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A review of mesoporous silica nanoparticles for targeted drug delivery, characterization and synthesis

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Abstract: Mesoporous silica nanoparticles (MSNs) possess uniform pore dimensions, excellent thermal stability, and are functionalized with various chemical groups, making them a reliable choice for diverse applications, including medicine, supercapacitors, food toxicity detection, and the chemical industry. MSNs are primarily chosen as drug carriers due to their unique tunability features, inert and porous nature, and resistance to chemical degradation. Compared to high-purity silica produced using synthetic organic precursors, MSNs are relatively cost-effective owing to their simple synthesis process. This paper reviews the properties, preparation, and synthesis of MSNs, as well as their applications in drug loading methodologies. These applications include tumor detection, food purification, biosensors, and drug delivery. The final section of the review discusses the effectiveness of MSNs and their interactions with biological systems, along with various issues that need to be addressed.

Keywords: *Drug delivery, Mesoporous silica nanoparticles, Synthesis, Applications.*

1. Introduction

The evolution of drug delivery has advanced significantly in the era of nanotechnology, transforming the traditional operations of the pharmaceutical industry. In drug delivery, nanoparticles with diameters ranging from 0.1 μm to 100 nm are used. The drug is initially dissolved and then compressed before being attached to the nanoparticle matrix. The size range of the nanoparticles often impacts their biodistribution and availability, hence serving as a crucial part in the drug carrier process. For drug loading and more effortless movement in the system, the hydroponic cores and hydrophilic surface block are used to prevent opsonization [1].

Nanoparticles have shown great potential in meeting the needs of these delivery systems. Hence, various studies have utilized nanoparticles for cancer vaccination not only to deliver immune activators to cells but also to act as tumour-related antigens to shrink the affected area. In this case, mesoporous Silica Nanoparticles (MSN), gold nanoparticles, polymers, and liposomes have Food and Drug Administration (FDA)-approved formulations and have also achieved success in chemotherapy treatments [2, 3].

The MSN structure is similar to honeycombs, as its design is mesoporous, which improves the bioavailability of the nanoparticles. The MSN is prepared using an emulsion technique and it is mainly used to carry drugs and release them in the affected region with increased stability. The surface area of MSN is large, hence it offers a higher absorption rate. MSN possesses different advantages such as targeted drug delivery to specific regions, biocompatibility, stability, personalized medicine applications, and high bioavailability [4].

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The MSN has crucial compounds that pave the way for cancer treatment and even serve as a pathway for challenging diseases. The advantages offered by MSN are numerous, including high pore volume, homogeneous guest molecule distribution, non-toxicity, high surface area, and biocompatibility. However, certain drawbacks of MSN also exist, such as inducing melanoma production due to the metabolic changes of the nanoparticles [5]. This review primarily highlights the significant advantages of MSN in various fields, as well as its preparation and synthesis process. This paper also summarizes the applications and challenges present in the design of MSN for different approaches.

2. Mesoporous Silica Nanoparticles

Most solid materials are naturally crystalline and composed of atoms. However, silica materials have two types of structures: both crystalline and amorphous [6]. In the amorphous materials, the atoms are mainly arranged in recurring patterns. By applying thermal treatments, the amorphous phase can be transformed into crystalline ones [7, 8]. Dynamic light scattering and electron microscope are the widely used techniques to identify the MSN particle size.

2.1. Structure of Mesoporous Nanoparticles

The MSN is smaller than the eukaryotic cells and is widely deployed in the biomedical field due to its subcellular-level functionality. The MSN collides with human beings and other species at both intra and extracellular levels. The structure of MSN is based on the following components.

- Surface area: To identify the absorption capacity of the drugs, the surface area is an important factor. The volume of the injected drug in the matrix can be increased and decreased by modifying the surface area. The drug absorption capacity (maximum drug loading capacity) is directly relative to the surface area. The surface area of the SBA-15 and MCM-41 is 719 m^2g^{-1} and 1157 m^2g^{-1} [9].
- Embedded structure: Fibrous MSN (Fe_3O_4) is an embedded form of MSN structure and retains sufficient magnetic response and redisperability during the drug release process.
- Pore size: Different parameters control the pore size of MSN and they are the packing capacity, silica source level, and surfactant. Based on the pH level and concentration, the surfactant is immersed in the solution. The synthesis of MSN for different pore structures happens at both different acidic and basic pH levels. For instance, the hexagonal structures can be derived using basic pH levels in the range 10 to 12 and the lamellomesar phases are derived in the pH range greater than 12 [10].
- Pore volume: The drug mainly interacts with the mesopores in a surface environment and a poor drug-to-drug interaction often results in pore filling. Using the pore volume, one can measure the amount of drug absorbed by the material. For a pore size of less than 15 nm, the pore volume will be nearly equal to 2cm^3g^{-1}. Pore volume and the loaded drug ratio are equivalent to each other.

MSN with different structures can be developed using different types of surfactants. Using sol-gel chemistry-based synthesis, the pore size and structure of the MSN can be automatically controlled [11]. During the synthesis process, surfactant molecules are dissolved in polar solvents to form liquid crystals, a phenomenon known as the liquid crystal templating mechanism. The surfactant molecules form micelles when the concentration exceeds the critical micellar concentration. Based on the surfactant used, the nature of the micelles varies. Supra-micellar structures are formed by integrating different micelles, which also depends on the type of surfactant used and the external environment[12, 13]. Based on the existing supra-micellar geometries, the new mesoporous framework is formed, and it can be of different shapes (cubic, laminar, and hexagonal). After the supra-micellar aggregates are formed, the associated precursors need to be added to the liquid crystals, such as alkoxysilanes, which undergo hydrolysis and condensation reactions to yield ordered mesoporous silica frameworks with tunable pore architecture and surface functionality.

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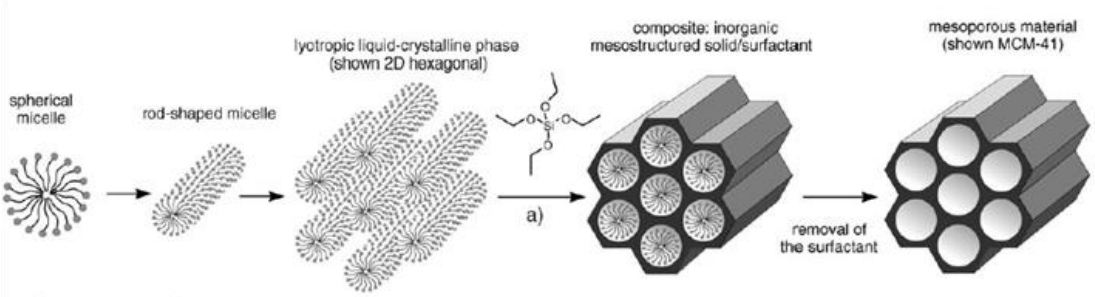

Figure 1.
Mesoporous structure formation (MCM-41).
Source: Jadhav, et al. [1] (Adapted with permission).

Mesoporous substances can also be obtained using different methods. For example, an assembly with a structure-directing agent and inorganic precursor also forms mesoporous materials. In this process, both ingredients should be added simultaneously, resulting in the simultaneous formation of mesophase and hydrolysis-condensation [10, 14]. Finally, the surfactant is removed from the product, resulting in a network of cavities. In this synthetic process, various procedures, such as solvent extraction or calcination at high temperatures, are applied within the inorganic framework to remove the surfactant [15, 16]. The ordered mesoporous generation process is depicted in Figure 1 which is an efficient mode for drug delivery.

2.2. Synthesis

MSNP is the most significant type of nanomaterial due to its unique features and potential applications, including imaging, sensing, catalysis, and drug delivery [17, 18]. This section describes the synthesis of MSNP. The base-catalyzed sol-gel technique is employed to produce silica nanoparticles of suitable sizes for biological applications [19]. The sol-gel technique uses organosilane precursors for condensation and hydrolysis processes.

$$Condensation: Si(OH)_4 + SiO^- \rightarrow OH^- + Si - O - Si \quad (1)$$

$$Hydrolysis: Si(OR)_4 + OH^- \rightarrow RO^- + Si(OR)_3OH \quad (2)$$

It initiates the new stage of sol formation. The sol contains small colloidal particles, whereas the gel phase is condensed. The procedure is used for manufacturing MSN nanoparticles, which range in size from 50 to 2000 nm [20, 21]. This was accomplished through the use of ammonia-catalyzed hydrolysis of tetraethyl orthosilicate (TEOS) and a water-alcohol solution. The templating agent, being a cationic surfactant, creates micelles. The micellar template condenses around the silica structure, directing the silicate source [22, 23]. Mesoporous silica materials are synthesized by two different research groups for catalytic applications. The initial material production technique used disordered morphologies with mesoporous silica sheets. Homogeneous form improves biocompatibility while also reducing material size [24].

Modified MCM-41 particles at the sub-micrometer scale were synthesized. The diluted surfactant solution contains 100 nm MCM-41 silica particles. The dialysis or double surfactant system produces less than 50 nm MSNP. Figure 2 depicts several examples of MSNP about MCM-41 based on SEM, TEM, MSNP enclose Zn-doped iron oxide, and MSNP encapsulate silver and mixed iron-oxide images, as illustrated in Figures 2 (i) to (iv). The ability to tailor particle size, morphology, and surface chemistry during synthesis is what enables MSNP to serve as a multifunctional platform for both therapeutic and diagnostic applications. Moreover, advances in synthetic strategies, such as evaporation-induced self-assembly, sol–gel templating, and aerosol-assisted processes, have further enabled the fabrication of highly ordered mesoporous structures with controlled pore sizes and high surface areas.

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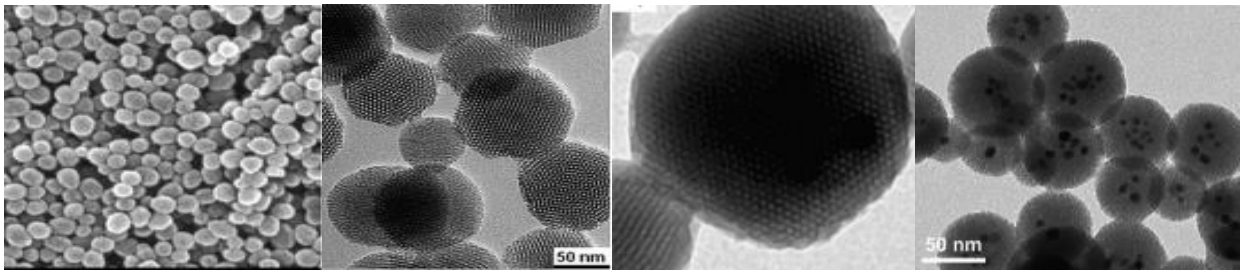

Figure 2.
The MSNP images for (i) MCM-41 based on SEM image, (ii) MCM-41 based on TEM image, (iii) MSNP encapsulate Zn-doped iron oxide and (iv) MSNP encapsulate silver and mixed iron-oxide.
Source: Li, et al. [15] (Adapted with permission).

In an aqueous solution with a basic pH (around 11), a templating surfactant is combined with tetraethyl orthosilicate (TEOS). This mixture results in the formation of micelle structures with a hexagonal packing arrangement through base-catalyzed sol-gel condensation. These micelles generate nanoparticles with a diameter of approximately 100 nm. During this process, interactions occur between the silica and the surfactant framework. Acidic alcohol is then used to reflux the resulting nanoparticles. Afterwards, the templating agent is removed from the mesopores. Electron microscopy and X-ray diffraction confirm that the pores remain intact and are arranged in 2D hexagonal arrays. These pores have a diameter of 2–3 nm and are roughly 100 nm in size, resembling the shape of spherical solvent particles.

3. Therapeutic MSN Applications

The MSN is widely applied in biomedical and imaging applications to enhance therapeutic molecules and to overcome the drawbacks associated with traditional drugs. The MSN degradation capability is associated with various parameters, including drug load, surface area, and morphology. The in vivo behavior of MSN is controlled in different ways [13]. The rod-shaped MSN takes a longer time to degrade than the spherical MSN. For efficient therapy, biocompatibility is an important concern, as the unwanted settlement of the drug in the body or cytotoxicity is unacceptable. Although MSN has shown great potential to enhance target drug delivery, there is still room for improvement, which can serve as potential areas for future research.

The biocompatibility of the MSN is typically high; however, the degradation rate of the product requires further improvement. To prevent long-term accumulation, the drug should be completely degraded once ingested. With surface functionalization only specific cells can be targeted and not the region of interest, hence accurate targeting mechanisms must be developed. The long-term side effects of MSN and the immune system reactions need to be identified through extensive clinical trials. A cost-efficient and reliable method needs to be developed for creating high-quality MSNs for drug delivery and cancer detection [16].

3.1. Characterization of Drug Delivery System

Once a target drug delivery system has been designed, it must be rigorously tested to guarantee its efficacy and safety [1, 17, 18]. Here are some often-used characterization techniques:

- Size and size distribution: The carrier's size determines its capacity to avoid the immune system and reach the target location. Particle size and distribution are measured using techniques such as dynamic light scattering (DLS).
- Surface features: The carrier's surface qualities, such as charge and hydrophobicity, might affect how it interacts with biological systems. Surface charge may be assessed using techniques such as zeta potential testing.

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- Drug loading and encapsulation efficiency: These factors determine the amount of drug encapsulated in the carrier and its level of protection. Quantification techniques include UV-V is spectroscopy and high-performance liquid chromatography (HPLC).
- In vitro and in vivo studies: These tests evaluate the effectiveness of the delivery system in cell cultures and animal models, respectively. They give essential information on drug release kinetics, targeting efficiency, and potential adverse effects.

3.2. Functionalization of MSN using Drug Loading

To improve the drug-loading properties and create a strong bonding, the MSN particles must be functionalized with organic groups between the MSN surface and the drug. The drug can be formulated based on the action, which comprises both solid-state and release functions. Drugs that are mostly in the solid state, such as Fenofibrate are often non-soluble in water hence, it is loaded onto the SBA-15 using a five-step process [19]. Functionalization of MSN surfaces not only improves drug-loading efficiency but also enables controlled release and enhances the stability of the loaded drug. The five-step process is shown in Figure 2. The work associated with Figure 2 is presented in Table 1.

These steps help to enhance the drug release rate when compared to an unprocessed drug. In multi-particle dosage forms, one of the widely conducted research studies is to identify the effects of coating drug particles using a polymer film [16, 20]. Although various techniques, such as microcrystalline cellulose and nonpareil sugar beads, have been employed, they exhibit low drug-loading properties due to their relatively low outer surface area for drug-loading particles. This increases the interest in using porous materials in the medical industry due to their higher surface area and drug-loading capacity. Porous materials not only enhance drug-loading efficiency but also provide a platform for achieving site-specific and sustained drug release. The main aim of the drug-loading materials is to offer controlled release and drug targeting [21]. In this way, the doses and bioavailability of poorly absorbed drugs can be reduced. The targeted drug delivery procedure is presented in Figure 4.

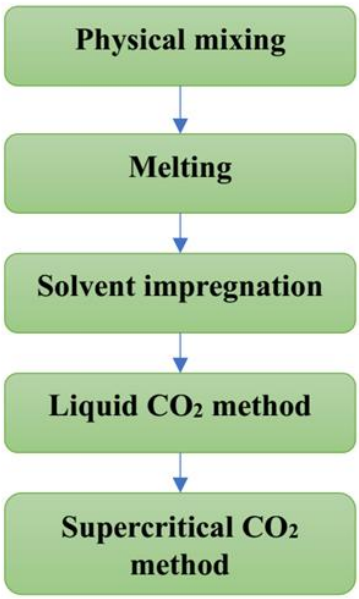

Figure 3.
MSN drug loading steps.

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Table 1.
Summary of the different MSN drug-loading steps.

Technique	Description	State	Drug loading type	Outcome
Physical mixing	The drug is mixed along with SBA-15 without any affinity	Crystalline	Heterogeneous	The drug is in the crystalline form without any indication of it in the mesopores
Melting	The drug is melted and then introduced into the mesopores	Non-crystalline	Homogeneous	The drug was dropped in the mesopores of SBA-15 upon cooling
Solvent Impregnation	The drug is either dissolved using ethanol or water	Non-crystalline	Homogeneous	The drug was found in the mesopores of SBA-15 after the solvent evaporated
Liquid CO_2 method	Dissolving the drug in liquid CO_2 under high pressure and temperature	Non-crystalline	Homogeneous	The drug was found in the mesopores of SBA-15 after the pressure was reduced
Supercritical CO_2 method	Supercritical CO_2 is used as a solvent to dissolve the drug	Non-crystalline	Homogeneous	The drug was found in the mesopores of SBA-15 under depressurization

Source: Jadhav, et al. [1].

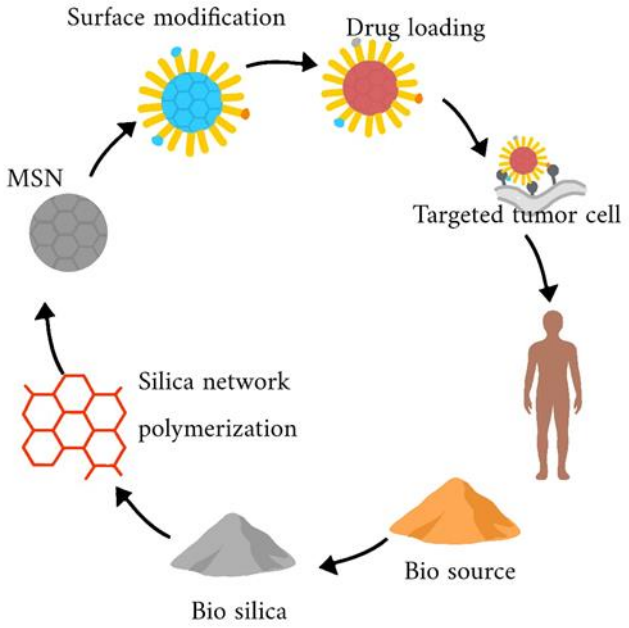

Figure 4.
Targeted drug delivery procedure.
Source: Porrang, et al. [16].

3.3. Applications of MSN

The MSN is used in different industries such as food, biosensors, bioimaging, and medicine [22, 23]. However, more amount of research is conducted in the biomedical field. This section shows the different sections where the MSN is applied.

3.3.1. Food Purification

Altunbas, et al. [8] utilized terbium-chelated MSN (Tb3+) to detect a toxic chemical named Ochratoxin A (OTA) commonly found in food particles. When the OTA is bonded near Tb3+, the sensor improves the fluorescence signal to identify the OTA even when it is present in a very low

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concentration (nanomolar) and offers a detection rate of 20 ppb. The experiments were conducted using the obtained fruit juice samples with different OTA concentrations. The TB3+ chelated nanoparticle sensor offers a high sensitivity and selectivity score showing that this biosensor is a promising tool for food safety analysis [24].

3.3.2. Biosensor

Abedi, et al. [9] designed an MSN-based chemical modifier using copper nitrate hydroxide with a C3N4 framework. The designed biosensor offered improved electrocatalytic activities when evaluated using the determination of clonazepam (CZP) test due to the modified glassy carbon electrode (GCE) used. Before modifying the electrode, they furnished the base GCE using alumina slurries and placed it in an ultrasonic bath for 2 minutes to remove the aluminum particles stuck in the electrode. The biosensor was mainly developed to identify the CZP levels in the tablet, urine, and serum samples. The results show that the biosensor improved the recovery rates by up to 94.2% and the relative standard deviation was nearly equal to 3.8% which shows that the sensor offers improved performance when tested using real-time samples.

The signal transducer with active sensing material present in the analytical device is a sensor [10]. Chemical and biosensors are two kinds of classes of sensors. Based on the environment, the major health issue is pollutants present at trace levels. Due to environmental pollution control, the growing demand met some rapid analytical models. Without extensive sample preparation, the nano-biosensors enable higher frequency pollutant monitoring, real-time and highly sensitive. Enlarger variability of pollutant monitoring and rapid screening of small devices integrates the nano-biosensors [25].

Due to salicylic acid, the 10–20 nm in diameter of nanosize grains with porous spherical and homogeneous morphology is indicated with TEM analysis [11]. The differential cyclic voltammetry and pulse voltammetry investigate the L-cysteine determination of salicylic acid and synthesize the nanocrystalline SiO2/CoFe2O4 electrochemical sensor application. The L-Cys determination with the remarkable sensitivity shown by sensors. According to the 0.02–425 μM L-Cys, there is a linear in SiO2/CoFe2O4 that modifies the glassy carbon electrode. The detection limit is 0.20 μM and the concentration range of L-Cys is 0.02–425 μM. To apply working potential, the negligible current response for citric acid, glutamic acid and tryptophan is produced by the electrode.

3.3.3. Tumor Therapy

Wu, et al. [12] developed a tumor microenvironment-sensitive gating system using a hollow MSN (HMSN) which has a higher surface area and large pore volume. Using the enhanced permeability and retention effect, the hollow MSN explores the tumor sites and offers effective drug delivery. The survival ratio of HMSN was nearly equal to 85% and tumor cells were nearly equal to 50%. This shows the cytotoxicity of the HMSN towards the cancer cells and the results show that the nanocarrier was efficient in reducing the anti-tumor activity.

3.3.4. Chemical Detection

To detect anions like cyanide and sulfide, seloneurea compounds are used and these sensors have different properties such as antioxidant activity, enzyme inhibitation, and DNA binding [14, 26]. The mesoporous silica sensors can also be used to detect nitrates which are visible in the form of red-violet products. Nitrates are a compound present in food that causes potential health risks [27, 28]. The chemical detection using mesoporous silica sensors offers higher accuracy and fast detection capability. Carcinoembryonic antigen [10, 29, 30] is a cancer marker that can slo be detected using MSN sensors powered with light-sensitive materials and specific compounds. Additionally, functionalized MSN-based sensors have been reported to provide high selectivity and sensitivity, making them effective tools for biomedical diagnostics and environmental monitoring

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3.3.5. Drug Delivery

Hybrid nanomaterials integrate organic and inorganic compounds to form new chemical conjugates that possess extraordinary properties [31, 32]. The nanoscale size of these particles enhances their stability and targeted delivery when encapsulating therapeutic agents, drugs, and genes [33, 34]. MSN is widely used for intracellular drug delivery due to the advantages it offers such as controlled release and biocompatibility [10, 35, 36]. The MSN minimizes the side effects of chemotherapy and enhances drug delivery efficiency. The MSN-based quantum dots serve as contrast agents for imaging techniques such as Magnetic Resonance Imaging (MRI) [11, 37, 38]. The MSN-based aerogels are applied in a wide range of applications such as drug delivery, biomarking, and cancer diagnosis due to their low density, high surface area, and cancer diagnosis [12, 39, 40]. Furthermore, the incorporation of targeting ligands and surface functional groups onto MSN enhances their specificity toward diseased cells, thereby improving therapeutic efficacy and reducing off-target effects. The active targeting strategy that targets cancer cells in stimuli-responsive drug delivery systems is shown in Figure 5.

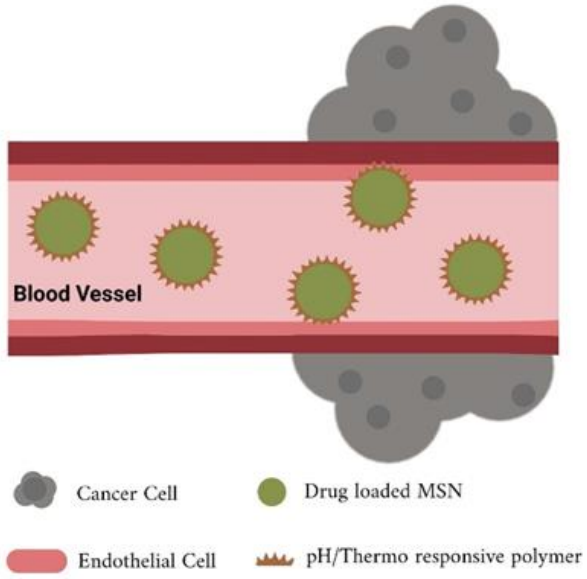

Figure 5.
MSN-based active targeting strategy.
Source: Porrang, et al. [16].

4. Quantitative Analysis and Existing Research Findings

The TEM image of 80 nm mesopores was obtained after calcination of MSN particles for 2 hours at 400°C. The results in Figure 6(a) demonstrate that the treatment did not alter the morphology of the particles nor induce nanoparticle aggregation. When evaluating the fluorescence intensity after applying 24 hours of UV radiation, no changes were found as per Figure 6 (b). This shows that the luminescence of MSN is stable when compared to the environmental changes since the different pH values (4-9) remain constant. When a 100 mm dithiothreitol (DTT) is evaluated under a strong environment, its luminescence remains constant [17, 41, 42]. Such high photostability and resistance to environmental fluctuations makes MSN highly suitable for long-term imaging and drug delivery applications in complex biological systems.

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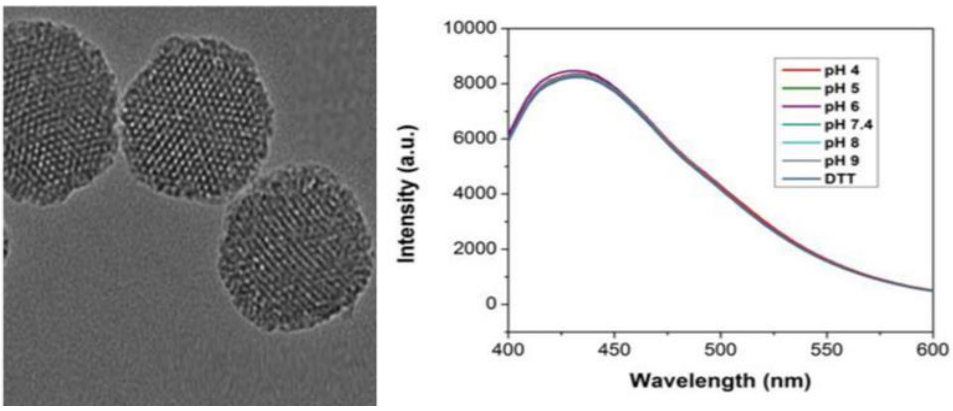

(a) (b)

Figure 6.
Fluorescence identification of MSN after calcination.
(a) TEM image after calcination (b) Fluorescence intensities for different pH levels.
Source: Chen, et al. [17].

Table 2 summarizes the diverse pore diameters and internal structures of various mesoporous silica nanoparticles (MSNPs). Existing research by Gisbert-Garzarán, et al. [4] reports an MSNP with a 3 nm pore diameter and a 3D cubic internal structure. Similarly, Gary-Bobo, et al. [5] describe an MSNP with a 9 nm pore diameter and a 3D cubic cage-like structure, while Selvam, et al. [6] present an MSNP with a 7.80 nm pore diameter and a 2D hexagonal structure. Finally, Vivero-Escoto and Luis [7] report an MSNP with a 10 nm pore diameter, although the specific internal structure is not specified in their work. This table highlights the range of pore sizes and internal configurations achievable in MSNPs, demonstrating their versatility and potential for various applications. The tunable pore sizes and diverse internal structures of MSNPs allow precise control over guest molecule loading, release kinetics, and surface functionalization, making them highly attractive for advanced biomedical and catalytic applications.

Table 2.
The results for various MSNP pore diameters and internal structure.

References	Internal structures	Pore diameter in nm
Gisbert-Garzarán, et al. [4]	3D cubic	3 nm
Gary-Bobo, et al. [5]	3D cubic cage-like	9 nm
Selvam, et al. [6]	2D hexagonal	7.80 nm
Vivero-Escoto and Luis [7]	2D hexagonal	10 nm

Figure 7 describes the graphical representation based on the number of papers published each year. Various years like 2001, 2009, 2012, 2015, 2017, 2019, 2020, and 2024-based papers were selected with different numbers. More papers were chosen from 2017 and the least number of papers were selected from different years. A comparative analysis is conducted between the conventional and MSN-based drug delivery systems using different features as shown in Table 3. The traditional techniques are cheaper and simpler to develop; however, the safety concerns and limited control over the drug release need to be improved [20, 24]. The MSN needs more improvement in controlled degradation and large-scale production. These trends suggest that future research should focus on addressing scalability, biodegradability, and clinical translation of MSN-based drug delivery systems to fully realize their potential in precision therapeutics.

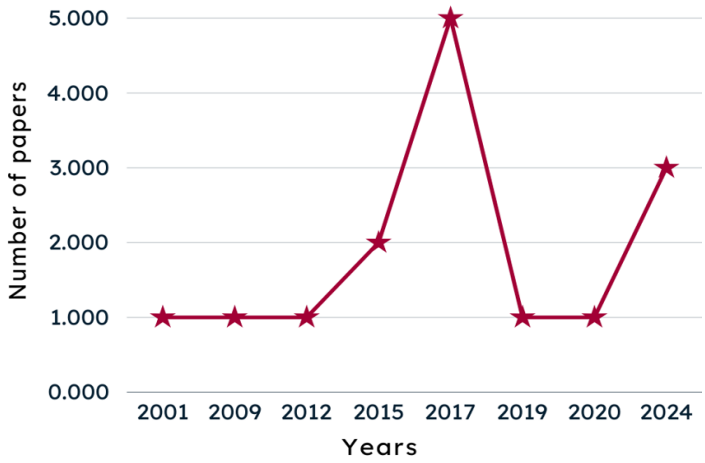

Figure 7.
Graphical plot for the number of papers published in each year.

Table 3.
Comparative analysis between traditional and MSN-based drug delivery system.

Features	**Traditional drug delivery systems [4, 10]**	**MSN based drug delivery system [1, 5, 7, 43]**
Controlled release	Limited control	Release can be triggered using different stimuli such as enzymes, pH, and lighting
Targeting	Non-targeted	Surface functionalized for targeted drug delivery to specific cells
Stability	Degrades over time	Stable
Targeted delivery	Limited	Possible with functionalization
Surface area	Lower	High
Cost	Varies	Moderate
Scale up-feasibility	Variable	Feasible
Drug loading capacity	Variable	High
Biocompatibility	Varied based on the material used	Easily tolerated by the body
Degradation rate	Unpredictable	Can be optimized
Characterization techniques	Limited	Different techniques is available for porosity, size, shape, and surface chemistry
Pore size	Variable	2-50 nm
Particle size	Not available	2-50 nm
Characterization techniques [10, 13, 20, 41]		
X-ray diffraction (XRD)	Less detailed	Crystal structure analysis
Brunauer Emmet Teller	Not applicable	Surface analysis and porosity analysis
Fourier Transform Infrared Spectroscopy	Limited to specific bonds	Chemical composition analysis
Transmission Electron Spectroscopy	Limited resolution	Detailed morphological analysis

5. Conclusion

This work presents a literature review of Mesoporous silica nanoparticles for targeted drug delivery, characterization, and synthesis. MSN has a well-defined pore structure, stability at high temperatures, functionalization, and a high surface area. The MSN synthesis is a cost-effective process and its biocompatibility makes it safe for use in biological systems. The tunable feature of MSN makes it an effective carrier for drug delivery. It is also used in other important applications such as tumor detection (cancer), food purification (contaminant detection), biosensors, and supercapacitors (energy

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storage devices for sustainable future applications). In the future, researchers can aim to minimize the potential toxicity associated with MSN and develop more advanced techniques for efficient controlled release mechanisms in various biomedical fields.

Transparency:

The authors confirm that the manuscript is an honest, accurate, and transparent account of the study; that no vital features of the study have been omitted; and that any discrepancies from the study as planned have been explained. This study followed all ethical practices during writing.

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