

Enhancing Therapeutic Efficacy Through Tailored Pharmacokinetics: A Review of Mesoporous Silica Nanoparticle-Based Delivery Systems

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Abstract: Low solubility and bioavailability represent major challenges in drug development, resulting in sub-optimal pharmacokinetic profiles, including poor gastrointestinal absorption and limited systemic exposure. Mesoporous silica nanoparticles (MSNs) have emerged as promising drug delivery systems due to their high surface area, tunable pore size, and high pore volume, which enable enhanced drug loading and stabilization of drugs in an amorphous state. These properties are critical for improving dissolution behavior. Numerous studies confirm that drug encapsulation into MSNs significantly enhances the dissolution rate, leading to substantial pharmacokinetic improvements—specifically increased Area Under the Curve (AUC) and higher Maximum Plasma Concentration (C_{max})—which are directly correlated with enhanced systemic exposure and the potential for improved therapeutic efficacy for poorly soluble drugs. These comprehensive findings indicate that MSN-based delivery systems offer a powerful strategy to overcome the intrinsic pharmacokinetic limitations of poorly soluble compounds and warrant further investigation into their long-term safety and clinical application.

Keywords: bioavailability, pharmacokinetics, mesoporous silica, in vivo studies, poorly water soluble-drugs

Introduction

Drug solubility is a major obstacle in the development of new drugs. Approximately 40% of commercialized products and 70–90% of drug candidates in development have poor solubility, resulting in low bioavailability, reduced therapeutic effects, and increased dosages.¹ BCS classifies drugs based on their solubility in the physiological pH range and permeability, to identify compounds that are low risk in terms of drug absorption.^{2,3} For BCS Class I compounds (high solubility, high permeability),⁴ BCS Class II compounds (low solubility, high permeability),⁵ BCS Class III compounds (high solubility, low permeability),⁶ and BCS Class IV compounds (low solubility, low permeability).⁷ Among these, BCS class II and class IV drugs present significant formulation challenges due to their limited dissolution and absorption in the gastrointestinal tract. These physicochemical limitations often result in poor and variable pharmacokinetic performance, ultimately reducing bioavailability and therapeutic effectiveness, due to reduced systemic absorption and altered gastrointestinal drug deposition, where poorly soluble drugs may precipitate or remain localized in the intestinal lumen, leading to incomplete dissolution and inconsistent absorption.⁸ This underscores that drug efficacy is governed not only by solubility and permeability but also by gastrointestinal deposition behavior, which plays a critical role in determining in vivo dissolution and subsequent absorption outcomes. Therefore, improving drug solubility is

a critical focus in pharmaceutical development to enhance absorption, optimize therapeutic outcomes, and minimize dose-related issues.⁹

Drug Delivery Systems (DDS) are a method of drug formulation that accelerate the delivery of drugs to specific target locations within the body.^{10,11} This continues to be developed to overcome the limitations of conventional systems, such as through controlled-release formulations, aiming to maximize therapeutic efficacy and minimize accumulation outside the target site.¹² Nanotechnology is fundamentally revolutionizing pharmaceutical drug delivery for poorly water-soluble drugs by enabling precise control over particle size, surface characteristics, and drug encapsulation at the nanoscale.¹³ These properties significantly enhance drug dissolution through increased surface area, improve cellular uptake via endocytosis, and enable protection of drug molecules from enzymatic degradation and premature clearance.^{14–16} In addition, nanoscale systems can modulate drug transport pathways, including enhanced permeation across biological membranes and potential lymphatic uptake, thereby improving bioavailability and therapeutic efficiency.¹⁷ Simultaneously, nanotechnology offers the ability to target diseased tissues more precisely, thereby minimizing off-target toxicity of active molecules, improving therapeutic selectivity, and potentially reducing healthcare costs.^{18–21} Mesoporous silica (MS) is one critical type of DDS that capitalizes on nano technology, enabling the efficient loading of hydrophobic drugs into the MSN pores, often using non-aqueous solvents, which is essential for improving solubility, bioavailability, and achieving controlled drug release.²² Mesoporous silica nanoparticles (MSNs) are porous nanomaterials characterized by highly ordered pore structures, large surface area, and tunable pore size. These structural properties facilitate the confinement of poorly water-soluble drugs within nanoscale pores, promoting their dispersion in an amorphous or semi-crystalline state, which enhances apparent solubility and dissolution rate. Additionally, MSNs possess abundant silanol groups that enable surface interactions with drug molecules and allow further functionalization for controlled and targeted drug delivery.^{23,24} These features collectively contribute to improved drug solubility, enhanced bioavailability, and optimized therapeutic performance. Furthermore, the ability of MSNs to be surface-functionalized enables site-specific drug delivery, including applications in vascular-targeted therapies such as atherosclerosis, where drug release can be concentrated at sites of vascular injury or plaque formation.²⁵

Pharmacokinetics (PK) plays an important role in drug development because it determines how drugs are absorbed, distributed, metabolized, and excreted, as well as determining therapeutic doses, potential toxicity, and the risk of drug interactions.^{26,27} Key PK parameters such as AUC, C_{max}, t_{1/2}, V_d, and clearance are benchmarks for bioavailability and therapeutic efficacy.²⁸ However, many hydrophobic drugs face additional challenges, such as low solubility, poor absorption, and rapid elimination, resulting in low bioavailability.²⁹ These limitations ultimately lead to a decrease in AUC and C_{max}, as only a small fraction of the administered dose reaches systemic circulation.³⁰ To address these issues, drug delivery systems (DDS), including nanoparticle, are widely used to improve solubility and enhance absorption.³¹ The small and uniformly distributed pore size of mesoporous silica results in an extremely large specific surface area, which facilitates the efficient loading and release of substances (eg, drugs).³² Additionally, it increases membrane permeability, thereby enhancing drug penetration across biological barriers. Nanoparticle-based delivery systems can also partially circumvent first-pass hepatic metabolism by protecting drug molecules from enzymatic degradation in the gastrointestinal tract and by facilitating alternative uptake pathways, such as lymphatic transport and intracellular protection within nanocarriers. This protection reduces premature metabolic breakdown and increases the fraction of drug reaching systemic circulation. Furthermore, these systems provide better formulation stability and enable more controlled drug release, which collectively improves pharmacokinetic performance.^{33–35} Through this mechanism, nanoparticle strategies can significantly modify pharmacokinetic behavior by increasing AUC and C_{max}, prolonging half-life (t_{1/2}), and reducing clearance, ultimately improving drug exposure and therapeutic outcomes.^{36,37}

A number of studies have reported on the effect of Mesoporous Silica Nanoparticles (MSNs) on drug pharmacokinetics, highlighting their crucial role in overcoming various physical and chemical challenges in the development of new drug formulations, such as low solubility or poor stability.³⁸ However, although several reviews have discussed nanotechnology-based drug delivery systems and mesoporous materials, most of them primarily focus on formulation development, material design, or general drug delivery.^{39–42} In contrast, a comprehensive analysis specifically integrating the pharmacokinetic outcomes of MSNs, particularly in terms of ADME (Absorption, Distribution, Metabolism, and Excretion) modulation and quantitative *in vivo* pharmacokinetic parameters, remains limited. Therefore, this review aims

to address this gap by summarizing and critically evaluating the pharmacokinetic effects of MSNs on drug absorption, distribution, metabolism, and excretion, with particular emphasis on in vivo performance and mechanistic insights a molecular pharmacy perspective.

Methods

This study is presented as a narrative review that explores and analyzes recent advancements pharmacokinetic (PK) studies mesoporous silica. Relevant studies were collected from major scientific databases, including PubMed, Scopus, ScienceDirect, and Google Scholar. The search strategy utilized combinations of keywords such as “nanoparticle,” “mesoporous silica,” “pharmacokinetic studies,” “pharmacological activities,” “dissolution,” “toxicity,” encompassing publications from 2000 to 2025. The review only incorporated articles from peer-reviewed journals that were published in English, with priority directed towards research that particularly explored pharmacokinetic studies in mesoporous silica. The included studies comprised original research articles and experimental reports focusing on in vitro and in vivo pharmacokinetic and biopharmaceutical evaluations of mesoporous silica nanoparticles, while review articles were used solely to support background and conceptual framework development. To ensure analytical rigor, only studies that reported quantitative in vivo pharmacokinetic parameters (eg, AUC, Cmax, $t_{1/2}$) with appropriate statistical measures were selected for the core analysis presented in Table 1; studies lacking complete quantitative PK data or focusing exclusively on in vitro characterization were excluded. Studies were also excluded if they are unrelated to nanoparticle study of mesoporous silica, or did not mention pharmacokinetic study, dissolution rate, toxicity, and pharmacological study. Information obtained from the chosen studies was gathered and extracted thematically emphasizing the dissolution rate, in vitro and in vivo performance, and comparative advantages over pharmacokinetic study in mesoporous silica. This focused, quality-driven selection process, while yielding a relatively modest number of core studies (n=17), was deliberately adopted to enable a thorough and critical examination of representative MSN formulations rather than a superficial survey of a larger but less homogeneous body of literature. The narrative review approach was considered suitable for encompassing the varying results of pharmacokinetic study in mesoporous silica investigated in the literature, enabling a thorough and comprehensive examination of their mechanisms and therapeutic implications concerning the enhancement of drug solubility, stability, and safety. The methodology’s flowchart is shown in Figure 1.

Mesoporous Silica Nanoparticles (MSNs)

Mesoporous silica nanoparticles (MSNs) have been widely utilized across various industries and scientific disciplines, including heterogeneous catalysis, electrochemistry, analytical chemistry, molecular biology, and several other areas.^{24,57} Their defining characteristic is a moderately sized pore range in diameter, which is vital for high-surface-area applications like drug delivery and catalysis,⁵⁸ and a substantial surface area, making them highly appealing to scientists involved in drug delivery research, given their ability to act as a carrier with minimal influence on the therapeutic process, alongside their capacity to be altered using diverse reagents to incorporate specific attributes or fine-tune their characteristics, eg, pore size, controlling the drug release, design it to target a specific organ or tissue, etc.⁵⁹

Physicochemical Properties of MSNs

Mesoporous silica nanoparticles (MSNs) possess unique physicochemical properties that make them highly suitable for drug delivery applications. A key feature is their exceptionally high specific surface area, typically ranging from several hundred to over one thousand m^2/g , which provides abundant active sites for drug adsorption and enables high drug loading capacity.^{60,61} MSNs also exhibit a well-defined and tunable pore diameter, generally within the mesoporous range of 2–50 nm, allowing efficient encapsulation of a wide variety of drug molecules with different sizes. In addition, their relatively large pore volume further enhances drug storage capacity and supports controlled release behavior.^{62,63} The particle size of MSNs, typically between 50 and 300 nm, plays a critical role in determining cellular uptake, biodistribution, and overall pharmacokinetic performance.⁶⁴ Collectively, these physicochemical characteristics enable MSNs to function as efficient nanocarriers that improve drug solubility, stability, and therapeutic efficacy through controlled loading and release mechanisms.

Table 1 Previous Studies of Drug-Loaded MSN

No.	Active Substance	Mesoporous Type (MSN)	Method Adsorption Preparation	Dissolution Study	Pharmacokinetic Study (°)	Pharmacological Activity	Toxicity	Year	Reference
1.	Indomethacin (IMC)	Mesoporous silica nanoparticles (MSNs)	Solvent Adsorption using acetone	IMC free: 66.67% within 120 min; Naked mesoporous silica nanoparticles (N-MSN): 70.44% within 120 min; Concealed body-D-mesoporous silica nanoparticles (Cb-D-MSN) and concealed body-L-mesoporous silica nanoparticles (Cb-L-MSN) was similar: up to 83.84% in pH 6.8	The IMC-MSNs showed up to 3.9x AUC increase AUC (0-∞) (µg h/L) from 297.88 ± 125.70 to 822.81 ± 364.03	Anti-inflammation: IMC-MSNs decreased level of swelling (swelling) in all groups of rats from 16.45% to 8.45% (1.95-fold) compared to the model group (saline)	–	2018	[43]
2.	Indomethacin (IMC)	Mesoporous silica nanoparticles (MSNs)	Solvent Adsorption using Acetone	IMC: 20% in 120 min IMC-MSN: 90% in 120 min (4.5x higher)	The IMC-MSNs showed up to 1.5x AUC increase AUC (0-∞) (µg h/L) from 1620.88 ± 34.68 to 2833.40 ± 73.14	Anti-inflammation: IMC-MSN reduces the swelling rate from 21.9% to 4.9% (4.47-fold) because MSN increases the solubility and controlled release of IMC, increases bioavailability, and distributes the drug more efficiently and is quickly absorbed into the tissue.	–	2020	[44]
3.	Fluorouracil (FU)	Amino-functionalized Mesoporous silica nanoparticles with Carboxymethyl Chitosan (AMSN-CMC)	Aqueous Adsorption using phosphate buffer pH 7.4	Free 5-FU: 100% released within 4 h (burst release). AMSN-CMC-FU: 83% released at 24 h (sustained release).	The AMSN-CMC-FU showed an increase in AUC _{0-∞} from 81.0 ± 13.3 to 497.6 ± 44.2 µg h mL ⁻¹ , corresponding to an approximately 6.14-fold (p < 0.01).	Antiproliferative: AMSN-CMC-FU showed sustained ocular delivery, maintaining FU levels > 0.2 µg/mL for > 24 h (2-fold improvement compared to pure FU)	–	2023	[41]

4.	Exenatide (EXT)	SBA-15	Aqueous Adsorption using phosphate buffer pH 7.4	Free EXT: 100% released within 1 day (rapid burst release). EXT-SBA-15: 33% released at day 1; 67% at 14 days (sustained release).	The EXT-SBA-15 showed an increase in $AUC_{0-\infty}$ from 1.71 ± 0.07 to 8.77 ± 0.76 ng h mL ⁻¹ (5.1-fold), and $t_{1/2}(\beta)$ extended from 0.6 h to 14.5 h ($p < 0.01$).	Antidiabetic: EXT-SBA-15 showed a sustained hypoglycemic effect for 25 days, maintaining glucose < 20 mmol/L, lowest 13 mmol/L on day 10 (vs. 4 h for EXT-Sol).	–	2017	[40]
5.	Puerarin (PUE)	PEGylated MSNs; bare MSNs.	Solvent Adsorption using pH 7.4 phosphate buffer	Free PUE: rapid burst release within hours. PUE-PEG-MSNs: 27–47% released at 72 h (pH 5.5–7.4; sustained, pH-responsive release).	The PUE-PEG-MSNs showed an increase in $AUC_{0-\infty}$ from 0.86×10^6 to 1.27×10^6 ng mL ⁻¹ min (1.47-fold); $t_{1/2}$ extended from 27 to 61 min ($p < 0.01$).	–	–	2016	[42]
6.	Captopril	MSNs type SBA-15 and SBA-15/APTES	Solvent Adsorption using Acetone		The AUC_{0-72} increased from 502.51 μ g h/mL (commercial) to 624.99–674.77 μ g h/mL (up to 1.34-fold) for SBA-15 (RT and 80 °C) and 645.15–705.22 μ g h/mL (up to 1.40-fold) for SBA-15/APTES (RT and 80 °C). The APTES-modified system, especially at 80 °C loading, showed the highest AUC (705.22 μ g h/mL; 140.33% of control), prolonged T_{max} up to 24 h, and extended half-life (>72 h)	More prolonged antihypertensive effect (over 72 h) compared to the commercial tablet (2–3 hours).	No significant signs of toxicity were observed in rats treated with either SBA-15 or SBA-15/APTES formulations with the 50% lethal dose value 7522 and 7180 mg/kg compared to pure captopril (6598 mg/kg). The animals showed normal clinical behavior	2011	[45]

(Continued)

Table 1 (Continued).

No.	Active Substance	Mesoporous Type (MSN)	Method Preparation	Dissolution Study	Pharmacokinetic Study (°)	Pharmacological Activity	Toxicity	Year	Reference
7.	Docetaxel (DTX)	Albumin-coated hollow mesoporous silica nanoparticles (A-HMSNs)	Aqueous Adsorption using phosphate buffer pH 7.4	Dissolution was reported as release rate. Pure DTX showed burst release (>90% at 24 h; 77.9 µg/h). DTX-HMSNs: 12.6 µg/h; DTX-NH ₂ -HMSNs: 11.6 µg/h; A-DTX-HMSNs : 8.1 µg/h (sustained up to 120 h)	AUC increased up to 8× compared to pure docetaxel. AUC _{0-∞} (ng h/mL) Pure DTX: 16,934.4 DTX-HMSNs: 46,866.5 A-DTX-HMSNs: 136,308.6	Stronger anticancer efficacy, with the potential to reduce both the required dose and dosing frequency.	–	2021	[46]
8.	Paclitaxel (PTX)	Mesoporous silica nanoparticles (MSNs)	Aqueous Adsorption using phosphate buffer pH 7.4	Pure PTX: <7% (dissolution rate at 120 min) MSN0: 23.1% MSN 1h: 32.9% MSN 2h: 41.3% MSN0, MSN1h, and MSN2h refer to MSN etched with NaBH ₄ for 0, 1, and 2 hours.	AUC values varied depending on the MSN formulation. PTX-MSN0 showed an increase in AUC (11.52 µg h/L) compared to pure paclitaxel (7.04 µg h/L), while PTX-MSN1h showed a moderate increase (8.57 µg h/L), and PTX-MSN2h showed a slightly lower AUC (6.95 µg h/L)	–	–	2013	[47]
9.	Paclitaxel (PTX)	Hollow Mesoporous Silica Nanoparticles (HMSNs)	Solvent Impregnation using methanol and hydrochloric acid	Using PBS pH 7.4 + Tween 80 Pure Paclitaxel: 0% PTX-MSN 24h: 60% PTX-MSN 7 days: 82%	The MSN formulation showed an increase 1.7-fold in AUC from 324.53 to 547.97 µg h/mL compared to pure paclitaxel. Plasma PK was also evaluated, showing lower systemic exposure for PTX-MSN.	Stronger anticancer activity, with ~3.5-fold higher cellular uptake and enhanced tumor growth inhibition compared to pure paclitaxel.	–	2016	[48]

10.	Mirtazapine (MRT)	SBA-15 (Santa Barbara Amorphous-15)	Impregnation, evaporation, and incipient using ethanol	Pure mirtazapine: 45% in 30 min Optimize MRT-SBA-15: 75% in 5 min; 100% in 30 min	The optimized MRT-SBA-15 formulation showed a ~2.14-fold increase in AUC, rising from 14,192.06 to 30,448.72 ng h/mL compared to plain mirtazapine	The $t_{1/2}$ increased ~1.56-fold (3.88 to 6.04 h), indicating enhanced pharmacological performance and prolonged systemic retention, with potential to reduce dose and dosing frequency compared to plain mirtazapine	–	2022	[49]
11.	Eprosartan	SBA-15 (Santa Barbara Amorphous-15) and NH ₂ -SBA-15 (Amino-functionalized SBA-15)	Wet impregnation using methanol	Pure Eprosartan: 22.13 ± 1.9% (6 hours). Eprosartan-MSNs: 93.00 ± 1.9% (6 hours).	The optimized Eprosartan-MSN buccal film showed a ~2.63-fold increase in AUC, rising from 13.48 µg h/mL to 35.46 µg h/mL, with a 2.88-fold rise in C _{max} and a shortened T _{max} (0.5 h) compared to pure Eprosartan.	Enhanced pharmacological performance, with improved dissolution, faster absorption, and higher systemic exposure, as evidenced by a 2.88-fold increase in C _{max}	–	2025	[50]
12.	Bevacizumab	Mesoporous silica nanoparticles (MSNs)	Nanocasting method	Pure bevacizumab: Immediate fast release Bevacizumab-MSN: 35% (3 h; sustained to 7 days) MSN-encapsulated bevacizumab: (35% in 2 days; sustained to 28 days)	MSN-encapsulated bevacizumab showed a 1.7-fold increase in AUC, rising from 561.43 to 963.34 µg day/mL, and extended the MRT by 2.7-fold (4.74 to 12.92 days).	Stronger antiangiogenic activity, supported by enhanced pharmacokinetics with a ~1.72-fold increase in AUC, leading to greater suppression of endothelial proliferation, migration, and tube formation, and improved inhibition of corneal and retinal neovascularization (absent after 14 days) compared to pure bevacizumab	–	2019	[51]

(Continued)

Table I (Continued).

No.	Active Substance	Mesoporous Type (MSN)	Method Preparation	Dissolution Study	Pharmacokinetic Study (°)	Pharmacological Activity	Toxicity	Year	Reference
13.	Velpatasvir	MCM-41 hexagonal ordered mesopores	Adsorption with methanol solvent	After loading onto MSN, VLP-MSN showing increased dissolution especially at pH 6.8. VLP-MSN released ~56% at pH 6.8 in the first 5 min, and >90% in 45 min. Whereas pure velpatasvir released less than 10% at pH 6.8	The overall amount of the drug that successfully reaches the systemic circulation is also increased. Pure Velpatasvir: $AUC_{0-t} = 214.41 \text{ ng mL}^{-1} \text{ h}$ Velpatasvir-MSN: $AUC_{0-t} = 400.50 \text{ ng mL}^{-1} \text{ h}$	–	In vitro (MTT, HepG2): good viability up to 100 $\mu\text{g/mL}$; LD50 ~448 $\mu\text{g/mL}$; decrease in viability is dose-dependent. In vivo (rats, 14 days): stable hematological/biochemical parameters; normal organ histopathology (heart, lung, liver, kidney); minimal weight change—indicating compatibility and non-toxicity at the test dose.	2020	[52]
14.	Neratinib Maleate (NM)	SYLOID XDP 3050	Solvent Evaporation Method	Free NM: <40% soluble (depending on pH) NM-MSN: Nearly 100% soluble at pH 3–6.8	The MSN formulation showed an increase in AUC last from 16.36 ± 2.28 to $28.29 \pm 3.59 \text{ h } \mu\text{g/mL}$ (1.73-fold) compared to pure NM ($p < 0.01$),	–	–	2024	[53]
15.	Indomethacin (IMC)	Mesoporous silica nanoparticles (MSNs)	Adsorption equilibrium and solvent evaporation	There was a substantial increase in drug release in the IMC-MSN formulation compared with free IMC IMC: <40% within 2 hours (slow and incomplete) IMC-MSN: >90% within 1 hour (fast and nearly complete)	The IMC-MSNs formulation increase (~2.24-fold) in AUC compared with free IMC. AUC (0– ∞) ($\mu\text{g h/L}$): IMC (free) = 3240 ± 117 IMC-MSNs (nanospheres) = 5398 ± 746 IMC-MSNRs (nanorods) = 7275 ± 608	–	Cytotoxicity of MSN against Caco-2 cells using MTT assay: Safe, Caco-2 cell viability 100% (24 hours incubation)	2018	[54]

16.	Carvedilol (CVD)	MSN (SMB-7)	Solvent adsorption	CVD: 5% dissolved within 60 min (very low) CVD-MZS 500: 13% within 60 min ($\approx 2.6\times$ higher) CVD-MZS 750: 12% within 60 min ($\approx 2.4\times$ higher) CVD-MZS 1000: 9% within 60 min ($\approx 1.8\times$ higher)	The solid self-nanoemulsifying drug delivery system (S-SNEDDS) demonstrated a marked increase in AUC ($0-\infty$), rising from 4.17 ± 1.02 to $90.41 \pm 5.91 \mu\text{g h/L}$ compared with free CVD, showing up to a 21.7-fold enhancement	–	–	2025	[55]
17.	Apigenin	Mesoporous silica nanoparticles (MSN)	Solvent adsorption	Apigenin (AP): 40.11% within 48 hour (low) AP-MSN: 95.2% within 48 hour	The IMC-MSNs showed up to 8.32x increased AUC increase AUC ($0-\infty$) ($\mu\text{g h/L}$) from 102.69 $\mu\text{g/Lh}$, to 854.89 $\mu\text{g/Lh}$	–	Safe, DMF residues AP-MSN solid dispersion was 0.055% lower than the ICH limit for the class II solvents	2019	[56]

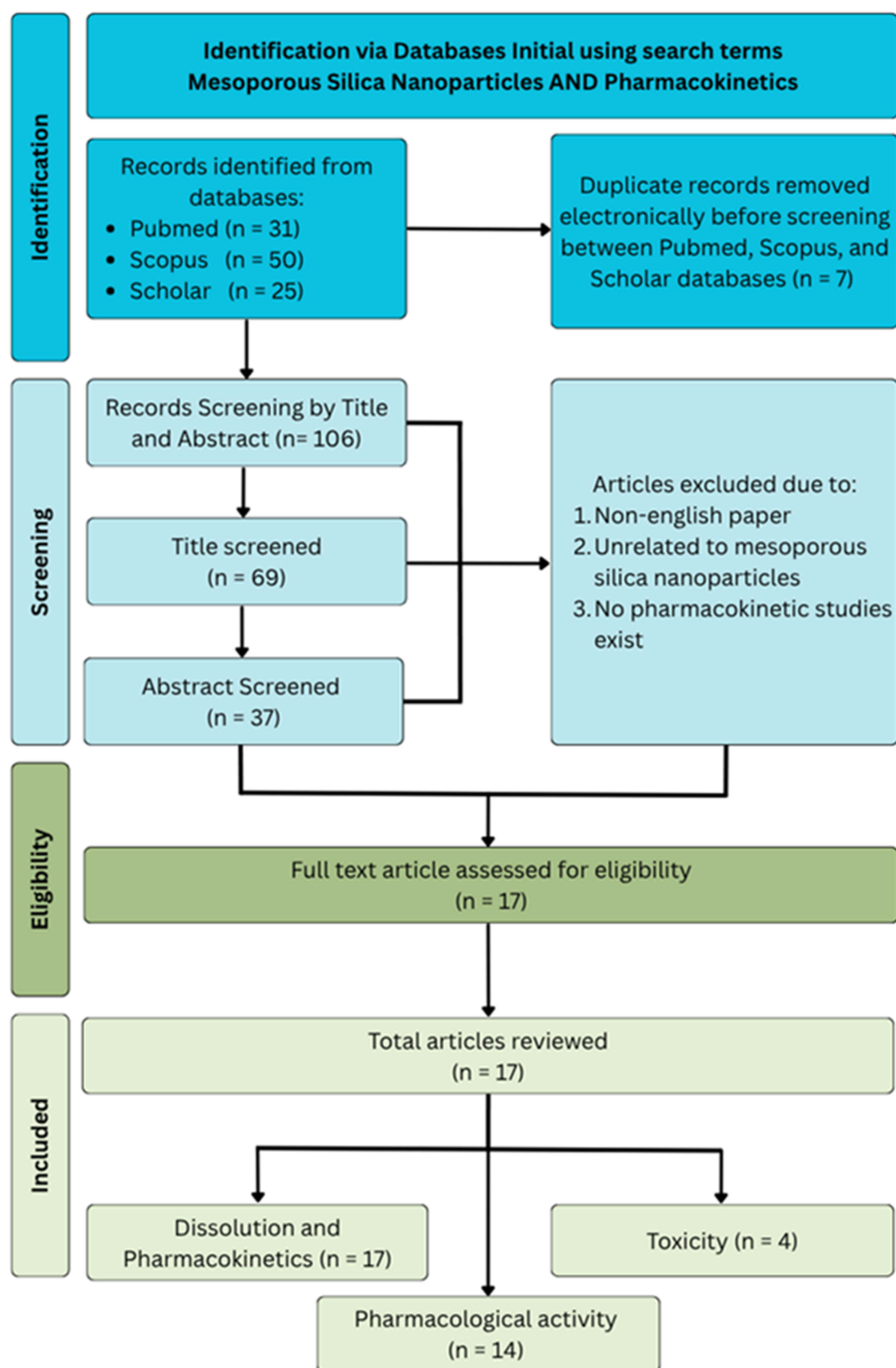


Figure 1 Methodology's Chart.

Classification of MSNs

Based on their mesoporous material categories, MSNs are generally classified into the M41S series, SBA series, FDU series, KIT series, and others.⁶⁵ MCM-41 features a highly ordered hexagonal pore architecture with comparatively small pore diameters, while SBA-15 possesses larger pore dimensions and thicker pore walls, resulting in enhanced hydro-thermal stability.⁶⁶ KIT and FDU-type MSNs exhibit distinct three-dimensional pore networks with tunable

mesostructures depending on synthesis conditions.^{67,68} These structural differences significantly influence drug loading capacity, release kinetics, and the stability of encapsulated compounds, where materials with larger pore volume and more robust interconnected frameworks generally demonstrate higher drug encapsulation efficiency and more sustained release behavior due to improved molecular accessibility and diffusion pathways within the mesoporous channels.⁵⁷ For instance, a comparative study on ibuprofen-loaded mesoporous silicas showed that SBA-15 exhibited the highest drug loading capacity, exceeding 100 wt% (>1:1 drug-to-carrier ratio), attributed to its larger pore diameter and higher pore volume, which facilitated efficient diffusion and near-complete pore filling. MCM-41 showed a much lower loading capacity (~11.7 wt% under low-concentration loading) and only approached maximal pore filling under high-concentration conditions, but remained limited compared to SBA-15 due to pore confinement and channel blockage. In contrast, TUD-1 displayed the lowest loading capacity despite its 3D interconnected pore network, primarily due to its lower total pore volume. TCPSi retained approximately 40% free mesopore volume after loading, indicating incomplete pore filling caused by pore-size heterogeneity and partial drug loss during washing. Collectively, these results confirm that drug loading capacity is mainly governed by mesopore volume and pore architecture rather than surface area alone.⁶⁹

Preparation of MSNs

MSNs are commonly synthesized using several primary approaches, including sol-gel synthesis, templating techniques, and surfactant-assisted synthesis, which enable precise control over particle morphology, pore architecture, and surface properties (Figure 2). The sol-gel method serves as the fundamental chemical route for most MSN preparations, involving the hydrolysis and condensation of silica precursors to form an amorphous silica network.⁷⁰ In addition, templating strategies both soft and hard templating are widely employed to generate well-ordered mesoporous structures through the use of structure-directing agents that guide pore formation.⁷¹ Surfactant-assisted synthesis is also extensively utilized, in which amphiphilic molecules self-assemble into micelles that act as templates for silica deposition.⁷²

In this context, the formation of MSNs is based on silica contains a tetrahedral network in which one silicon atom is covalently linked to four oxygen atoms, forming the structural foundation of mesoporous silica with pore sizes ranging from 2 to 50 nm.⁷³ In the synthesis process, soluble silica precursors organize into liquid-crystalline mesophases through

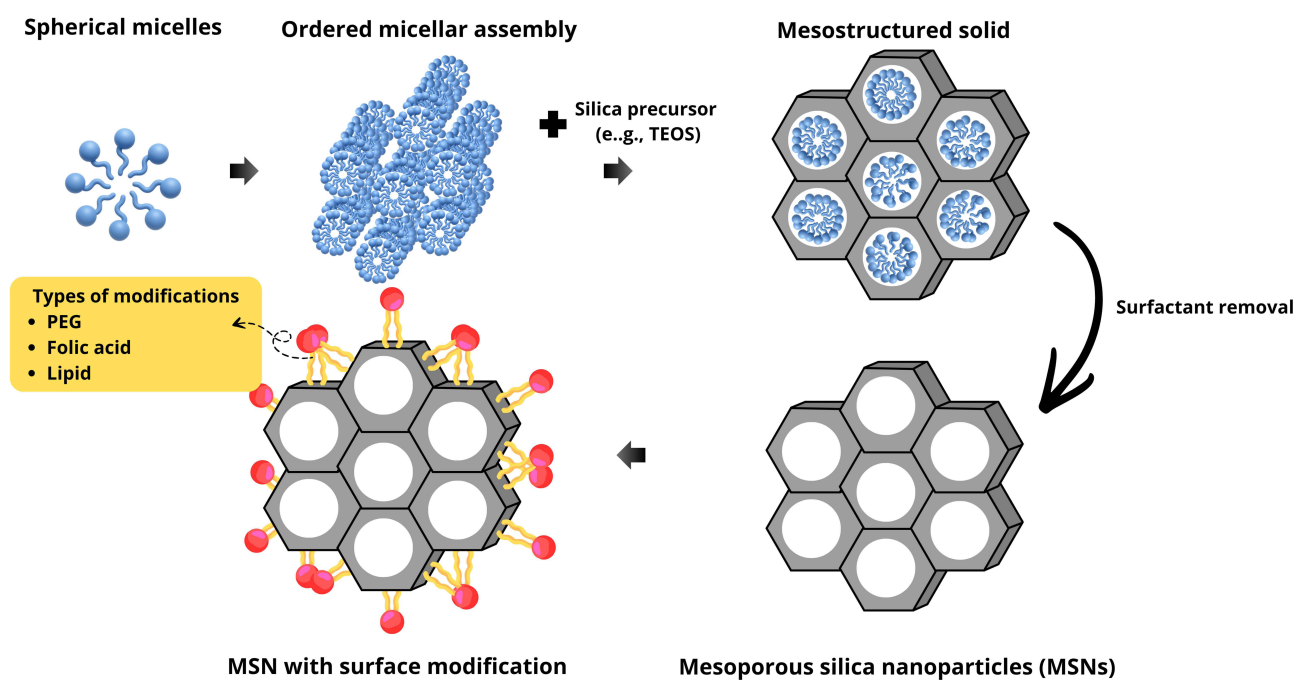


Figure 2 Schematic illustration of mesoporous silica nanoparticle (MSN) synthesis. Formation of MSNs starting from spherical micelles, self-assembly into ordered phases, deposition of silica precursors (eg, TEOS), and surfactant removal to yield porous MSNs. Surface modifications (eg, PEGylation, ligand conjugation) are optional and can enhance targeting, biocompatibility, and pharmacokinetic performance. Adapted from Hoffman F, Cornelius M, Morell J, Froba M. Silica-based mesoporous organic-inorganic hybrid materials. *Angew Chem Int Ed* 2006; 45: 3216–51.

interactions with block copolymers or amphiphilic surfactants acting as structure-directing agents.^{74,75} Following this, silane condensation occurs, and the surfactant templates are removed by solvent extraction or calcination, producing amorphous mesoporous silica with diverse pore architectures, including hexagonal, cubic, lamellar, and disordered forms.⁷⁶ MCM-41 was first introduced as a new mesoporous material featuring a highly ordered hexagonal arrangement of uniform pores, with tunable channel sizes ranging from 1.5 to 10 nm.⁷⁷ Typically, it is synthesized using cetyltrimethylammonium bromide (CTAB) as the surfactant and tetraethyl orthosilicate (TEOS) as the silica precursor. Under strongly alkaline conditions, CTAB molecules form rod-shaped micelles that assemble into hexagonal structures.^{78,79} When TEOS is added, the resulting silicate species deposit around these micellar arrays, driven by electrostatic attraction between negatively charged Si–O groups and the positively charged N+(CH₃)₃ headgroups, promoting silane hydrolysis and condensation.⁸⁰ Subsequent calcination removes the surfactant template, yielding the final mesoporous material. Several years later, SBA-15 was introduced to have a similar feature as MCM-41 and shown to be a highly promising nanomaterial for biomedical applications.^{81,82} In 2001, the first biomedical application of mesoporous silica for drug delivery was documented, showing that MCM-41 could successfully load and release the anti-inflammatory drug ibuprofen at a loading capacity of 30% by weight.^{83,84}

For MSNs synthesis, numerous parameters can be modified, such as pH, the type of surfactant, and the silica precursor.^{85,86} They can be fabricated using several approaches, including soft-templating techniques (such as single-vessel, vesicle, and microemulsion templating), hard-templating strategies, polymer-latex templating, the Stöber process, sol–gel methods, and various others.⁸⁷ MSNs are typically produced using a surfactant-templated sol–gel method. Their structural and morphological characteristics are shaped by various factors, including the choice of surfactant, the silica precursor,⁸⁸ the catalyst used, as well as external conditions like pH and temperature.⁸⁹ Three primary types of structure-directing agents are commonly used in MSNs synthesis for example cationic surfactants (CTAB and CTAC), anionic surfactants (including phosphoric acid, sodium dodecyl sulfate, and alkyl carboxylic acids),⁹⁰ and non-ionic surfactants (Pluronic F123, F127, PEO, and PPO).⁹¹

Characterization of MSNs

A thorough characterization of mesoporous silica nanoparticles (MSNs) is fundamental to verifying their structural integrity, surface properties, and overall suitability for advanced drug delivery. Scanning Electron Microscopy (SEM) and Transmission Electron Microscopy (TEM) are the primary techniques employed to evaluate particle morphology, size distribution, and pore architecture. SEM analysis typically reveals monodisperse spherical particles with uniform size distributions, often exhibiting distinct hexagonal symmetry on the surface—a hallmark of a highly ordered mesoporous framework.⁵⁷ Meanwhile, TEM provides superior resolution for probing the internal matrix, validating the presence of ordered hexagonal channels and enabling the precise quantification of both particle diameter and pore dimensions. For instance, Huang et al (2014) identified MSNs with a mean particle size of ~105 nm and pore widths of ~2.1 nm, confirming a well-defined architecture optimized for molecular encapsulation.⁹² Furthermore, evidence suggests that tuning synthesis parameters, such as surfactant-to-silica ratios, can yield diverse morphologies ranging from lamellar outer shells to dendritic pore networks, underscoring the indispensable role of TEM in refining formulation design.^{76,93}

The specific surface area and pore volume of MSNs are conventionally quantified using Brunauer–Emmett–Teller (BET) analysis via nitrogen adsorption–desorption isotherms. Most MSNs demonstrate characteristic Type IV isotherms with pronounced hysteresis loops, which definitively confirm their mesoporous nature.⁵⁷ Reported BET surface areas vary substantially depending on the synthesis conditions, ranging from approximately 380 m²/g to over 1190 m²/g, with corresponding pore volumes between 0.7 and 1.0 cm³/g.^{93,94} These exceptional surface-to-volume ratios are directly responsible for the high drug-loading capacities and the amorphous stabilization effects observed in MSN-based systems—both of which are critical drivers for enhancing dissolution kinetics and subsequent systemic absorption.

Complementary insights into the hydrodynamic behavior and colloidal stability of MSNs in suspension are obtained through Dynamic Light Scattering (DLS) and Zeta Potential (ZP) analyses. DLS measurements typically indicate narrow polydispersity indices, with hydrodynamic diameters ranging from 65 to 100 nm for well-dispersed formulations, thereby confirming minimal particle aggregation.^{95,96} Simultaneously, Zeta potential evaluates the surface charge, a key parameter influencing interactions with biological membranes and plasma proteins. Unmodified MSNs generally exhibit

negative zeta potential values (approximately -17 to -25 mV at physiological pH) due to the deprotonation of surface silanol groups, which provides sufficient electrostatic repulsion to maintain colloidal stability in aqueous media.⁹⁴ These surface characteristics can be further tailored through functionalization to optimize biodistribution and cellular uptake. Ultimately, the precise control and characterization of these parameters guarantee a stable and predictable pharmacokinetic profile by preventing premature clearance and ensuring consistent, controlled drug release.

Drug Loading Mechanisms of MSNs

Drug loading into MSNs is primarily achieved through physical adsorption within their high-surface-area mesoporous architecture (2–50 nm). In this process, drug molecules diffuse into the pore channels and interact with the silica surface via hydrogen bonding, electrostatic interactions, and van der Waals forces.⁹⁷ Common loading approaches include adsorption from concentrated drug solutions and solvent evaporation techniques, where solvent removal facilitates the deposition of drug molecules within the mesopores.⁹⁸ In addition to these conventional methods, alternative strategies such as covalent conjugation, hybrid matrix encapsulation, and diffusion-supported loading have been explored to further enhance loading efficiency and modulate drug release behavior, particularly for complex or high-molecular-weight compounds.^{99,100} The efficiency of drug loading is strongly influenced by several physicochemical properties of MSNs, including surface area, pore volume, pore size, and surface functionalization. Materials with larger pore volumes and tunable surface chemistry generally exhibit higher loading capacity due to improved molecular accessibility and stronger drug–carrier interactions.¹⁰¹

Following incorporation into the mesoporous framework, MSNs also play a crucial role in stabilizing drugs in an amorphous state (Figure 3). The spatial confinement of drug molecules within nanoscale pores restricts molecular mobility and inhibits nucleation and crystal growth, thereby preventing recrystallization.¹⁰² Moreover, interactions between drug molecules and surface silanol groups further contribute to the stabilization of the amorphous phase.^{103–105} This effect is particularly significant for poorly water-soluble drugs, where confinement within mesoporous carriers promotes disordered molecular arrangements, resulting in enhanced apparent solubility and dissolution rates. Numerous studies have demonstrated the significant impact of mesoporous confinement on poorly water-soluble drug performance. For instance, fenofibrate-loaded SBA-15 exhibited an approximately 3–5-fold increase in dissolution rate compared to its crystalline counterpart, attributed to its amorphous dispersion within large mesopores.¹⁰⁶ Similarly, curcumin-loaded MSNs showed a 10–20-fold enhancement in solubility and a 2–3-fold improvement in oral bioavailability.¹⁰⁶ In another study, indomethacin confined within MCM-41 achieved a ~4–6-fold increase in dissolution efficiency, with X-ray diffraction (XRD) and nuclear magnetic resonance (NMR) analysis confirming complete suppression of crystallinity.¹⁰⁷ Collectively, these findings highlight that nanoscale confinement within MSNs effectively stabilizes drugs in an amorphous state, leading to substantial improvements in solubility, dissolution behavior, and pharmacokinetic performance.

Drug Release Behavior of MSNs

The therapeutic effectiveness of MSN-based drug delivery systems is primarily governed by the kinetics of drug release from their mesoporous structure. Typically, the release process follows a diffusion-controlled mechanism (Figure 3), where the release rate is determined by the pore geometry and the physicochemical interactions between the drug and the silanol groups on the MSN surface.¹⁰⁷ This mechanism operates through concentration gradients, with drug molecules migrating from regions of higher concentration within the nanopores to areas of lower concentration in the surrounding environment.¹⁰⁸ The sustained release enabled by diffusion-controlled mechanisms is particularly advantageous in optimizing therapeutic outcomes, as it extends the duration of drug action, stabilizes plasma concentrations, and reduces dosing frequency, thus improving patient adherence to treatment.¹⁰⁹

In addition to passive diffusion, stimulus-responsive nanoformulations have been engineered to offer more precise control over drug release.^{22,110,111} These advanced systems incorporate “gatekeepers” or molecular valves that respond to internal physiological signals (eg, pH, redox potential, and enzymes) or external stimuli (eg, light and magnetic fields), ensuring that the drug is released exclusively at the intended site of action.^{112–115} This targeted approach allows for both spatial and temporal control over drug delivery, reducing off-target effects and enhancing the precision of treatment. Research has demonstrated the effectiveness of these systems in improving site-specific drug delivery, particularly for

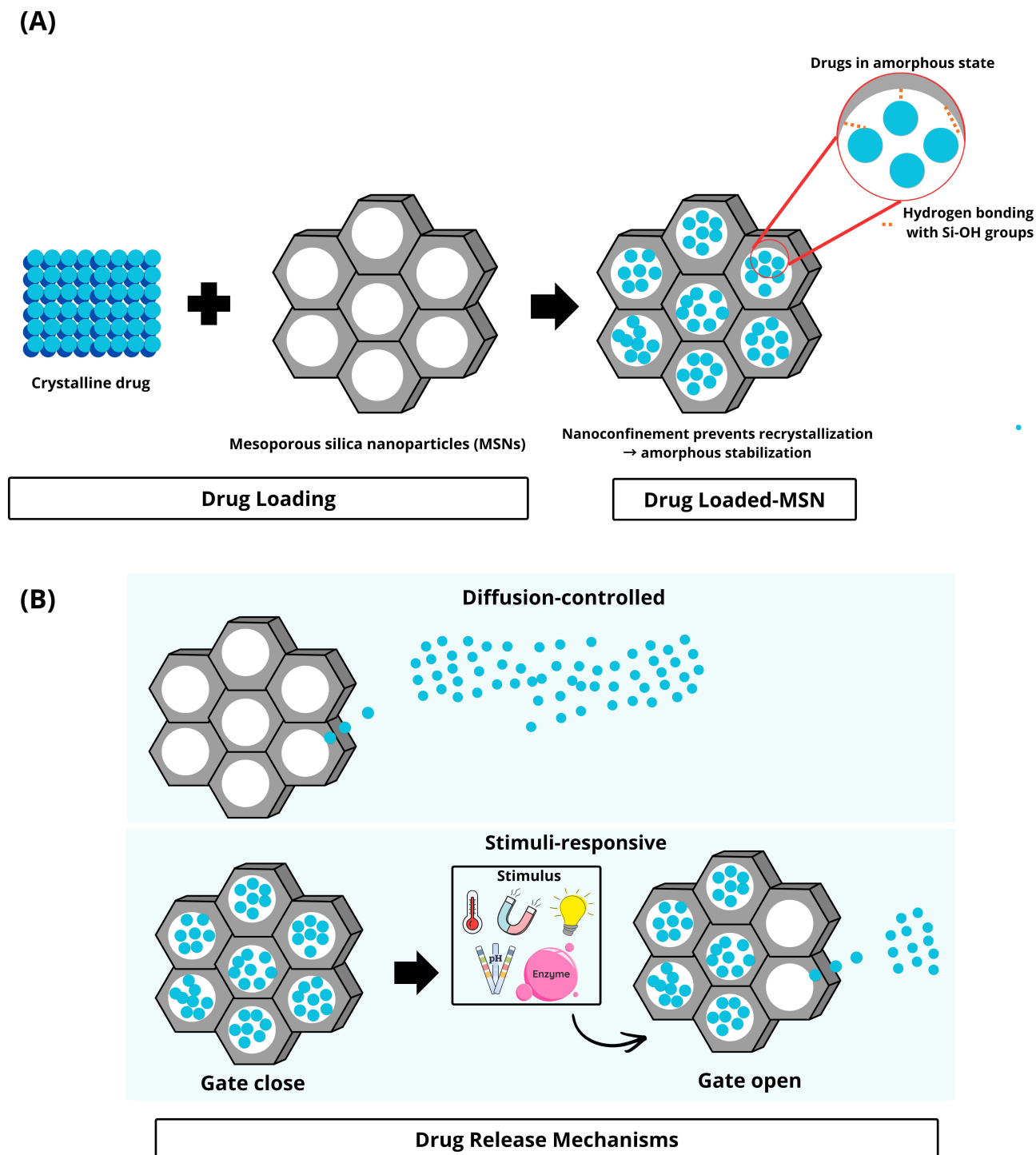


Figure 3 Schematic illustration of **(A)** drug loading and amorphous stabilization within mesoporous silica nanoparticles (MSNs), and **(B)** drug release mechanisms from MSNs.

treating localized diseases such as cancer, where the acidic tumor microenvironment or other disease-specific markers can trigger controlled drug release.¹¹⁶

Numerous recent studies highlight how different release mechanisms from MSNs impact drug delivery efficacy. For instance, in systems governed by passive diffusion, Mahajan and Rajput (2018) demonstrated that ritonavir (RTV) encapsulated in MCM-48 MSNs significantly enhanced pharmacokinetics compared to the free drug. Specifically, the

C_{max} and AUC_{0-t} of RTV-MCM-48NPs increased by approximately 2.48-fold and 1.94-fold, respectively, relative to unencapsulated ritonavir, indicating a marked improvement in systemic exposure due to sustained drug release from the mesoporous structure.¹¹⁷ Another example of diffusion-controlled release is seen with MSNs enhancing the dissolution profiles of hydrophobic anticancer agents like paclitaxel and docetaxel. In these cases, MSN formulations achieved significantly higher cumulative release percentages over 8 hours compared to free drug suspensions, with approximately 72.6–85.1% cumulative release versus negligible release from the unencapsulated drug, illustrating how the porous structure of MSNs facilitates controlled passive release.¹¹⁸ In contrast, stimulus-responsive MSNs are engineered to respond to specific environmental triggers. For instance, Ortiz et al (2024) developed pH-sensitive MSN systems functionalized with transferrin gatekeepers, which remain closed at physiological pH but open in acidic conditions, enabling on-demand drug release at tumor sites and enhancing site-specific delivery.¹¹⁹ Similarly, histidine-modified poly-L-lysine (PLL-His) serves as a pH-responsive gatekeeper on MSNs, enabling controlled release of anti-inflammatory drugs in acidic microenvironments, demonstrating how stimulus-responsive modifications allow for drug release exclusively in targeted physiological conditions.¹²⁰

Surface Modifications of MSNs

Surface functionalization of MSNs plays a pivotal role in improving targeting, biocompatibility, and stability, all of which are essential for optimizing pharmacokinetic performance. The abundant silanol (Si–OH) groups on the MSN surface offer a flexible platform for both covalent and non-covalent modifications, allowing for precise adjustments in the physicochemical and biological properties of MSNs.^{121,122} Functionalization strategies include grafting targeting ligands (eg, folic acid, peptides, antibodies) to enhance receptor-mediated uptake, applying polymer coatings (eg, PEGylation) to improve colloidal stability and reduce opsonization, and introducing stimulus-responsive moieties that enable controlled release in response to specific microenvironmental cues.^{123,124} These modifications not only allow for targeted drug delivery to disease sites but also optimize the pharmacokinetics by extending circulation time, reducing premature drug release, and improving the therapeutic index of the encapsulated drugs.¹²⁵

Recent studies highlight the significant impact of surface functionalization on MSN pharmacokinetics. For example, pH-responsive MSNs functionalized with folic acid (FA) and chitosan have been designed for targeted delivery of epirubicin in breast cancer models. These MSNs exhibited a high drug loading capacity (~79.5%) and improved in vitro and in vivo pharmacokinetics, showing superior tumor targeting and enhanced therapeutic efficacy with minimal off-target toxicity, resulting in improved systemic exposure.¹²⁶ Similarly, redox- and pH-triggered surface modifications have been used to enable dual stimuli-responsive release, enhancing the ability of MSNs to deliver drugs specifically to diseased microenvironments while maintaining stability in systemic circulation, thus improving bioavailability and reducing off-target effects.¹²⁷ Additionally, surface functionalization of MSNs with polymers or ligands has also been shown to significantly improve cellular uptake and biocompatibility, which directly contributes to enhancing pharmacokinetics in imaging, theranostics, and drug delivery applications.¹²⁸

Pharmacokinetic Improvements of MSNs-Based Formulations

Pharmacokinetics Consideration in MSN-Based Drug Delivery

Pharmacokinetics is a term that describes how the concentrations of drugs and their metabolites in body fluids and tissues change over time.^{129,130} It also explains the journey of a drug within the body through four main processes, namely absorption, distribution, metabolism, and excretion, which are collectively referred to as ADME.¹³¹ Pharmacokinetics models the concentration–time profile using key parameters such as volume of distribution, area under the curve (AUC), clearance (CL), half-life ($t_{1/2}$), maximum concentration (C_{max}), and bioavailability (F).¹³² These parameters provide essential information on how a drug is distributed within the body. Pharmacokinetic parameters depend on the physicochemical properties of the drug, such as solubility, membrane permeability, plasma protein binding, and the ability to cross biological barriers.¹³³ In addition, physiological factors of the body also play a role, including blood flow, liver function, and kidney function, which are involved in the processes of metabolism and excretion.¹³⁴ Individual variability, such as age, sex, genetics, disease conditions, and drug–drug interactions, can lead to differences in

pharmacokinetic profiles among patients.¹³⁵ A thorough understanding of pharmacokinetic parameters is therefore crucial in drug development and in determining the optimal dosing regimen, to ensure the achievement of therapeutic concentrations that are both effective and safe for patients.¹³⁶

Among these parameters, the area under the concentration–time curve (AUC), clearance (CL), maximum concentration (C_{max}), and half-life (t_{1/2}) are particularly important for evaluating drug exposure and elimination. AUC represents the total systemic exposure of a drug, determined by both the extent of absorption and the rate of elimination.¹³⁷ A higher AUC indicates greater absorption, which may enhance therapeutic efficacy but also raise the risk of toxicity, whereas a lower AUC suggests poor absorption, potentially leading to subtherapeutic drug levels.^{138,139} Clearance describes the body's efficiency in eliminating a drug from systemic circulation: high clearance results in rapid removal and lower exposure,¹⁴⁰ while low clearance slows elimination and prolongs systemic exposure.¹⁴¹ Under first-order kinetics, clearance remains constant even though the elimination rate varies with drug concentration. Physiologically, total body clearance is the sum of clearance via multiple elimination routes, including hepatic, renal, and other pathways.¹⁴² In the context of nanomaterial-based formulations such as mesoporous silica nanoparticles (MSNs), the concept of clearance remains relevant but involves more complex interactions due to the distinct biological behavior of nanoparticles compared to small-molecule drugs.¹⁴³

C_{max} reflects the peak plasma concentration, where excessively high levels can trigger concentration-dependent toxicities,¹⁴⁴ while low values may lead to insufficient therapeutic effect.¹⁴⁵ Half-life (t_{1/2}) indicates how long a drug persists in the body; a prolonged t_{1/2} extends therapeutic effects but may cause accumulation and adverse outcomes,¹⁴⁶ whereas a short t_{1/2} requires more frequent dosing to maintain efficacy.²⁸

Pharmacokinetics is a branch of pharmaceutical science that studies the path of drugs in the body, encompassing four main processes: absorption, distribution, metabolism, and excretion (ADME).¹⁴⁷ After administration, drugs undergo an absorption process from the site of administration into systemic circulation, which can occur through passive diffusion, active transport, or endocytosis, depending on the drug's physicochemical properties.¹⁴⁸ After entering the bloodstream, drugs are distributed to various tissues and organs, influenced by blood flow, membrane permeability, and drug binding to plasma proteins.¹⁴⁹ Next, drugs undergo metabolism, primarily in the liver through cytochrome P450 enzymes,¹⁵⁰ to be converted into more polar metabolites for easier excretion, this process can produce active or inactive metabolites.¹⁵¹ The final stage is excretion, which is the removal of drugs or their metabolites from the body through the kidneys (urine), bile (feces), sweat, or respiration.¹⁵² Overall, pharmacokinetic mechanisms determine drug levels in the blood, the duration of therapeutic effects, and the potential for drug interactions and toxicity.¹⁵³

Research conducted by Huynh et al (2022) discusses the pharmacokinetic mechanisms of ACT-1004-1239, a CXCR7 receptor antagonist being developed for the treatment of inflammatory diseases and cancer. A Phase I study in six healthy subjects showed that the drug was well absorbed through the gastrointestinal tract and rapidly detected in plasma, indicating efficient absorption. After entering the circulation, ACT-1004-1239 undergoes primary metabolism in the liver by the CYP3A4 enzyme through oxidation and amide hydrolysis, resulting in two main metabolites, M1 and M23. Elimination of the drug occurs primarily through feces (69.6%) and a small portion through urine (14.5%), indicating that the dominant excretion route is the biliary pathway. Overall, the ADME mechanism of ACT-1004-1239 reflects the characteristics of a lipophilic drug with good absorption, extensive hepatic metabolism, and excretion primarily through the biliary system without the formation of toxic metabolites.¹⁵⁴

Pharmacokinetics plays a crucial role in determining the success of therapy and disease recovery. Pharmacokinetic variability, whether influenced by the physicochemical properties of the drug or the patient's physiological condition, can affect the attainment of therapeutic concentrations in the body. Imbalances in the pharmacokinetic profile, such as poor absorption, uneven distribution, excessively rapid or slow metabolism, and impaired excretion, may result in drug levels falling below or exceeding the therapeutic range.^{155,156} These conditions can potentially reduce therapeutic effectiveness or increase the risk of toxicity. Several studies have demonstrated that monitoring pharmacokinetic parameters, such as in antiretroviral therapy for HIV patients.¹⁵⁷ Antibiotic therapy in critically ill patients,¹⁵⁸ and personalized therapy in hemophilia A.¹⁵⁹

Pharmacokinetics Performance of MSN-Based Formulations

Prior studies have shown that drug-loaded MSNs can improve the pharmacokinetic performance, as summarized in Table 1.

Analysis of Pharmacokinetics Parameters of Drug Loaded-MSN

Table 2 summarizes the quantitative pharmacokinetic improvements achieved by the representative MSN formulations discussed in this section. The selected studies highlight significant enhancements in pharmacokinetic parameters, including increases in AUC (ranging from 1.47-fold to 21.7-fold), C_{max} (up to 15.7-fold), and half-life/MRT (up to 24-fold) across various drug classes.

Area Under Curve

Pharmacokinetic evaluation of three selected studies showed that mesoporous silica nanoparticles (MSNs) increased the systemic bioavailability of drugs, as evidenced by a significant increase in the area under the plasma concentration-time curve (AUC). Chen et al (2017) evaluated the pharmacokinetic profile of exenatide (EXT) loaded into SBA-15 mesoporous silica (EXT-SBA-15) compared with an aqueous solution of EXT (EXT-Sol). The results indicated

Table 2 Representative Pharmacokinetic Improvements Achieved with MSN-Based Formulations

Active Substances	Mesoporous Type (MSN)	Key Pharmacokinetic Outcomes (vs Pure Active Substances)				Other Key Findings	Ref.
		Area Under Curve (AUC)		Maximum Concentration (C _{max})			
		Value	Improvement	Value	Improvement		
Exenatide (EXT)	Santa Barbara Amorphous (SBA) -15	8.77 ± 0.76 vs 1.71 ± 0.07 ng h mL ⁻¹	5.2-fold	–	–	t _{1/2} : extended from 0.60 ± 0.08 h to 14.53 ± 0.70 h	[160]
Puerarin (PUE)	PEGylated MSNs	1.27 × 10 ⁶ vs 0.86 × 10 ⁶ ng mL ⁻¹ min	1.47-fold	–	–	t _{1/2} : extended from 27 h to 61 h	[40]
Carvedilol (CVD)	MSN-S-SNEDDS	90.41 ± 5.91 vs 4.17 ± 1.02 µg h/L	21.7-fold	11.31 ± 1.15 vs 0.72 ± 0.11 ng/mL	15.7-fold	No significant change in T _{max}	[42]
Paclitaxel (PTX)	Hollow MSNs	547.97 ± 26.9 vs 324.53 ± 33.32 µg h/mL	1.69-fold	–	–	Mean residence time: increased from 17.83 to 56.86 hours	[56]
Eprosartan	SBA-15	35.46 vs 13.48 µg h/mL	2.63-fold	0.52 ± 0.5 vs 1.58 ± 0.6 µg/mL	2.88-fold	T _{max} shortened	[51]
Indomethacin (IND)	Mesoporous silica nanorods (IMC-MSNRs)	7275 ± 608 vs 3240 ± 117 µg h/L	2.24-fold	928.0 ± 24.8 vs 234.2 ± 16.0 mg/mL	3.96-fold	T _{max} shortened	[54]
Mirtazapine (MRT)	SBA-15	30,448.72 vs 14,192.06 ng h/mL	2.14-fold	2918.22 ± 320.62 vs 1455.71 ± 210.85 ng/mL	2-fold	t _{1/2} : extended from 6.04 ± 0.58 h to 3.88 ± 0.23 h	[161]
Velpatasvir (VLP)	MCM-41 hexagonal ordered mesopores	400.50 vs 214.41 ng mL ⁻¹ h	1.87-fold	31.84 ± 0.054 vs 16.44 ± 0.48 ng/mL	1.94-fold	t _{1/2} : decreased from 10.76 ± 0.155 to 9.20 ± 0.52 h	[52]

a pronounced enhancement of drug exposure, where the $AUC_{0-\infty}$ of EXT-SBA-15 was significantly higher ($8.77 \pm 0.76 \text{ ng}\cdot\text{h}\cdot\text{mL}^{-1}$) than that of EXT-Sol ($1.71 \pm 0.07 \text{ ng}\cdot\text{h}\cdot\text{mL}^{-1}$), accompanied by a remarkable extension of half-life from $0.60 \pm 0.08 \text{ h}$ to $14.53 \pm 0.70 \text{ h}$. These findings highlight the ability of SBA-15 carriers to prolong systemic circulation and achieve sustained release of peptide drugs.⁴⁰ In another example, Liu et al (2016) assessed the pharmacokinetic profile of puerarin encapsulated in PEGylated MSNs. Compared with puerarin injection, PUE-PEG-MSNs achieved a 1.47-fold increase (from 0.86×10^6 to $1.27 \times 10^6 \text{ ng}\cdot\text{mL}^{-1}\cdot\text{min}$) in AUC and a 2.3-fold prolongation of half-life (from 27 to 61 min), demonstrating the dual benefits of enhanced drug exposure and extended circulation time. The PEG surface modification was particularly important in reducing rapid clearance and improving systemic retention.⁴²

A study by Jang et al (2015) on a solid self-nanoemulsifying drug delivery system (S-SNEDDS) based on MSN for carvedilol found that this combination was able to form an emulsion with very small droplet sizes ($\sim 130 \text{ nm}$) when it came into contact with gastrointestinal fluids. This result is consistent with the high surface-area-to-volume ratio of MSNs, which promotes rapid supersaturation and maximizes the concentration gradient for intestinal absorption. As a result, carvedilol in the 500 MSN formulation showed a 21.7-fold increase in AUC (4.17 ± 1.02 to $90.41 \pm 5.91 \mu\text{g}\cdot\text{h}/\text{L}$) and a 15.7-fold increase in C_{max} (from 0.72 ± 0.11 to $11.31 \pm 1.15 \mu\text{g}/\text{mL}$) compared to the pure drug, with no significant change in T_{max} . Collectively, the observed enhancements in AUC can be mechanistically attributed to the intrinsic physicochemical properties of MSNs. The high specific surface area and ordered mesoporous architecture of carriers such as SBA-15 and PEG-MSNs promote efficient drug loading and stabilize the encapsulated payload in a high-energy amorphous state. This nanoscale confinement enhances apparent solubility and dissolution rate while enabling sustained, diffusion-controlled release from the pore channels, thereby prolonging therapeutic plasma concentrations and substantially increasing total systemic exposure.

Clearance

Clearance describes the body's efficiency in eliminating a drug from systemic circulation: high clearance results in rapid removal and lower exposure, while low clearance slows elimination and prolongs systemic exposure.¹⁶² A study by Fu et al (2016) demonstrated that incorporating paclitaxel into mesoporous silica nanoparticles (MSNs) markedly altered the disposition of the drug following intraperitoneal (IP) administration. The MSN formulation produced a sustained drug-release profile within the peritoneal cavity, resulting in a substantial prolongation of drug retention compared to free paclitaxel. Pharmacokinetic evaluation showed that the MSN-based system increased the peritoneal AUC from 324.53 ± 33.32 to $547.97 \pm 26.9 \mu\text{g}\cdot\text{h}/\text{mL}$, representing a 1.69-fold enhancement in exposure. Because clearance is inversely proportional to AUC ($CL \propto 1/\text{AUC}$), this increase in peritoneal exposure corresponds to an estimated 41% reduction in apparent peritoneal clearance relative to the control formulation. The mean residence time (MRT) similarly increased from 17.83 to 56.86 hours, indicating prolonged local drug persistence. Together, these findings highlight that MSNs significantly slow the elimination of paclitaxel from the peritoneal cavity, promoting sustained locoregional drug availability and enhancing tumor accumulation by 6.5-fold.⁵¹ Mechanistically, this reduction in clearance is a direct consequence of the sustained, diffusion-controlled release enabled by the ordered mesoporous architecture of the hollow MSNs employed in the study. The high pore volume and tortuous diffusion pathways inherent to mesoporous carriers retard drug efflux from the administration site, effectively decoupling local drug disposition from rapid systemic elimination. The reduction in clearance, combined with improved retention and targeted delivery, underscores the potential of MSN-based carriers for optimizing paclitaxel pharmacokinetics.

Maximum Concentration

C_{max} reflects the peak plasma concentration, where excessively high levels can trigger concentration-dependent toxicities, while low values may lead to insufficient therapeutic effect. Abdellatif and Gebreel (2025) the pharmacokinetic profile of eprosartan loaded into spheroidal mesoporous silica SBA-15 and aminofunctionalized mesoporous silica SBA-15 was evaluated to assess the improvement in drug exposure. The results demonstrated a significant enhancement in systemic availability, where the C_{max} of the MSNs film increased by 2.88-fold ($C_{\text{max}}, 4.52 \pm 0.5 \mu\text{g}/\text{mL}$) compared to the oral dispersion of eprosartan ($C_{\text{max}}, 1.58 \pm 0.6 \mu\text{g}/\text{mL}$), with a statistically significant difference (unpaired t -test, $p = 0.029$). This elevation in C_{max} can be mechanistically linked to the amino-functionalization of the SBA-15 surface. The introduction of

amine groups enhances mucoadhesion and membrane permeability, promoting faster drug absorption across the buccal mucosa and consequently elevating peak plasma concentrations. These findings indicate that incorporating eprosartan into a mesoporous silica nanosystem notably enhances the absorption rate and the extent of drug exposure, suggesting an improvement in bioavailability attributed to better dissolution and permeability characteristics provided by the MSN-based delivery system.¹⁶³ In addition, differences in the shape of mesoporous silica can also affect C_{max} . Indomethacin as a drug is loaded in mesoporous silica with different structures, namely mesoporous silica nanospheres (IMC-MSNs) and mesoporous silica nanorods (IMC-MSNRs). In the C_{max} evaluation, IMC-MSNRs had a higher concentration in blood plasma (2.22-fold) with a value of 928.0 ± 24.8 mg/mL compared to IMC-MSNs which had a C_{max} of 417.4 ± 36.3 mg/mL. While in free IMC the C_{max} value only showed 234.2 ± 16.0 mg/mL. The superior performance of IMC-MSNRs is directly attributable to particle morphology. The elongated nanorod geometry provides a higher surface area-to-volume ratio and a unique helical pore structure. These features accelerate dissolution kinetics and prolong systemic circulation time compared to isotropic nanospheres, thereby maximizing the peak plasma concentration. Furthermore, in the dissolution test, IMC-MSNRs had a faster dissolution profile. This is because IMC-MSNRs have a helical pore structure and a larger surface area ratio.⁵⁰ These examples underscore that rational manipulation of MSN size, shape, and surface chemistry can be strategically employed to fine-tune C_{max} and optimize the onset of therapeutic action.

Half-Life

Half-life ($t_{1/2}$) indicates how long a drug persists in the body; a prolonged $t_{1/2}$ extends therapeutic effects but may cause accumulation and adverse outcomes, whereas a short $t_{1/2}$ requires more frequent dosing to maintain efficacy.²⁸ Mussalam et al (2022) the pharmacokinetic study comparing MRT oral suspension and optimized MRT-SBA-15, the $t_{1/2}$ of the optimized formulation (604 ± 0.58 hr) was significantly longer than that of the oral suspension (3.88 ± 0.23 hr). This 1.56-fold increase in elimination half-life suggests that the mesoporous silica-based delivery system slowed down the drug's elimination rate, thereby maintaining therapeutic concentrations for a longer duration. This prolongation of $t_{1/2}$ is mechanistically linked to the ordered mesoporous architecture of SBA-15, which functions as a drug reservoir enabling sustained, diffusion-controlled release. The gradual liberation of mirtazapine from the pore channels prolongs the absorption phase and delays the onset of elimination, thereby extending the apparent terminal half-life. Such an extended $t_{1/2}$ may contribute to improved patient compliance and enhanced therapeutic efficacy, supporting the potential of MRT-SBA-15 as a sustained-release formulation.⁵⁴ Furthermore, a study conducted by Mehmood et al (2020) evaluated the pharmacokinetic profiles of free velpatasvir namely an antiviral that has low solubility in water and velpatasvir loaded in mesoporous silica (VLP-MSN) which is expected to increase the bioavailability of velpatasvir. One of the parameters evaluated was the half-life ($t_{1/2}$) to find out how long it takes for a drug to reach half of its initial concentration in the body. The test results reported that the $t_{1/2}$ for VLP-MSN was 9.20 ± 0.52 , indicating a decrease compared to free MSN, which had a $t_{1/2}$ value of 10.76 ± 0.155 . This apparent shortening of half-life paradoxically reflects improved bioavailability. By stabilizing velpatasvir in an amorphous state within the mesoporous matrix, the MSN carrier dramatically accelerates dissolution, shifting the rate-limiting step from absorption to elimination. The drug is absorbed more rapidly and completely, leading to faster systemic clearance and a shorter observed $t_{1/2}$, yet with achieving an overall systemic exposure.⁴⁹

Pharmacological Activity of MSN-Based Formulations

In addition to pharmacokinetic improvements, the three selected studies also showed significant increases in pharmacological activity after MSN-based drug delivery. Chen et al (2017) reported that exenatide encapsulated in SBA-15 (EXT-SBA-15) produced a markedly prolonged hypoglycemic effect in diabetic mice, with blood glucose levels significantly reduced for up to 25 days after a single administration, in contrast to the rapid decline observed with EXT solution. This sustained pharmacodynamic effect closely aligned with the extended half-life and increased AUC reported in the pharmacokinetic study, thereby confirming the therapeutic advantage of MSN encapsulation for peptide drugs.⁴⁰ Similarly, Alhowyan et al (2023) demonstrated that ocular delivery of 5-fluorouracil using carboxymethyl chitosan-coated MSNs (AMSN-CMC-FU) not only enhanced ocular bioavailability but also translated into superior anticancer efficacy *in vitro*, while histopathological examination in rabbits confirmed good ocular tolerance without signs of irritation. These results suggest that pharmacokinetic gains achieved through MSN formulations directly support

improved therapeutic activity and safety in ophthalmic drug delivery.⁴¹ Furthermore, Liu et al (2016) showed that puerarin loaded into PEGylated MSNs (PUE@PEG-MSNs) conferred superior cardioprotective effects in a rat model of myocardial ischemia compared with puerarin injection. The enhanced activity was attributed to increased bioavailability and extended systemic circulation, which allowed the antioxidant and vasodilatory properties of puerarin to be sustained at therapeutically relevant levels.⁴²

Safety and Toxicity of MSN-Based Formulations

The translational potential of MSNs is fundamentally tied to their biocompatibility and long-term fate in vivo. Although amorphous silica is generally regarded as safe due to its degradation into orthosilicic acid ($\text{Si}(\text{OH})_4$) a naturally excretable metabolite the biological behavior of MSNs is governed by multiple physicochemical parameters, including particle size, surface charge, porosity, and coating chemistry.⁵² Unmodified MSNs, particularly those containing residual surfactants, have been shown to induce oxidative stress and membrane damage at elevated concentrations ($>200 \mu\text{g/mL}$) in vitro.¹⁶⁴ However, surface functionalization with polymers such as PEG, chitosan, or phospholipids substantially reduces nonspecific protein adsorption and improves hemocompatibility, often maintaining hemolysis rates below 5% under physiological conditions.¹⁶⁵ While cationic surface moieties enhance cellular uptake, they may also trigger platelet activation and hemolysis, underscoring the importance of charge-neutral or zwitterionic coatings for systemic administration.¹⁶⁶ With respect to long-term biodistribution, systemically administered MSNs are predominantly sequestered by the mononuclear phagocyte system (MPS) within the liver and spleen. Particle size critically influences clearance kinetics: smaller particles ($<50 \text{ nm}$) exhibit partial renal excretion, whereas larger particles ($>150 \text{ nm}$) undergo slower degradation via hydrolysis of siloxane (Si-O-Si) bonds, followed by urinary elimination of orthosilicic acid.^{167,168} Chronic exposure studies in rodent models have revealed minimal organ accumulation and no significant histopathological abnormalities at therapeutic doses ($<50 \text{ mg/kg}$).¹⁶⁹ Additionally, the formation of a dynamic protein corona upon contact with biological fluids modulates opsonization and immune recognition. PEGylated or zwitterionic surfaces preferentially adsorb dysopsonins such as albumin and clusterin, thereby prolonging systemic circulation.¹⁷⁰ Collectively, while well-engineered MSNs exhibit a favorable acute safety profile, comprehensive evaluation of chronic exposure, immunotoxicity, and organ-specific retention remains essential for clinical advancement.¹⁷¹

Despite robust preclinical efficacy, the clinical translation of MSN-based pharmaceutical products is hindered by the absence of standardized regulatory pathways and the inherent complexity of hybrid nanomaterials. Unlike conventional small-molecule drugs, MSNs reside in a regulatory grey zone, necessitating case-by-case evaluation by agencies such as the FDA and EMA. Key translational challenges include ensuring batch-to-batch consistency in particle size, pore architecture, and surface chemistry—parameters that directly influence pharmacokinetic performance and immunogenicity.¹²⁷ Establishing quality control protocols aligned with international standards (eg, ISO 10993 for biocompatibility and ICH Q8–Q10 for pharmaceutical development) is a prerequisite for Good Manufacturing Practice (GMP) production.^{172–175} Furthermore, regulatory approval requires comprehensive ADME profiling, including definitive data on silica degradation products and acceptable thresholds for residual surfactants or solvents.^{176,177} Although silica-based platforms such as “Cornell dots” have advanced to early-phase clinical trials for imaging applications the development pathway for drug-loaded MSNs remains in its infancy. Accelerating clinical translation will require harmonized pharmacological endpoints, standardized immunotoxicity assays, and long-term toxicological data generated under Good Laboratory Practice (GLP) conditions.¹⁷⁸

Bridging the divide between laboratory-scale innovation and industrial application demands a fundamental shift toward scalable and reproducible manufacturing processes. The conventional sol–gel synthesis of MSNs is highly sensitive to minor fluctuations in pH, temperature, and stirring rate, often resulting in significant batch-to-batch variability in pore morphology and drug loading efficiency. Recent advances in continuous-flow microfluidic reactors offer a promising solution, enabling precise control over reactant mixing and residence time to achieve uniform particle size distributions on a multi-kilogram scale.¹²⁹ Concurrently, the adoption of “green synthesis” strategies—employing biotemplates, ionic liquids, or supercritical fluids—addresses environmental concerns associated with traditional surfactant removal and organic solvent use. From a formulation perspective, maintaining long-term colloidal stability necessitates optimized lyophilization protocols incorporating cryoprotectants such as trehalose or mannitol.¹⁷⁹ Post-

synthetic modifications, including polymer grafting and ligand conjugation, must also be standardized to ensure consistent functionalization density, a factor that directly impacts pharmacokinetic behavior and therapeutic efficacy. Looking ahead, the integration of artificial intelligence (AI)-driven quality control and high-throughput screening will be instrumental in de-risking the manufacturing pipeline. By establishing robust, GMP-compliant supply chains and adhering to evolving regulatory guidelines. MSN-based delivery systems can transition from promising preclinical tools to clinically viable, next-generation therapeutics.

Discussion

A critical synthesis of the reviewed studies reveals a consistent yet highly tunable pharmacokinetic enhancement conferred by MSN-based delivery. The magnitude of improvement in AUC and C_{max} is not uniform but varies substantially depending on the interplay between drug properties, MSN architecture, and surface functionalization strategies. Each drug integrated into MSNs demonstrates unique pharmacokinetic characteristics shaped by its physico-chemical attributes, therapeutic category, and the particular alterations made to the MSN carrier. Numerous pharmaceuticals characterized by inherently inadequate oral absorption—such as peptides, natural compounds, and anticancer agents—encounter significant constraints, including low solubility, rapid enzymatic degradation, and brief systemic residence durations. These problems often lead to diminished bioavailability and inadequate therapeutic results. Although dose escalation may mitigate inadequate absorption, this strategy frequently increases the likelihood of systemic toxicity and treatment-related side effects. In this context, MSNs present a viable approach to surmount pharmacokinetic limitations by improving solubility, stabilizing unstable molecules, and regulating drug-release profiles via their distinctive structural and chemical characteristics. Their extensive surface area, adjustable pore structure, and tailored surface chemistry provide substantial drug loading, enhanced absorption, and extended systemic circulation, hence improving therapeutic effectiveness.

Numerous studies have demonstrated the ability of MSN formulations to significantly enhance pharmacokinetic performance. Quantitatively, the reviewed studies demonstrate substantial variability in pharmacokinetic enhancement, with reported AUC improvement ranging from 1.47-fold (puerarin-loaded MSNs) to 21.7-fold (carvedilol-loaded MSNs), and C_{max} enhancements reaching up to 15.7-fold, underscoring the high tenability of MSN carrier. These quantitative findings are consistent with the pharmacokinetic data summarized in Table 1, where multiple MSN-based formulations demonstrate measurable improvements in systemic exposure. As illustrated in Figure 4, improvements in key

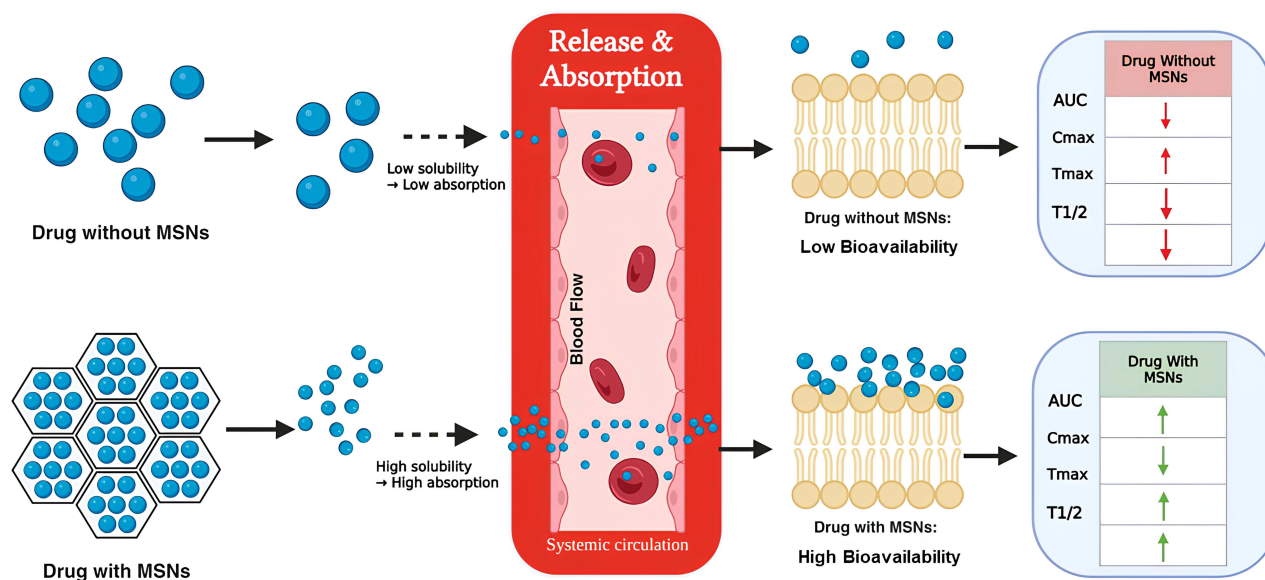


Figure 4 Comparative pharmacokinetic profiles of Drug without MSNs and Drug with MSNs. Upward arrows (↑) indicate an increase in pharmacokinetic parameters (eg, C_{max}, AUC), while downward arrows (↓) indicate a decrease. Rightward arrows (→) represent a shift in the absorption or elimination profile.

pharmacokinetic parameters—including area under the curve (AUC), maximum plasma concentration (C_{max}), and elimination half-life ($t_{1/2}$)—arise from synergistic mechanisms intrinsic to the MSN platform. Confinement within mesoporous channels promotes drug amorphization or nanodispersion, reducing crystallinity and increasing the surface-area-to-volume ratio. At the molecular level, the spatial confinement of drug molecules within nanoscale pores restricts molecular mobility and prevents the organization required for nucleation and crystal growth. In addition, interactions between drug molecules and the silanol groups on the silica surface – such as hydrogen bonding and electrostatic interactions – further inhibit recrystallization and stabilize the drug in a high-energy amorphous state. This dual effect of physical confinement and interfacial interaction plays a critical role in maintaining amorphous stability during storage and dissolution. As a result, this structural transformation enhances apparent solubility and accelerates dissolution kinetics, thereby increasing the fraction of drug available for absorption. Importantly, elevated AUC values often reflect an improved extent of absorption rather than merely accelerated absorption rates.

The ordered porous architecture further enables controlled and sustained release, minimizing burst effects while prolonging systemic exposure. Such release modulation can extend plasma residence time and, in some cases, increase the apparent half-life without fundamentally altering intrinsic elimination pathways. Surface functionalization amplifies these effects: modifications such as PEGylation or ligand conjugation reduce opsonization, limit recognition by the reticuloendothelial system, and decrease nonspecific plasma protein interactions. Collectively, these strategies prolong circulation time and enhance the probability of drug accumulation at target tissues.

The enhanced systemic exposure noted in [Table 1](#) and [Table 2](#) is a direct result of the interplay between diffusion-controlled and stimulus-responsive release mechanisms intrinsic to the MSN platform. In diffusion-controlled systems, the mesoporous channels act as a reservoir, where drug release is primarily governed by Fickian diffusion. For instance, Fu et al (2016) utilized hollow MSNs to achieve sustained, diffusion-mediated release of paclitaxel, leading to extended retention in the peritoneal cavity (mean residence time [MRT] increased from 17.8 to 56.9 hours) and improved tumor accumulation.¹⁸⁰ Similarly, Liu et al (2016) demonstrated that PEGylation of MSNs for puerarin encapsulation altered the diffusion characteristics by creating a hydrophilic barrier, which mitigated the initial burst release and enhanced the AUC by 1.47-fold. Beyond passive diffusion, surface functionalization facilitates stimulus-responsive activity, which further optimizes pharmacokinetic profile.⁵¹ For example, Jang et al (2015) incorporated carvedilol into an MSN-based self-nanoemulsifying drug delivery system (S-SNEDDS), creating a supersaturated condition upon interaction with gastrointestinal fluids. This stimulus-responsive process promoted rapid and complete absorption, resulting in a 21.7-fold increase in AUC.⁴² Similarly, Alhowyan et al (2023) employed carboxymethyl chitosan-coated MSNs for ocular delivery of 5-fluorouracil, where the coating enabled pH-triggered controlled release in the eye, maintaining therapeutic levels and resulting in a 6.14-fold enhancement in ocular AUC.⁵⁶ These examples emphasize the critical role that controlling the timing and location of drug release plays in optimizing pharmacokinetics, whether through manufactured diffusion barriers or environmental triggers.

The magnitude of pharmacokinetic enhancement is highly dependent on formulation-specific parameters, including pore size, particle size, surface chemistry, and drug-to-carrier ratio. Suboptimal design may result in insufficient loading, premature leakage, or excessively slow release. Therefore, pharmacokinetic modulation by MSNs should be viewed as a tunable process requiring rational optimization to balance solubility enhancement, release kinetics, biodistribution, and systemic stability. Through careful engineering of mesoporous architecture and surface properties, MSNs can translate physicochemical modifications into meaningful alterations in systemic drug exposure. These pharmacokinetic improvements are closely linked to therapeutic performance. Increased systemic exposure and prolonged retention can enhance pharmacodynamic response, reduce dosing frequency, and potentially mitigate peak-related toxicity by smoothing plasma concentration fluctuations. Thus, the principal contribution of MSNs extends beyond bioavailability enhancement to the strategic reshaping of drug exposure profiles in order to optimize therapeutic outcomes.

Despite the promising pharmacokinetic advancements, the clinical application of MSN-based drug delivery systems faces several significant challenges. Aggregation remains a major concern, particularly in aqueous environments, where MSNs can cluster, negatively impacting their stability, drug-loading capacity, and controlled release properties. Additionally, premature drug release can occur when MSNs are exposed to physiological conditions that compromise their structural integrity, leading to reduced therapeutic efficacy and potentially increased toxicity. Another challenge is

the biodegradability of MSNs, as their slow degradation rate may result in accumulation over time, causing long-term toxicity or triggering immune responses. Notably, The toxicity and tolerability of MSNs are significantly dependent on the formulation. According to the Safety and Toxicity section, unmodified MSNs can cause oxidative stress at high doses (>200 µg/mL), but surface-functionalized MSNs demonstrate much enhanced hemocompatibility, with hemolysis rates around 5%. Particle size determines clearance routes, with diminutive particles promoting renal excretion and bigger particles collecting in the liver and spleen. This heterogeneity highlights the necessity for rigorous, formulation-specific safety assessments.

To overcome these challenges, surface functionalization plays a crucial role in improving stability, targeting, and biocompatibility of MSNs. Modifications such as PEGylation or grafting targeting ligands (eg, folic acid) enhance colloidal stability, extend circulation time, and enable targeted drug delivery, which optimizes pharmacokinetics. For example, Liu et al (2016) demonstrated that PEGylation of MSNs for puerarin encapsulation altered diffusion characteristics, reducing the initial burst release and improving AUC by 1.47-fold. These functionalizations help mitigate premature drug release, enhance therapeutic efficacy, and improve drug retention at the target site, ultimately boosting the therapeutic index.⁴¹ The integration of MSN with other targeting ligands or hybrid systems, as seen in recent nanomedicine developments, could further refine the precision of drug delivery.^{42,181,182} Moreover, while many studies show favorable short-term biocompatibility, long-term safety data remain limited. Concerns such as chronic accumulation, organ-specific retention, immunological modulation, and prolonged degradation require further investigation. The absence of standardized toxicological evaluation frameworks complicates regulatory assessments and inter-study comparability. Addressing these issues requires ongoing innovations in surface functionalization, encapsulation techniques, and release rate control to ensure that MSNs are biodegradable or can be safely eliminated after completing their therapeutic role. Future advancements in MSN-based systems will need to integrate pharmacokinetic optimization with clearance pathway investigations, biodegradation kinetics, and chronic safety profiles to ensure that enhanced systemic exposure is met with consistent and reliable safety assurance.

Conclusion

In conclusion, mesoporous silica nanoparticles (MSNs) show strong potential as drug delivery systems to improve the solubility, bioavailability, and pharmacokinetic profiles of poorly soluble drugs. Their high surface area, tunable pore size, and versatile surface modification enable efficient drug loading, stabilization of drugs in an amorphous form, and controlled release, leading to enhanced absorption and systemic exposure. However, despite promising preclinical results, the clinical translation of MSN-based formulations remains challenged by concerns regarding long-term safety, clearance mechanisms, large-scale manufacturing, and the lack of standardized regulatory frameworks. Future research should focus on chronic toxicity studies in large animal models to enhance predictions of human biodistribution and organ retention, the development of physiologically based pharmacokinetic (PBPK) models to simulate the *in vivo* fate of MSNs, and the development of standardized characterization protocols to guarantee batch-to-batch consistency under Good Manufacturing Practice (GMP) conditions. Moreover, meticulously designed early-phase clinical trials would be crucial to confirm the safety and pharmacokinetic benefits demonstrated in preclinical studies. By methodically addressing these translational limitations, MSN-based delivery systems can progress from promising laboratory instruments to clinically viable platforms for next-generation medicines.

Author's Perspective

Current evidence positions mesoporous silica nanoparticles (MSNs) as one of the most adaptable nanoplatforms for overcoming fundamental pharmacokinetic barriers across diverse therapeutic classes. Improvements in solubility, molecular stability, and systemic exposure have been demonstrated repeatedly, suggesting that the advantages of MSNs extend far beyond any single drug category. Yet, despite this breadth of potential, most advances remain confined to preclinical exploration. A pronounced gap still separates mechanistic promise from clinically deployable technology. Bridging this divide requires a shift from predominantly empirical optimization toward predictive, design-oriented development frameworks capable of translating physicochemical enhancements into reproducible therapeutic benefit.

Several entrenched challenges continue to limit the progression of MSNs toward clinical maturity. Formulation-dependent variability in loading efficiency, release kinetics, and systemic stability remains substantial, undermining reproducibility both within and across research groups. The absence of standardized characterization protocols further complicates cross-study interpretation, while long-term human data on biodistribution, clearance, biodegradation, and chronic exposure remain markedly insufficient to establish regulatory confidence. Manufacturing constraints compound these issues: achieving batch-to-batch control over pore architecture and surface chemistry—parameters central to performance—remains technically demanding and difficult to scale. Without decisive solutions to these interconnected obstacles, MSNs risk remaining confined to proof-of-concept demonstrations rather than advancing toward meaningful clinical implementation.

Realizing the clinical promise of MSNs demands a decisive evolution in research strategy. Progress will rely on rational design principles supported by computational modeling, machine-learning-based prediction of drug-carrier interactions, and quantitative structure-property frameworks that enable anticipatory formulation design. Equally critical is comprehensive evaluation of long-term safety, biodegradation pathways, and in vivo fate under clinically relevant dosing paradigms to define realistic translational boundaries. Parallel development of scalable, quality-assured manufacturing pipelines is essential to ensure physicochemical uniformity across production sites and regulatory jurisdictions. Momentum in these areas would reposition MSNs not merely as experimental enhancers of pharmacokinetics, but as robust, clinically credible platforms with the capacity to support next-generation therapeutics—particularly those constrained by poor solubility, structural fragility, or rapid systemic clearance.

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Disclosure

The authors report no conflicts of interest in this work.

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