Chapter

Fabrication of Mesoporous Silica Nanoparticles and Its Applications in Drug Delivery

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Abstract

Mesoporous Silica Nanoparticles (MSNs) are nano-sized particles with a porous structure that offers unique advantages for drug delivery systems. The chapter begins with an introduction to MSNs, providing a definition of these nanoparticles along with a brief historical overview. The distinctive properties of MSNs, such as high surface area, tunable pore size, and excellent biocompatibility, are discussed, highlighting their potential in drug delivery applications. The synthesis methods for MSNs are presented, including template-assisted synthesis, sol-gel method, co-condensation method, and other approaches. The chapter also covers the characterization techniques used for evaluating MSNs, including morphological, structural, and chemical characterization, which are crucial for assessing their quality and functionality. The surface modification of MSNs is explored, focusing on the functionalization of surface groups, attachment of targeting ligands, and surface charge modification to enhance their interactions with specific cells or tissues. The chapter then delves into the diverse applications of MSNs, with a particular focus on drug delivery. The use of MSNs in cancer theranostics, drug delivery, imaging, biosensing, and catalysis is discussed, emphasizing their potential to revolutionize these areas. Furthermore, the toxicity and biocompatibility of MSNs are addressed, covering both in vitro and in vivo studies that evaluate their safety and efficacy.

Keywords: mesoporous silica nanoparticles, surface modification, cancer theranostics, template-assisted synthesis, Co-condensation, biosensing

1. Introduction

1.1 Definition of mesoporous silica nanoparticles (MSNs)

Mesoporous silica nanoparticles (MSNs) are nano-sized particles composed of silica (SiO_2) with a unique porous structure. They possess a regular arrangement

of mesopores, which are cylindrical channels or voids within the particle structure [1]. These mesopores typically range in size from 2 to 50 nm, offering a large surface area for drug loading and delivery [2].

The term "mesoporous" refers to the intermediate pore size between micropores (less than 2 nm) and macropores (greater than 50 nm). This mesoporous structure allows for the efficient encapsulation, storage, and controlled release of therapeutic agents, making MSNs highly desirable for drug delivery applications [3].

MSNs can be fabricated with precise control over their size, shape, and pore characteristics, enabling tailored drug delivery systems. The synthesis of MSNs involves the use of various templating agents or surfactants that serve as a template around which the silica precursor is deposited, followed by the removal of the template to create the desired pore structure [4].

The unique properties of MSNs make them versatile platforms for drug delivery. Their large surface area facilitates high drug-loading capacity, while the tunable pore size allows for the selective encapsulation of different types of drugs, including small molecules, proteins, nucleic acids, and even imaging agents. Additionally, the surface of MSNs can be functionalized with targeting ligands, making them capable of targeted drug delivery to specific cells or tissues [5].

1.2 Brief history of MSNs

The development and exploration of mesoporous silica nanoparticles (MSNs) as versatile materials for drug delivery applications have evolved over several decades. The following provides a detailed overview of the historical milestones and key contributions in the field of MSNs [6, 7].

1.2.1 Discovery of mesoporous materials

The study of mesoporous materials traces its origins to the late 1960s and early 1970s when researchers discovered the existence of ordered porous structures in various materials. Initial investigations focused on mesoporous materials like MCM-41 and SBA-15, which laid the foundation for the development of MSNs [8].

1.2.2 Introduction of MSNs

The concept of mesoporous silica nanoparticles (MSNs) emerged in the early 1990s when researchers introduced a template-assisted synthesis method to create highly ordered porous structures within silica nanoparticles. This breakthrough led to the realization of MSNs as promising candidates for drug delivery systems due to their unique properties [9].

1.2.3 Pioneering synthesis methods

In the late 1990s and early 2000s, researchers developed and refined various synthesis methods for MSNs. The sol-gel method and co-condensation method gained significant attention as effective approaches to fabricate MSNs with controlled pore size and surface properties. These methods allowed for the synthesis of MSNs with tailored characteristics suitable for drug delivery applications [10].

1.2.4 Advancements in surface modification

During the 2000s, considerable progress was made in surface modification techniques for MSNs. Researchers explored different strategies to functionalize the surface of MSNs with organic groups, polymers, or targeting ligands. These modifications enabled the introduction of specific functionalities, such as controlled drug release, enhanced stability, and targeted drug delivery [11].

1.3 Unique properties of MSNs

Mesoporous silica nanoparticles (MSNs) possess several distinct properties that make them highly desirable for drug delivery applications. Understanding these unique characteristics is crucial for harnessing the full potential of MSNs in the field of drug delivery [12–15]. The following provides a detailed exploration of the key properties of MSNs:

1.3.1 High surface area

MSNs have an exceptionally high surface area due to their porous structure. The presence of mesopores enables a large surface area-to-volume ratio, providing ample space for drug loading and adsorption. The high surface area allows for efficient interaction with drugs, leading to improved encapsulation efficiency and enhanced drug loading capacity.

1.3.2 Tunable pore size and volume

MSNs offer the advantage of tunable pore size and volume, enabling customization based on specific drug delivery requirements. The pore size can be precisely controlled during the synthesis process, allowing for the selective encapsulation of different types of drugs, including small molecules, macromolecules, and even imaging agents. This tunability facilitates the optimization of drug release kinetics and enhances therapeutic efficacy.

1.3.3 Controlled drug release

MSNs exhibit controlled drug release behavior, which is critical for achieving sustained and targeted drug delivery. The porous structure of MSNs provides a reservoir-like effect, allowing for controlled release of encapsulated drugs over an extended period. The release kinetics can be further modulated through surface modifications, such as the introduction of stimuli-responsive systems or functional groups that respond to specific environmental cues.

1.3.4 Excellent biocompatibility

MSNs demonstrate excellent biocompatibility, ensuring their compatibility with biological systems and minimizing adverse effects. The silica material used in MSNs is generally considered biologically inert, reducing the likelihood of cytotoxicity and immunogenicity. Furthermore, MSNs can be surface-modified with biocompatible polymers or targeting ligands to enhance their biocompatibility and reduce potential toxicity concerns.

1.3.5 Surface functionalization

The surface of MSNs can be easily functionalized, allowing for the introduction of specific functionalities to facilitate targeted drug delivery. Functional groups, polymers, or targeting ligands can be attached to the surface of MSNs, enabling selective interactions with specific cells, tissues, or biological molecules. Surface functionalization also enables the incorporation of imaging agents for real-time monitoring or diagnostic purposes.

1.3.6 Stability and ease of fabrication

MSNs exhibit good stability, making them suitable for long-term storage and transportation. The synthesis methods for MSNs are well-established and relatively straightforward, offering reproducibility and scalability. This ease of fabrication facilitates their translation from the laboratory to industrial-scale production for practical applications.

MSNs hold significant potential for the development of advanced drug delivery systems. Their high surface area, tunable pore size, controlled drug release behavior, excellent biocompatibility, surface functionalization capabilities, and stability make them versatile platforms for efficient and targeted drug delivery, ultimately improving therapeutic outcomes [16–20].

2. Synthesis of MSNs

The synthesis of mesoporous silica nanoparticles (MSNs) involves various methods that allow for the controlled fabrication of their unique porous structure [21–23]. The following describes the key synthesis methods commonly employed for the production of MSNs:

2.1 Template-assisted synthesis

Template-assisted synthesis is a widely employed method for fabricating mesoporous silica nanoparticles (MSNs) with precise control over their porous structure [24–26]. This approach involves the use of a sacrificial template or surfactant, around which the silica precursor is deposited and subsequently removed, leaving behind the desired porous architecture within the nanoparticles. The template provides a framework that determines the size, shape, and arrangement of the mesopores, allowing for tailored drug loading and release properties. The following steps outline the template-assisted synthesis process:

2.1.1 Template selection

The choice of template plays a crucial role in determining the characteristics of the resulting MSNs. Commonly used templates include organic surfactants, such as cetyltrimethylammonium bromide (CTAB) or Pluronic block copolymers, and inorganic templates like colloidal silica or polymer micelles. The template's structure and size dictate the dimensions and arrangement of the mesopores within the silica network.

2.1.2 Silica precursor deposition

The silica precursor, often tetraethyl orthosilicate (TEOS) or other alkoxysilanes, is added to a solution containing the template. Under appropriate conditions, hydrolysis and condensation reactions occur, leading to the formation of silica species.

2.1.3 Template removal

After the deposition of the silica precursor, the template is selectively removed to generate the porous structure within the nanoparticles. The template removal can be achieved through either calcination or extraction processes. Calcination involves heating the MSNs to high temperatures, typically above 400°C, to burn off the organic template. On the other hand, extraction involves dissolving the template using solvents that are selective for the template material. This step leaves behind an interconnected network of mesopores within the MSNs.

2.1.4 Post-synthesis treatment

To further refine the MSNs' properties, post-synthesis treatments can be performed. These treatments may include washing with solvents to remove residual impurities, surface functionalization to introduce specific functionalities or targeting ligands, or modification of the pore surface to alter the release kinetics or enhance biocompatibility.

Template-assisted synthesis offers several advantages for MSN fabrication. It allows precise control over the pore size, distribution, and connectivity, enabling the customization of drug loading and release profiles. The use of different templates and adjustments in synthesis conditions enable the creation of MSNs with specific properties tailored for various drug delivery applications. Additionally, template-assisted synthesis is a relatively straightforward and scalable method, making it suitable for large-scale production of MSNs.

By utilizing template-assisted synthesis, researchers can create MSNs with a well-defined mesoporous structure, offering improved drug encapsulation capacity, controlled release behavior, and enhanced therapeutic efficacy. This synthesis approach contributes to the development of advanced drug delivery systems with precise control over drug release kinetics and targeted delivery to specific tissues or cells (**Figure 1**).

2.2 Sol-gel method

The sol-gel method is a widely used approach for the synthesis of mesoporous silica nanoparticles (MSNs) [27–31]. This method involves the hydrolysis and condensation of silica precursors in a solution, leading to the formation of silica nanoparticles with a porous structure. The sol-gel process allows for the precise control of reaction parameters to tailor the size, shape, and pore characteristics of the resulting MSNs. The following steps outline the sol-gel method for MSN synthesis:

2.2.1 Selection of silica precursors

The sol-gel method typically utilizes alkoxysilane precursors, such as tetraethyl orthosilicate (TEOS) or tetramethyl orthosilicate (TMOS). These precursors undergo hydrolysis and subsequent condensation reactions to form the silica network. The

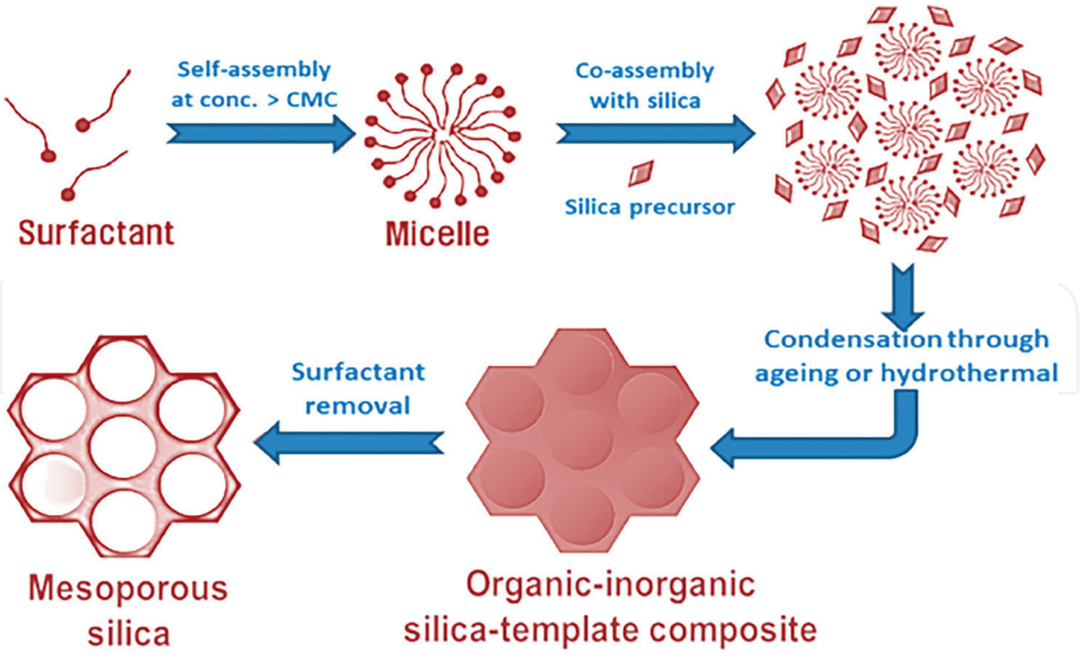

Figure 1.
Template assisted synthesis of mesoporous silica nanoparticles.

choice of precursor depends on factors such as reactivity, availability, and desired properties of the MSNs.

2.2.2 Hydrolysis

The silica precursor is hydrolyzed by adding a controlled amount of water or a hydrolyzing agent, such as an acid or base, to initiate the hydrolysis reaction. This step involves the breaking of the alkoxide groups in the precursor, resulting in the formation of silanol groups (Si-OH) on the silica precursor.

2.2.3 Condensation

The hydrolyzed silica precursor undergoes a condensation reaction, where the silanol groups react with each other to form siloxane bonds (Si-O-Si) and release water molecules as byproducts. The condensation reaction can be controlled by adjusting reaction parameters such as pH, temperature, and concentration of precursors. The condensation leads to the formation of a three-dimensional silica network.

2.2.4 Pore formation

During the hydrolysis and condensation reactions, the addition of a structure-directing agent or a surfactant can lead to the formation of mesopores within the silica network. The surfactant molecules self-assemble and organize themselves to create micelles, which act as templates for the pore formation. The surfactant can be removed later to generate the mesopores within the MSNs.

2.2.5 Aging and drying

The synthesized MSNs are subjected to aging and drying processes to promote further condensation and solidification. Aging refers to the continuation of

the condensation reaction over an extended period, allowing the particles to grow and the pore structure to develop. Drying involves the removal of solvent and water from the MSNs, typically through evaporation or freeze-drying.

The sol-gel method offers several advantages for MSN synthesis. It allows precise control over the particle size, pore size, and pore structure of the MSNs by adjusting reaction parameters. The process is relatively simple, scalable, and compatible with the incorporation of various functional groups or additives for tailored drug delivery applications.

By employing the sol-gel method, researchers can produce MSNs with well-defined mesopores, high surface area, and customizable properties. These MSNs offer advantages for drug delivery, including high drug loading capacity, controlled release profiles, and the potential for targeted delivery to specific tissues or cells. The sol-gel method contributes to the development of efficient and precise drug delivery systems using MSNs as carriers (**Figure 2**).

2.3 Co-condensation method

The co-condensation method is a commonly used technique for the synthesis of mesoporous silica nanoparticles (MSNs) [32–37]. This method involves the simultaneous hydrolysis and condensation of two or more silica precursors, resulting in the formation of MSNs with enhanced structural and chemical properties. The co-condensation method offers advantages such as improved control over pore size, surface functionality, and composition of the MSNs. The following steps outline the co-condensation method for MSN synthesis:

2.3.1 Selection of silica precursors

The co-condensation method utilizes two or more silica precursors, typically alkoxysilanes, such as tetraethyl orthosilicate (TEOS), tetramethyl orthosilicate (TMOS), or organosilanes. The choice of precursors depends on the desired properties and functionalities of the resulting MSNs.

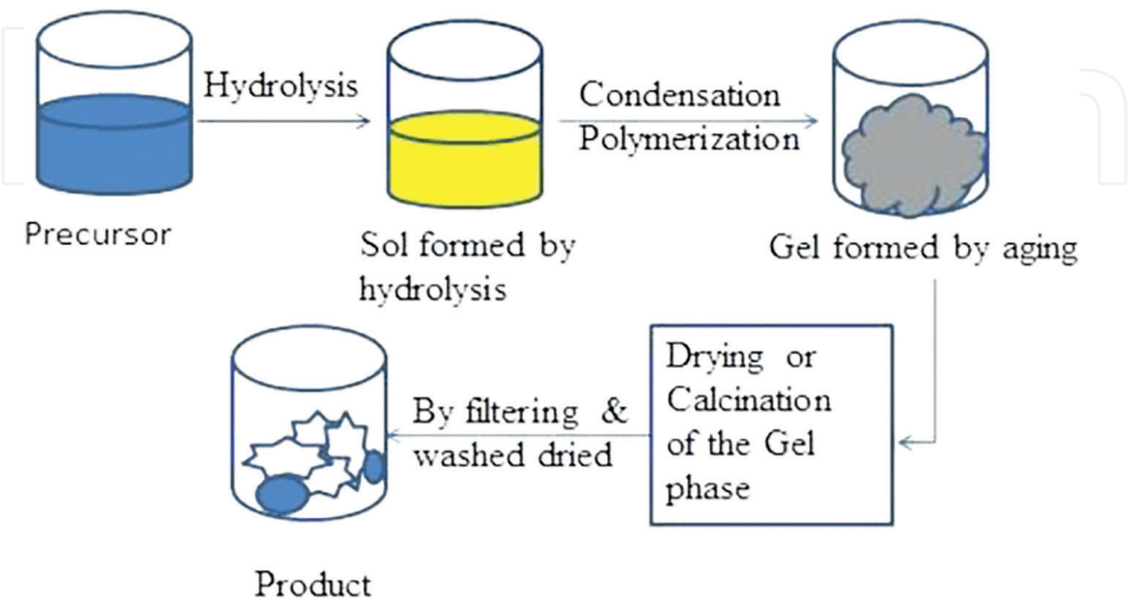

Figure 2.
Sol-gel method for synthesis of mesoporous silica nanoparticles.

2.3.2 Hydrolysis

The selected silica precursors are hydrolyzed by adding water or a hydrolyzing agent, such as an acid or base, to initiate the hydrolysis reaction. Hydrolysis breaks the alkoxide groups in the precursors, leading to the formation of silanol groups (Si-OH) on the silica precursors.

2.3.3 Co-condensation

The hydrolyzed silica precursors undergo co-condensation, where the silanol groups from different precursors react with each other to form siloxane bonds (Si-O-Si). This simultaneous condensation results in the formation of a hybrid silica network containing different types of siloxane linkages.

2.3.4 Pore formation

Similar to other synthesis methods, the addition of structure-directing agents or surfactants can be incorporated during the co-condensation process to induce the formation of mesopores within the silica network. These agents self-assemble and organize themselves to create micelles, which act as templates for pore formation. The subsequent removal of the template generates the desired mesoporous structure within the MSNs.

2.3.5 Aging and drying

The synthesized MSNs undergo aging and drying processes to promote further condensation and solidification. Aging allows the particles to grow and the pore structure to develop over time. Drying involves the removal of solvent and water from the MSNs, typically through evaporation or freeze-drying, resulting in the formation of solid MSNs.

The co-condensation method provides enhanced control over the composition and properties of the MSNs by combining different silica precursors. This method allows the incorporation of organic groups, such as functional molecules or polymers, into the silica network, enabling the introduction of specific functionalities or surface modifications. The resulting MSNs exhibit improved stability, enhanced drug loading capacity, and tailored release profiles, making them suitable for various drug delivery applications.

By utilizing the co-condensation method, researchers can design and synthesize MSNs with specific pore structures, tailored surface functionalities, and controlled drug delivery properties. These MSNs offer advantages in terms of targeted drug delivery, increased stability, and improved therapeutic efficacy. The co-condensation method contributes to the advancement of MSNs as versatile carriers in drug delivery systems (**Figure 3**).

2.4 Other synthesis methods

In addition to template-assisted synthesis and the sol-gel method, there are several other methods available for the synthesis of mesoporous silica nanoparticles (MSNs). These methods offer alternative approaches to tailor the size, shape, and pore characteristics of the MSNs. Here are some of the commonly employed methods:

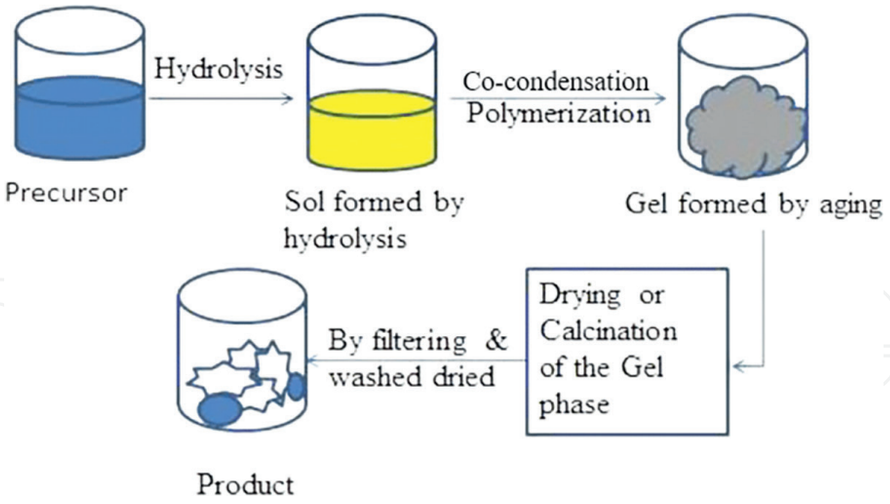

Figure 3.
Co-condensation method for synthesis of mesoporous silica nanoparticles.

2.4.1 Stöber method

The Stöber method, also known as the classical silica nanoparticle synthesis method, involves the hydrolysis and condensation of silica precursors in the presence of a stabilizing agent, such as ammonia or ethanol. The resulting silica nanoparticles can be further etched to generate mesopores, or surfactants can be added during the synthesis process to induce pore formation [38–40].

2.4.2 Microemulsion method

The microemulsion method utilizes water-in-oil or oil-in-water microemulsions as reaction media for the synthesis of MSNs. In this method, silica precursors are dispersed within the microemulsion, and the hydrolysis and condensation reactions take place within the confined nanodroplets. The microemulsion method allows for precise control over the size and morphology of the resulting MSNs [41–44].

2.4.3 Emulsion-droplet coalescence method

The emulsion-droplet coalescence method involves the formation of water-in-oil emulsions containing silica precursors and a hydrophilic solvent. Subsequently, the emulsion droplets are subjected to coalescence, leading to the formation of silica nanoparticles. The resulting nanoparticles can be further treated to introduce mesoporous structures [45–49].

2.4.4 Aerosol-assisted synthesis

The aerosol-assisted synthesis method involves the generation of aerosol droplets containing silica precursors, which are then passed through a high-temperature furnace or reactor. The high temperature promotes the hydrolysis and condensation reactions, resulting in the formation of MSNs. This method allows for the production of MSNs with controlled particle size and narrow size distribution [50, 51].

2.4.5 Solvothermal method

The solvothermal method involves the synthesis of MSNs in a high-pressure, high-temperature environment using organic solvents as reaction media. This method allows for the formation of MSNs with unique structures and properties. The solvothermal conditions facilitate the control of particle size, surface area, and pore characteristics of the MSNs [52].

Each of these alternative methods offers specific advantages in terms of controlling the size, morphology, and pore structure of the resulting MSNs. Researchers can choose the most suitable method based on the desired properties and applications of the nanoparticles. The flexibility and versatility provided by these various synthesis methods contribute to the advancement of MSNs as promising drug delivery systems, enabling tailored approaches to meet specific therapeutic needs.

3. Characterization of MSNs

3.1 Morphological characterization of mesoporous silica nanoparticles

3.1.1 Particle size

Surfactant, which may be charge or neutral, is utilized in aqueous solution to generate mesoporous silica nanoparticles. Surfactant polymerizes silicates, an ester of orthosilicic acid.

The following factors can affect how big and how shaped mesoporous silica nanoparticles are:

- Hydrolysis rate.
- How well the constructed template interacts with the silica polymer.
- Source condensation of silica.

We can modify all of these variables by adjusting the pH and utilizing various templates and co-solvents. Using a high concentration of template and hydrophobic auxiliaries, Stucky et al. created hard mesoporous silica spheres with sizes ranging from hundreds of microns to millimeters at the oil-water interface. The pace of stirring is crucial in determining the particle size of MSNs; if the rate is slow, lengthy fibers are produced, whereas when the rate is fast, one powder is created. Impact of pH on the morphology of MSNs shows that spherical mesoporous particles with a size range of 1–10 m develop in mildly acidic conditions [29].

Although dynamic light scattering is currently favored, electron microscopy was once utilized to measure the particle size of MSNs. MSNs are frequently employed in the biomedical field because, while being smaller than eukaryotic cells, they can function at the subcellular level. MSN interacts with living things like plants, animals, and bacterial cells at both the extracellular and intracellular levels. Spherical MSNs are less likely to be taken up by cancer and non-cancer cells than tubular ones on spherical and tubular MSNs on cancer and non-cancer cells [53].

3.1.2 Pore size

The following variables are employed to regulate the pore shape of MSNs:

- Amount of surfactant and silica source.
- The surfactant's capacity for packing.

Surfactant aggregation in solutions is influenced by pH and solution concentration. Different pore shapes are used to synthesize MSNs at both acidic and basic pH levels. For instance, hexagonal structures are formed at basic pH, but lamellar mesophases are synthesized at high pH (>12). By converting cylindrical channels in an ionic liquid containing MSNs to twisted channels. During or after synthesis, hydrothermal treatment is employed to modify the pore width. In order to produce the required pore size, it is crucial to use a surfactant with varying hydrophobic chain lengths or to use mesitylene as a swelling agent. Since additives have the ability to alter the hydrophobic-hydrophilic equilibrium, further tuning is necessary for pore expansion when applying them during synthesis. Mesitylene is utilized to increase the pore size of MSNs from 3 to 5 nm without changing the particle size, and these MSNs with larger pores are then used as a delivery system for proteins that are membrane impermeable to cancer cells [54]. To enhance pore size without altering the morphology of pre-formed particles, a freshly synthesized material is subjected to autogenic pressure during post-synthesis at temperatures between 373 K and 423 K with or without additions. By combining a fluorocarbon-based and polymer-based surfactant. X-ray diffraction and transmission electron microscopy (TEM) are used to measure the pore structure of MSNs, and nitrogen sorption is used to calculate the pore diameter. The lamellar p2 (MCM-50), the 3D cubic Ia3d, and the 2D hexagonal p6m (MCM-41) are the three most prevalent mesophases in silicas with pore sizes between 2 and 5 nm, respectively. This is comparable to the discovery of large pore size 6–20 nm MSNs with 2D hexagonal p6m [55].

3.1.3 Surface area

The number of medicinal drugs absorbed depends primarily on the surface area of the MSNs. Two distinct methods are utilized to adjust the amount of medication integrated into the matrix: raising or reducing the surface area and changing the surface drug affinity. This shows that the relationship between surface area and drug absorption is direct. Surface area (SBET value) 1157 $m^2 g^{-1}$ and SBA-15 with surface area value 719 $m^2 g^{-1}$ are used to create MCM-41. When alendronate is loaded in MSNs under the identical circumstances, MCM-41 and SBA-15 each receive 139 mg g^{-1} of the medication. It suggests that the relationship between surface area and maximum drug loading is strong [56].

3.1.4 Pore volume

When the surface area is around 1000 $^2 g^{-1}$ and the pore size is smaller than 15 nm, the pore volume is typically in the range of 2 $cm^2 g^{-1}$. Poor drug-drug interactions can cause pore illness while drug interactions with mesopores are a surface phenomenon. The pore volume can be used to calculate the amount of drug adsorbed.

Drug-intermolecular interactions inside the pore width are amplified when drugs are repeatedly loaded into mesopores in ordered mesoporous material. It suggests that the relationship between pore volume and the amount of drug loaded is linear.

Based on the size of their pores, mesoporous materials fall within the category of porous materials. Micro, meso, and microporous are the three categories that can be used to classify the three types of pores. Mesoporous materials typically have pores with a diameter between 2 and 50 nm. Usually, silica is formed around template micelle assemblies to manufacture these materials, and then the templates are removed by calcination. Mesoporous materials' use as drug delivery vehicles has now been expanded due to their distinct pore size, large surface area, and high pore volume. By employing several types of templates and altering the reaction parameters, the pore size of the mesoporous material for such an application can be adjusted. Mesoporous silica nanoparticles (MSN) are stable and expanded mesopores produced by organized mesoporous materials based on silicates produced by sol-gel and hydrothermal synthesis. MSNs are renowned for having excellent characteristics like uniformly shaped pores with well-defined diameters. In addition, altering the template molecule's length can change the pore size of MSNs. By altering the silica sources, surfactants, or reaction parameters, such as temperature, aging time, mole ratio of reactants, and medium pH, a new mesoporous system can also be created [57]. Tetraethyl orthosilicate (TEOS), a precursor to silica, is soluble in alcohol but not in water, hence ethanol is typically used as a homogenizing agent in the reaction. Tetrakis(2-hydroxyethyl) orthosilicate (THEOS), a novel silica precursor with ethylene glycol as a water-soluble residue, was developed to address this problem [58]. THEOS is hydrolyzed into glycol and silicic acid when dissolved in water, and these two substances eventually condense to form silica. The advantage of using THEOS for structured silica fabrication is that it is an environmentally benign technique because the produced silica is readily hydrolyzed and polymerized at neutral pH conditions and can go through jellification at room temperature [59, 60]. Additionally, THEOS as a precursor for silica synthesis only releases glycol rather than alcohols, making it more biocompatible [61].

3.2 Structural characterization of mesoporous silica nanoparticles

Mesoporous nanoparticles have a sizable framework, a porous structure, and a sizable quantity of surface area that allow for the attachment of numerous functional groups for targeting the drug moiety. Chemically, MSNs have a structure resembling a honeycomb and an active surface.

Mesoporous silica nanoparticles (MSNs) combine the benefits of nanomaterials with mesoporous silica materials. This class of materials is characterized by large surface areas, controllable pore size, and ordered pore structures. Particle size, morphology, pore size, and mesostructured can all be controlled through study; a new class of stimuli-responsive aminated MSNs with shape-shifting behavior is introduced. MSNs can change shape by being vacuum-dried from water-rich solvents, being evaporated at high humidity for MSN suspensions in ethanol, or being exposed to water vapor in solid form for 24 h. With the loss of mesostructured long-range hexagonal order, a decrease in surface area and mesopore volume, an increase in micropore volume, and further condensation of the silica matrix, animated MSNs' cross-sectional shapes can change from hexagonal to six-angle stars under these conditions. Finally, a class of quasicrystalline MSNs' synthesis and thorough characterization are addressed. Dodecagonal (12-fold) symmetry is present in these MSNs, which have particles smaller than 100 nm [62].

High surface area, huge pore volume, and consistent and controllable pore size are characteristics of mesoporous silica materials. Because silica is safe, has chemical stability, and can be combined with other materials, it has attracted interest from a variety of fields, including biorelated ones. Nano-sized ordered mesoporous silica particles are one such example.

It has taken a lot of work to create mesoporous silica particles with various shapes, functions, and sizes. On the other hand, the creation mechanism of these particles has received relatively little attention in investigations to date.

The production and characterization of ordered mesoporous silica nanoparticles with and without incorporated magnetic nanoparticles are covered in the first section. By recording particle production at various times during the synthesis, the formation mechanism of silica nano composites is examined. To describe the structure evolution of the resultant materials, transmission electron microscopy (TEM) and small angle x-ray scattering (SAXS) are combined. Ordered mesoporous silica nanoparticles are given additional functionalities by the addition of organic moieties to the silica matrix. However, it frequently results in pore blockage or an unorganized pore structure.

X-ray diffraction (XRD-Pan Analytical X'Pert Pro) was used to determine the crystalline structure, and Fourier transform infrared (FTIR-Thermo Scientific Nicolet IS10) was used to assess the chemical bonding. Microscop electron (SEM-FEI Inspect S50 and TEM) microstructure examination was conducted. Using a Quantochrome surface analyzer and the Brunauer Emmett-Teller (BET) Nitrogen adsorption-desorption method, the specific surface area, pore size, and pore distribution were calculated [63].

4. Surface modification of MSNs

4.1 Functionalization of mesoporous silica nanomaterials

Surface changes have been made for the silica nanoparticles expansion in the bio-domain. By doing so, it is possible to improve biocompatibility, avoid non-specific adsorption, and supply functional groups for future biomolecule conjugation activities. Layer by layer self-assembly (LSA) and chemical surface functionalization are the two most popular surface modifications. The integration of the mesoporous silica nanoparticles during the manufacture of metal or metal oxide nanocrystals can functionalize them. To produce a metal-functionalized silica, a surfactant solution (such as hexadecyltrimethylmonium bromide) must be mixed with a heterogeneous mixture made up of the surfactant-coated metal nanocrystals in an organic solvent. As a result, gold, silver, and iron oxide are embedded into the mesoporous silica. Next, a silicate source is added to the mixture to enhance the condensation reaction. These functionalized systems can exhibit a variety of bio-activities, such as antibacterial activity, which is guaranteed by the presence of dissolved metallic ions [64].

Research has been made to create colloidal core-shell mesoporous silica with various linear PEG (polyethylene glycol) modifications in order to assess the significant impact of various functionalization techniques. Because the PEG matrix is present on the surface of the nanomaterial, silica functionalization can reduce the degradation rate compared to unfunctionalized ones. PEG is hydrophilic, which prevents proteins from adhering to it and minimizes undesirable interactions between the physiological environment and Nano silica. In other studies, silica surface functionalization with

hydroxyl, carboxyl, and PEG groups was highlighted. The nanomaterials were largely removed by the renal pathway according to in vivo optical measurements from the urinary bladder, demonstrating that these alterations are independent of the renal clearance. In contrast to the hydroxyl and carboxyl derivates, PEG showed longer blood circulation and reduced liver absorption [65].

The silica functionalization of SBA-15 was the subject of numerous studies. Kim et al. investigated the biodegradation of functionalized SBA-15, modified with hydroxyl, amine, and carboxyl moieties on the surface, in order to assess the impact of surface functionalization onto deterioration behavior. The least amount of degradation was present in the carboxyl functionalized silica. According to these studies, the SBA-15 surface functionalization reduces the degradation rate compared to neat silica, highlighting the possibility that the functionalization may affect silica shell corrosion by interacting with the cations in biological media and thereby slowing the SBA-15 clearance rate. The therapy is typically digested through adsorption, and the mesoporous silica nanoparticles are typically charged by immersion in the active component solution. When the silica surface is functionalized, the cargo can be released in a controlled manner only at the specific damaged tissue; there is no evidence of a premature release into the bloodstream, which minimizes any unwanted side effects and boosts therapeutic effectiveness. The functionalization of SBA-15 mesoporous silica with amino groups from organic amines (aminopropyl triethoxysilane) for the transport of bioactive coordination complexes. The hydrophobic contact with the hydrophobic active principle improved as a result of a linkage between the functional groups from the coordination compound and the amino groups from the silica surface. The rate of medication release will increase once sialylation has been reduced via amination [66].

5. Applications of mesoporous silica nanoparticles (MSNs)

5.1 Drug delivery

Different therapeutic agents, including chemotherapy drugs, small interfering RNA (siRNA), or photo-thermal agents, can be loaded into MSNs. The high drug loading capacity and controlled release made possible by the mesoporous structure increase the efficacy of cancer treatment. Additionally, targeting delivery to particular cancer cells is made possible by functionalizing the MSNs' surface, which minimizes off-target effects [67].

5.2 Imaging

Imaging agents, such as fluorescent dyes, magnetic nanoparticles, or radioactive isotopes, can be added to MSNs. This enables non-invasive imaging of tumor sites, tracking of nanoparticle dispersion, and tracking of therapeutic response. The large surface area of MSNs also enables multi-modal imaging, which combines various imaging modalities for improved diagnostic precision [68].

5.3 Photothermal therapy

MSNs can be used for photothermal therapy by incorporating photothermal agents, such as gold or carbon nano-materials, into them. The photothermal agents

produce heat when exposed to near-infrared (NIR) light, selectively ablating cancer cells while sparing healthy tissue. MSNs' mesoporous structure makes it easier to load and deliver photothermal agents to tumor sites effectively [69].

5.4 Combination therapy

MSNs may be made to carry several different therapeutic agents, allowing for the use of combination therapy strategies. Combinations of chemotherapeutic drugs, photothermal agents, immunotherapeutic agents, or gene therapy agents may be used in this. By focusing on multiple pathways involved in cancer progression, these combination therapies have the potential to increase treatment efficacy [70].

5.5 Biosensing and early detection

Functionalized MSNs may be used in biosensing applications to identify particular cancer biomarkers or abnormal cellular processes. These nanoparticles have the ability to bind to target molecules with preference, producing a discernible signal. Early cancer biomarker detection can help with prompt diagnosis and enhance treatment outcomes [71].

5.6 Theranostic nanoplatforms

By combining various functionalities, MSNs can act as adaptable theranostic nanoplatforms. For instance, a single MSN system can be designed to combine photothermal therapy, imaging, and drug delivery capabilities, enabling individualized and accurate cancer treatment.

Although MSNs show great promise in cancer theranostics, more research is still needed to improve their design, increase the effectiveness of their targeting, improve biocompatibility, and guarantee long-term safety. In the coming years, it is anticipated that the clinical translation of MSN-based theranostics will advance as a result of ongoing research in this field [72].

5.7 Catalysis

Mesoporous silica nanoparticles (MSNs) have demonstrated great potential as catalysts in a number of catalytic reactions, including reaction number seven. MSNs are appealing for catalytic applications due to their distinctive structural characteristics, such as their high surface area, large pore volume, and tunable pore size [73–76]. The following are some significant uses of MSNs in catalysis:

5.7.1 Heterogeneous catalysis

To catalyze a variety of reactions, MSNs can be functionalized with different catalytic species, such as metal nanoparticles or metal complexes. Mesoporous channels in MSNs enable effective mass transport of reactants and products, and their large surface area and pore structure provide a sufficient number of active sites for catalytic reactions. In reactions like oxidation, hydrogenation, and selective organic transformations, heterogeneous catalysis using MSNs has been investigated.

5.7.2 Enzyme immobilization

MSNs can effectively support the immobilization of enzymes, enabling the creation of enzyme-based catalysts. Improved stability, reusability, and ease of separation from the reaction mixture are all displayed by enzymes immobilized on MSNs. This makes it possible for enzymatic catalysis in a variety of bio-catalytic processes, such as enzyme-mediated transformations and the creation of biofuels.

5.7.3 Chiral catalysis

To make enantioselective catalysts, MSNs can be functionalized with chiral ligands or chiral metal complexes. These catalysts allow for asymmetric catalysis, which allows for the selective production of particular enantiomers of a compound. Enantiomer separation and effective chiral transformations are made possible by the immobilization of chiral catalysts on MSNs.

5.7.4 Photo-catalysis

To enable photo-catalytic reactions, MSNs can be modified with photo-catalytic species, such as semiconductor nanoparticles (such as TiO2, and ZnO). MSNs' mesoporous structure facilitates the interaction of photo-catalysts and reactants and enables effective light harvesting. For uses like water splitting, pollutant degradation, and organic synthesis when exposed to light, photo-catalytic MSNs have been investigated.

5.7.5 Acid-base catalysis

By modifying the surface chemistry of MSNs, acid or base sites can be added, enabling acid-base catalysis. Bronsted or Lewis acid-base sites can be created on the surface of MSNs by grafting functional groups like -SO3H or -NH2. Aldol condensation, trans-esterification, and other reactions have all used MSNs with acid-base functionalities.

The use of MSNs in catalysis offers several advantages, including high catalytic activity, improved selectivity, and recyclability. However, challenges still exist, such as optimizing the catalyst loading, stability under reaction conditions, and mass transfer limitations. Further research is focused on the development of novel MSN-based catalysts and their integration into practical catalytic processes.

6. Toxicity and biocompatibility

6.1 Toxicity

Before using mesoporous silica nanoparticles (MSN) in biomedical applications, it is essential to assess their toxicity [77–79]. MSN's toxicity can change depending on the biological system being studied as well as factors like particle size, surface characteristics, shape, and surface charge. Here are some key points regarding the toxicity of MSN:

6.1.1 Physicochemical characteristics

MSN's toxicity can be greatly influenced by its physicochemical characteristics, such as particle size, surface charge, and surface functionalization. Due to their

improved interactions with cellular components, smaller particles and particles with larger surfaces may manifest increased toxicity.

6.1.2 Inflammatory response

MSN may cause the release of pro-inflammatory cytokines like interleukin-6 (IL-6) or tumor necrosis factor-alpha (TNF-alpha), which are indicative of an inflammatory response in cells or tissues. Long-lasting or excessive inflammation can have cytotoxic effects and damaged tissue.

6.1.3 Effects that are dose-dependent

Like many other nanoparticles, MSN's toxicity frequently shows a dose-dependent relationship. MSN may have negligible or no negative effects at low concentrations, but at higher concentrations, its toxicity may increase.

6.1.4 Cell type specificity

Depending on the cell type, exposure to MSN may have different effects. For instance, some studies have indicated that compared to normal cells, some cancer cell lines may be more vulnerable to the toxic effects of MSN. Thus, the toxicity of MSN may vary depending on the type of cell being exposed.

6.1.5 Cellular uptake and internalization

MSN can enter cells via a number of different processes, including passive diffusion or endocytosis. The extent of cellular uptake can influence the toxicity of MSN, as internalized nanoparticles may interact with cellular components and induce specific responses.

6.1.6 Reactive oxygen species (ROS) generation

MSN can produce ROS that can cause oxidative stress in cells, such as hydrogen peroxide or superoxide radicals. Increased ROS levels have the potential to be cytotoxic by damaging cellular components like proteins, lipids, and DNA.

6.1.7 Biodistribution and systemic effects

MSN can interact with different organs and tissues while dispersing throughout the body when taken systemically. When evaluating MSN's toxicity and potential long-term effects on various organ systems, the biodistribution of MSN is a crucial factor to consider.

6.2 Biocompatibility

6.2.1 IN-VIVO studies

Due to their potential use in drug delivery, imaging, and diagnostics, mesoporous silica nanoparticles (MSN) have drawn a lot of interest in biomedical research. Before MSN is put to use in clinical settings, biocompatibility studies are essential for

determining its safety and effectiveness. MSN interactions with living organisms are examined in vivo studies, particularly in terms of biocompatibility, bio-distribution and potential toxicity [80–83].

Animal models like mice, rats, or non-human primates are frequently given these nanoparticles in biocompatibility studies of MSN. Depending on the intended use, the nanoparticles can be given through a variety of routes, such as intravenous injection, oral administration, or inhalation. The animals are then observed for a predetermined amount of time to evaluate any negative effects or biological reactions.

To evaluate the biocompatibility of MSN, several aspects are typically investigated:

6.2.1.1 Acute and chronic toxicity

Animals are watched closely for any indications of acute toxicity, such as modifications in behavior, body weight, or organ function. Studies on chronic toxicity examine the long-term consequences of MSN exposure, such as possible organ accumulation, inflammation, or organ dysfunction.

6.2.1.2 Bio-distribution

To comprehend the uptake, localization, and clearance mechanisms of MSN, the distribution of MSN in various organs and tissues is examined. The distribution of nanoparticles can be seen and measured using methods like fluorescence imaging, electron microscopy, and radiolabeling.

6.2.1.3 Immunological response

To determine any potential immune toxicity, the immune response induced by MSN is examined. To ascertain whether MSN causes an inflammatory response or immune cell activation, immune cells, cytokine levels, and histological analysis of immune-related organs are examined.

6.2.1.4 Organ-specific effects

To assess any potential harm or dysfunction brought on by MSN, specific organ systems, such as the liver, kidneys, lungs, and spleen, are carefully examined. It is common practice to evaluate tissue morphology and spot any anomalies through histopathological analysis.

6.2.1.5 Metabolism and excretion

To comprehend the biotransformation and excretion pathways of MSN, the metabolic fate of the substance is investigated. To determine their potential toxicity, metabolites and degradation products are examined.

6.2.2 IN-VITRO studies

For mesoporous silica nanoparticles (MSN), in-vitro studies are a crucial part of biocompatibility evaluations. Insights into their potential toxicity, cellular uptake mechanisms, and biological responses can be gained from these studies by analyzing the interactions between MSN and various biological components at the cellular and molecular levels [84–89].

Here are a few typical in vitro techniques for evaluating MSN's biocompatibility:

Tests for cytotoxicity and cell viability: These tests examine the viability, proliferation, and metabolic activity of cultured cells after they have been exposed to MSN. The MTT assay, the Cell Counting Kit-8 (CCK-8) assay, or the lactate dehydrogenase (LDH) release assay are examples of frequently used assays. Potential side effects may be indicated by any appreciable decrease in cell viability or rise in cytotoxicity when compared to control groups.

6.2.2.1 Cellular uptake and internalization

In vitro studies investigate the interactions between MSN and cells, including the internalization processes and intracellular fate of MSN. To see and measure the uptake of MSN by cells, techniques like fluorescence microscopy, flow cytometry, or electron microscopy can be used.

6.2.2.2 Inflammatory response

The ability of MSN to cause an inflammatory response is determined by monitoring the release of pro-inflammatory cytokines by immune cells or other pertinent cell types, such as interleukin-6 (IL-6) or tumor necrosis factor-alpha (TNF-alpha). To measure the expression of cytokines, real-time PCR or enzyme-linked immunosorbent assays (ELISA) are frequently used.

6.2.2.3 Oxidative stress assessment

MSN may produce reactive oxygen species (ROS) inside of cells, which causes oxidative stress. Studies conducted in vitro measure oxidative stress markers like lipid peroxidation, superoxide dismutase activity, intracellular ROS levels, and other antioxidant enzyme activities. These analyses aid in assessing the possibility of oxidative damage brought on by MSN.

6.2.2.4 Genotoxicity and DNA damage

In vitro genotoxicity assays, such as the micronucleus assay or the comet assay, assess the likelihood that MSN will result in genomic instability or DNA damage in cells. The results of these tests shed light on the potential long-term consequences of MSN exposure.

6.2.2.5 Cell-specific assays

Additional cell-specific assays may be carried out depending on the intended use of MSN. Studies may assess the release of encapsulated drugs, therapeutic efficacy, or particular cellular reactions to the delivered cargo, for instance, if MSN is intended for drug delivery.

7. Conclusions

MSNs offer unique properties that make them highly attractive for drug delivery systems. Their high surface area, tunable pore size, and excellent biocompatibility

make them suitable for efficient encapsulation, controlled release, and targeted delivery of therapeutic agents.

The chapter discusses various synthesis methods for MSNs, including template-assisted synthesis, sol-gel method, co-condensation method, and other approaches. Each method offers specific advantages and allows for the customization of MSNs with desired characteristics. The characterization techniques for evaluating MSNs, such as morphological, structural, and chemical characterization, are also presented, emphasizing the importance of assessing the quality and functionality of these nanoparticles.

Surface modification of MSNs is explored, highlighting the strategies for functionalizing surface groups, attaching targeting ligands, and modifying surface charge. These modifications enable improved interactions with specific cells or tissues, enhancing the efficacy and specificity of drug delivery.

The chapter further discusses the diverse applications of MSNs, focusing on cancer theranostics, drug delivery, imaging, biosensing, and catalysis. MSNs show great potential in revolutionizing these areas by enabling precise drug delivery, multimodal imaging, sensitive biosensing, and efficient catalytic reactions.

Toxicity and biocompatibility of MSNs are addressed, covering in vitro and in vivo studies that evaluate the safety and efficacy of these nanoparticles. The understanding of their biocompatibility is essential for their successful translation into clinical applications.

Finally, the chapter concludes by highlighting future research directions in the field of MSNs. Ongoing research aims to improve the design and fabrication of MSNs, enhance their drug loading and release capabilities, explore new applications, and address any potential challenges related to toxicity and biocompatibility. The significant potential of MSNs in advancing drug delivery systems is underscored, emphasizing their role in the development of innovative and targeted therapeutic strategies.

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Conflict of interest

The authors declare no conflict of interest.

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