Advancing Drug Delivery through Metal-Organic Frameworks

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Abstract. Metal–organic frameworks (MOFs) have emerged as promising platforms for drug delivery owing to their high porosity, tunable structures, and multifunctional design. Built from metal nodes and organic linkers, MOFs offer exceptionally high drug loading capacities and controllable release behaviours that outperform many conventional nanocarriers. Their modular nature enables precise adjustment of pore size, surface chemistry, and degradation properties, allowing improved drug stability, reduced premature release, and enhanced therapeutic efficacy. This review summarizes recent advances in MOF-based drug delivery systems, focusing on framework design, drug loading strategies, and surface engineering approaches that improve biocompatibility and targeting. Fundamental host–guest interactions and release mechanisms, including diffusion-controlled and stimuli-responsive pathways triggered by pH, redox conditions, or external stimuli, are discussed. Additionally, the ability of MOFs to deliver a diverse range of therapeutic agents, including small-molecule drugs, biomacromolecules, and gasotransmitters, is highlighted. Finally, key challenges related to in vivo stability, biodegradation, scalable manufacturing, and regulatory translation are outlined, together with perspectives on the future development of MOF-based nanomedicines.

1 Introduction

1.1 What is MOF

Given these unmet needs, materials with high tunability and exceptional loading capacity are required—features that are intrinsic to metal-organic frameworks (MOFs). MOFs are crystalline hybrid materials formed via the self-assembly of metal-containing nodes (secondary building units, SBUs) and multitopic organic linkers. This modular construction yields a vast, designable, and porous network. Since their popularization in the late 1990s, thousands of MOFs with diverse structures and properties have been developed, primarily for applications in gas storage and separation. More recently, their potential in biomedicine has been vigorously explored, driven by the unique structural advantages they offer for therapeutic delivery.

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1.2 Suitability for biomedical applications

The remarkable properties of MOFs stem directly from their hybrid composition and crystalline porous architecture, conferring several distinct advantages for drug delivery as shown in Fig. 1. High Porosity and Surface Area: MOFs possess record-high surface areas, often exceeding 6000 m^2/g. This extensive porosity directly translates to exceptionally high drug loading capacities, unmatched by most other nanocarriers like liposomes or mesoporous silica.

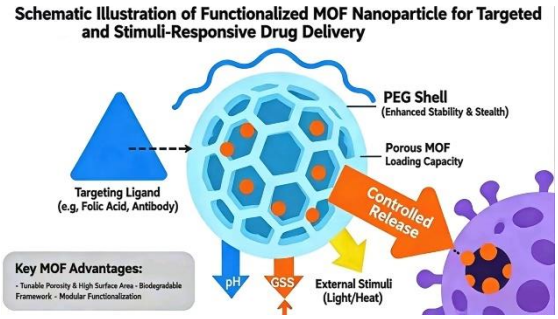

Fig. 1. Schematic illustration of functionalized MOF nanoparticle for targeted and stimuli-responsive drug delivery.

Tunable Pore Size and Functionality: Pore dimensions can be precisely adjusted by selecting linkers of different lengths, allowing for the accommodation of specific therapeutic molecules. Furthermore, organic linkers can be pre- or post-synthetically functionalized to tailor the chemical environment within the pores, thereby optimizing host-guest interactions for enhanced drug loading and controlled release.

Biodegradability: Unlike many non-degradable inorganic nanoparticles, certain MOFs can be designed to decompose under physiological conditions, releasing their cargo and minimizing long-term accumulation. This programmable degradation is a critical safety feature for clinical translation.

2 Design and synthesis of MOFs for drug delivery

To translate the inherent advantages of Metal-Organic Frameworks (MOFs) into effective drug delivery systems (DDSs), rational design and synthesis that prioritize biocompatibility and functionality are paramount. The strategic construction of an MOF-based delivery platform generally involves three coordinated fundamental aspects: the selection of biocompatible framework components, the implementation of efficient drug loading strategies, and tailored surface functionalization, all aimed at ensuring colloidal stability, targeted delivery, and controlled therapeutic efficacy. The initial choice of the framework is critical, with several well-established classes of bio-relevant MOFs forming the cornerstone of current research. These prominently include iron-based MOFs (e.g., MIL-100(Fe), MIL-101(Fe)) known for their low toxicity and biodegradability [1]; zirconium-based MOFs (e.g., UiO-66, UiO-67) valued for exceptional chemical stability; zinc-based frameworks such as Zeolitic Imidazolate Framework-8 (ZIF-8), popular for their ease of synthesis and pH-responsive degradation [2]; and Bio-MOFs constructed from endogenous building blocks like metal ions (e.g., Ca^{2+}) and biomolecules (e.g., adenine), which are designed for enhanced biocompatibility [3]. The selection among these materials establishes the foundation for subsequent drug loading and surface engineering steps.

2.1 Surface engineering

The design of an effective MOF-based drug delivery platform requires the integrated optimization of both internal drug incorporation and external surface properties, as these factors collectively govern loading capacity, release kinetics, colloidal stability, and *in vivo* biodistribution (Table 1). Drug loading is primarily achieved through three strategic pathways, each imparting distinct characteristics. Encapsulation during synthesis (one-pot method) involves co-precipitating the drug molecules with the MOF precursors, potentially entrapping them within the evolving framework; this method is advantageous for loading fragile biomolecules under mild conditions but may be limited by compatibility with the synthesis environment. The more prevalent post-synthetic loading (diffusion/impregnation) leverages the porous architecture of pre-formed, activated MOFs, where drugs diffuse into the pores from a concentrated solution, offering high loading efficiency and broad applicability. Alternatively, covalent or coordinative post-synthetic modification chemically grafts therapeutic molecules onto the organic linkers or metal clusters of the MOF, which typically provides a stronger, stimulus-responsive release profile compared to physical encapsulation. Concurrently, surface engineering is crucial for translating high drug payloads into therapeutic efficacy *in vivo*. The native surface of MOF nanoparticles often requires modification to prevent aggregation, evade immune clearance, and achieve targeted delivery. Common strategies include coating with hydrophilic polymers, such as polyethylene glycol (PEGylation), to enhance stealth properties and prolong the circulation half-life, or functionalizing with specific targeting ligands (e.g., folic acid, peptides, antibodies) that recognize receptors overexpressed on target cells, thereby promoting selective cellular uptake [4]. While surface engineering critically determines the biological trajectory and targeting capability of the carrier, the internal drug loading mechanism and the host-guest interactions within the pores remain the core determinants of the system's drug release function and capacity. The following section, therefore, delves into the fundamental interactions and kinetics that govern drug retention and controlled release from MOF matrices.

Table 1. Representative MOFs for Drug Delivery.

MOF	Metal node	Pore size	Drug type	Stimulus	Advantage
ZIF-8	Zn^{2+}	~11 Å	DOX / protein	pH	Acid-responsive
MIL-101(Fe)	Fe^{3+}	29–34 Å	Small molecules	Diffusion	High loading
UiO-66	Zr^{4+}	~6 Å	Cisplatin	Stability	High chemical stability

3 Drug loading mechanisms and controlled release kinetics

Although surface engineering is indispensable for optimizing in vivo performance, the core functionality of a drug delivery system is dictated by the internal drug loading and release mechanisms. The following section examines the fundamental drug–MOF interactions that govern encapsulation and controlled release behaviour. Pivotal as surface engineering may be, the intrinsic mechanisms governing drug loading and release are paramount for DDS efficacy. Accordingly, the subsequent analysis will address these fundamental processes. The efficacy of a MOF-based DDS is governed by a sequence of critical events: how the drug is loaded, how it is released, how that release is controlled, and finally, how the carrier behaves in vivo. This section examines these aspects in detail.

3.1 Encapsulation pathways and host-guest interactions

The selection of a drug-loading strategy directly determines the host-guest interactions between the drug and the porous carrier, which subsequently govern the drug release profile and pharmacokinetic behaviour. Drug loading primarily occurs through physical adsorption via non-covalent interactions—such as van der Waals forces, π–π stacking, or hydrogen bonding—or through direct coordination to unsaturated metal sites within the framework, forming stronger bonds that often require specific stimuli for release. The resulting drug-release behaviour is governed by the nature of these loading interactions. Drugs loaded by physical adsorption generally exhibit passive diffusion or sustained release, influenced by the local microenvironment. In contrast, drugs bound via coordination chemistry typically demonstrate stimuli-responsive release, activated by endogenous factors such as pH variation, redox potential, or enzyme activity, as well as exogenous triggers like light, heat, or ultrasound. Release kinetics can be finely modulated through rational material design. By adjusting the framework's composition, pore size, surface properties, or the incorporation of stimuli-responsive polymers, the system can be programmed to achieve zero-order, pulsatile, or on-demand release patterns tailored to specific therapeutic needs. Upon administration, the in vivo fate of the drug is influenced by carrier properties and physiological conditions. Parameters such as particle size, surface charge, and functionalization affect circulation time, biodistribution, and targeting efficiency. Ultimately, the pharmacological efficacy is determined by the drug's absorption, distribution, metabolism, and excretion (ADME), where controlled release plays a critical role in maintaining effective drug concentrations at the target site while minimizing systemic exposure and adverse effects.

3.2 Release kinetics and mathematical models

The release profile is crucial for therapeutic efficacy. It is often governed by diffusion and can be modelled using established equations such as the Higuchi model (for matrix systems) and the Korsmeyer-Peppas model, which helps determine the underlying release mechanism (Fickian diffusion or polymer relaxation) [5]. Zero-order and first-order kinetics models are also applied to describe constant release and concentration-dependent release, respectively. Understanding this kinetics is foundational for designing the stimuli-responsive systems discussed next. Table 2 provides a conceptual classification based on representative literature reports and is intended to summarize general drug–MOF loading and release mechanisms.

Table 2. Drug Loading Strategies and Release Mechanisms.

Strategy	Interaction	Release control	Pros	Cons
One-pot	Physical entrapment	Degradation	Mild conditions	Limited compatibility
Post-loading	Adsorption	Diffusion	High versatility	Burst release risk
Covalent	Coordination	Stimuli	Precise control	Complex synthesis

3.3 Stimuli-responsive ("smart") RELEASE SYSTEMS

MOFs excel as platforms for stimuli-responsive delivery, releasing their payload only upon encountering a specific biological trigger. This "smart" release enhances specificity and minimizes off-target effects.

pH-Triggered: The acidic microenvironment of tumor tissues (pH ~6.5) or endo/lysosomes (pH ~5.0) can degrade acid-labile MOFs like ZIF-8, leading to controlled drug release [2].

Redox-Triggered: The high concentration of glutathione (GSH) in cancer cells can break disulfide bonds or reduce metal nodes, triggering the release of encapsulated drugs.

Other Triggers: Exogenous stimuli like light, temperature, or magnetic fields can also be used to remotely control drug release from appropriately designed MOF composites.

3.4 Biocompatibility, degradation, and in vivo behaviour

Beyond sophisticated release mechanisms, the ultimate clinical success of MOF DDSs hinges on their safety profile and fate within the body. The ultimate clinical success of MOF DDSs hinges on their safety profile. Hydrolysis is the primary degradation pathway, influenced by pH, ligand-metal bond stability, and the biological milieu. The metabolic fate of the metal ions and organic linkers must be carefully evaluated. Studies on in vivo circulation and biodistribution show that size, surface charge, and coating significantly influence pharmacokinetics and tumor accumulation via the Enhanced Permeability and Retention (EPR) effect [6].

4 Delivery of diverse therapeutic agents

The versatility of metal-organic frameworks (MOFs) extends beyond sophisticated release mechanisms to the broad spectrum of therapeutic agents they can encapsulate and deliver, thereby demonstrating their exceptional potential as a universal delivery platform. Their structural and chemical tunability allows for the precise accommodation of agents varying dramatically in size, polarity, and stability, addressing key challenges in modern therapeutics.

4.1 Chemotherapeutic small molecules

Conventional chemotherapeutic drugs often suffer from poor solubility, rapid clearance, and severe off-target toxicity. MOFs offer an effective strategy to overcome these limitations. Doxorubicin and cisplatin have been successfully loaded into porous MOFs like MIL-100 and UiO-66, showing enhanced efficacy and reduced side effects in cancer models due to improved tumor accumulation and controlled release [1]. Beyond these classic examples, other chemotherapeutic agents such as 5-fluorouracil, gemcitabine, and camptothecin have also been incorporated into various MOF matrices (e.g., ZIF-8, MIL-101), demonstrating improved pharmacokinetics and therapeutic outcomes [7]. The high surface area and porosity of MOFs allow for substantial drug payloads, while their surface functionality can be tailored for targeted delivery.

4.2 Biomacromolecules

The delivery of sensitive biomacromolecules—including proteins, peptides, and nucleic acids (DNA, siRNA)—is particularly challenging due to their susceptibility to enzymatic degradation and rapid in vivo clearance. The large, tailorable pores and protective microenvironments of some MOFs can shield these fragile cargoes. For instance, CRISPR-Cas9 machinery has been efficiently delivered using nanoscale MOFs (NMOFs) for gene editing applications [8]. Furthermore, MOFs have shown promise in the delivery of therapeutic antibodies, vaccines, and enzymes. A notable example is the use of zeolitic imidazolate framework-8 (ZIF-8) to encapsulate and preserve the activity of proteins under

harsh conditions, facilitating their cytosolic delivery for intracellular therapeutic applications [9]. The controlled decomposition of MOFs in the cellular environment enables the efficient and timely release of these large biomolecules.

4.3 Gasotransmitters

Gaseous signaling molecules, or gasotransmitters, such as nitric oxide (NO), carbon monoxide (CO), and hydrogen sulfide (H_2S), play crucial roles in physiological and pathological processes but are extremely difficult to store, target, and administer in a controlled manner. MOFs provide an ideal solution by acting as porous sponges that can adsorb and stabilize large quantities of these gases within their frameworks. The gas molecules can then be released in a controlled manner via stimuli-responsive decomposition of the MOF or through ligand displacement reactions. For example, nitric oxide (NO) donors have been integrated into MOF pores, enabling sustained, localized release for antibacterial applications or vasodilation [10]. Recent advances also explore the use of MOFs for the delivery of CO and H_2S, offering new avenues for treating inflammation, ischemia-reperfusion injury, and cardiovascular diseases.

5 Conclusion

Despite the exciting progress, significant hurdles remain. The translation of these promising laboratory findings into clinically viable products faces several key challenges.

5.1 Stability, degradation, and toxicity

A comprehensive understanding of the *in vivo* stability profile, degradation pathways, and systemic biocompatibility of MOFs is paramount. While many MOFs, particularly those based on endogenous metals like iron or zinc, demonstrate favourable short-term toxicity profiles, their long-term fate requires rigorous investigation. Key concerns include the potential for accelerated or incomplete degradation in specific biological microenvironments (e.g., the acidic tumor niche), the pharmacokinetics and clearance routes of both metal ions and organic linkers, and the chronic biological impact of their accumulation in reticuloendothelial system organs. Furthermore, the potential immunogenicity of certain MOF structures or their degradation products must be systematically evaluated, as unintended immune activation or suppression could significantly affect therapeutic efficacy and safety. Consequently, extensive long-term toxicological studies are indispensable.

5.2 Manufacturing scalability and regulatory considerations

The reproducible, cost-effective, and large-scale synthesis of clinical-grade MOFs under Good Manufacturing Practice (GMP) standards presents a formidable barrier. Many laboratory-scale synthesis protocols involve organic solvents, extreme conditions, or complex purification steps that are unsuitable for industrial-scale production. Ensuring batch-to-batch consistency in critical quality attributes—such as particle size, porosity, drug loading efficiency, and surface chemistry—is exceptionally challenging for nanoscale coordination polymers. Moreover, the regulatory pathway for MOF-based therapeutics is nascent and complex. Regulatory agencies like the FDA and EMA have limited precedent for evaluating such hybrid inorganic-organic materials, raising questions regarding their classification, the required characterization dossier, and the appropriate benchmarks for

demonstrating quality, safety, and efficacy. Addressing these challenges necessitates close collaboration between chemists, engineers, and regulatory scientists from an early stage.

5.3 Future directions

Looking ahead, emerging research trends are pushing the boundaries of functionality. One promising direction is the development of bioactive or theranostic MOFs**,** where the framework itself is integral to the therapy. Examples include MOFs constructed from therapeutic metal ions (e.g., Gd^{3+} for imaging and therapy, Zn^{2+} for antibacterial action) or linkers with pharmacological activity, and frameworks designed for sustained *in situ generation* of therapeutic agents like reactive oxygen species. Another vibrant area is the creation of sophisticated hybrid or composite systems, such as MOF-polymer core-shell structures for enhanced stealth and stability, MOF-inorganic nanoparticle composites for multimodal imaging and therapy, and MOF-coated implants or devices. Successfully addressing the fundamental challenges of stability, scalability, and safety will be the critical enabler that paves the way for these next-generation, intelligent, and multifunctional material platforms to transition from the laboratory bench to the patient's bedside.

MOFs represent a highly versatile and promising class of materials for advanced drug delivery. Their superior drug loading capacity, tunability, and potential for multifunctionality position them at the forefront of nanomedicine research. While challenges in biocompatibility, scalable manufacturing, and regulatory approval are non-trivial, the continuous advancements in the design of safer, smarter, and more effective MOF-based systems provide a strong and optimistic outlook for their future clinical translation.

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