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Advances in Mesoporous Silica Nanoparticles for Targeted and Controlled Drug Delivery

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Abstract

Mesoporous Silica Nanoparticles (MSNs) have emerged as a versatile and highly tunable platform for controlled and targeted therapeutic applications. Their unique structural features including high surface area, tunable pore size, adjustable morphology, and abundant surface silanol groups enable efficient drug loading, precise surface functionalization, and stimuli-responsive release. Advances in synthesis methods, including sol–gel, soft-template, hard-template, and microemulsion approaches, allow precise control over particle size, pore architecture, and surface properties, which are critical for optimizing biological performance. Surface functionalization strategies, such as post-synthesis grafting, co-condensation, polymer coating, and ligand conjugation, enhance biocompatibility, targeting efficiency, and controlled drug release, while minimizing premature drug leakage and systemic toxicity. MSNs support diverse drug loading mechanisms, including physical adsorption, covalent attachment, and encapsulation with pore capping, enabling sustained and stimuli-responsive therapeutic release in response to pH, redox potential, enzymes, or external triggers. Targeting strategies, encompassing passive accumulation, active ligand-mediated targeting, biomimetic coatings, and organelle-specific delivery, further enhance therapeutic specificity and efficacy. Despite these advances, challenges remain in clinical translation, including long-term toxicity, immunogenicity, and large-scale reproducible synthesis. Future research is expected to focus on multifunctional, stimuli-responsive, and theragnostic MSNs that integrate combination therapies, biomimetic targeting, and real-time monitoring, thereby advancing personalized and precision medicine. This review provides a comprehensive overview of MSN structure, synthesis, functionalization, drug loading, targeting strategies, and future perspectives, highlighting their potential as next-generation nanotherapeutic platforms.

Keywords: Mesoporous silica nanoparticles, Controlled drug delivery, Targeted therapeutics, Surface functionalization, Stimuli-responsive release, Nanomedicine.

1 | Introduction

Over the past few decades, rapid advances in nanotechnology have profoundly influenced biomedical sciences, leading to the development of innovative strategies for disease diagnosis, monitoring, and treatment. One of the most significant contributions of nanomedicine is the emergence of advanced drug delivery systems designed to overcome the inherent limitations of conventional therapeutic approaches. Traditional

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drug administration often suffers from non-specific biodistribution, poor penetration across biological barriers, high required dosages, fluctuating plasma drug levels, and severe systemic side effects [1–3]. These issues are particularly critical in the treatment of complex and chronic diseases such as cancer, neurological disorders, and inflammatory conditions. In response to these challenges, nanocarriers have been extensively investigated as powerful tools to improve the pharmacokinetic and pharmacodynamic profiles of therapeutic agents. An ideal nanocarrier should provide high drug loading capacity, protect the therapeutic payload from premature degradation, enable controlled and site-specific release, and exhibit minimal toxicity toward healthy tissues. Various nanocarrier systems, including polymeric nanoparticles, liposomes, metallic nanoparticles, and silica-based nanostructures, have been explored. Among them, Mesoporous Silica Nanoparticles (MSNs) have gained particular prominence due to their distinctive structural and functional characteristics [4].

MSNs are characterized by an ordered mesoporous framework with pore sizes typically ranging from 2 to 50 nm, offering exceptionally high surface area and large pore volume. These properties allow efficient encapsulation of a broad spectrum of therapeutic agents with diverse molecular sizes and chemical natures. Moreover, the particle size, pore diameter, and morphology of MSNs can be precisely tailored by adjusting synthesis parameters, which is crucial for optimizing their biological behavior, cellular uptake, and therapeutic performance. A remarkable advantage of MSNs lies in the facile chemical modification of their internal and external surfaces. The abundance of silanol groups enables conjugation with a wide variety of functional moieties, including biocompatible polymers, targeting ligands, and molecular gatekeepers [5]. Such surface engineering strategies enhance colloidal stability, improve biocompatibility, reduce immune recognition, and enable active targeting toward specific cells or tissues. Furthermore, stimuli-responsive MSN-based systems have been developed to achieve controlled drug release in response to endogenous triggers (such as pH variations, enzymatic activity, and redox conditions) or exogenous stimuli (including light, temperature, ultrasound, and magnetic fields).

Owing to the integration of structural versatility, surface functionalization, and stimuli-responsiveness, MSNs have emerged as multifunctional platforms for both therapeutic and diagnostic applications. They have been widely explored in targeted cancer therapy, gene and RNA delivery, protein and peptide transport, antimicrobial treatments, and theranostic systems. Despite substantial progress, several challenges remain to be addressed before clinical translation, including long-term biosafety, controlled biodegradability, clearance pathways, and scalable manufacturing processes. This review provides a comprehensive and systematic overview of recent advances in MSNs for controlled and targeted therapeutics. The structural features and physicochemical properties of MSNs, synthesis methodologies, drug loading strategies, controlled release mechanisms, targeting approaches, therapeutic applications, and current challenges and future perspectives are critically discussed.

2 | Structure and Physicochemical Properties of Mesoporous Silica Nanoparticles

MSNs are considered one of the most advanced nanocarriers in drug delivery due to their ordered structure, tunable physicochemical properties, and versatile surface modification capabilities. MSNs consist of a silica framework containing mesopores with diameters ranging from 2 to 50 nm, typically organized into hexagonal channels or three-dimensional interconnected networks. This ordered mesoporous architecture provides exceptionally high surface area (commonly exceeding 700 m^2/g) and substantial pore volume, allowing for high drug loading capacity [6]. The particle size, pore diameter, and overall morphology of MSNs can be precisely engineered by adjusting synthesis parameters, including the type and concentration of surfactants, silica precursor concentration, pH, and reaction temperature. Particle sizes are typically controlled within 50–300 nm, which is optimal for overcoming biological barriers, enhancing cellular uptake, and achieving preferential accumulation in target tissues, such as tumors. The internal and external surfaces of MSNs are rich in silanol (Si–OH) groups, providing versatile sites for covalent or non-covalent functionalization with ligands, biocompatible polymers, and gatekeeping systems [7]. Surface modification enhances colloidal

stability, surface charge, hydrophilicity/hydrophobicity balance, and interactions with cellular membranes, thereby enabling active targeting and controlled release of therapeutic agents. From a physicochemical perspective, MSNs exhibit excellent chemical and thermal stability, essential for maintaining drug integrity under physiological conditions [8–10]. The high porosity and interconnected pore network facilitate efficient diffusion of solvents and biomolecules, supporting uniform and controlled drug release. Moreover, these properties allow MSNs to encapsulate a wide range of therapeutics, including small molecules, proteins, nucleic acids, and imaging agents. The combination of ordered mesoporous structure, high surface area, tunable size and morphology, and extensive surface functionalization capabilities makes MSNs an ideal platform for designing controlled and targeted drug delivery systems. Furthermore, physicochemical characteristics such as particle size, shape, surface charge, and pore distribution directly influence biological behavior, including cellular uptake, intracellular trafficking, and drug release kinetics. Thus, a deep understanding of the structure and physicochemical properties of MSNs is fundamental for the rational design of effective nanotherapeutic platforms for diverse biomedical applications (*Fig. 1*).

2.1 | Synthesis Methods of Mesoporous Silica Nanoparticles

The synthesis methods of MSNs play a pivotal role in defining their structural organization, pore architecture, particle size, morphology, surface chemistry, and ultimately their performance in controlled and targeted therapeutic applications. In general, the fabrication of MSNs is based on sol-gel chemistry combined with structure directing agents (templates) that guide the self-assembly of silica precursors into ordered mesoporous frameworks. Careful selection and control of synthesis routes and parameters enable the rational design of MSNs with tailored physicochemical properties suitable for drug delivery, imaging, and biomedical applications [11].

2.2. | Soft Template Assisted Sol-Gel Method

The soft-template-assisted sol-gel method is the most widely employed and fundamental approach for the synthesis of MSNs. In this method, surfactants such as Cetyltrimethylammonium Bromide (CTAB), Cetyltrimethylammonium Chloride (CTAC), or amphiphilic block copolymers including Pluronic P123 and F127 act as structure-directing agents. These surfactants self-assemble into micellar structures in aqueous or alcoholic media, which serve as templates for mesopore formation. Silica precursors, most commonly Tetraethyl Orthosilicate (TEOS) or Tetramethyl Orthosilicate (TMOS), undergo hydrolysis followed by condensation reactions under controlled pH, temperature, and reaction time, resulting in the formation of a silica framework around the micelles. The pore size of MSNs synthesized via this method is mainly determined by the type of surfactant and the presence of pore-expanding agents such as trimethylbenzene, while particle size and morphology can be tuned by adjusting parameters including the water-to-precursor ratio, pH, stirring rate, and reaction temperature. After framework formation, the surfactant template is removed either by calcination or solvent extraction. Although calcination yields highly ordered mesoporous structures, solvent extraction is generally preferred for biomedical applications as it better preserves surface silanol groups required for subsequent surface functionalization [12].

2.3 | Evaporation-Induced Self-Assembly

Evaporation-Induced Self-Assembly (EISA) is an effective strategy for producing highly ordered mesoporous silica structures with well-defined pore arrangements. In this approach, gradual solvent evaporation increases the concentration of surfactants and silica precursors, promoting micelle organization and mesophase formation. The EISA method offers precise control over pore ordering, morphology, and structural uniformity, and is particularly suitable for the fabrication of uniform mesoporous nanoparticles, thin films, and coatings.

2.4 | Hard Template Assisted Synthesis

Hard-template-assisted synthesis employs rigid templates such as polymeric nanoparticles, carbon spheres, metal oxides, or biological scaffolds to generate mesoporous silica architectures. In this approach, silica is deposited onto the surface of the hard template through sol-gel reactions, followed by removal of the template via chemical etching or thermal treatment. This method enables the fabrication of complex architectures, including hollow MSNs, core-shell structures, and multi-shelled or hierarchical mesoporous systems. However, hard-template synthesis generally involves more elaborate procedures, longer processing times, and higher costs compared to soft-template methods.

2.5 | Microemulsion-Based Synthesis

Microemulsion-based synthesis relies on nanoscale droplets of immiscible phases that function as confined nanoreactors for silica formation. These droplets provide spatial confinement, allowing controlled particle growth and resulting in MSNs with narrow size distributions and uniform morphology. Despite these advantages, the need for large amounts of surfactants and the complexity of microemulsion systems limit their scalability and practical industrial application.

2.6 | Hydrothermal and Solvothermal Methods

Hydrothermal and solvothermal synthesis methods are carried out under elevated temperature and pressure conditions, which enhance pore ordering, structural uniformity, and framework stability of MSNs. These approaches facilitate improved condensation of the silica network and allow fine control over particle morphology and pore architecture. Nevertheless, the requirement for specialized equipment and strict control of reaction parameters can restrict their widespread use.

2.7 | Control of Structural Parameters

Precise control over synthesis parameters including pH, surfactant type and concentration, silica precursor ratio, reaction temperature, reaction time, and template removal conditions is essential for tailoring the particle size, pore diameter, morphology, and surface properties of MSNs. Rational manipulation of these parameters enables the design of MSNs optimized for controlled drug loading, stimuli-responsive release, and targeted therapeutic applications. The synthesis of MSNs can be achieved using various approaches, each offering distinct advantages and limitations in terms of pore structure, particle morphology, and functionalization potential. As summarized in *Table 1*, different synthesis methods offer distinct advantages and limitations, which can be exploited to tune MSN properties for specific biomedical applications [12–18].

Table 1. Comparison of common synthesis methods for mesoporous silica nanoparticles, including key features, advantages, limitations, and applications.

Typical Applications	Limitations	Advantages	Key Features	Synthesis Method
Drug delivery, imaging	Possible pore blockage, requires surfactant removal	Simple, versatile, tunable pore size	Surfactant-directed micelle formation	Soft-Template Sol-Gel
Thin films, coatings	Requires controlled evaporation	Highly ordered pores, uniform morphology	Solvent evaporation drives micelle ordering	EISA
Controlled release, multimodal therapy	Time-consuming, costly, template removal	Hollow, core-shell, hierarchical structures	Silica deposited on rigid templates	Hard-template
Targeted drug delivery	Large surfactant usage, complex	Narrow size distribution, uniform morphology	Nanoreactors confine particle growth	Microemulsion
In vivo applications	Specialized equipment, strict control	High pore ordering and stability	High temp and pressure for condensation	Hydrothermal/ Solvothermal

3 | Surface Functionalization of Mesoporous Silica Nanoparticles

Surface functionalization of MSNs is a critical step in transforming these materials from simple porous carriers into highly efficient and multifunctional nanoplatforms for controlled and targeted therapeutic applications. Although pristine MSNs possess advantageous properties such as high surface area, large pore volume, and tunable mesostructures, their unmodified surfaces often suffer from limited selectivity, premature drug leakage, nonspecific protein adsorption, and suboptimal biological interactions. Surface functionalization addresses these challenges by enabling precise control over interfacial chemistry, biological interactions, and stimulus-responsive behavior. The presence of abundant silanol (–Si–OH) groups on both the external surface and internal pore walls of MSNs provides versatile reactive sites for chemical modification. Through appropriate surface engineering, key properties such as surface charge, hydrophilicity/hydrophobicity balance, colloidal stability, drug loading efficiency, release kinetics, cellular uptake, biodistribution, and targeting specificity can be systematically optimized *(Fig. 1)* [19–21].

3.1 | Functionalization Strategies

Surface functionalization strategies for MSNs can generally be classified into two main approaches: post-synthesis grafting and co-condensation during synthesis. Each method offers distinct advantages and limitations depending on the intended biomedical application.

3.2 | Post-Synthesis Grafting

Post-synthesis grafting is the most widely employed functionalization strategy due to its simplicity and versatility. In this approach, functional organosilanes are chemically attached to the silanol groups on pre-synthesized MSNs through siloxane bond formation. Commonly used silane coupling agents include Aminopropyltriethoxysilane (APTES), Mercaptopropyltrimethoxysilane (MPTMS), carboxyethylsilanes, and epoxy-functionalized silanes. This method allows selective functionalization of either the external surface or the internal pore walls by controlling reaction conditions such as solvent polarity, temperature, and reaction time. Post-grafting is particularly advantageous for introducing specific functional groups without disturbing the pre-formed mesoporous structure. However, excessive grafting may lead to partial pore blockage, which can reduce pore accessibility and negatively impact drug loading capacity.

3.3 | Co-Condensation Method

In the co-condensation approach, functional organosilanes are incorporated into the silica framework during the sol-gel synthesis process alongside conventional silica precursors such as TEOS. This results in a more homogeneous distribution of functional groups throughout the MSN structure, including both the pore walls and external surface. Co-condensation minimizes pore blockage and preserves meso-structural order, making it attractive for applications requiring uniform functionality. Nevertheless, this approach requires careful optimization to maintain structural integrity and typically offers less flexibility in post-synthesis modification compared to grafting methods [22].

3.4 | Surface Charge Engineering

Surface charge plays a pivotal role in determining the interaction of MSNs with drug molecules, cell membranes, and biological fluids. Functionalization with amine-containing groups introduces a positive surface charge, which enhances electrostatic interactions with negatively charged drugs, nucleic acids, and cellular membranes, thereby improving drug loading efficiency and cellular uptake. Conversely, carboxyl, phosphate, or sulfonate groups impart negative surface charges, improving colloidal stability and reducing nonspecific interactions in physiological environments. Fine-tuning surface charge is essential for balancing cellular internalization and systemic circulation behavior, particularly in in vivo applications [23].

3.5 | Hydrophobic and Hydrophilic Surface Modification

The hydrophobicity or hydrophilicity of MSN surfaces strongly influences drug loading and release behavior. Hydrophobic functional groups, such as alkyl or aromatic moieties, enhance the encapsulation of poorly water-soluble drugs and slow down their release through hydrophobic interactions. In contrast, hydrophilic modifications improve aqueous dispersibility and biocompatibility, which are critical for intravenous administration. By combining hydrophobic and hydrophilic functional groups, MSNs can be engineered to achieve optimal drug retention while maintaining favorable biological interactions.

3.6 | Polymer Coating and Stealth Functionalization

Polymer-based surface modification is a widely used strategy to enhance the biocompatibility and circulation time of MSNs. Among various polymers, Polyethylene Glycol (PEG) is the most extensively employed due to its ability to reduce protein adsorption, minimize opsonization, and evade recognition by the reticuloendothelial system. PEGylation significantly prolongs blood circulation time and improves passive tumor accumulation via the Enhanced Permeability and Retention (EPR) effect. Other polymers such as chitosan, Polyethylenimine (PEI), and Poly(Lactic-co-Glycolic Acid) (PLGA) have also been explored. These polymers can impart additional functionalities, including pH responsiveness, enhanced endosomal escape, and gene delivery capability [20–25].

3.7 | Stimuli-Responsive Surface Functionalization

Advanced surface functionalization strategies focus on the development of stimuli-responsive MSNs that enable on-demand and site-specific drug release. pH-responsive functional groups exploit the acidic microenvironment of tumors or intracellular compartments such as endosomes and lysosomes. Redox-responsive systems utilize disulfide linkages that are cleaved in the presence of high intracellular glutathione concentrations, particularly in cancer cells.

Enzyme-responsive coatings enable drug release in the presence of disease-specific enzymes, while externally triggered systems respond to light, temperature, magnetic fields, or ultrasound. These smart functionalization strategies significantly enhance therapeutic precision and reduce systemic side effects.

3.8 | Targeting Ligand Conjugation

Surface functionalization also enables the conjugation of targeting ligands that facilitate selective accumulation of MSNs in diseased tissues. Common targeting moieties include antibodies, peptides, aptamers, folic acid, transferrin, and small-molecule ligands. These ligands promote receptor-mediated endocytosis, thereby enhancing cellular uptake and improving therapeutic efficacy while minimizing off-target toxicity. Ligand conjugation is typically achieved through stable covalent bonding using linker chemistry, ensuring ligand integrity and functionality under physiological conditions [26].

3.9 | Impact on Therapeutic Performance

The surface functionalization strategy directly influences the overall therapeutic performance of MSN-based delivery systems, including drug loading efficiency, release kinetics, biodistribution, cellular uptake pathways, and treatment outcomes. Rational surface engineering enables the integration of multiple functionalities into a single nanoplatform, facilitating controlled release, active targeting, and combined therapeutic and diagnostic (theranostic) applications. Surface functionalization and targeting strategies play a pivotal role in enhancing the biocompatibility, cellular uptake, and therapeutic efficacy of MSNs. *Table 2* summarizes the main functionalization and targeting approaches, their purposes, key features, advantages, and representative examples. This overview provides a concise reference for designing MSN-based therapeutic platforms with tailored properties and targeted delivery capabilities [27].

Table 2. Overview of mesoporous silica nanoparticle surface functionalization and targeting strategies, highlighting purpose, key features, advantages, and representative examples.

Example	Advantages	Key Features	Purpose	Functionalization/ Targeting Strategy
Enhanced drug loading, pH responsiveness	Flexible, selective	Amines, thiols, carboxyls	Introduce functional groups	Post-Synthesis Grafting
Covalent drug attachment	Preserves pore order	Homogeneous distribution	Incorporate functional groups during synthesis	Co-condensation
PEGylated MSNs for tumor targeting	Reduced immune recognition, prolonged circulation	Hydrophilic, stealth effect	Improve biocompatibility, circulation	Polymer Coating (PEG, Chitosan, PEI)
Folate-targeted cancer therapy	Enhanced specificity	Antibodies, peptides, folic acid, RGD	Receptor-mediated uptake	Ligand-Mediated Active Targeting
Membrane-coated MSNs for selective delivery	Immune evasion, homotypic targeting	RBC, cancer, immune cell membranes	Cell membrane camouflaging	Biomimetic targeting
Redox-sensitive MSNs for cancer therapy	On-demand drug release	pH, redox, enzyme, temperature, light	Controlled release at target site	Stimuli-Responsive

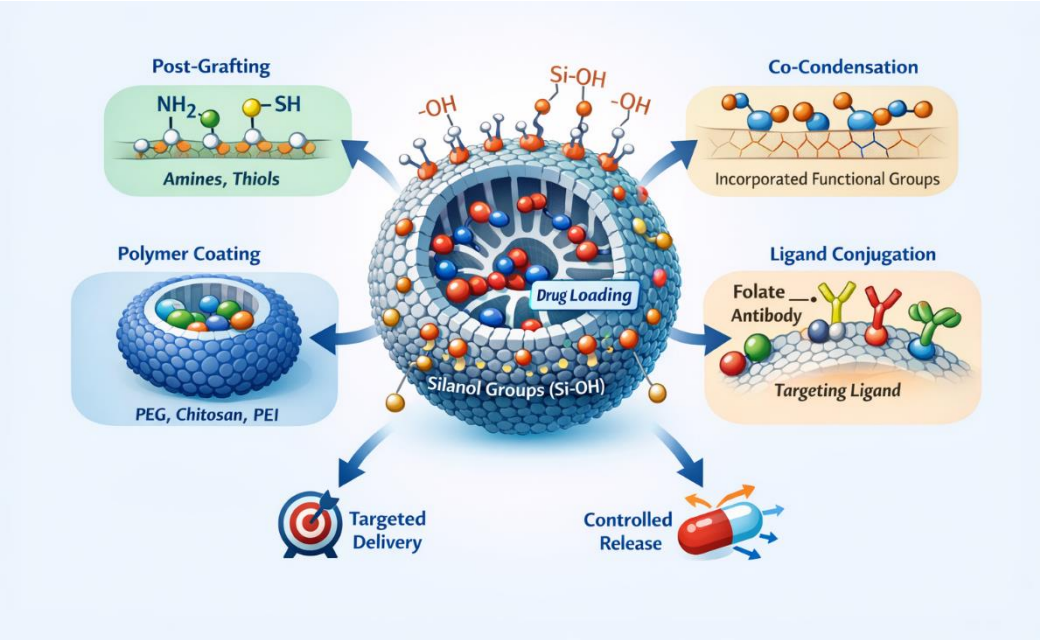

Fig. 1. Structure and surface functionalization of mesoporous silica nanoparticles for controlled drug delivery.

4 | Drug Loading Strategies and Controlled Release Mechanisms in Mesoporous Silica Nanoparticles

MSNs have attracted significant attention as drug delivery systems due to their exceptionally high surface area, large pore volume, tunable pore size, and versatile surface chemistry. These intrinsic properties enable efficient drug loading and provide multiple opportunities for controlled and stimuli-responsive drug release. The ability to precisely control both drug encapsulation and release behavior is a defining advantage of MSN-based nanocarriers in therapeutic applications (*Fig. 2*).

4.1 | Drug Loading Strategies

Drug loading into MSNs can be achieved through several mechanisms depending on the physicochemical properties of the therapeutic agent, the surface functionality of the nanoparticles, and the desired release profile.

4.2 | Physical Adsorption

Physical adsorption is the simplest and most widely used drug loading strategy. In this approach, drug molecules are loaded into the mesoporous channels of MSNs through non-covalent interactions such as electrostatic attraction, hydrogen bonding, van der Waals forces, and hydrophobic interactions. The high surface area and well-defined pore network of MSNs allow high drug loading capacities, particularly for small-molecule therapeutics. While physical adsorption is straightforward and does not require chemical modification of the drug, premature drug leakage may occur due to weak interactions between the drug and the silica matrix. Therefore, this method is often combined with surface functionalization or pore-capping strategies to improve drug retention [19].

4.3 | Covalent Attachment

Covalent drug loading involves the chemical conjugation of drug molecules to functional groups on the MSN surface through cleavable or non-cleavable linkers. This strategy provides enhanced drug retention and minimizes premature release during circulation. Cleavable linkers, such as disulfide bonds, ester bonds, or hydrazone linkages, enable controlled drug release in response to specific stimuli. Although covalent attachment offers excellent control over drug release kinetics, it requires chemical modification of the drug molecule, which may affect its bioactivity and necessitates careful linker design [25].

4.4 | Encapsulation and Pore Entrapment

Encapsulation strategies rely on loading drug molecules into mesopores followed by pore sealing or capping to prevent premature release. Pore capping can be achieved using nanoparticles, polymers, biomolecules, or supramolecular assemblies that block pore openings. This approach allows high loading efficiency while enabling triggered release upon removal or degradation of the pore cap.

4.5 | Controlled Release Mechanisms

Controlled drug release from MSNs can be achieved by exploiting internal physiological stimuli or applying external triggers. These mechanisms enable site-specific drug delivery and reduce systemic toxicity.

4.6 | pH-Responsive Release

pH-responsive MSNs are designed to exploit the acidic microenvironment of tumors or intracellular compartments such as endosomes and lysosomes. pH-sensitive linkers or surface coatings undergo protonation or cleavage under acidic conditions, leading to accelerated drug release. This strategy is particularly effective for cancer therapy, where tumor tissues typically exhibit lower pH compared to normal tissues.

4.7 | Redox-Responsive Release

Redox-responsive MSNs utilize disulfide bonds that are stable under extracellular conditions but cleaved in the presence of high intracellular glutathione concentrations. This mechanism enables selective drug release within cancer cells, which often exhibit elevated redox potential, thereby enhancing therapeutic efficacy and minimizing off-target effects [27].

4.8 | Enzyme-Responsive Release

Enzyme-responsive drug delivery systems exploit disease-specific enzymatic activity to trigger drug release. Surface coatings or linkers that are degradable by enzymes such as proteases, esterases, or matrix metalloproteinases allow site-specific release in pathological tissues where these enzymes are overexpressed.

4.9 | Thermo, Light, and Magnetically Triggered Release

Externally triggered release mechanisms provide spatial and temporal control over drug delivery. Thermo-responsive polymers release drugs in response to temperature changes, while photo-responsive systems utilize light to induce bond cleavage or structural changes. Magnetic field-responsive MSNs enable controlled release through localized heating or mechanical effects shown by magnetic nanoparticles incorporated into the MSN structure [28].

4.10 | Factors Influencing Drug Loading and Release

Several parameters influence drug loading efficiency and release behavior, including pore size and volume, surface functionalization, drug carrier interactions, particle size, and pore connectivity. Optimization of these parameters is essential for achieving high loading capacity, sustained release, and precise therapeutic control.

4.11 | Therapeutic Implications

The versatility of drug loading strategies and controlled release mechanisms makes MSNs highly adaptable nanocarriers for a wide range of therapeutic agents, including small-molecule drugs, proteins, nucleic acids, and combination therapies. By integrating surface functionalization with stimuli-responsive release systems, MSNs enable sophisticated drug delivery platforms capable of maximizing therapeutic efficacy while minimizing adverse effects [19].

5 | Targeting Strategies for Mesoporous Silica Nanoparticle-Based Therapeutics

Targeting strategies are a fundamental component in the design of MSN-based therapeutic systems, as they significantly enhance treatment efficacy while minimizing systemic toxicity and off-target effects. By enabling preferential accumulation at diseased sites and improving cellular and subcellular drug delivery, targeting strategies transform MSNs into highly precise and efficient nanotherapeutic platforms. These strategies can be broadly classified into passive targeting, active targeting, and advanced bioinspired or stimuli-responsive targeting approaches.

5.1 | Passive Targeting

Passive targeting relies on the unique pathophysiological characteristics of diseased tissues, particularly the EPR effect commonly observed in solid tumors and inflamed tissues. Leaky vasculature and deficient lymphatic drainage allow nanoparticles within an optimal size range (typically 50–200 nm) to preferentially accumulate at these sites. MSNs are well suited for passive targeting due to their tunable particle size, controllable surface charge, and high colloidal stability. Surface modification with hydrophilic polymers, most notably PEG, plays a critical role in enhancing passive targeting efficiency. PEGylation reduces protein adsorption, minimizes opsonization, and prolongs systemic circulation time, thereby increasing the probability of nanoparticle accumulation at target sites. PEGylated MSNs have consistently demonstrated improved pharmacokinetics and enhanced tumor accumulation in vivo [27–29].

5.2 | Active Targeting

Active targeting involves the functionalization of MSNs with specific ligands that recognize and bind to overexpressed receptors on target cells, thereby promoting receptor-mediated endocytosis and enhanced

intracellular drug delivery. This strategy provides higher specificity than passive targeting alone and is particularly effective in overcoming biological barriers at the cellular level. A wide range of targeting ligands has been explored, including antibodies and antibody fragments, peptides, aptamers, vitamins, carbohydrates, and small-molecule ligands. Folic acid is one of the most extensively studied targeting agents due to the overexpression of folate receptors in various cancer types. Transferrin and lactoferrin target transferrin receptors involved in iron uptake, while peptides such as RGD specifically bind to integrin receptors associated with tumor angiogenesis and metastasis. The effectiveness of active targeting depends strongly on ligand density, spatial orientation, and binding affinity. Covalent conjugation using stable linker chemistry is typically employed to ensure ligand stability and functionality under physiological conditions.

5.3 | Dual and Multivalent Targeting Strategies

To address tumor heterogeneity and receptor variability, dual and multivalent targeting strategies have been developed. These approaches involve the simultaneous incorporation of multiple targeting ligands or the combination of passive and active targeting mechanisms within a single MSN platform. Dual-targeted MSNs can recognize multiple receptor types or exploit complementary targeting pathways, leading to improved cellular uptake and enhanced therapeutic efficacy. Multivalent targeting, achieved through high ligand density on the MSN surface, enhances binding avidity and promotes more efficient receptor clustering and internalization [21].

5.4 | Microenvironment-Responsive Targeting

In addition to ligand-based approaches, targeting can be achieved by exploiting specific features of the disease microenvironment. Tumor tissues often exhibit acidic pH, elevated glutathione concentrations, hypoxia, and overexpression of specific enzymes. MSNs can be engineered to respond selectively to these stimuli, enabling site-specific drug release and functional activation. pH-responsive targeting takes advantage of acidic extracellular tumor environments and intracellular endo/lysosomal compartments, while redox-responsive systems utilize disulfide linkages that are cleaved in high-glutathione conditions. Enzyme-responsive MSNs are designed to release their payload in the presence of disease-associated enzymes such as matrix metalloproteinases or proteases [28].

5.5 | Biomimetic Targeting Approaches

Biomimetic targeting strategies represent an emerging and highly promising direction in MSN-based therapeutics. In these systems, MSNs are coated with cell membranes derived from red blood cells, cancer cells, immune cells, or platelets. Membrane-coated MSNs inherit the biological functions and surface proteins of the source cells, enabling immune evasion, prolonged circulation, and homotypic targeting to specific tissues. Cancer cell membrane-coated MSNs, for example, can selectively target tumors through homotypic recognition, while immune cell membrane coatings facilitate targeting of inflamed or metastatic sites.

5.6 | Intracellular and Organelle-Specific Targeting

Beyond tissue- and cell-level targeting, MSNs can be engineered for intracellular and organelle-specific delivery. Targeting moieties such as nuclear localization signals, mitochondrial targeting peptides, or lysosome-disrupting agents enable precise delivery of therapeutics to specific intracellular compartments. This approach is particularly valuable for gene therapy, apoptosis induction, and treatments requiring subcellular precision.

5.7 | Impact on Therapeutic Efficacy

The integration of advanced targeting strategies significantly influences the biodistribution, cellular uptake pathways, intracellular trafficking, and overall therapeutic performance of MSN-based drug delivery systems. By combining passive accumulation, ligand-mediated recognition, and stimuli-responsive activation, MSNs can achieve highly selective and efficient therapeutic outcomes with reduced systemic side effects [30].

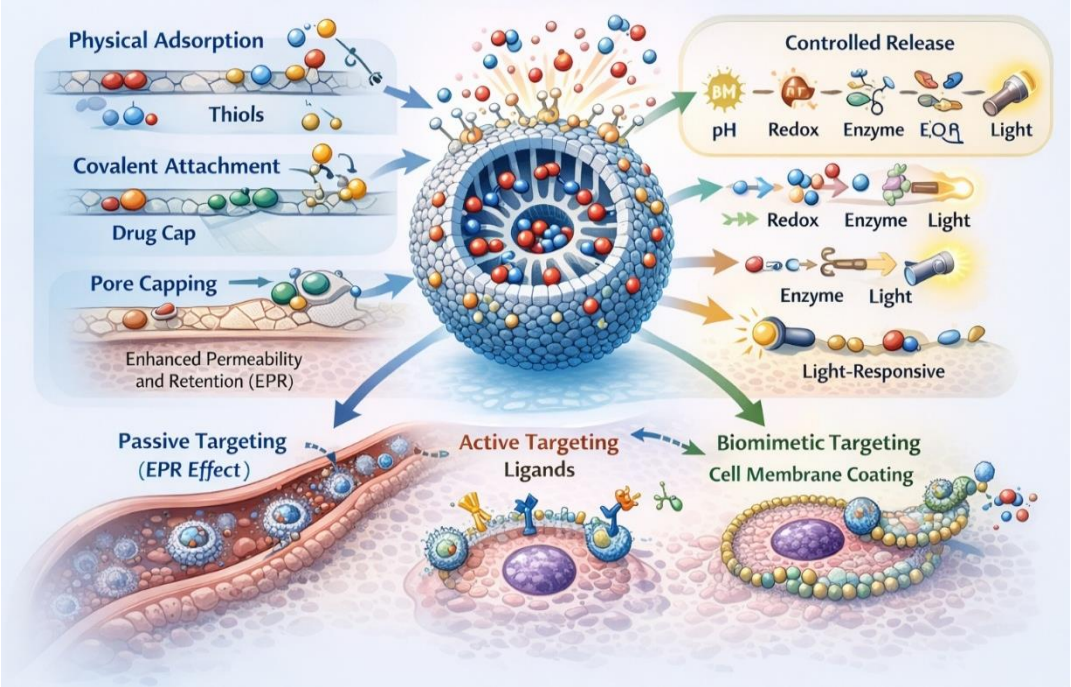

Fig. 2. Drug loading, stimuli-responsive release, and targeting strategies of MSN-based therapeutic systems.

6 | Conclusion

MSNs have emerged as highly versatile and robust nanoplatforms for controlled and targeted therapeutic applications. Their unique structural features including tunable pore size, high surface area, adjustable particle morphology, and rich surface chemistry provide unparalleled opportunities for drug encapsulation, functionalization, and stimuli-responsive release. As reviewed in this article, advances in MSN synthesis, surface engineering, drug loading strategies, and targeting approaches have collectively contributed to the development of sophisticated nanotherapeutics capable of overcoming many limitations of conventional drug delivery systems. Despite these significant achievements, several challenges remain before MSNs can be fully translated into clinical applications. Biocompatibility, biodistribution, long-term toxicity, and immune clearance are critical considerations that require systematic in vivo evaluation. Surface functionalization and PEGylation have proven effective in mitigating immune recognition, yet comprehensive studies on chronic administration and organ accumulation are still needed. Furthermore, scalable and reproducible synthesis methods that preserve the uniformity of pore structure, particle size, and functionalization are essential for regulatory approval and industrial production. Future research on MSN-based therapeutics is expected to concentrate on several critical aspects aimed at enhancing their clinical potential and therapeutic performance. One major direction involves the development of multifunctional and stimuli-responsive platforms that integrate multiple capabilities, such as dual or multimodal targeting, combination therapy, and controlled release triggered by pH, redox potential, enzymes, temperature, or light. Such sophisticated designs allow MSNs to adapt dynamically to the complex microenvironments of diseased tissues, thereby maximizing precision and therapeutic efficacy [25–30].

Another promising area focuses on biomimetic and smart targeting strategies. By employing cell membrane coatings, organelle-specific targeting, and microenvironment-responsive release mechanisms, MSNs can achieve unparalleled specificity and efficiency, ensuring selective accumulation at disease sites while minimizing off-target effects. These approaches not only improve targeting precision but also enhance biocompatibility and circulation time, moving MSN-based systems closer to clinical relevance. The integration of combination therapies and theranostic functionalities is also anticipated to expand in future research. MSNs have the inherent capacity to co-deliver multiple therapeutic agents, including small molecules, nucleic acids, and proteins, and can incorporate diagnostic or imaging agents to enable real-time monitoring of therapeutic

responses. This convergence of therapy and diagnostics offers the possibility of synergistic treatment outcomes while providing critical feedback on drug release and therapeutic efficacy. Finally, translating MSN-based therapeutics from preclinical research to clinical application requires addressing pharmacokinetics, immunogenicity, long-term toxicity, and large-scale manufacturing challenges. Standardized characterization protocols and adherence to regulatory frameworks are essential to ensure reproducibility, safety, and scalability, which are crucial for successful commercialization and clinical adoption [24], [27].

In conclusion, MSNs have established themselves as a transformative platform in nanomedicine, offering precise control over drug delivery, targeting, and release. Continuous advances in synthesis, surface functionalization, targeting strategies, and translational research are likely to unlock their full potential, paving the way for the next generation of personalized, safe, and highly effective therapeutic systems. The synergy between material science, nanotechnology, and biomedical research will ultimately enable routine clinical application of MSNs, contributing significantly to the advancement of precision medicine.

Authors' Contributions

The author solely conducted the research and prepared the manuscript and has approved its final version.

Data Availability

The data are available from the corresponding author upon reasonable request.

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Conflict of Interest

There are no competing interests to declare.

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