REVIEW ARTICLE

Formulation, Characterization and Stability Aspects of Mesoporous Silica Nanoparticles

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ABSTRACT

Mesoporous silica nanoparticles are a type of inorganic nanoparticles having mesopores of 2 to 50 nm in size. The nanosized mesoporous particles of silica facilitate endocytosis in drug targeting without any side effects. Mesoporous silica nanoparticle (MSN) can be used to deliver a variety of therapeutic agents or gene delivery through active or chemical adsorption. MSNs can be used in the field of biomedical for the detection and treatment of various diseases like cancers, infection, inflammation, diabetes, bone-related disorders, cardiac diseases, neurodegenerative diseases, etc. The unique characteristics of MSNs in the form of easily adjustable pore size, surface area, particle size, pore volume, and surface morphology are advantageous not only in the biomedical field but also in the fields of biosensors, imaging, agriculture, thermal energy, and catalysis, etc. MSNs provide high surface area, easy surface functionalization, and controlled drug release. MSNs are formulated after condensation of silica in the presence of molecular templates like surfactants and polymers. This review article focused on giving in-depth knowledge about formulation techniques. Various types of excipients, such as catalysts, silica, solvents and surfactants utilized for the formulation of silica-based nanoparticles, have been summarized. The characterization of MSNs using suitable techniques was also reviewed. The stability of MSNs and factors affecting their stability is a crucial part of formulation development that is discussed here.

Keywords: Mesoporous silica nanoparticles, Formulation, Excipients, Evaluation, Stability.

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INTRODUCTION

Nanoparticulate drug delivery is a potential technique that has recently gained much interest in detecting, monitoring, and treating various diseases, including cancer.[1-3] The use of nanotechnology in cancer treatment[4-6] and diagnosis has raised the bar for millions of patients who now have higher expectations for better, safer, and more affordable healthcare.[7-9] To provide more precise targeting of therapeutic molecules to the tumors and reduce the toxic effect associated with treatments, nanotechnology will probably help in cancer treatments.[10-12] Researchers[13-15] have increasingly concentrated on creating nanoformulations that provide therapeutic benefits without any side effects.[16] Liposomes, micelles, polymeric, and silica-based nanoparticleshave been researched in various cancer studies.[17-23] Controlled drug delivery of anticancer medications to tumors has been a major challenge of cancer therapy.[24,25] In addition, the most challenging factor of better cancer treatment is the low water solubility of most anticancer medicines.[26] Developing effective and targeted therapies without any side effects is critical for improving patient outcomes.[27-31] As per the International Union of Pure and Applied Chemistry (IUPAC),mesoporous materials are porous materials with 2 to 50 nm particle size. At the beginning of 1990, scientists presented significant articles on mesoporous materials.[32-34] Scientists produced M41S and KSW-n mesoporous materials using surfactants as structure-directing agents.[35] However, the breakthrough research done by American and Japanese scientists at the beginning of 1990 was just the start of the tremendous growth in mesoporous solids research over the past 20 years.[36,37]

Mesoporous Silica Nanoparticles

Mesoporous nanoparticles possess a large surface area, substantial porous characters, and nano size that facilitates the attachment of a variety of functional groups for drug targeting.[38,39] Mesoporous silica nanoparticle (MSN), with their distinct mesoporous structure and good chemical stability, surface activity, and biocompatibility, are ideal for novel drug delivery systems.[40,41] The MSNs provide the sustained

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Table 1: List of excipients used in MSNs

Excipients	*Examples*	*Properties*	*Role*	*References*
Catalyst	Gold, silver, platinum, palladium, sulfonic acid, carboxylic acid, amine, and imidazole, *etc*.	high activity, selectivity, stability, dispersion, accessibility, and regenerability.	improving the efficiency and selectivity of chemical reactions by providing a high surface area support for the reaction to proceed, enabling effective diffusion of reactants and products, and lowering the activation energy of the reaction	48
Silica	Tetraethyl orthosilicate (TEOS), Tetramethyl orthosilicate, Sodium silicate (Na2SiO3), Ethyl silicate (ES), Octadecyl trichlorosilane (OTS), and SBA-15 (Santa Barbara), *etc.*	Biocompatibility, thermal and chemical stability, large pore volume, high surface area	the main component of MSN synthesis	49
Solvents	Water, alcohol, (ethanol, methanol), organic solvents (toluene, chloroform, hexane) Acidic solvents (hydrochloric acid, acetic acid), *etc.*	High solubility, reactivity, viscosity, surface tension, and non-toxicity.	regulates the hydrolysis and condensation reactions, determines the size and shape of the nanoparticles, eliminates the surfactant template, and influences stability and biocompatibility.	50
Surfactants	tetraethyl ortho silicate (TEOS), cetyltrimethylammonium ammonium bromide (CTAB), Hexadecyltrimethylammonium bromide (HTAB), Sodium dodecyl sulfate (SDS), Pluronic P123 and F127, *etc.*	Charge, chain length, hydrophobicity or hydrophilicity, and concentration affect the size, shape, pore size distribution, and surface properties of MSNs.	form micelles in solution, and help in mesopores formation in silica matrix	51

release of drugs and other molecules at the site of action for a prolonged period, thus reducing dosing frequency and the possibility of side effects.[42] The chemical structure of MSNs resembles a honeycomb or hexagonal array of pores like molecular sieves with an active surface. Active surfaces allow functionalization to change surface characteristics and bind bioactive constituents.[43] MSNs are made of silicon dioxide (SiO_2) structure. A variety of production techniques areused to create MSNs with a variety of properties.[44] MSNs are more stable to biodegradation and mechanical stresses than other nanomaterials like dendrimers, niosomes, liposomes, etc., due to the weak silicon-oxygen (Si-O) bond. Therefore, these materials do not require any external stabilizer during the production of MSNs.[45] To create a smart drug delivery system, researchers[46] generated a unique approach for incorporating medicines into spherical-shaped MSNs. An innovative technique for preparing and loading MSNs is rotary evaporation, whose efficiency of drug loading is more as compared to the standard impregnation loading technique,[47] etc. The mesoporous nature of MSNs makes them suitable for use in biomedical and pharmaceutical applications due to their distinct characteristics, as shown in Figure 1. In addition to biomedical applications, MSNs also have potential uses in catalysis and sensing.

Excipients used in MSNs

Excipients are added to MSN formulations to increase the stability of the particles, help with drug loading, regulate the particle size, or give other desired properties. The common examples of excipients that are used in the formulation of MSNs are given in Table 1. Overall, the excipients utilized in MSN formulations are chosen based on the application and desirable particle qualities. Excipients can significantly enhance the loading, stability, and release of pharmaceuticals or other active components from MSNs.

Properties of MSNs

MSNs have unique characteristics that make them desirable for drug administration, catalysis, sensing, and imaging. The key propertiesof MSNs include:

Easily adjustable particle size

MSNs have easily adjustable particle sizes, making it simple for living beings and plant cells to endocytose them without cytotoxicity.

Rigid framework and good stability

In comparison to the other polymer-derived drug carriers, MSNPs exhibit significantly greater resistance to pH, physical loading, temperature, and hydrolysis-induced degradations.[52]

Homogeneous and easily adjustable pore size

The uniform and easily adjustable pores of MSNs are between 2 to 6 nm. This capability allows MSNsto load drug molecules and conduct studies on the drug release and their pharmacokinetics properties.

Pore capacity and surface area

MSNs have significantly high surface area surfaces (> 800 m^2/g) and good pore volumes (more than 0.9 cm^3 per gm) that provide significant drug loading and encapsulation.

Surface functionalization

MSNs have internal and external surfaces with various functions. This characteristic allows different pharmacological substances to be selectively functionalized on the interior and/or exterior surfaces of MSNPs.

Easy fabrication

MSNs can be produced with minimal effort and at a reasonable cost[53]

Encapsulation efficiency

MSNs can absorb or encapsulate significant amounts of bioactive compounds.[54] The significant benefits and drawbacks of MSNs are shown in Figure 2.

Method of Preparation of Mesoporous Silica Nanoparticles

The commonly used methods for mesoporous carriers are sol-gel, template-assisted, chemical etching, and microwave-assisted techniques.

Stober or sol-gel method

In the wet chemical method, sol-gel is a commonly employed method of materials research and ceramic engineering. This method is also known as the chemical solution deposition method.[55] The Stober approach enables the formation of a sequential pore system using structure-regulating chemicals. According to certain investigations, spherical MSNs were synthesized by employing sodium silicate rather than tetraethyl orthosilicate (TEOS) as a silica source.[56] In general, the silica source is TES, the solvent is distilled water or ethanol and the catalyst is ammonia for MSN synthesis. Soluble TEOS monomers in homogenous liquids produce solid particles by nucleation. When TEOS is hydrolyzed to create silicic acid, the resultant silicic acid condenses to create silica particles with siloxane bridges (Si-O-Si).[57] The stober approach provides flexibility to customizethe particle size, shape, and surface area. These characteristics can be adjusted by adjusting the pH, temperature, silica supply and surfactant of the reaction.[58] Figure 1 depicts the formulation of MSNs using the Stober method. The formation of mesoporous materials with desired morphologies is now possible using a sol-gel process. To produce mesoporous material by this method cationic surfactants, organic small molecules, and triblock copolymers can be used as structure-directing agents. Hydrothermal synthesis is another technique utilized to make silica nanoparticles. As a source of silica, TEOS or sodium silicate can be employed. However, the hydrothermal method has drawbacks like high costs and energy consumption that hinder large-scale production.

Template assisted technique

A popular and more affordable method to create ordered mesoporous material is the template-assisted process. This technique is categorized as (1) endotemplate or soft matter templating and (2) exotemplate approach or hard matter templating, as shown in Figure 2.

Endotemplate is a method for synthesizing ordered mesoporous materials using surfactant as a template. Endotemplate is also referred to as a "soft matter templating method" because it does not require hard template solids. The exotemplate or hard matter temptation approach, also known as "Nano casting," substitutes a porous solid for the surfactant as the template.[59] The gaps that serve as the exotemplate's structure are filled with an inorganic precursor, which is then transformed when the right circumstances are present (cured). After the filled exotemplate framework is removed, the material is added to create a product with a specific surface area by replicating the template's pore system as a "negative image." The final physicochemical characteristics of the nanoformulations, like pore size, surface properties, and surface area, are influenced by the choice of template surfactant and synthesis circumstances. By adjusting these parameters, it is possible to generate MSNs with features useful for medicinal applications.

Microwave assisted method

The microwave-assisted hydrothermal technique was developed in 1992. It has been widely used to swiftly manufacture various ceramic oxides, hydroxylated phases, porous materials, and metal powders. In recent years, molecular sieves have been made employing this technique. This technique provides benefits over the traditional procedures, such as a quicker crystallization period than traditional autoclave heating, quick supersaturation caused by the precipitated gels dissolving quickly, and fast heating to the crystallization temperature.[60] This approach involves stirring a structure-directing agent and deionized water constantly at 40 °C for 4 to 6 hours. Then, while the homogenous solution is still being stirred, a solution of hydrochloric acid, deionized water, and 1, 2-bis(triethoxysilyl)ethane (ethane group containing silica source) is incorporated. The finished liquid was poured into teflon pans and heated at 100°C temperature in a microwave oven. Microwave irradiation was used to facilitate the hydrothermal treatment that followed the self-assembly of block copolymer and organosilane precursors. In the first stage,magnetic stirrers were used to stir the synthesis mixture for 2 to 24 hours at 40°C. After the preliminary phase, the temperature was kept at 100°C for 8 to 48 hours in a microwave oven with no magnetic stirring. The product was properly filtered, washed with deionized water, and dried in an oven set to 80°C.[61] The periodic mesoporous organosilica containing ethane and disulfide groups were effectively produced as mesoporous hectorites using the microwave-assisted technique. The manufacture of mesoporous materials has also been accepted using microwave-assisted procedures. It was discovered that this method produced highly ordered

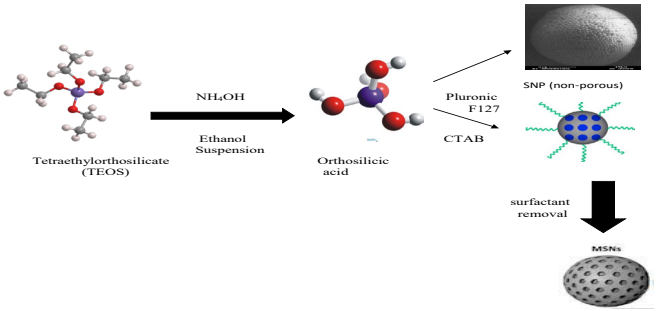

Figure 1: Formulation of MSNs using the Stober method

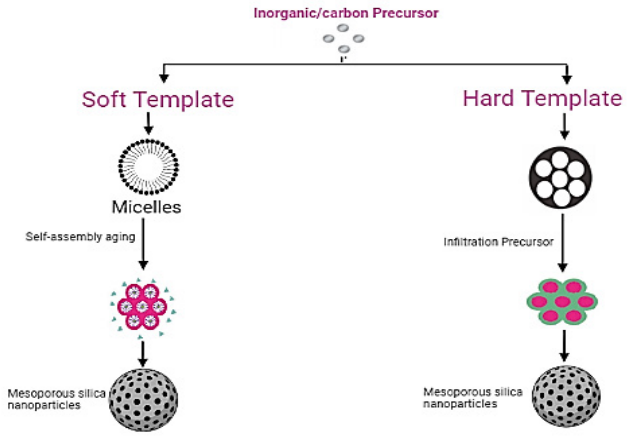

Figure 2: Soft/Hard template method of MSN formulation

mesoporous materials in a very short amount of time by using cetyl trimethyl ammonium bromide (CTAB) as a template to create MCM-41 mesoporous materials.[62] The microwaves can produce excessive localized heating that is more than the reaction vessel's measured temperature. Thus, using a microwave to produce mesoporous materials and other non-materials can be the best option in some circumstances.

Chemical etching technique

The chemical etching technique structurally alters the shell and core of a silica core/mesoporous silica structure, resulting in hollow-type mesopores that are subsequently used to make hollow interiors. The chemical etching technique enables the production of the most dispersed hollow mesoporous silica with tunable pores. Doxorubicin, an anticancer medication, may be efficiently loaded and transported using the mesoporous nanoparticles prepared by this technique. The chemical etching technique can be utilized to fabricate different heterogeneous hollow-type nanostructures, with the shell made of mesoporous silica and the core consisting of inorganic nanomaterials such as gold (Au), iron oxides ($Fe_2O_{3)}$ and (Fe_3O_4). The conventional processes for creating mesoporous materials, like materials self-templating and soft/hard templating techniques, have occasionally been successful in controlling morphology and preparing particle/pore size.

For hollow materials, conventional soft/hard template fabrication techniques are used to provide consistent soft/hard templates; heterogeneous shell deposition is used to functionalize the surfaces of these templates. Furthermore, compositional alterations have a major influence on the removal of the cores by calcination utilizing the soft templating process.[63] However, the chemical etching techniques utilize homogenous templating or structural difference-based selective etching to prepare porous material with different core or shell characteristics. The use of suitable etching agents provides selective itching in the interior. However, the exterior shell typically stays unaltered, which leadsto the creation of a hollow structure.[64] To create fluorescent meso- and macroporous particles, scientists[65] changed the internal structure of fluorescent simple silica utilizing a base-induced chemical etching method. By applying successive calcination, alkali activation, and acid etching processes to natural kaolin, tiantian Li *et al.*[66] developed mesoporous silica with a kaolin foundation that had increased specific surface area (604 m^2/g) and big pore size (4.41 nm) at the highest likelihood. By adopting a wet chemical etching approach, ellipsoid silica nanoshells are created from silica nanoparticles. The wet-etching technique is an advantageous alternative technique since it just requires one step and produces ellipsoidal silica nanoshells with a diameter of less than 100 nm without the need for a template. By using a suitable etchant to efficiently regulate the roughness of the silica shells, it is possible to produce tunable, uniform-sized particles of different shell thicknesses.[67]

Factor Affecting MSNs Formulation

The performance of MSNs depends on various factors like method of formulation, excipients, size, surface properties, charges and environmental interactions.

Some key factors include:

Method of preparation

The method of preparation of MSNs affects the size of pores, particle size and surface area as well as their surface morphology.

Size of pores and structure

Size and the the structures of mesopores affect the loading, encapsulation and release of therapeutic agents from the MSNs. Fabricating MSNs with suitable pore sizes helps in the customization of MSNs for specific purposes.

Size and surface appearance

Both properties of MSNs affect the dispersibility, drug targeting, cellular uptake and distribution of MSNs in the biological system.

Surface charge

The colloidal stability, cellular absorption, and interactions of MSNs with biomolecules depend on the presence of the charge on the surface. The surface charge can be determined by measuring zeta potential.

Surface chemistry

The surface chemistry of MSNs can be altered by functionalization with various groups or coating. It can change the physicochemical properties, improve stability and enable specific interactions with target molecules. Surface modification can be done to make the MSNs more biocompatible.

External factors

pH, temperature, and ionic strength of biological systems are some external causes affecting the stability, dissolution, and biological performance of MSNs.

Biological interactions

Interactions of MSNs with cells, proteins, and other biomolecules can affect their biodistribution, biodegradability, and *in-vivo* performance.

Table 2: Evaluation characteristics of msns

Characteristics	Evaluation technique
Specific surface area	Gas sorption (Nitrogen, Argon)
Micropore volume and external surface area	Gas sorption (Nitrogen, Argon)
Mesopore size analysis	Gas sorption (Nitrogen, Argon)
Porosity	Gas (Nitrogen, Argon) sorption, liquid intrusion (Mercury Porosimetry), light X-ray, atomic force microscopy (AFM), optical and electron microscopy, and neutron scattering.
Ordered structures	X-ray diffraction
Pore structure and particle morphology	Scanning electron microscopy (SEM), Transmission electron microscopy (TEM)
Incorporation efficiency	Percentage loading and entrapment efficiency
Drug release (*in-vitro*)	USP Dissolution apparatus

Evaluation Characteristics of MSNs

The evaluation of dosage forms is crucial to ensure their efficacy, quality, and safety in treating a particular disease. All evaluation parameters must be evaluated using suitable techniques to confirm that the formulation can provide the desired effect. The evaluation methods of MSNs for various characteristics using suitable techniques are given in Table 2.

Stability issues of MSNs

Despite the attractive characteristics of MSNs, the stability issues may affect the performance of MSNs.[68,69] Some challenges of stability are discussed here:

Pore collapse or pore blockage

The mesoporous structure of MSNs can be altered by changes in temperature, pH, and certain chemicals. The surface modification can also lead to undesirable changes in the structure of functionality of MSNs.

Agglomeration

The high surface energy of MSNs can lead to agglomeration and aggregation, mainly in the aqueous medium.

Leaching or dissolution

MSNs are susceptible to the leaching and dissolution of silica in biological conditions. The acidic or enzymatic reaction can result in the degradation and possible loss of drugs encapsulated within the MSNs.

In addition to the environmental causes, the physicochemical properties of MSNs also affect their stability. Careful engineering of MSNs is frequently required to address stability issues. This includes synthesis condition optimization, functional group or surface coating selection, or resistance shielding to protect them from harsh environmental conditions of pH, temperature, etc., the incorporation of suitable crosslinkers or stabilizers, and the development of hybrid MSNs with better stability and efficacy. Stimuli-responsive MSNs have the potential to alter their structural makeup in reaction to stimuli, which improves their stability in a variety of settings.

CONCLUSION

MSNs are regarded as an effective way to deliver therapeutic agents as they can encapsulate a wide range of therapeutic molecules and have biocompatibility, nanosize, and multifunctional surface features. Additionally, MSNs have demonstrated significant potential for combination therapy by co-delivering several drug therapies to produce synergistic benefits. However, MSNs still face some issues that need to be resolved, including the long-term stability and biocompatibility of MSNs, the optimizationof drug release profiles, and the potential for immune system recognition and clearance. MSNs provide advancement in the field of nanotechnology. It is therefore required to conduct more clinical studies to explore the potential of MSNs in life-threatening diseases like cancer, brain disorders, virus infections, and respiratory ailments.

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AUTHOR'S CONTRIBUTION

The collaborative efforts of Padiyar Neha and Dr. Nidhi Nainwal mainly draft this manuscript. All the other authors helped in the formatting, language, and grammar editing, referencing, and citation of this manuscript as per journal guidelines.

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