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Metal–Organic Frameworks for Drug Delivery: Recent Advances, Challenges and Future Perspectives

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Abstract: Metal–Organic Frameworks (MOFs) have emerged as one of the most promising classes of porous materials for advanced drug delivery owing to their exceptionally high surface areas, tunable pore architectures, structural diversity, and versatile surface chemistry. These characteristics enable efficient drug encapsulation, controlled release, and the development of multifunctional therapeutic platforms. In recent years, substantial progress has been achieved in the rational design of MOFs with tailored physicochemical properties, resulting in improved drug-loading capacity, enhanced physiological stability, and greater therapeutic efficacy compared with many conventional delivery systems. This review provides a comprehensive and up-to-date analysis of MOF-based drug delivery systems, with particular emphasis on the relationships between synthesis strategies, structural characteristics, drug-loading mechanisms, and therapeutic performance. Various fabrication approaches, including conventional and advanced synthesis methods, are discussed alongside one-pot and post-synthetic drug-loading techniques. Particular attention is devoted to the influence of pore structure, surface functionality, particle size, and framework composition on drug encapsulation efficiency and release behavior. Recent advances in stimuli-responsive and multifunctional MOFs capable of responding to pH, redox conditions, enzymes, light, magnetic fields, and other biological triggers are also critically examined.

Keywords: drug delivery, nanocarrier, metal organic frameworks drug release, drug loading.

Introduction

In recent decades, remarkable advances in nanotechnology have provided novel approaches to overcome the limitations of traditional drug delivery. Many effective drugs for the treatment of chronic and intractable diseases such as cancer, resistant infections, or neurological disorders fail in clinical trials due to poor bioavailability, high systemic toxicity, and lack of targeted delivery [1]. Meanwhile, the use of nanoscale carriers with controllable properties, such as liposomes, polymeric nanoparticles, and mesoporous silicas, has opened new horizons in the design of smart drug-delivery systems. However, each of these systems still faces challenges such as limited loading capacity, poor stability, or biodegradability problems [2].

Metal–Organic Frameworks (MOFs), as a group of hybrid materials with porous three-dimensional networks composed of metal ions or clusters and organic ligands, have rapidly become the focus of biomedical research in recent years. The unique properties of MOFs in having very high specific surface area, tunable pore size and volume, and chemical flexibility have made them an ideal platform for loading a variety of pharmaceutical and bioactive molecules [3]. Furthermore, the ability to engineer surfaces and intelligently select metals and ligands allows the design of systems that respond to biological or environmental stimuli such as changes in pH, light, temperature, and the presence of enzymes; thus, drug release can occur in a targeted manner in the pathological environment (such as the tumor microenvironment or inflamed tissues). In recent years, several studies have shown that the use of MOFs such as ZIF-8, UiO-66, and MIL-100 not only improves the rate and efficiency of drug loading, but also increases the stability and time-controlled release [4]. These properties, together with the ability to biodegrade and reduce toxicity when the metal components and ligands are properly selected, have pushed the prospect of using MOFs towards clinical applications. In addition to chemotherapy

drug delivery, recent research focuses on the integration of these materials into theranostic systems, gene transfer, and protein delivery, which could lead to the realization of personalized therapies.

Despite these advances, the path to clinical translation of MOFs still faces significant obstacles, such as reproducibility of synthesis, accurate biocompatibility assessment, long-term effects of consumable metals, and drug regulatory constraints. Hence, a comprehensive assessment of recent advances, existing challenges, and future directions in the design and application of MOFs for targeted drug delivery is essential for the development of this emerging technology [5,6]. The present article aims to analytically review these aspects, compare the performance of MOFs with other nanocarriers, and outline future prospects for their commercialization and clinical utilization. Table 1 shows other names of ligands used in the construction of MOFs.

Table 1. Names of some ligands used in the preparation of MOFs

Abbreviated name	full name	Type of ligand	Related famous MOFs
BDC	1,4-Benzenedicarboxylic acid (Terephthalic acid)	Dicarboxylic	MOF-5, UiO-66, MIL-53, MIL-101
BTC	1,3,5-Benzenetricarboxylic acid (Trimesic acid)	Tricarboxylic	HKUST-1 (Cu-BTC), MIL-100
BPDC	4,4'-Biphenyldicarboxylic acid	Dicarboxylic	UiO-67, MOF-177
ABTC	3,3',5,5'-Azobenzenetetracarboxylic acid	Tetracarboxylic	PCN-250, Fe-soc-MOF
BTB	1,3,5-Tris(4-carboxyphenyl)benzene	Tricarboxylic	MOF-177, MOF-205
NDC	2,6-Naphthalenedicarboxylic acid	Dicarboxylic	UiO-68, DUT-4
Imidazolate	Imidazolate / 2-Methylimidazolate	Nitrogenous (azole)	ZIF-8, ZIF-67
BPy	4,4'-Bipyridine	Nitrogenous (dipyridine)	Many mixed-ligand MOFs
FDA	2,5-Furandicarboxylic acid	Dicarboxylic	Some aliphatic/heterocyclic MOFs
TCPP	Tetrakis(4-carboxyphenyl)porphyrin	Tetracarboxylic (porphyrin)	PCN-222, MOF-525

To address the breadth of topics in the initial version and to improve the analytical depth, this review focuses primarily on the critical aspects governing the performance and translational limitations of MOF-based drug-delivery systems, with particular emphasis on stability, structure–function relationships, and biological barriers.

Structure and properties of MOFs

Metal–Organic Frameworks (MOFs) are crystalline porous structures formed by the coordination of metal ions or clusters with multidentate organic ligands. Due to their unique physicochemical properties, such as exceptionally high specific surface areas (ranging from 1,000 to 10,000 m^2/g) and tunable pore sizes, they have attracted significant attention from researchers [7]. The structure of these materials is based on two main components: the Primary Building Unit (PBU), where metal ions (such as Cr^{3+}, Fe^{3+}, Cu^{2+}, and Zn^{2+}) and organic ligands (including sulfonate, amine, phosphate, nitrile, and carboxylate groups) act as building blocks, and the coordination number of the metals (ranging from 2 to 7) leads to the formation of diverse geometric shapes such as tetrahedral, square planar, linear, octahedral, pyramidal, and square pyramidal. Fig 1 shows the general structure of MOFs. Additionally, the Secondary Building Unit (SBU) plays a key role in determining the final topology and geometry of the network; these units typically possess rigid, polyhedral structures, and their use results in frameworks with very high mechanical and chemical stability [8,9]. Finally, the strength of the coordination bonds between these components can be explained based on the "Hard and Soft Acids and Bases" (HSAB) principle: soft metal ions (such as Mn^{2+}, Cu^{2+}, Zn^{2+}, Ag^{+}, and Ni^{2+}) tend to interact more readily with soft ligands (such as azolates with high pKa), whereas hard metal ions (such as Al^{3+}, Fe^{3+}, Zr^{4+}, and Cr^{3+}) bond with harder ligands (such as carboxylates with low pKa), thereby offering better chemical stability. Stability is the most critical factor in the design and application of MOFs and is directly dependent on the strength of the bond between the metal and the ligand. It encompasses four key aspects: chemical stability, which is enhanced by using high-valence metal ions and soft ligands, or by combining nitrogen heterocycles with softer metals [10], where strong metal-nitrogen or metal-oxygen bonds lead to excellent stability in aqueous environments; thermal stability, which improves with higher metal center valences and the use of oxy-anionic linkers, resisting the breaking of the node bond and ligand combustion; hydrothermal stability, which involves resistance to moisture at high temperatures and is enhanced by intermolecular or intramolecular forces, hydrophobic functional groups, and cross-linked bonds in the structure; and mechanical stability, which is directly related to the porous structure but typically decreases as porosity increases, requiring a precise balance between porosity and structural strength.

Biocompatibility, biodegradability, and functionalization are key characteristics of Metal–Organic Frameworks (MOFs) that play a vital role in their biological and medical applications. The biocompatibility of MOFs primarily depends on the type of metal ions and organic ligands used in their structure; specifically, the use of biologically relevant metals such as iron (Fe^{3+}), calcium (Ca^{2+}), magnesium (Mg^{2+}), and zinc (Zn^{2+}), combined with natural or derived ligands (such as amino acids, vitamins, and peptides), leads to reduced cytotoxicity and enhanced compatibility with living systems [11]. In contrast, MOFs based on heavy metals or toxic ligands may require surface coating or modification to prevent adverse immune responses. On the other hand, the controlled biodegradability of these materials in physiological environments (such as the acidic pH of tumors or the presence of specific enzymes) enables the gradual and targeted release of drugs or therapeutic agents, a process typically occurring through the hydrolysis of coordination bonds or the degradation of pH- and enzyme-sensitive ligands. Finally, functionalization refers to the possibility of chemically modifying the surface or the interior pores of MOFs with various functional groups (such as hydroxyl, amine, thiol groups [12,13], or targeting ligands like antibodies and aptamers), which not only improves stability and biocompatibility but also facilitates precise cellular targeting, enhanced water solubility, and increased therapeutic efficacy. Together, these three features transform MOFs into ideal candidates for smart drug delivery, medical imaging, and tissue engineering. Table 2 provides an overview of the MOF type, specific surface area, pore size, drug delivery agents, and cells/animals tested.

Table 2. Summary of the MOF type, surface area, pore size, agents delivered, and cells/animals tested for drug delivery [14].

MOF	Surface area (m^2/g)	Pore size (Å)	Drug	Loading (%)	Cell/Model
ZIF	1300	12	DOX, CPT	–	MCF-7, MDA-MB-468, B16F10
MIL-100	1800	25-29	ICG, BT	–	MCF-7, 661W
PCN-333	4000	42-55	Tyrosinase	–	RPMI-1640
UiO-66	1200	8-12	TAMRA-DNA	–	HeLa
MIL-53(Fe)	–	8.6	IBU	22	–
UiO-66-NH_2	–	100 nm	5-FU	3.1	–
MIL-88@ZIF-8	–	1.3 nm	DOX/ICG	21.69/3.58	–
MOF-74-Zn	–	12.7	IBU	50	–

Although higher surface area and larger pore volume are generally considered beneficial for drug loading, the data presented in Table 2 demonstrate that these parameters alone do not determine loading efficiency or therapeutic performance. For example, PCN-333 possesses a remarkably high BET surface area (~4000 $m^2\ g^{-1}$) and large pore sizes (42-55 Å), suggesting excellent cargo accommodation capability. However, several studies have reported that drug loading and release behavior are also strongly influenced by host-guest interactions, framework stability, surface chemistry, and the physicochemical properties of the therapeutic agent [15,16].

Similarly, ZIF-based materials exhibit considerably lower surface areas than PCN-333, yet they remain among the most extensively investigated drug delivery platforms. The mentioned observation highlights that pH-responsive degradation, facile synthesis, and favorable cellular uptake can compensate for lower porosity. Furthermore, direct comparison among studies remains challenging because drug loading efficiencies are often determined using different analytical methods, drug concentrations, loading protocols, and release media. Consequently, variations reported in the literature may not solely reflect intrinsic material properties but also differences in experimental design.

Another important consideration is that larger pore sizes do not always guarantee superior performance. While large pores facilitate encapsulation of macromolecules, they may also lead to premature drug leakage and reduced control over release kinetics [17]. Conversely, materials with smaller pores may provide stronger confinement effects and more sustained release profiles. Therefore, an optimal balance between pore architecture, framework stability, and drug-framework interactions is required for efficient drug delivery applications.

The drug loading efficiencies summarized in Table 2 exhibit substantial variability, ranging from 3.1% for 5-FU loaded UiO-66-NH_2 to 50% for ibuprofen loaded MOF-74-Zn. These differences indicate that drug loading capacity cannot be solely predicted from pore size or particle dimensions. Instead, loading performance is governed by a combination of structural and physicochemical factors, including pore accessibility, surface functionality, framework-drug interactions, drug molecular size, polarity, and loading methodology. For example, despite the excellent chemical stability and biocompatibility of UiO-66-NH_2, its reported loading efficiency for 5-FU is relatively low (3.1%). This may be attributed to limited host-guest interactions and restricted pore accessibility under the experimental conditions employed [18,19]. In contrast, MOF-74-Zn demonstrates substantially higher ibuprofen loading, likely due to favorable interactions between the drug molecules and the open metal sites present within the framework. The dual-drug delivery system MIL-88@ZIF-8 further illustrates

the influence of drug properties on encapsulation behavior. In the same carrier, the loading efficiency of DOX (21.69%) is considerably higher than that of ICG (3.58%), suggesting that molecular structure, charge distribution, hydrophobicity, and affinity toward the framework play important roles in determining loading performance. It is also important to note that direct comparison among studies should be approached cautiously. Reported loading efficiencies are often affected by differences in synthesis procedures, activation methods, drug concentration, solvent systems, loading duration, and quantification techniques [20]. Therefore, the wide variation observed in the literature reflects not only intrinsic differences among MOFs but also the lack of standardized experimental protocols. This limitation complicates cross-study comparisons and remains a significant challenge for the translation of MOF-based drug-delivery systems toward clinical applications [21,22].

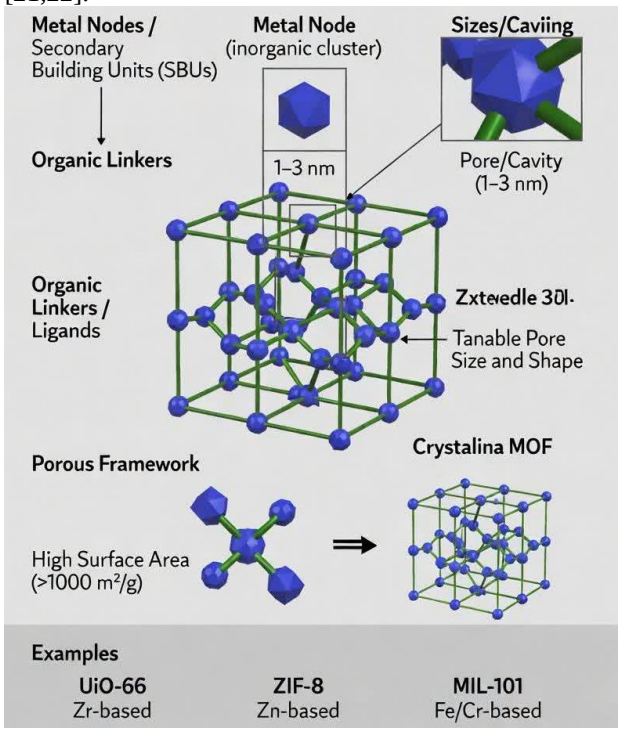

Fig 1. General structure of metal-organic frameworks (MOFs).

Synthesis of MOFs

The synthesis of Metal–Organic Frameworks necessitates the precise assembly of metal ions/clusters and organic linkers to achieve the desired network topology and resulting properties. Generally, synthetic strategies can be categorized into two fundamental approaches: top-down and bottom-up techniques. Top-down methods involve the chemical dismantling of a pre-existing MOF structure into smaller units, followed by their subsequent reassembly into a novel architecture [23, 24]. Conversely, the bottom-up approach relies on the self-assembly of individual metal ions/clusters and organic ligands to directly construct the coordination compound or complex structure [25]. The bottom-up strategy often affords superior control over the final structural features and physicochemical characteristics of the resulting MOF, making it the preferred route when precise assembly control is paramount [26, 27].

The outcome of the synthesis is fundamentally governed by a complex interplay of numerous reaction parameters. These critical factors include reaction time and temperature, the nature and concentration of the metal ions and organic ligands, the solvent system employed, the size and structural characteristics of the nodes, the presence of counterions, and the crystallization kinetics (which dictates nucleation and subsequent crystal growth).

The predominant method for MOF synthesis remains the liquid-phase reaction, where solutions of the metal salt and the organic ligand are mixed. The selection of the solvent is crucial, as it influences the reaction thermodynamics, activation energy, as well as the inherent reactivity and solubility of the precursors. Most commonly, MOFs are prepared under solvo(hydro)thermal conditions, involving high temperature and pressure—often referred to as the 'classic' method. To facilitate the growth of high-quality single crystals, techniques such as the slow evaporation of the reaction solution are frequently utilized.

However, driven by the need for sustainability, cost-effectiveness, and faster throughput, several alternative synthetic methodologies have gained prominence in recent years. These items include mechanochemical, electrochemical, microwave-assisted, and sono-chemical methods. These modern techniques often result in lower energy consumption, reduced reaction times, and cleaner products with fewer byproducts (Fig 2) [28, 29], although difficulties in single-crystal growth have sometimes been noted with solid-state variations.

Slow Evaporation and Diffusion Methods

Both procedures are typically carried out at the room temperature and do not require external heating. In the slow evaporation approach, reagent solutions are mixed and maintained under conditions that allow gradual solvent loss. As the concentration increases to a critical level, nucleation becomes favorable and crystal growth proceeds. To shorten the process, solvents with lower boiling points are often employed [30,31].

In the diffusion method, the reagent solutions are layered on top of one another, separated by a solvent gap, or they are brought into contact gradually through physical diffusion barriers. In some cases, gels are used as the medium to enable controlled diffusion and crystallization. Crystals form mainly at the interface between layers, where the precipitating solvent diffuses gradually into the adjacent compartment, leading to supersaturation and

subsequent framework formation [32]. This technique is particularly useful when the target products exhibit low solubility.

For example, MOF-5 (or IRMOF-1), with the approximate formula (where = 1,4-benzenedicarboxylate), was synthesized by diffusing Et3N into a solution of and in dmf/chlorobenzene, along with a small amount of hydrogen peroxide to promote the formation of species that can bind at the core of the SBU [33].

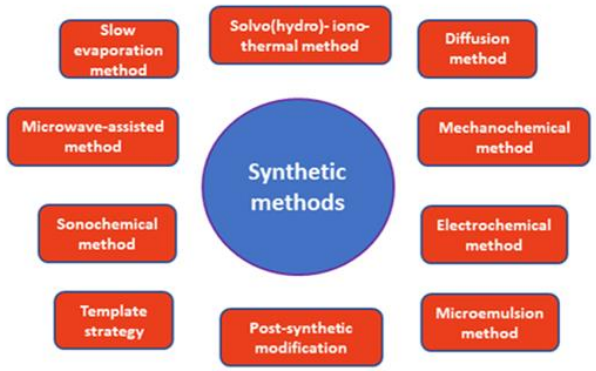

Fig 2. Synthetic methods used to obtain MOFs [34].

Solvo(hydro)thermal and Iono-thermal Methods

Solvo(hydro)thermal synthesis is performed in sealed vessels (autoclaves) under autogenous pressure at temperatures above the solvent boiling point [35]. To date, a large fraction of reported MOFs has been prepared under these conditions [36–40]. Reactions are typically carried out in polar solvents within 50–260 °C and often require extended durations (hours, and sometimes days). For temperatures exceeding 400 °C, Teflon-lined autoclaves are commonly used. Raising temperature can improve bond formation—particularly for systems involving kinetically inert ions—and promotes crystallization. However, higher temperatures and prolonged reaction times may also alter crystal morphology and increase the risk of framework decomposition [41,42]. Controlled (often slow) cooling is important for achieving desirable crystal growth. Because these methods rely on high-boiling solvents, DMF, DEF, MeCN, MeOH, EtOH, H_2O, Me_2CO, or their mixtures are frequently selected. Notably, harsher conditions may induce in situ chemical transformations of the starting materials that do not occur under milder routes, thereby generating new ligands in situ. Iono-thermal synthesis is based on using ionic liquids as both solvents and templates, and can be regarded as a subclass of solvo(hydro)thermal methods. Ionic liquids are considered more environmentally compatible than many conventional organic solvents due to their low vapor pressure, high solubilizing ability, thermal stability, and nonflammability. They can also provide both cations and anions that act as counterions and/or participate as structural templates, making them attractive alternatives for MOF synthesis [43]. As shown in Fig 3, the process of thermal solvent synthesis and alternative methods for preparing MOFs are explained.

Microwave-assisted Synthesis

Microwave irradiation, as an alternative heating strategy, has recently been applied in nanotechnology and pharmaceutical research for the preparation of nanoparticles and porous frameworks. This approach was first used for synthesizing organic materials and porous inorganic compounds, and later extended to the synthesis of metal clusters and MOFs. Its key benefits include shorter reaction times, higher yields, and lower processing costs. In the microwave-assisted synthesis of HKUST-1 (with the formula; where denotes 1,3,5-benzenetricarboxylate), the resulting products have been reported to exhibit improved yields and physicochemical properties while forming in substantially less time than conventional hydrothermal routes [44]. From a mechanistic viewpoint, microwave irradiation enhances molecular mobility and thereby facilitates the nucleation process, enabling the formation of crystals with controlled size and morphology, provided that parameters such as concentration and temperature are properly optimized. In drug-delivery applications, controlling MOF features—particularly particle size, shape, and surface chemistry—can increase drug loading capacity and improve interactions with biological systems, including the potential for targeted delivery to specific tissues or cells. For example, MIL-100(Cr) [45] has been synthesized in approximately 4 hours under microwave conditions instead of the several days required for typical conventional synthesis, and it has been reported that this route can produce narrower size distributions and higher porosity. Moreover, microwave processing has been considered especially suitable for producing single-dispersed MOF particles with sizes below 100 nm, as well as for scaling up synthesis for biomedical applications. Overall, microwave-assisted synthesis has been reported for a wide range of MOFs, including HKUST-1, MIL-53, MIL-101-NH2, MIL-100, and ZIF-8, as well as MOFs based on metal nodes such as Zr, Zn, and Ca [46,47].

Sonochemical Method

Sonochemistry refers to molecular and materials transformations driven by high-energy ultrasonic fields (typically 20 kHz–10 MHz). When an ultrasonic pulse is applied to a liquid reaction mixture, cavitation occurs: microbubbles repeatedly grow and collapse, generating transient “hot spots” characterized by elevated temperature and pressure. These extreme local conditions accelerate chemical reactions and favor the rapid creation

of crystallization nuclei, thereby enabling fast framework assembly and improved control over crystal formation. In practice, sono-assisted routes have been used to obtain high-quality MOFs under significantly shortened reaction times, often relying on convenient polar solvents such as 1-methyl-2-pyrrolidone. For example, MOF-5 and MOF-177 have been synthesized through sono-chemical processing to yield crystals with distinct size regimes, demonstrating that ultrasound can tune nucleation and subsequent crystal growth. Beyond solid-state outcomes, the method has also shown potential for producing Zn-based MOFs such as MOF-177 with high-quality crystallinity and improved yields, while additional formulations (including the use of suitable deprotonating agents) can further influence particle morphology and mesostructure formation [48]. The reported ultrasonic conditions (e.g., specific power and frequency ranges) have enabled the preparation of several ZIF members as well, supporting the view that sonochemistry is a versatile and relatively green strategy for MOF synthesis.

Mechanochemical Method

Mechanochemical synthesis is an increasingly attractive route for MOF preparation, in which mechanical energy is used to promote coordination between metal sources and organic linkers. Rather than relying on conventional solvothermal conditions, the reactants are typically combined by manual grinding or, more commonly, ball milling, allowing framework formation under ambient temperature and, in many cases, with little or no solvent. This approach improves mixing, enhances mass transfer, reduces particle size, and can locally heat or partially melt the reagents, all of which contribute to faster crystallization and shorter reaction times. Because it minimizes solvent consumption, energy input, and equipment demands, mechanochemistry is widely regarded as a green and cost-effective alternative for MOF synthesis. It has been successfully applied to the preparation of diverse coordination polymers and MOFs, including Zn-based SPCP-Zn, which was obtained in high yield within minutes, and the water-stable indium framework InOF-1, which showed notable CO_2 uptake and gas selectivity. Despite these advantages, a key limitation remains the frequent formation of amorphous or poorly crystalline products, which can complicate structural characterization by single-crystal X-ray diffraction. [49].

Green synthesis

Green synthesis in the context of MOFs refers to the preparation of MOF materials using sustainable, safer, and environmentally friendly approaches. The central idea is to design synthesis routes that reduce energy consumption, limit the use of hazardous chemicals, and minimize waste generation. In contrast, conventional MOF synthesis methods (often solvent-based) typically rely on elevated temperatures and, in some cases, high pressures, while also requiring the use of organic solvents; consequently, they can pose challenges in terms of safety, environmental impact, and long-term sustainability [50]. Therefore, green MOF synthesis is being developed by decreasing dependence on harsh conditions and solvents. More sustainable strategies—such as low-solvent/solvent-free processes and rational surface engineering (e.g., coating or functionalization)—can improve stability, reduce cytotoxicity, and enhance performance in applications such as drug delivery and therapeutic treatments.

Critical Comparison of MOF Synthesis Methods for Drug Delivery Applications

Although numerous synthetic approaches have been developed for MOF production, their suitability for drug delivery applications differs substantially with respect to reproducibility, scalability, particle size control, and product consistency. Solvo(hydro)thermal synthesis remains the most widely used approach because it generally produces highly crystalline frameworks with well-defined pore structures. However, the requirement for elevated temperatures, long reaction times, and large volumes of organic solvents increases production costs and may complicate industrial-scale manufacturing. Furthermore, slight variations in temperature, precursor concentration, and cooling rate can significantly influence crystal size and morphology, leading to batch-to-batch variability. Microwave-assisted synthesis offers substantially reduced reaction times and improved energy efficiency. The rapid heating process often generates smaller particles with narrower size distributions, which is advantageous for drug delivery applications. Nevertheless, achieving homogeneous heating in large reaction volumes remains challenging, potentially limiting scalability and reproducibility during industrial production. Sonochemical synthesis enables rapid nucleation and the formation of nanoscale MOFs with relatively uniform particle sizes. Despite these advantages, the final product characteristics are highly dependent on ultrasonic frequency, power intensity, and reactor geometry. These parameters Standardization remains limited, making cross-study comparisons difficult. Mechanochemical synthesis is particularly attractive from a sustainability perspective because of its minimal solvent consumption and low energy requirements. However, the frequent formation of partially crystalline or amorphous products can adversely affect porosity, drug-loading capacity, and release behavior. In addition, quality control and product consistency remain important concerns for large-scale

production. Green synthesis strategies have attracted increasing attention because they reduce environmental impact and improve the overall sustainability of MOF production. Nevertheless, many green synthesis protocols remain at the laboratory scale, and comprehensive evaluations of long-term reproducibility, pharmaceutical-grade quality control, and manufacturing feasibility are still limited.

Overall, while each synthesis strategy offers unique advantages, no single method currently satisfies all requirements for clinical translation. Future efforts should focus on developing scalable, reproducible, and standardized synthesis protocols capable of producing MOFs with consistent physicochemical properties and predictable biological performance.

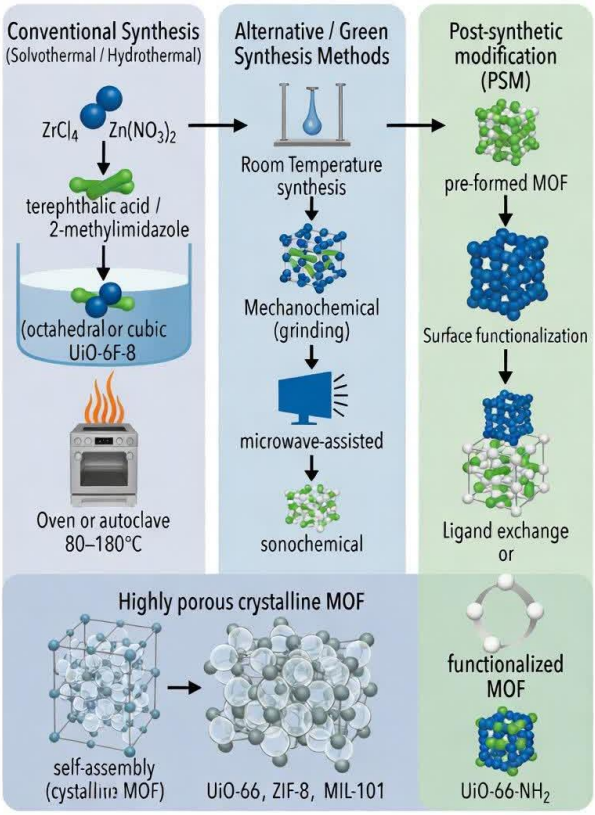

Fig 3. Solvothermal synthesis and alternative methods for MOFs.

Metal Centers in MOFs for Drug Delivery

MOFs, as versatile drug-delivery platforms, are important for targeted delivery and controlled release due to their high porosity, structural tunability, and the ability to engineer drug–carrier interactions. In these systems, the choice of the metal ion is a key determinant of the material's properties—such as porosity, stability, and biocompatibility—and therefore strongly influences drug loading capacity, release kinetics, and targeting performance. Transition metals, owing to their flexible coordination chemistry and potential redox activity, enable the design of MOFs with adjustable pore structures and stimulus-responsive behavior. In contrast, lanthanide ions, with their distinctive optical and magnetic features, can transform MOFs into platforms for imaging or theranostics, supporting simultaneous monitoring of disease progression and drug release. Moreover, integrating metal ions with biological functions (e.g., cofactor-like roles or metalloenzyme activity) can produce synergistic effects, improving therapeutic efficacy beyond drug encapsulation and even enabling catalytic functions in biological environments [51,52]. Overall, advances in MOFs based on common metal families (including Fe-based systems, Zn/ZIF, Zr-based, as well as Cr- and Cu-based frameworks) demonstrate that by tuning structure, surface characteristics, and intrinsic interactions, more effective release, enhanced accumulation in target tissues, and improved therapeutic outcomes can be achieved. At the same time, rational surface modification and intelligent design can mitigate biosafety concerns such as toxicity and stability under realistic conditions.

Ligands as Key Components in MOF Drug Delivery Systems

MOFs are considered promising candidates for drug delivery due to the wide diversity of metal precursors and organic ligands they offer. In these frameworks, organic ligands act as structural organizers and directly influence the physicochemical properties of MOFs. Ligands such as carboxylates, phosphates, sulfates, and various heterocyclic derivatives, owing to their diverse functional groups and chemical functionalities, enable the rational design of MOFs with tunable characteristics—including enhanced framework stability and engineered porosity—thereby improving their performance in applications such as drug delivery, catalysis, and gas storage. In the literature, early examples of biocompatible MOFs based on amino-acid ligands date back to previous decades, after which MOF-enabled drug delivery studies expanded systematically [53]. In many reports, ligand selection—particularly ligands capable of strong interactions with drug molecules—is a key factor in increasing drug loading and controlling the release kinetics. For instance, ligands bearing groups complementary to drugs can enhance drug uptake through coordination interactions, π–π stacking, hydrogen bonding, and/or anion–cation interactions, which helps suppress undesired burst release. Consequently, drug release is often shifted toward a more gradual and sustained profile. Also, it has been shown that engineering the pore channels and pore size through appropriate ligand selection can affect the release duration. Moreover, modifications to ligands—such as introducing hydrophobic groups or incorporating

structural effects (e.g., partial occupation of pore surfaces)—can improve framework stability under different conditions and lead to higher effective drug loading. Overall, the available evidence indicates that the deliberate design of ligands, with respect to their type, their interactions with drug molecules, and the resulting pore architecture, is essential for achieving MOF-based systems with controlled release and improved drug delivery performance [54].

Functionalization Strategies for Advanced MOF-Based Drug Delivery Systems

As can be seen in Fig 4, the functionalization processes of MOFs are presented as pre-synthetic and post-synthetic. The therapeutic potential of Metal–Organic Frameworks (MOFs) as drug delivery vehicles is significantly amplified through strategic functionalization. By precisely modifying the surface or incorporating specific moieties, MOFs can be engineered to exhibit enhanced drug loading, controlled release kinetics, improved stability, and targeted accumulation at disease sites. This section explores the diverse functionalization approaches that transform pristine MOFs into sophisticated drug-delivery systems, addressing key challenges in current therapeutic interventions.

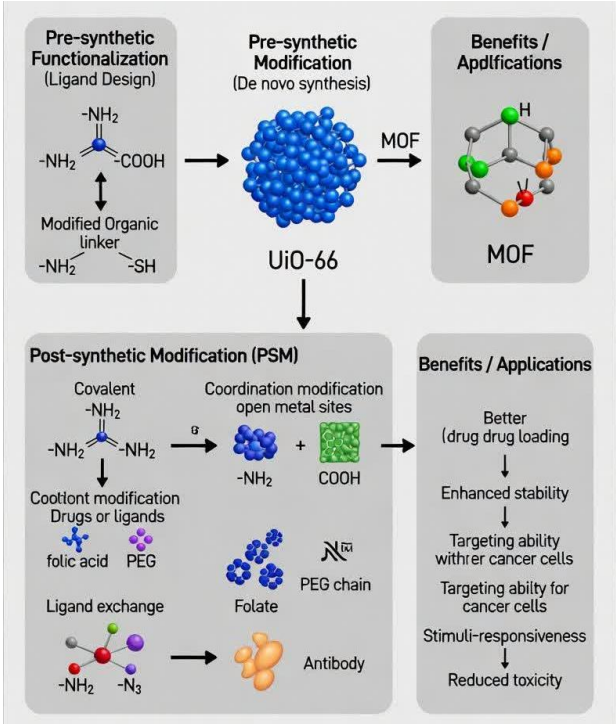

Fig 4. MOF functionalization via pre- and post-synthetic modification.

Pre-synthetic Functionalization

In the pre-synthetic approach, the desired functional groups are incorporated into the organic linkers or metal precursors prior to the final assembly of the MOF. This strategy allows for a homogeneous and uniform distribution of functional sites throughout the framework structure, while simultaneously ensuring robust coordination between the metal centers and the ligands. Common strategies in this regard include the utilization of functionalized ligands, such as amine (–NH_2), carboxyl (–COOH), hydroxyl (–OH), or thiol (–SH) groups, which are employed to modulate properties like hydrophilicity, enhance drug-molecule interactions, or confer sensitivity to pH changes [55]. Furthermore, the incorporation of heterometallic nodes using biocompatible metals such as iron (Fe), zinc (Zn), and zirconium (Zr) enables precise tuning of the framework's stability profile and degradation rate. Overall, this approach facilitates the accurate and predictable adjustment of the MOF's chemical composition, making it an ideal choice for drug-delivery systems that demand high reproducibility and structural uniformity.

Post-synthetic Modification (PSM)

Post-synthetic modification (PSM) is a process carried out after the formation of the primary MOF framework, enabling targeted alterations without disturbing the crystalline structure. This approach is particularly important for loading sensitive biomolecules or introducing targeting and stimulus-responsive functionalities. Various techniques are employed in PSM, including the covalent grafting of polymers, peptides, or targeting ligands such as folic acid and antibodies onto the MOF surface to enable selective targeting of cancer cells or specific tissues [56]. In addition, coordination processes and ion-exchange reactions are used to replace exchangeable metal sites with bioactive species or catalytic centers. Furthermore, surface coating or encapsulation with biocompatible materials such as polyethylene glycol (PEG), silica, or lipid layers plays a crucial role in enhancing the stability, biocompatibility, and circulation time of MOFs in biological environments.

Stimuli-Responsive Functionalization

An emerging trend in the functionalization of MOFs involves the design of stimuli-responsive systems capable of releasing therapeutic agents in response to internal or external triggers such as pH, temperature, enzymes, light, or magnetic fields. The incorporation of such responsive functional groups enables precise spatiotemporal control over drug release [57], thereby minimizing systemic toxicity and enhancing therapeutic efficacy. For instance, acid-sensitive ligands can facilitate drug release within the acidic tumor microenvironment, whereas redox-active or photoresponsive components provide externally controllable release mechanisms. This approach

significantly improves the selectivity and efficiency of MOF-based drug delivery platforms, making them highly promising for advanced biomedical applications.

Biomolecular Conjugation and Hybrid Architectures

To enhance biocompatibility and functionality, MOFs are often conjugated with biomolecules (e.g., proteins, nucleic acids, polysaccharides) or integrated into hybrid nanostructures that combine MOFs with liposomes, dendrimers, or polymers. These architectures merge the high porosity and tunable chemistry of MOFs with the specific biological properties and soft interfaces of organic materials, leading to multifunctional and theranostic drug-delivery systems. This synergistic approach leverages the strengths of each component to create advanced platforms with improved targeting, imaging, and therapeutic capabilities [58].

In general, the choice of functionalization method depends on the desired biomedical function, stability in physiological environments, and compatibility with therapeutic agents. By strategically selecting and optimizing functionalization pathways, researchers can transform conventional MOFs into smart, responsive, and high-performance drug delivery platforms with significant clinical potential.

MOFs Based Composites

Advancements in drug-delivery systems have recently gained significant momentum, focusing on maximizing therapeutic efficacy while mitigating adverse reactions. Within this context, metal-organic frameworks (MOFs) have emerged as highly promising materials, largely attributed to their distinct physicochemical characteristics. This versatility has driven the creation of MOF-based composites, where the incorporation of diverse functional materials enables highly precise and responsive drug release. This discussion examines the architecture, design methodologies, and transformative potential of these composites within the therapeutic landscape [59,60]. By integrating the unique attributes of MOFs with complementary functional agents, researchers are effectively overcoming the traditional hurdles of drug administration and paving the way for more efficient, targeted, and personalized medical solutions. Fig 5 depicts the various types of MOF-based composites utilized in drug-delivery systems (DDS).

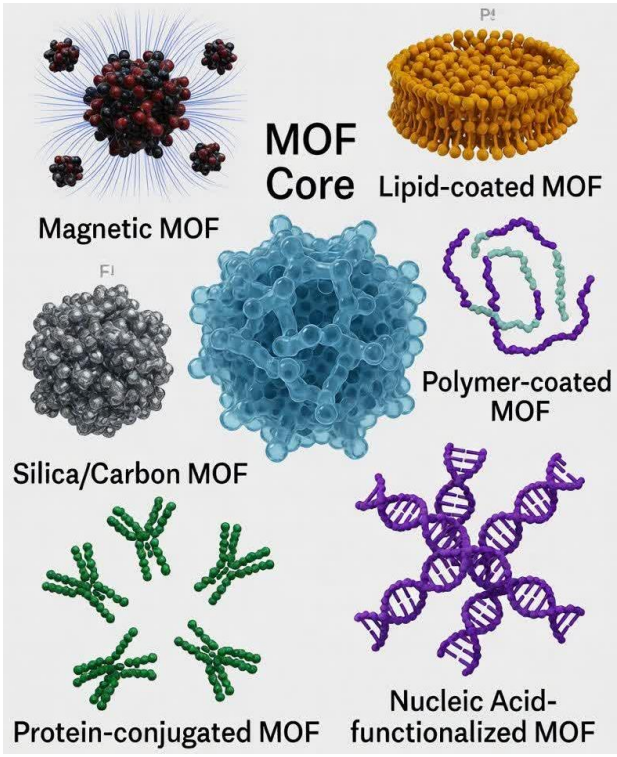

Fig 5. Schematic representation of various MOF-based composites.

Nucleotide-Based MOF Composites in Drug Delivery

Nucleic acids, such as siRNA, are crucial tools for gene-targeting therapies, capable of inhibiting specific protein production by silencing gene expression. However, due to their high molecular weight and negative charge, these molecules often require a delivery system to efficiently cross cell membranes. Metal–Organic Frameworks (MOFs) have emerged as promising novel carriers for nucleic acid delivery, particularly for molecules like siRNA and mRNA. MOFs offer significant potential for effective drug delivery, owing to their high loading capacities and tunable pore sizes. Research indicates that MOFs can be effective in reducing gene expression via siRNA and are also utilized for delivering gene-editing tools like CRISPR/Cas9, as well as other RNA molecules. Challenges such as drug degradation within endosomes after cellular uptake are being addressed through the development of modified MOFs or their combination with auxiliary agents (e.g., proton sponges) [61]. Furthermore, the biocompatibility and stability of certain MOFs, like MIL-100(Fe), position them as hopeful candidates for future therapeutic applications.

Lipid-MOF Composites in Drug Delivery

Coating nanoparticles (NPs) with lipid layers is an effective approach to enhance their cellular uptake and

colloidal stability. This method has also been applied in combination with MOFs. In the present approach, MOFs are combined with lipid materials to improve their therapeutic properties. For instance, MOFs based on metals such as lanthanum (La), zinc (Zn), and iron (Fe), when coated with lipids, have shown higher efficacy against cancer cells. These composites, containing anti-cancer drugs like cisplatin and oxaliplatin, have demonstrated longer blood circulation half-lives in animal studies and exhibited lower uptake by the mononuclear phagocyte system. Furthermore, their effectiveness in tumor reduction compared to free drugs has been significant. In addition, combining MOFs with lipids facilitates cell targeting. For example, by adding groups like triphenylphosphonium (TPP), MOFs can be directed towards specific cells, such as mitochondria, enabling targeted delivery of drugs into cancer cells like MCF-7 breast cancer cells [62]. These composites can also incorporate additional therapeutic functions, such as photodynamic therapy (PDT).

Protein-MOF Composites in Drug Delivery

Protein-MOF composites are formed by enclosing proteins within or around MOF structures, which helps protect the proteins from degradation. This approach also improves the chemical and thermal stability of the MOF system. A significant advantage of these composites is their ability to safeguard environment-sensitive proteins and enable their controlled release in response to changes in conditions such as pH. In addition, these systems can be used to induce oxidative stress in tumor cells. By employing MOFs capable of converting prodrugs into active oxidizing species, reactive oxygen species (ROS) can be generated, which may contribute to tumor suppression [63].

Magnetic Nanoparticles

Magnetic nanoparticles (MNPs) incorporated into metal-organic frameworks (MOFs) enable targeted delivery through an external magnetic field. This approach is also useful in magnetic resonance imaging (MRI) and helps reduce magnetic relaxation times. These composites allow for easy collection of particles after use by applying a magnetic field. Their structure features a high specific surface area and large pore volume, which influence interactions with materials in aqueous environments and significantly shorten the diffusion distance. One of the key advantages of this approach is the reduction of equilibrium time for the selective extraction and separation of materials. This is achieved by leveraging the selective adsorption ability of MOFs, which capture released molecules while preventing other attached molecules from entering the MOF pores. In addition, the thin-layer structure of these composites accelerates the diffusion of substances into the MOF framework. This section also highlights innovative uses of MNPs combined with MOFs for advanced therapeutic and diagnostic applications. A major aspect is controlled drug release. MOF-based composites can load drugs and release them in response to environmental changes, such as the low pH of tumor sites. This enables a stable local drug concentration and improves therapeutic effectiveness. Moreover, these composites serve as contrast agents in MRI. Their strong magnetic properties produce negative contrast (signal darkening) in MRI images, facilitating the detection and monitoring of lesions or tumors. The spin-spin relaxation times (T2 and T2*) of these nanocomposites are reduced, and their high transverse relaxivity leads to high-quality MRI images. In addition, targeting these nanocomposites with molecules such as folate can significantly improve drug accumulation at tumor sites and enhance treatment efficacy [64,65].

Table 3. Comparison of Various MOFs composites [66].

MOF based Composites	Composite type	Ligand used	Application	Ref.
$Fe_3O_4/Cu_3(BTC)_2$	Magnetic	BTC	Anti cancer medication	[67]
Fe_3O_4@MIL 100 (Fe)	Magnetic	BTC	Sorption studies of toxic materials	[65]
γ-Fe_2O_3 @MOFs	Magnetic	H_2BDC, 2MI	Drug delivery	[68]
PMP@MIL 88A	Magnetic	Fumaric acid	Drug delivery	[69]
NCPs	Lipid	DSCP	Cisplatin loading	[70]
Zn(II) bisphosphonate NCP	Lipid	DOPA	Anti Cancer activity	[71]
NCP@Pyrolipid	Lipid	DOPA	Tumour regression	[72]
ZIF-8/BSA biocomposite	Protein	2-MI	Bioactivity	[63]
TYR@NPCN 333	Protein	TATB	Anti cancer activity	[73]
cal@MOF	Nucleotide	Pyrene	Drug release	[74]
CC-ZIFs	Nucleotide	2-MI	Gene editing	[75]

Methods for Drug Loading onto MOFs

Drug incorporation into MOFs is a crucial step for developing advanced drug-delivery systems. This process involves encapsulating therapeutic agents within the porous structure of MOFs, which offers several advantages, such as protecting the drug from degradation, enabling controlled release kinetics, and ultimately enhancing therapeutic outcomes [76,77]. Various methodologies, broadly categorized into one-step and two-step approaches, are employed for effectively loading drugs into MOFs, catering to diverse therapeutic applications. In Table 4, different methods of drug loading into MOFs are presented.

Table 4. Various methods of drug loading in MOFs [66].

MOF	Drug loading mechanism	Synthetic method	Reference
UiO-66-NH_2/Curcumin	One-pot (in situ encapsulation)	Solvothermal	[78]
UiO-66 (DOX release system)	Post-synthetic loading	Solvothermal	[79]
PEG-phosphate functionalized UiO-66	Post-synthetic loading (DOX)	Surface-functionalized UiO-66	[80]
Au/ZIF8/ZIF67/FA hybrid MOF	One-pot co-encapsulation of 5-FU and curcumin	Solvothermal	[81]
Fe_3O_4@UiO-66	Post-synthetic impregnation (Curcumol)	In situ growth + supercritical impregnation	[82]
DNA-decorated UiO-66-NH_2	Post-synthetic co-loading (DOX + Sorafenib)	Solvothermal	[83]

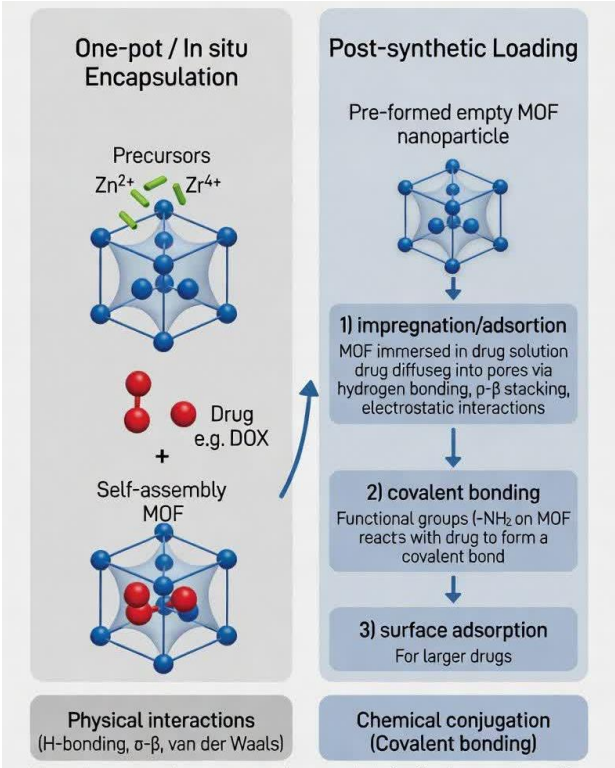

Fig 6. MOF drug encapsulation: In situ vs. Post-synthetic loading.

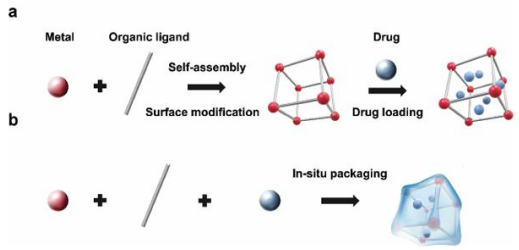

Fig 7. Schematic illustration of MOF formation, surface modification, and drug loading strategies

One-step or One-pot synthesis

The one-step synthesis method, also known by names such as in-situ synthesis, One-Pot Method, or In Situ Encapsulation, is a simple and efficient approach for incorporating drugs into Metal-Organic Framework (MOF) structures. Fig 6 and 7 shows two approaches, in situ and post-synthetic, for drug delivery/encapsulation in metal-organic frameworks. In this method, the drug is directly added to the reaction mixture of metal precursors and organic ligands. Concurrently with the MOF synthesis process, the drug is entrapped within the pores or channels of the forming crystalline framework. This mechanism, where the drug acts as a guest molecule, is ideal for compounds sensitive to solvents or harsh post-synthesis conditions [84]. Additionally, in cases where the

drug possesses suitable functional groups (such as carboxyl or amine), it can act as a ligand itself, coordinating with metal ions or covalently combining with framework components, leading to a very high loading capacity.

Key advantages of this integrated approach include greater simplicity and efficiency due to fewer experimental steps, potentially higher loading capacities (as the MOF structure is still forming and more accessible), and protection of the drug from degradation within the reaction environment. However, challenges also exist, including ensuring drug stability under synthesis conditions, preventing interference with MOF nucleation and growth, precise control of loading efficiency, and achieving uniform drug distribution. Despite these challenges, one-step synthesis is particularly attractive when drug stability is not the primary concern and the goal is to achieve high drug loading without the need for complex post-synthesis processing [85,86].

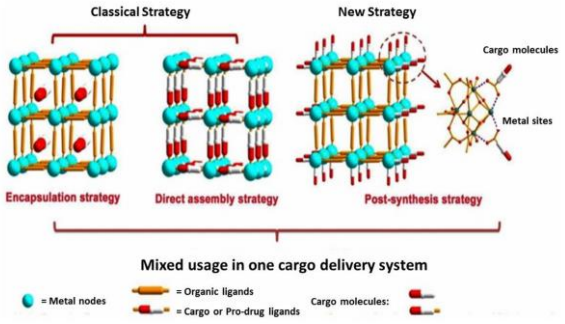

Fig 8. Encapsulation,directassembly,andpost-synthesisofcargo-loadingstrategiesforMOFs [87].

Two-step or Post-synthetic loading

The two-step method, also known as post-synthetic loading, involves synthesizing the Metal-Organic Framework (MOF) first, followed by the introduction of the drug into the pre-formed structure. This sequential approach grants enhanced control over both MOF fabrication and drug incorporation, as these processes are managed independently. Drug loading in this method can occur via two primary interaction types: physical (non-covalent) or chemical (covalent). Physical loading, the more common approach, relies on the physical entrapment or adsorption of drug molecules within the MOF's pores and channels. This is achieved by exposing the MOF to a drug solution, allowing diffusion into void spaces driven by concentration gradients, with retention via weaker forces like van der Waals or hydrogen bonding. Some factors such as pore size, drug solubility, MOF affinity, and loading conditions critically influence its efficiency. Conversely, chemical loading involves forming stable covalent bonds between the drug and the MOF framework [88]. This can be accomplished through MOF functionalization followed by reaction with the drug, in situ activation, or the use of pre-functionalized linkers during MOF synthesis. While offering superior drug retention, controlled release, and protection, chemical loading presents challenges in terms of selecting compatible reactive functionalities and potential complexity in synthesis. Key advantages of the two-step method overall include greater control, compatibility with drugs sensitive to synthesis conditions, broader versatility, and the potential for higher drug loading [89]. However, it also faces challenges like diffusion limitations for large molecules, the risk of framework degradation by loading solvents, and the inherent need for more experimental steps compared to one-step synthesis. The selection between physical and chemical loading hinges on the desired drug release profile, drug stability, and the chemical characteristics of both the drug and the MOF.

The Post-synthetic loading method is the most common approach, involving the immersion of a pre-synthesized MOF into a concentrated drug solution. Within this approach, several sub-methods and mechanisms exist. Impregnation or Adsorption is the simplest and most prevalent technique, where the MOF is submerged in a drug solution (typically in ethanol, water, or DMSO), allowing the drug to diffuse into the pores. This process relies on non-covalent interactions such as hydrogen bonding, π–π stacking between aromatic rings of the drug and MOF ligands, van der Waals forces, and electrostatic interactions, especially in MOFs functionalized with NH_2 or COOH groups. The size and shape of the MOF's pores (micropores/mesopores) play a crucial role in confinement [90,91]. This method is suitable for most small-molecule drugs like ibuprofen (IBU), doxorubicin (DOX), 5-fluorouracil (5-FU), and curcumin. Loading capacity often increases with higher BET surface area and pore volume, reaching up to 0.5 g/g for 5-FU via hydrogen bonding. A variation, surface adsorption, is applicable for larger drugs that cannot enter the pores, where the drug adsorbs primarily onto the external surface of the MOF, though this typically results in faster drug release. Another sophisticated technique is Covalent bonding or Post-synthetic modification (PSM), where functional groups on the MOF ligands (e.g., NH_2 in UiO-66-NH_2 or MIL-101-NH_2) react with drug moieties to form stable covalent bonds. This significantly enhances loading stability and prevents premature leakage, as exemplified by the covalent attachment of camptothecin to amine-functionalized MIL-101(Fe). Finally, Co-loading enables the simultaneous incorporation of multiple drugs (e.g., a chemotherapy agent and a photosensitizer) for combination therapy. Fig 8 shows different cargo loading strategies in metal-organic frameworks (MOFs),

including encapsulation, direct assembly, and post-synthesis [92].

Beyond common methods, advanced approaches for drug loading into MOFs have been developed. These include Grinding or Co-crystallization, primarily used for oral MOFs like CD-MOFs (based on cyclodextrin and potassium), where the drug is loaded via mechanical milling or co-crystallization with the MOF. Microfluidic or Continuous Methods are employed for integrated MOF synthesis and loading on a large scale, allowing for more precise control and improved efficiency. Furthermore, Stimuli-responsive MOFs are designed to respond to environmental triggers such as changes in pH, redox potential, temperature, or light, controlling pore opening/closing and thus modulating drug loading and release; for instance, ZIF-8 degrades in the acidic pH found in cancerous tumor microenvironments, facilitating controlled drug release [93]. As can be seen in Fig 9, the distinct features of covalent and non-covalent loading mechanisms in MOFs are shown in a comparative manner.

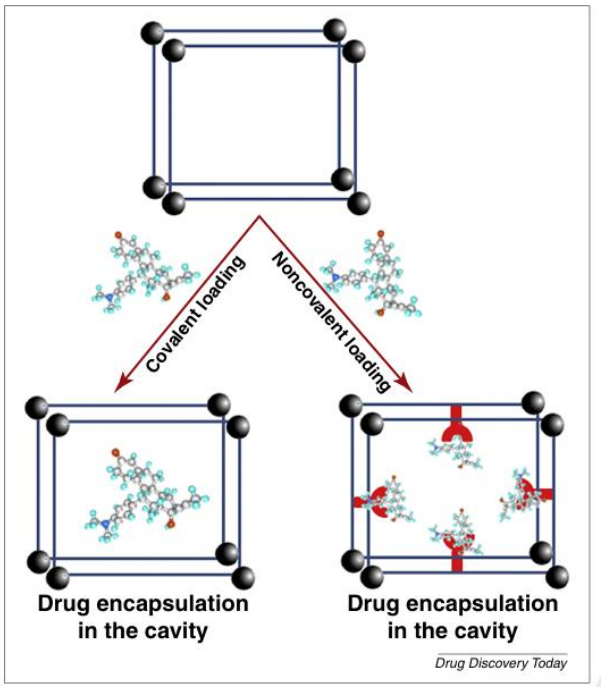

Fig 9. Drug loading strategies in MOFs, indicating characteristic differences between covalent and noncovalent drug loading mechanisms [94].

Mechanisms of drug release from MOFs

Drug release mechanisms from Metal–Organic Frameworks (MOFs) are one of the most critical aspects of their application in controlled drug-delivery systems. MOFs, owing to their tunable porous structure, the ability to be designed as stimuli-responsive, and high loading capacity, enable the control of drug release in a mechanism-driven and on-demand manner. These features significantly reduce non-specific and premature drug leakage, thereby enhancing therapeutic efficacy, particularly in applications such as the treatment of cancer, infections, and chronic diseases. Drug release mechanisms from Metal–Organic Frameworks (MOFs) can be broadly categorized into two main types: passive release, which operates based on diffusion, gradual degradation, or interactional equilibrium without requiring an external stimulus; and active or stimuli-responsive (smart) release, which is triggered by internal (e.g., pH or enzymes) or external (e.g., light or heat) stimuli. Often, a combination of these two mechanisms is observed, beginning with an initial burst release followed by a transition to more controlled and sustained release [95]. Fig 10 shows a schematic illustration of the stimulated drug release from MOFs.

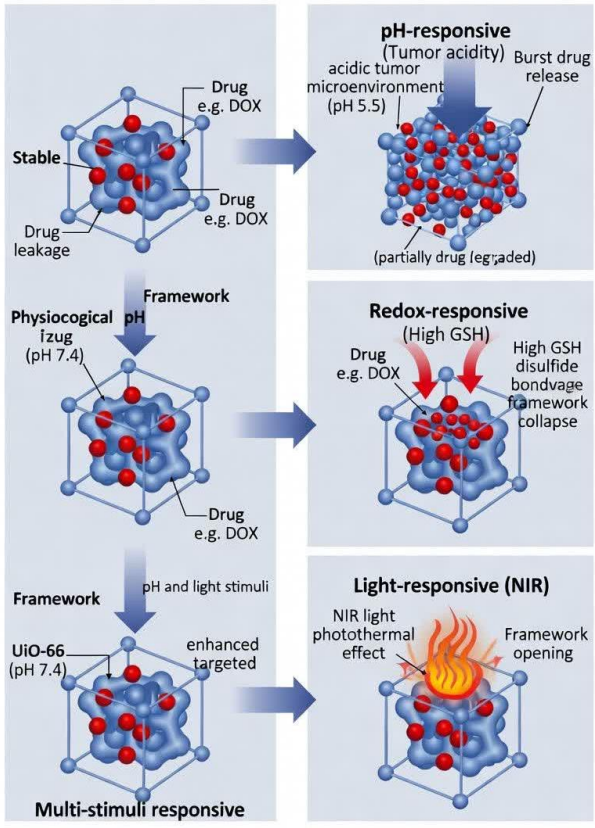

Fig 10. Schematic illustration of stimuli-responsive drug release from MOFs.

Passive Drug Release Mechanisms from MOFs

Passive drug release mechanisms from Metal–Organic Frameworks (MOFs) are primarily governed by three distinct processes, each contributing to the controlled liberation of therapeutic agents. Firstly, diffusion-controlled release is a cornerstone mechanism,

particularly prevalent in robust MOFs like UiO-66. This process involves the drug molecules gradually migrating from the MOF's internal porous structure to the external environment. The rate and efficiency of this diffusion are intricately influenced by several factors, including the precise dimensions and volume of the MOF's pores, as well as the nature of host-guest interactions within these pores. These interactions encompass phenomena such as hydrogen bonding, π–π stacking between drug molecules and MOF linkers, and weaker van der Waals forces, all of which modulate the drug's ability to move through the framework [96]. Secondly, degradation or erosion of the framework presents another significant pathway for passive drug release. This mechanism is more pronounced in MOFs that exhibit inherent structural instability, such as ZIF-8. In such cases, the MOF structure itself undergoes gradual decomposition or dissolution when exposed to the physiological milieu. This breakdown can be instigated by various biological components and conditions, including the presence of specific ions, enzymatic activity, or variations in the local pH. As the MOF lattice disintegrates, the entrapped drug molecules are released into circulation. Thirdly, ion exchange offers a unique mechanism for passive drug release in certain MOF architectures. This process occurs when ions present in the surrounding biological fluid are exchanged with either the metal ions forming the nodes or the organic ligands that constitute the framework of the MOF. This substitution disrupts the MOF's structural integrity, leading to conformational changes or partial dissolution that facilitates the release of the loaded drug. This mechanism highlights the dynamic nature of some MOFs in response to their chemical environment [97].

Stimulus-responsive mechanisms

These mechanisms represent the most advanced approach, enabling release at the target site (e.g., the tumor microenvironment). Table 5 presents examples of metal–organic frameworks used for controlled release.

Endogenous Stimuli

Endogenous triggers are internal physiological stimuli or conditions within the body that initiate a biological response. In the context of drug-delivery systems, particularly those designed for targeted release, endogenous triggers refer to specific physiological cues present at the target site that can activate the release of a therapeutic agent from its carrier. These triggers are highly desirable for targeted drug delivery because they are inherently associated with the disease state or specific physiological conditions, meaning they are naturally found at the site where the drug is needed and are less likely to present elsewhere in the body. This selectivity helps to minimize off-target effects and maximize the therapeutic efficacy of the drug. In summary, endogenous triggers are internal biological signals that drug-delivery systems can be designed to read [98]. By utilizing these signals, researchers strive to create intelligent drug carriers that release their therapeutic payload precisely when and where it is most needed, heralding a new era of precision medicine.

pH-responsive

The abnormal expansion of tumor cells leads to rapid nutrient consumption and increased CO2 generation, consequently lowering the local pH of the tumor microenvironment to approximately 5.5–6.8, which is significantly more acidic than the bloodstream (pH 7.4). Metal–Organic Frameworks (MOFs) can passively target and accumulate in these tumor locations. Upon entering the acidic tumor microenvironment, MOFs can undergo dissociation, changes in surface charge, and shape alterations, facilitating controlled drug release. The most prevalent method to achieve pH-responsive drug release from MOFs involves inducing intrinsic protonation of specific chemical groups within their structure, such as imidazole, carboxylate, or pyridyl moieties. This protonation disrupts the crucial coordination bonds between the metal ions and organic ligands, leading to the decomposition of the MOF framework. Classic examples of such pH-sensitive MOFs include ZIF-8, which rapidly degrades in acidic conditions to release drugs like doxorubicin or 5-FU, and several MOFs from the MIL and UiO series [99,100]. This mechanism is driven by alterations in electrostatic and hydrogen bonding interactions alongside framework dissolution. The inherent pH differences across various physiological environments, including the acidic tumor microenvironment due to increased glycolysis and the even lower pH within intracellular compartments like endosomes and lysosomes, make MOFs a promising platform for precisely triggered drug delivery. By designing drug carriers with pH-sensitive polymers or bonds that respond to these specific pH levels, researchers can engineer systems that precisely control the release of therapeutic agents [101]. As shown in Fig 12, taking DOX as a pharmaceutical model, Gd/Tm-MOFs@mSiO$_2$−FA has a promising drug performance and pH responsiveness.

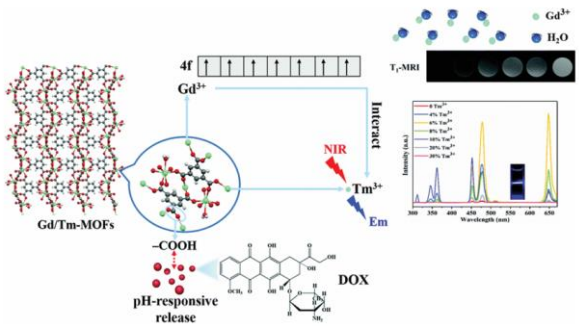

Fig 11. Synthetic procedure, anti-tumor drug loading and possible receptor-mediated endocytosis pathway of the targeted Gd/Tm-MOFs@mSiO$_2$-FA [102].

Zhu et al [103]. developed a dendritic cell-based platform in which gold nanoparticles and the anticancer drug doxorubicin were simultaneously incorporated into a dendrimer scaffold. In addition to serving as a drug delivery system, this nanoplatform also enabled computed tomography (CT) imaging of tumors. In this design, DOX was linked to the nanocarrier through a cis-aconityl bond, which is sensitive to acidic conditions and therefore makes drug release pH-dependent. The results showed that under physiological conditions at pH 7.4, DOX release remained minimal, with less than 15% released even after 80 hours. However, as the environment became more acidic, the release rate increased markedly; after 80 hours, approximately 62.7% and 86.5% of DOX were released at pH 6.0 and 5.0, respectively. Moreover, compared with the conventional iodine-based contrast agent Omnipaque, these nanoparticles exhibited superior X-ray attenuation properties. Accordingly, this gold–dendrimer–DOX system offers a combined approach for targeting folate receptor–expressing cancer cells, effective chemotherapy, and CT imaging (Fig 11).

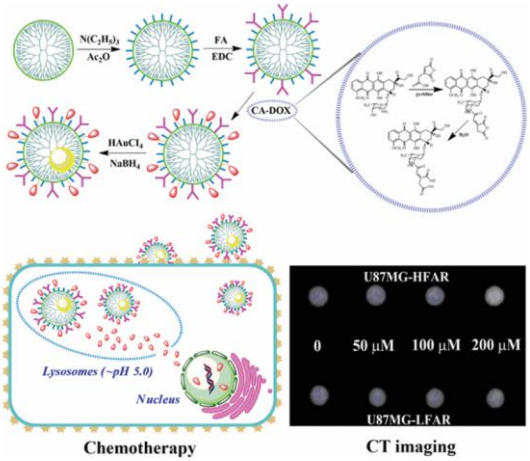

Fig 12. Schematic Illustration of the Synthesis of {(Au 0) 50 -G5·NHAc-FA-DOX} (for Short, Au-G5-F-D) DENPs [106].

Redox-responsive

Tumor cells are characterized by a high concentration of glutathione (GSH); this concentration reaches 2 to 10 mM in the cytoplasm, which is 102 to 103 times higher than its concentration in the blood and extracellular matrix (approximately 2 μM). Glutathione is a potent reducing agent that can reduce disulfide bonds or certain active oxidizing groups. This unique characteristic forms the basis for designing many GSH-responsive Metal–Organic Frameworks (MOFs). GSH-responsive mechanisms in these MOFs are mainly divided into two categories: disulfide bond cleavage and GSH-induced sensitization. The disulfide bond cleavage mechanism is a common method for controlled drug release from MOFs in GSH-rich environments. The process occurs in three stages: first, drug-loaded MOF nanoparticles are exposed to an environment with a high GSH concentration. Then, the disulfide bonds within the MOF structure are reduced and cleaved by GSH. Finally, the loaded drugs are released in target tissues or sites upon the decomposition of these nanoplatforms. The high GSH concentration in cancer cells makes the intracellular environment significantly more reductive than the extracellular environment. This difference in redox potential provides an opportunity for precise drug targeting [104,105]. MOFs designed with disulfide bonds or redox-active metals (such as iron or copper) can decompose in the presence of high GSH concentrations and release their payload. Drug delivery systems utilizing disulfide bonds are engineered to release their therapeutic cargo after entering the intracellular reductive environment. This approach enables more precise and effective therapies by leveraging the biochemical characteristics of cancer cells.

Enzyme-responsive

Cancer cells and diseased tissues often possess unique microenvironments that can be utilized for targeted drug release. One of these characteristics is the presence of specific enzymes at high concentrations or activity levels in these areas. Enzymes such as esterase, protease, or hyaluronidase, which are found in lower amounts under normal physiological conditions, are abundant in pathological microenvironments like tumors or inflammatory regions. These enzymes can hydrolyze sensitive linkages (such as ester, peptide, or glycosidic bonds) incorporated into the structure of Metal–Organic Frameworks (MOFs) or other drug-delivery systems. This hydrolysis leads to a change in the MOF structure and consequently, the release of the drug at the intended site. For instance, certain types of cancer are associated with the overexpression of enzymes like matrix metalloproteinases (MMPs) or esterases. By designing drug-delivery systems with linkages that are specifically cleaved by these enzymes, it can be ensured that the drug is released only at the time and location where these enzymes are present (i.e., at the disease site) [106]. In addition to enzymes, high concentrations of other molecules like adenosine triphosphate (ATP) or specific ions can also serve as indicators of pathological microenvironments. Changes in the concentration of these molecules can alter the MOF structure, leading to drug release. This approach enables the creation of smart drug-delivery systems capable of selectively responding to diseased cells or tissues, thereby enhancing treatment efficacy and minimizing side effects.

External stimuli

Smart drug-delivery systems based on Metal–Organic Frameworks (MOFs), by leveraging external stimuli, enable advanced and targeted control over drug release. These stimuli, applied from outside the body, offer advantages such as being non-invasive, allowing for precise adjustability, and enabling localized targeting.

Light-responsive

Metal–Organic Frameworks (MOFs) as novel platforms in intelligent drug-delivery systems, by integrating light-sensitive components, provide controlled and targeted drug release under irradiation of specific wavelengths of light. This capability has opened up significant therapeutic potential, especially in the field of combination therapies. These systems utilize key mechanisms to respond to light, including photolysis and bond cleavage, conformational change, photothermal effect, and generation of reactive oxygen species. In photolysis, MOFs are designed with photon-sensitive linkers that break upon light irradiation, particularly in the UV or visible range, leading to MOF structure degradation and drug release. This method enables precise temporal control of drug release. In conformational change, light-sensitive molecules (like azobenzenes) are embedded within the MOF structure [107]. Light irradiation causes isomerization of these molecules, leading to changes in the overall MOF structure, pore opening, and subsequent drug release. The photothermal effect is another crucial mechanism where MOFs are combined with photothermal materials. These materials convert irradiated light into heat, primarily in the near-infrared (NIR) range. The generated heat causes MOF expansion, structural degradation, or increased cell membrane permeability, facilitating drug release. This mechanism is highly effective for chemo-photothermal combination therapies. MOFs can also be combined with photosensitizers to generate reactive oxygen species (ROS) upon light irradiation. ROS not only have direct anti-cancer effects but can also contribute to MOF structure degradation and simultaneous drug release. The use of near-infrared light (NIR) has high clinical appeal due to its deeper penetration into biological tissues compared to UV and visible light. This allows for targeted treatment of deeper lesions and enhances synergy with therapeutic methods like PDT and PTT. Combining MOF-based drug delivery with light stimulation enables complex combination therapies, significantly enhancing therapeutic efficacy while minimizing systemic side effects. In conclusion, MOF-based drug-delivery systems responsive to light, particularly those utilizing NIR wavelengths, represent a significant step towards achieving precise, non-invasive, and efficient treatments. Fig 13 shows the synthesis of the O_2@UiO-66@ICG@RBC system and the schematic mechanism of NIR-activated oxygen release/generation [108].

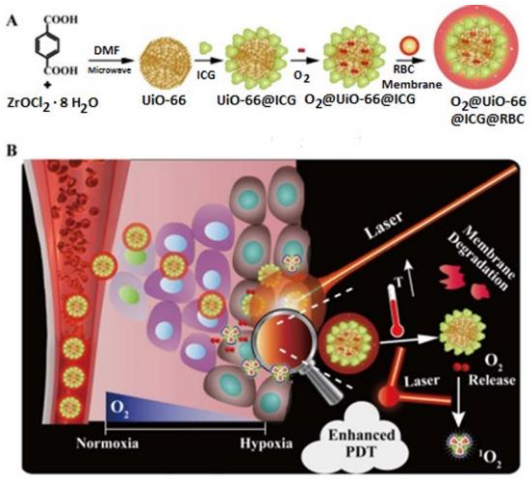

Fig 13. Synthesis of O_2@UiO-66@ICG@RBC. Schematic mechanism of NIR-triggered O2 [87].

Temperature-responsive

Thermally responsive MOF-based drug-delivery systems represent an advanced and highly tunable approach for achieving targeted and controlled therapeutic release. These systems operate by utilizing temperature elevation—induced through external sources such as near-infrared (NIR) lasers, ultrasound irradiation, magnetic hyperthermia, or direct localized heating—to trigger structural or chemical transitions within the MOF or its polymeric coatings. The primary mechanisms involve the weakening of host–guest interactions or the induction of thermal effects such as swelling, phase transition, or controlled structural degradation at defined threshold temperatures (typically above 40–42 °C), ultimately facilitating drug release [109]. A major advantage of these systems is the simplicity and precision with which thermal stimuli can be applied, along with their strong compatibility and synergistic potential with hyperthermia-based cancer therapies. Collectively, these features position thermally responsive MOFs as powerful and versatile platforms in the development of next-generation smart nanotherapeutic systems.

Magnetic-responsive

The integration of Metal–Organic Frameworks (MOFs) with magnetic nanoparticles, particularly iron oxides such as, establishes an advanced and versatile platform for targeted and stimuli-responsive drug delivery. Upon application of an external magnetic field, these hybrid nanocarriers can simultaneously perform several crucial functions. Firstly, they enable magnetic targeting, guiding the drug delivery system towards the tumor site and enhancing its local accumulation. Secondly, the external magnetic field can induce localized heating through

magnetic hyperthermia. This thermal elevation weakens host–guest interactions within the MOF structure or triggers phase transitions and structural alterations in the accompanying coatings, ultimately facilitating drug release. Thirdly, the applied field can induce mechanical stress and physical perturbations within the nanocarrier, further aiding in the controlled release of the therapeutic payload [110]. This integrated approach concurrently offers two significant advantages: targeted magnetic guidance, which enhances tissue penetration and accumulation within the tumor microenvironment, and magnetic hyperthermia induction, serving as a precise, non-invasive external stimulus for controlled drug release kinetics. Consequently, magnetic MOFs are considered highly promising not only for improving the efficacy of localized drug delivery but also for synergistic combination with hyperthermia therapies, enabling multi-modal treatment strategies (e.g., chemo-hyperthermia). These attributes position MOFs incorporating magnetic nanoparticles as one of the most compelling smart systems in the field of cancer nanomedicine [111].

Ultrasound-Responsive

The focused ultrasound waves, acting as a precise and adjustable external stimulus, can activate MOF-based drug delivery through several simultaneous mechanisms. In these systems, ultrasound energy is converted into physical and biological effects within the focal region, ensuring that drug release primarily occurs at the target site. Firstly, under the certain ultrasound irradiation conditions, a portion of the energy leads to a localized temperature increase. This issue can weaken the interactions between the MOF and the drug molecules, facilitate diffusion pathways within the porous network, and ultimately enhance the release rate. Secondly, the phenomenon of acoustic cavitation plays a key role; microscopic bubbles are generated in the fluid and then collapse violently. This event can create intense local shockwaves and currents, resulting in the disruption or weakening of the MOF structure (or its surrounding coatings), thereby opening up pathways for drug exit. Thirdly, focused ultrasound can induce sonoporation, which means creating transient disruptions in the lipid bilayer and temporarily increasing cell membrane permeability, thereby facilitating more effective entry of the drug into the cell (after release from the MOF) [112]. In summary, this approach leverages the deep tissue penetration of ultrasound, its external non-invasive actuation, the ability to precisely focus energy on the target area, and consequently its relative non-invasiveness, making it highly suitable for therapeutic applications. By adjusting ultrasound parameters, a balance can be struck between release efficiency and minimizing unwanted effects on healthy tissues.

Electric Field-Responsive

The application of external electric fields in MOF-based drug-delivery systems offers an innovative mechanism for the precise and dynamic regulation of drug release. This approach operates on electrical stimulation, controlling drug transfer through several simultaneous or independent mechanisms: 1) Alteration of MOF Surface Charge: The application of an electric field can modify the surface charge distribution of MOF nanoparticles. This change in surface charge modulates the electrostatic interactions between the MOF and the drug molecule (especially if the drug is charged), leading to drug adsorption or desorption from the porous framework. 2) Induction of Changes in Stimuli-Responsive Bonds: If the MOF is designed with linkers or bonds sensitive to electric fields (such as certain covalent or hydrogen bonds), applying a field can cause these bonds to break, rearrange, or change configuration. This structural alteration increases the framework's permeability, facilitating drug release. 3) Stimulation of Ion Migration: The external electric field can induce the migration of ions within the MOF framework or surrounding counter-ions [113,114]. This ionic migration can lead to changes in the overall MOF structure, increase pore volume, or create electrochemical imbalances, ultimately affecting drug loading capacity or stability and accelerating or modulating the release process. Collectively, these systems allow for precise control over the intensity and duration of stimulation, and due to their high programmability and adjustability, they hold significant potential in the development of smart implants for targeted and long-term therapies, particularly in areas such as targeted drug delivery to tumor sites or controlled release in damaged tissues.

Despite their considerable promise, electric field-responsive MOF systems remain at an early stage of development. Most studies reported to date are limited to proof-of-concept demonstrations and in vitro evaluations, while comprehensive in vivo investigations regarding their safety, therapeutic efficacy, long-term stability, and clinical translatability are still lacking. Therefore, further preclinical studies are required before these systems can be considered for practical biomedical applications.

Multi-stimuli-responsive

The integration of multiple stimuli, such as combining pH and redox conditions or pH and light, represents a sophisticated advancement in drug-delivery systems, aiming for enhanced precision and smarter release profiles. This synergistic approach has garnered substantial attention in recent years. By leveraging both external stimuli (like electric fields, light, or magnetic fields) and internal microenvironmental cues characteristic of disease states (such as specific pH levels, enzyme concentrations, or redox potentials), it becomes possible to design multi-responsive drug-delivery systems. These advanced systems offer significant advantages, including increased therapeutic efficacy through targeted and on-demand drug release, reduced

systemic toxicity by minimizing off-target exposure, and the potential for personalized treatment regimens tailored to individual patient needs and disease progression [115]. The ability of these systems to respond selectively to a unique combination of triggers ensures that drug release occurs only at the intended site and under specific pathological conditions, thereby optimizing therapeutic outcomes while mitigating adverse effects.

Table 5. MOFs for controlled release [102].

MOF	Drugs	Stimuli	Tested cell	Ref.
DSF@Z-NPs	Doxorubicin (DOX)	pH	MCF-7	[116]
DS@ZJU-801	diclofenac sodium (DS)	Temperature	PC12	[117]
PPy@MIL-100(Fe) NCs	Doxorubicin (DOX)	Light	HepG-2	[118]
Mn-SS/DOX@PDA-PEG NCPs	Doxorubicin (DOX)	Glutathione(GSH)	HeLa, and K7M2	[119]
MS/PNIPAM-MAA/EuW10 hydrogel	DOX	Temperature/pH	HeLa	[120]
PEG–FA-NH2-Fe-BDC	DOX	pH/ultrasound	MCF-7	[121]
ZDOS NPs	DOX	pH/Redox	HeLa and MCF-7	[122]
AP-ZIF-90@DOX	DOX	ATP/pH	MDA-MB-231	[123]

Challenges

Despite significant advances in the application of metal–organic frameworks (MOFs) as drug nanocarriers, several fundamental challenges still hinder their widespread clinical translation. These challenges are mainly centered on stability, biocompatibility, scalability, and clinical applicability. One of the most critical challenges is the chemical and colloidal stability of MOFs in physiological environments. Many MOFs, particularly Zn- and Zr-based structures, are unstable in the presence of serum proteins (such as albumin), phosphate ions, and fluctuations in the pH of blood or tissues, leading to rapid degradation. This phenomenon results in premature drug leakage, reduced carrier efficiency, and undesirable alterations in pharmacokinetics. In addition, the thermal and chemical instability of some MOFs during manufacturing and storage processes creates practical limitations. Biocompatibility and toxicity issues represent another major challenge requiring serious attention from researchers. The release of metal ions, such as Zn^{2+}, Fe^{3+}, or Cu^{2+}, as well as organic ligands, may induce cytotoxicity or chronic inflammation. Although iron- and zirconium-based MOFs are generally considered safer, comprehensive in vivo studies—particularly long-term repeated-dose investigations and evaluations of cumulative effects—remain insufficient. The structural diversity of MOFs makes it difficult to predict toxicity solely based on chemical composition, and important factors such as particle size, morphology, and route of administration must be assessed individually.

Scalability of synthesis and production cost are also key barriers. Most MOF synthesis methods are currently performed at the laboratory scale, and translating them to industrial production while maintaining crystalline quality, uniform particle size, and high purity remains highly challenging. Moreover, the use of toxic solvents in some synthesis methods is not consistent with the principles of green chemistry.

From the perspective of clinical translation, the lack of standardized protocols for evaluating in vivo degradation, long-term pharmacokinetics, and toxicity, together with regulatory hurdles, has slowed the progress of MOFs into clinical phases. To date, only a limited number of MOF-based systems have entered clinical trials, highlighting a substantial gap between preclinical research and practical clinical application.

Despite the remarkable progress achieved in the development of MOF-based drug-delivery systems, several critical challenges continue to hinder their successful clinical translation. One of the primary concerns is the potential toxicity associated with framework degradation and metal ion release. Although many MOFs are generally considered biocompatible, their safety profiles can vary significantly depending on metal composition, particle size, surface chemistry, and degradation behavior. In particular, the release of metal ions from unstable frameworks may induce oxidative stress, inflammatory responses, or dose-dependent cytotoxicity. Furthermore, favorable in vitro results do not always correlate with in vivo performance, highlighting the need for comprehensive long-term biosafety studies.

Another major challenge is the stability of MOFs under physiological conditions. While numerous frameworks exhibit excellent structural integrity under laboratory conditions, exposure to biological fluids containing salts, proteins, and phosphate ions may trigger partial degradation, pore collapse, or ligand displacement. Such instability can result in premature drug leakage, reduced targeting efficiency, and unpredictable therapeutic outcomes. Therefore, maintaining structural integrity while preserving biodegradability remains a delicate balance in the design of MOF-based nanocarriers.

Reproducibility and batch-to-batch consistency also represent significant obstacles for practical implementation. Small variations in synthesis parameters, including reaction temperature, precursor concentration, solvent composition, reaction time, and post-synthetic treatment, can substantially alter particle size, crystallinity, porosity, and drug-loading capacity. Consequently, materials prepared using nominally

identical procedures may exhibit different physicochemical properties and biological performances. This variability complicates quality control and limits the reliable large-scale production required for pharmaceutical applications.

Scalability presents an additional challenge. Although a vast number of MOFs have been successfully synthesized at the laboratory scale, relatively few studies have demonstrated economically viable large-scale production processes. Conventional synthesis methods often require high temperatures, long reaction times, large volumes of organic solvents, and extensive purification steps, all of which increase manufacturing costs and reduce industrial feasibility. The development of scalable and environmentally sustainable production routes therefore remains a key priority for future research.

Moreover, despite the extensive number of publications reporting promising preclinical outcomes, the clinical translation of MOF-based drug-delivery systems remains limited. This discrepancy highlights the substantial gap between laboratory-scale success and real-world therapeutic application. Factors such as long-term toxicity, biodistribution, biodegradation pathways, immune responses, pharmacokinetics, and manufacturing reproducibility must be thoroughly evaluated before clinical implementation can be achieved.

Regulatory considerations further complicate the translational pathway. Currently, standardized regulatory frameworks specifically addressing MOF-based nanomedicines are still evolving. Regulatory agencies require comprehensive information regarding material characterization, quality control, biodegradation behavior, toxicological profiles, and manufacturing consistency. The absence of universally accepted testing protocols and evaluation criteria creates additional barriers to regulatory approval and commercialization.

Looking forward, future research should focus on the development of biodegradable and highly biocompatible MOFs, standardized synthesis and characterization procedures, scalable manufacturing technologies, and comprehensive long-term safety assessments. Greater collaboration among materials scientists, pharmaceutical researchers, clinicians, and regulatory authorities will be essential to bridge the gap between fundamental research and clinical application. Addressing these challenges will ultimately determine whether MOF-based drug-delivery systems can fulfill their considerable promise in next-generation precision medicine.

Future Perspectives

Despite these challenges, promising prospects exist for drug-delivering MOFs. Future focus will be on designing more biocompatible MOFs (e.g., Fe-, Zr-, or Mg-based structures) and enhancing stability through surface coating with polymers (like PEG), lipids, or polysaccharides. The development of multi-stimuli-responsive and intelligent systems that can simultaneously respond to multiple signals (pH, redox, NIR light, and enzymes) will enable more precise drug release and combination therapies (chemo-photothermal, chemo-immunotherapy).

One emerging trend is the integration of artificial intelligence and machine learning in the design and synthesis optimization of MOFs, which can significantly reduce the discovery time for new structures. Furthermore, a shift towards non-systemic or localized applications (such as topical delivery to tumors, wounds, or implantable devices) can mitigate the risk of systemic toxicity and increase the chances of clinical translation.

Ultimately, overcoming translation barriers necessitates increased interdisciplinary collaboration among researchers in reticular chemistry, pharmaceutical sciences, tissue engineering, and regulatory affairs. Conducting standardized preclinical studies, developing more human-relevant animal models, and performing life cycle assessments (LCA) of MOFs are essential steps to transform these materials into next-generation drug delivery platforms. By addressing these challenges, MOFs hold immense potential to deliver precise, personalized, and multifunctional spatio-temporal drug-delivery systems for precision medicine.

Conclusion

Recent investigations into metal-organic frameworks (MOFs) as drug delivery nanocarriers and multisponsive systems have introduced transformative approaches to targeted and intelligent drug delivery. These nanoscale platforms, leveraging their tunable architectures and responsiveness to biological and physical stimuli, possess significant potential for optimizing drug pharmacokinetics, enhancing solubility and bioavailability, and minimizing systemic toxicity. Nevertheless, the transition from laboratory research to widespread clinical application faces considerable hurdles, primarily concerning chemical and colloidal stability within physiological environments, comprehensive assessment of biocompatibility and long-term toxicity profiles, challenges in industrial-scale production while maintaining batch uniformity and quality control, and the imperative for establishing standardized regulatory frameworks.

Looking forward, several critical research directions should be prioritized to facilitate the clinical translation of MOF-based drug-delivery systems. First, the development of highly stable MOFs capable of maintaining their structural integrity under physiological conditions while preserving stimuli-responsive behavior remains a major objective. Surface engineering approaches, including polymer coatings, biomimetic membranes, and hybrid nanocomposites, may provide effective solutions for enhancing stability and prolonging

circulation time. Second, comprehensive safety evaluation protocols must be established. Future studies should move beyond short-term in vitro assessments and focus on long-term in vivo investigations, including biodistribution, biodegradation pathways, immunogenicity, and chronic toxicity. The generation of standardized datasets will be essential for comparing different MOF platforms and supporting regulatory approval processes. Third, scalable and environmentally sustainable manufacturing strategies should receive greater attention. Continuous-flow synthesis, solvent-free approaches, and green chemistry methodologies have the potential to improve reproducibility while reducing production costs and environmental impact. Such developments will be crucial for industrial implementation and commercialization. Furthermore, the integration of computational modeling, machine learning, and artificial intelligence is expected to accelerate the rational design of MOFs with optimized pore structures, drug-loading capacities, and biological performance. Data-driven approaches may significantly reduce the time and cost associated with experimental screening and material development. Finally, future efforts should focus on bridging the gap between laboratory-scale success and clinical application through interdisciplinary collaborations involving materials scientists, pharmacologists, toxicologists, clinicians, and regulatory experts. Only through such coordinated efforts can MOF-based nanotherapeutics progress from promising experimental platforms to clinically approved systems for the treatment of cancer, infectious diseases, and other complex disorders. The future trajectory of this field will hinge on advancing strategies for augmenting MOF stability, engineering multifunctional nanodispersions capable of sequential and coordinated responses to multiple stimuli, and integrating cutting-edge technologies such as artificial intelligence for the discovery and optimization of novel materials. The realization of effective and safe therapeutic applications necessitates a holistic approach, encompassing precise molecular design, in-depth preclinical studies, and robust interdisciplinary collaborations. In light of these advancements, this new generation of nanotherapeutics is poised to usher in a novel era in the treatment of complex diseases, including cancer and chronic inflammatory conditions.

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