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Review Article:

Recent Advances in Porous Carriers for Drug Delivery: Materials, Loading Strategies, and Applications

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Abstract

Background: Poor aqueous solubility and low bioavailability of many drugs remain major challenges in pharmaceutical development and often limit the therapeutic efficacy. To overcome these limitations, considerable attention has been directed towards advanced drug delivery systems that can improve drug stability, release behavior, and pharmacokinetic profile. Among these systems, porous carriers have emerged as versatile platforms. These carriers include polymeric, lipid-based, and inorganic materials that possess diverse physicochemical properties enabling efficient drug incorporation and controlled release. **Aim**: To provide a comprehensive overview of porous carriers in the manufacturing of solid dosage forms and drug delivery systems, focusing on their classification, structural and physicochemical characteristics, drug loading mechanisms, pharmaceutical applications and current challenges associated with their use. **Methods:** This review is based on previously published scientific studies on porous carriers and their applications in drug delivery systems. Relevant research and review articles were carefully examined to present a clear scientific summary of current knowledge in this field. **Conclusion:** Porous carriers have gained significant attention as a result of their high surface area, tunable pore size/volume, and modifiable surface chemistry, which enhance drug loading efficacy, dissolution behavior, and controlled release. Various porous materials, including mesoporous silica, Neusilin®, calcium phosphates, and hybrid organic-inorganic frameworks, have demonstrated promising potential in improving drug delivery and therapeutic outcomes. Continued research is essential to optimize these systems and expand their pharmaceutical applications.

1. Introduction

Any active pharmaceutical ingredient (API) may present a limitation if it fails to achieve its intended therapeutic action or cannot be formulated in a suitable dosage form due to its physicochemical, physico-mechanical, and pharmacokinetic properties. Limitations such as poor aqueous solubility, low permeability, and instability therefore represent major obstacles in drug development (1). Consequently, a large proportion of drug candidates are classified as Class II or IV according to the biopharmaceutical classification system (BCS), making them difficult to formulate and deliver the correct doses in conventional dosage forms (2).

To overcome such challenges, researchers have developed novel carriers and advanced drug delivery systems that are capable of improving dissolution and drug bioavailability (3). However, conventional approaches for drug delivery remain insufficient for complex medical fields such as oncology, cardiovascular diseases, pain management, and tissue engineering, where precise control over drug performance and, in some cases, multi-drug strategies are required (4).

It's within this context that porous carriers emerged as a revolutionary platform. Historically, porous materials were engineered for industrial applications, serving as structural materials, adsorbents, or catalysts (5). However, over the past two decades, their application has dramatically shifted toward the biomedical field. Early studies in 2019 demonstrated that their unique structural features such as, their remarkably high surface area and large pore volume, allowed them to act as passive reservoirs for physically entrapping APIs (6,7). Currently, porous drug carriers function as highly adaptable drug delivery systems rather than simple passive matrices. By encapsulating APIs

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within their mesoporous network structures, these carriers restrict and stabilize the drug moieties in their amorphous form. This physical confinement prevents crystallization, which significantly enhances dissolution rate of poorly soluble drugs. Furthermore, their extensive pore framework provides high drug loading capacity and allows co-loading of multiple therapeutic ingredients within a single carrier (8).

Among these advanced materials, mesoporous silica nanoparticles (MSNs) recently represent the most extensively studied and well-established class of inorganic porous carriers. Their transition from basic silica frameworks to advanced delivery platforms is attributed to their simplicity of manufacture, excellent biocompatibility and reliable prevention of premature drug release. Moreover, their amorphous silica framework also gives them high mechanical stability while allowing precise control over pore shape, size, and connectivity. This interesting architecture, combined with the modern surface modifications, directly governs drug diffusion pathways, release kinetics, and overall delivery performance under physiological conditions (6, 9-11). To highlight these developments, this review focuses on recent advances in porous carriers for drug delivery systems, comprehensively discussing their classification, structural characteristics, physicochemical properties, loading and release mechanisms, applications and future perspectives.

2. Methodology

A comprehensive analysis was carried out across academic databases, including PubMed, ScienceDirect, Google Scholar, RSC Advances, for literature published between 2000 and 2025. The search strategy employed the terms “porous carriers,” “mesoporous silica nanoparticles,” “loading methods,” “release mechanisms,” “surface functionalization,” “solubility enhancement”, utilized individually or in diverse combinations.

3. Porous carriers: Types and classifications

Porous carriers are solid materials characterized by the presence of open or closed pore networks within their structure, resulting in a honeycomb-like architecture with low density and high internal surface area. Within porous carriers, pores function as pathways that regulate the molecular transport, diffusion, and interaction between the carrier and its surrounding environment (12). Pores are not merely internal channels or voids; they have different shapes and sizes, enabling them to provide different loading capacities and modifiable release patterns. Porous systems may be composed of organic or inorganic materials and are used in various biological and pharmaceutical fields. Accordingly, they can be classified based on their multiple features, such as pore size, structure, geometry, and pharmaceutical application.

3.1. Classification by pore size according to IUPAC

Porous materials can present ordered pore arrangements as well as disordered pore networks. This classification is important in pharmaceutical applications, as pore size directly influences molecular accessibility, diffusion behavior, and transport pathways within the porous carriers.

3.1.1. Microporous

Are carriers of less than 2 nm pore size, formed by irregular arrangement or stacking of the active ingredients forming amorphous alignment with micro-channels, which are subdivided by their microporosity to ultramicropore (<0.5 nm), micropores (0.5-1.4 nm), and supermicropores (1.4-2 nm). The adsorption in each is different and highly related to microporosity; hence, it’s inversely proportional to pore size. In ultramicropores, molecules actively diffuse because the similarity between pore and particle size that will hinder the molecular movement; however, unlike in micropores, molecules will adsorb more rapidly due to the overlapping potentials of the pore walls. In supermicropores, adsorption will take place by forming a monolayer and then filling the pores cooperatively (13-15).

3.1.2. Mesoporous

Carriers with diameter between (2-50 nm), as shown in the previous table. With pore sizes between the micro- and the macro-porous systems, they also possess different shapes (sphere, cube, ellipsoid, and rod). Mesoporous carriers typically formed due to structural irregularities in the solid framework, which creates channels that aid in the transport of drug molecules inside them. The application of mesoporous carriers in drug delivery began in the early 1990s, following their initial development for various scientific and industrial purposes (16,17). Mesoporous silica was first introduced by Mobil Oil Corporation in 1992 and its potential in pharmaceutical applications was demonstrated in 2001 when MCM-41 silica was used for ibuprofen release, marking one of the earliest drug delivery applications. Since then, MSNs have gained popularity as a method of administrating medicines. The filling process of such pores is achieved by multilayer formation leading to capillary condensation followed by pore filling (18-21).

3.1.3. Macroporous

Carriers can be observed using optical microscopy and scanning electron microscopy, as these techniques can detect features that are 50 nm and larger. The diameter of the pores does not have a definitive upper limit; however, it typically ranges from 1 to 2 mm. Offering high drug loading capacity due to their large pore size and pore volume with a modifiable release profile that can be either fast or prolonged release depending on the macroporous design (12,22). **Figure1** shows the most commonly used mesoporous nanoparticles (MSNs) in drug formulation and their classification according to pore size. It also provides an overview of the most widely utilized mesoporous materials in drug delivery systems (DDS) (7).

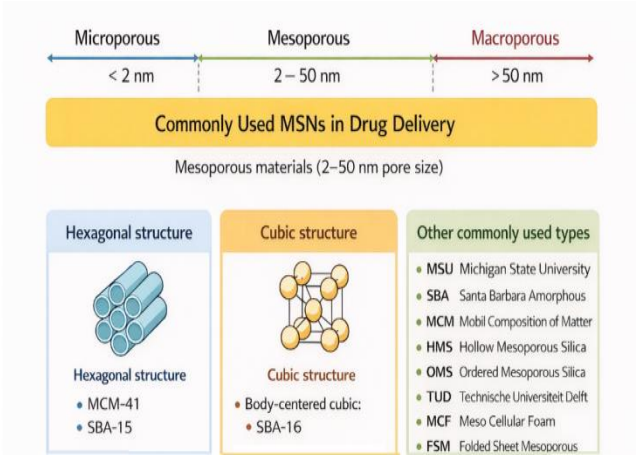

Figure 1. Schematic illustration of different mesoporous carriers used in drug delivery systems (DDS) (7).

3.2. Classification by Pore Structure and Geometry

Open pores are channels that connect the internal part of the solid to its external surface, allowing the passage of the gas or fluid through the material (12). In drug delivery, open pores are highly advantageous as they facilitate efficient API loading and release. In contrast, closed podres are isolated spaces that are enclosed within the solid without any connection to the surface, preventig mass transport. Among open pores, transport pores function as primary pathways facilitating the movement of materials within the internal pore network. Blind pores represent branches of transport pores that terminate within the solid matrix without passage to the external surface. From a pharmaceutical perspective, blind pore presents a structural limitation, since they restrict the material exchange and can irreversibly trap drug molecules reducing delivery efficiency (12,23,24).

While pore accessibility determines whether and how the surrounding medium ingredients can enter the carrier pores, pore organization and spatial arrangement also play a critical role in diffusion pathway and release behavior within the porous carrier. Mesoporous carriers may exhibit either ordered or disordered pore structures depending on their synthesis conditions and structural design (23,16). Ordered mesoporous materials have regular homogenous pore arrangements and highly defined internal frameworks, which allow specified control over pore geometry and transport pathways. In contrast, disordered mesopores have a random pore network distribution with low pore uniformity, leading to uneven diffusion and variable transport behavior. Consequently, the degree of pore ordering directly influences the release kinetics, mass transport and overall carrier performance. Therefore, ordered structures are highly preferred choices as reproducible drug delivery tools (20, 24-26).

3.3. Classification according to pharmac-eutical application

Porous carriers are classified based on their pharmaceutical use, which may include improving drug dissolution and bioavailability, achieving controlled or sustained release, improving flowability and compressibility in tablet formulation, and targeted or site-specific drug delivery. as summarized in **Table 1**.

Table 1. Classification of porous carriers according to their pharmaceutical application

Application	Mechanism	Type of the carrier	Reference
Increase solubility	Transform the drug from crystalline to amorphous form and stabilize it	Mesoporous silica Neusiline	(27)
Control or sustain the drug release	Regulation the drug diffiusion through different pore network	Macroporous and mesoporous carriers	(28)
Targeted drug delivery	Surface functionalizing to target specific tissues	Functionalized Mesoporous Nanoparticles MSNs	(29) (30)
Combination therapy	Dual drug loading to co-deliver different APIs with varying solubility profiles within single carrier	Mesoporous and Macroporous carriers	(4) (2)

4. Surface modification and functionalization of mesoporous silica nanoparticles (MSNs)

To transition from simple porous structure into “smart” drug delivery tools, MSNs can be structurally and chemically modified. Through surface functionalization, charge tuning and pore engineering, these carriers achieve high drug loading capacity, controlled release and targeted delivery.

4.1. Modified mesoporous silica nanoparticles

The surface of mesoporous silica nanoparticles is rich in silanol groups, providing reactive sites for functionalization with organic groups, polymers, and targeting moieties. These surface modifications play a key role in regulating drug adsorption, release behavior, and targeting efficiency. Covalent attachment of functional groups is accomplished by co-condensation or post-synthetic grafting, resulting in the introduction of silane-based organic functionalities. The co-condensation procedure involves adding a functional organosilane and a silica source directly into the

synthesis gel solution (31). Co-condensation offers several advantages, including simplicity of operation, uniform functionalization, and high drug loading within the internal surface of mesopores. In contrast, functional groups can be introduced via post-synthetic grafting, a process that depends on both covalent bond formation and electrostatic interaction. A key advantage of the post-synthetic grafting is its ability to selectively functionalize the external surface to prevent premature drug leakage, while keeping the internal pores available for maximum drug loading (32).

4.2. Surface property control of mesoporous silica nanoparticles

Due to their large surface area, mesoporous nanoparticles enable control over surface charge by incorporating specific functional groups; for instance, doxorubicin can be loaded into MSNs by functionalizing the surface of the carriers with polyacrylic acid. This polymer provides a negatively charged carboxyl group that interacts with the positively charged DOX, thereby improving the loading capacity and stabilizing the drug–carrier complex (33).
Functional moieties such as folic acid (FA), RGD peptide, and transferrin (TF) have been widely used to enhance targeting efficiency. Among these, FA has been frequently employed due to its affinity for folate receptors, which are overexpressed on malignant cells. In this approach, carboxyl-functionalized mesoporous silica nanoparticles (MSN/COOH) were chemically linked to FA through a PEG spacer, resulting in the targeted construct MSN/COOH-PEG-FA (34,35). By modifying the pores of MSNs, it is possible to design gated drug-delivery systems. For example, adding octyl and octadecyl chains to SBA-15 reduces the pore size and wettability. This strategic modification successfully slowed the release of erythromycin, creating highly effective controlled-release profile (36).

5. Pharmaceutical applications of porous carriers

Porous carriers have emerged as advanced solutions for poorly soluble oral drugs, which account for approximately 70% of pharmaceutical formulations. This section discusses the different applications of porous systems across various fields, as illustrated in **Figure 2** (20).

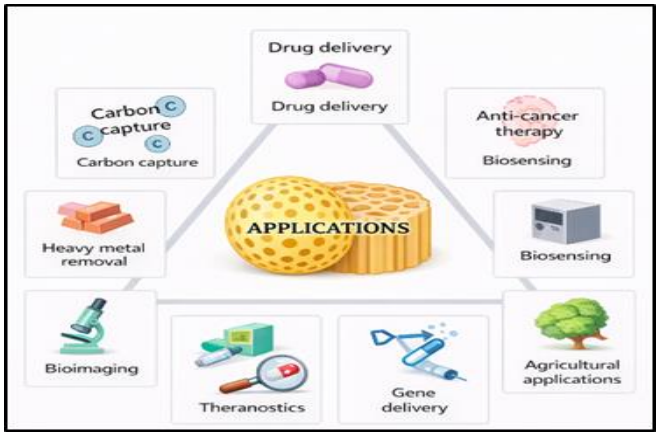

Figure 2. Various applications of mesoporous silica nanoparticles (MSNs) in different fields (20).

5.1. Improving bioavailability

Functioning as solubility enhancers, MSNs have gained considerable interest because their ability to improve therapeutic efficacy. Their contribution to increasing drug bioavailability is mainly driven by their nanoscale pores, which effectively confine and transform crystalline API molecules into their amorphous form. Moreover, the intrinsic properties of the porous carriers include a large surface area, high pore volume, well-defined pore size, ordered pore arrangement, and the presence of surface silanol groups in several porous nanomaterial types that can interact with various pharmacological compounds. Together, these characteristics improve wettability and dissolution of hydrophobic drugs when loaded into ordered MSN systems (37,38).
Specific types of porous carriers like Florite RE (FLR), a calcium silicate, have two types of pores: inter- and intra-particles pores in sizes ranging from 12 to 0.15µm. FLR not only has different pore patterns, but it can also be dispersed in all aqueous solutions and used as a solubilizing agent for oily soluble drugs. Low-density porous carriers like porous silicon dioxide (Sylysia), polypropylene foam powder (Accurel), porous calcium silicate (Florite), magnesium alumino-metasilicate (Neusilin), and porous ceramics with open or closed pore structures provide a large surface area for dissolution, thus enhancing the bioavailability of poorly soluble drugs such as meloxicam, aspirin, and indomethacin (39 ,40).

5.2. Controlled and targeted drug delivery

Building upon their success in enhancing bioavailability, porous nanomaterials are now engineered as advanced platforms for targeted drug delivery. Mesoporous silica (e.g., MCM-41, SBA-15), Neusilin®, and calcium phosphates are extensively studied as drug carriers for oral administration systems due to their pore size, biocompatibility, and surface characteristics (7,41). After loading these carriers with a specific drug, their surface can be functionalized with stimuli-responsive groups to control release through precise manipulation of open/closed pore architectures (42). They can react to internal stimuli of the human body, including pH, enzymes, and redox agents, as well as exterior stimuli such as temperature, light, and magnetic fields (43,44). Furthermore, hybrid PNMs like metal–organic frameworks MOFs and organo-silica provide many benefits, improving stability, selective adsorption, and facilitating the co-loading of several medicines or synergistic therapeutic agents (45) .These characteristics enable PNMs to control drug release, enhance therapeutic efficacy, and decrease dosing frequency.
Recent *in vivo* and *in vitro* studies validate the capability of such carriers to act as a precise delivery tools. For instance, Safat et al. evaluated the cholesterol-lowering activity of Cynara scolymus (CS) extract when incorporated into Santa Barbara Amorphous-15 (SBA-15) MSNs and compared it with the non-encapsulated extract. Rats treated with the MSN-based formulation had considerably lower triglyceride (TG), total cholesterol (TC), and VLDL levels than those given the free extract, indicating improved drug delivery effectiveness. In another study regarding oncology, Jia et al. found that paclitaxel loaded into MSNs had better cytotoxicity against MCF-7 cells, resulting in a lower IC_{50} value and enhanced apoptosis compared to free paclitaxel (46,47). All these studies demonstrate that porous carriers possess an extraordinary ability as multifunctional drug delivery platforms, allowing for

targeted, controlled, and efficient drug administration, indicating their potential utility in enhanced therapeutic formulations. Recently, porous systems are investigated for applications in tissue engineering, biomedical imaging, and bio-sensing.

5.3 Porous Carriers in the food industry: Cross-industry versatility

Porous carriers possess unique physicochemical features that allow their adsorption mechanisms to be translated across both the food and the pharmaceutical sectors. Their vast surface area, adjustable pore shape, and high adsorption capacity make them excellent candidates for decolonization, purification, and controlled release of bioactive chemicals. For example, bio-char made from sugar-industry bagasse and treated with hydroxyapatite is a porous carbonaceous carrier that has a large internal surface area and a strong attraction to colorants during sugar-juice purification. Cha et al. (2022) found that these kinds of combinations could hold about 313 mg/g of colorants in cane juice. In the same way, powdered mesoporous activated carbon waste from sugar factory procedures (with a BET surface area of around 600 m^2/g) was able to get rid of almost 81% of the color from turbid sugar juice. These results indicate that porous carbon-based materials could be used as eco-friendly and cheap adsorbents in industry, especially for cleaning food, making beverages, and treating wastewater. Pharmaceutical formulation and environmental cleanup can also benefit from the same surface-driven adsorption concepts that enhance food purification effectiveness. This shows how versatile porous carriers can be for many different purposes (48).

5.4. Porous carriers in tissue engineering

Recent advances have expanded the use of porous carriers beyond conventional drug formulation toward tissue engineering applications. Due to their high porosity and interconnected structures, porous carriers are considered scaffolds for cell proliferation and growth. Their architecture resembles the extracellular matrix (ECM), the body's natural framework that supports natural cell attachment, nutrient exchange, and cellular development. Such structural similarity converted porous carriers into bioactive materials in tissue engineering.

Subsequently, researchers advanced these platforms by tailoring the size, shape, and surface chemistry of pores of the porous materials to actively modulate cellular behavior during growth. A well-designed porous scaffold not only allows for oxygen and nutrient exchange, but it also promotes the proliferation of cells like osteoblasts and chondrocytes, which produce new tissue. In the engineering of bone and cartilage, hybrid carriers composed of silica, calcium, and polymers became essential for promoting osteogenesis and chondrogenesis, as well as aiding the repair of injured tissues with both strength and biological harmony (49,50,51).

Sun et al. (2024) demonstrated that porous materials are not only used in drug delivery systems but also have the ability to target and release growth factors and therapeutic molecules. Sun et al. (2024) found that their porous organic materials (POMs) facilitated axonal regeneration over damaged facial nerves, enabling the formation of novel neural pathways and the restoration of tissue function. The success of this approach relied on the careful balance between the shape and type of the pores, which provided physical guidance, while the surface chemistry facilitated cells adhesion and regenerate (50).

6. Drug loading methods

The transformation of a raw porous silica materials into an effective drug delivery tool, heavily relies on the method used to load the active compounds. Currently, porous carriers are widely utilized to design these targeted drug delivery systems. In pharmaceutical applications, mesoporous amorphous silica is the most common due to its reduced toxicity relative to the crystalline form. Thus, various types have been examined, including porous and non-porous silica, fumed silica, and silica gels, among others. The characteristics of these materials can be enhanced through precise modification of pore structural properties, leading to the formation of ordered mesoporous particles, which are currently the most prevalent variety (52-55).

Owing to their organized porous architecture (channels lacking connectivity), high surface area (exceeding 700 m^2/g), and large pore volume (surpassing 1 cm^3/g), they provide accurate control over drug loading and drug release kinetics (56). MSNs possess two functional surfaces: an internal cylindrical pore surface and external surface. Both surfaces can be selectively modified by certain functional groups to enhance loading and release characteristics. Particularly, the external surface can be modified to enhance the efficacy of drug delivery to specific targets within the body (57,58).

The primary benefit from a pharmaceutical perspective is the enhancement of API's solubility upon incorporation into the mesoporous network, alongside the establishment of stable drug-carrier dispersion systems (59). Drugs can be loaded into theses pores using several methods, as illustrated in **Figures 3**. They can be categorized into two principal approaches: solvent-free methods and solvent-based methods (often referred to as wet methods) (59) (60). The percentages of entrapment efficiency (EE%) and drug loading (DL%) are calculated based on the following equations (61,62).

$$\text{Entrapment efficiency (\%)} = \frac{\text{Entrapped drug}}{\text{Total drug}} \times 100$$

$$\textit{Drug loading (\%)} = \frac{\textit{Weight of drug loaded in MSN}}{\textit{Total weight of loaded MSN}} \times 100$$

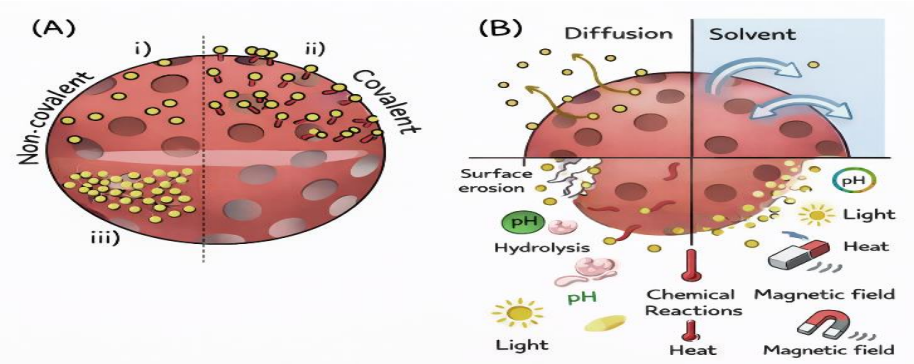

Figure 3. (A) Drug loading methods in porous nanomaterials (PNMs) include: (i) direct adsorption of drugs on the surface or within the pores, (ii) linker-mediated loading (covalent grafting) on the surface or within the pores, and (iii) cavity loading inside porous capsule. (B) Drug release mechanisms of PNMs are categorized based on non-covalent interactions, diffusion-controlled release, solvent control, chemical reaction control, and stimuli-responsive release (7).

According to recent literature, solvent-based methods, including solvent evaporation, adsorption, and incipient wetness impregnation, are often used for encapsulating different types of drugs. Among the solvent-free techniques, melting and co-milling are recommended for incorporating drugs into the pores of mesoporous silica nanoparticles (MSNs). The encapsulation method relies on the adsorption of drug molecules onto the inner and outer surfaces of the porous silica under conditions suitable for drug-carrier interactions, such as van der Waals forces, hydrogen bonding, electrostatic attraction, or covalent bonding (8).

The optimal loading method must efficiently pack large amounts of the drug into the carrier and subsequently release it according to the specified profile (60). Crucially, minimizing the proportion of the drug adsorbed on the external surface is essential to prevent potential re-crystallization and burst release effect. The degree of drug loading is dependent upon various criteria; the most critical factors are the available surface area and the drug's affinity for the silica substrate (63,64). In wet methods, the pore volume, solvent polarity, and drug concentration are also determinants (65). Ultimately, the selected loading technique influences the extent of encapsulation, the drug's spatial distribution within the pores, and the physicochemical properties of the final formulation (66). For any successful drug delivery system, formulating a reproducible technique is essential. API loading is the most critical step in engineering these porous carriers, highly dependent on the intended clinical application. However, the most commonly reported loading methods remain limited to laboratory-scale application. Translating these techniques into large-scale method for pharmaceutical manufacturing present a significant challenge (67). Industrial scalability demands simple, reproducible and cost-effective protocols that satisfy both the economic and the environmental requirements. The commonest drug loading strategies along with carrier types, are summarized in **Table 2** and discussed below.

Table 2. Drug loading strategies for porous carriers and their representative drug systems

Drug	BSC Classification	MSP	Method of loading	Reference
Atenolol	III	SBA-16	Adsorption	(68)
Atorvastatin	II	SBA-15	Solvent evaporation	(69)
Ezetimibe	II	OMS	Incipient wetness (Impregnation)	(70)
Felodepin	II	MSN	Solvent evaporation	(71)
Fenofibrate	II	SBA-15 MCM-41 OMS	Supercritical CO2 Incipient wetness Physical mixing Incipient wetness Co-spray drying Supercritical CO2	(72) (73) (74) (75) (76)
Ibuprofen	II	MCM-41 SBA-15	Diffusion Supported Loading Liquid Co2 Co-spray drying Incipient wetness Adsorption Covalent grafting Adsorption Incipient wetness Solvent evaporation Melting Co-spray drying Co-milling	 (77) (78) (79) (80) (80) (81) (82) (82) (82)

6.1. Solvent-based method

The solvent-based methods remain the most commonly used techniques for encapsulating active ingredients in MSNs because they stabilize APIs in their amorphous form, significantly enhances dissolution and release. However, these methods involve complex multi-step procedures and require large volumes of organic solvents, making it difficult to guarantee pore-filling efficiency (83). consequently, removing excess solvent to acceptable levels is a critical challenge. For instance, Eren et.al. demonstrate that trace amount of hexane remaining within the pores of SBA-15 carriers negatively affected the viability of incubated cells (HT-29, HLA116), highlighting major toxicological drawback of solvent-based methods (78, 84).

6.1.1. Adsorption

Adsorption is one of the most widely used methods for drug loading into MSN-carriers ,as it can be utilized for both hydrophilic (85), hydrophobic (86) drugs and heat sensitive APIs. The simplicity of this procedure arises from immersing porous carriers into concentrated drug solutions. Over time, drug molecules will be adsorbed and trapped inside carrier's pores, followed by filtration and drying to remove the excess solvent (87). However, the primary drawbacks of this technique is time-consuming, the requirement for high drug concentrations and unpredictable loading capacity. Using excessive amounts of drugs can lead to rapid surface adsorption, which blocks the mesopores and restricts the release (88).

6.1.2. Solvent evaporation

Another highly used method for drug loading combines both adsorption and rapid solvent drying (77). In this approach, the carrier is immersed in a volatile organic solution consist of the drug and usually ethanol, followed by solvent removal using a rotatory evaporator or controlled heating to achieve loaded MSNs (67,89,90). Unlike simple adsorption, which can cause significant drug loss, the solvent evaporation directly influences the physical state, location and release profile of the drug within the MSNs. This was proven by Mellaerts et al. who showed that while Ibuprofen will be located inside the microspores of SBA-15 silica regardless to the loading method (wet impregnation or adsorption). In contrast, itraconzole will be distributed differently depending on the loading technique used, as illustrated in **Figure 4** (82).

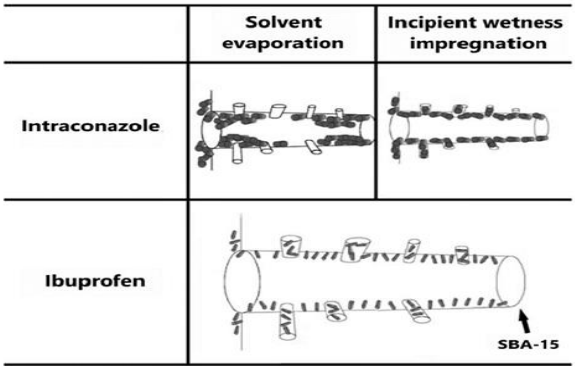

Figure 4. Physical state of itraconazole and ibuprofen after loading into SBA-15 using the solvent evaporation method and the incipient wetness impregnation method (67).

6.1.3. Wet impregnation (WIM)

Wet Impregnation has emerged as one of the most efficient strategies for drug loading, overcoming many limitations of the conventional methods. In this technique, the volume of drug solution is adjusted to match the pore size and volume of the carrier. This enables the capillary penetration of solution droplets and their distribution inside the pores. This controlled diffusion causes deeper encapsulation of the APIs and prevents surface crystallization of the drug, which is a major drawback in simple adsorption. In WIM, the volume of drug solutions is precisely measured to ensure complete drug entrapment inside the pore network. As it's described in the patent (91), which was published in 2022, the technique will control wetting and cause homogenous distribution inside the porous matrix.

Because the WIM technique requires minimal solvent volumes and mild operating temperatures, it is highly suitable for loading thermolabile, hydrophilic, and even poorly soluble drugs. Furthermore, previous studies have emphasized two critical features of wet impregnation, which are, after initial impregnation, the wet powder being subjected to mild washing with solvent to remove any extra drug particles attached to the external surface of the carrier. Charnay et al. found a decrease in the quantity of ibuprofen encapsulated in MCM-41 following the ethanol washing of silica, from 1350 to 500 mg/g (80). They have also shown that successive impregnations facilitate full pore filling and markedly enhance the concentration of ibuprofen. Their research indicates that the incipient wetness impregnation approach is more effective than the conventional solvent immersion process. Ibuprofen within the pores existed in an amorphous condition, resulting in enhanced dissolution rates relative to the crystalline form of the medication (80). Overall, the wet impregnation provides high loading capacity, uniform intra-pore distribution, and stabilization of the drug in its amorphous form. These characteristics position WIM as superior to traditional drug loading methods.

6.1.4. Supercritical fluid technology (SCF)

This method, is commonly used in the food industry and chromatography, as well as in drug loading into porous carriers (72,76,92). The effectiveness of supercritical carbon dioxide is due to its adjustable physicochemical characteristics such as liquid-like density and gas-like viscosity, which enhance the diffusion of the drug particles into the pores of the carrier (93). Comparative studies support the efficacy of this technique; for example, research on ibuprofen and fenofibrate revealed that SCCO2 impregnation achieves superior drug loading capacity and provides faster process kinetics, which decrease the loading time from 48 hours to 2 hours compared to conventional adsorption or incipient wetness methods (76,94). Furthermore, the supercritical fluid method inhibits the drug crystallization, leading to improved drug release profiles in comparison to physical mixing or melting methods (74). The limited solubility of BCS class II drugs remains a challenge in the SCCO2 method; nonetheless, this technology offers a compensatory mechanism to facilitate pore filling through decreasing drug viscosity and lowering drug melting points, without using hazardous co-solvents.

6.2 Solvent methods

In contrast to wet methods, solvent-free techniques are more efficient and can achieve higher degree of drug loading levels. Furthermore, the drug concentrations inside the porous materials can easily be predicted, as its directly influenced by the ratio between the APIs and MSNs.

6.2.1 Melting method

This method, commonly known as the thermal solvent-free technique, involves heating the drug-porous carrier mixture beyond the melting point of the API (66,95). this method decreases processing duration and improves drug delivery, for example Potrzebowski et al. uses solid-state NMR to illustrate that the melt method produced a superior filling factor of roughly 60% (w/w) for ibuprofen in MCM-41 relative to the incipient wetness method (96). The value of this approach is determined by the physicochemical parameters of the API. Despite the advantages, the melting method has some limitations, since it's limited to thermally stable compounds and it is affected by the molten viscosity of the drugs. Mellaerts et al. illustrate that low-viscosity drugs, such as ibuprofen, can be effectively incorporated into SBA-15 pores in an amorphous form, whereas high-viscosity drugs like itraconazole cannot infiltrate the mesopores, leading to accumulation on the external surface and suboptimal loading efficiency (82,95).

6.2.2. Co-milling

Co-milling is a mechano-chemical technique used to generate sub-micrometric particles and to promote solid-state amorphization. Planetary ball milling has been reported as an efficient solvent-free approach for incorporating organic molecules, such as benzoic acid and 4-fluorobenzoic acid, into the pores of MCM-41, achieving loading capacities exceeding 50%. In addition, Hedous et al. observed that co-milling SBA-15 with ibuprofen facilitates drug incorporation with the porous matrix, which increases the filling degree up to 40% (97,98). The distribution of these guest molecules within the internal pores, external surface, and interstitial spaces is illustrated in **Figure 5**. Therefore, this indicates that milling techniques serve as alternatives to solvent-based methods. Despite its simplicity and time efficiency, the co-milling applications can affect the porous material stability. Abu-Zied et al. highlight that high mechanical stress of the ball milling can compromise the structural integrity of the porous carrier leading to potential collapse of carrier framework as the milling process continue (99).

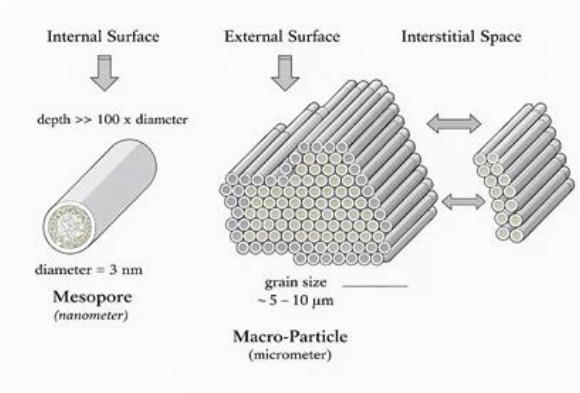

Figure 5. Illustration of the internal and external space accessible to drug molecules in the powder samples of MCM-41 silica. A single pore, about 3 nm in diameter and with depth exceeding 100 nm, contributes to an increase in the internal volume (left). The ordered pores are arranged in a honeycomb pattern (center), leading to large external surface area (the gray region). The external surface forms interstitial space (right) created between the randomly arranged crystallites (see to the horizontal arrows)(96).

7. Comparative evaluation of drug loading methods

Based on the methods discussed in the previous paragraph, **Table 3** provide a comprehensive summary of both solvent-based and solvent-free drug loading mechanisms. This comparative evaluation systemically emphasizes critical aspects, including loading efficiency, drug stability upon loading and overall scalability**.**

8. Mechanisms of drug release

The release of the APIs from porous carriers like Neusilin and Fujicalin, is a unique process controlled by the physical state of the loaded drug and the surface chemistry of the carrier (9,117). A key advantage of these porous systems is their ability to entrap the API within their mesopores in an amorphous state. By preventing drug crystalization, the energy barrier for dissolution is reduced. This amorphous stabilization, combined with the carrier's high surface area, facilitates wetting and rapid dissolution upon contact with the biological fluids, therefore leading to an immediate release (105). In addition, sustained release profiles can be achieved by surface functionalization, where the pore walls are chemically modified with specific functional groups. This modification increases the binding affinity between the drug and the carrie, thereby slowing API outward diffusion (25). Furthermore, many advanced applications depend on dual-release profiles to achieve rapid onset and long action. This is often managed by stimuli-responsive mechanisms (e.g., pH, temperature, or enzymes), which act as gatekeepers regulating drug release and delivery (27,60, 106-108).

9. Current challenges in drug loading into porous carriers

Despite the numerous advantages in porous drug carrier systems, loading multiple APIs onto a single porous matrix remains a significant challenge. One of the common hurdles is the potential of drug-drug interaction within the confine porous structure, which may result in undesirable chemical reactions or altered release profiles (109). Furthermore, competitive binding affinities between the two medications for the carrier's internal surface can obstruct drug release; for instance, a medication with higher affinity may displace or delay the release of the second drug. Another obstacles arise from the difference in solubility and physicochemical properties of the co-loaded drugs. When these APIs differ significantly in hydrophobicity, molecule size, or charge, achieving simultaneous or sequential release becomes exceedingly difficult (110).
Moreover, the inherent limited loading capacity of porous structures, especially microporous or low-surface-area materials, pores became the major constraint (45). From formulation aspect, guaranteeing the stability, flowability, and compressibility of the drug-carrier composite is critical,

especially when the final product is intended for oral solid dosage forms (111). These factors affect the end product's manufacturability and scalability. Beyond *in vitro* formulation constraints, predicting the in-vivo behavior of these systems remains a critical research gap. Recent literature highlights that the spontaneous formation of a biomedical corona around the porous matrix upon entering systemic circulation can prematurely abstract pores. This phenomenon often alters the intended release kinetics and compromises targeting efficiency (112,113). Additionally, long-term biological fate and *in-vivo* degradation pathways of highly functionalized carriers are still not fully understood, complicating their clinical translation (114,115).

These collective limitations highlight significant research gaps in the current literature. To address these issues, ongoing research must focus on developing hybrid porous carriers with tailored pore topologies, advanced surface functionalization, and stimuli-responsive release mechanisms (116).

Table 3. Comparative evaluation of drug loading methods

Loading Method	Loading Efficiency	Impact On Drug Stability	Complexity and Scalability	Reference
Adsorption	Unpredictable loading & with risk of pore blockage	Suitable for heat-sensitive drugs but with risks for surface crystallization.	Simple but Time-consuming: Requires immersion, filtration, and drying.	(20,7)
Solvent Evaporation	Provide better control over the API's physical state and location within pores.	Stablize the drug in it's amorphous form, mitigates drug loss compared to simple adsorption.	Moderate: Requires rapid solvent drying via rotatory evaporation or heating.	(7,100,117)
Wet Impregnation	High loading efficiency and capacity with full pore filling	Stabilizes drugs in an amorphous state; suitable for thermolabile and hydrophilic APIs.	Moderate: Requires precise volume measurements and mild solvent washing steps.	(101,7,102,117)
Supercritical Fluid	high loading capacity; limited by the solubility of BCS class II drugs.	Inhibits drug crystallization; provides excellent stability without hazardous solvents.	Complex but Fast: Requires SCCO2 setup but cut the loading time (e.g., from 48h to 2h).	(7,103)
Melting	High loading capacity (e.g., >25%w/w filling for Ibuprofen.	Limited: only for thermally stable APIs .	Simple and Fast: Solvent-free thermal process, depends on drug viscosity.	(7,20)
Co-Milling	High (exceeding 50% capacity; ~40% filling degree).	Promotes solid-state amorphization; Carrier Risk: mechanical stress may cause framework collapse.	Fast and Simple: Mechano-chemical solvent-free approach, highly time-efficient	(7,104)

10. Future perspectives

To overcome the persistent challenge of industrial scalability discussed previous, recent inventions have demonstrated that continuous manufacturing processes can be applied to multiple drug loading onto porous carriers. For example, in the patent WO 2021 126829 A1 which describes a scalable method using drug solutions are sprayed on porous matrix inside continuous high-shear mixer, followed by solvent evaporation to obtain drug loaded carriers. This approach achieves a uniform drug distribution across the pore's networks. Such continuous loading techniques will bridge the gap between laboratory preparation methods and real commercial scale methods. Furthermore, to address the complex release requirement of co-loaded APIs, modern research is shifting towards Anisotropic carriers and hierarchical pore structures. These advanced designs enable multistage or programmable release profiles, which demonstrate how the carrier design and drug loading processes can work synergistically to support the next generation of oral dosage forms (91).

11. Conclusion

Porous silica-based carriers have emerged as groundbreaking platforms for drug delivery, because of their physicochemical properties such as pore morphology and size, massive surface area and tunable surface chemistry which all serve as structural foundation that provide control over drug loading and release. A key advantage of the porous carriers comes from their ability to stabilize the active pharmaceutical ingredient in the amorphous form inside the pores therefore enhance the available surface area for dissolution. This amorphization will overcome the poor aqueous solubility of BCS class II and IV drugs, through enhancing their dissolution rate and bioavailability.

Beyond the solubility enhancements, Surface functionalization of MSNs provides targeted delivery and stimuli- responsive release. The incorporation of responsive surface modifications such as" gatekeepers" allows drug release in the exact amount at specific targeted area as a response to certain trigger stimuli (e.g. pH, temperature or enzymatic activity), thereby limiting premature drug release and improving drug delivery (101). However, as discussed in this review, the successful clinical translation of these enhanced delivery techniques is dependent on overcoming considerable formulation and biological obstacles. Issues such as the reproducibility of large-scale manufacturing, the control of drug-drug interactions in co-loaded systems, and the prediction of long-term in vivo behavior continue to pose significant bottlenecks. Overall, the recent studies indicate that while porous carrier hold high therapeutic potential, future research must strike a careful balance between nanoscale engineering and practical, scalable manufacturing to fully realize their clinical viability (102,52).

12. Conflict of Interest

The authors declare that there are no conflicts of interest regarding the publication of this manuscript.

13. References

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التطورات الحديثة في الحوامل المسامية لتوصيل الأدوية: المواد، واستراتيجيات التحميل، والتطبيقات

الخلاصة:

الخلفية: لا تزال ذوبانية العديد من الأدوية في الماء وانخفاض توافرها الحيوي من التحديات الرئيسية في تطوير الأدوية، وغالبًا ما تحد من فعاليتها العلاجية. وللتغلب على هذه القيود، وُجّه اهتمام كبير نحو أنظمة توصيل الأدوية المتقدمة التي تُحسّن استقرار الدواء، وسلوك إطلاقه، وخصائصه الحركية الدوائية. ومن بين هذه الأنظمة، برزت الحوامل المسامية كمنصات متعددة الاستخدامات. تشمل هذه الحوامل مواد بوليمرية، ودهنية، وغير عضوية، تتميز بخصائص فيزيائية وكيميائية متنوعة تُمكّن من دمج الدواء بكفاءة وإطلاقه بشكل مُتحكم فيه. **الهدف**: تقديم نظرة شاملة على الحوامل المسامية في تصنيع الأشكال الصيدلانية الصلبة وأنظمة توصيل الأدوية، مع التركيز على تصنيفها، وخصائصها التركيبية والفيزيائية والكيميائية، وآليات تحميل الدواء، وتطبيقاتها الصيدلانية، والتحديات الحالية المرتبطة باستخدامها. **طرق العمل**: تستند هذه المراجعة إلى دراسات علمية منشورة سابقًا حول الحوامل المسامية وتطبيقاتها في أنظمة توصيل الأدوية. تم فحص الأبحاث والمقالات الاستعراضية ذات الصلة بدقة لتقديم ملخص علمي واضح للمعرفة الحالية في هذا المجال. **الاستنتاج**: حظيت الحوامل المسامية باهتمام كبير نظرًا لمساحة سطحها العالية، وإمكانية ضبط حجم مسامها، وتعديل تركيبها الكيميائي السطحي، مما يُحسّن من فعالية تحميل الأدوية، وسلوك ذوبانها، وإطلاقها المُتحكم به. وقد أظهرت مواد مسامية متنوعة، بما في ذلك السيليكا المسامية المتوسطة، ونيوسيلين®، وفوسفات الكالسيوم، والأطر الهجينة العضوية-غير العضوية، إمكانات واعدة في تحسين توصيل الأدوية والنتائج العلاجية. ويُعد استمرار البحث ضروريًا لتحسين هذه الأنظمة وتوسيع نطاق تطبيقاتها الصيدلانية.

الكلمات المفتاحية: تحميل الأدوية؛ السيليكا المسامية المتوسطة؛ الحوامل المسامية؛ تعديل السطح