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From Mesoporous Silica to MOF–Silica Composites: Advancements in Nanostructured Drug Delivery Systems

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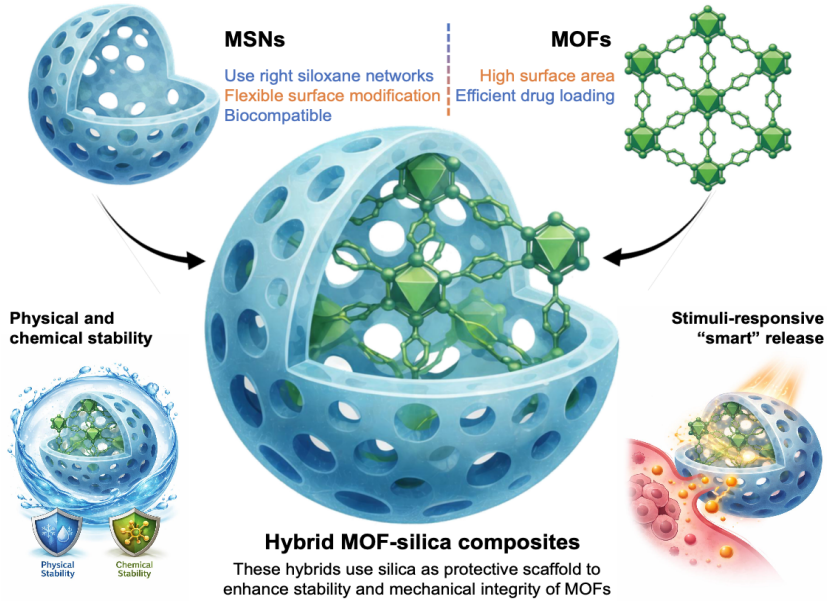
GRAPHICAL ABSTRACT



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ABSTRACT

Recent advances in nanotechnology have enabled the development of versatile drug delivery systems (DDS) using nanoscale carriers, offering significant improvements over conventional therapies. Mesoporous silica nanoparticles (MSNs) and metal–organic frameworks (MOFs) are highly porous nanomaterials with tunable structures and large surface areas, making them promising platforms for drug delivery. MSNs provide controllable particle size, pore size, and surface functionality, allowing efficient loading and controlled release of both hydrophilic and hydrophobic drugs. MOFs, with their high surface area, adjustable pore structures, and chemical versatility, enable high drug loading capacity and stimuli-responsive release. Integrating MOFs with silica to form MOF–silica composites further enhance structural stability, biocompatibility, and drug delivery efficiency. Stimuli-responsive composites can minimize premature drug release and enable targeted delivery in response to environmental triggers,

such as pH or near-infrared irradiation. This review highlights the structural and functional differences among MSNs, MOFs, and MOF–silica composites, and discusses their applications in delivering model therapeutic agents, including curcumin, quercetin, and doxorubicin. The advantages, limitations, and future perspectives of these nanocarriers for precision medicine are also addressed, emphasizing their potential to improve therapeutic efficacy while reducing off-target effects.

1. INTRODUCTION

Over the past decade, the delivery of conventional therapeutic compounds has remained a major challenge in the treatment of many diseases. Most conventional drugs are administered orally or intravenously and, despite their ease of use, often suffer from limited efficacy, poor biodistribution, and low selectivity. Low selectivity may cause drugs to interact with non-target tissues, leading to severe adverse effects, an issue particularly evident in cancer patients receiving traditional chemotherapeutic agents [1]. These limitations highlight the need for controlled drug-delivery strategies capable of enhancing therapeutic efficiency while minimizing systemic toxicity.

Drug delivery systems (DDS) provide a means to transport therapeutic agents specifically to targeted sites, thereby reducing unwanted interactions with healthy tissues and improving treatment outcomes [2]. DDS can also protect drugs from premature degradation or rapid clearance, increase their accumulation in target tissues, and ultimately enable the use of lower drug dosages [3]. Such modern therapeutic approaches are especially important when there is a narrow margin between the therapeutic and toxic concentrations of a drug.

The emergence of nanotechnology has positioned nanoparticles as highly promising candidates for advanced DDS platforms. Nanoparticles—typically defined as particles with diameters ranging from 10 to 1000 nm—can enhance drug efficacy by prolonging systemic circulation [4], improving the solubility of hydrophobic drugs, and enabling controlled or sustained release [4]. Stimuli-responsive nanoparticles further offer the ability to reduce toxicity and modulate biodistribution in a spatiotemporally precise manner. A wide variety of nanoparticle-based DDS have been developed, including organic nanoparticles (e.g., liposomes [5], dendrimers [6], and polymeric micelles [7], inorganic nanoparticles (e.g., carbon nanotubes [8], metal nanoparticles [9], and mesoporous silica [10]), and metal–organic frameworks (MOFs) [11].

2. MESOPOROUS SILICA NANOPARTICLES (MSNs)

Mesoporous silica was first reported in the early 1990s by Kuroda and co-workers in Japan. The synthesis of mesoporous silica typically involves the use of surfactant molecules as templates around which silica precursors condense. Subsequent removal of the surfactant template produces well-defined pores within the material. Mesoporous silica exhibits an ordered pore arrangement, uniform pore size ranging from 2–20 nm, a large pore volume of approximately 1 $cm^3\ g^{-1}$, a high specific surface area (up to ~1000 $m^2\ g^{-1}$), and a surface rich in silanol groups that can be readily functionalized with a wide range of chemical moieties. The excellent physical properties and tunable surface chemistry of mesoporous silica make it highly attractive for biomedical applications. This has motivated extensive research into the development of nanoscale mesoporous silica materials.

Mesoporous silica nanoparticles (MSNs) can be synthesized by several methods. The most commonly used route (Figure 1) is a hydrolytic sol–gel process, which involves the hydrolysis and condensation of silicon alkoxide precursors under acidic or basic catalysis. During polycondensation, the silica network forms around surfactant molecules acting as structure-directing agents, generating a colloidal solution (sol) that gradually evolves into a gel or discrete nanoparticles. Under sufficiently dilute conditions, this process yields monodisperse, spherical MSN particles with well-defined mesoporous structures.

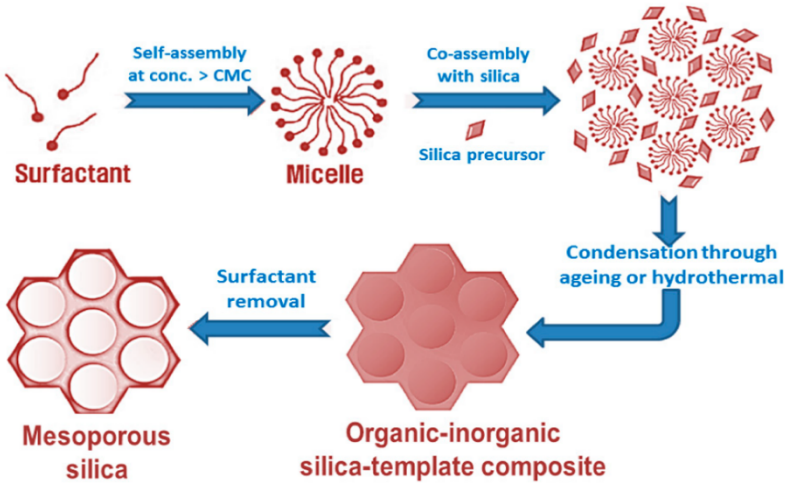

Figure 1. General scheme in synthesis of MSNs via surfactant template method. The figure is reused under CC BY 3.0 from ref. [12].

The MSNs possess highly tunable physicochemical properties, including particle size, pore size, pore volume, surface area, pore architecture, and surface functionalization. Their well-defined mesoporous network provides internal cavities capable of loading and releasing a wide range of therapeutic molecules. The formation of MSNs is strongly influenced by the self-assembly of surfactants, which act as structure-directing agents, together with silica oligomers derived from hydrolyzed precursors.

Controlled growth during synthesis enables precise adjustment of key parameters, including particle diameter, pore dimensions, pore volume, and overall surface area. By modulating synthesis conditions such as surfactant type, precursor concentration, pH, reaction temperature, and additives, MSNs with tailored aspect ratios and morphologies can be produced to meet specific requirements for biomedical applications.

Particle size is one of the most critical parameters influencing the biomedical performance of MSNs. It plays a central role in their pharmacokinetic behavior, cellular uptake, biodistribution, and in vivo clearance. Therefore, controlling particle size is essential for achieving effective drug loading and delivery. Several agents, including amines, alcohols, salts, and inorganic bases, affect the hydrolysis and condensation of silica precursors, thereby influencing the particle size of MSNs. Reaction temperature, reagent concentration, and stirring rate also significantly impact the final size of MSNs. For example, Lv et al. (2016) reported that stirring speed markedly affects MSN size [13]. In addition, the concentration of reagents such as triethanolamine (TEA) plays a key role in regulating particle size. TEA can terminate particle growth and prevent aggregation during MSN formation. Mou et al. examined the effect of MSNs' size on cellular uptake in HeLa cells. They observed that 50-nm MSNs exhibited the highest cellular uptake, followed by particles of 30, 110, 280, and 170 nm [14]. These findings highlight particle size as a crucial factor in the design of MSN-based drug-delivery systems.

Surfactants play a crucial role in determining the pore volume of MSNs. Short-chain surfactants generate smaller pores, whereas surfactants with longer hydrocarbon chains produce larger pore sizes [15]. A high pore volume is essential for achieving high drug-loading capacities. In addition, the concentration of TEOS strongly influences the structural order of mesoporous nanoparticles. Chiang et al. (2011) reported that lower TEOS concentrations result in poorly ordered mesoporous frameworks, whereas increasing the TEOS concentration improves the structural quality of the mesopores [16]. Furthermore, surface functionalization with amino groups enables MSNs to act as efficient carriers for various therapeutic agents. Typical non-functionalized MSNs synthesized under standard conditions exhibit particle diameters of approximately 160 nm as observed by TEM. After amine functionalization, the particle diameter increases to around 260 nm. Pristine MSNs exhibit a pore volume of about 0.87 $cm^3\ g^{-1}$, whereas functionalized MSNs show a reduced pore volume, consistent with the partial occupation of pore channels by surface modifiers [17].

The morphology of MSNs plays a crucial role in determining their biodistribution and cellular uptake. Therefore, precise control over particle shape is essential for optimizing in vivo performance.

Spherical MSNs are the most widely used in biomedical applications due to their superior cellular internalization compared with non-spherical counterparts. MSNs can be synthesized in a variety of shapes—such as platelets, cubes, films, rods, and ellipsoids—depending on reaction conditions [18]. Parameters, including the concentration of basic catalysts, surfactants, silica precursors, and water, significantly influence the resulting morphology. Cellular uptake studies using FITC-labeled MSNs in HeLa cells demonstrated that spherical MSNs exhibit the highest internalization efficiency compared with particles of other shapes. This highlights that particle morphology is a key determinant in designing MSNs for effective drug-delivery applications [19].

Pore size and pore structure are additional key features of MSNs that strongly influence the amount of drug that can be loaded into the nanoparticle system. An optimal pore diameter is essential to prevent premature leakage of loaded therapeutic molecules and to ensure efficient encapsulation [20]. As the structure-directing agent, the surfactant plays a central role in controlling pore size. At the same time, parameters such as the type of silica precursor, reaction time, temperature, and base catalyst concentration also contribute to the final pore architecture [21]. Significant pore-size variation has been observed when mixtures of water and ethanol are used as the reaction medium. Specifically, pore size increases as the ethanol-to-water ratio decreases from 7.5 to 3.6 mL. This indicates that variations in reagent concentrations and solvent composition can profoundly affect the pore dimensions of MSNs [22].

MSNs have been extensively developed as drug-delivery platforms due to their high surface area, tunable mesopore size, chemical stability, and excellent biocompatibility [23]. The presence of abundant silanol groups enables versatile surface functionalization, allowing attachment of targeting ligands, polymers, and stimuli-responsive moieties. These features have positioned MSNs among the most established inorganic nanocarriers for controlled drug release [24]. Nevertheless, as therapeutic strategies advance toward higher molecular complexity and precision medicine, several intrinsic limitations of MSNs become apparent. Drug encapsulation in MSNs is largely governed by physical adsorption and diffusion-controlled mechanisms, which may result in premature leakage or burst release, particularly for weakly interacting drugs. Furthermore, although mesopore size can be adjusted within a limited range, the rigid silica framework offers restricted structural tunability at the molecular level [25]. Achieving sophisticated stimuli-responsive release often requires extensive post-synthetic surface modification rather than intrinsic framework adaptability.

3. Metal-Organic Frameworks (MOFs)

In this context, metal–organic frameworks (MOFs) emerged as a next-generation class of porous materials offering a fundamentally different design philosophy. Unlike MSNs, whose framework is based on siloxane networks, MOFs are constructed from coordination bonds between metal nodes and organic linkers, enabling modular and highly programmable architectures. This hybrid organic–inorganic composition allows precise control over pore size, internal surface chemistry, topology, and framework flexibility at the molecular level. As a result, MOFs provide exceptionally high surface areas, tunable pore environments, and versatile host–guest interaction mechanisms, including coordination bonding, π–π stacking, and electrostatic interactions. These features significantly expand the design space for drug loading and stimuli-responsive release compared with purely inorganic silica systems.

MOFs are highly ordered crystalline porous coordination polymers composed of inorganic metal ions or clusters (e.g., transition metals and lanthanides) linked by organic ligands such as carboxylates, phosphonates, imidazolates, or phenolates. In 1999, Yaghi and colleagues first reported the design and synthesis of MOF-5, a zinc–carboxylate framework constructed from Zn_4O clusters and 1,4-benzenedicarboxylate (BDC), which exhibited an exceptionally high Langmuir surface area of 2900 $m^2\ g^{-1}$. Over the past two decades, MOFs have attracted significant interest due to their ultrahigh surface areas, large pore volumes, tunable pore sizes, and versatile chemical compositions, enabling their application in gas storage, chemical separation, catalysis, semiconductors, and bioimaging.

In the last decade, the biomedical applications of MOFs—particularly for drug delivery—have grown rapidly. When MOF particle sizes are reduced to the nanoscale, these nano-MOFs (NMOFs) function as efficient carriers capable of delivering imaging agents, chemotherapeutic drugs, and photothermal or photodynamic therapeutic molecules. To date, various nanoparticle-based drug-

delivery systems—including liposomes, dendrimers, and mesoporous silica—have been widely explored. The properties of MOF nanoparticles and mesoporous silica nanoparticles are summarized in Table 1.

TABLE I. Summary of properties of MOF and MSN

Parameters	MOFs	MSNs	Reference
Synthesis	Solvothermal, microwave, ultrasound	Sol–gel, hydrothermal	[26, 27]
Morphology	Spherical, ellipse, Cubes, hexagonal, octahedral	Spherical, cylinder	[26, 27]
Size distribution	Mono-/polydisperse	Mono-/polydisperse	[26, 27]
Pore shape	Tunable	Hexagonal, cube	[26, 27]
Pore feature	Amphiphilic	Hydrophobic	[26, 27]
Structural tunability	Depend on metal cluster and organic ligand	Depend on synthesis condition	[26, 27]
Surface area	1000 -7000 m^2 g^{-1}	700- 1200 m^2 g^{-1}	[28]
Volume Pori	1.04-4.40 cm^3 g^{-1}	0.6- 2 cm^3 g^{-1}	[28]
Loading capacity	350-395 mg g^{-1}	261 mg g^{-1}	[28]

Compared with other porous materials, MOFs offer several remarkable advantages, such as exceptionally high surface areas and porosities for high drug-loading capacity, easily tunable pore size and architecture, chemically versatile frameworks derived from both inorganic clusters and organic ligands, straightforward functionalization either through predesigned ligands or ex-situ ligand modification, and open channels that facilitate substrate diffusion and interactions with encapsulated guest molecules. Additional benefits include adjustable coordination bond strength, inherent degradability, and highly ordered structures that allow detailed host–guest interaction analysis. Owing to these unique features, MOFs have emerged as one of the most promising platforms for drug delivery and cancer therapy.

The modular design of MOF, based on coordination bonds between metal nodes and organic linkers, enables precise control over pore size, geometry, and internal chemical environment. This structural programmability has encouraged extensive investigation into their use in gas separation, storage, catalysis, and drug-delivery systems [29-31]. However, despite their superior physicochemical versatility, many MOFs exhibit weak coordination bonds, leading to poor chemical stability and low mechanical strength [32]. A major challenge in MOF development is therefore enhancing chemical, thermal, and water stability to withstand biological environments. To address these limitations, researchers have developed MOF composites by integrating MOFs with reinforcing materials such as polymers, silica, graphene, or carbon nanotubes [33-36].

4. MOFs-Silica Composites

To reconcile the structural programmability of MOFs with the robustness and biocompatibility of silica, hybrid MOF-silica composites have been developed as an evolutionary integration of both material classes. In these hybrid systems, silica functions as a mechanically stable scaffold or protective shell, while the MOF component provides high porosity, chemical tunability, and responsive release behavior. This synergistic combination addresses the intrinsic limitations of each material: silica enhances water stability and mechanical integrity of MOFs, whereas MOFs introduce molecular-level structural adaptability that is not achievable in conventional MSNs.

Incorporating silica not only enhances the mechanical stability of MOFs but also improves water resistance and framework integrity through covalent anchoring or protective encapsulation. Two primary fabrication strategies are commonly employed: (i) in situ growth of MOF crystals on silica substrates and (ii) sol–gel coating of silica layers onto pre-formed MOF particles. Thus, MOF–silica composites have demonstrated strong performance across a wide range of applications, including gas adsorption, separation, catalysis, and biomedicine. In the field of drug delivery, MOF-based materials offer significant advantages owing to their hybrid organic–inorganic architecture,

tunable porosity, and adaptable surface chemistry. The biological stability and structural diversity of MOFs can be further enhanced through silica integration, making MOF–silica composites even more suitable for biomedical applications. MOF–silica composites can be characterized using various analytical techniques, including X-ray diffraction (XRD), scanning electron microscopy (SEM), transmission electron microscopy (TEM), Fourier-transform infrared spectroscopy (FTIR), and thermogravimetric analysis (TGA). Depending on the intended application, three fabrication methods are commonly employed: in situ synthesis, sol–gel coating, and impregnation.

In the in-situ approach, silica particles are first synthesized and subsequently used as substrates for MOF growth via one-pot or layer-by-layer techniques. For example, to prepare UiO-66@SiO_2, Gao et al. (2019) first synthesized silica with carboxyl-functionalized surfaces, then coordinated Zr^{4+} ions onto the silica surface and reacted them with 1,4-benzenedicarboxylic acid (H_2BDC) to form the UiO-66 shell [37]. This method produces composites with uniform size distribution and well-defined morphology, which is essential for many advanced applications.

In the sol–gel process, MOF crystals are first synthesized and subsequently coated with a silica layer. During this method, silica precursors undergo hydrolysis, condensation, and gelation to form a porous SiO_2 shell on the MOF surface. The silica coating produced through this technique not only preserves the intrinsic performance of the MOF but also significantly enhances its mechanical strength and overall stability. As illustrated in Figure 2, MIL-101(Cr) crystals were successfully encapsulated within an ultrathin layer of hydrophobic mesoporous silica using a sol–gel procedure followed by calcination [38]. When evaluated as catalysts for the oxidation of indane with H_2O_2 in acetonitrile, MIL-101(Cr)@mSiO_2 exhibited markedly higher catalytic activity compared to pristine MIL-101(Cr), demonstrating the beneficial synergistic effect of the silica shell.

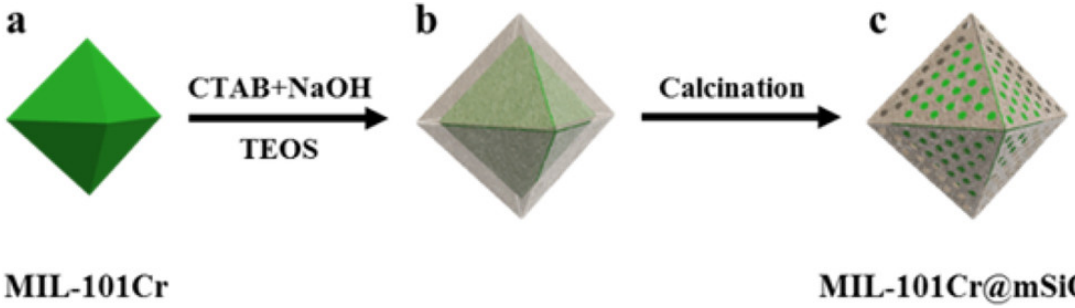

Figure 2. Synthesis scheme of MIL-101(Cr)@mSiO_2. The Figure is reused with permission from [38], © 2018, American Chemical Society.

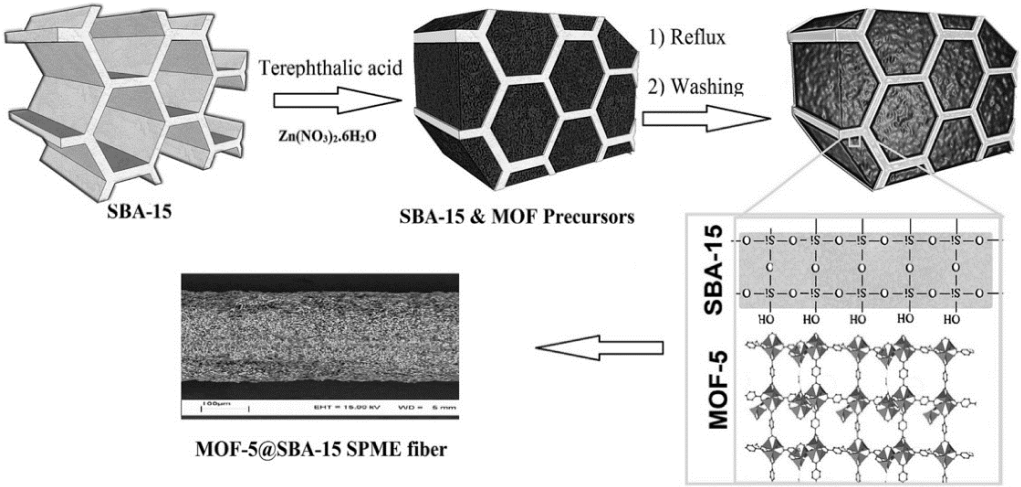

Figure 3. Synthesis of MOF-5@SBA-15. This figure is reused with permission from ref. [39], © 2015 WILEY-VCH Verlag GmbH & Co. KGaA, Weinheim.

The morphology of MOF/silica composites can be effectively controlled using the impregnation technique, in which MOF crystals are grown within the porous network of silica-based supports. As illustrated in Figure 3, mesoporous silica (SBA-15) with large and uniform pore

channels is impregnated with MOF precursors dissolved in a suitable solvent. Under these conditions, MOF crystallization occurs predominantly on the pore surfaces and within the confined spaces of the silica support [39]. The resulting MOF-5@SBA-15 nanocomposite exhibits enhanced adsorption capacity for small molecules due to its hierarchical porous structure, large surface area, and well-defined composite morphology.

5. Applications as Drug Delivery System (DDS)

Strategies to overcome the limitations of conventional drug-delivery systems have been extensively developed in recent years. The unique physicochemical properties of MSNs have attracted considerable attention in biomedical and drug-delivery research. One of the major advantages of MSNs is the ease with which their surface can be modified for various applications, particularly to achieve controlled drug release.

The surface chemistry of MSNs has been widely explored to enhance drug delivery and minimize adverse effects. MSNs serve as highly adaptable carriers that can encapsulate therapeutics with diverse physicochemical characteristics and can be further functionalized to achieve more effective therapy. In addition to MSNs, metal–organic frameworks (MOFs) have also emerged as promising candidates for drug delivery. MOF-based drug-delivery performance relies on precise control over pore size, structure, and dimensionality; surface functionalization; high drug-loading capacity; controlled therapeutic release within biological environments; and stabilization of biomolecular therapeutics. Synthetic strategies can be tuned to generate nano-sized MOFs or to modify their pore dimensions, thereby improving drug-loading efficiency or enabling controlled release. Thus, both MSNs and MOFs, each with its own structural advantages, represent highly promising platforms for advanced drug-delivery systems.

Drug loading in MSNs is primarily governed by the interplay between pore architecture and surface chemistry [40]. The large internal surface area and interconnected mesoporous network enable substantial adsorption of therapeutic molecules through electrostatic interactions, hydrogen bonding, and van der Waals forces [41]. Importantly, pore diameter directly influences loading efficiency: pores that closely match the molecular dimensions of the drug enhance confinement effects and reduce premature leakage, whereas excessively large pores may increase burst release due to weak diffusional resistance [42]. In addition, surface functionalization with amine, thiol, or carboxyl groups modulates drug–matrix interactions, thereby increasing loading capacity through complementary electrostatic attraction or specific hydrogen bonding [43]. Stronger interfacial interactions typically result in slower release kinetics due to increased desorption energy barriers.

In contrast to MSNs, drug loading within MOFs is influenced not only by pore dimensions but also by framework flexibility and the chemical nature of metal nodes and organic linkers. The hybrid organic–inorganic composition of MOFs enables multiple host–guest interaction modes, including coordination bonding with unsaturated metal sites, π–π stacking with aromatic ligands, hydrogen bonding, electrostatic interactions, and specific molecular recognition, such as Watson–Crick base pairing in nucleic-acid-based MOFs [44, 45]. These interactions can significantly enhance loading efficiency and enable higher drug payloads compared with purely inorganic silica systems. Moreover, the dynamic, or “breathing,” behavior of certain MOFs creates adaptive pore environments that respond to guest-molecule size, further influencing encapsulation efficiency.

The release profile of drugs from MSNs is predominantly diffusion-controlled and can be described by Fickian transport through the mesoporous channels [46]. Notably, loading followed by amine functionalization often provides better release control compared to systems that are functionalized before drug loading [47]. Parameters such as pore length, tortuosity, and surface charge density collectively determine the effective diffusion coefficient of encapsulated molecules [48]. Smaller pore diameters and higher surface functionalization densities increase diffusional resistance, suppress burst release, and promote sustained release behavior [42]. Conversely, weakly interacting hydrophobic drugs may exhibit rapid initial release if pore confinement and surface interactions are insufficient. Therefore, rational control of pore size and surface chemistry is essential to tailor release kinetics for specific therapeutic applications.

In contrast, drug release from MOFs often involves a combination of diffusion and framework degradation mechanisms. Under physiological conditions, stable MOFs exhibit relatively controlled

diffusion-based release. However, in acidic or reductive microenvironments—such as tumor tissues or intracellular endosomal compartments—coordination bonds may weaken, leading to partial framework collapse and accelerated drug release [49]. Thus, the intrinsic stability of the MOF framework directly determines release kinetics, making metal–ligand bond strength and water stability critical parameters for biomedical performance.

MOF–silica composite systems integrate these mechanisms by introducing hierarchical diffusion barriers and structural stabilization. In core–shell architectures, the silica layer can function as a semipermeable barrier, increasing the diffusional path length and reducing premature drug leakage under physiological conditions [50]. Simultaneously, the MOF component retains its high porosity and host–guest interaction capabilities. The overall release kinetics in such composites are therefore governed by a coupled mechanism involving: (i) diffusion through MOF pores, (ii) possible framework degradation under stimuli-responsive conditions, and (iii) secondary diffusion across the silica shell. The thickness, porosity, and surface chemistry of the silica coating further modulate release rates by altering permeability and interaction strength.

Faaizatunnisa et al. (2022) developed MIL-100(Fe)-silica composites with two distinct architectures (MIL-100(Fe)@SiO_2 and SiO_2@MIL-100(Fe)) to evaluate how structural configuration influences curcumin loading and release behavior. The incorporation of silica enhanced the overall adsorption capacity, achieving up to 97.96% loading at an initial concentration of 30 mg/L; however, partial pore coverage by SiO_2 slightly reduced accessibility to the MIL-100(Fe) internal pores at lower concentrations. Drug adsorption was governed by multiple host–guest interactions, including hydrogen bonding, dipole–dipole, and ion–dipole interactions with silanol groups on silica, as well as coordination and non-covalent interactions within the MIL-100(Fe) framework. Release studies revealed that MIL-100(Fe) exhibited the highest curcumin release at pH 7.4 due to its high surface area and pore volume, whereas silica integration reduced release rates by introducing additional diffusion barriers and stronger interfacial interactions. Under acidic conditions (pH 5.8), MIL-100(Fe) showed accelerated release due to framework degradation, particularly when positioned as the outer shell (SiO_2@MIL-100(Fe)). In contrast, when silica served as a protective outer layer (MIL-100(Fe)@SiO_2), degradation of the MOF core was suppressed, leading to slower, more sustained release. These findings demonstrate that pore accessibility, shell configuration, interfacial interactions, and framework stability collectively govern adsorption efficiency and pH-responsive release kinetics in MOF–silica composite systems [51].

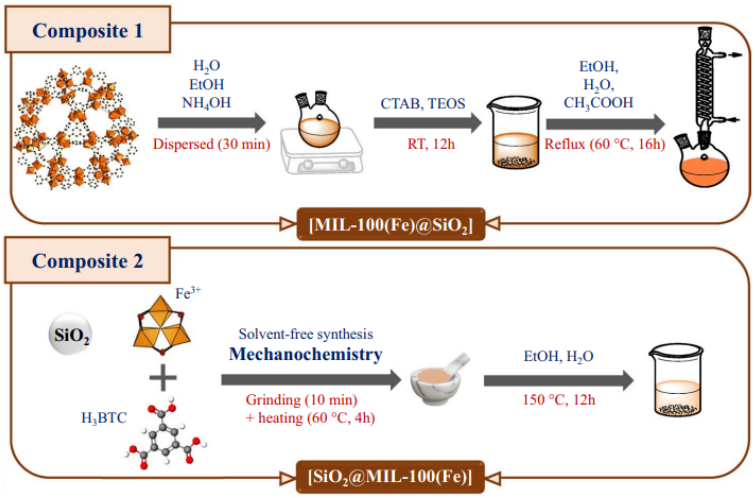

Figure 4. Synthesis scheme of MOF/SiO_2 composites. This figure is reused with permission from ref. [51], © 2022, The Author(s), under exclusive licence to Springer Science Business Media, LLC, part of Springer Nature.

Stimuli-responsive MOF composites have received considerable attention as drug-release systems because they can effectively prevent premature drug leakage. Zeolitic imidazolate frameworks such as ZIF-8, which are synthesized from zinc ions and 2-methylimidazole, represent a prominent class of pH-responsive MOFs. Under physiological pH, ZIF-8 exhibits high structural stability; however, in acidic environments, it readily dissociates. This property makes ZIF-8 highly

suitable for controlled drug loading and release. To construct the DOX/HMS@ZIF-8 composite capsule (Figure 5), Jia et al. (2018) first loaded doxorubicin (DOX) into hollow mesoporous silica (HMS) particles and subsequently coated the HMS surface with a ZIF-8 layer. Under physiological conditions (pH 7.4), DOX encapsulated within HMS@ZIF-8 showed negligible release, whereas a substantial release occurred at pH 5. These findings highlight that HMS@ZIF-8 can function as an efficient pH-responsive drug-delivery platform with favorable cellular compatibility [52].

The in-situ deposition of MOFs on core–shell gold nanorods and mesoporous silica nanoparticles was reported by Guo et al. (2021) as a straightforward strategy to construct multifunctional nanocarriers (GNRs-MSNs). The resulting GNRs-MSNs-MA platform successfully integrates targeted chemo-photothermal therapy with trimodal imaging, including magnetic resonance imaging (MRI), computed tomography (CT), and photoacoustic (PA) imaging, through further surface modification with hyaluronic acid (HA). This approach also enables the direct growth of an MOF shell onto MSN cores containing magnetic or convertible nanoparticles. Importantly, GNRs-MSNs-MA exhibited enhanced drug-loading efficiency and laser-induced drug release upon near-infrared (NIR) irradiation. The in-situ growth of the MOF layer increased the effective surface area and pore complexity, leading to a DOX loading efficiency of 23.56%, compared to 12.87% for the system without the MOF coating. This improvement reflects the contribution of expanded porosity and additional host–guest interaction sites provided by the MOF framework. Drug release studies demonstrated clear pH-responsive behavior, with more than 20% of DOX released within 12 h at pH 5.0, whereas only 9.3% was released at pH 7.4. The accelerated release under acidic conditions was attributed to partial MOF instability and enhanced DOX solubility due to protonation of its daunosamine groups. Furthermore, near-infrared (NIR) irradiation accelerated drug release via the photothermal effect of gold nanorods, thereby enhancing molecular diffusion and weakening drug–matrix interactions. Compared to GNRs-MSNs without MOF integration, the hybrid MOF–silica composite exhibited reduced premature leakage under physiological conditions, demonstrating improved release controllability under biologically relevant conditions [53].

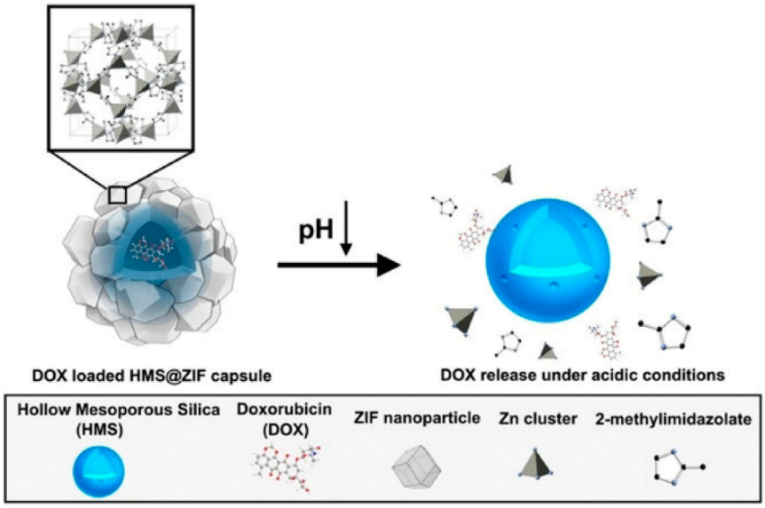

Figure 5. Synthesis scheme of HMS@ZIF-8. The figure is reused with permission from ref. [52], © 2018 Wiley-VCH Verlag GmbH & Co. KGaA, Weinheim.

Chen et al. (2019) developed a hybrid organic–inorganic nanocomposite in which MOFs were effectively integrated with hollow mesoporous organosilica nanoparticles (HMONs) and a polydopamine (PDA) interlayer, forming HMONs-PMOF. The resulting nanostructure exhibited well-defined PMOF architecture templated by HMONs and demonstrated excellent biocompatibility. Doxorubicin (DOX) was independently loaded with high efficiency into both the inner cavity of the HMON core and the porous outer MOF shell. The dual-drug-loaded nanocomposite showed promising photothermal properties and a pH/NIR-triggered DOX release mechanism. Furthermore, in vitro studies confirmed that HMONs-PMOF efficiently delivered DOX into cancer cells [54]. Comparative drug loading and release profiles for these materials are summarized in Table 2.

TABLE II. Comparison of drug-loading capacity and release behavior of MSN- and MOF-based systems for anticancer drug delivery.

Drug Carriers	Drugs	Drug Loading (wt%)	Drug Release (%, hour)	Ref.
MSN	Doxorubicin	48.16	-	[55]
HMSNs	Doxorubicin	112.12	70, 70 h	[55]
MSN	Curcumin	16.45	25, 40 h	[56]
MSN	Quercetin	45.48	25, 72 h	[57]
MIL-100	Curcumin	36.1	20, 72 h	[58]
CuS@ZIF-8	Quercetin	24	45, 48 h	[59]
NH_2-MIL-125	Doxorubicin	55	80, 30 h	[60]
MIL-100(Fe)@SiO_2	Curcumin	97.82	2.5, 5 h	[51]
SiO_2@MIL-100(Fe)	Curcumin	97.96	3.5, 5 h	[51]
HMS@ZIF-8	Doxorubicin	28	71.4, 10 h	[52]
GNRs-MSNs-MA	Doxorubicin	23.56	29, 60 h	[53]
HMONs-PMOF	Doxorubicin	59.4	35, 120 h	[54]

6. CONCLUSIONS

Mesoporous silica nanoparticles (MSNs), metal–organic frameworks (MOFs), and MOF–silica composites represent versatile platforms for advanced drug delivery systems due to their tunable structural and chemical properties. MSNs offer high surface areas, adjustable pore sizes, and facile surface functionalization, enabling effective loading and controlled release of both hydrophilic and hydrophobic drugs. MOFs offer exceptionally high surface areas, customizable pore structures, and diverse chemical functionalities, enabling high drug loading capacities and stimuli-responsive release.

Integrating MOFs with silica to form MOF–silica composites leverage the advantages of both materials, enhancing mechanical stability, dispersibility, biocompatibility, and drug-delivery efficiency. Stimuli-responsive MOF-based and composite systems further allow precise control over drug release in response to environmental triggers, such as pH or near-infrared irradiation. Dual-functional or multifunctional nanocomposites, such as HMONs-PMOF and GNRs-MSNs-MA, demonstrate the potential for combined therapy, targeted delivery, and multimodal imaging, highlighting the versatility of these platforms for personalized medicine.

Overall, MSNs, MOFs, and their composites offer significant promise for the development of next-generation drug delivery systems. Continued optimization of particle size, shape, pore structure, surface functionality, and composite design will be critical to maximize therapeutic efficacy while minimizing off-target effects and toxicity. Future research should focus on improving in vivo performance, biodegradability, and clinical translation potential of these nanocarriers.

References

[1] R. K. Harrison, “Phase II and phase III failures: 2013–2015,” *Nat. Rev. Drug Discov.*, vol. 15, no. 12, pp. 817–818, Dec. 2016, doi: 10.1038/nrd.2016.184.

[2] J. K. Patra *et al.*, “Nano based drug delivery systems: recent developments and future prospects,” *J. Nanobiotechnology*, vol. 16, no. 1, p. 71, Dec. 2018, doi: 10.1186/s12951-018-0392-8.

[3] R. M. Raj and V. Raj, “Polymers in drug delivery and targeting,” in *Handbook of Polymers in Medicine*, Elsevier, 2023, pp. 595–634. doi: 10.1016/B978-0-12-823797-7.00022-8.

[4] M. Sarfraz *et al.*, “Development of Dual Drug Loaded Nanosized Liposomal Formulation by A Reengineered Ethanolic Injection Method and Its Pre-Clinical Pharmacokinetic Studies,” *Pharmaceutics*, vol. 10, no. 3, p. 151, Sep. 2018, doi: 10.3390/pharmaceutics10030151.

[5] J. Li *et al.*, "Galloylated liposomes enable targeted drug delivery by overcoming protein corona shielding," *Nat. Commun.*, vol. 16, no. 1, p. 7926, Aug. 2025, doi: 10.1038/s41467-025-63198-4.

[6] R. J. Sarode and H. S. Mahajan, "Dendrimers for drug delivery: An overview of its classes, synthesis, and applications," *J. Drug Deliv. Sci. Technol.*, vol. 98, p. 105896, Sep. 2024, doi: 10.1016/j.jddst.2024.105896.

[7] A. Chaudhuri *et al.*, "Polymeric micelles: A novel drug delivery system for the treatment of breast cancer," *J. Drug Deliv. Sci. Technol.*, vol. 77, p. 103886, Nov. 2022, doi: 10.1016/j.jddst.2022.103886.

[8] H. Zare *et al.*, "Carbon Nanotubes: Smart Drug/Gene Delivery Carriers," *Int. J. Nanomedicine*, vol. Volume 16, pp. 1681–1706, Mar. 2021, doi: 10.2147/IJN.S299448.

[9] Neha Desai, M. Momin, T. Khan, S. Gharat, R. S. Ningthoujam, and A. Omri, "Metallic nanoparticles as drug delivery system for the treatment of cancer," *Expert Opin. Drug Deliv.*, vol. 18, no. 9, pp. 1261–1290, Sep. 2021, doi: 10.1080/17425247.2021.1912008.

[10] O. A. Saputra, W. N. S, A. Istiqomah, M. R. Kumalasari, M. Irmawan, and F. R. Wibowo, "Advances in Mesoporous Silica Nanoparticles: Synthesis, Characterization, and Biomedical Uses," *IJCA (Indonesian Journal of Chemical Analysis)*, vol. 7, no. 2, pp. 108–131, Sep. 2024, doi: 10.20885/ijca.vol7.iss2.art9.

[11] H. D. Lawson, S. P. Walton, and C. Chan, "Metal–Organic Frameworks for Drug Delivery: A Design Perspective," *ACS Appl. Mater. Interfaces*, vol. 13, no. 6, pp. 7004–7020, Feb. 2021, doi: 10.1021/acsami.1c01089.

[12] V. Pande, S. Kothawade, S. Kuskar, S. Bole, and D. Chakole, "Fabrication of Mesoporous Silica Nanoparticles and Its Applications in Drug Delivery," 2023. doi: 10.5772/intechopen.112428.

[13] X. Lv, L. Zhang, F. Xing, and H. Lin, "Controlled synthesis of monodispersed mesoporous silica nanoparticles: Particle size tuning and formation mechanism investigation," *Microporous and Mesoporous Materials*, vol. 225, pp. 238–244, May 2016, doi: 10.1016/j.micromeso.2015.12.024.

[14] R. Huang *et al.*, "MXene Composite Nanofibers for Cell Culture and Tissue Engineering," *ACS Appl. Bio Mater.*, vol. 3, no. 4, pp. 2125–2131, Apr. 2020, doi: 10.1021/acsabm.0c00007.

[15] R. Narayan, U. Y. Nayak, A. M. Raichur, and S. Garg, "Mesoporous silica nanoparticles: A comprehensive review on synthesis and recent advances," Sep. 01, 2018, *MDPI AG*. doi: 10.3390/pharmaceutics10030118.

[16] Y. D. Chiang, H. Y. Lian, S. Y. Leo, S. G. Wang, Y. Yamauchi, and K. C. W. Wu, "Controlling particle size and structural properties of mesoporous silica nanoparticles using the taguchi method," *Journal of Physical Chemistry C*, vol. 115, no. 27, pp. 13158–13165, Jul. 2011, doi: 10.1021/jp201017e.

[17] E. Juère, R. Caillard, and F. Kleitz, "Pore confinement and surface charge effects in protein-mesoporous silica nanoparticles formulation for oral drug delivery," *Microporous and Mesoporous Materials*, vol. 306, Oct. 2020, doi: 10.1016/j.micromeso.2020.110482.

[18] N. Hao, L. Li, and F. Tang, "Shape matters when engineering mesoporous silica-based nanomedicines," Apr. 01, 2016, *Royal Society of Chemistry*. doi: 10.1039/c5bm00589b.

[19] T. P. S. , and C. C. W. Albanese Alexandre, "The Effect of Nanoparticle Size, Shape, and Surface Chemistry on Biological Systems," *Annu. Rev. Biomed. Eng.*, vol. 14, pp. 1–16, 2012.

[20] N. Varga, M. Benkő, D. Sebők, G. Bohus, L. Janovák, and I. Dékány, "Mesoporous silica core–shell composite functionalized with polyelectrolytes for drug delivery," *Microporous and Mesoporous Materials*, vol. 213, pp. 134–141, Sep. 2015, doi: 10.1016/j.micromeso.2015.02.008.

[21] L. Xiong, X. Du, B. Shi, J. Bi, F. Kleitz, and S. Z. Qiao, "Tunable stellate mesoporous silica nanoparticles for intracellular drug delivery," *J. Mater. Chem. B*, vol. 3, no. 8, pp. 1712–1721, Feb. 2015, doi: 10.1039/c4tb01601g.

[22] Y. He, J. Li, M. Long, S. Liang, and H. Xu, "Tuning pore size of mesoporous silica nanoparticles simply by varying reaction parameters," *J. Non. Cryst. Solids*, vol. 457, pp. 9–12, Feb. 2017, doi: 10.1016/j.jnoncrysol.2016.11.023.

[23] J. Chen *et al.*, "Mesoporous silica nanoparticles: A Synthesis Guide and Research Progress in the Biomedical Field," *Mater. Today Chem.*, vol. 42, p. 102426, Dec. 2024, doi: 10.1016/j.mtchem.2024.102426.

[24] S. Mohanan, X. Guan, M. Liang, A. Karakoti, and A. Vinu, "Stimuli-Responsive Silica Silanol Conjugates: Strategic Nanoarchitectonics in Targeted Drug Delivery," *Small*, vol. 20, no. 39, Sep. 2024, doi: 10.1002/smll.202301113.

[25] V. Mamaeva, C. Sahlgren, and M. Lindén, "Mesoporous silica nanoparticles in medicine—Recent advances," *Adv. Drug Deliv. Rev.*, vol. 65, no. 5, pp. 689–702, May 2013, doi: 10.1016/j.addr.2012.07.018.

[26] C. Argyo, V. Weiss, C. Bräuchle, and T. Bein, "Multifunctional mesoporous silica nanoparticles as a universal platform for drug delivery," Jan. 14, 2014. doi: 10.1021/cm402592t.

[27] S. Wang, C. M. McGuirk, A. d'Aquino, J. A. Mason, and C. A. Mirkin, "Metal–Organic Framework Nanoparticles," Sep. 13, 2018, *Wiley-VCH Verlag*. doi: 10.1002/adma.201800202.

[28] S. Wuttke, M. Lismont, A. Escudero, B. Rungtaweevoranit, and W. J. Parak, "Positioning metal-organic framework nanoparticles within the context of drug delivery – A comparison with mesoporous silica nanoparticles and dendrimers," *Biomaterials*, vol. 123, pp. 172–183, Apr. 2017, doi: 10.1016/j.biomaterials.2017.01.025.

[29] L. Jiao, Y. Wang, H. L. Jiang, and Q. Xu, "Metal–Organic Frameworks as Platforms for Catalytic Applications," Sep. 13, 2018, *Wiley-VCH Verlag*. doi: 10.1002/adma.201703663.

[30] L. He *et al.*, "Recent progress in nanoscale metal-organic frameworks for drug release and cancer therapy," 2019, *Future Medicine Ltd.* doi: 10.2217/nnm-2018-0347.

[31] R. D. Arrua, A. Peristyy, P. N. Nesterenko, A. Das, D. M. D'Alessandro, and E. F. Hilder, "UiO-66@SiO_2 core-shell microparticles as stationary phases for the separation of small organic molecules," *Analyst*, vol. 142, no. 3, pp. 517–524, Jan. 2017, doi: 10.1039/c6an02344d.

[32] N. Yuan, S. Li, and G. Li, "Sodium alginate coated mesoporous silica for dual bio-responsive controlled drug delivery," *J. Drug Deliv. Sci. Technol.*, vol. 46, pp. 348–353, Aug. 2018, doi: 10.1016/j.jddst.2018.05.026.

[33] S. Ehrling, C. Kutzscher, P. Freund, P. Müller, I. Senkovska, and S. Kaskel, "MOF@SiO_2 core-shell composites as stationary phase in high performance liquid chromatography," *Microporous and Mesoporous Materials*, vol. 263, pp. 268–274, Jun. 2018, doi: 10.1016/j.micromeso.2018.01.003.

[34] B. Ma *et al.*, "Electrocatalysis of Cu−MOF/Graphene Composite and its Sensing Application for Electrochemical Simultaneous Determination of Dopamine and Paracetamol," *Electroanalysis*, vol. 31, no. 6, pp. 1002–1008, Jun. 2019, doi: 10.1002/elan.201800890.

[35] L. Peng, S. Yang, D. T. Sun, M. Asgari, and W. L. Queen, "MOF/polymer composite synthesized using a double solvent method offers enhanced water and CO_2 adsorption properties," *Chemical Communications*, vol. 54, no. 75, pp. 10602–10605, 2018, doi: 10.1039/c8cc05428b.

[36] Q. Wu *et al.*, "MOF-derived rambutan-like nanoporous carbon/nanotubes/Co composites with efficient microwave absorption property," *Mater. Lett.*, vol. 244, pp. 138–141, Jun. 2019, doi: 10.1016/j.matlet.2019.02.023.

[37] B. Gao *et al.*, "Hybridization of metal–organic framework and monodisperse spherical silica for chromatographic separation of xylene isomers," *Chin. J. Chem. Eng.*, vol. 27, no. 4, pp. 818–826, Apr. 2019, doi: 10.1016/j.cjche.2018.06.016.

[38] J. Ying *et al.*, "Nanocoating of Hydrophobic Mesoporous Silica around MIL-101Cr for Enhanced Catalytic Activity and Stability," *Inorg. Chem.*, vol. 57, no. 3, pp. 899–902, Feb. 2018, doi: 10.1021/acs.inorgchem.7b01992.

[39] M. M. Abolghasemi, V. Yousefi, and M. Piryaei, "Synthesis of a metal-organic framework confined in periodic mesoporous silica with enhanced hydrostability as a novel fiber coating for solid-phase microextraction," *J. Sep. Sci.*, vol. 38, no. 7, pp. 1187–1193, Apr. 2015, doi: 10.1002/jssc.201400916.

[40] V.-P. Lehto and J. Riikonen, "Drug loading and characterization of porous silicon materials," in *Porous Silicon for Biomedical Applications*, Elsevier, 2014, pp. 337–355. doi: 10.1533/9780857097156.3.337.

[41] Z. Li, Y. Zhang, and N. Feng, "Mesoporous silica nanoparticles: synthesis, classification, drug loading, pharmacokinetics, biocompatibility, and application in drug delivery," *Expert Opin. Drug Deliv.*, vol. 16, no. 3, pp. 219–237, Mar. 2019, doi: 10.1080/17425247.2019.1575806.

[42] F. Baumann, T. Paul, S. Wassersleben, R. Regenthal, D. Enke, and A. Aigner, "Characterization of Drug Release from Mesoporous SiO_2-Based Membranes with Variable Pore Structure and Geometry.," *Pharmaceutics*, vol. 14, no. 6, May 2022, doi: 10.3390/pharmaceutics14061184.

[43] A. Matadamas-Ortiz *et al.*, "Effect of Amine, Carboxyl, or Thiol Functionalization of Mesoporous Silica Particles on Their Efficiency as a Quercetin Delivery System in Simulated Gastrointestinal Conditions," *Foods*, vol. 13, no. 8, p. 1208, Apr. 2024, doi: 10.3390/foods13081208.

[44] W. Y. Zhu *et al.*, "Interface Engineering and Phase Regulation in CoP/$CePO_4$Heterostuctures for Boosting Oxygen Evolution Electrocatalysis," *Energy and Fuels*, vol. 35, no. 20, pp. 16760–16767, Oct. 2021, doi: 10.1021/acs.energyfuels.1c02438.

[45] J. E. Cun *et al.*, "Copper-based metal–organic frameworks for biomedical applications," Jul. 01, 2022, *Elsevier B.V.* doi: 10.1016/j.cis.2022.102686.

[46] M. Sha'at *et al.*, "Development of Modified Drug Delivery Systems with Metformin Loaded in Mesoporous Silica Matrices: Experimental and Theoretical Designs.," *Pharmaceutics*, vol. 17, no. 7, Jul. 2025, doi: 10.3390/pharmaceutics17070882.

[47] A. Nieto, M. Colilla, F. Balas, and M. Vallet-Regí, "Surface electrochemistry of mesoporous silicas as a key factor in the design of tailored delivery devices," *Langmuir*, vol. 26, no. 7, pp. 5038–5049, Apr. 2010, doi: 10.1021/la904820k.

[48] F. Elwinger, P. Pourmand, and I. Furó, "Diffusive Transport in Pores. Tortuosity and Molecular Interaction with the Pore Wall," *The Journal of Physical Chemistry C*, vol. 121, no. 25, pp. 13757–13764, Jun. 2017, doi: 10.1021/acs.jpcc.7b03885.

[49] X. Li *et al.*, "New insights into the degradation mechanism of metal-organic frameworks drug carriers," *Sci. Rep.*, vol. 7, no. 1, p. 13142, Oct. 2017, doi: 10.1038/s41598-017-13323-1.

[50] P. S. Chauhan, M. Kumarasamy, A. M. Carcaboso, A. Sosnik, and D. Danino, "Multifunctional silica-coated mixed polymeric micelles for integrin-targeted therapy of pediatric patient-derived glioblastoma," *Materials Science and Engineering: C*, vol. 128, p. 112261, Sep. 2021, doi: 10.1016/j.msec.2021.112261.

[51] N. Faaizatunnisa, W. W. Lestari, O. A. Saputra, T. E. Saraswati, L. Larasati, and F. R. Wibowo, "Slow-Release of Curcumin Induced by Core–Shell Mesoporous Silica Nanoparticles (MSNs) Modified MIL-100(Fe) Composite," *J. Inorg. Organomet. Polym. Mater.*, vol. 32, no. 5, pp. 1744–1754, May 2022, doi: 10.1007/s10904-022-02230-2.

[52] X. Jia *et al.*, "Hollow Mesoporous Silica@Metal–Organic Framework and Applications for pH-Responsive Drug Delivery," *ChemMedChem*, vol. 13, no. 5, pp. 400–405, Mar. 2018, doi: 10.1002/cmdc.201800019.

[53] H. Guo *et al.*, "In situ formation of metal organic framework onto gold nanorods/mesoporous silica with functional integration for targeted theranostics," *Chemical Engineering Journal*, vol. 403, Jan. 2021, doi: 10.1016/j.cej.2020.126432.

[54] L. Chen *et al.*, "Merging metal organic framework with hollow organosilica nanoparticles as a versatile nanoplatform for cancer theranostics," *Acta Biomater.*, vol. 86, pp. 406–415, Mar. 2019, doi: 10.1016/j.actbio.2019.01.005.

[55] F. Chen *et al.*, "Engineering of hollow mesoporous silica nanoparticles for remarkably enhanced tumor active targeting efficacy," *Sci. Rep.*, vol. 4, May 2014, doi: 10.1038/srep05080.

[56] S. Ghosh, S. Dutta, A. Sarkar, M. Kundu, and P. C. Sil, "Targeted delivery of curcumin in breast cancer cells via hyaluronic acid modified mesoporous silica nanoparticle to enhance anticancer efficiency," *Colloids Surf. B Biointerfaces*, vol. 197, Jan. 2021, doi: 10.1016/j.colsurfb.2020.111404.

[57] O. A. Saputra *et al.*, "Organically surface engineered mesoporous silica nanoparticles control the release of quercetin by pH stimuli," *Sci. Rep.*, vol. 12, no. 1, p. 20661, Nov. 2022, doi: 10.1038/s41598-022-25095-4.

[58] Y. Zhang *et al.*, "Engineering Metal-Organic Frameworks for Photoacoustic Imaging-Guided Chemo-/Photothermal Combinational Tumor Therapy," *ACS Appl. Mater. Interfaces*, vol. 10, no. 48, pp. 41035–41045, Dec. 2018, doi: 10.1021/acsami.8b13492.

[59] W. Jiang *et al.*, "CuS@MOF-Based Well-Designed Quercetin Delivery System for Chemo-Photothermal Therapy," *ACS Appl. Mater. Interfaces*, vol. 10, no. 40, pp. 34513–34523, Oct. 2018, doi: 10.1021/acsami.8b13487.

[60] A. Rengaraj *et al.*, "Porous NH_2-MIL-125 as an efficient nano-platform for drug delivery, imaging, and ROS therapy utilized Low-Intensity Visible light exposure system," *Colloids Surf. B Biointerfaces*, vol. 160, pp. 1–10, Dec. 2017, doi: 10.1016/j.colsurfb.2017.09.011.