

The Application of Mesoporous Silica Nanoparticles in Enhancing the Efficacy of Anti-Atherosclerosis Therapies: A Review

Arif Budiman¹, Luthfiyyah Mutmainah¹, Martina Anjelina¹, Mila Karisma Fitriawati¹,
Eufasia Ine Pilihanto¹, Salma Amaliah¹, Diah Lia Aulifa²

¹Department of Pharmaceutics and Pharmaceutical Technology, Faculty of Pharmacy, Universitas Padjadjaran, Bandung, West Java, Indonesia;

²Department of Pharmaceutical Analysis and Medicinal Chemistry, Faculty of Pharmacy, Universitas Padjadjaran, Bandung, West Java, Indonesia

Correspondence: Arif Budiman, Department of Pharmaceutics and Pharmaceutical Technology, Faculty of Pharmacy, Universitas Padjadjaran, Jl. Raya Bandung-Sumedang Km. 21, Bandung, 45363, Indonesia, Email arif.budiman@unpad.ac.id

Abstract: Atherosclerosis (AS) is a chronic inflammatory condition of large arteries and a major contributor to cardiovascular disease (CVD) and stroke. The prevention of AS diseases involves numerous anti-atherosclerosis agents, including antihyperlipidemic and antihypertensive drugs. However, these drugs often exhibit poor aqueous solubility, which can affect their bioavailability and therapeutic efficacy. Mesoporous silica nanoparticles (MSNs) have emerged as effective drug delivery systems due to their high surface area, tunable pore sizes, surface functionalization potential, and physicochemical stability. These characteristics enable enhanced drug loading, regulated release, and stabilization of amorphous drug forms, thereby improving solubility, permeability, pharmacokinetics, and therapeutic efficacy. This review offers an in-depth look at MSN-based strategies for optimizing the delivery of anti-atherosclerosis drugs, particularly those targeting cholesterol levels and blood pressure control. Relevant data were sourced from PubMed, Scopus, and Google Scholar using the keywords “mesoporous silica nanoparticle”, “atherosclerosis”, “antihyperlipidemic”, and “antihypertensive.” Numerous studies have demonstrated the ability of MSN formulations to significantly enhance drug performance, with reported enhancements in solubility and bioavailability ranging from 1.4-fold to 88-fold, depending on the drug and formulation. For example, nifedipine-loaded MSNs showed an 88-fold increase in solubility compared to the pure drug and a 10-fold improvement over marketed tablets. Simvastatin-loaded MSNs achieved a 6.1-fold enhancement in oral bioavailability, while efendipine-loaded MSNs exhibited up to a 3.5-fold increase in dissolution and permeability. These advancements may result in decreased dosing frequencies, reduced drug dosages, and fewer adverse effects, ultimately improving patient compliance. However, clinical translation remains limited due to the lack of early-phase clinical trials, insufficient long-term safety data, and challenges associated with large-scale MSN manufacturing. This review highlights the therapeutic potential of MSNs in cardiovascular applications and points out that it requires further research to address translational barriers. With continued development, MSN-based delivery systems hold strong potential to enhance the clinical effectiveness of anti-atherosclerosis therapies.

Keywords: atherosclerosis, mesoporous silica, antihyperlipidemic, antihypertensive, bioavailability

Introduction

The World Health Organization (WHO) reported that in 2021, atherosclerosis (AS) was associated with approximately 19 million deaths annually, positioning it as one of the leading chronic diseases globally. In the United States, AS was a major contributor to cardiovascular diseases, including myocardial infarction (MI), heart failure, and stroke, with more than 50% related deaths each year.¹ AS underlies various arterial diseases, including ischemic stroke, heart attack, and peripheral arterial disease.^{2,3} AS is closely associated with both aging and premature biological aging, as atherosclerotic plaques exhibit features of cellular senescence marked by reduced proliferation, cell cycle arrest, increased apoptosis, and elevated DNA destruction. These instances of cellular senescence play a significant role in the progression of AS.^{4,5}

Currently, pharmacological treatments focus on managing major risk factors, particularly hypercholesterolemia/hyperlipidemia and elevated blood pressure, using lipid-lowering and antihypertensive agents.

Various pharmacological agents used to inhibit the progression of AS, including antihyperlipidemic and antihypertensive drugs, often encounter challenges such as poor aqueous solubility and adverse effects like myopathy and hepatotoxicity. These limitations compromise systemic bioavailability and reduce therapeutic efficacy.^{6,7} To address these challenges, several strategies have been explored, including the use of nanocarriers. Among various nanocarriers, mesoporous silica nanoparticles (MSNs) offer distinct advantages, including high physicochemical stability, biocompatibility, substantial drug loading capacity, tunable pore sizes, and ease of surface functionalization.^{8,9} Compared to liposomes and dendrimers, MSNs demonstrate superior scalability and structural integrity, making them particularly suitable for oral drug delivery systems.^{10–12}

Recently, mesoporous silica has emerged as a promising carrier for oral drug delivery, particularly in enhancing the dissolution profiles of poorly soluble drugs.^{13–15} These mesoporous materials possess nanoscale pores capable of accommodating drug molecules in a non-crystalline or amorphous state, thereby improving their solubility and dissolution rate.^{16,17} The drug is encapsulated within the pores, adapting to their nanosize and leveraging their high surface area. Additionally, due to the confined space within the pores, the drug molecules are unable to arrange in a regular pattern to form a crystal lattice structure, leading to the formation of an amorphous form or semi-crystalline structures.^{18,19} The high surface area of mesoporous silica further supports efficient drug loading. Moreover, oral toxicity studies have demonstrated the safety of silica-based carriers for oral drug delivery systems.^{19,20} Accordingly, the MSN represents a promising strategy to enhance the bioavailability of antihyperlipidemic and antihypertensive drugs while minimizing their side effects, leading to the improvement of their efficacy, safety, and stability.

Significant attention has been given to the incorporation of antihyperlipidemic and antihypertensive drugs into MSNs.^{21–23} The ability of MSNs to encapsulate and protect antihyperlipidemic and antihypertensive drugs, along with enhancing bioavailability, presents an innovative strategy in drug delivery systems.^{17,24,25} However, despite extensive research on MSNs for drug delivery, there is a lack of review articles explicitly addressing their use in the delivery of antihyperlipidemic and antihypertensive drugs. While previous reviews have broadly explored the potential of MSNs in drug delivery, focused analyses of these two therapeutic classes remain limited in the current literature.

This review addresses the identified gap by presenting a comprehensive analysis of the use of MSNs to enhance the delivery and therapeutic efficacy of antihyperlipidemic and antihypertensive drugs. It begins with an overview of the structural and physicochemical properties of MSNs, followed by a detailed analysis of their application in the delivery of cholesterol-lowering and blood pressure-regulating drugs. Additionally, the review discusses the pharmacological mechanisms, *in vitro* and *in vivo* efficacy, and MSN-drug interactions.

Furthermore, this review underscores key challenges in the clinical translation of MSN-based therapies, including limited long-term safety data, a lack of Phase I/II clinical studies, regulatory uncertainties, and scalability issues in pharmaceutical manufacturing. It aims to elucidate the potential of MSNs in advancing cardiovascular therapy and to encourage further research and innovation in this emerging field.

Methods

This review compiled relevant literature from PubMed, Scopus, and Google Scholar using keywords such as “mesoporous silica nanoparticles”, “atherosclerosis”, “antihyperlipidemic”, and “antihypertensive.” After the removal of duplicates, titles and abstracts were screened for relevance, followed by full-text evaluations to assess methodological rigor and contribution to the review’s objectives. Studies emphasizing solubility enhancement, pharmacokinetic improvement, and therapeutic applications of MSNs in cardiovascular-related treatments were prioritized. The selection process was conducted collaboratively by the review team to ensure consistency and minimize the risk of selection bias.

Atherosclerosis

Cardiovascular diseases (CVDs) have remained the leading cause of global mortality, accounting for nearly 20 million deaths worldwide in 2021, which has established them as the primary cause of death in middle- and high-income nations for decades.²⁶ Atherosclerosis leads to the formation of plaques within blood vessels. This obstruction significantly

contributes to the initiation and progression of cardiovascular diseases. The term “atherosclerosis” originates from the Greek terms “athero” (gruel or paste), which describes the characteristic hardened tissue appearance of atherosclerotic plaque.²⁷ This condition develops when fat accumulates in the bloodstream, leading to chronic inflammation and further exacerbation within the artery walls.²⁸

Atherosclerosis initiates with the deposition of low-density lipoprotein (LDL) in the subendothelial layers of arteries.²⁹ LDL adheres to extracellular matrix proteins exposed by activated endothelial cells and is then oxidized by reactive oxygen species (ROS), resulting in oxidized LDL (ox-LDL). Macrophages then internalize both LDL and ox-LDL through scavenger receptors to generate foam cells. Foam cells and macrophages, secrete numerous pro-inflammatory cytokines, including soluble cluster of differentiation 40 (CD40) ligand, interleukin-1 (IL-1), IL-3, IL-6, IL-8, and tumor necrosis factor- α (TNF- α). IL-1 β , IL-6, and TNF- α induce the liver to synthesize C-reactive protein (CRP), a significant inflammatory biomarker. Endothelial cells play a crucial role in the production of atherosclerotic plaques, particularly when stimulated by dyslipidemia or hypertension. These cells enhance the transcription of nuclear factor- κ B (NF- κ B) and express adhesion molecules including E-selectin, P-selectin, intercellular adhesion molecule-1 (ICAM-1), and vascular cell adhesion molecule-1 (VCAM-1). In conjunction with ox-LDL, these adhesion molecules facilitate leukocyte migration past the compromised endothelium into the intima of the blood vessel, resulting in the production of additional pro-inflammatory mediators that extend the inflammatory response. Arterial smooth muscle cells react to chemoattractants, small soluble molecules that bind to leukocyte receptors and enhance their activity, produced by activated leukocytes like platelet growth factor. This reaction triggers smooth muscle cells to migrate from the tunica media toward the intimal layer, contributing to the structural formation of mature atherosclerotic plaques. T cells exhibit both preventive and detrimental functions in the development of atherosclerosis. T regulatory cells (Tregs) and Th-17 cells reinforce plaques by secreting anti-inflammatory cytokines and augmenting the fibrous cap, while T helper 1 (Th1) cells exacerbate atherosclerosis through the secretion of interferon- γ and TNF- α . Platelets exacerbate plaque development by adhering to endothelial cells, secreting chemokines and adhesion molecules, and facilitating LDL oxidation and macrophage ingestion. Collectively, these processes sustain chronic inflammation and plaque development, which are key features of atherosclerosis.³⁰ Figure 1 illustrates the mechanism of atherosclerotic formation.

Currently, pharmacological treatments primarily focus on effectively managing major risk factors such as hypercholesterolemia/hyperlipidemia and elevated blood pressure. Several regimens are widely used in managing those risk factors, such as lipid-modifying agents for hyperlipidemia risks and antihypertensive agents for uncontrolled hypertension risks.

Antihyperlipidemics

Mechanism of Action of Antihyperlipidemic Drugs

Hyperlipidemia disrupts lipid metabolism in the bloodstream, resulting in elevated lipid levels. Lipids in the body consist of unesterified cholesterol, triglycerides (TG), phospholipids, and proteins.³¹ Lipids are transported in the bloodstream as lipoproteins: chylomicrons, very low-density lipoprotein (VLDL), intermediate-density lipoprotein (IDL), low-density lipoprotein (LDL), and high-density lipoprotein (HDL). Each type plays a distinct role in transporting cholesterol and triglycerides in the body. Hyperlipidemia is associated with numerous disorders, including atherosclerosis, which illustrates the importance of drugs that can reduce elevated lipid levels.³² Healthcare providers commonly utilize lipid-lowering therapies, such as statins, fibrates, bile acid sequestrants, cholesteryl ester transfer protein (CETP) inhibitors, proprotein convertase subtilisin kexin 9 (PCSK9) inhibitors, and ezetimibe, to prevent cardiovascular disease (CVD).³³ Moreover, the mechanisms of action of antihyperlipidemic drugs are illustrated in Figure 2.

Statin

Statins are primary lipid-lowering drugs that inhibit the enzyme 3-hydroxy-3-methylglutaryl-coenzyme A (HMG-CoA) in the liver, reducing the conversion of HMG-CoA to mevalonic acid, a key step in cholesterol production. The activate sterol-regulated binding protein-2 (SREBP-2) pathway increases LDL receptor expression and enhances liver uptake of apo-B-containing lipoproteins, leading to lower plasma lipid levels.^{34,35} Examples of statins include fluvastatin, pravastatin, rosuvastatin, cerivastatin, lovastatin, simvastatin, and atorvastatin.³⁶

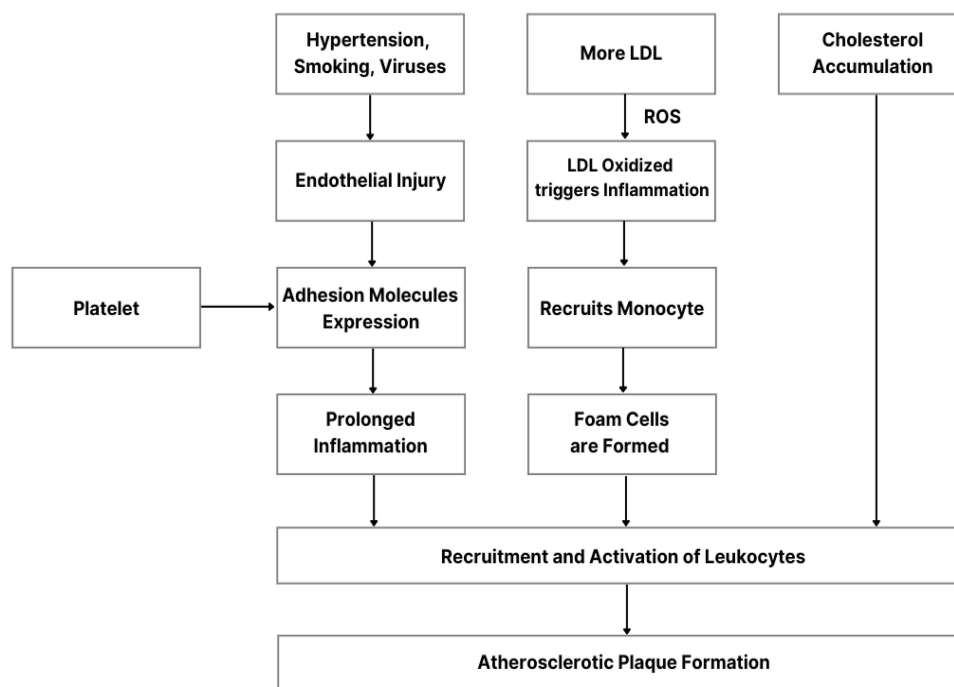


Figure 1 Illustrates the mechanisms of atherosclerotic plaque formation. Adapted from Szwed P, Gasecka A, Zawadka M, Eyileten C, Al. E. Infections as novel risk factors of atherosclerotic cardiovascular diseases: Pathophysiological links and therapeutic implications. *J Clin Med.* 2021;10(12):2539. Licensed under Creative Commons Attribution 4.0 International License (CC BY 4.0).³⁰

Cholesteryl Ester Transfer Protein (CETP)

CETP is a hydrophobic glycoprotein that facilitates lipid transfer; inhibiting its activity raises HDL levels and reduces CE concentrations in VLDLs and LDLs. Notable CETP inhibitors include torcetrapib, dalcetrapib, evacetrapib, and anacetrapib.³⁷ Fibrates, such as gemfibrozil and fenofibrate, act as agonists of peroxisome proliferator-activated receptors (PPAR α), enhancing HDL production by diminishing CETP activity, which lowers triglycerides and VLDL production.³⁸

Bile Acid Sequestrants (BAS)

BAS are cationic polymeric that prevent the conversion of cholesterol into bile in the liver, thereby enhancing low-density lipoprotein (LDL) receptor activity and facilitating the clearance of low-density lipoprotein cholesterol (LDL-C). Cholestyramine, colestipol, and colesvelam are FDA-approved drugs used to treat hypercholesterolemia.³⁹ Due to side effects when combined with statins as well as BAS's benefits for other conditions like diabetes, their clinical uses are being reevaluated.⁴⁰

Proprotein Convertase Subtilisin Kexin 9 (PCSK9)

The inhibitory effect of PCSK9 diminishes LDL receptor (LDL-R) degradation, enhancing hepatic absorption of LDL-C to lower LDL-C concentrations. Evolocumab and alirocumab are monoclonal antibodies that inhibit PCSK9, limiting its binding to LDL receptors in hepatocytes and so averting the degradation of LDL receptors mediated by PCSK9.⁴¹ Small interfering RNA (siRNA) therapy, such as inclisiran, blocks the production of PCSK9. Inclisiran is a type of siRNA made of two strands of RNA and linked to a sugar molecule called N-acetylgalactosamine (GalNAc), which helps it target the liver. Its main goal is to block the production of PCSK9.³⁴

Niemann–Pick C1-Like 1 Protein (NPC1L1) Inhibitor

Ezetimibe is an established inhibitor of the NPC1L1. Ezetimibe diminishes the hepatic cholesterol reservoir and enhances the expression of LDL receptors on hepatocytes, resulting in increased elimination of LDL cholesterol from the circulation.⁴² Bempedoic acid works by directly and competitively inhibiting an enzyme called ATP citrate lyase (ACL), reducing acetyl-CoA production and cholesterol synthesis in the liver.³⁴

Presenting profiles of approved anti-hyperlipidemic drugs currently available can be seen in [Table 1](#).

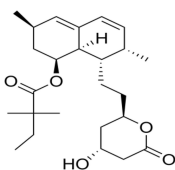
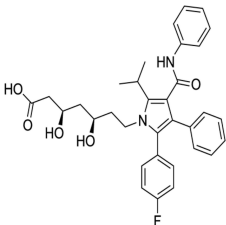
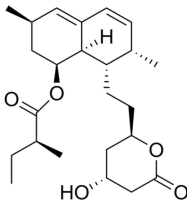
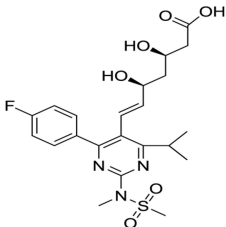
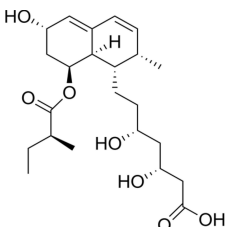
Antihypertensive

Mechanism of Action of antihypertensive Drugs

Diuretics

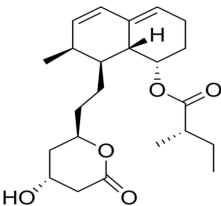
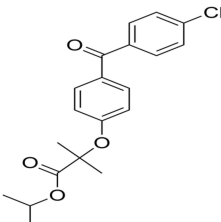
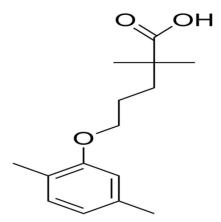
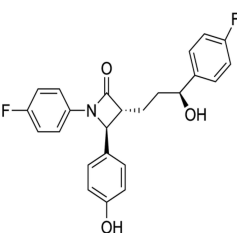
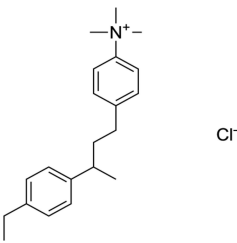
Diuretics are a diverse group of drugs that increase urine output.⁵⁷ Diuretics are classified by their mechanism of action and their effect site in the nephron.⁵⁸ Carbonic anhydrase inhibitors (eg, acetazolamide) act on the proximal tubule, reducing Na^+ and HCO_3^- reabsorption, causing mild diuresis. Loop diuretics (eg, furosemide) act on the ascending loop of Henle, strongly inhibiting Na^+ reabsorption, and are effective even with low GFR. Thiazide diuretics (eg, hydrochlorothiazide) act on the distal tubule, reduce Na^+ reabsorption, and are used for hypertension and edema.⁵⁹

Table 1 Antihyperlipidemic Drugs Profile

No	Antihyperlipidemic	Structure	Molecular weight	Mechanism of Action	Solubility in Water	Ref.
1.	Simvastatin		418.6 g/mol	Inhibit the conversion of HMG-CoA into mevalonic acid as a precursor of de novo cholesterol by the rate-limiting enzyme 3-hydroxy-3-methylglutaryl-coA reductase (HMGCR).	Slightly soluble (30 µg/mL)	[43,44]
2.	Atorvastatin		558.6 g/mol		Slightly soluble (20.4 µg/mL)	[45]
3.	Lovastatin		404.5 g/mol		Practically insoluble (0.4 µg/mL)	[46]
4.	Rosuvastatin		481.5 g/mol		Slightly soluble (10 µg/mL)	[47]
5.	Pravastatin		424.5 g/mol		Insoluble in water (1.3–1.5 µg/mL)	[48]

(Continued)

Table I (Continued).

No	Antihyperlipidemic	Structure	Molecular weight	Mechanism of Action	Solubility in Water	Ref.
6.	Mevastatin		390.5 g/mol		Very poorly soluble (36.8 µg/mL)	[49]
7.	Fenofibrate		360.8 g/mol	Peroxisome proliferator activated receptors (PPARα) agonist and act through various transcription factors to regulate lipoprotein metabolism to lower fasting and postprandial TG levels.	Practically insoluble (0.21 ± 0.05 µg/mL)	[50,51]
8.	Gemfibrozil		250.33 g/mol		Slightly soluble (19 µg/mL)	[48]
9.	Ezetimibe		409.4 g/mol	Niemann–Pick C1-like 1 protein (NPC1L1) protein blocker to prevent the uptake of cholesterol micelles into enterocytes in the intestinal epithelium or hepatocytes, reducing cholesterol absorption and upregulates the expression of LDL receptors on hepatocytes, leading to an increase in LDL-C removal from the blood.	Slightly soluble (12 µg/mL)	[52,53]
10.	Cholestyramine	 Cl ⁻	382.6 g/mol	Bind the negatively charged bile acids in the small intestine, avoiding their reabsorption, and causing fecal bile acid excretion, thus induces the conversion of cholesterol into bile within the liver, which promotes an increase in low density lipoprotein (LDL) receptors and LDL-C clearance.	Insoluble in water (< 100 µg/mL)	[54]

Calcium Channel Blocker (CCB)

CCBs work by blocking calcium movement at L-type voltage-gated calcium channels, leading to vasodilation.⁶⁰ Calcium channel blockers (CCBs) are divided into dihydropyridines (DHPs) and non-DHPs. DHP-CCBs are vascular-selective vasodilators, while non-DHP-CCBs are cardiac-selective, used for tachyarrhythmia, but decrease cardiac contractility and heart rate.⁶¹ Examples of DHP include amlodipine and nimodipine, while non-DHP examples are diltiazem and verapamil.^{62,63}

Angiotensin-Converting Enzyme Inhibitor (ACEI)

ACE inhibitors block angiotensin-converting enzymes therefore inhibit hydrolyzing angiotensin I to produce angiotensin II that promote vasodilator and lowers blood pressure.^{64,65} Lisinopril is the most commonly used antihypertensive regimen worldwide.⁶⁶

Angiotensin II Receptor Blockers (ARBs)

ARBs inhibit the effects of angiotensin II by preventing it from binding to the angiotensin II type 1 receptor (AT1 receptor), thereby contributing to lower blood pressure.⁶⁷ Irbesartan, losartan, telmisartan, and valsartan are examples of ARBs.⁶⁸

Angiotensin Receptor-Neprilysin Inhibitor (ARNI)

The mechanism of action of ARNI entails the inhibition of both the angiotensin II receptor and the neprilysin enzyme (NEP), which inhibits atrial natriuretic peptide (ANP) and brain natriuretic peptide (BNP).⁶⁹ This dual inhibition mitigates the detrimental effects of the renin-angiotensin-aldosterone system (RAAS) and amplifies the advantageous effects of natriuretic peptides.⁷⁰ Sacubitril/valsartan is the first of the class of ARNI.⁷¹

Mineralocorticoid Receptor Antagonists (MRAs)

MRAs block mineralocorticoid receptors to counteract aldosterone's harmful effects, improving fluid balance and protecting the heart, vessels, and kidneys from inflammation and damage.⁷² Some examples of MRAs are spironolactone and eplerenone.⁷³

Furthermore, the mechanism of action of antihypertensive medications is illustrated in [Figure 3](#).

Profiles of approved antihypertensive drugs can be seen in [Table 2](#).

Limitation of Current Drugs

These antihyperlipidemic and antihypertensive drugs exhibit poor water solubility, according to the data on their physical and chemical properties presented in [Tables 1](#) and [2](#). Limited aqueous solubility can significantly impact the drug's distribution inside the body,^{93,94} thereby diminishing its bioavailability and rendering the prescribed dose ineffective.^{95,96} To overcome this challenge, researchers have utilized various approaches to enhance the solubility of the active ingredient. Numerous chemical and physical techniques have been developed to improve drug solubility.⁹⁷

Examples of chemical approaches include manipulating salt formation through acid-base reactions to enhance drug solubility. However, salt formation improves solubility without necessarily decreasing the required drug dosage. Cocrystallization is another promising technique that enhances solubility and dissolution, and improves both the physical and chemical properties of drugs. Cocrystals are multicomponent crystalline structures composed of active compounds and a co-former that establish hydrogen and van der Waals interactions to produce crystals. The selection of an appropriate co-former and the quality of the co-crystal remain the primary challenges in this process.⁹⁸ Another approach is co-solvency, which involves the addition of a water-soluble solvent to reduce surface tension between water and the drug. However, this method can be restricted by uncontrolled solid formation and the incompatibility of numerous insoluble compounds with available co-solvents.⁹⁹

Various physical procedures, in addition to chemical approaches, frequently enhanced drug solubility. One such method is particle size reduction; as particle size decreases, the surface area available for interaction with the solvent increases.¹⁰⁰ Nonetheless, this approach can lead to aggregation and degradation of active materials due to physical or mechanical stress. Another approach involves altering the crystal habit via polymorphism. Polymorphism refers to the

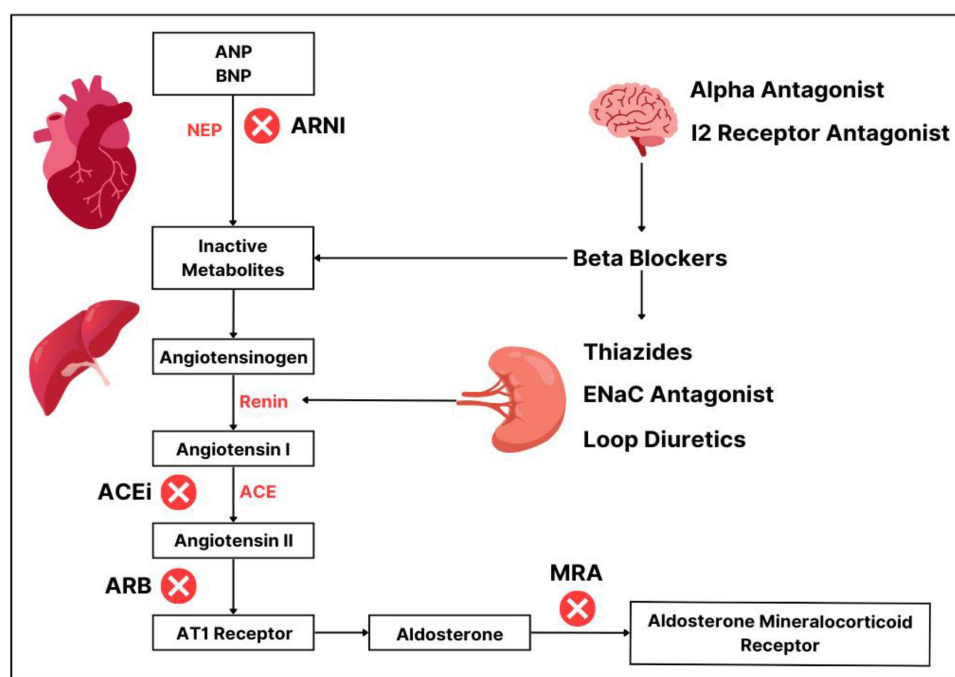


Figure 3 Mechanisms of action for antihypertensive drugs. Adapted from Kreutz R, Algharably E. Encyclopedia of Molecular Pharmacology. Springer; 2021. Permission conveyed through Copyright Clearance Center, Inc.⁷⁴

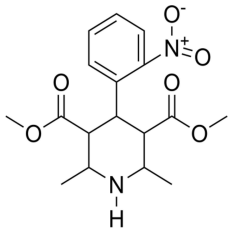
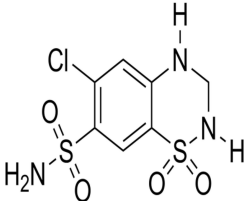
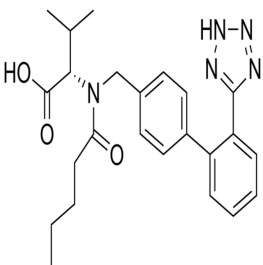
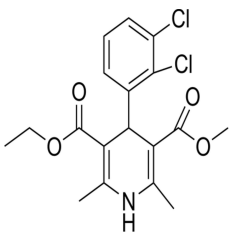
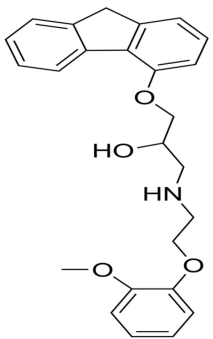
ability of a substance to crystallize in more than one distinct crystalline form. Despite having identical chemical compositions, several pharmacological polymorphs exhibit unique physicochemical properties. The amorphous form of a drug generally exhibits higher apparent solubility and faster dissolution rates compared to its crystalline form, primarily due to its higher free energy and greater molecular mobility.⁹⁹ Nonetheless, polymorphic transitions can lead to solid-

Table 2 Antihypertensive Drug Profile

No	Antihypertensive	Structure	Molecular weight	Mechanism of Action	Solubility in Water	Ref.
I.	Amlodipine Besylate		567.1 g/mol	Inhibits selected membrane calcium channels.	Slightly soluble (2930 µg/mL)	[75,76]

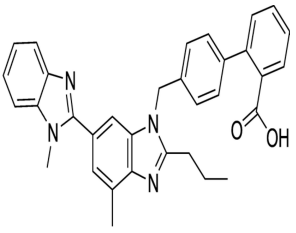
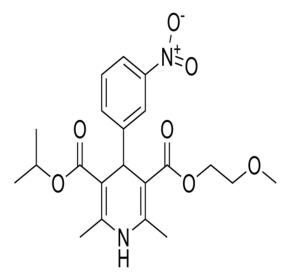
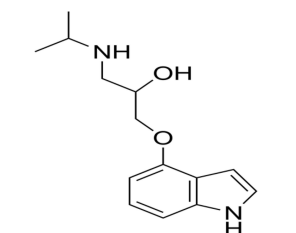
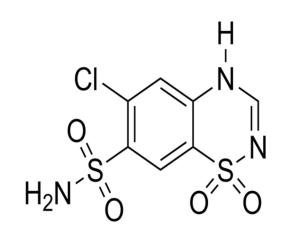
(Continued)

Table 2 (Continued).

No	Antihypertensive	Structure	Molecular weight	Mechanism of Action	Solubility in Water	Ref.
2.	Nifedipine		346.3 g/mol	Inhibit L-type voltage gated calcium channels.	Insoluble (< 100 µg/mL)	[77,78]
3.	Hydrochlorothiazide		297.7 g/mol	Prevents the reabsorption of sodium and water from the distal convoluted tubule.	Slightly soluble (700 µg/mL)	[79,80]
4.	Valsartan		435.5 g/mol	Inhibits the pressor effects of angiotensin II.	Slightly soluble (45.12 µg/mL)	[81,82]
5.	Felodipine		384.2 g/mol	Blocks the transmembrane influx of calcium ions into vascular and cardiac smooth muscle, producing direct relaxation of vascular smooth muscle.	Practically insoluble in water (19.7 µg/mL)	[83–85]
6.	Carvedilol		406.5 g/mol	Adrenergic antagonist with non-selective beta- and alpha-1 receptor blocking.	Practically insoluble in water (93 µg/mL)	[87]

(Continued)

Table 2 (Continued).

No	Antihypertensive	Structure	Molecular weight	Mechanism of Action	Solubility in Water	Ref.
7.	Telmisartan		514.6 g/mol	Blocking a substance in the body that causes blood vessels to tighten	Practically insoluble in water (4 µg/mL)	[86,88]
8.	Nimodipine		418.44 g/mol	Stabilizing voltage-gated L-type calcium channels in their inactive conformation.	Practically insoluble in water (4.6 µg/mL)	[89,90]
9.	Pindolol		248.32 g/mol	Inhibits the release of renin, especially inhibits angiotensin II and aldosterone release.	Practically insoluble in water (<100 µg/mL)	[91]
10.	Chlorothiazide		295.72 g/mol	Interference with the renal tubular mechanism of electrolyte reabsorption	Very slightly soluble in water (693 µg/mL)	[92]

state instability and clinical failure.¹⁰¹ In addition to these methods, mesoporous silica nanoparticles (MSNs) serve as an effective method by enhancing solubility and minimizing drug dosage without inducing adverse effects.

Mesoporous Silica Nanoparticles (MSNs)

Mesoporous silica nanoparticles (MSNs) represent an extensively developed nanotechnology for diagnostic and therapeutic applications. Current research predominantly focuses on the use of MSNs for the delivery of anticancer drugs. Compared to other methods, MSNs offer precise drug release due to their pore volume and large surface area. MSNs can increase the solubility of poorly water-soluble drugs while providing greater physical and chemical stability, thus increasing drug bioavailability and reducing drug dosage.¹⁰²

Characteristic of MSNs

The sol-gel process is the primary method for the synthesis of MSNs. The size, shape, and porosity of the resulting MSNs are influenced by several factors, including the choice of surfactant, the type of cosolvent and its volume ratio to water, the reaction temperature, and the stirring speed. The final morphology of the MSN core, which commonly adopts a spherical or rod-like structure, plays a crucial role in determining its *in vivo* behavior and physiological fate.¹⁰³ MSNs exhibit greater resistance to physical and chemical environmental changes compared to other delivery systems.¹⁰⁴ The material for MSNs primarily consists of silanol groups, which are biodegradable and biocompatible, thereby reducing the risk of side effects. Additionally, MSNs demonstrate stability across a wide range of pH values, temperatures, and hydrolysis reactions.¹⁰²

Synthesis Methods of MSNs

MSNs can be synthesized through various methods, with the sol-gel and surfactant-templating techniques being the most widely utilized. The sol-gel method typically involves the hydrolysis and condensation of alkoxysilanes under acidic or basic conditions, producing silica frameworks with tunable porosity.¹⁰⁵ This technique is straightforward, cost-effective, and highly suitable for surface functionalization.¹⁰⁶ However, conventional sol-gel methods often yield MSNs with broad particle size distributions, irregular morphology, and potential for agglomeration, which can compromise reproducibility and drug delivery performance.¹⁰⁷

Such inhomogeneity primarily arises from uncontrolled hydrolysis and condensation kinetics during the sol-gel process, which significantly affect nucleation and particle growth. Xu et al⁹ reported that base-catalyzed sol-gel processes commonly yield particles ranging from 50 to 200 nm, often accompanied by variability in pore structure and size, factors that contribute to inconsistent drug loading and release profiles. Recent advancements, including hydrothermally assisted sol-gel synthesis and hard-template approaches, have enabled the production of MSNs with narrower size distributions and improved structural uniformity, thereby expanding the method's applicability for pharmaceutical use.¹⁰⁸

In contrast, the surfactant-templating technique utilizes structure-directing agents that self-assemble into highly ordered micellar or liquid crystalline phases.¹⁰⁹ Silica precursors such as tetraethyl orthosilicate (TEOS) condense around these templates to form well-organized mesoporous structures, allowing for precise control over pore size, particle morphology, and nanostructural consistency.¹¹⁰ Fujii et al¹¹¹ demonstrated that the use of surfactant-templating agents, specifically cetyltrimethylammonium bromide (CTAB) and sodium dodecyl sulfate (SDS), in combination with hard templates facilitated the synthesis of MSN with finely tunable structural properties, including pore size of approximately 12 nm, shell thickness ranging from 5 to 9 nm, and surface areas reaching up to 553 m²/g. This approach enabled a remarkably high ibuprofen loading capacity (3009 mg/g) and exhibited sustained-release behavior, underscoring the utility of this method for producing structurally optimized drug delivery carriers. Supporting evidence by Elimbinzi et al¹¹² further confirmed that surfactant composition could be strategically adjusted to achieve pore sizes around 43 nm and surface areas of approximately 209 m²/g. Collectively, these findings underscore the superior batch-to-batch reproducibility and architectural precision of surfactant-templated MSNs, making them especially suitable for pharmaceutical formulations requiring reliable *in vivo* behavior and consistent therapeutic outcomes.

Structure of MSNs

The hexagonal, honeycomb-like structure of MSNs creates tunnels with numerous uniform pores, providing various advantages, including the capacity to carry a higher amount of active substances.¹¹³ Additionally, MSNs coat their outer surface with silanol groups, allowing for various functionalizations. This uniform pore size contributes to consistent drug loading and distribution, thereby increasing the bioavailability of the drug in the body. Furthermore, due to the utilization of both internal and external surfaces, MSNs exhibit a large surface area. This large surface area facilitates a high drug-loading capacity, reduces diffusion resistance, and enables controlled drug release, ultimately allowing for a reduction in the required dosage.¹⁰²

Characterization of MSNs

Scanning Electron Microscopy (SEM)

Scanning Electron Microscopy (SEM) is an essential method for characterizing MSNs, providing comprehensive insights into their morphology, dimensions, pore architecture, surface characteristics, elemental composition, size distribution, porous structure, and surface modifications.¹¹⁴ SEM images also reveal details such as particle size distribution, shape (eg, spherical or rod-like), surface roughness, and pore architecture.¹¹⁵

Huang et al¹¹⁶ employed SEM to analyze the surface morphology of MSNs. The findings revealed that the particles predominantly possessed a spherical shape with a uniform size distribution, accompanied by hexagonal-symmetry patterns on their surfaces, signifying a well-ordered mesoporous structure (Figure 4a). Similarly, AbouAitah et al¹¹⁷ utilized SEM to analyze the structural morphology of MSNs, demonstrating a uniform spherical shape with a pronounced 3D dendritic mesoporous architecture and the absence of aggregation, signifying successful synthesis and excellent colloidal stability.

Transmission Electron Microscopy (TEM)

Transmission Electron Microscopy (TEM) is a crucial technique for characterizing MSNs, offering high-resolution insights into their morphology, particle size, and well-ordered pore architecture, including hexagonal channels.¹¹⁸ It also allows for precise particle size measurement, which can be correlated with disc centrifuge data, and, like SEM, TEM analyzes structural features using thin-sectioned samples.¹¹⁹

Huang et al¹¹⁶ employed TEM to examine the internal structure and morphology of MSNs, revealing a hexagonal-symmetry pore configuration with a particle size of 105.66 ± 23.11 nm and a pore size of 2.13 ± 0.21 nm, signifying a well-ordered mesoporous framework appropriate for drug delivery applications (Figure 4b). Similarly, Arcos et al¹²⁰ utilized TEM to examine the morphology and internal architecture of MSNs, revealing that samples with differing surfactant/silica ratios displayed spherical morphology with poorly crystalline mesopores, lamellar outer structures characterized by a periodicity of 8.5 nm, and partially decomposed polygonal particles, demonstrating that composition and thermal treatment substantially influence the structural order and stability of the mesoporous framework.

Brunauer-Emmett-Teller (BET)

Brunauer–Emmett–Teller (BET) analysis is a standard method used to determine the specific surface area and pore size distribution of MSNs through nitrogen adsorption–desorption isotherms.¹¹⁵ These measurements are critical for understanding the suitability of MSNs for applications such as drug delivery and catalysis.¹²¹

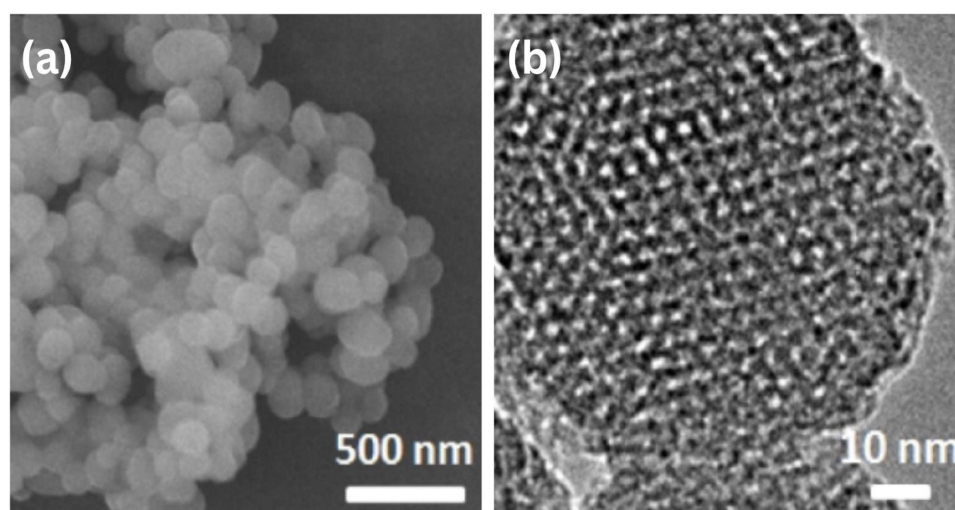


Figure 4 Characterization of mesoporous silica nanoparticles (MSNs) by electron microscopy: (a) scanning electron microscopy (SEM), (b) transmission electron microscopy (TEM). Reproduced from Huang X, Young NP, Townley HE. Characterization and comparison of mesoporous silica particles for optimized drug delivery. *Nanomater Nanotechnol.* 2014;4(1):1–15. Licensed under Creative Commons Attribution 3.0 International License (CC BY 3.0).¹¹⁶

AbouAitah et al¹¹⁷ reported that the MSNs demonstrated a substantial BET surface area of 380.1 m²/g and a considerable total pore volume of 0.772 cm³/g, signifying a well-structured mesoporous architecture commonly linked to type IV nitrogen adsorption–desorption isotherms, characterized by a steep uptake at relative pressures (P/P_0) of 0.4–0.9 and a distinct hysteresis loop resulting from capillary condensation (Figure 5). Kumar et al¹²² also conducted BET analysis and determined that the MSNs displayed an extraordinarily high specific surface area of 1193.19 m²/g, hence corroborating the existence of a highly developed porous structure.

Dynamic Light Scattering (DLS)

Dynamic Light Scattering (DLS) is frequently employed to ascertain the hydrodynamic diameter and size distribution of MSNs, offering insights into particle populations and agglomeration tendencies.¹²³ Despite its utility, DLS exhibits limitations in resolution, is inappropriate for highly concentrated or opaque samples, and relies on precise knowledge of solvent viscosity.¹¹⁵

Paris et al¹²⁴ conducted DLS studies on MSNs, revealing a peak particle diameter of around 100 nm, indicating a very homogeneous nanoscale distribution throughout the colloidal suspension. Guerrero-Flórez et al¹²⁵ employed DLS to characterize the seed MSNs, determining an average hydrodynamic diameter of around 65 nm, which suggests a uniform and well-dispersed colloidal suspension.

Zeta Potential (ZP)

Zeta potential (ZP) is commonly employed to evaluate the surface charge and colloidal stability of MSNs.¹¹⁵ ZP data, often acquired using electrophoretic light scattering, assess nanoparticle dispersion behavior, surface modifications, and aggregation tendencies while being influenced by parameters such as pH, ionic strength, and medium composition.¹²⁶

Attia et al¹²⁷ assessed the zeta potential of MSNs and determined an average value of −16.84 mV, signifying the existence of negatively charged surface groups and moderate colloidal stability in aqueous dispersion. Kumar et al¹²² measured the zeta potential of MSNs and determined a value of roughly −25 mV at pH 7.4, indicative of deprotonated

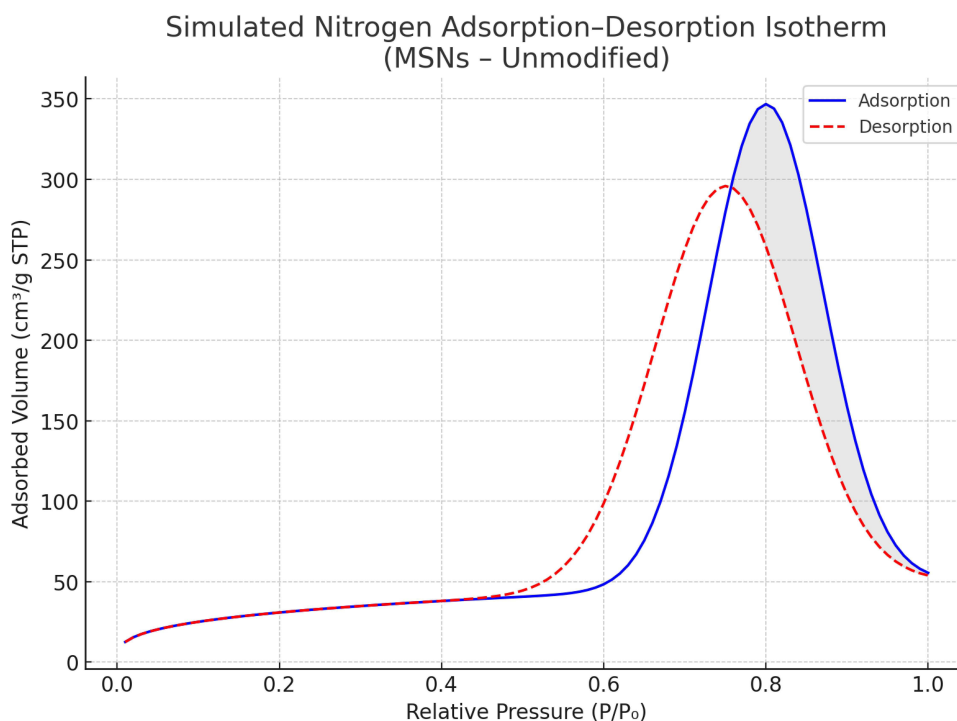


Figure 5 Characterization of mesoporous silica nanoparticles (MSNs) by Brunauer-Emmett-Teller (BET). Adapted from Abouaitah K, Hassan HA, Swiderska-Sroda A et al. Targeted nano-drug delivery of colchicine against colon cancer cells by means of mesoporous silica nanoparticles. *Cancers (Basel)*. 2020;12(1):1–30. Licensed under Creative Commons Attribution 3.0 International License (CC BY 4.0).¹¹⁷

silanol groups on the MSN surface. The presence of this negative surface charge signifies excellent colloidal stability and is characteristic of silica-based nanoparticles in neutral water conditions.

Safety Profiles of MSNs

MSNs have demonstrated excellent safety profiles in both in vitro and in vivo studies, reinforcing their potential for therapeutic applications. MSNs are widely regarded as biocompatible and biodegradable, breaking down into non-toxic orthosilicic acid, which is naturally eliminated through renal and hepatobiliary pathways.¹²⁸ Numerous preclinical investigations have confirmed their low immunogenicity, minimal hemolytic activity, and high cellular compatibility.¹²⁹

In a recent study, Cheng et al¹³⁰ demonstrated that rod-like MSNs induced minimal oxidative stress and did not cause significant tissue damage in both in vitro and in vivo models, suggesting their favorable biocompatibility under physiological conditions. Furthermore, degradation rates and clearance efficiency can be modulated by adjusting particle size, pore structure, shell porosity and surface chemistry.¹³¹ For example, Fiedler et al¹³² demonstrated that the degradation rate and clearance efficacy of MSNs can be precisely controlled by postsynthetic modulation of shell porosity, without altering particle size. Using mesoporous silica shell-superparamagnetic iron oxide nanoparticles (SPION) core nanoparticles in the J774.A1 macrophage cell line, they observed that the silica shell underwent substantial lysosomal degradation within three days, indicating favorable intracellular biodegradability. Moreover, extracellular dissolution occurred even more rapidly, supporting the potential for efficient clearance. Both environments exhibited consistent degradation kinetics, underscoring the predictability and tunability of MSN behavior in biological systems.

Despite these promising results, clinical translation remains limited, primarily due to regulatory uncertainties and challenges in achieving scalability.¹²⁸ Nevertheless, the current body of evidence strongly supports the biosafety and pharmacokinetic manageability of well-engineered MSNs, highlighting their strong potential for safe integration into clinical drug delivery systems.⁹

Effect of MSNs on Dissolution and Bioavailability Enhancement

MSNs are recognized as next-generation pharmaceutical carriers due to their capacity to improve therapeutic efficacy by increasing water solubility and bioavailability. The ability of MSNs to increase drug solubility and dissolution rate is attributed to their nanoscale pores, which facilitate the transformation of crystalline molecules into amorphous form. The enhancement of drug solubility is supported by several distinctive characteristics of MSNs, including a high specific surface area, large pore volume, appropriately sized molecular pores, a well-organized pore structure, and the presence of surface silanol groups capable of interacting with various pharmacological compounds. Additionally, the wettability and porosity of hydrophobic drugs loaded into ordered MSNs can be enhanced.^{102,133}

MSNs have demonstrated significant potential to improve the oral bioavailability of poorly soluble drugs by enhancing drug dissolution rate and permeability. The porous structure of MSNs provides a high surface area for drug loading, thereby maximizing the contact between the drug and the surrounding medium and promoting faster dissolution. Moreover, MSNs can be constructed to enable controlled drug release by increasing the diffusion resistance, thereby improving drug absorption and ultimately allowing for dose reduction.^{134,135}

Effect of MSNs on Pharmacological Activity

As a drug delivery system, MSNs significantly increase pharmacological activity by enabling targeted drug delivery to specific tissues, providing controlled drug release over time, increasing bioavailability, and frequently allowing for reduced dosage requirements due to their large surface area and adjustable pore size. Targeted drug delivery using MSNs provides an efficient and safe treatment approach by concentrating the drug at the site of action while minimizing adverse effects on nearby healthy tissue, thereby improving therapeutic efficacy and potentially reducing side effects.¹³⁶ Safat et al¹³⁷ compared the cholesterol-lowering effect of *Cynara scolymus* (CS) extract loaded into Santa Barbara Amorphous-15 (SBA-15) MSNs (T group) with extract administered alone (CS group). The group of rats receiving the *Cynara scolymus* extract - SBA 15 formulation significantly lowered triglyceride (TG), total cholesterol (TC), and VLDL compared to the group treated with *Cynara scolymus* extract alone, indicating improved drug delivery in group T. In another study, Jia et al¹³⁸ evaluated the in vitro antitumor effect of paclitaxel. A higher antitumor effect was observed

for paclitaxel incorporated into MSNs, as reflected by a lower eqn value, indicating a lower concentration needed to inhibit 50% of cancer cell viability. Furthermore, paclitaxel-loaded MSNs induced a higher apoptotic effect on MCF-7 cells compared to paclitaxel alone.

Antihyperlipidemic and Antihypertensive Drugs Loaded MSNs

Therefore, based on the discussion above, MSNs represent a promising strategy to address the poor water solubility of antihyperlipidemic and antihypertensive drugs.¹⁰² Many studies have shown positive results for using MSN technology in creating drugs to lower blood pressure and cholesterol, as summarized in Table 3.

Dissolution

Dissolution is the process in which two phases combine to form a new, homogenous phase known as a solution.¹⁵⁴ In the pharmaceutical field, the term refers to the quantity of drug that dissolves per unit time under standardized conditions, which include defined interfaces between the liquid and solid phases, controlled temperature, and composition of the solvent. Dissolution testing is an essential quality control assessment for pharmaceutical dosage forms and is widely utilized as a prediction instrument for evaluating drug bioavailability.¹⁵⁵ The dissolving characteristics of a drug significantly affect its pharmacological efficacy, rendering it a critical factor in drug development and formulation.¹⁵⁶

The dissolution studies conducted by Bharati et al in 2024 utilized a USP type II apparatus with distilled water, hydrochloric acid, and phosphate buffer.¹⁴² The mesoporous silica loaded with efonidipine hydrochloride ethanolate (EFE-loaded MSNs) showed a 3.54-fold and 3.02-fold increase in the dissolution rate when tested in distilled water and phosphate buffer (pH 6.8) containing 0.05% w/v sodium lauryl sulfate (SLS), respectively. The high surface area of the mesoporous silica positively influenced the dissolving rate, in contrast to efonidipine hydrochloride ethanolate (EFE), which exhibited a lower dissolution rate across all three media. Furthermore, Farooq et al (2016) conducted ex vivo real-time release tests to examine the release profiles of the control and magnetic nanoparticles (MNPs).¹⁴⁹ The results show that MNPs with sodium nitroprusside (SNP) rapidly release 61.93% within the first 20 minutes. The peak relaxation of 64.16% occurred at 35 minutes; the highest relaxation reached 77.08% at 125 minutes. In a study by Kiwilsza et al, a design suitable for class II BCS active pharmaceutical ingredients (APIs) was used.¹³⁹ The results indicated that the crystalline nifedipine (NF) reached only approximately 30% after 700 minutes, while the encapsulated NF exhibited a significantly higher dissolution rate, achieving 60%, which is 83 times more than the crystalline NF.

In vitro Studies

Hypertension and dyslipidemia are major contributors to the development of atherosclerosis. However, the poor water solubility of drugs used to manage these conditions can hinder their absorption and therapeutic efficacy, limiting treatment outcomes. To address this issue, MSNs have emerged as a promising drug delivery platform. MSNs can enable targeted drug delivery, thereby increasing drug accumulation at the intended site of action while minimizing adverse effects on healthy tissue. This targeted approach has the potential to enhance therapeutic efficacy and reduce side effects.¹³⁶ Dyslipidemia drugs typically function by reducing LDL-C and TG while elevating HDL levels. Although heparin is primarily classified as an anticoagulant, studies have shown its potential in decreasing LDL-C levels. A study by Jin et al in 2024 demonstrated that in vitro tests, including the injection of heparin (HP)/MSN into mice plasma, resulted in a considerable enhancement ($p < 0.05$) of LDL-C adsorption relative to the control group.¹⁵³ Several mechanisms were proposed to explain the LDL-C-lowering effect of HP/MSN. First, HP/MSN served as a solid-phase extraction medium that directly adsorbed LDL-C, which reduced the plasma concentration of LDL-C. LDL-C bound to HP/MSN could subsequently be released using a high-concentration sodium chloride solution, confirming that HP/MSN adsorbs LDL-C via physical sequestration. Second, the development of HP/MSN-LDL-C complexes disrupted the usual interaction between blood lipids and lipase, leading to diminished lipase activity. This work employs PMS, a kind of mesoporous silica, as the control, which possesses the capacity to adsorb LDL-C directly. The PMS was subsequently amalgamated with heparin, resulting in the HP/MSN test chemical. The profile test results obtained using TEM show irregular shapes, suggesting that both PMS and HP/MSN can substantially adsorb LDL-C. Nevertheless, the capacity of HP/MSN to bind LDL-C is significantly greater than that of PMS alone. Furthermore, HP/MSN exhibits a reduced

Table 3 Previous Studies of Antihyperlipidemic and Antihypertensive-Loaded MSN

No	Extract/ Compound	Type of MSN	Particle Size of MSN	Preparation Methods	Loading Efficacy of MSN	Dissolution Studies	In vitro Studies	In vivo Studies	Ref.
1.	Nifedipine (NF)	Santa Barbara Amorphous-15 (SBA-15)	Total pore volume = 0.845 l cm ³ /g Mean pore diameter = 62.4 Å	Solvent Evaporation	35%	Crystalline NF after 700 minutes was around 30%, while for the encapsulated NF it was higher, reaching 60%.	-	-	[139]
2.	Breviscapine (BRE)	Mesoporous Silica Nanoparticles (MSNs)	BREMSNs = 177.24 nm	Ultrasound Assisted Solution Enhanced Dispersion by Supercritical Fluids (USEDs)	8.63%	The breviscapine Mesoporous Silica Nanoparticles (BRE-MSNs) showed a more rapid dissolution (80%) of breviscapine than the breviscapine powder (26%).	-	Bioavailability of drug-loaded MSNs was increased 1.96 times compared to that of the breviscapine powder (p<0.05)	[133]
3.	Nifedipine	Syloid	Not mentioned	Solvent loading method	Not mentioned	Nifedipine with Syloid showed 88 folds increase in solubility and dissolution compared with Nifedipine pure drug and 10 folds compared with marketed oral tablet.	-	-	[140]
4.	Rosuvastatin calcium (RSV)	CD9-modified MSN coated with hyaluronic acid (CD9-HMSN@RSV)	MSN@RSV = 86.6 nm CD9-HMSN@RSV = 137.5 nm	Solvent evaporation	48.15 ± 0.95%	CD9-HMSN@RSV accelerates RSV release to 82.6% at atherosclerotic pH of 5 compared to less than 60% for pure RSV and achieves 45.1% release at pH 7.4, compared to less than 40% for pure RSV (p<0.01)	CD9-HMSN@RSV exhibited the lowest level of LDL oxidation associated with plaque formation (2.8%) in comparison with free RSV (10.6%) (p<0.01)	CD9-HMSN@RSV treatment reduced the plaque formation in atherosclerotic lesions to 6%, significantly lower than the 12.5% observed in free RSV (p<0.001)	[3]
5.	Simvastatin (SIM)	Silica-lipid hybrid (SLH)	Pure SLH = 7–3.5 µm SLH after spray drying = 7–8.5 µm	Spray dry	SLH-A@ (Aerosil® 300 silica type) = 75.8 ± 2.08% SLH-A2x (Aerosil® 300 silica type) = 86.9 ± 1.33% SLH-A4x (Aerosil® 300 silica type) = 64.0 ± 1.88% SLH-S2x (Syloid® 244 silica type) = 6.7 ± 0.10	SLH formulation exhibited rapid SIM release, achieving a maximum dissolution concentration up to 3.5 times higher than the pure unmodified drug (p<0.05)	-	SLH formulations increased the oral bioavailability of SIM by up to 6.1-fold compared to pure SIM powder and by 2.9-fold compared to the commercially available tablet formulation Simvastatin Sandoz (p<0.05)	[141]

(Continued)

Table 3 (Continued).

No	Extract/ Compound	Type of MSN	Particle Size of MSN	Preparation Methods	Loading Efficacy of MSN	Dissolution Studies	In vitro Studies	In vivo Studies	Ref.
6.	Fenofibrate	Hexagonal mesoporous silica (HMS)	Brunauer-Emmett-Teller (BET) Surface area of HMS = 974 m ² /g Pore size average of HMS = 2.6 nm	Solvent evaporation	Loaded with dichloro-methane (DCM) solvent = 44 ± 2.0% Loaded with Chloroform solvent = 41 ± 1.5% Loaded with tetrahydrofuran (THF) solvent = 39 ± 1.5%	Fenofibrate-loaded HS improved the aqueous dissolution to 90 ± 0.5% in comparison with commercial fenofibrate tablet which achieved only 74 ± 2% of dissolution	-	Fenofibrate-loaded HMS enhanced cholesterol-lowering activity, reducing cholesterol levels to 50.64 ± 8.4 mg/dl compared to 80.52 ± 12.2 mg/dl achieved by the plain drug, 48 hours after administration (p<0.001)	[19]
7.	Efonidipine hydrochloride ethanolate (EFE)	Mesoporous Silica	Not mentioned	Solvent evaporation	1 EFE: 1 MSN = 64.20 ± 1.98% 1 EFE: 2 MSN = 74.87 ± 1.25% 1 EFE: 3 MSN = 62.35 ± 2.15%	EFE-loaded mesoporous silica exhibited a 3.54-fold and 3.02-fold increase in the dissolution rate in distilled water and phosphate buffer (pH 6.8) (0.05% w/v SLS), respectively	EFE-loaded mesoporous silica exhibited a 2-fold increase in the rate of permeation and apparent permeability coefficient compared to pure EFE.	EFE-loaded mesoporous silica enhanced antihypertensive activity by lowering the mean arterial pressure to 73.33 ± 2.22 mmHg compared to 83.82 ± 3.13 mmHg achieved by pure EFE (p<0.0001)	[142]
8.	Selexipag	KIT-6, Santa Barbara Amorphous-15 (SBA-15), and Mobil Composition of Matter No. 41 (MCM-41)	Untreated SBA-15: BET Surface Area = 589.55 m ² /g Pore volume (cm ³ /g) = 1.19 (BJH), 1.11 (NLDFT) Pore diameter (nm) = 7.95 (BJH), 8.78 (NLDFT/GMC) SXP-loaded SBA-15: BET Surface Area = 536.81 m ² /g Pore volume (cm ³ /g) = 1.07 (BJH), 1.01 (NLDFT) Pore diameter (nm) = 7.83 (BJH), 8.58 (NLDFT/GMC)	Rotary Evaporation	Monolayer loading: MCM-41 = 10.5% SBA-15 = 5.7% KIT-6 = 5.5% Double layer loading: MCM-41 = 21.1% SBA-15 = 11.4% KIT-6 = 11.1%	All selexipag loaded MSN formulations have significantly improved dissolution rates up to 4-fold compared to pure selexipag.	-	-	[143]

9.	Metoprolol Tartrate (MPT)	Mobil Composition of Matter No. 41 (MCM-41), Santa Barbara Amorphous-15 (SBA-15), and Mesoporous Cellular Foam 26 (MCF-26)	Surface area (m ² /g): MCM-41 = 809.1 SBA-15 = 652.1 MCF-26-1 = 382.1 MCF-26-2 = 305.9 Pore diameter (nm): MCM-41 = 2.889 SBA-15 = 6.570 MCF-26-1 = 11.82 MCF-26-2 = 15.61 Pore volume (cm ³ /g): MCM-41 = 0.5843 SBA-15 = 1.058 MCF-26-1 = 1.117 MCF-26-2 = 1.189	Vacuum dried	MCM-41 = 6% SBA-15 = 9% MCF-26-1 = 15% MCF-26-2 = 25%	-	MPT loaded MSN with the pore size was doubled from 3 nm to 6 nm, the diffusion coefficient increased from $3.37 \times 10^{-10} \text{ m}^2/\text{s}$ to $14.49 \times 10^{-10} \text{ m}^2/\text{s}$ with a 3.3-fold increase.	-	[144]
10.	Simvastatin (SIM)	Highly ordered mesoporous carbon (HMC)	Hexagonal HMC (HHMC) = 700 nm Spherical HMC (SHMC) = 400–900 nm Fibrous HMC (FHMC) = 1–4 μm	Solvent evaporation	HHMC = $37.6 \pm 2.3\%$ SHMC = $39.5 \pm 2.2\%$ FHMC = $34.6 \pm 3.4\%$ SHMC-2 = $40.1 \pm 2.0\%$	SIM-loaded HMC improved the SIM dissolution nearly 100% as opposed to only 56% achieved by commercial pure SIM tablet. SIM-loaded HMC improved the SIM saturation solubility approximately 4.5-fold higher than pure crystalline SIM	-	Concentration maximum of SIM-HMC was higher (106.62 ± 24.50) than control (57.30 ± 19.06) ($p < 0.05$)	[145]
11.	Atorvastatin Calcium (ATC)	Syloid 244-FP mesoporous silica	Range of 2.5 to 3.7 μm	Rotary evaporation	Solubility I ATC: $2.5 \text{ S244} = 5.42 \times 10^{-1} \text{ mg/mL}$ compared to pure ATC = $1.9 \times 10^{-1} \text{ mg/mL}$	The result showed that % cumulative atorvastatin tablet with S244 (reach 90% at 60 minutes) are higher than without S244 (only 30% at 60 minutes).	-	-	[146]
12.	Hydrochlorothiazide (H2T)	MSN-41	Average Diameter = 150 nm Diameter of pore (Dp) = 4.64 nm BET Surface Area = 1047.6 m ² /g	Solvent evaporation	$50 \pm 0.5\%$	H2T-MSN-41 was released in the first 5 minutes of assay and the concentration reach 85%. HTZ had a high desorption in the first stage, because it dissolves rapidly in water (722 mg/mL at 25 °C)	-	-	[147]

(Continued)

Table 3 (Continued).

No	Extract/ Compound	Type of MSN	Particle Size of MSN	Preparation Methods	Loading Efficacy of MSN	Dissolution Studies	In vitro Studies	In vivo Studies	Ref.
13.	Valsartan (VAL)	Modified-MSN (M-MSN) (combination of (aminopropyl-MSN) AP-MSN coated by Eudragit L 100–55)	BET Surface Area (m ² /g): MSN = 467.38 MSN-VAL = 83.35 AP-MSN-VAL = 68.92 AP-MSN-VAL-L100-55 = 16.53 Average Particle Size (nm): MSN = 119.52±4.2 MSN-VAL = 126.92±3.3 AP-MSN-VAL = 133.38±6.2 AP-MSN-VAL-L100-55 = 179.23 ± 8.5	Solvent evaporation	MSN-VAL = 43.25% AP-MSN-VAL-L100-55 = 54.16%	Compared to the commercial product (Diovan) that only 44% dissolved within 60 minutes, M-MSN released 50% of contained drug showed first pulse immediately followed by a lag time of 240 min and then a sustained release over a period of 960 min	-	Relative bioavailability of the group of albino male rats treated with Formulation M-MSNs was found 1.82 fold higher than the group treated with marketed formulation Diovan. The commercial formulation showed only 47.36% bioavailability.	[148]
14.	Sodium nitroprusside (SNP)	MNPs	MNPs = 95 ± 13 nm Fluorescein isothiocyanate (FITC) MNPs = 109 ± 18 nm	Solvent evaporation	MNPs = 86.30% Fluorescein isothiocyanate (FITC) MNPs = 96.46%	Rapid initial release in 10 minutes, faster compared to SNP control	The MNPs loaded with SNP led to an initial sharp release of SNP within the first 20 min leading to 57.74% relaxation compared to SNP control. The maximum relaxation was 77.08% and was reached at 125 min (p<0.001)	-	[149]
15.	Valsartan	AP-MSN	BET Surface Area AP-MSN-VAL = 68.92 m ² /g Average Particle Size AP-MSN = 128.58±6.8 nm	Solvent evaporation	59.77%	Compared to the commercial product (Diovan) that only 44% dissolved within 60 minutes, almost 30% of VAL was released in the first 60 min, while the remaining amount followed a typical sustained release pattern and dissolved completely over a time period of about 600 min.	-	-	[148]

16.	Simvastatin (SIM)	HA-MSN	MSN = 178.3 ± 5.2 nm HA-MSN = 185.4 ± 6.1 nm SIM@HA-MSN = 189.1 ± 5.8 nm	Solvent evaporation	$21.32 \pm 1.31\%$	Pure SIM (no sustained release) was released >30% around 1 hour, meanwhile SIM@HA-MSN was released $70.11 \pm 4.64\%$ over 48 h (sustained release) ($p < 0.05$)	SIM@HA-MSN make decrease of foam cell formation around $6.77 \pm 0.85\%$, which was around one fifth that in the positive control group ($p < 0.05$)	Almost 37% SIM@HA-MSNs remains in blood stream after 48 hours, meanwhile control group almost eliminated in 10 hours ($p < 0.05$)	[7]
17.	Carvedilol	Mobil composition of Matter (MCM 41), Zeolite Socony Mobil (ZSM 5), SBA 16	MCM-41 = $76.60 \text{ nm} \pm 4.350$ SBA-16 = $68.06 \text{ nm} \pm 0.0$ ZSM-5 = $132.8 \text{ nm} \pm 0.8956$	Solvent evaporation, Kneading	MCM 41 (Solvent evaporation method) = 90.0% MCM 41 (Kneading method) = 77.0% ZSM-5 (Solvent evaporation method) = 82.0% ZSM-5 (Kneading method) = 74.0% SBA-16 (Kneading method) = 64.5%	Pure carvedilol was only 33% dissolute at 15 minutes, compared to MCM-41 was drug was released 100% around the same time ($p > 0.05$)	-	-	[150]
18.	Atorvastatin	SBA-16 with Dopamine	BET Surface Area = 510 m ² /g Average Pore Size = 3.85nm	Grafting using electrostatic method	Not mentioned	-	-	No significant difference in serum TC, TG, HDL, and LDL-C levels between the SBA-16 silica/dopamine group and the group treated with SBA-16 silica/dopamine together with atorvastatin.	[151]
19.	Telmisartan (TEL)	Hiroshima Mesoporous Material and AP-MSNs	BET Surface Area (m ² /g): MSNs-1 = 585 MSNs-2 = 628 MSNs-3 = 694 TEL-MSNs-1 = 140 TEL-MSNs-2 = 126 TEL-MSNs-3 = 153 AP-MSNs = 527 TEL-AP-MSNs = 119 Particle Size (nm): MSNs-1 = 3.6 ± 0.8 MSNs-2 = 7.8 ± 1.1 MSNs-3 = 12.9 ± 2.5 TEL-MSNs-1 = 1.4 ± 0.5 TEL-MSNs-2 = 1.6 ± 0.6 TEL-MSNs-3 = 2.3 ± 0.9 AP-MSNs = 10.4 ± 2.3 TEL-AP-MSNs = 1.7 ± 0.3	Adsorption using loading solvent	Thermogravimetric analysis (TGA): TEL-MSNs = 48.9% TEL-MSNs = 59.1% TEL-MSNs = 59.7% TEL-AP-MSNs = 50.2% High Performance Liquid Chromatography (HPLC): TEL-MSNs = 50.7% TEL-MSNs = 61.2% TEL-MSNs = 60.3% TEL-AP-MSNs = 48.5%	The amount of dissolved for TEL-MSNs-3 at sampling times of 30 min accumulated to 100.3%, compared to the TEL at the sampling time of 90 min accumulated no more than 1%.	-	-	[152]
20.	Heparin (HP)	PMS (Periodic Mesoporous Silica Nanoparticles)	100 nm	Dispersion	Not mentioned	-	PMS-HP exhibited a greater capacity 1.4 fold for adsorbing LDL-C in comparison to PMS ($p < 0.05$)	PMS-HP demonstrated the higher ability to reduce LDL-C levels up to 1.5 fold in plasma than PMS ($p < 0.001$)	[153]

capacity for HDL adsorption in comparison to MSN, suggesting its potential for greater efficacy. These findings suggest a mechanistic basis for potential LDL-C reduction *in vivo*, which could contribute to plaque stabilization.

Conversely, statins represent a category of antidiyslipidemic drugs extensively utilized in treatment. Senescent foamy macrophages are prevalent and exert harmful effects across all stages of atherosclerosis, as evidenced by a comprehensive transmission electron microscopy analysis of atherosclerotic plaques. The removal of these cells has been associated with lesion regression. It has been suggested that the senescent cells present in both early and mature atherosclerotic plaques may correspond to pro-inflammatory macrophages, and their elimination could suppress plaque development and enhance plaque stability. Modified LDL, including oxLDL, can trigger the accumulation of monocytes and macrophages in the subendothelial region during inflammatory atherosclerosis, facilitating their differentiation into foam cells, which contributes to the formation of detrimental atherosclerotic plaque. A 2021 *in vitro* study by Pham et al demonstrated that rosuvastatin encapsulated in MSN resulted in significantly ($p < 0.01$) lower LDL oxidation (2.8%), in contrast to free rosuvastatin (10%), indicating a potential role in mitigating plaque development.³

In addition to antidiyslipidemic agents, researchers also studied antihypertensive drugs. Antihypertensives are crucial in mitigating the onset of atherosclerosis. In the research performed by Farooq et al¹⁴⁹ on MSNs loaded with sodium nitroprusside (SNP), a potent vasodilator used in hypertension treatment. SNP relaxes vascular smooth muscle, resulting in the dilation of peripheral arteries and veins. MSNs and fluorescein isothiocyanate (FITC) MSNs were introduced into the organ-bath system at a concentration of $1.96 \times \text{eqn}$. The observed trend in the vasodilation of aortic arteries incubated with MSNs containing SNP resulted in a notable decrease in constriction. The MSNs containing SNP exhibited a rapid release of SNP within the initial 20 minutes, yielding a 57.74% relaxation relative to the SNP control. The maximum relaxation was 77.08%, achieved at 125 minutes. The result suggests that MNPs-SNP may be more efficacious than employing only SNP. These results highlight the potential of MSN formulations in improving vascular responsiveness and reducing blood pressure, key therapeutic targets in atherosclerosis prevention.

Bharati et al¹⁴² further investigated Efonidipine hydrochloride ethanolate (EFE) in 2024 using the non-everted sac technique to assess its permeation across three specific rat intestinal segments: the duodenum, jejunum, and ileum. The study compared the permeability of pure EFE and EFE with Solid Dispersion (EFESD). Results indicated that EFESD exhibited approximately a twofold enhancement in the permeability coefficient and permeation rate relative to EFE, as observed in the KRS (pH 7.4) and isopropyl alcohol (70:30 v/v) mixture. This contributed to enhancement in EFE's solubility and favorable distribution across the intestinal barrier. The non-specific absorption of EFE via the small intestine was evidenced by the absence of notable differences in penetration across the three intestinal regions.

While these *in vitro* results suggest promising physicochemical and pharmacological enhancements, direct correlations with clinical outcomes—such as plaque regression or blood pressure normalization—remain limited. Future research should prioritize the integration of pharmacodynamic data to substantiate the translational relevance of these findings.

In vivo Studies

An *in vivo* study by Bharati et al¹⁴² in 2024 using Wistar rats with acute renal hypertension demonstrated the enhanced antihypertensive efficacy of mesoporous silica-based amorphous formulations of the BCS class II drug EFE. The EFE-loaded mesoporous silica enhances solubilization in the gastrointestinal tract (GIT), increasing its concentration at the absorption site and resulting in better antihypertensive efficacy. Notably, the EFE-loaded mesoporous silica achieved a rapid reduction in mean arterial blood pressure (MABP) to 73.33 ± 2.22 mmHg, compared to 83.82 ± 3.13 mmHg with pure EFE, indicating statistically significant improvement ($p < 0.0001$). This suggests greater potential for clinical blood pressure control and atherosclerosis prevention.

Concurrently, Jadhav and Vavia developed a dodecylamine template-based MSN carrier to enhance the delivery of poorly soluble fenofibrate by improving drug loading and *in vivo* efficacy.¹⁹ The formulation was evaluated using a two-phase Triton-induced hyperlipidemia model in male Wistar rats. In Phase I, the MSN-based formulation significantly reduced both cholesterol (46.4 ± 5.8 mg/dL, $p < 0.001$) and triglyceride (78.88 ± 10.6 mg/dL, $p < 0.001$) levels at 24 hours post-administration, compared to the plain drug, which only reduced cholesterol to 197.70 ± 20.6 mg/dL and triglycerides to 321.67 ± 16.8 mg/dL. Similarly, in Phase II, further reductions were observed at 48 hours, with

cholesterol at 50.64 ± 8.4 mg/dL ($p < 0.001$) and triglycerides at 67.63 ± 7.2 mg/dL ($P < 0.001$), while the plain drug achieved levels of 80.52 ± 12.2 mg/dL and 111.65 ± 20.1 mg/dL. These results highlight the superior lipid-lowering efficacy of the MSN-based formulation in both phases of the Triton test, which can be attributed to the MSN carrier's enhancement of fenofibrate dissolution, potentially leading to improved absorption and consequently higher blood concentrations (bioavailability). This pharmacokinetic improvement translates into a meaningful enhancement in therapeutic lipid regulation, which is critical in the management of atherosclerosis.

Additionally, Jin et al proposed a novel method using MSN to create HP-MSN, which allows selective removal of LDL-C from the bloodstream without lowering the HDL-C levels or interfering with total protein in blood.¹⁵³ In vivo studies using Sprague–Dawley rats fed a high-fat diet showed MSN-HP selectively adsorbed LDL-C (6.5 ± 0.73 mM vs 8.6 ± 0.76 mM, $p < 0.001$) without affecting other plasma components, thereby reducing collagen content subsequent to intravascular plaque formation ($3.66\% \pm 1.06\%$ vs $1.87\% \pm 0.79\%$, $p < 0.05$) on the aortic wall and inhibiting vascular remodeling ($27.2\% \pm 6.55\%$ vs $38.3\% \pm 1.99\%$, $p < 0.05$) compared to the control group treated with phosphate buffered saline (PBS). These findings provide strong evidence that MSN-HP not only modulates plasma lipid levels but also attenuates atherogenesis at the tissue level, an effect driven by electrostatic interaction between the negatively charged surface of MSN-HP and positively charged LDL-C, facilitating selective adsorption, similar to the mechanism observed with MSN.

Yang et al¹³³ developed a novel drug delivery system, breviscapine-loaded MSN prepare using Ultrasound Assisted Solution Enhanced Dispersion by Supercritical Fluids (BRE-MSN USEDS), a natural flavonoid extracted from *Erigeron breviscapus* (Vant) with known cardiovascular benefits, within mesoporous silica nanoparticles (MSNs). To assess the enhanced pharmacokinetic profile of BRE-MSN USEDS, an in vivo study was conducted. The plasma concentration profile of BRE-MSNs demonstrated a significantly enhanced drug absorption compared to BRE powder. After oral administration, the AUC_{0–∞} and C_{max} for the BRE powder were 3.07 µg/h·mL and 0.46 µg/mL, respectively. The BRE-MSNs showed substantially higher AUC_{0–∞} and C_{max} values than the BRE powder ($P < 0.05$). Specifically, the AUC_{0–∞} of BRE-MSNs-USEDS was 1.96 times greater, and the C_{max} was 2.13 times higher compared to BRE powder. While this study focused on pharmacokinetic improvements, the known cardiovascular activity of BRE supports its potential relevance for clinical outcomes such as improved endothelial function or reduced vascular inflammation.

Collectively, these in vivo studies substantiate the pharmacological advantages of MSN-based formulations, demonstrating statistically significant improvements in blood pressure regulation, lipid profile modulation, and attenuation of atherosclerotic plaque. Despite these promising biological effects, future investigations should incorporate standardized clinical endpoints and long-term outcome evaluations to strengthen the translational validity of these findings.

Discussion

Each drug formulation requires its own criteria according to the type of preparation to be produced. In solid preparations, there are criteria that need to be considered, such as physicochemical properties and solubility. High solubility can increase the bioavailability of a drug in the body due to its efficient absorption and distribution at the site of action. Conversely, low solubility can hinder dissolution, resulting in reduced bioavailability and suboptimal therapeutic effects, which may necessitate higher doses. However, increasing the dosage can lead to drug accumulation in the body and a higher risk of adverse effects. MSNs serve as a solution to enhance the solubility of poorly water-soluble compounds, including antihyperlipidemics and antihypertensives drugs. Both types typically exhibit low solubility, necessitating a modification.

The use of MSN in the statin group can enhance the effectiveness of the drug's action in the body. The effect can be seen in Figure 6. Statins are categorized under the BCS class II, which means the drugs have poor solubility. The poor solubility can result in a low concentration of the drug in the target, which can lead to the drug's low bioavailability in the body. This low solubility often leads to insufficient drug concentrations at the target site and reduced bioavailability, requiring higher doses to achieve therapeutic efficacy. However, increasing the dose can increase the risk of side effects. MSNs offer an effective solution due to their unique physicochemical properties. The presence of silanol groups on the MSN surface contributes to improved solubility of hydrophobic drugs like statins. In addition, the large surface area and porous structure of MSNs facilitate enhanced drug loading, accelerated release, and improved interaction with biological

membranes. These features collectively contribute to increased dissolution rates, improved absorption, and subsequently higher bioavailability. Furthermore, due to their high absorption in the bloodstream and the attainment of therapeutic dosages, statins/MSN can block the enzyme HMG-CoA reductase, a crucial element in cholesterol synthesis, more effectively compared to pure statins. Inhibiting HMG-CoA reductase prevents HMG-CoA from being converted to mevalonate, which inhibits the synthesis of cholesterol and impacts the clinical profile by lowering the total cholesterol value, thereby resolving the dyslipidemia problem.

The pharmacological activity of antihypertensive drugs, such as ARBs, is significantly enhanced when loaded into MSNs compared to the pure drug forms, as shown in Figure 7. This enhancement is attributed to the nanosized particles of MSNs, which increase drug solubility and facilitate a controlled, gradual release of ARBs into the body, improving bioavailability via a diffusion-driven mechanism. The passive diffusion process enables ARBs to dissolve more effectively in the body's aqueous compartments, such as the interstitial spaces, by maintaining a concentration gradient. This gradient drives ARBs from regions of higher to lower concentration until equilibrium is achieved. Furthermore, the incorporation of ARBs into MSNs allows them to traverse water-filled pores in the endothelial lining of blood vessels. The distribution of ARB molecules in an individual, single-molecule form within the pores of the MSNs creates a supersaturated solution in the aqueous environment, further enhancing solubility.²³ A supersaturated solution of ARB will increase the amount of molecules of ARB to block the action of angiotensin II by inhibiting its binding to the angiotensin II type 1 (AT1) receptor compared to pure ARBs, leading to significant enhancement of the efficacy of ARBs.¹⁵⁷ ARBs loaded into MSNs exhibit more competitive binding to the angiotensin II receptor (AT1) that inhibits the attachment of angiotensin II compared to pure ARB. This inhibition prevents oxidative damage to endothelial cells, thereby preventing endothelial dysfunction, which is a primary contributor to the pathogenesis of atherosclerosis. Blocking AT1 receptor activation helps widen blood vessels by reducing signals that cause them to narrow, leading to a notable drop in blood pressure.¹⁵⁸

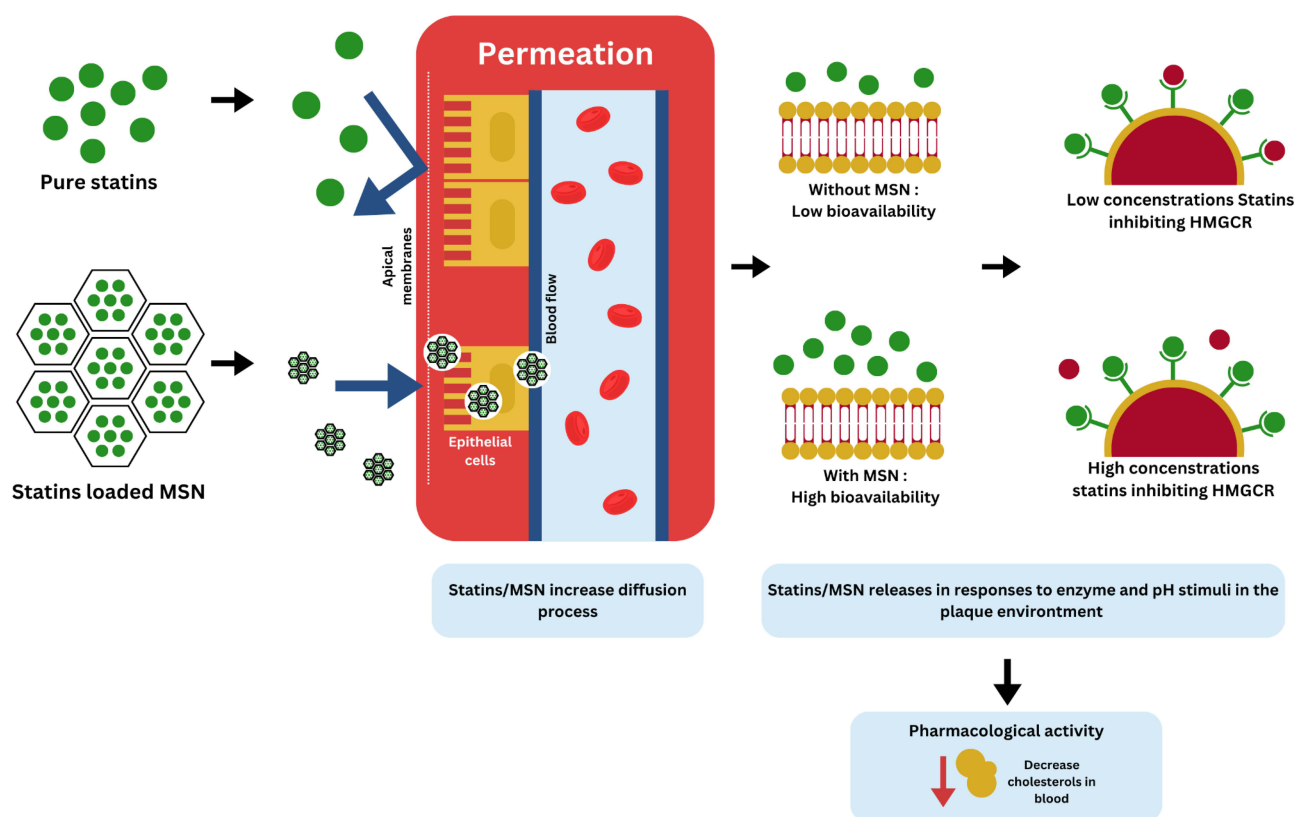


Figure 6 Speculated mechanism by which mesoporous silica nanoparticles (MSNs) improve the efficacy of statins.

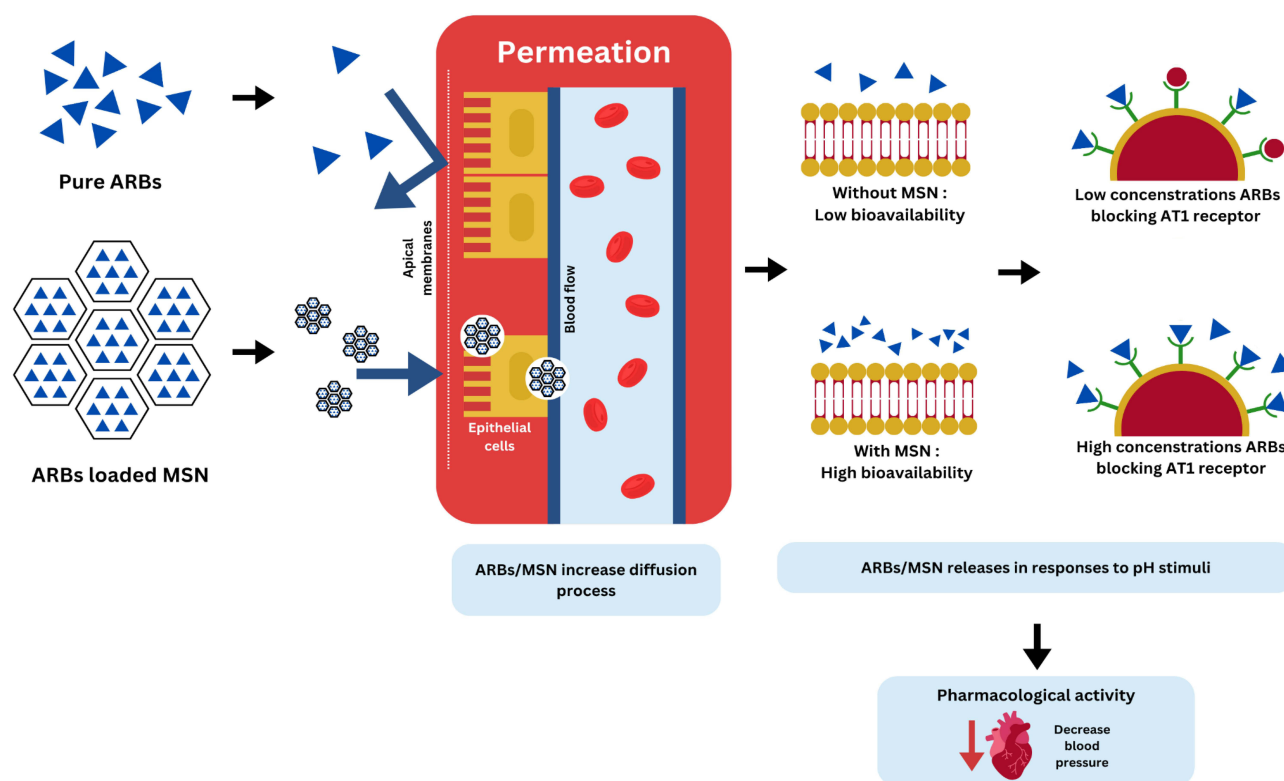


Figure 7 Speculated mechanism of the improvement of angiotensin receptor blockers (ARBs) with mesoporous silica nanoparticles (MSNs).

Despite their therapeutic potential, particularly in enhancing the efficacy of anti-atherosclerosis treatments, the clinical application of MSNs remains significantly limited. Most MSN-related studies are still confined to preclinical investigations, including in vitro and small-animal in vivo models. Only a few MSN-based formulations have advanced to early-phase clinical trials, and comprehensive data on their long-term safety, biodistribution, metabolism, and pharmacodynamic behavior in humans are lacking. These gaps reduce regulatory confidence and hinder the approval of MSNs as viable drug delivery systems.

Additionally, the large-scale industrial production of MSNs faces considerable challenges. Conventional batch-based sol-gel synthesis methods are difficult to scale due to their multistep procedures, high material and energy demands, and inconsistencies in particle size uniformity and surface characteristics. In response, microfluidic-based synthesis has attracted growing attention for its potential to enable continuous, scalable, and reproducible MSN production with precise control over size, morphology, and drug-loading efficiency. The adoption of such advanced manufacturing technologies could help bridge the gap between laboratory-scale research and industrial pharmaceutical production.

Moreover, recent studies have shown that MSN synthesis methods—such as sol-gel and surfactant-templating—can significantly influence particle uniformity, surface characteristics, and drug loading capacity. However, the lack of standardized, head-to-head comparisons conducted under consistent conditions continues to hinder the optimization of MSN design for therapeutic applications. In parallel, the safety profiles of MSNs, including long-term toxicity, immunogenicity, and clearance pathways, remain insufficiently characterized. While emerging research has begun to address these concerns, more comprehensive and systematic evaluations are essential to determine the clinical feasibility of MSN-based formulations, particularly for long-term therapeutic use.

Compared to other well-established nanocarriers—such as liposomes, dendrimers, and polymeric nanoparticles—MSNs offer several unique advantages, including high surface area, tunable pore size, and exceptional physicochemical stability. These features enable efficient drug loading, protection of labile compounds, and controlled drug release. In addition, MSNs can be readily surface-functionalized to achieve targeted drug delivery without compromising their

structural integrity. However, unless the clinical and industrial limitations are systematically addressed, the broader translation of MSNs into real-world therapeutic applications will remain restricted.

While this review highlights promising outcomes regarding the use of MSNs, it is important to acknowledge the methodological limitations of the cited studies. Although many investigations have utilized *in vivo* models, relatively few have conducted integrated *in vitro* and *in vivo* assessments within the same study. This lack of comprehensive, multi-tiered evaluation limits the understanding of mechanistic correlations and weakens the interpretation of translational relevance. Additionally, inconsistencies in experimental design, dosing strategies, and outcome measures across studies further complicate efforts to draw consistent and generalizable conclusions regarding the clinical potential of MSN-based drug delivery systems. These challenges underscore the need for more standardized, methodologically rigorous, and cohesively designed research moving forward.

Conclusions

In conclusion, MSNs have demonstrated significant potential in enhancing the solubility, bioavailability, and pharmacological efficacy of antihyperlipidemic and antihypertensive drugs, as supported by both *in vitro* and *in vivo* studies. Unlike conventional enhancement methods that are hindered by issues such as aggregation and polymorphism, MSNs offer unique physicochemical advantages, such as tunable pore size, high surface area, and modifiable surface chemistry, that enable efficient drug loading, stabilization, and targeted delivery. However, the clinical translation of MSN-based formulations remains limited by concerns related to long-term toxicity, immunogenicity, clearance pathways, and challenges in large-scale manufacturing. These difficulties are further compounded by regulatory uncertainties due to the absence of standardized evaluation frameworks for nanoparticle-based systems. Future research should prioritize comprehensive safety profiling, the development of scalable synthesis methods, and well-designed clinical trials to support the safe and effective integration of MSNs into therapeutic practice, particularly in the treatment of atherosclerosis.

Author's Perspective

In the Asia-Pacific region, the prevalence of hypertension ranges between 10.6% and 48.3%, and elevated low-density lipoprotein (LDL) levels range between 7.8% and 47.2%, highlighting the urgent need for pharmacists to develop innovative therapeutic strategies. Mesoporous silica nanoparticles (MSNs) have been acknowledged as a promising strategy for next-generation pharmaceutical carriers due to their remarkable capacity to enhance the therapeutic efficacy of antihyperlipidemics and antihypertensives. Compared to conventional physical and chemical methods currently employed to address low solubility issues in antihyperlipidemic and antihypertensive drugs, these existing approaches primarily improve solubility, dissolution rate, and physicochemical properties without significantly reducing the required dose, potentially leading to drug toxicity. Furthermore, traditional methods often fail to prevent uncontrolled polymorphism, which poses a risk of clinical failure due to undesirable solid-state conversion. Besides only enhancing solubility and dissolution profiles, MSNs also promote uniform drug distribution by enabling targeted drug delivery. This approach significantly increases drug concentration at the intended site of action while minimizing adverse effects on surrounding healthy tissues, thereby improving therapeutic efficacy and potentially reducing side effects.

This review presents a comprehensive overview of previous studies on antihypertensive and antihyperlipidemic drugs loaded into MSNs, emphasizing their effects on dissolution and pharmacological activity based on both *in vitro* and *in vivo* studies. The types of MSNs developed by various researchers, including SBA-15, SLH, CD9-HMS N@RSV, KIT-6, MCM-41, MCF-26, and HMC, are briefly summarized. Furthermore, this review discusses the key attributes of MSNs that contribute to the enhancement of solubility, dissolution rate, and bioavailability, which consequently improve pharmacological efficacy. This review also presents the underlying mechanisms by which MSN-based drug delivery systems enhance the bioavailability of antihyperlipidemic and antihypertensive drugs. This review is expected to provide valuable insights into the potential of MSNs as innovative carriers in cholesterol and hypertension therapies.

Despite significant advancements in the development of MSNs as advanced drug delivery systems for hypertension and hyperlipidemia, several challenges hinder their translation into commercially available therapeutic regimens. One of the primary obstacles is the limited progression of MSNs into clinical trials, as most studies are confined to preclinical in

vitro and in vivo studies. The absence of comprehensive clinical investigations regarding their long-term safety, pharmacokinetics, and pharmacodynamic profiles poses a critical barrier to regulatory approval. Secondly, the large-scale industrial production of MSNs becomes challenging due to the complexity of synthesis protocols, which often involve multiple steps, high-cost materials, and stringent physicochemical control to ensure uniform particle size, pore structure, and drug loading efficiency. Developing simple, cost-effective, and reproducible fabrication methods is essential to facilitate and develop MSN industrialization as well as meet the demands of large-scale pharmaceutical manufacturing. Addressing these challenges through interdisciplinary collaboration and technological advancements is crucial to unlocking the full potential of MSNs as commercially viable platforms for antihyperlipidemic and antihypertensive therapies.

Acknowledgments

We would like to thank Universitas Padjadjaran for APC.

Funding

This research was funded by the National Research and Innovation Agency (BRIN, RIIM2) and the Indonesia Endowment Funds for Education (LPDP) to Diah Lia Aulifa (No.: 61/IV/KS/5/2023; No.: 2131/UN6.3.1/PT.00/2023).

Disclosure

The authors declare no conflicts of interest for this review article.

References

1. Report WH. Obesity & cardiovascular disease. Available from: https://world-heart-federation.org/wp-content/uploads/World_Heart_Report_2025_Online-Version.pdf. Accessed August 05, 2025.
2. Herrington W, Lacey B, Sherliker P, Armitage J, Lewington S. Epidemiology of atherosclerosis and the potential to reduce the global burden of atherothrombotic disease. *Circ Res*. 2016;118(4):535–546. doi:10.1161/CIRCRESAHA.115.307611
3. Pham TT, Kim EC, Ou W, et al. Targeting and clearance of senescent foamy macrophages and senescent endothelial cells by antibody-functionalized mesoporous silica nanoparticles for alleviating aorta atherosclerosis. *Biomaterials*. 2021;269(120677):120677. doi:10.1016/j.biomaterials.2021.120677
4. Zhang L, Connelly JJ, Peppel K, et al. Aging-related atherosclerosis is exacerbated by arterial expression of tumor necrosis factor receptor-1: evidence from mouse models and human association studies. *Hum Mol Genet*. 2010;19(14):2754–2766. doi:10.1093/hmg/ddq172
5. Wang JC, Bennett M. Aging and atherosclerosis: mechanisms, functional consequences, and potential therapeutics for cellular senescence. *Circ Res*. 2012;111(2):245–259. doi:10.1161/CIRCRESAHA.111.261388
6. Wong YJ, Qiu TY, Ng GK, Zheng Q, Teo EK. Efficacy and safety of statin for hepatocellular carcinoma prevention among chronic liver disease patients: a systematic review and meta-analysis. *J Clin Gastroenterol*. 2021;55:615–623. doi:10.1097/MCG.0000000000001478
7. Song K, Tang Z, Song Z, et al. Hyaluronic acid-functionalized mesoporous silica nanoparticles loading simvastatin for targeted therapy of atherosclerosis. *Pharmaceutics*. 2022;14(6):1265. doi:10.3390/pharmaceutics14061265
8. Noureddine A, Maestas-Olguin A, Tang L, et al. Future of Mesoporous silica nanoparticles in nanomedicine: protocol for reproducible synthesis, characterization, lipid coating, and loading of therapeutics (chemotherapeutic, proteins, siRNA and mRNA). *ACS Nano*. 2023;17(17):16308–16325. doi:10.1021/acsnano.3c07621
9. Xu B, Li S, Shi R, Liu H. Multifunctional mesoporous silica nanoparticles for biomedical applications. *Signal Transduct Target Ther*. 2023;8(1):435. doi:10.1038/s41392-023-01654-7
10. Bouchoucha M, Côté MF, C-Gaudreault R, Fortin MA, Kleitz F. Size-controlled functionalized mesoporous silica nanoparticles for tunable drug release and enhanced anti-tumoral activity. *Chem Mater*. 2016;28(12):4234–4258. doi:10.1021/acs.chemmater.6b00877
11. Islam S, Ahmed MM, Islam S, Hossain N, Chowdhury MA. Advances in nanoparticles in targeted drug delivery—A review. *Results in Surfaces and Interfaces*. 2025;19:100529. doi:10.1016/j.rsufi.2025.100529
12. Santhamoorthy M, Asaithambi P, Ramkumar V, Elangovan N, Perumal I, Kim SC. A Review on the recent advancements of polymer-modified mesoporous silica nanoparticles for drug delivery under. *Polymers*. 2025;17(12):1640. doi:10.3390/polym17121640
13. Abbaraju PL, Kumar Meka A, Jambhrunkar S, et al. Floating tablets from mesoporous silica nanoparticles. *J Mater Chem B*. 2014;2(47):8298–8302. doi:10.1039/C4TB01337A
14. Summerlin N, Qu Z, Pujara N, et al. Colloidal mesoporous silica nanoparticles enhance the biological activity of resveratrol. *Colloids Surf B Biointerfaces*. 2016;144:1–7. doi:10.1016/j.colsurfb.2016.03.076
15. Budiman A, Aulifa DL. Characterization of drugs with good glass formers in loaded-mesoporous silica and its theoretical value relevance with mesopores surface and pore-filling capacity. *Pharmaceutics*. 2022;15(1):93. doi:10.3390/ph15010093
16. Xu W, Riikonen J, Lehto VP. Mesoporous systems for poorly soluble drugs. *Int J Pharm*. 2013;453(1):181–197. doi:10.1016/j.ijpharm.2012.09.008
17. Budiman A, Wardhana YW, Ainurofiq A, et al. Drug-coformer loaded-mesoporous silica nanoparticles: a review of the preparation, characterization, and mechanism of drug release. *Int J Nanomed*. 2024;19:281–305. doi:10.2147/IJN.S449159

18. Khanfar M, Fares MM, Qandil AM, Qandil AM. Mesoporous silica based macromolecules for dissolution enhancement of Irbesartan drug using pre-adjusted pH method. *Microporous Mesoporous Mater.* **2013**;173:22–28. doi:10.1016/j.micromeso.2013.02.007
19. Jadhav NV, Vavia PR. Dodecylamine template-based hexagonal mesoporous silica (HMS) as a carrier for improved oral delivery of fenofibrate. *AAPS Pharm Sci Tech.* **2017**;18:2764–2773. doi:10.1208/s12249-017-0761-x
20. Kim YR, Lee SY, Lee EJ, et al. Toxicity of colloidal silica nanoparticles administered orally for 90 days in rats. *Int J Nanomed.* **2014**;9(2):67. doi:10.2147/IJN.S57925
21. Trewyn BG, Slowing G II, Chen S, HT LVSY, Lin VS-Y. Synthesis and functionalized of a mesoporous silica nanoparticle based on the sol-gel process and applications in controlled release. *Acc Chem Res.* **2007**;40:846–853. doi:10.1021/ar600032u
22. de Lima HHC, Kupfer VL, Moises MP, et al. Bionanocomposites based on mesoporous silica and alginate for enhanced drug delivery. *Carbohydr Polym.* **2018**;196:126–134. doi:10.1016/j.carbpol.2018.04.107
23. Aulifa DL, Amarilis B, Ichsani LN, et al. A comprehensive review: mesoporous silica nanoparticles greatly improve pharmacological effectiveness of phytoconstituent in plant extract. *Pharmaceuticals.* **2024**;17(12):1684. doi:10.3390/ph17121684
24. Tam D, Ashley CE, Xue M, Carnes EC, Zink JJ, Brinker CJ. Mesoporous silica nanoparticle nanocarriers: biofunctionality and biocompatibility. *Acc Chem Res.* **2013**;46:792–801. doi:10.1021/ar3000986
25. Mohapatra S, Rout SR, Narayan R, Maiti TK. Multifunctional mesoporous hollow silica nanocapsules for targeted co-delivery of cisplatin-pemetrexed and MR imaging. *Dalton Trans.* **2014**;43:15841–15850. doi:10.1039/C4DT02144D
26. Tsao CW, Aday AW, Almaraz ZI, Al E. Heart disease and stroke statistics—2022 update: a report from the American Heart Association. *Circulation.* **2022**;145(8):153–639.
27. Perera K, Kuruppuarachchi D, Kumarasinghe S, Sulemen M. The impact of carbon disclosure and carbon emissions intensity on firms' idiosyncratic volatility. **2023**;128(107053).
28. Benslaiman S, Garcia U, Sebal A, et al. Pathophysiology of atherosclerosis. *Int J Mol Sci.* **2022**;23(6).
29. Zhang X, Fernández-Hernando C. Transport of LDLs into the arterial wall: impact in atherosclerosis. *Curr Opin Lipidol.* **2020**;31(5). doi:10.1097/MOL.0000000000000701
30. Szwed P, Gasecka A, Zawadka M, Eyileten C, Al E. Infections as novel risk factors of atherosclerotic cardiovascular diseases: pathophysiological links and therapeutic implications. *J Clin Med.* **2021**;10(12):2539. doi:10.3390/jcm10122539
31. Feingold K. Lipid and Lipoprotein Metabolism. *Endocrinol Metab Clin N Am.* **2022**;51:437–458. doi:10.1016/j.ecl.2022.02.008
32. Narasimhulu CA, Fernandez-Ruiz I, Selvarajan K, et al. Atherosclerosis — do we know enough already to prevent it? *Curr Opin Pharmacol.* **2016**;27:92–102. doi:10.1016/j.coph.2016.02.006
33. Michaeli D, Michaeli J, Albers S, Boch T, Michaeli T. Established and emerging lipid-lowering drugs for primary and secondary cardiovascular prevention. *Am J Cardiovasc Drugs.* **2023**;23(5):477–495. doi:10.1007/s40256-023-00594-5
34. Ferri N, Ruscica M, Fazio S, Corsini A. Low-density lipoprotein cholesterol-lowering drugs: a narrative review. *J Clin Med.* **2024**;13(16):4582. doi:10.3390/jcm13164582
35. Zabetakis I, Lordan R, Tsoupras A. *The Impact of Nutrition and Statin on Cardiovascular Diseases*. Academic Press; **2019**.
36. Tiwari V. Mechanism of action of anti-hypercholesterolemia drugs and their resistance. *Eur J Pharmacol.* **2014**;741:156–170. doi:10.1016/j.ejphar.2014.07.048
37. Shrestha S, Wu B, Guiney L, Barter P, Rye K. Cholesteryl ester transfer protein and its inhibitors. *J Lipid Res.* **2018**;59:772–783. doi:10.1194/jlr.R082735
38. Yamashita S, Masuda D, Matsuzawa Y. Pemafibrate, a new selective PPAR α modulator: drug concept and its clinical applications for dyslipidemia and metabolic diseases. *Curr Atheroscler Rep.* **2020**;22(5):1–17. doi:10.1007/s11883-020-0823-5
39. Wang X, Jing S, Qiu X, Zhao S, Liu Y, Tan Y. Novel bile acid sequestrant: a biodegradable hydrogel based on amphiphilic allylamine copolymer. *Chem Eng J.* **2016**;304:493–502. doi:10.1016/j.cej.2016.06.104
40. Stanciu MC, Nichifor M, Teacă CA. Bile acid sequestrants based on natural and synthetic gels. *Gels.* **2023**;9(6):500. doi:10.3390/gels9060500
41. Nair T. Role of PCSK9 inhibitors in the management of dyslipidaemia. *Indian Hear J.* **2024**;76(1):44–50. doi:10.1016/j.ihj.2023.12.011
42. Kang M. *Stroke Revisited: Dyslipidemia in Stroke*. In: Springer; **2021**.
43. Murtaza G. Solubility enhancement of simvastatin: a review. *Acta Pol Pharm.* **2012**;69(4):581–590.
44. Gryn SE, Hegele RA. Ezetimibe plus simvastatin for the treatment of hypercholesterolemia. *Expert Opin Pharmacother.* **2015**;16(8):1255–1262. doi:10.1517/14656566.2015.1041504
45. Wei J, Chen S, Fu H, et al. Measurement and correlation of solubility data for atorvastatin calcium in pure and binary solvent systems from 293.15 K to 328.15 K. *J Mol Liq.* **2021**;324:115–124. doi:10.1016/j.molliq.2020.115124
46. Górniak A, Gajda M, Pluta J, Irzabek H, Karolewicz B. Thermal, spectroscopic and dissolution studies of lovastatin solid dispersions with acetylsalicylic acid. *J Therm Anal Calorim.* **2016**;125(1):777–784. doi:10.1007/s10973-016-5279-z
47. Kamble P, Shaikh K, Chaudhari P. Application of liquisolid technology for enhancing solubility and dissolution of rosuvastatin. *Adv Pharm Bull.* **2013**;4(2):197–204. doi:10.5681/apb.2014.029
48. Enna S, Bylund D. *xPharm: The Comprehensive Pharmacology Reference*. In: Elsevier; **2008**.
49. Guoquan Z. Study of solute-solvent intermolecular interactions and preferential solvation for mevastatin dissolution in pure and mixed binary solvents. *J Chem Thermodyn.* **2022**;174:106902.
50. Yousaf A, Kim D, Oh Y, Yong C, Kim J, Choi H. Enhanced oral bioavailability of fenofibrate using polymeric nanoparticulated systems: physicochemical characterization and in vivo investigation. *Int J Nanomed.* **2015**;10(1):1819–1830. doi:10.2147/IJN.S78895
51. Jung JY, Choi Y, Suh CH, Yoon D, Kim HA. Effect of fenofibrate on uric acid level in patients with gout. *Sci Rep.* **2018**;8:16767. doi:10.1038/s41598-018-35175-z
52. Górniak A, Złocińska A, Trojan M, Pęcak A, Karolewicz B. Preformulation studies of ezetimibe-simvastatin solid dispersions in the development of fixed-dose combinations. *Pharmaceutics.* **2022**;14(5):912. doi:10.3390/pharmaceutics14050912
53. Phan BAP, Dayspring TD, Toth PP. Ezetimibe therapy: mechanism of action and clinical update. *Vasc Heal Risk Manag.* **2012**;8:415–427.
54. Ha J, Jo K, Kang B, Kim M, Lim D. Cholestyramine use for rapid reversion to euthyroid states in patients with thyrotoxicosis. *Endocrinol Metab.* **2016**;31(3):476–479. doi:10.3803/EnM.2016.31.3.476

55. Carnovale C, Perrotta C, Baldelli S, et al. Antihypertensive drugs and brain function: mechanisms underlying therapeutically beneficial and harmful neuropsychiatric effects. *Cardiovasc Res.* **2023**;119(3):647–667. doi:10.1093/cvr/cvac110
56. Felkle D, Jarczyński M, Kaleta K, Zięba K, Nazimek K. The immunomodulatory effects of antihypertensive therapy: a review. *Biomed Pharmacother.* **2022**;153.
57. Olivas-Morales FJ. Diuretics use in the management of hypertension. *Hipertens y Riesgo Vasc.* **2024**;41(3):186–193. doi:10.1016/j.hipert.2024.03.004
58. Kehrenberg MCA, Bachmann HS. Diuretics: a contemporary pharmacological classification? *Naunyn Schmiedebergs Arch Pharmacol.* **2022**;395(5):619–627. doi:10.1007/s00210-022-02228-0
59. Blebea N, Pușcașu C, Ștefănescu E, Stănișu A. Diuretic therapy: mechanisms, clinical applications, and management. *J Mind Med Sci.* **2025**;12(1):26. doi:10.3390/jmms12010026
60. Jones KE, Hayden SL, Meyer HR, et al. The evolving role of calcium channel blockers in hypertension management: pharmacological and clinical considerations. *Curr Issues Mol Biol.* **2024**;46(7):6315–6327. doi:10.3390/cimb46070377
61. Lee EM. Calcium channel blockers for hypertension: old, but still useful. *Cardiovasc Prev Pharmacother.* **2023**;5(4):113–125. doi:10.36011/cpp.2023.5.e16
62. Mosa FES, Suryanarayanan C, Feng T, Barakat K. Effects of selective calcium channel blockers on ions' permeation through the human Cav1.2 ion channel: a computational study. *J Mol Graph Model.* **2021**;102:107776. doi:10.1016/j.jmgm.2020.107776
63. Meyer M, Wetmore JB, Weinhandl ED, Roetker NS. Association of non-dihydropyridine calcium channel blockers versus beta-adrenergic receptor blockers with risk of heart failure hospitalization. *Am J Cardiol.* **2023**;197:68–74. doi:10.1016/j.amjcard.2023.04.013
64. Borghi C, Cicero AFG, Agnoletti D, Fiorini G. Pathophysiology of cough with angiotensin-converting enzyme inhibitors: how to explain within-class differences? *Eur J Intern Med.* doi:10.1016/j.ejim.2024.03.012
65. Silva-Velasco DL, Cervantes-Pérez LG, Sánchez-Mendoza A. ACE inhibitors and their interaction with systems and molecules involved in metabolism. *Heliyon.* **2024**;10(2):e24655. doi:10.1016/j.heliyon.2024.e24655
66. Chen R, Suchard MA, Krumholz HM, et al. Comparative first-line effectiveness and safety of ACE (angiotensin-converting enzyme) inhibitors and angiotensin receptor blockers: a multinational cohort study. *Hypertension.* **2021**;78(3):591–603. doi:10.1161/HYPERTENSIONAHA.120.16667
67. Khalil H, Zeltser R. *Antihypertensive Medications*. In: StatPearls Publishing; **2023**.
68. de Souza GA P, Osman IO, Le Bideau M, et al. Angiotensin II receptor blockers (ARBs antihypertensive agents) increase replication of SARS-CoV-2 in Vero E6 cells. *Front Cell Infect Microbiol.* **2021**;11:639177. doi:10.3389/fcimb.2021.639177
69. Sutanto H, Dobrev D, Heijman J. Angiotensin receptor-neprilysin inhibitor (ARNI) and cardiac arrhythmias. *Int J Mol Sci.* **2021**;22(16):8994. doi:10.3390/ijms22168994
70. Tsai Y, Cheng W, Chang Y. Mechanism of angiotensin receptor-neprilysin inhibitor in suppression of ventricular arrhythmia. *J Cardiol.* **2021**;78(4):275–284. doi:10.1016/j.jcc.2021.04.011
71. Pascual-Figal D, Bayés-Genis A, Beltrán-Troncoso P, et al. Sacubitril-Valsartan, clinical benefits and related mechanisms of action in heart failure with reduced ejection fraction: a review. *Front Cardiovasc Med.* **2021**;8:754499. doi:10.3389/fcvm.2021.754499
72. Rico-Mesa J, White A, Ahmadian-Tehrani A, Anderson A. Mineralocorticoid receptor antagonists: a comprehensive review of finerenone. *Curr Cardiol Rep.* **2020**;22(11):140. doi:10.1007/s11886-020-01399-7
73. Jhund PS, Talebi A, Henderson AD, et al. Mineralocorticoid receptor antagonists in heart failure: an individual patient level meta-analysis. *Lancet.* **2024**;404(10458):1119–1131. doi:10.1016/S0140-6736(24)01733-1
74. Kreutz R, Algharably E. *Encyclopedia of Molecular Pharmacology*. Springer; **2021**.
75. Luo Y, Ren L, Jiang M, Chu Y. Anti-hypertensive efficacy of amlodipine dosing during morning vs evening: a meta-analysis. *Rev Cardiovasc Med.* **2019**;20(2):91–98.
76. Behboudi E, Soleymani J, Martinez F, Jouyban A. Solubility of amlodipine besylate in binary mixtures of polyethylene glycol 400 + water at various temperatures: measurement and modelling. *J Mol Liq.* **2022**;347.
77. Yang W, Villiers M, D M. The solubilization of the poorly water soluble drug nifedipine by water soluble 4-sulphonic calix[n]arenes. *Eur J Pharm Biopharm.* **2004**;58(3). doi:10.1016/j.ejpb.2004.04.010
78. Uzieline I, Bernotiene E, Rakauskienė G, et al. The antihypertensive drug nifedipine modulates the metabolism of chondrocytes and human bone marrow-derived mesenchymal stem cells. *Front Endocrinol.* **2009**;10(1).
79. Rashmi VT, Pravin SA, Jayashree BT, Jayashri GM, Milind JU. Solubility enhancement studies of hydrochlorothiazide by preparing solid dispersions using losartan potassium and urea by different methods. *Pharm Lett.* **2011**;3(6):8–17.
80. Raffin EP, Penniston KL, Antonelli JA, et al. The effect of thiazide and potassium citrate use on the health related quality of life of patients with urolithiasis. *J Urol.* **2018**;200(6):1290. doi:10.1016/j.juro.2018.06.023
81. Abdullah A, Rusli MF. Valsartan: a brief current review. *Pharmacophore Pharmacophore.* **2020**;11(2):58–64.
82. Józó M, Simon N, Yi L, Móczó J, Pukánszky B. Improved release of a drug with poor water solubility by using electrospun water-soluble polymers as carriers. *Pharmaceutics.* **2021**;14(1):34. doi:10.3390/pharmaceutics14010034
83. Bhole P, Patil V. Enhancement of water solubility of felodipine by preparing solid dispersion using poly-ethylene glycol 6000 and poly-vinyl alcohol. *Asian J Pharm.* **2009**;3(3):240–244. doi:10.4103/0973-8398.56305
84. Aronson JK. *Meyler's Side Effects of Drugs*. Elsevier; **2016**.
85. Chadha R, Sharma M, Haneef J. Multicomponent solid forms of felodipine: preparation, characterisation, physicochemical and in-vivo studies. *J Pharm Pharmacol.* **2017**;69(3):254–264. doi:10.1111/jphp.12685
86. O'Neil MJ. *The Merck Index - an Encyclopedia of Chemicals, Drugs, and Biologicals*. Cambridge: Merck and Co. Inc.; **2006**.
87. Fernandes GJ, Rathnanand M, Kulkarni V. Mechanochemical synthesis of carvedilol cocrystals utilizing hot melt extrusion technology. *J Pharm Innov.* **2019**;14:373–381. doi:10.1007/s12247-018-9360-y
88. Kundu S, Kumari N, Soni S, Al E. enhanced solubility of telmisartan phthalic acid cocrystals within the ph range of a systemic absorption site. *ACS Omega.* **2018**;3(11):15380–15388. doi:10.1021/acsomega.8b02144
89. Al-Omar MA. Nimodipine: physical profile, profiles of drug substances. *Excipients Relat Methodol.* **2005**;31:337–354.

90. Wei R, Wang H, Chen B, et al. Preparation and characterization of a modified nimodipine injection: an in vitro and in vivo study. *J Drug Deliv Sci Technol.* **2025**;107(1):106769. doi:10.1016/j.jddst.2025.106769
91. Hu Y, Kim H, Shinde VV, Jeong D, Choi Y, Cho E. Carboxymethyl cyclophosphoroses as a flexible Ph-responsive solubilizer for pindolol. *Carbohydr Polym.* **2017**;174:101–107.
92. Khoyi M, Westfall DC. *xPharm Compr Pharmacol Ref.*
93. Budiman A, Kalina K, Aristawidya L, Al SAA, Rusdin A, Aulifa DL. Characterizing the impact of chitosan on the nucleation and crystal growth of ritonavir from supersaturated solutions. *Polymers.* **2023**;15(5):1282. doi:10.3390/polym15051282
94. Aulifa DL, Al Shofwan AA, Megantara S, Fakhri TM, Budiman A. Elucidation of molecular interactions between drug–polymer in amorphous solid dispersion by a computational approach using molecular dynamics simulations. *Adv Appl Bioinforma Chem.* **2024**;17. doi:10.2147/AABC.S441628
95. Budiman A, Megantara S, Apriliani A. Solid dosage form development of glibenclamide-aspartame cocrystal using the solvent evaporation method to increase the solubility of glibenclamide. *Int J Appl Pharm.* **2019**;11(3):150–154. doi:10.22159/ijap.2019v11i3.32121
96. Pinal R. Enhancing the bioavailability of poorly soluble drugs. *Pharmaceutics.* **2024**;16(6):758. doi:10.3390/pharmaceutics16060758
97. Bhalani DV, Nutan B, Kumar A, Singh Chandel AK. Bioavailability enhancement techniques for poorly aqueous soluble drugs and therapeutics. *Biomedicines.* **2022**;10(9):2055. doi:10.3390/biomedicines10092055
98. Bavishi DD, Borkhataria CH. Spring and parachute: how cocrystals enhance solubility. *Prog Cryst Growth Charact Mater.* **2016**;62(3):1–8. doi:10.1016/j.pcrysgrow.2016.07.001
99. Jagtap S, Magdum C, Jadge D, Jagtap R. Solubility enhancement technique: a review. *J Pharm Sci Res.* **2018**;10(9):2205–2211.
100. Kumar R, Thakur A, Chaudhari P, Banerjee N. Particle size reduction techniques of pharmaceutical compounds for the enhancement of their dissolution rate and bioavailability. *J Pharm Innov.* **2020**;17(1).
101. Censi R, Martino D. Polymorph impact on the bioavailability and stability of poorly soluble drugs. *Molecules.* **2015**;20(10):18759–18776. doi:10.3390/molecules201018759
102. Djayanti K, Maharjan P, Cho KH, et al. Mesoporous silica nanoparticles as a potential nanopatform: therapeutic applications and considerations. *Int J Mol Sci.* **2023**;24(7):6349.
103. Kolimi P, Narala S, Youssef AAA, Nyavanandi D, Dudhipala N. A systemic review on development of mesoporous nanoparticles as a vehicle for transdermal drug delivery. *Nanotheranostics.* **2023**;7(1):70–89. doi:10.7150/ntno.77395
104. Frickenstein A, Hagood J, Britten C, Abbott B, McNally M, Al E. Mesoporous silica nanoparticles: properties and strategies for enhancing clinical effect. *Pharmaceutics.* **2021**;13(4):570. doi:10.3390/pharmaceutics13040570
105. Sato Y, Iwashina T, Tanihata N, et al. Sol–gel reaction of tetraethoxysilane, hexaethoxydisiloxane, and octaethoxytrisiloxane: differences in siloxane precursor oligomers depending on raw materials. *ACS Appl Polymer Mater.* **2024**;6(19):12197–12206. doi:10.1021/acsapm.4c02305
106. Steinbach JC, Fait F, Mayer HA, Kandelbauer A. Sol–gel-controlled size and morphology of mesoporous silica microspheres using hard templates. *ACS Omega.* **2023**;8(33):30273–30284. doi:10.1021/acsomega.3c03098
107. Han Y, Zhang L, Yang W. Synthesis of mesoporous silica using the sol–gel approach: adjusting architecture and composition for novel applications. *Nanomaterials.* **2024**;14(11):903. doi:10.3390/nano14110903
108. AlMohaimadi KM, Albishri HM, Thumayri KA, AlSuhaimi AO, Mehdar YTH, Hussein BHM. Facile hydrothermal assisted basic catalyzed sol gel synthesis for mesoporous silica nanoparticle from alkali silicate solutions using dual structural templates. *Gels.* **2024**;10(12):839. doi:10.3390/gels10120839
109. Liu J, Du G, Chen T. Synthesis of ordered mesoporous silica with nonionic surfactant/anionic polyelectrolyte as template under near-neutral pH conditions. *Langmuir.* **2024**;40(27):14016–14026. doi:10.1021/acs.langmuir.4c01338
110. Bae JY, Jang SG, Cho J, Kang M. Amine-functionalized mesoporous silica for efficient CO₂ capture: stability, performance, and industrial feasibility. *Int J Mol Sci.* **2025**;26(9):1–27. doi:10.3390/ijms26094313
111. Fujii Y, Zhou S, Shimada M, Kubo M. Synthesis of monodispersed hollow mesoporous organosilica and silica nanoparticles with controllable shell thickness using soft and hard templates. *Langmuir.* **2023**;39(13):4571–4582. doi:10.1021/acs.langmuir.2c03121
112. Elimbinzi E, Mgya JE. Mixed bio-based surfactant-templated mesoporous silica for supporting palladium catalyst. *Heliyon.* **2024**;10(20):e39168. doi:10.1016/j.heliyon.2024.e39168
113. Bose S, Sarkar N, Jo Y. Natural medicine delivery from 3D printed bone substitutes. *J Control Release.* **2024**;365:848–875. doi:10.1016/j.jconrel.2023.09.025
114. Das D, Yang Y, O'Brien JS, et al. Synthesis and physicochemical characterization of mesoporous sio₂ nanoparticles. *J Nanomater.* **2014**;2014. doi:10.1155/2014/176015
115. Trzeciak K, Chotera-ouda A, Bak-sypien II, Potrzebowski MJ. Mesoporous silica particles as drug delivery systems—the state of the art in loading methods and the recent progress in analytical techniques for monitoring these processes. *Pharmaceutics.* **2021**;13(7):950. doi:10.3390/pharmaceutics13070950
116. Huang X, Young NP, Townley HE. Characterization and comparison of mesoporous silica particles for optimized drug delivery. *Nanomater Nanotechnol.* **2014**;4(1):1–15. doi:10.5772/58290
117. Abouaitah K, Hassan HA, Swiderska-Sroda A, et al. Targeted nano-drug delivery of colchicine against colon cancer cells by means of mesoporous silica nanoparticles. *Cancers.* **2020**;12(1):1–30. doi:10.3390/cancers12010144
118. Lyu X, Wu X, Liu Y, Huang W, Lee B, Li T. Synthesis and characterization of mesoporous silica nanoparticles loaded with Pt catalysts. *Catalysts.* **2022**;12(2):183. doi:10.3390/catal12020183
119. Ruiz-González ML, Torres-Pardo A, González-Calbet JM. The role of transmission electron microscopy in the early development of mesoporous materials for tissue regeneration and drug delivery applications. *Pharmaceutics.* **2021**;13(12):2200. doi:10.3390/pharmaceutics13122200
120. Arcos D, López-Noriega A, Ruiz-Hernández E, Ruiz L, González-Calbet JM, Vallet-Regí M. Synthesis of mesoporous microparticles for biomedical application. *Key Eng Mater.* **2008**;377:181–194. doi:10.4028/www.scientific.net/KEM.377.181
121. VigneshKrishnan SM, Kalaivani T, Kalaivani T. Synthesis and characterization of mesoporous SiO₂ nanoparticles for bio medical applications. *IOP Conf Ser Mater Sci Eng.* **2022**;1219(1):012038. doi:10.1088/1757-899x/1219/1/012038

122. Kumar B, Kulanthaivel S, Mondal A, et al. Mesoporous silica nanoparticle based enzyme responsive system for colon specific drug delivery through guar gum capping. *Colloids Surf B Biointerfaces*. 2017;150:352–361. doi:10.1016/j.colsurfb.2016.10.049
123. Abedi M, Abolmaali SS, Abedanzadeh M, Farjadian F, Mohammadi Samani S, Tamaddon AM. Core-shell imidazoline-functionalized mesoporous silica superparamagnetic hybrid nanoparticles as a potential theranostic agent for controlled delivery of platinum(II) compound. *Int J Nanomed*. 2020;15:2617–2631. doi:10.2147/IJN.S245135
124. Paris JL, Vora LK, Pérez-Moreno AM, et al. Dissolving microneedle array patches containing mesoporous silica nanoparcles of different pore sizes as a tunable sustained release platform. *bioRxiv*. 2023;(669). doi:10.1016/j.ijpharm.2024.125064
125. Guerrero-Florez V, Barbara A, Kodjikian S, Oukacine F, Trens P, Cattoën X. Dynamic light scattering unveils stochastic degradation in large-pore mesoporous silica nanoparticles. *J Colloid Interface Sci*. 2024;676:1098–1108. doi:10.1016/j.jcis.2024.07.151
126. Clemens D, Lee BY, Plamthottam S, et al. Nanoparticle formulation of moxifloxacin and intramuscular route of delivery improve antibiotic pharmacokinetics and treatment of pneumonic tularemia in a mouse model. *ACS Infect Dis*. 2019;5:281–291. doi:10.1021/acsinfectdis.8b00268
127. Attia MS, Hasan AA, Ghazy FES, Gomaa E. Mesoporous silica nanoparticles-embedded hydrogel: a potential approach for transdermal delivery of carvedilol to pediatric population. *Int J Pharm*. 2025;676:125605. doi:10.1016/j.ijpharm.2025.125605
128. Lérica-Viso A, Estepa-Fernández A, García-Fernández A, Martí-Centelles V, Martínez-Máñez R. Biosafety of mesoporous silica nanoparticles; towards clinical translation. *Adv Drug Deliv Rev*. 2023;201:115049. doi:10.1016/j.addr.2023.115049
129. Solarska-ściuk K, Pruchnik H. A critical view on the biocompatibility of silica nanoparticles and liposomes as drug delivery systems. *Mol Pharm*. 2025;22(6):2830–2848. doi:10.1021/acs.molpharmaceut.5c00501
130. Cheng Y, Tao J, Zhang Y, et al. Shape and shear stress impact on the toxicity of mesoporous silica nanoparticles: in vitro and in vivo evidence. *Mol Pharm*. 2023;20(6):3187–3201. doi:10.1021/acs.molpharmaceut.3c00180
131. Zhang Y, Lin X, Chen X, et al. Strategies to regulate the degradation and clearance of mesoporous silica nanoparticles: a review. *Int J Nanomed*. 2024;19:5859–5878. doi:10.2147/IJN.S451919
132. Fiedler R, Sivakumaran G, Mallén J, Lindén M. Superparamagnetic core-mesoporous silica shell nanoparticles with tunable extra- and intracellular dissolution rates. *Chem Mater*. 2024;36(6):2790–2798. doi:10.1021/acs.chemmater.3c02986
133. Yang G, Li Z, Wu F, et al. Improving solubility and bioavailability of breviscapine with mesoporous silica nanoparticles prepared using ultrasound-assisted solution-enhanced dispersion by supercritical fluids method. *Int J Nanomed*. 2020;15:1661–1675. doi:10.2147/IJN.S238337
134. Zhang Y, Wang J, Bai X, Jiang T, Zhang Q, Wang S. Mesoporous silica nanoparticles for increasing the oral bioavailability and permeation of poorly water soluble drugs. *Mol Pharm*. 2012;9:505–513. doi:10.1021/mp200287c
135. Porrang S, Davaran S, Rahemi N, Allahyari F, Mostafavi E. How advancing are mesoporous silica nanoparticles? A comprehensive review of the literature. *Int J Nanomed*. 2022;17:1803–1827. doi:10.2147/IJN.S353349
136. Fang L, Zhou H, Cheng L, Wang Y, Liu F, Wang S. The application of mesoporous silica nanoparticles as a drug delivery vehicle in oral disease treatment. *Front Cell Infect Microbiol*. 2023;13:1124411. doi:10.3389/fcimb.2023.1124411
137. Safat A, Sheibani H, Mohammadi P, Hasanabadi N, Sakhaee E. Evaluation of lipid-lowering effect of Cynara scolymus extract-loaded mesoporous silica nanoparticles on ultra-lipid-fed mice. *Comp Clin Pathol*. 2018;27:513–518. doi:10.1007/s00580-017-2621-1
138. Jia L, Shen J, Li Z, Zhang D, Al E. In vitro and in vivo evaluation of paclitaxel-loaded mesoporous silica nanoparticles with three pore sizes. *Int J Pharm*. 2013;445:12–19. doi:10.1016/j.ijpharm.2013.01.058
139. Kiwilsza A, Milanowski B, Druzbicki K, et al. Molecular dynamics and the dissolution rate of nifedipine encapsulated in mesoporous silica. *Microporous Mesoporous Mater*. 2017;250:186–194. doi:10.1016/j.micromeso.2017.05.019
140. Prathusha P, Bhargavi L, Belsen D, Al E. Formulation development and in-vitro evaluation of nifedipine sublingual tablets using mesoporous silica. *Pharma Innov J*. 2015;4(10):76–82.
141. Meola T, Schultz H, Peressin K, Al E. Enhancing the oral bioavailability of simvastatin with silica-lipid hybrid particles: the effect of supersaturation and silica geometry. *Eur J Pharm Sci*. 2020;150(1):10537. doi:10.1016/j.ejps.2020.105337
142. Bharati S, Gaikwad V, Chellampillai B. Biopharmaceutical advancement of efendipine hydrochloride ethanolate through amorphous solid dispersion of a partek Slc mesoporous silica polymer. *RSC Pharm*. 2024;1:765–774. doi:10.1039/D4PM00113C
143. Attia M, Ghazy F. Ameliorating the poor dissolution rate of selexipag in aqueous acidic conditions following confinement into mesoporous silica. *Ind J Pharm Edu Res*. 2023;57(4):1002–1011. doi:10.5530/ijper.57.4.122
144. Luo S, Hao J, Gao Y, Al E. Pore size effect on adsorption and release of metoprolol tartrate in mesoporous silica: experimental and molecular simulation studies. *Mater Sci Eng C*. 2019;100:789–797. doi:10.1016/j.msec.2019.03.050
145. Zhang Y, Wang H, Gao C, Al E. Highly ordered mesoporous carbon nanomatrix as a new approach to improve the oral absorption of the water-insoluble drug, simvastatin. *Eur J Pharm Sci*. 2013;49(5):864–872. doi:10.1016/j.ejps.2013.05.031
146. Madan J, Patil S, Mathure D. Improving dissolution profile of poorly water-soluble drug using non-ordered mesoporous silica. *Marmara Univ Press*. 2018;22(2):249–258.
147. Diadrio A, Sánchez-Montero J, Diadrio J, Salinas A, Vallet-Regi M. Mesoporous silica nanoparticles as a new carrier methodology in the controlled release of the active components in a poly pill. *Eur J Pharm Sci*. 2017;97:1–8. doi:10.1016/j.ejps.2016.11.002
148. Biswas N. Modified mesoporous silica nanoparticles for enhancing oral bioavailability and antihypertensive activity of poorly water soluble valsartan. *Eur J Pharm Sci*. 2017;99:152–160. doi:10.1016/j.ejps.2016.12.015
149. Farooq A, Tosheva L, Azzawi M, Whitehead D. Real-time observation of aortic vessel dilation through delivery of sodium nitroprusside via slow release mesoporous nanoparticles. *J Colloid Interface Sci*. 2016;478:127–135. doi:10.1016/j.jcis.2016.06.004
150. Mahdi H, Muhana F, Al-Ani I, Al-Sanabrah A. Preparation and evaluation of SBA-16, ZSM-5 and MCM-41 Mesoporous silica nanoparticles as drug delivery system for carvedilol. *Int J Drug Deliv Technol*. 2022;12(3):1033–1048. doi:10.25258/ijddt.12.3.20
151. Sayadi K, Rahdar A, Hajinezhad M, Nikazar S, Susan M. Atorvastatin-loaded SBA-16 nanostructures: synthesis, physical characterization, and biochemical alterations in hyperlipidemic rats. *J Mol Struct*. 2019;1202:127296. doi:10.1016/j.molstruc.2019.127296
152. Zhang Y, Zhi Z, Jiang T, Zhang J, Wang Z, Wang S. Spherical mesoporous silica nanoparticles for loading and release of the poorly water-soluble drug telmisartan. *J Control Release*. 2010;145(3):257–263. doi:10.1016/j.jconrel.2010.04.029
153. Jin H, Lu W, Zhang Y, et al. Functionalized periodic mesoporous silica nanoparticles for inhibiting the progression of atherosclerosis by targeting low-density lipoprotein cholesterol. *Pharmaceutics*. 2024;16(1):74. doi:10.3390/pharmaceutics16010074

154. Kumari L, Choudhari Y, Patel P, et al. Advancement in solubilization approaches: a step towards bioavailability enhancement of poorly soluble drugs. *Life*. 2023;13(5):1099. doi:10.3390/life13051099
155. Brown C, Friedel H, Barker A, et al. FIP/AAPS Joint Workshop Report: dissolution/in vitro release testing of novel/special dosage forms. *AAPS Pharm Sci Tech*. 2011;12(2):782–794. doi:10.1208/s12249-011-9634-x
156. Joshi K, Chandra A, Jain K, Talegaonkar S. Nanocrystallization: an Emerging Technology to Enhance the bioavailability of poorly soluble drugs. *Pharm Nanotechnol*. 2019;7(4):259–278. doi:10.2174/2211738507666190405182524
157. Messerli F, Bangalore S, Bavishi C, Rimoldi S. Angiotensin-converting enzyme inhibitors in hypertension. *J Am Coll Cardiol*. 2018;71(13):1474–1481. doi:10.1016/j.jacc.2018.01.058
158. Nickening G. Should angiotensin II receptor blockers and statins be combined? *Circulation*. 2004;110(8):1013–1020. doi:10.1161/01.CIR.0000139857.85424.45

International Journal of Nanomedicine

Publish your work in this journal

The International Journal of Nanomedicine is an international, peer-reviewed journal focusing on the application of nanotechnology in diagnostics, therapeutics, and drug delivery systems throughout the biomedical field. This journal is indexed on PubMed Central, MedLine, CAS, SciSearch®, Current Contents®/Clinical Medicine, Journal Citation Reports/Science Edition, EMBase, Scopus and the Elsevier Bibliographic databases. The manuscript management system is completely online and includes a very quick and fair peer-review system, which is all easy to use. Visit <http://www.dovepress.com/testimonials.php> to read real quotes from published authors.

Submit your manuscript here: <https://www.dovepress.com/international-journal-of-nanomedicine-journal>

Dovepress
Taylor & Francis Group