



A review on mesoporous silica nanoparticles:” Based on comprehensive synthesis and recent advances”

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Abstract

Mesoporous silica nanoparticles (MSNs) have emerged as versatile nanomaterials with considerable potential in pharmaceutical and biomedical applications because of their highly tunable pore architecture, large specific surface area, accessible surface chemistry, and adaptable particle morphology. Since the development of ordered mesoporous silica materials, particularly MCM-41, considerable progress has been made in controlling particle size, pore diameter, morphology, surface functionality, drug loading, and release behaviour. This review provides a comprehensive overview of the synthesis and recent advances in MSN-based nanomedicine. It discusses the historical development and structural characteristics of MSNs, classification of different MSN architectures, mesopore formation mechanisms, conventional sol-gel and surfactant-templated synthesis, and advanced, emerging, and green synthesis strategies. Particular attention is given to the control of particle size, morphology, pore structure, and surface chemistry because these characteristics strongly influence drug loading, cellular interactions, biodistribution, degradation, and therapeutic performance. The review also examines drug encapsulation and release mechanisms, targeted and stimuli-responsive delivery, and applications in cancer therapy, gene and nucleic-acid delivery, antimicrobial therapy, imaging, biosensing, and theranostics. Recent developments involving multifunctional, biodegradable, responsive, and combination-delivery systems are highlighted. Despite substantial progress, challenges related to reproducible manufacturing, scale-up, long-term toxicity, biodistribution, biodegradation, pharmacokinetics, and regulatory characterization remain important barriers to clinical translation. Future development will require integration of materials science, pharmaceutical technology, toxicology, manufacturing science, and data-driven approaches to establish predictable structure-property-biological performance relationships. Overall, MSNs represent a flexible platform for advanced drug delivery, but their successful translation requires simultaneous optimization of functionality, safety, reproducibility, and manufacturability.

Keywords: Mesoporous silica nanoparticles (MSNS), sol-gel synthesis, cancer therapy, theranostics, targeted drug delivery

Introduction

Mesoporous Silica Nanoparticles

Mesoporous silica nanoparticles (MSNs) are nanoscale silica-based materials containing an organized network of mesopores. Their central pharmaceutical value comes from the combination of a high internal surface area, adjustable pore dimensions, relatively rigid silica frameworks, and chemically accessible surfaces. Unlike a conventional nonporous particle, an MSN can accommodate a therapeutic molecule inside its pore system while the outer surface can be engineered for dispersion, targeting, protection, or controlled release. This makes the material a platform rather than a single formulation. The concept of using ordered mesoporous silica as a drug carrier emerged soon after the development of ordered mesoporous molecular sieves, with MCM-41 becoming a landmark example for pharmaceutical loading [1].

The usefulness of MSNs is closely connected with their ability to address formulation problems. Hydrophobic drugs may show poor aqueous dissolution, unstable crystalline forms, or inadequate exposure after administration. Confinement inside mesopores can reduce molecular

aggregation and may stabilize an amorphous or molecularly dispersed state. At the same time, the hydrophilic silica interface promotes wetting when the loaded material contacts aqueous media. These features can influence dissolution and apparent bioavailability, although the final performance depends on drug properties, pore size, surface chemistry, loading method, and dosage-form design. Early pharmaceutical work merely as an adsorbent [2].

The current concept of an MSN extends beyond passive drug storage. Surface groups can be introduced to alter charge, hydrophilicity, ligand recognition, degradation, or interactions with biomolecules. MSNs can also be combined with polymers, magnetic components, fluorescent probes, photosensitizers, nucleic acids, and biological ligands. Such combinations support applications in targeted delivery, imaging, biosensing, gene delivery, and theranostics. Nevertheless, multifunctionality must be balanced against manufacturing complexity, reproducibility, biological safety, and clearance. Thus, the rational design of an MSN requires simultaneous consideration of materials science and pharmaceutical performance [3].

Historical Evolution and Development of MSNs

The modern history of mesoporous silica is rooted in the development of ordered molecular-sieve materials. In the early 1990s, researchers demonstrated that surfactant assemblies could direct the formation of silica with regularly arranged mesopores. The landmark M41S family, including MCM-41, established that pore ordering could be controlled by the interaction between inorganic silica species and organic structure-directing assemblies. This discovery initially stimulated work in catalysis, adsorption, separation, and molecular transport because the materials combined accessible pores with comparatively high surface area [4].

The next stage involved broadening the range of pore geometries and silica architectures. Researchers developed materials with three-dimensional interconnected networks, larger mesopores, thicker walls, and different degrees of structural order. SBA-type materials, especially SBA-15, became important because their larger pore dimensions and robust walls were attractive for accommodating larger molecules and studying controlled adsorption. These advances established general principles linking surfactant chemistry, silica condensation, solvent composition, acidity, and aging conditions with final pore architecture [5].

A major transition occurred when ordered mesoporous materials were deliberately adapted to biomedical delivery. The demonstration that an MCM-41-type material could load and release a pharmaceutical compound provided a conceptual bridge between porous materials chemistry and pharmaceuticals. Subsequent studies moved from microscale porous solids toward nanoparticles with controlled dimensions and dispersibility. This nanoscale transition increased interest in cellular uptake, biodistribution, intracellular delivery, and targeting. Contemporary MSNs therefore represent the cumulative development of ordered mesoporous chemistry, nanoscale particle engineering, and pharmaceutical formulation science [6].

Structural Characteristics and Physicochemical Properties of MSNs

An MSN generally contains a silica network surrounding channels or cavities with dimensions in the mesoporous range. Depending on synthesis conditions, the pore arrangement may be hexagonal, cubic, radial, dendritic, or partially disordered. The pore system contributes a large internal interface where drug molecules, proteins, dyes, or other cargos can be accommodated. Important measurable characteristics include particle diameter, pore diameter, pore volume, specific surface area, wall thickness, morphology, surface charge, and degree of structural order. These parameters are not independent; changing one synthesis variable may influence several properties simultaneously [7]. Particle size is particularly important for pharmaceutical behavior because it can affect colloidal stability, cellular interaction, tissue distribution, and clearance. Pore diameter determines which molecules can enter the internal network

and how rapidly they can diffuse out. Larger pores may be advantageous for macromolecules, while smaller pores can provide stronger confinement for many small-molecule drugs. The silica surface contains silanol groups that can be used as chemical anchors. Amines, carboxyls, thiols, phosphonates, polymers, peptides, and other groups can therefore be introduced to change surface charge and drug affinity [8].

The structural advantages of MSNs should not be interpreted as automatically producing biological safety or therapeutic superiority. High surface area can improve loading but can also increase interactions with proteins and cell membranes. Surface charge may improve cellular association while simultaneously increasing nonspecific interactions or toxicity. Particle aggregation can change the effective size seen by biological systems. Consequently, characterization should connect physical properties with biological behavior rather than treating surface area or pore volume as isolated quality attributes [9].

Classification and Types of Mesoporous Silica Nanoparticles

MSNs can be classified according to pore organization, particle architecture, composition, and functional design. Ordered MCM-41 is associated with a hexagonal arrangement of cylindrical pores, whereas MCM-48 contains a three-dimensional interconnected cubic network. SBA-15 is notable for comparatively large mesopores and thicker silica walls. These classical materials provide useful reference structures for understanding how pore geometry affects loading, diffusion, and mechanical stability. The selection of a structure should be based on the intended cargo and route of administration rather than on structural order alone [10].

Hollow and core-shell architectures introduce an additional internal compartment. Hollow MSNs contain a central void surrounded by a porous silica shell, allowing separation of the cargo environment from the external medium and creating opportunities for high loading. Core-shell particles can combine a silica shell with magnetic, metallic, polymeric, or other cores. The core can contribute imaging, magnetic manipulation, photothermal conversion, or another function, while the silica shell provides a chemically modifiable porous interface [11].

Dendritic and radial MSNs are characterized by branched pore pathways that can provide high accessibility and large pore volumes. Biodegradable MSNs are designed so that the silica framework or its functional connections can break down under physiological conditions. Stimuli-responsive MSNs incorporate gates, linkers, coatings, or caps that react to pH, redox conditions, enzymes, light, temperature, magnetic fields, or combinations of stimuli. This classification is therefore increasingly functional: the architecture is selected according to the desired loading, release, targeting, imaging, or degradation behaviour [12].

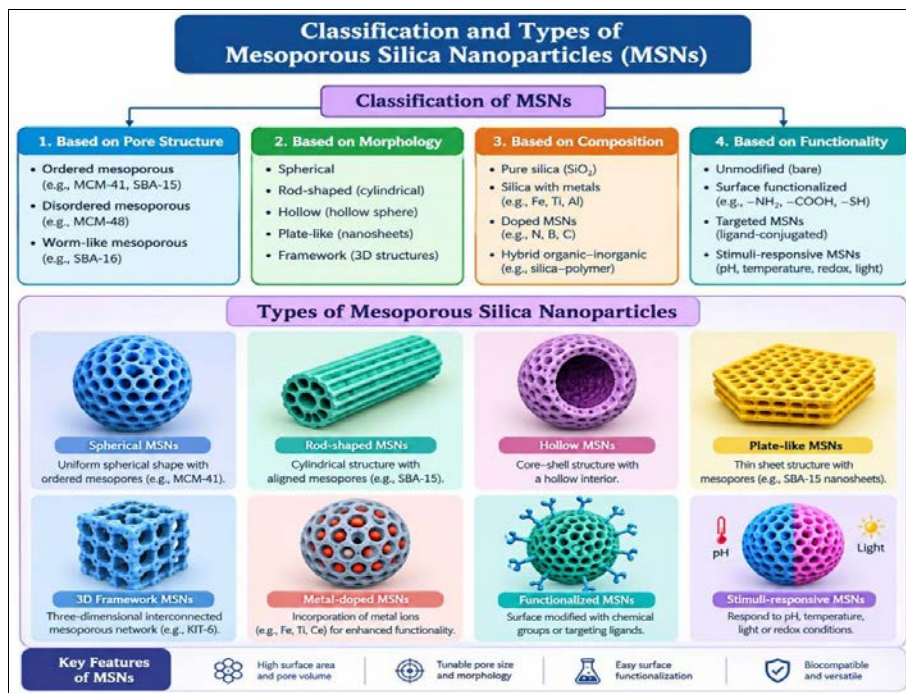


Fig 1: Classification and Types of (MSNs)

Mesopore Formation and Self-Assembly Mechanisms

The formation of ordered mesopores is commonly described through cooperative interactions between silica precursors and structure-directing agents. Surfactant molecules can assemble into micelles or other supramolecular structures once their concentration and solution conditions permit aggregation. Hydrolyzed silica species interact with these assemblies and condense around or between them. Subsequent removal of the organic template leaves a pore system that reflects the dimensions and organization of the original template. The process is dynamic rather than a simple one-step molding event, because silica condensation and surfactant organization occur together and influence each other [13].

Electrostatic interactions, hydrogen bonding, hydrophobic effects, and solvent-mediated interactions can all contribute to self-assembly. pH is especially important because it changes the ionization state of silica species and influences

hydrolysis and condensation rates. Surfactant concentration, silica precursor concentration, temperature, solvent composition, ionic strength, additives, and aging time can alter nucleation, particle growth, pore diameter, wall thickness, and morphology. Small changes in reaction conditions can therefore produce substantial differences in the final nanoparticle population [14].

Template removal is the final step required to expose the pore network. Calcination is effective for removing many organic templates, but the heat treatment can destroy temperature-sensitive surface groups or incorporated molecules. Solvent extraction is gentler and may preserve organic functionality, although residual template and extraction efficiency must be carefully controlled. A reproducible MSN process therefore requires control over both self-assembly and post-synthesis treatment. Modern studies increasingly combine mechanistic understanding with process monitoring to improve batch consistency [15].

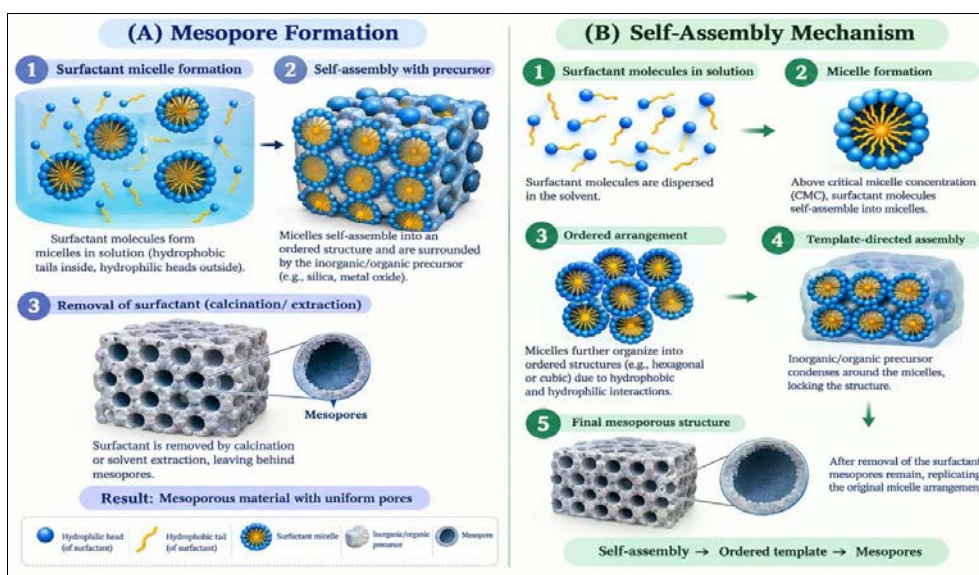


Fig 2: Mesopore Formation and Self Assembly Mechanism

Materials and Precursors Used in MSN Synthesis

Tetraethyl orthosilicate (TEOS) is a widely used silica precursor because its hydrolysis and condensation can be controlled under aqueous, alcoholic, acidic, or basic conditions. Other alkoxy silanes can be introduced when a different hydrolysis rate or organic functionality is required. Organosilane co-precursors can become incorporated into the framework or can provide reactive groups for later functionalization. The precursor system consequently affects nucleation, particle growth, framework composition, and the availability of functional sites [16].

Surfactants and block copolymers serve as structure-directing agents. Cationic surfactants such as acetyltrimethylammonium bromide have been extensively used for ordered silica with relatively small mesopores. Block copolymers can produce larger pore systems and different structural organizations. The concentration and identity of the template influence micelle dimensions and interactions with the growing silica network. The choice of template must therefore be matched with the desired pore size and final application [17].

The reaction medium commonly contains water, alcohol, bases or acids, salts, and selected additives. These components regulate precursor hydrolysis, silica condensation, micelle formation, and particle growth. Swelling agents can enlarge pores, while amines can modify the local reaction environment and influence particle dimensions. For biomedical MSNs, an additional requirement is that residual template, solvent, and by-products can be adequately removed. Pharmaceutical-quality development therefore considers not only whether a precursor produces the desired morphology but also whether the resulting process is reproducible, purifiable, and scalable [18].

Conventional Methods for the Synthesis of MSNs

Conventional MSN synthesis commonly combines sol-gel chemistry with template-directed self-assembly. A silica precursor is hydrolyzed and condensed in the presence of a structure-directing agent, followed by particle growth,

aging, and template removal. The approach is attractive because particle size, pore dimensions, and surface chemistry can be adjusted by changing the reaction variables. Batch synthesis is relatively accessible to academic laboratories, but mixing and heat transfer can become more difficult as the reaction volume increases [19].

Hydrothermal or solvothermal treatment can be applied after initial particle formation to promote further condensation and structural organization. Temperature and treatment time can influence wall thickness, pore order, and mechanical properties. Precipitation-based procedures provide another route in which changes in concentration, pH, temperature, and mixing determine nucleation and growth. These approaches can be adapted for spherical, hollow, or other morphologies, but the sensitivity of nanoparticle formation to local conditions requires careful experimental control [20]. Evaporation-induced self-assembly is useful when solvent removal itself becomes a driving force for organization. As the solvent evaporates, the relative concentration of silica and surfactant increases, allowing ordered domains to develop. This strategy has been especially useful for mesoporous films and selected highly organized materials. Across conventional routes, the major practical variables are precursor ratio, surfactant concentration, pH, temperature, aging, mixing, and template removal. Optimizing these variables together is more reliable than treating each as an isolated factor [21].

Sol-Gel and Surfactant-Templated Synthesis

The sol-gel route is based on two connected chemical processes: hydrolysis of alkoxy silane groups and condensation of silanol species. Hydrolysis converts Si-OR groups into Si-OH groups, while condensation produces Si-O-Si bonds and water or alcohol as by-products. Repeated condensation generates an inorganic silica network. When this chemistry occurs around organized surfactant assemblies, the growing network adopts a mesostructured arrangement. The balance between hydrolysis and condensation is therefore central to particle nucleation and pore formation [22].

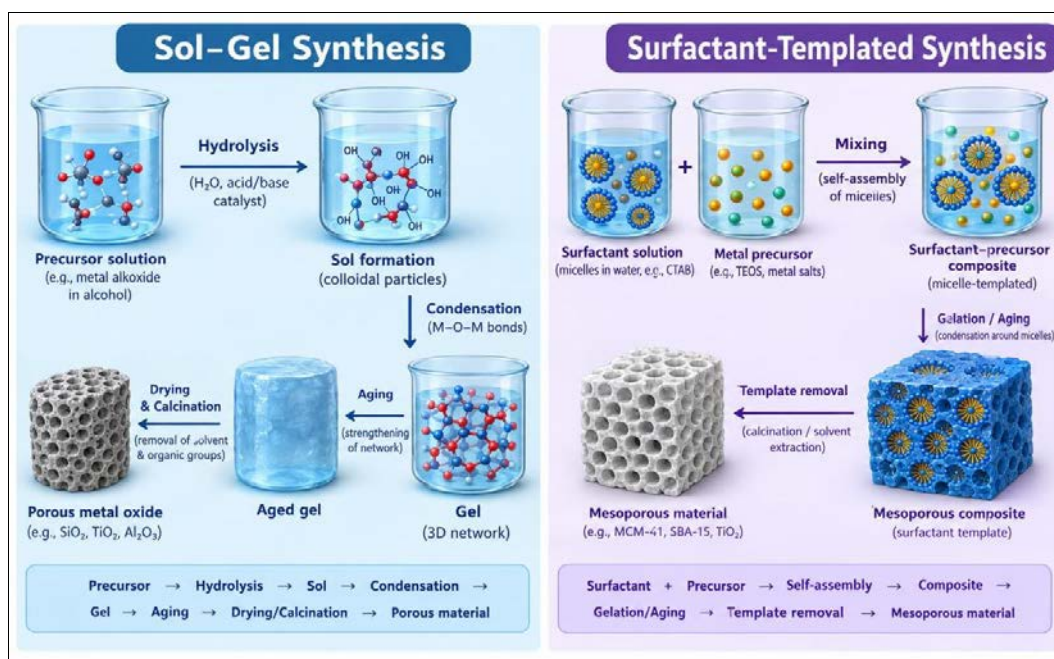


Fig 3: Sol-Gel Synthesis and Surfactant-Templated Synthesis

Surfactant templating determines the dimensions and organization of the future mesopores. Micellar aggregates act as nanoscale structure-directing environments, while silica species accumulate around them. After condensation, removal of the surfactant exposes the pore channels. The final pore diameter can be influenced by surfactant chain length, concentration, swelling additives, solvent composition, and temperature. The particle diameter and morphology are additionally affected by silica concentration, base concentration, mixing, and reaction time [23].

The pH of the reaction mixture has a particularly strong influence because silica speciation and condensation kinetics change with acidity or basicity. In basic systems, rapid condensation can support nanoparticle formation, while acidic conditions may produce different nucleation and growth behaviour. Temperature and aging influence the development of the silica framework after nucleation. The major strength of sol-gel templating is its flexibility: a controlled combination of precursor, template, additives, and reaction conditions can generate a wide range of pore structures and surface chemistries [2].

Advanced and Emerging Synthesis Strategies

Advanced synthesis strategies seek better control over mixing, nucleation, growth, morphology, and scale-up. Microfluidic systems are attractive because small reaction volumes and rapid mixing can reduce local concentration gradients. This can improve particle uniformity and provide a more reproducible relationship between reaction conditions and product properties. Continuous-flow platforms similarly offer controlled residence time and potentially improved process monitoring. Their successful translation, however, requires understanding how laboratory batch chemistry changes when mixing and heat-transfer conditions are altered [25].

Microwave-assisted synthesis can accelerate heating and reduce reaction times in selected formulations. Aerosol-assisted methods create precursor-containing droplets that act as individual reaction environments; rapid solvent evaporation can then produce particles with distinctive morphologies. Seed-mediated synthesis separates the nucleation stage from subsequent particle growth. This approach can reduce uncontrolled secondary nucleation and provide narrower particle-size distributions when carefully optimized [26].

Emerging methods should be assessed against practical pharmaceutical requirements. A method that produces a visually attractive morphology but has poor batch reproducibility, difficult purification, or uncertain residual-template levels may not be suitable for translation. Continuous manufacturing is particularly promising because process variables can be monitored in real time, but scale-up still involves challenges in precursor residence time, mixing, heat transfer, and downstream isolation. Advanced synthesis therefore represents a shift from simply making nanoparticles toward designing a controllable manufacturing process [27].

Green and Sustainable Approaches for MSN Synthesis

Green synthesis of MSNs aims to reduce environmental burden without sacrificing structural quality or pharmaceutical performance. Conventional synthesis can involve surfactants, organic solvents, high temperatures,

multiple washing steps, and energy-intensive template removal. A more sustainable process may reduce hazardous solvent use, lower reaction temperature, shorten processing time, recover templates, or replace selected reagents with safer alternatives. However, a process should not be considered green merely because one ingredient is renewable; solvent consumption, energy, purification, waste, and life-cycle impacts also need to be considered [28]. Water-based and solvent-minimized strategies are especially relevant for pharmaceutical materials. Safer reaction media can reduce volatile-organic-compound emissions and simplify handling. Biological molecules and naturally derived compounds have also been explored as additives or structure-directing components because they provide multiple functional groups capable of interacting with silica species. Such approaches may generate hierarchical structures while reducing reliance on conventional synthetic additives. Their limitations include variability of biological materials and the need for strict control of composition [29]. Sustainability must be integrated with product quality. For MSNs intended for biomedical use, the process still needs predictable particle size, pore structure, surface chemistry, purity, sterility where applicable, and degradation behaviour. Template recovery and solvent recycling may become increasingly important during scale-up. Life-cycle thinking also encourages comparison of energy requirements, raw-material sourcing, water use, waste treatment, and downstream processing. The long-term objective is therefore a synthesis platform that is environmentally responsible while remaining reproducible and compatible with pharmaceutical manufacturing [30].

Control of Particle Size, Morphology, Pore Size, and Surface Area

Particle size is one of the most important design variables in MSN development. It can influence colloidal stability, protein adsorption, cellular uptake, tissue distribution, and clearance. Size is controlled through precursor concentration, surfactant concentration, pH, temperature, solvent composition, ionic strength, additives, and mixing conditions. Because several variables can act simultaneously, optimization should focus on reproducible size distributions rather than only the mean diameter [31].

Pore diameter and pore volume determine how easily a cargo can enter, occupy, and leave the internal network. For small-molecule drugs, conventional mesopores may provide sufficient accessibility and strong surface interactions. Proteins, nucleic acids, and other macromolecules generally require larger pores or specially designed dendritic structures. Pore size also affects release kinetics: when diffusion is restricted by narrow channels, release may become slower, whereas large accessible pores can facilitate faster transport [32].

Morphology provides another level of control. Spherical particles, rods, hollow particles, and dendritic structures can exhibit different cellular interactions and transport through biological barriers. Surface area is valuable for loading, but maximizing surface area is not necessarily equivalent to maximizing therapeutic performance. Very high porosity can influence framework stability and degradation. Rational MSN design therefore seeks a balanced combination of particle size, shape, pore structure, loading capacity, release behaviour, degradation, and safety rather than optimizing a single parameter in isolation [33].

Surface Functionalization and Chemical Modification of MSNs

Silica surfaces contain reactive silanol groups that make chemical modification relatively accessible. Functionalization can be performed during particle formation by co-condensation or after synthesis by post-synthetic grafting. Common groups include amines, carboxyl, thiols, phosphonates, polyethylene glycol chains, peptides, carbohydrates, and targeting ligands. The location of modification is important because functional groups may be introduced on the external surface, inside the pores, or both. Spatial control can therefore separate loading functions from biological targeting functions^[34].

Surface chemistry changes drug-carrier interactions. Cationic groups can associate with anionic cargos such as nucleic acids, while hydrophobic groups can increase affinity for poorly water-soluble compounds. Hydrogen bonding and electrostatic interactions can slow release, whereas hydrophilic coatings can improve dispersion in aqueous media. Polyethylene glycol and related coatings are often used to reduce nonspecific interactions and improve colloidal behaviour, although dense coatings may also reduce cell association or pore accessibility^[35].

Targeting ligands such as folic acid, peptides, antibodies, carbohydrates, and hyaluronic acid can be attached to the surface to promote receptor-mediated interactions. The ligand density, orientation, accessibility, receptor expression, and particle characteristics all influence the outcome. Excessive functionalization can decrease pore volume, change surface charge, or destabilize the particle. Therefore, surface engineering should be accompanied by measurements of grafting density, particle size, zeta potential, surface area, pore volume, and release behaviour^[36].

Drug Loading and Encapsulation Strategies

Drug loading into MSNs may occur through adsorption, pore filling, hydrophobic interactions, hydrogen bonding, electrostatic attraction, or covalent attachment. The porous structure provides a large interface for drug-carrier contact, and confinement can help disperse drug molecules throughout the pore network. For poorly soluble compounds, this can reduce crystallinity or molecular aggregation and may increase apparent dissolution. The loading method should be selected according to the drug's polarity, molecular size, ionization state, solubility, and chemical stability^[37].

Passive loading is commonly performed by exposing empty MSNs to a drug solution followed by solvent removal. The drug diffuses into accessible pores and interacts with the silica surface. Pore diameter and surface chemistry influence both loading capacity and the fraction of drug located near pore entrances. Functionalized surfaces can improve loading of charged compounds through electrostatic interactions, while hydrophobic modifications may increase affinity for lipophilic drugs. The amount loaded should be quantified together with loading efficiency and recovery because high nominal drug input does not necessarily indicate high incorporation^[38].

Covalent attachment can provide stronger retention and may reduce premature leakage, but it introduces the additional requirement of a chemically cleavable linkage. Co-former or co-amorphous strategies represent another emerging option for poorly soluble drugs because the drug can be stabilized

in a less crystalline state while the mesoporous carrier provides confinement. These approaches highlight an important formulation principle: MSN loading should be designed together with the intended release mechanism and dosage form rather than considered as a separate preliminary step^[39].

Drug Release Mechanisms from MSNs

Drug release from MSNs can occur by diffusion, desorption, dissolution of the silica framework, cleavage of a covalent or supramolecular linkage, or a combination of mechanisms. In a simple diffusion-controlled system, drug molecules move from the internal pore environment toward the external release medium. The rate is influenced by pore diameter, tortuosity, surface chemistry, drug solubility, loading distribution, and interactions with the silica wall. Release testing should therefore be interpreted together with the physical characteristics of the carrier^[40].

Surface modification can deliberately slow or accelerate release. Strong ionic interactions between a drug and a functionalized silica surface may reduce mobility, whereas hydrophilic environments may improve wetting and transport. Pore size is also important because small channels can restrict diffusion. Hollow structures and multilayer coatings can create additional diffusion barriers. When a drug is covalently attached, release depends on cleavage of the linker, so the chemistry of the bond becomes a critical design parameter^[41].

Stimuli-responsive release introduces a gate or switch that changes under a selected condition. Acid-sensitive groups can open in acidic environments; disulfide-containing systems can respond to reducing conditions; enzyme-cleavable caps can react to disease-associated enzymes; and externally triggered systems may use light, temperature, magnetic fields, or ultrasound. The desired profile depends on therapy: an immediate release, sustained release, or triggered pulse can each be appropriate in different circumstances. Consequently, release kinetics should be engineered from the therapeutic objective backward^[42].

Targeted and Stimuli-Responsive Drug Delivery

Targeted MSNs attempt to increase the probability that a carrier interacts with a desired cell or tissue while reducing nonspecific exposure. Targeting can be passive, based on physicochemical behaviour and tissue characteristics, or active, using ligands that recognize receptors. Active ligands include antibodies, peptides, carbohydrates, aptamers, and small molecules. Their effectiveness depends on ligand density, receptor abundance, particle size, protein corona formation, tissue penetration, and the biological barriers encountered after administration^[43].

Stimuli-responsive systems add a second layer of control by linking release to a biological or externally applied trigger. Endogenous triggers include acidic pH, glutathione-rich reducing environments, reactive oxygen species, enzymes, ATP, or disease-associated biochemical conditions. Exogenous triggers include light, magnetic fields, temperature, and ultrasound. A gatekeeper may remain associated with the pore opening until the trigger changes its structure or breaks a chemical connection. This can reduce premature leakage during circulation and promote release after localization^[44].

Dual- or multi-responsive systems are increasingly explored because biological environments are heterogeneous. For

example, a carrier may combine pH sensitivity with receptor targeting, or redox sensitivity with a targeting ligand. The design challenge is to ensure that each component remains functional without creating excessive complexity. Recent work emphasizes that smart delivery systems should be evaluated not only for release in simplified laboratory media but also for stability, targeting specificity, penetration, and therapeutic performance in realistic biological environments [45].

MSNs for Cancer Therapy

Cancer therapy is one of the most extensively studied applications of MSNs because the platform can combine high drug loading with surface engineering and controlled release. Conventional anticancer agents can be incorporated into pores, while surface ligands or protective coatings can be added to alter distribution and cellular uptake. This architecture is particularly attractive for drugs that suffer from poor solubility, rapid degradation, nonspecific distribution, or dose-limiting toxicity. However, MSN performance in cancer models depends strongly on the tumour type and the biological barriers encountered [46].

Passive accumulation through abnormal tumour vasculature has been widely investigated, while active targeting uses ligands that recognize receptors on tumour cells or associated stromal cells. Folic acid, mannose, antibodies, hyaluronic acid, and other ligands have been studied. Targeting is not guaranteed simply by attaching a ligand: receptor heterogeneity, protein corona formation, vascular transport, tumour penetration, and endocytosis can limit the effect. Therefore, active targeting should be demonstrated with appropriate receptor-positive and receptor-negative controls [47].

MSNs can also support combination therapy. A single platform may carry two therapeutic agents, or combine chemotherapy with photothermal, photodynamic, imaging, or gene-based components. Such multifunctionality can create opportunities for complementary mechanisms, but it also increases formulation and characterization requirements. Preclinical evidence should therefore distinguish between increased cellular uptake, increased cytotoxicity in vitro, tumour growth inhibition in vivo, and actual clinical benefit. These are related but not interchangeable outcomes [48].

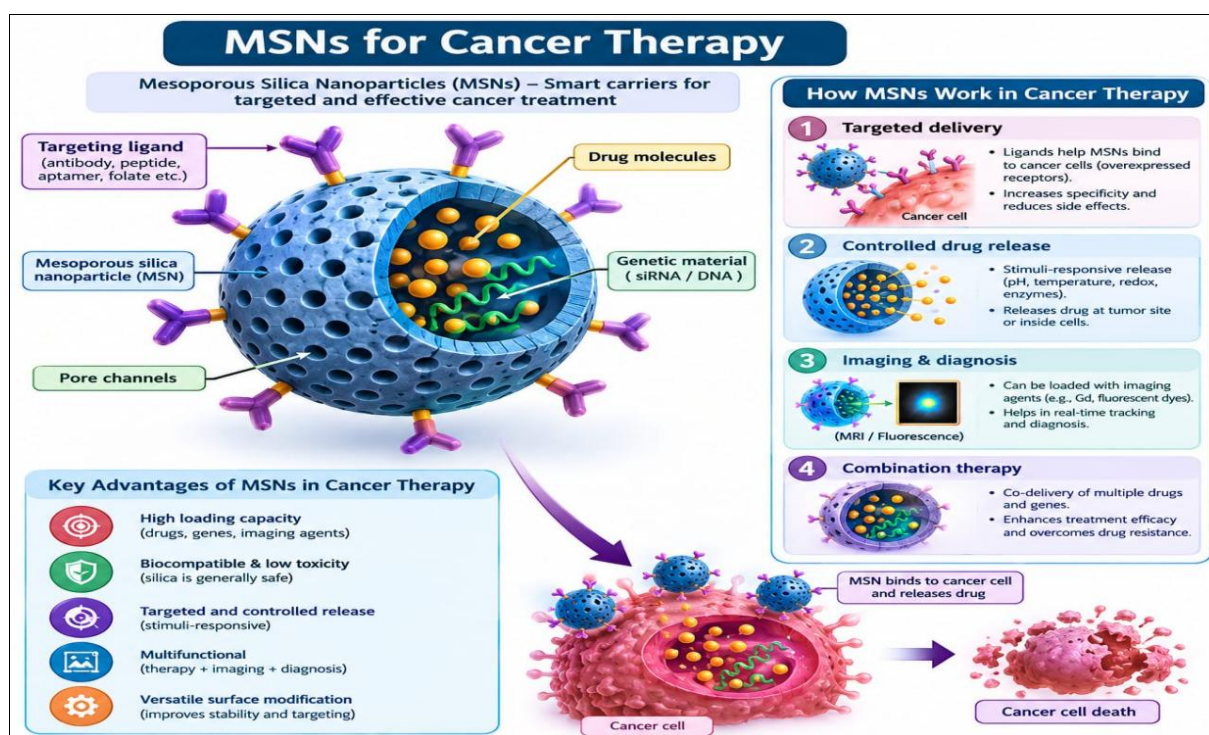


Fig 4: MSNs for Cancer Therapy

MSNs for Gene and Nucleic-Acid Delivery

MSNs have been investigated as carriers for plasmid DNA, siRNA, miRNA, mRNA, and other nucleic-acid cargos. Their pores can provide physical protection from extracellular degradation, while surface modification can promote association with negatively charged nucleic acids. Cationic groups and polymers are commonly used to improve electrostatic binding and cellular uptake. However, overly strong binding can make intracellular release difficult, so an effective carrier must balance extracellular protection with efficient cargo liberation [49].

Endosomal entrapment is a major biological barrier. After internalization, nanoparticles may remain within endosomes and lysosomes rather than reaching the cytosol. Strategies

such as protonatable polymers, membrane-active peptides, pH-responsive coatings, and carefully designed surface charge have therefore been explored to facilitate endosomal escape. Large-pore MSNs can additionally improve physical accommodation of nucleic acids inside the pore network. The carrier architecture must be selected according to the size and structure of the nucleic acid rather than applying a single pore design to all cargos [50].

Co-delivery is another important opportunity. MSNs can be engineered to carry a small-molecule drug together with siRNA or another nucleic acid, allowing complementary mechanisms to be addressed in the same cell. This has been explored for multidrug-resistant tumors and other settings where gene modulation can alter drug sensitivity. Nevertheless, transfection efficiency, inflammatory

responses, cytotoxicity of cationic components, intracellular trafficking, and long-term safety remain important considerations. Translation therefore requires rigorous comparison with established nonviral delivery systems ^[51].

MSNs for Antimicrobial and Other Therapeutic Applications

MSNs can deliver antimicrobial compounds by providing a porous reservoir with controlled release. Antibiotics, antifungal agents, antiseptics, and other active substances can be incorporated, while surface chemistry can be modified to influence interactions with microbial cells. Controlled local release may be useful when prolonged exposure at a wound or implant surface is desired. The antimicrobial effect depends on the released compound as well as nanoparticle size, charge, pore structure, and the surrounding biological environment ^[52].

Beyond drug carriage, MSNs can be combined with antimicrobial components such as metals or other active materials. These hybrid systems can provide more than one mechanism, although the addition of a second active component also changes toxicity, stability, and regulatory considerations. For wound care, the ability to combine local delivery with tissue-compatible materials is particularly relevant. Recent work has examined MSN-based formulations for wound healing, tissue adhesion, controlled drug delivery, and approaches that may support local antimicrobial management ^[53].

Other therapeutic applications include anti-inflammatory delivery, regenerative medicine, tissue engineering, and bone-related systems. The porous structure can accommodate bioactive molecules and can be integrated with polymeric or mineral matrices. For tissue applications, degradation rate and interfacial behaviour become especially important because the carrier must perform its function without producing an undesirable persistent residue. These applications illustrate that MSN technology is not restricted to cancer or conventional drug delivery ^[54].

MSNs for Imaging, Biosensing, and Theranostics

The pore system of MSNs can accommodate imaging molecules such as fluorescent dyes and can be combined with magnetic, radioactive, or photoactive components. Encapsulation may protect sensitive imaging agents from environmental degradation and can reduce their direct interaction with biological components. The outer surface can simultaneously be modified with hydrophilic coatings or targeting ligands, creating particles that combine imaging and delivery functions ^[55].

Fluorescent MSNs are useful for tracking cellular uptake and intracellular localization in experimental systems. Magnetic core-shell designs can add magnetic resonance imaging or magnetic manipulation, while gold-containing structures can support photothermal functions. Up-conversion components and other optical materials have also been combined with mesoporous silica to create multimodal platforms. The major advantage of these architectures is integration: a single particle can potentially carry a therapeutic payload while reporting its location or responding to an external stimulus ^[56].

Biosensing uses the large surface area and chemically addressable interface of MSNs to immobilize recognition molecules. A target-binding event can be linked to a measurable signal or to opening of a pore gate. This creates

an opportunity for Theranostics in which diagnosis, monitoring, and treatment are integrated. However, practical translation requires reproducible signal generation, appropriate specificity, stability in biological fluids, and validated relationships between the measured signal and the biological state ^[57].

Biocompatibility, Toxicity, Biodistribution, and Biodegradation

Biological safety is a central requirement for MSN-based nanomedicine. Toxicity can be affected by particle size, concentration, morphology, surface charge, functional groups, aggregation, administration route, and degradation rate. In vitro cytotoxicity alone is insufficient to define safety because a material may behave differently after protein adsorption, systemic distribution, or repeated exposure. Appropriate evaluation should therefore connect physicochemical properties with cellular, tissue, and whole-animal responses ^[58].

After administration, MSNs interact with proteins and biological membranes and may acquire a protein corona that changes their effective biological identity. This can influence circulation, uptake by the mononuclear phagocyte system, tissue distribution, and clearance. Size and surface modification affect whether particles remain in circulation or are preferentially taken up by organs such as the liver and spleen. Repeated dosing is particularly important because a low single-dose response does not establish the absence of cumulative effects ^[59].

Biodegradation is another key translational parameter. Silica frameworks can dissolve under physiological conditions, but the rate depends on pore architecture, particle dimensions, surface chemistry, and the surrounding environment. Toxicological studies should consider inflammation, oxidative stress, blood compatibility, immune responses, organ accumulation, and clearance. Recent reviews emphasize that clinical translation requires a systematic evidence base covering biodistribution, biodegradation, and long-term safety rather than relying on isolated short-term assays ^[60].

Recent Advances in MSN-Based Nanomedicine

Recent MSN research increasingly emphasizes multifunctionality, biological responsiveness, and more predictable degradation. Modern platforms may combine drug delivery with imaging, targeting, gene modulation, phototherapy, or immunological functions. The objective is shifting from simply increasing loading capacity toward controlling where, when, and under what biological conditions the cargo becomes available. Such designs require integration of materials chemistry, pharmaceutical formulation, cell biology, and quantitative characterization. Recent work has also expanded the role of MSNs in immunotherapy and tissue repair. Immunotherapy-oriented systems explore the ability of engineered nanoparticles to deliver immune-active cargos while providing targeting or controlled release. Wound-healing research has investigated MSNs as local carriers, tissue-interface materials, and components of formulations designed for controlled delivery. Drug Coformer approaches are another recent formulation direction, using Co-amorphous or related systems together with mesoporous silica to stabilize poorly soluble drugs and improve dissolution behaviour.

The newest perspective is increasingly translational. Recent comprehensive reviews emphasize surface engineering, theranostic integration, antibacterial and vaccine-related applications, and the need to connect laboratory design with manufacturing scalability and long-term biological compatibility.

Artificial intelligence and data-driven optimization may also help identify relationships between synthesis conditions, nanoparticle properties, and biological outcomes. The challenge is to convert this increasing design flexibility into reproducible products with clearly defined quality attributes [61, 65].

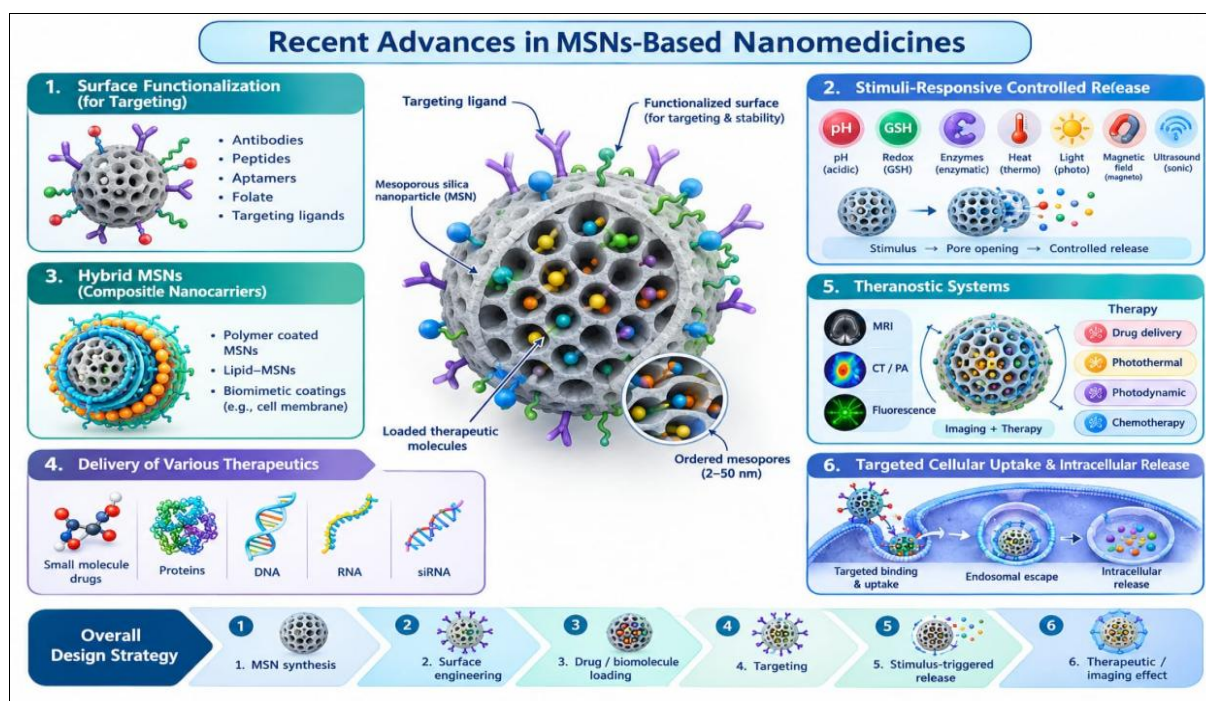


Fig 5: Recent Advances in MSNs-Based Nanomedicines

Challenges in Clinical Translation, Scale-Up, and Regulatory Considerations

The movement of MSNs from laboratory research to clinical products is limited by the need for reproducible manufacturing and well-defined biological performance. Small changes in mixing, precursor concentration, surfactant concentration, temperature, or aging can alter particle size and pore structure. At larger scale, heat transfer and mixing patterns change, potentially creating batch-to-batch differences. A scalable process therefore needs defined critical process parameters and analytical methods capable of detecting meaningful changes in product quality [66].

Regulatory characterization must address both the therapeutic cargo and the nanocarrier. Relevant attributes may include particle-size distribution, morphology, pore structure, surface chemistry, residual template or solvent, purity, drug loading, release kinetics, stability, sterility where appropriate, and degradation behaviour. For functionalized systems, the identity and quantity of surface ligands or polymers can also become critical quality attributes. These requirements are more complex than those for a conventional small-molecule dosage form because the carrier itself can influence pharmacokinetics and safety [67]. Clinical translation is also constrained by incomplete knowledge of long-term exposure. Biodistribution, chronic toxicity, immune interactions, clearance, and degradation products must be understood for the intended route and dosing schedule. Standardized reporting would make studies easier to compare by requiring consistent descriptions of particle size, pore characteristics, surface chemistry, loading efficiency, release conditions, biological models, and

experimental dose. The practical goal is not simply to demonstrate that an MSN works in a model, but to establish a reproducible product profile that can be manufactured and controlled [68].

Future Perspectives and Research Opportunities

Future MSN development is likely to focus on biodegradable and biologically predictable architectures. A useful biodegradable MSN should retain sufficient pore volume and structural integrity during the delivery phase but subsequently undergo controlled breakdown and clearance. Achieving this balance may involve thinner silica walls, chemically labile frameworks, degradable linkers, or hybrid compositions. The degradation rate must be matched with the intended therapeutic window rather than maximized without regard to function.

Precision nanomedicine provides another research direction. Targeting ligands, molecular biomarkers, responsive release systems, and imaging can be integrated to create more individualized delivery platforms. However, increasingly complex particles may also increase manufacturing variability and regulatory burden. Future research should therefore prioritize modular designs in which each functional component has a clearly defined purpose and measurable quality attribute. Predictive computational tools may support formulation screening, synthesis optimization, and analysis of structure property performance relationships. Sustainable production is also expected to become more important. Water-based processing, safer solvents, lower-energy synthesis, continuous manufacturing, template recovery, and efficient downstream purification can reduce environmental impact. Standardized experimental reporting

will be equally important because reproducibility is a prerequisite for meaningful comparison between laboratories. The strongest future opportunities are therefore likely to come from integrating advanced materials design with manufacturing science, toxicology, pharmacokinetics, and clinical development rather than treating each discipline separately [69-70].

Conclusion

Mesoporous silica nanoparticles have evolved from ordered porous materials developed for adsorption and catalysis into versatile platforms for pharmaceutical and biomedical research. Their high internal surface area, adjustable pore architecture, accessible silanol chemistry, and adaptable particle morphology permit substantial control over loading and release. These features have supported applications involving poorly soluble drugs, anticancer agents, nucleic acids, imaging molecules, antimicrobial compounds, and multifunctional theranostic systems.

The development of sol-gel and surfactant-templated synthesis established the basic toolkit for controlling pore structure, while hollow, dendritic, core-shell, biodegradable, and stimuli-responsive architectures have expanded the design space. Surface functionalization provides additional control over colloidal behaviour, drug affinity, targeting, and triggered release. Recent advances increasingly combine these functions with imaging, immunotherapy, tissue repair, and other biomedical applications. Nevertheless, increasing complexity must be accompanied by better characterization and manufacturing control.

The major remaining barriers concern reproducibility, scale-up, long-term safety, biodistribution, biodegradation, pharmacokinetics, and regulatory definition. Future progress will depend on establishing reliable links between MSN structure, manufacturing variables, biological fate, and therapeutic outcome. A clinically useful MSN will need to be more than highly functional: it must also be reproducible, sufficiently stable, appropriately degradable, controllable in manufacture, and supported by convincing safety and efficacy evidence. These principles provide a framework for the continued development of MSNs as advanced nanomedicine platforms.

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