating method**: The second method is the hard templating method, employing solid templates like colloidal crystals. In this process, a silica precursor is deposited onto the template, forming a silica network. Once the template is removed, a mesoporous structure remains.

REASONS FOR UTILIZING MSNs IN DRUG DELIVERY SYSTEM

Based on the designing of mesoporous silica nanoparticles, there are several drugs that are loaded into MSNs for their immediate, targeted as well as sustained release systems. As the drugs with hydrophobic nature are poorly water soluble which automatically leads to decrease in absorption rate in gastrointestinal tract. A study by Zhang *et al.* (30)showed that the hydrophobic drugs got the improvement in both the solubility and bioavailability i.e. Telmisartan loaded with MSNs had enhanced dissolution rate as compared to raw Telmisartan powder with 154.4% ± 28.4% relative bioavailability compared to that of marketed drug product Micardis. When the process behind this drastically change in oral bioavailability is investigated on the human colon cancer (Caco-2) cell line for permeability tests. The results of permeability indicated that MSNs boosted TEL's permeability considerably and lowered the rate of medication efflux, which improved oral absorption.

As for our knowledge immediate release MSNs cannot utilize its action for longer period, thereby, leading to the discovery of sustained release drug delivery systems which is divided into two levels: unmodified and modified silica materials. With the unmodified version of silica materials the pore structure, diameter of the pore and particle size of the carrier is regulated and the latter is conjugated with organo silanes (31). The dissolution rate gets delayed with the help of interaction between the functional group and drug molecules. In essence, food and drug administration considered silica material as Generally Regarded as Safe (GRAS), for food additives and cosmetics and for clinical purposes, mesoporous silica nanoparticles are versatile being a drug delivery system (32–34).

The studies demonstrated that pore structure and its size affect the rate of release of drug. This helps to achieve the system in sustained release. Qu *et al.* (35) reported the effect of particle size with respect to behavior of drug release which had proportionality to the length of pore channel. In addition to the particle size, the drug content also affects the rate of release, which was in decreasing order when the drug content gets increased demonstrated by Carriazo *et al.* (36) due to low penetration of solvents into the pore channels.

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Advantages of selecting an MSN for the drug delivery: -

- As mesoporous silica nanoparticles offer larger surface area with tunability in its shape and size that can be regulated from 50 to 300mm, this, in terms, also leads to have a capability of load drug content in high ratio.
- Silica-derived porous materials are highly beneficial compounds that can enhance cancer treatment projects and provide a way to treat challenging diseases.
- The porous structure of MSN is in long range order that enables for precise tuning by not connecting individual porous channels and controlling the kinetics of drug loading and release (37).
- Here, silica is used as a precursor for the preparation of MSNs, which is considered as safe with good biocompatibility by USFDA.

Disadvantages balancing upsides of MSNs: -

- Increased particle size enhances urine elimination, affecting the breakdown rate and biocompatibility.
- Preparing a well-organized distribution is challenging, often resulting in scattered distribution. Moreover, formulating stable colloidal suspensions is complex.
- Porous silica nanoparticles have a significant drawback: the high surface density of silanol groups interacts with red blood cell phospholipids, leading to hemolysis at the membrane level.
- Additionally, porous silica nanoparticles may induce metabolic changes that could potentially promote melanoma (38,39).

KEY DETERMINANTS OF Msns

Ideally, there are three main constituents that act as decisive factors for the formation of MSNs, it includes a silica precursor like TEOS, TMOS, Sodium Silicate etc., a structure directing agent commonly surfactant such as CTAB, PEG, Tween 80 etc. and a catalyst like ammonium hydroxide, ammonium chloride, sodium hydroxide etc. apart from this, there are other factors which cannot be negotiated during the synthesis of MSNs (40,41).

1. **Regulating particle size**: Tuning of pore size is a determining factor in designing nano drug carriers such as mesoporous silica nanoparticles. To control pore size, pH plays a key role by tailoring the hydrolysis process along with condensation for silica pioneer. This adjustment increases the reaction kinetics, resulting in smaller particle size (42).
2. **Regulating the pore size, volume including ordering of meso-structure:** The adjustment of pore size of MSNs has been altered based on type of the surface-active agent which is usually increases with the chain length of the surfactant and vice versa. While for the implication of MSNs ordering, it depends on the concentration of TEOS (43,44).
3. **Controlling the shape and drug loading:** The shape of MSNs is crucial for optimizing their performance in drug delivery which can be controlled by template selection, synthesis conditions, solvent type, and various other factors. The demonstration of particle shape is illustrated by controlling the conditions during synthesis which gives the idea of how particle shape is being formed, and there is hydrogen bonding, hydrophobic interactions between the surfactant and organo-alkoxy silane found (45). The drug is generally gets loaded into pores of MSNs because of adsorptive properties of MSNs as well as their larger pore volume and the MSNs can load both hydrophobic and hydrophilic drugs in it.
4. **Cellular uptake of MSNs:** MSNs are up-taken in the cell by the process called endocytosis which includes entrapping the particle by caveola mediated endocytosis (CME), afterwards early endosomes are formed (a stage in the formation of lysosomes), which in terms forming various vesicular structures, these structures escape from these compartments and gets distributed in the body organs after the blood stream entry through exocytosis (46,47).

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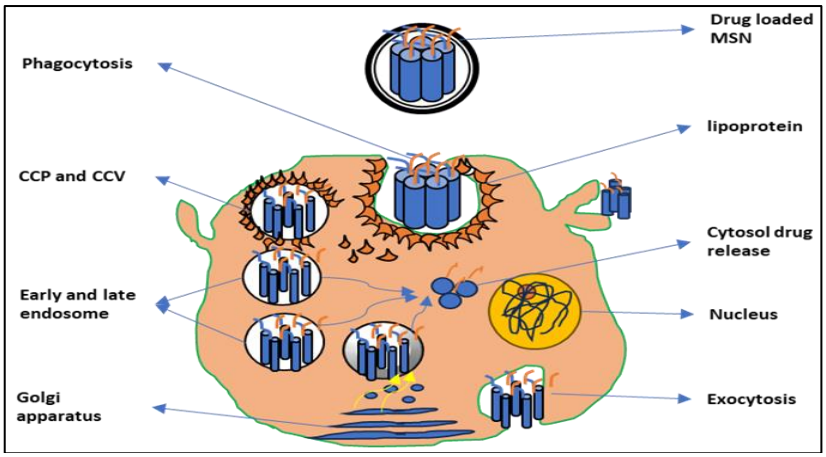

Figure 1: Uptake of MSN and its distribution in the cell, endocytosis, escaping from endosomal compartment, afterwards entering blood stream *(48)*

MECHANISM OF FORMATION OF MSN NETWORK

The formation mechanism of MSNs suggested that, as per previous reports, the network of silica work was formed through the solution phase of the non-ionic surfactants. Notably, the cases of materials made from additive solutions for surfactants, where irregular meso-structure was not observed, are particularly noteworthy (48). The hydrolyzed silica gets separated from their micelles in preparation for SBA-15, conversely, the interaction of surfactant with silica mixture at the initial stage acts as a core shell-like structure for MCM-41 (48).

Time-resolved small-angle neutron scattering (SANS) was employed in situ to examine the formation of MSNs, allowing researchers to predict simultaneous changes occurring throughout the process. During the initial hydrolysis of TMOS from silica (around 40 seconds), it was observed that silica ions were seen to adsorb around the surfactant micelles during the growth stage. From the starting, hydrolysis followed by condensation of the silica precursor diminished charge surrounding the surfactant, reducing the repulsive forces between the micelles and allowing the formation of small silica aggregates. After approximately 400 seconds, the reaction mixture contained well-distributed, hexagonally arranged silica mesoporous, is assessed by Transmission Electron Microscopy (TEM). This observation aligns with the formerly proposed "Current Bun model" for the mechanism of MSN creation (49,50).

Table 1. List of drugs loaded into MSNs with their loading methods *(51)*

Drug	Carrier	Loading procedures	Structure material	References
Carbamazepine	MCM-41	Adsorption	2D hexagonal (44)	(52)
Chlorhexidine		Adsorption		(53)
Celecoxib		Adsorption		(54)
Ibuprofen		Adsorption		(55)
Fenofibrate		Incipient wetness		(56)
Aceclofenac		Solvent evaporation		(57)
Furosemide		Solvent evaporation		(58)
Methotrexate		Adsorption		(59)
Prednisolone	SBA-3	Adsorption	2D hexagonal (60)	(61)
Naproxen	SBA-15	Adsorption	2D hexagonal (60,62)	(63)
Piroxicam		Adsorption		(64)
Carbamazepine		Physical mixing		(65)
Fenofibrate		Incipient wetness		(56)
Itraconazole		Incipient wetness		(66)
Atenolol	SBA-16	Adsorption	Cubic (67)	(68)
Carvedilol		Solvent evaporation		(69)
Indomethacin		Solvent evaporation		(70)
Itraconazole	COK-12	Incipient wetness	2D hexagonal (71)	(66)
Prednisolone	FDU-12	Adsorption	Face centered (72)	(61)
Itraconazole		Incipient wetness		(73)
Itraconazole	KIT-6	Incipient wetness	Bi-continuous (74)	(66)

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CHARACTERIZATION AND ASSESSMENT OF MSNs

Once MSNs are formulated, it is essential to assess such type of nanoparticles to ensure that the formulation takes place in an efficient and correct manner. For this, there are such methods that are used to assess the MSNs, they are:

a. Particle size, its distribution and structure analysis of MSNs: The particle size and its shape can be characterized using TEM micrographs, which shows that both method of preparation and the polymer being used act as capping agent and helps to prevent formation of agglomerates as well as maintaining its shape in spherical form. While the variation might be due to nucleation change and generated MSN's growth rate during method of preparation (75).

b. Zeta potential analysis (Surface Charge): For the analysis of zeta potential, Malvern Scientific analyzer can be used which can also predict the mean particle size as well as zeta potential. Dynamic light of scattering measures the surface's electrical charge as well as physical mixture of formulation being loaded (76).

c. Adsorption-desorption analysis of Nitrogen (Surface Area as well as Pore Volume): This is a method in which nitrogen gas is used as template to measure adsorption as well as desorption of MSNs for the estimation of BET surface area and porosity. In this, MSN sample is degassed to remove any adsorbed contaminants, then, nitrogen gas is adsorbed onto the surface of MSN at liquid temperature at various relative pressures. The nitrogen gas is then desorbed, and the measurement of gas released is checked. The plot between adsorption and desorption data is plotted to form an isotherm which is analyzed using models like BET method for surface area, BJH method for pore size distribution (77).

d. Characterization of materials (Pore Size and Structure): The characteristics of surface area, meso-structure of samples formed can be observed using TEM microscopy, BET analysis. The consistency of the MSN throughout the sample can be evaluated by X-Ray diffraction methods and FTIR analysis (78).

e. Surface functionalization: Functional groups can be attached superficially at the surface to enhance and withstand the conditions during drug loading and its release. These modifications can be evaluated using FTIR and NMR spectroscopy (79,80).

f. Drug loading efficacy and capacity: for the drug to load into MSN, several factors are desirable like pore size, pore volume, structure etc. and drug loading can be effective for the desired rate of drug delivery. This can be evaluated by determining the amount of drug loaded into MSN. UV-Visible spectroscopy is the method that can help to measure the absorbance of the drug solution before and after loading into MSNs by calculating the difference. Other methods can ne HPLC, TGA, etc. (81,82).

g. *In-vitro* Drug dissolution studies: The drug's release kinetics for MSNs can be checked using dissolution apparatus i.e., USP Apparatus Type II or any other dissolution based on the dosage form. The drug's loading efficacy, its kinetics of release and what type of mechanism behind the release can be evaluated using *in-vitro* drug dissolution studies (83).

BIOSAFETY PROFILE OF MSNs

With the aim of developing a new technique, obstacles always come along with it. Same as for MSNs, in which biosafety is a crucial aspect to consider, especially for their applications in drug delivery in medical fields. The most important aspects to consider are Biodegradability, Toxicity, Cellular Interaction, i*n vivo* Behavior. While Silica derived nanomaterials are generally viewed as safe for human use, controversies still arise and some data are raised against this delivery during the progression of this nano delivery. Although, along with the concerns, the efforts are made to clear out the objections and their optimization. As the MSNs synthesis greatly depends on the pore size, volume, particle size crystallinity, shape, etc., the complexity makes it tedious to accept as a good nano carrier (84–89).

a. **Particle size:** It is a crucial factor for determining the particle size of MSN's effect pharmacologically. When the study is conducted on various size ranges of MSNs, the outcomes revealed that the size of particle has somewhat resulted in the biocompatibility of mesoporous nanocarrier (90). The revelations are high rate of cell damage and upper hand of hemolysis by smaller size particles as compared to larger particles (11).

b. **Surface characteristics:** It is also evaluated as another marker that has influenced the biocompatibility of MSNs. The neutral and anionic MSNs might have low loading efficacy than the cationic MSNs but comes with longer circulation throughout the body as well as less cytotoxic (91,92). While surface modification of MSNs coated with PEG (PEGylated-MSNs) does not only increases the half-life, but also, there is a decrease in cytotoxic behavior and hemolysis than unmodified MSN (93–95). But as mentioned on the first line of this profile, there are some reports suggesting production of anti-PEG IgM with repetitive use of former MSNs that has effects of hypersensitivity reactions with increase in elimination of modified versions by a natural immunogenic response known as ABC (96).
Another example of surface modification is particle-protein corona which is an outer-covering of MSNs with proteins that covers as a shield for the surface of nanoparticles, also known as former "protein corona" (97–101). This layer inhibits the interaction between particles and cells (RBC's) which reduces the hemolytic activity of MSN to blood cells (100,102).

c. Study of particle structure: The study of structure of particles conducted using both spherical and tubular shapes to scrutinize the interrelation among structure, shape, and its effect on uptake of MSN on cellular level (103)showed that the former's endocytosis and its rate of uptake is faster than the latter (104,105). Nevertheless, various

concentrations among samples are collected of both spherical and tubular MSNs indicated that on increasing the concentration up to 250 and 500 mg/ml caused more hemolytic damage for tubular NPs as compared to spherical NPs while at lower concentrations (20,50 and 100 mg/ml) showed no hemolytic activity (106).

CONCLUSION AND FUTURE STANDPOINT

Currently, nanoparticles are an effective key to unlock the occurring problems. There are too many reasons for researchers to attract towards MSNs as an effective approach to drug delivery, but their side-effects can also not to be neglected. Just simple MSN (unmodified or non-functionalized) have showed optimum activity for drug delivery and stimuli responsive MSNs, functionalized versions are like even greater versions of that. It can be concluded that though the MSNs can benefit the market as well as world, they must overcome the obstacles and present themselves as perfect candidate before marketing and commercial production.

MSNs, as biological point of view, are no doubt one of the strongest candidates, but their in-vivo studies show lack of completion which needs to be completed (107). May be, not now, but in future it can be utilized and gets encouraged into clinical trials after further modifications as it has high potential as an effective nano-carrier for drug delivery. In conclusion, MSNs offer a promising platform for drug delivery and other biomedical application due to their customizable properties and multifunctionality. However, careful consideration of their biocompatibility, functionalization, synthesis, and regulatory requirements is essential for their successful application.

ABBREVIATIONS:

MCM: Mobil Composition of Matter
SBA: Santa Barbara Amorphous
CTAB: Cetyl Trimethyl Ammonium Bromide
CTAC: Cetyl Trimethyl Ammonium Chloride
TMOS: Tetra Methyl Ortho Silicate
TEOS: Tetra Ethyl Ortho Silicate
NaOH: Sodium Hydroxide
NH_4OH: Ammonium Hydroxide
USFDA: United States Food and Drug Administration
PEG: Polyethylene glycol
BET: Brunauer-Emmett-Teller method
BJH: Barrett-Joyner-Halenda method
FTIR: Fourier Transfer Infrared Spectrometry
NMR: Nuclear Magnetic Resonance
HPLC: High Performance Liquid Chromatography
TGA: Thermogravimetric Analysis
NPs: Nanoparticles

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