REVIEW ARTICLE

Optimizing Poorly Soluble Drugs: Advances in Mesoporous Silica-Based Formulations

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ABSTRACT
The challenge of improving the solubility of poorly water-soluble drugs has become increasingly critical in oral drug delivery, where low bioavailability can limit therapeutic effectiveness. Mesoporous silica materials (MSMs), with their high surface area, tuneable pore sizes, and biocompatibility, have emerged as a powerful tool for enhancing drug dissolution rates. This review provides a comprehensive overview of MSMs, particularly focusing on commercially available variants, and their application in formulating amorphous solid dispersions for solubility enhancement. We discuss various drug-loading techniques, including solvent-based and non-solvent-based methods, highlighting their impact on drug stability, amorphization, and release profiles. The review also addresses key factors influencing drug release from MSMs, such as particle characteristics and environmental conditions, alongside successful case studies demonstrating improved bioavailability. Despite the promising results, challenges in scaling up MSM-based formulations for industrial production remain. Future directions in MSM technology development and regulatory considerations are explored, emphasizing the potential of these materials in revolutionizing drug delivery systems for poorly soluble drugs.

Keywords: Mesoporous silica materials, Solubility enhancement, poorly water-soluble drugs, Amorphous solid dispersions, Drug delivery systems.
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INTRODUCTION

The oral route is the most preferred and widely accepted method for drug delivery due to its simplicity, cost-effectiveness, and patient compliance. Approximately 60% of the drug formulations on the market are administered orally, making it a crucial area of focus for pharmaceutical development. Oral drug administration is attractive because it allows for self-administration without the need for medical assistance, and it generally offers a non-invasive, convenient option for patients. Despite these advantages, achieving optimal therapeutic outcomes via oral delivery remains challenging due to several factors, primarily the solubility, dissolution, and permeability of drugs. These three parameters are critical in determining a drug's bioavailability, which in turn governs its therapeutic efficacy.[1] When a drug is administered orally, it must undergo disintegration in the gastrointestinal (GI) tract, dissolution into GI fluids, and then absorption across the GI membrane into the bloodstream. These processes are influenced by the physicochemical properties of the drug, such as solubility and permeability, as well as the physiological environment of the GI tract. Among these, poor water solubility is a major bottleneck in achieving adequate oral bioavailability, especially for the majority of newly discovered drug candidates, which often exhibit poor solubility in water and other biological fluids. [2] This trend can be attributed to modern drug design approaches, such as combinatorial chemistry and high-throughput screening, which tend to yield molecules with high lipophilicity, large molecular weight, and complex structures traits that are generally unfavorable for oral absorption. It is estimated that approximately 40% of marketed drugs and nearly 90% of compounds in the drug development pipeline suffer from poor water solubility, classifying them as poorly water-soluble drugs (PWSDs).This high prevalence of PWSDs presents a significant challenge for drug developers, as low solubility often leads to suboptimal absorption in the GI tract, limiting the drug's ability to reach therapeutic concentrations at the site of action as presented in Figure 1. As a result, PWSDs exhibit poor oral bioavailability, which can compromise their efficacy and require higher dosages to achieve desired therapeutic effects, potentially leading to increased side effects and reduced patient compliance.[3]

The Biopharmaceutical Classification System (BCS) is a framework widely used to categorize drugs based on their solubility and permeability, with the goal of understanding their bioavailability characteristics and identifying appropriate formulation strategies. According to the BCS, drugs are divided into four classes: Class 1 drugs exhibit high solubility and high permeability, and thus are well absorbed and readily bioavailable. Class 2 drugs, although possessing high permeability, are limited by poor solubility,

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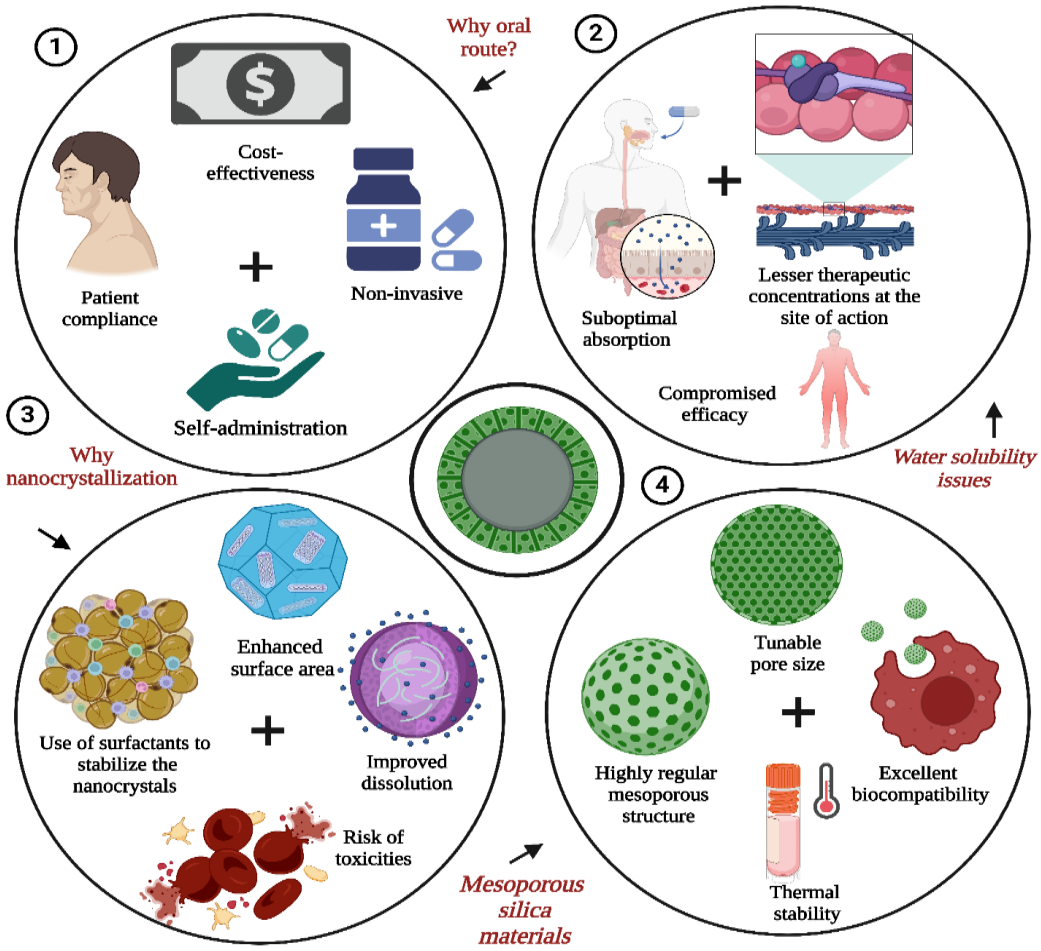

Figure 1: It illustrates about 1: The need of oral drug delivery route 2: The impact of water insolubility issues for active pharmaceutical ingredients 3: The requirement of nanocrystallization for enhanced surface area, improved dissolution involving with risk of toxicities. 4. Advantages of mesoporous silica materials for effective therapeutics.

making dissolution the rate-limiting step in their absorption. Class 3 drugs have high solubility but poor permeability, and their absorption is restricted by their ability to cross the intestinal epithelium.[4] Finally, Class 4 drugs suffer from both poor solubility and low permeability, making them the most challenging to formulate for oral delivery. For Class 2 drugs, which represent a significant portion of the PWSDs, improving solubility is a key formulation challenge. Poorly soluble drugs often exhibit poor dissolution rates, which is critical in limiting their absorption in the GI tract. According to the Noyes-Whitney equation, the dissolution rate of a solid in a solvent is directly proportional to its surface area and solubility. Therefore, strategies aimed at reducing particle size, such as nano crystallization, have been employed to increase the effective surface area of drug particles, thereby enhancing the dissolution rate and improving bioavailability.[5] Nano crystallization is a well-established approach for increasing the oral bioavailability of PWSDs by reducing the drug's particle size to the nanometer range. This top-down technique typically involves milling large drug crystals into smaller nanoparticles, increasing their surface area and improving their dissolution profile. However, while this method is effective in enhancing dissolution, the use of surfactants to stabilize the nanocrystals often introduces safety concerns. Surfactants can lead to potential side effects and reduced drug-loading efficiency, thereby increasing the overall chemical burden on patients.[6] In addition, the stabilizers used to maintain the nanocrystal size distribution may negatively impact the drug's pharmacokinetics and increase the risk of toxicity. In recent years, mesoporous silica materials (MSMs) have emerged as promising alternatives to traditional nano crystallization techniques for improving the dissolution of PWSDs. MSMs offer several advantages, including their highly regular mesoporous structure, high surface area, large pore volume, tunable pore size, excellent biocompatibility, and thermal stability. The unique structure of MSMs allows them to encapsulate drug molecules within their pores, preserving the drug in its amorphous form and preventing crystallization. Amorphous forms of drugs tend to dissolve more readily than their crystalline counterparts, making MSMs highly attractive for enhancing the dissolution and bioavailability of poorly soluble drugs. Since the first application of MSMs for drug delivery, as demonstrated by Vallet-Regí et al with the use of MCM-41 mesoporous silica to prolong the release of ibuprofen, interest in MSMs as carriers for PWSDs has grown significantly.[7] MSMs offer the ability to trap drug molecules within their porous network, reducing the energy required for dissolution and promoting faster

drug release in the GI tract. Additionally, the large surface area of MSMs facilitates better wetting and dispersion of the encapsulated drug, further enhancing dissolution rates.

Despite the promising potential of MSMs in improving drug solubility and dissolution, challenges remain. For example, while MSMs have shown efficacy in in vitro dissolution studies, their in vivo performance is not always superior to that of commercial formulations. Studies have indicated that the bioavailability of some drugs, such as Itraconazole, loaded onto MSMs can be lower than that of conventional drug products.[8] This discrepancy underscores the need for further optimization of MSM-based drug delivery systems, particularly in terms of drug loading capacity, release kinetics, and overall bioavailability. The Lipinski "rule of five" is often used as a guideline to assess the oral drug-likeness of a compound, indicating that drugs with poor solubility and high molecular weight are less likely to be successfully absorbed when administered orally[20]. MSMs, by offering an approach to encapsulate and maintain PWSDs in their amorphous state, provide a potential solution to these limitations. However, future advancements in MSM technology must focus on optimizing drug release profiles and improving the in vivo absorption of these formulation.[9]

Table 1: Solvent and non-solvent-based methods for preparing ordered and non-ordered mesoporous silica materials for pharmaceutical applications.

Preparation Method	Silica Type	Description	Advantages	Disadvantages
Sol-Gel Method	Ordered (OMS) & Non-Ordered (NOS)	Hydrolysis and condensation of silane precursors with surfactants to form silica networks.	High control over pore size and structure, adaptable for both OMS and NOS.	Requires precise control; potential for incomplete drug release if pores are too tight.
Hydrothermal Synthesis	Ordered (OMS)	Surfactant-assisted method with heat treatment to enhance pore organization.	Produces highly ordered mesoporous structures; uniform pore size.	High temperature and long processing time; complex setup.
Evaporation-Induced Self-Assembly (EISA)	Ordered (OMS)	Uses solvent evaporation to organize surfactants and silica precursors into ordered structures.	Scalable; allows control over pore arrangement.	Sensitive to environmental conditions; risk of pore collapse.
Solvent-Based Methods	Ordered (OMS) & Non-Ordered (NOS)	Includes solvent immersion, incipient wetness, rotary evaporation, spray drying, supercritical CO_2 methods.	Simple, effective for high drug loading; suitable for heat-sensitive drugs.	Risk of non-uniform drug distribution; solvent residue may remain.
Non-Solvent-Based Methods	Ordered (OMS) & Non-Ordered (NOS)	Includes melting, hot melt extrusion, microwave irradiation, mechanical energy.	Avoids use of solvents, reducing risk of solvent-related toxicity; can be energy-efficient.	Limited to heat-stable drugs; may lead to irregular drug distribution.
Impregnation and Solvent Evaporation	Ordered (OMS) & Non-Ordered (NOS)	Drug molecules are dissolved, mixed with silica, and then evaporated to load into pores.	Easy to scale; suitable for heat-sensitive drugs.	May lead to non-uniform drug distribution; incomplete drug loading.
Incipient Wetness Impregnation	Non-Ordered (NOS)	Drug solution is applied dropwise onto silica until pores are filled.	Efficient for high drug loading; cost-effective.	Limited to small-scale; uneven drug distribution.
Co-Spray Drying	Ordered (OMS) & Non-Ordered (NOS)	Drug and silica are simultaneously sprayed and dried, forming drug-loaded particles.	Enhances stability and solubility of drugs; scalable and fast.	Requires specialized equipment; risk of pore blockage.
Microwave-Assisted Synthesis	Ordered (OMS)	Uses microwave energy to accelerate sol-gel reaction, creating ordered structures.	Faster synthesis; uniform pore size.	Requires specialized equipment; less common.
Acid/Base Catalyzed Sol-Gel Process	Non-Ordered (NOS)	Chemical reaction at ambient temperature using acidic or basic conditions.	Cost-effective; adaptable for various drugs.	Produces irregular pores; less control over structure.

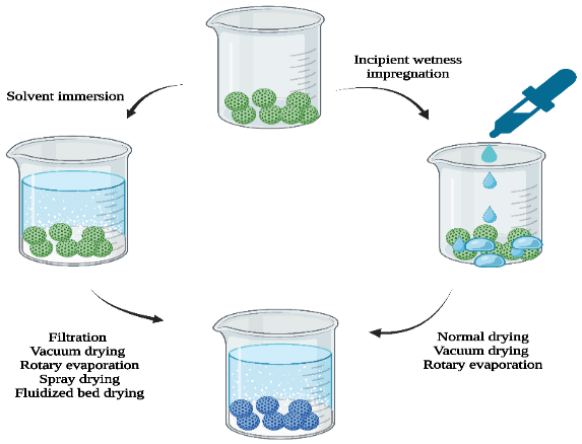

Figure 2: solvent based method for preparing ordered and non-ordered mesoporous silica materials

Type of mesoporous silica materials (MSMs)

Applications and benefits of ordered MSMs

Ordered mesoporous silica materials (OMS) have garnered significant attention as novel drug carriers, especially for the oral delivery of poorly water-soluble drugs. These materials, characterized by their uniform mesoporous structures (with pore diameters ranging from 2 to 50 nm) and ordered arrangement, offer unique advantages in drug delivery. Their ability to suppress recrystallization of drug molecules, enhance dissolution rates, and generate supersaturated drug solutions has made them a promising alternative to traditional drug delivery systems, particularly for bioavailability enhancement. One of the most compelling advantages of OMS is its ability to stabilize drugs in their amorphous state. Amorphous forms of drugs are known to have higher solubility compared to their crystalline counterparts, but they are also thermodynamically unstable and prone to recrystallization. OMS materials overcome this challenge by confining drug molecules within their mesoporous structure, where the finite-size effects prevent nucleation and crystal growth. This size-constraining effect ensures that drug molecules remain in an amorphous state, thus enhancing their solubility and dissolution rates upon administration. Studies have shown that drugs loaded into OMS not only dissolve faster than their crystalline forms but also often generate supersaturated solutions, providing higher concentrations of the drug in the gastrointestinal tract and consequently improving bioavailability. The process of drug loading into OMS is typically achieved through solvent-based impregnation techniques, such as solvent evaporation or incipient wetness impregnation.[10] During these processes, the drug molecules are deposited into the mesopores of the silica carrier, resulting in a homogeneous dispersion of the drug within the porous matrix. This uniform dispersion is crucial for preventing drug crystallization and ensuring that the drug remains in its amorphous state. Upon exposure to an aqueous medium, the drug is rapidly released from the pores, offering a faster dissolution rate compared to its crystalline counterpart. This accelerated release has been demonstrated with various poorly water-soluble drugs, including Itraconazole, Glibenclamide, and Ezetimibe, where OMS-based formulations resulted in enhanced dissolution rates and increased bioavailability in non-clinical models. The ability of OMS to generate supersaturated solutions is particularly important for improving drug bioavailability.[11] When a poorly soluble drug is released from OMS, it often exceeds its equilibrium solubility, resulting in a supersaturated state. In this state, the concentration of the drug in solution is higher than that of its crystalline form, which can significantly improve the drug's absorption in the gastrointestinal tract. This supersaturation phenomenon has been observed in studies involving drugs like Itraconazole, where the OMS-based formulation maintained a higher drug concentration in solution for extended periods, enhancing its bioavailability. Supersaturation also enables a more efficient drug absorption profile, as demonstrated in human clinical studies where Fenofibrate formulated with OMS showed a 77% increase in maximum concentration (C_{max}) and a 54% increase in the area under the curve (AUC) compared to a micronized form of Fenofibrate.[12] Moreover, OMS offers several advantages over traditional polymer-based amorphous solid dispersions (ASDs). While ASDs are widely used to enhance drug solubility, they often suffer from stability issues, particularly under conditions of high humidity and temperature. In contrast, OMS materials provide a more stable environment for amorphous drugs due to their rigid and inorganic silica matrix, which is less prone to degradation. The high specific surface area (SSA) of OMS (ranging from 500 to 1000 m^2/g) also allows for a higher drug-loading capacity compared to ASDs, while still maintaining the amorphous nature of the drug.[13] Another key benefit of OMS is its tunable pore size and surface chemistry. By adjusting the synthesis conditions, the pore size of OMS can be tailored to match the size of drug molecules, allowing for optimal drug loading and release kinetics. The surface of OMS can also be functionalized to improve drug compatibility, enhance drug loading efficiency, or modify the release profile. For example, functional groups such as amines or thiols can be introduced onto the surface of the silica to interact with specific drug molecules, improving their stability and release properties. This flexibility in design makes OMS a versatile platform for formulating a wide range of drugs with varying physicochemical properties. Furthermore, the use of OMS in drug delivery extends beyond solubility enhancement. These materials have been explored for controlled and targeted drug delivery applications, where the drug release can be modulated over time or directed to specific sites within the body. The ordered pore structure of OMS allows for precise control over the release rate of the drug, which can be adjusted by modifying the pore size, surface chemistry, or drug-loading method.[14] This capability is particularly useful for drugs that require sustained release or site-specific delivery, such as in cancer therapy or chronic disease management. Despite the numerous advantages of OMS, challenges remain in optimizing their performance as drug carriers. One common issue is incomplete drug release from the mesopores, particularly under non-sink conditions. Studies have shown that while OMS can enhance the dissolution rate of poorly soluble drugs, the total amount of drug released may plateau before

reaching 100%. This phenomenon has been attributed to a dynamic adsorption equilibrium between the drug and the silica surface, where a portion of the drug remains adsorbed within the pores rather than being fully released into solution. Further research is needed to better understand the factors influencing drug release from OMS and to develop strategies for overcoming this limitation.

Applications and benefits of non-ordered MSMs

Non-ordered silica materials (NOS) also serve as effective drug carriers for poorly water-soluble drugs, although they differ from ordered mesoporous silica (OMS) in their structure. Unlike OMS, which has a uniform and organized pore arrangement, NOS materials feature irregular, non-uniform pores. Despite this, they still offer advantages such as increased surface area and the ability to stabilize drugs in an amorphous state, enhancing solubility and dissolution rates. The amorphous drug is confined within the irregular pores of NOS, preventing crystallization and maintaining higher solubility. Like OMS, NOS materials improve drug bioavailability by enabling faster dissolution and the formation of supersaturated solutions. However, due to their less structured pore network, NOS may offer different release profiles, which can be beneficial for specific formulations where a gradual or sustained release is desired. The drug loading process for NOS often involves techniques similar to OMS, such as solvent impregnation, ensuring even drug dispersion. While NOS materials may not match the precise control over drug release seen with OMS, their flexibility in accommodating various drug types and modifying surface chemistry still makes them a versatile choice for enhancing drug delivery.[15]

Overview and applications of commercially available MSMs

Non-porous silica

Non-porous silica, particularly colloidal anhydrous silica (commonly referred to as hydrophilic fumed silica), is a widely utilized material in pharmaceuticals and cosmetics. Its functions include serving as an anti-tacking agent to prevent stickiness during manufacturing, an adsorbent, an emulsion stabilizer, a glidant, and a viscosity enhancer. Examples of commercially available non-porous silica include *Aerosil®* by Evonik Industries and *Cab-O-Sil®* from Cabot Corporation, both of which have been explored as drug delivery vehicles. Their high surface area, typically between 50–300 m^2/g, and hydrophilic properties make them favorable candidates for enhancing drug dissolution. Recently published work demonstrated the enhancement of the dissolution rate of Nisoldipine by adsorbing it onto *Cab-O-Sil® M5* using a supercritical CO_2-based method.[16] Another reearch reported improved dissolution rates for carbamazepine and Nifedipine adsorbed onto *Aerosil®* grades (200, 300, and 380), regardless of the solvents used for preparing solid dispersions, thanks to their high surface area. Despite these advantages, non-porous silica materials often show limitations in dissolution enhancement compared to their porous counterparts. For instance, a group of researcher found that *Sylysia® 350,* a mesoporous silica, significantly outperformed *Aerosil® 200* in

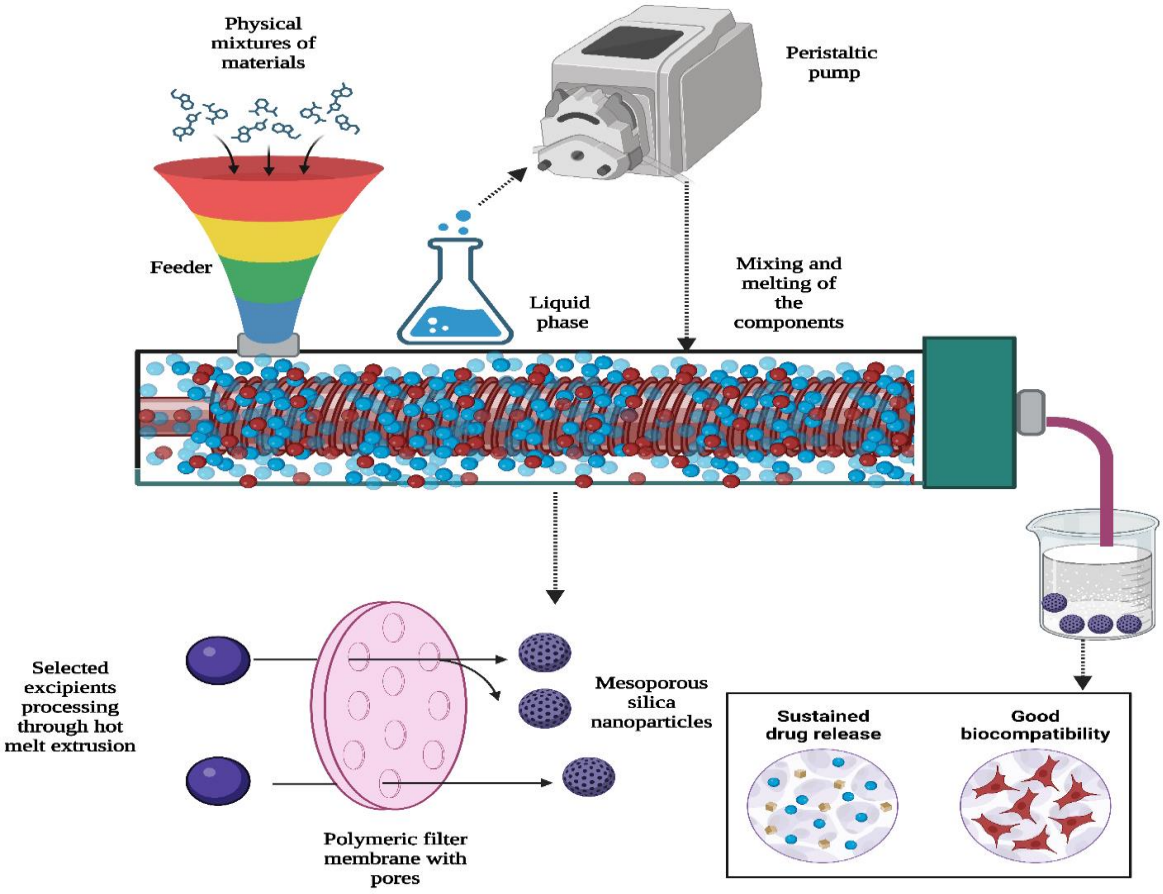

Figure 3: It illustrates about the hot melt extrusion set up for preparation of silica nanoparticles.

improving the dissolution rate of indomethacin in solid dispersions prepared via spray drying. Therefore, while non-porous silica has its uses, porous media like mesoporous silica often offer superior performance in drug delivery applications, which will be the focus of the following sections.[17]

Mesoporous silica materials (MSMs)

The International Union of Pure and Applied Chemistry (IUPAC) classifies porous materials by pore size: microporous materials have pore sizes smaller than 2 nm, mesoporous materials range from 2 to 50 nm, and macroporous materials have pores larger than 50 nm. Mesoporous silica materials have gained attention in drug delivery due to their large surface areas and ability to stabilize drug molecules in their amorphous state. This stabilization is achieved by the high free energy of MSMs, which adsorb drug molecules and shift the system to a lower energy state Additionally, the small pore size of MSMs can prevent crystal nucleation and growth, further stabilizing the amorphous form of the drug.[18] A variety of MSMs are commercially available and commonly used as pharmaceutical excipients. These materials exhibit diverse physicochemical properties that influence both drug loading and release characteristics. However, understanding the interplay of different material properties on solid dispersion behavior can be challenging. For example, *Parteck® SLC* and *Syloid® AL-1 FP* have small particle sizes, which enhances drug loading and release but may negatively affect powder flow and tableting properties due to their small mesopore sizes.[19,20] In contrast, *Aeroperl® 300*, with its larger particle size and round-shaped morphology, offers better flow properties, facilitating the production of final dosage forms. However, its larger particle size may reduce drug loading and release efficiency. Thus, selecting the appropriate MSM depends on the formulation's specific requirements. For formulations where amorphous drug stability is critical and dose requirements are low, materials like *Parteck® SLC* and *Syloid® AL-1 FP* may be suitable. Conversely, when higher drug content and better flow properties are needed, materials with larger particle sizes and pores, such as *Aeroperl® 300* or *Syloid® XDP*, may be more appropriate. The choice of MSM should be carefully tailored to optimize drug delivery performance based on the target product profile.[20]

Table 2: Recently published case studies based mesoporous silica as a carrier for the solubility and bioavailability enhancement.

Therapeutic used	Method of preparation	Pore volume Before/after drug loading	Particle size	Solubility/Drug release data	Outcome	Ref
Paclitaxel	Solvent evaporation	0.76/0.60 (cm^3/g)	188.7 ± 5.4 nm	The cumulative release of PTX increased from 23% in free PTX after 12 hours to 34.41% from MSN@PTXdic after 48 hours.	PTX-loaded MSN exhibited stronger cytotoxic effects against HepG2 cells compared to free PTX, due to better cellular uptake, suggesting improved therapeutic potential	[58]
Vorinostat	Sol-gel-based templating	0.99/0.48 (cm^3/g)	~140–200 nm	The solubility of Vorinostat was improved by 2.6-fold, when encapsulated in MCM-41.	Amino-functionalized MCM-41 greatly enhanced vorinostat's permeability and improved its anti-tumor activity in colorectal and cutaneous T-cell lymphoma cells.	[59]
Atorvastatin calcium (AC)	Solvent evaporation	2.26/1.36 (cm^3/g)	-	After 45 minutes, mesoporous silica formulation (MSF) released 99% of its initial drug content, while the pure drug released only 68%.	Atorvastatin calcium showed a significantly enhanced release profile with both SBA-15 and MSF as drug carriers. Additionally, MSF demonstrated a faster release rate than SBA-15 in enzyme-free simulated gastric fluid (pH 1.2).	[60]
Telmisartan	Solvent-Based Loading	917.6 /1.15 (cm^3/g)	0.5 µm	TEL-loaded MSMs achieved about 80% drug release, higher than the 60% release from marketed	The study showed that TEL-loaded MSMs increased bioavailability by about 29% compared to conventional formulations,	[61]

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Therapeutic used	Method of preparation	Pore volume Before/after drug loading	Particle size	Solubility/Drug release data	Outcome	Ref
				tablet, suggesting efficient dissolution.	indicating improved absorption, though still less effective than TEL-loaded MSNs	
Telmisartan	Organic template method	1.04/0.22 (cm^3/g)	90 nm	At 90 minutes, pure TEL showed less than 1% dissolution, while TEL-MSNs-1 significantly enhanced the dissolution rate, reaching 25.6% at 5 min, 65.7% at 15 min, and 83.5% at 30 min, demonstrating improved solubility.	The drug loading capacity of MSNs depends largely on their total pore volume and pore diameter. Additionally, ionic interactions between the carboxyl groups of TEL and amine groups on AP-MSNs enable effective control over the drug release rate.	[62]
Griseofulvin (GRIS)	Rotary evaporation technique	0.86/0.24 (cm^3/g)	100–200 nm	The solubility of griseofulvin was increased approximately three fold in MCM-41-GRIS (62.3 µg/mL) compared to GRIS alone (21.5 µg/mL)	Surface functionalization of MCM-41 significantly affects the in vitro release and solubility of griseofulvin. Both negatively and positively charged surfaces enhance griseofulvin's solubility and drug release.	[63]
Fenofibrate	Solvent impregnation	1.03/0.41 (cm^3/g)	-	Under sink conditions, larger pore sizes increased the release rate, while smaller pore sizes enhanced supersaturation duration and degree under supersaturating conditions (FaSSIF).	The study found that in a fasted state, Fenofibrate absorption improved with slower drug release rates: 102±34 µMh for 2.7 nm, 86±19 µMh for 4.4 nm, and 20±13 µMh for 7.3 nm pore diameters, suggesting that reduced supersaturation benefits absorption.	[10]
Naproxen	Sol-gel-based templating	1.09/ 0.40 (cm^3/g)	200 nm	The advantage of the relatively short pore channel was also a major factor to improve the dissolution.	The morphology of mesoporous silicas affects naproxen (Nap) dissolution, with longer pores extending diffusion pathways. Functionalized materials provide better control over Nap release than unmodified ones.	[64]

Mechanisms of solubility enhancement with MSMs

Drug loading into mesoporous particles

Several methods have been employed for loading various drugs into mesoporous particles (Table 1). In addition to the factors influencing drug loading method used to prepare solid dispersions plays a crucial role in determining the amount of drug loaded, its distribution within the carrier, its physical state, and ultimately its release profile.[21] As a result, it is essential to assess each case individually to identify the most appropriate method for drug loading. Additionally, not all methods are feasible for industrial-scale applications, which is an important consideration in the development process. Generally, these drug-loading

techniques can be categorized into two broad groups: solvent-based methods and non-solvent-based methods.

Solvent-based methods

Solvent-based methods, as the name implies, utilize organic solvents to facilitate the loading of drugs into mesoporous carriers. These methods typically consist of two fundamental steps: first, the drug solution is combined with the mesoporous material, and second, the solvent is evaporated or otherwise removed. The classification of these methods in the literature is often ambiguous, as variations exist based on either the solvent addition step or the solvent removal step. This review seeks to encompass all these methodological variations as documented in existing literature. The initial two categories are centered on the solvent addition phase, while the subsequent methods pertain to the solvent removal stage (Figure 2). Additionally, the supercritical CO_2 ($scCO_2$)-based method is included here; although $scCO_2$ is technically a solvent, it is frequently treated as a separate category in the literature.[22]

The solvent immersion method

The solvent immersion method is a widely utilized approach for drug loading, where the mesoporous carrier is immersed in an excess of drug solution dissolved in an organic solvent. This mixture is typically stirred for a designated period, followed by vacuum filtration and drying to eliminate the solvent. The duration of stirring varies among studies, with times reported as short as 10 minutes, or even 24 hours. Despite its frequent use in research, this method faces challenges for industrial application due to its labor-intensive nature and economic limitations.[23] In addition to the physicochemical properties of the mesoporous carrier, several factors significantly impact the degree of drug loading. For instance, it was found that carvedilol exhibited much lower loading into Syloid® XDP 3050 compared to ibuprofen (7.1% vs. 33.0%, as determined by thermal gravimetric analysis). This difference was attributed to stronger and more favorable interactions between carvedilol and the solvent, specifically methanol. This illustrates the critical role of solvent selection in influencing process yield.[24] Limnell et al compared drug release profiles from solid dispersions produced via solvent immersion, rotary evaporation, and fluid bed methods. They observed notably rapid drug release from solid dispersions prepared using the solvent immersion technique, attributing this to limited diffusion into the particles, which results in a shorter diffusion path (Figure 3). However, the overall fraction of drug released from these solid dispersions was lower compared to other methods.[25] For comparison, the release profile of bulk indomethacin is also included (dashed line). The data represent the mean ± standard deviation (n = 3). The different loading methods for Syloid are labeled as follows: SFLU (fluid bed method), SROT (rotary evaporation method), and SIMM (solvent immersion method).

The incipient wetness impregnation method

The incipient wetness impregnation method involves adding a concentrated drug solution dropwise to a mesoporous carrier while continuously stirring. To eliminate any residual solvent, the mixture is subsequently dried using either a hot air dryer, a vacuum dryer, or via rotary evaporation. The impregnation process can be performed once or repeated multiple times, with the solvent evaporating after each cycle. Typically, the amount of drug solution added matches the pore volume of the carrier. One major advantage of this method over solvent immersion is the precise control over the amount of drug loaded, making it particularly useful for costly active pharmaceutical ingredients (APIs). However, surface crystallization can be an issue, and achieving higher drug loading often requires multiple impregnation cycles. Sun et al used the incipient wetness impregnation method to load carbamazepine, celecoxib, griseofulvin, and ritonavir into Aeroperl® 300, achieving drug loading of 0.05%–10.0% by adjusting solution concentration. SEM analysis showed that Aeroperl® particles retained their spherical shape and smooth surface, indicating drugs were mainly adsorbed within the mesopores. No significant changes were observed after six months of accelerated stability testing (40°C/75% RH), suggesting the drugs remained well-dispersed and amorphous, contributing to enhanced stability.[26]

Rotary evaporation method

The rotary evaporation method is a widely utilized technique for loading drugs into mesoporous carriers, particularly in the preparation of solid dispersions. This method involves adding the carrier to a drug solution, followed by either soaking or stirring, and then removing the solvent through vacuum rotary evaporation. One key advantage of this technique over other solvent-based methods, such as solvent immersion, is the ability to precisely control the concentration gradient of the drug solution during the drying process. This makes it especially suitable for industrial-scale production, as the initial drug concentration does not need to be high, reducing solvent and drug waste. A major benefit of this method is that it enhances drug release by promoting supersaturation. Studies, such as those by Lai et al, have shown that lower starting drug concentrations can lead to faster release rates due to higher supersaturation levels. However, higher drug concentrations can drive more of the drug into the inner pores of the carrier, which may reduce dissolution rates and limit or prevent supersaturation entirely. This highlights the need to carefully optimize drug concentration during the rotary evaporation process.[27] An interesting finding by Kovacic et al revealed that performing the rotary evaporation in multiple steps—by reintroducing the mesoporous carrier into fresh drug solution between cycles—can lead to a higher drug loading and a completely amorphous drug form, even at high concentrations (50-60%). This multi-step approach enhances drug dispersion and reduces the risk of crystallization. However, despite these promising results, the technique remains underreported in the literature, suggesting potential for further exploration and application in pharmaceutical research.[28]

Spray drying method

Spray drying is an efficient method for incorporating drugs into solid dispersions, offering rapid conversion of solutions or suspensions into dry powders in a single step.

Table 3: Recent patents on mesoporous silica-based formulations

Title	Therapeutics	Inventor/assignee/applicant	Outcome	Patent application number
Mesoporous silica drug-loaded nanoparticle (MSN) and preparation method and application thereof	Tumor-oriented penetrating peptide iRGD, Docetaxel (DOX) and poly (2-ethyl-2-oxazoline) (PEOz)	Xian Medical University	The MTT assay showed that the DOX @ MSN- Polydopamine-PEOz-iRGD formulation exhibited a significantly higher inhibition rate on Bel-7402 liver cancer cells, achieving 80% inhibition at a concentration of 0.5 μg/mL	CN110693851 B
Composition, particulate materials and methods for manufacturing particulate materials	Spinosad	University of Queensland UQ	Nano-spinosad loaded into the Rough-surfaced hollow mesoporous silica (MSHSs-RS) cavity demonstrated effective activity against cattle tick (Rhipicephalus microplus) larvae, showing enhanced water solubility, UV stability, and fur adhesion compared to standard formulations	ES2908677T3
Mesoporous silica nanosphere, preparation method thereof and application thereof in drug loading	Itraconazole	Huazhong University of Science and Technology	Loading Itraconazole into mesoporous silica nanospheres enhanced its crystalline state, preventing crystallization and boosting dissolution from 35.9% to 95.7%, significantly improving its bioavailability.	CN109896528 B
Formulation of silymarin with high efficacy and prolonged action and the preparation method thereof	Silymarin	Jiangsu University	This long-acting silymarin formulation, comprising solid dispersion, silica nanoparticles, slow-release matrix, and release enhancer, shows a drug loading rate of 51.95%-52.87%. In vivo testing on Beagle dogs demonstrated continuous release for 72 hours.	WO 20110201680
Mesoporous material excipients for poorly aqueous soluble ingredients	Ibuprofen	Agency for science, technology and research, Singapore	The amorphous drug is stabilized within nanosized pores via co-spray drying, preventing re-crystallization, and improving dissolution rates and storage stability.	WO 2010/050897

The process involves atomizing a drug-carrier suspension into fine droplets, with solvent evaporation happening almost instantly, forming a fine powder. This technique provides better control over particle size, high reproducibility, and ease of scale-up compared to other solvent-based methods. Studies confirm its high drug loading efficiency and reduced surface deposition, although drug concentrations in solid dispersions are usually below 25%.[29] Kamboj et al demonstrated the use of spray drying to enhance the oral bioavailability of nelfinavir mesylate, utilizing a Quality by Design (QbD) approach to optimize key process parameters such as inlet temperature, drug loading, and solid substrate type. Syloid® 244 FP was identified as the most effective carrier, emphasizing the need to evaluate these parameters case by case, especially in industrial settings. The original Syloid® particles appeared as irregular, fine, and loosely aggregated structures. In contrast, the SDNPs formed spherical granules, indicating successful encapsulation, which contributed to improved flow properties and potential bioavailability enhancement.[30]

Supercritical CO_2 method

Supercritical CO_2 ($scCO_2$) offers an alternative to traditional solvent-based methods by providing low toxicity and environmental impact, along with high dissolution capacity under mild conditions. It is the most widely used supercritical fluid and holds promise for scalable and continuous manufacturing in the pharmaceutical industry, though it has not yet been widely adopted.[31] There are two main approaches for using $scCO_2$ in solid dispersion production: as a solvent and as an anti-solvent. In the solvent method, the drug and carrier (such as silica) are placed in a pressure-resistant vessel, where CO_2 is added under heat and pressure. The drug dissolves in $scCO_2$, diffuses into the porous carrier, and precipitates once the CO_2 is released. In the anti-solvent method, the drug and carrier are initially dissolved in an organic solvent before CO_2 is added, inducing drug supersaturation. This process allows for solvent removal by increasing the temperature

and adding fresh CO_2. Silica can be added to prevent particle agglomeration, which is a common issue.[32] Studies have shown $scCO_2$ to significantly improve the dissolution rate of poorly water-soluble drugs compared to solvent immersion techniques. For instance, recently published work reported a much higher dissolution rate (70.2% vs. 13.3%) for drug-loaded Sylysia® 350 using $scCO_2$. However, the drug loading achieved was relatively low (17%), with some of the drug remaining in a crystalline state. While the potential for enhanced performance is clear, only a few studies have compared solid dispersions prepared via $scCO_2$ to other methods, highlighting the need for further investigation.[31]

Non-solvent based methods

While solvent-based drug loading methods are commonly used for producing solid dispersions with mesoporous silica, they have notable disadvantages, primarily related to the use of organic solvents. One significant concern is that residual solvent levels in the final product must meet the strict standards set by the International Conference on Harmonisation guidelines. Additionally, these methods pose environmental challenges and incur high production costs due to the extensive use of organic solvents. As a result, non-solvent-based methods are emerging as attractive alternatives to address these issues. These methods typically involve the application of elevated temperatures or mechanical energy to achieve drug loading without the use of solvents.[33]

Elevated temperature method: melting process

The melting method, one of the earliest techniques used for preparing solid dispersions in pharmaceutical applications, involves heating a system just above the drug's melting point, allowing the molten drug to diffuse into a porous carrier. After heating, the system is cooled and the resulting mixture is processed, either by milling, sieving, or crushing with a pestle and mortar. [34]While this method is simple and cost-effective, it is limited to thermally stable drugs. Additionally, the viscosity of the molten drug plays a crucial role; if too viscous, the drug may not flow effectively into the carrier pores. Since its first use in 1961, various modifications have improved the scalability and application of this method.[35]

Hot melt extrusion (HME)

Hot melt extrusion (HME) is a continuous, solvent-free process that involves forcing a drug–silica mixture through a die under high temperature and pressure to create a product with uniform shape and density as presented in Figure 3. This method typically uses rotating screw extruders to move the feed material towards the die. Due to its cost-effectiveness, scalability, and ability to work with relatively thermally sensitive drugs, HME has become one of the most successful technologies for preparing solid dispersions in marketed products. Genina et al studied ibuprofen and carvedilol loaded into Syloid® XDP 3050 using HME. They found that drug-to-carrier ratios below 50% were not feasible for extrusion due to blockage caused by silica particles. To overcome this, a polymer (Soluplus®) was added. However, with carvedilol, the dissolution rate decreased, likely due to the gelling properties of Soluplus®, whereas ibuprofen showed a significantly improved dissolution profile. In another work, HME used to prepare indomethacin solid dispersions with Syloid® XDP 3050 and hydroxypropyl methylcellulose (HPMC), reporting improved dissolution without manufacturing issues. They emphasized that process conditions like screw speed and feed rate are crucial, as they significantly impact the miscibility, dissolution, and stability of the final product. Thus, while HME is effective, its complexity requires careful optimization of process variables.[24,36]

Microwave irradiation

Microwave irradiation is a non-conventional technique used to prepare solid dispersions, which heats the drug and carrier mixture through microwave energy. This method offers more uniform heating and is controlled by a feedback system to prevent overheating, making it energy-efficient and cost-effective.[37] One key challenge is temperature control, as constant power doesn't always ensure stable temperatures. Some materials heat more easily under microwave irradiation than others, making direct temperature measurement and computerized power control essential. Similar to the traditional melting method, viscosity is a critical factor. For instance, a group of researcher found that the high viscosity of molten apremilast in solid dispersions with Syloid® 244 FP led to pore blockages, causing the drug to deposit between the pore walls.[38]

Mechanical energy

Mechanical energy can also be employed to produce solid dispersions through methods like co-milling or kneading. This approach disrupts the crystalline structure of the drug without causing significant chemical degradation.[39] Co-milling involves grinding the drug and silica using either a pestle and mortar or a milling device. In contrast, kneading creates a paste by mixing the drug, silica, an optional third component, and a liquid (such as water or water-ethanol). After kneading, the mixture is dried and sifted. These mechanical methods are cost-effective and scalable, requiring minimal equipment. However, there is limited research on their application for producing solid dispersions with mesoporous materials.[40]

Drug amorphization and stabilization

One of the primary goals of formulating solid dispersions is to achieve amorphisation and stabilize the amorphous state of the drug, which significantly improves its dissolution characteristics[59]. It is essential to confirm whether amorphisation has been effectively realized in these formulations. The most widely used methods for characterizing the solid state of a drug within a mesoporous carrier are Powder X-ray Diffraction (PXRD) and Differential Scanning Calorimetry (DSC) (Xu et al., 2013). Both techniques assess the crystallinity and the extent of the crystalline state within a sample.[41]

Powder X-ray diffraction (PXRD)

Amorphisation is evidenced by the absence of Bragg peaks and the emergence of a broad halo in the diffraction pattern.

Differential scanning calorimetry (DSC)

The absence of a melting peak, along with the observation of a glass transition event, indicates that amorphisation has occurred.

Some studies suggest that if the drug is entirely adsorbed onto the surface of the porous silica, thermal events may not be observed. However, the detection of glass transition or melting temperatures can indicate that the drug exceeds the available silanol binding sites, suggesting the presence of some drug in either an amorphous or crystalline state, likely outside the pores. If crystallization occurs within the pores, DSC may reveal a depressed melting point due to the nanoscale size of the crystals. DSC is particularly advantageous over PXRD for detecting crystallinity at the nanoscale. For example, small crystals may still present as an amorphous halo in PXRD, while DSC can identify a depressed melting peak. Research has revealed that the characteristics of solid dispersions can vary significantly based on the drug-to-silica ratio. Several studies have reported contrasting findings regarding the amorphous state of drugs within different mesoporous silica matrices. For instance, recent report observed signs of crystalline K-832 at a 15% drug loading in Sylysia® 740, while other group successfully achieved complete amorphous solid dispersions of carvedilol in Sylysia® 350 at a higher loading of 60%.[42] Conversely, Genina et al[24] demonstrated that solid dispersions with ibuprofen were entirely amorphous at higher ratios compared to those with carvedilol (33% vs. 7%) when using the solvent immersion method. They attributed this difference to the stronger interactions (primarily hydrogen bonds) between ibuprofen and the silica surface, although they did not provide direct experimental evidence to support this hypothesis. Additionally, the larger molecular weight of carvedilol (406 g/mol) compared to ibuprofen (206 g/mol) may also play a role in these outcomes. The method of drug loading has also been identified as a critical factor affecting the degree of amorphization. Recently published work found that performing rotary evaporation in multiple steps could influence the amorphization of carvedilol in Sylysia® 350. Miura et al. (2010) employed both the supercritical CO_2 ($scCO_2$) method and solvent immersion for K-832 in Sylysia® 350, reporting that while some drug recrystallized during $scCO_2$ processing, complete amorphisation was achieved through solvent immersion. However, there remains a limited number of studies that have systematically compared various drug loading methods in commercially available mesoporous silica matrices, particularly focusing on achieving high loading with a completely amorphous drug.[28] Ensuring the stability of the solid-state drug within the mesoporous carrier during storage is equally important. Recrystallization during storage can compromise the product's dissolution properties, resulting in reduced solubility, absorption, and ultimately bioavailability. Evaluating product stability requires careful consideration of testing conditions, including temperature and relative humidity. For instance, storing at temperatures above the glass transition temperature (T_g) can lead to rapid recrystallization due to increased molecular mobility. Similarly, moisture presence can have a plasticising effect, lowering T_g and contributing to physical instability.[41] Additionally, certain drugs may degrade in the presence of water, which can participate in both chemical reactions and instabilities.[43] According to the International Conference on Harmonisation (ICH) guidelines, new products must undergo stability testing for a minimum of 12 months under ambient conditions or for at least 6 months at 40°C and 75% relative humidity (European Medicines Agency, 2003). Several studies that have adhered to these guidelines reported stability in formulated solid dispersions throughout the testing period.[44]

Formulation considerations and factor influencing solubility and drug release

Porosity characteristics

One of the significant advantages of MSMs is their high pore volume and appropriately sized pores, which fall within the molecular range. The unique characteristics of these pores facilitate the effective adsorption of drug molecules, keeping them in a submicrometric environment that can prevent crystallization.[45] Specifically, the width of the pores is typically only about ten times the size of the drug molecules. This intimate confinement is critical as it helps maintain the drug in an amorphous state, which is associated with faster dissolution rates compared to its crystalline counterparts.[46] The capability of MSMs to prevent crystallization is particularly noteworthy. The size of the pores necessary to inhibit the crystallization process can be estimated for cylindrical pores using the following equation:

$$d^* = \frac{-\Delta H_m}{\sigma_{cl} \cdot T_m^{\infty} \cdot \rho_c} \cdot 4 \left(\frac{T - T_m^{\infty}}{T} \right) \quad \ldots(1)$$

Where,

d* is critical pore diameter needed to prevent crystallization

σ cl is surface energy between the crystal and melt

ΔH_m is heat of melting

ρc is crystal density

In this context, d* typically ranges in the few nanometer scale. This is significant because the pore sizes of MSMs can be finely tuned from approximately 1.5 nm to tens of nanometers, with common pore sizes typically falling between 2 to 10 nm. This tunability makes MSMs particularly suitable for preventing drug crystallization and enhancing solubility.[47] The release behaviour of drugs from MSMs is significantly influenced by pore size. Mellaerts et al[35] investigated the in vitro release performance of Itraconazole from four different SBA-15 silicas characterized by varying pore widths (from 4.5 to 9.0 nm). The results indicated that increasing the pore size from 4.5 to 6.4 nm significantly enhanced the release of Itraconazole. However, further increases in pore size to 7.9 and 9.0 nm yielded only minor improvements in release rates. These findings suggest the existence of a critical pore width that affects drug diffusion, where smaller pores create steric hindrance that slows down the release. In another research, it was observed the loading of Ibuprofen into different silicas (MCM-41, SBA-15, and SBA-15-LP) with increasing pore sizes. The physical state of ibuprofen was affected by pore size; loading into SBA-15-LP (20 nm pores) resulted in nanocrystals, while loading into MCM-41 and SBA-15 (pore sizes smaller than 10 nm) resulted in an amorphous state. The amorphous ibuprofen demonstrated rapid dissolution. Although increasing pore

size from 2 to 6 nm had a slight influence on dissolution rate, larger pores (20 nm) led to slower dissolution rates despite facilitating drug diffusion due to the presence of larger ibuprofen particle.[48] In conclusion, while increasing pore size can facilitate drug release, there exists a critical range where optimal release occurs. Beyond this range, the physical state of the drug and its organization within the pores play a vital role in determining the dissolution behaviour. The interplay between pore size and drug state (amorphous vs. crystalline) is crucial for optimizing the formulation of solid dispersions for enhanced bioavailability.

Influence of mesoporous structure

The Higuchi equation identifies pore connectivity and geometry, represented by tortuosity (τ), as critical factors influencing drug diffusion from porous matrices. Recently, a group of researchers investigated the effects of different mesoporous materials—specifically, MCM-41 and SBA-15 (unidirectional), thermally carbonized porous silicon (TCPSi, 2D), and TUD-1 (3D)—on ibuprofen dissolution rates. The study found that the drug loading capacity was primarily determined by the total pore volume, with SBA-15 achieving the highest loading ratio (~1:1, w: w) and TUD-1 the lowest, despite its accessible mesopores. Ibuprofen release was tested under various pH conditions to simulate small intestine environments. All MSMs enhanced ibuprofen release, significantly outperforming the bulk drug. In a phosphate buffer (pH 5.5), 25% of ibuprofen dissolved within 45 minutes, compared to a 2.5–3.5-fold increase in release from MSMs. TUD-1 exhibited the fastest release, attributed to its accessible 3D mesopore network, followed by SBA-15 and MCM-41, with MCM-41's narrower pores hindering drug transfer. Overall, SBA-15 emerged as the most effective dissolution-enhancing matrix due to its high drug loading capacity and rapid release profile.

Effect of surface functionalization

Surface functionalization is a strategic approach used to enhance the controlled release properties of MSMs by fostering specific interactions between the functional groups on the carrier surface and the incorporated drug molecules.[50] Although functionalization typically aims to retard drug release, it has been explored in limited studies for improving dissolution rates. For instance, adding basic amine groups (NH_2) to mesoporous silica can promote interactions with acidic drugs, while carboxylic acid groups (COOH) can enhance interactions with basic drugs. During drug loading, strong interactions stabilize the drug in its amorphous state, while during release, strong repulsion is preferred for rapid drug liberation. This transition is facilitated by performing loading under non-polar conditions and releasing in aqueous environments, where electrostatic interactions play a crucial role.[51] The presence of residual silanols on the silica surface, along with functional groups, significantly influences the release behaviour of drugs, which are often weak acids or bases. Additionally, non-ionizable surface groups can hydrophobize the silica, delaying drug release by affecting wetting and hydrolytic stability. However, excessive loading of hydrophobic drugs may hinder release due to wetting challenges.[46]

Effect of precipitation inhibitors

The poor water solubility of drugs poses significant challenges, including inadequate dissolution, low bioavailability, and suboptimal clinical outcomes. Therefore, ensuring effective drug release from solid dispersions formulated with mesoporous materials is essential. Numerous studies have demonstrated improved dissolution profiles for various drugs when incorporated into non-ordered mesoporous silica materials, with some formulations outperforming their free crystalline counterparts in vivo. Notable examples include celecoxib, puerarin, cefuroxime axetil, and Fenofibrate. It is important to recognize that the incorporation of a drug into mesoporous silica can enhance both its solubility and dissolution rate.[50-52] When a drug exists in an amorphous state within a mesoporous carrier, it creates a supersaturated solution where the drug concentration exceeds its saturated solubility. This state, while metastable, can lead to precipitation.[53] However, if precipitation can be prevented long enough for drug absorption, it may enhance the oral bioavailability of poorly water-soluble drugs. To achieve this, precipitation inhibitors, typically hydrophilic polymers, are used to stabilize the supersaturated state by exploiting intermolecular forces between the drug and polymer and providing steric hindrance against crystallization.[54] The "spring and parachute" model illustrates this mechanism: the amorphous drug acts as the "spring" that rapidly elevates drug concentration, while the precipitation inhibitor functions as the "parachute" that prolongs the supersaturated state. Several studies have applied this model in formulating mesoporous silica-based solid dispersions. For instance, Price et al[56] examined the inclusion of HPMC acetate succinate (HPMCAS) as a precipitation inhibitor with Glibenclamide and Parteck® SLC, demonstrating that co-incorporation of HPMCAS during the drug-loading process resulted in significantly improved dissolution and sustained supersaturation in fasted-state simulated intestinal fluid. In contrast, adding HPMCAS post-loading did not maintain the amorphous state. Similarly, Laine et al. (2016) co-incorporated HPMCAS with celecoxib in a solid dispersion, observing faster absorption rates and higher peak concentrations compared to crystalline suspensions, although bioavailability was similar between the formulations, highlighting discrepancies between in vitro and in vivo outcomes.

MSMs based formulations and their success in enhancing drug solubility: Case studies

Nanotechnology has significantly advanced biomedical fields, particularly in drug delivery, with mesoporous silica nanoparticles (MSNs) emerging as promising carriers. MSNs enhance the solubility of guest molecules by converting unstable crystalline forms into stable amorphous states without changing lattice energy. They provide a larger surface area for better drug adsorption and protect therapeutic cargo from external factors. Their tunable pore sizes and surface functionalization allow for controlled drug release. Additionally, free MSNs with negatively charged

silanol groups facilitate the rapid release of negatively charged drugs, due to weak ionic interactions. Considering this fact, Biswas et al.[56] developed modified MSNs to enhance the oral bioavailability and antihypertensive activity of the poorly soluble drug valsartan (VAL). The MSNs were functionalized with aminopropyl groups (AP-MSN) and coated with a pH-sensitive polymer, Eudragit L100-55 (AP-MSN-L100-55), for controlled release. Characterization showed a high entrapment efficiency of 59.77% due to strong ionic interactions with VAL. In vitro studies demonstrated an initial rapid release followed by sustained release, achieving 96% dissolution over 960 minutes, attributed to VAL's amorphisation. The modified MSNs showed no significant cytotoxicity and resulted in a 1.82-fold increase in bioavailability compared to the commercial Diovan tablet in rabbits. Blood pressure monitoring in rats indicated that the M-MSN formulation effectively controlled blood pressure for over 840 minutes, significantly longer than the Diovan tablet's 360 minutes. This study highlights the potential of modified MSNs to improve the therapeutic efficacy of poorly soluble drugs like valsartan. The solubility and absorption of weakly basic drugs are significantly influenced by gastric acidity, which enables the formation of supersaturated solutions. In an acidic environment, basic compounds dissolve more effectively through protonation, preventing crystal precipitation. However, maintaining a supersaturated state in the small intestine, where the pH shifts to neutral, can enhance the absorption of poorly water-soluble compounds. Recent research investigates whether ordered mesoporous silica (OMS) can serve as a carrier to induce supersaturation of Itraconazole, a weakly basic compound (pKa = 3.7), in a neutral medium. This study seeks to establish a pH-independent dissolution enhancement strategy to improve intestinal absorption and provide consistent results under varying gastrointestinal conditions. Mellaerts et al[57] evaluated the pH-independent generation of intraluminal supersaturation of Itraconazole and its effect on absorption in Caco-2 cells and the rat in situ perfusion system. Using a solvent shift method and OMS as a carrier, both techniques created a supersaturated state of Itraconazole in fasted state simulated intestinal fluid (FaSSIF) without prior acidic dissolution. The solvent shift method achieved supersaturation exceeding 21.9, while OMS maintained a level of 9.6 for at least 4 hours. Both methods increased itraconazole transport across Caco-2 cell monolayers more than 16-fold compared to saturation conditions, with basolateral appearances of 2.20 ± 0.29 µg and 1.46 ± 0.03 µg after 90 minutes for the solvent shift and OMS, respectively. In contrast, the marketed product Sporanox® achieved only 0.12 ± 0.03 µg. These results suggest that OMS effectively creates intraluminal supersaturation without prior acidic dissolution, facilitating efficient intestinal absorption. Moreover, drug nanosizing using mesoporous inorganic systems is an innovative approach for improving the dissolution of poorly soluble drugs. Mesoporous silica materials, known for their highly regular structures, large surface areas, tunable pore sizes, and good biocompatibility, have emerged as significant drug carriers. Recently published study highlights a nano-amorphous strategy that utilizes mesoporous silica nanospheres to enhance the loading and release behaviors of the poorly soluble drug Itraconazole (ITZ). It was found that the size and specific surface area of the MSNs significantly influence the amorphous state of ITZ, thereby impacting its loading capacity and release rates. MSNs with approximately 50 nm diameters achieved a high ITZ loading (around 37.5 wt%) in a pure amorphous form, leading to nearly 100% in vitro release in simulated gastric fluid and a 1.5-fold increase in in vivo bioavailability compared to the commercial product Sporanox. Carvedilol dissolution was improved using solid dispersions with porous silica (Sylysia). The researchers loaded carvedilol into the silica pores via solvent evaporation and acetone solution adsorption, then characterized the carriers using nitrogen adsorption, X-ray diffraction, and thermal analysis. The results indicated enhanced drug release from the solid dispersions compared to pure carvedilol or its physical mixtures. When carvedilol precipitated as a thin layer within the carrier, it maintained high specific surface area and micropore volume, improving release rates. However, higher drug loads led to decreased surface area and release rates due to pore precipitation. The study concluded that the amorphous form of carvedilol, along with improved wettability and weak interactions with the carrier, enhanced dissolution.[23] The recently published MSMs based drug delivery systems for solubility enhancement are depicted in Table 2.

Recent patents on mesoporous silica-based formulations

Recent patents (Table 3) on mesoporous silica-based formulations have highlighted significant advancements in drug delivery and therapeutic applications. These patents focus on enhancing drug solubility, stability, and controlled release properties, utilizing the unique porous structure of mesoporous silica. Innovations include formulations for poorly soluble drugs, targeted delivery systems, and multifunctional carriers for co-delivery of therapeutic agents. The integration of mesoporous silica with various polymers and surface modifications has led to more efficient and versatile drug delivery platforms.

Conclusion and future perspective

Mesoporous silica materials offer significant advantages in enhancing the solubility, stability, and bioavailability of poorly water-soluble drugs. Their high surface area and adjustable pore sizes enable efficient drug loading and controlled release, leading to improved therapeutic outcomes. While promising, challenges like scalability and consistent in vivo performance remain. Future efforts should focus on scalable, cost-effective manufacturing, improved biocompatibility, and clear regulatory guidelines to streamline the development and market transition of MSM-based formulations, expanding their potential to include biologic drugs.

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