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**Review Article**

# Advancing Drug Delivery with Metal-Organic Frameworks: Challenges, Synthesis and Application

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## ABSTRACT

Metal-Organic Frameworks (MOFs), a novel class of crystalline hybrid materials composed of metal ions or clusters bridged by organic linkers, have emerged as promising candidates in drug delivery due to their high porosity, exceptional surface area, and customizable structural features. This review provides a comprehensive analysis of the design, functionalization, and application of MOFs in advanced drug delivery systems. The synthesis methods, including solvothermal, microwave-assisted, are discussed in relation to tailoring MOF properties for specific therapeutic purposes. Particular focus is placed on the capacity of MOFs to encapsulate a wide variety of therapeutic agents, ranging from small-molecule drugs to macromolecules such as peptides, proteins, and nucleic acids, with high efficiency. Key mechanisms of drug release, including pH-sensitive, enzyme-responsive, and photo-thermal triggered systems, are explored, showcasing the potential of MOFs to enable targeted and controlled release profiles. The role of functionalized MOFs in enhancing biocompatibility, reducing systemic toxicity, and improving pharmacokinetics is examined in depth, along with the incorporation of MOFs in multi-modal therapeutic strategies such as combined chemotherapy and photodynamic therapy. Furthermore, the review highlights recent breakthroughs in leveraging MOFs for challenging therapeutic applications, including cancer treatment, antimicrobial resistance, and precision medicine. This review emphasizes ongoing efforts to address these challenges through innovative material design, offering a roadmap for future research. By synthesizing the current knowledge and identifying gaps in the field, this article underscores the transformative role of MOFs in advancing drug delivery technologies and their promise to revolutionize therapeutic interventions in the near future.

## INTRODUCTION

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With the rapid progress in materials science, considerable attention has been focused on the development of advanced nanoplatforms for the controlled and intelligent release of drugs, aiming to enhance therapeutic efficacy while minimizing unwanted side effects.[1] Metal- Organic Frameworks (MOFs) have emerged as a promising class of hybrid materials, which are made up of metal ions or metal clusters bonded with organic linkers to form highly porous crystalline networks.[2] Since their inception in 1989 by Hoskins and Robson, MOFs have attracted a great deal of interest because of their molecular-level tunability, ultrahigh porosity, and modular design.[3] The Cambridge Structural Database currently has over 20,000 MOF structures, demonstrating the field's rapid expansion and the materials' promise for a range of uses, including drug delivery.[4] MOFs are perfect for biomedical applications because of their special physicochemical characteristics, which include large surface area, tunable pore size, adjustable morphology, and the capacity to alter their hydrophilicity or hydrophobicity. In addition to medication delivery, MOFs have shown promise in a number of other areas, including gas storage, separations, imaging, catalysis, sensing, and energy storage.[5] However, MOFs are especially promising for biomedical applications, where drug delivery has seen the quickest progress in recent years, due to their customisable porosity, functionalizability, and structural plasticity.[6]

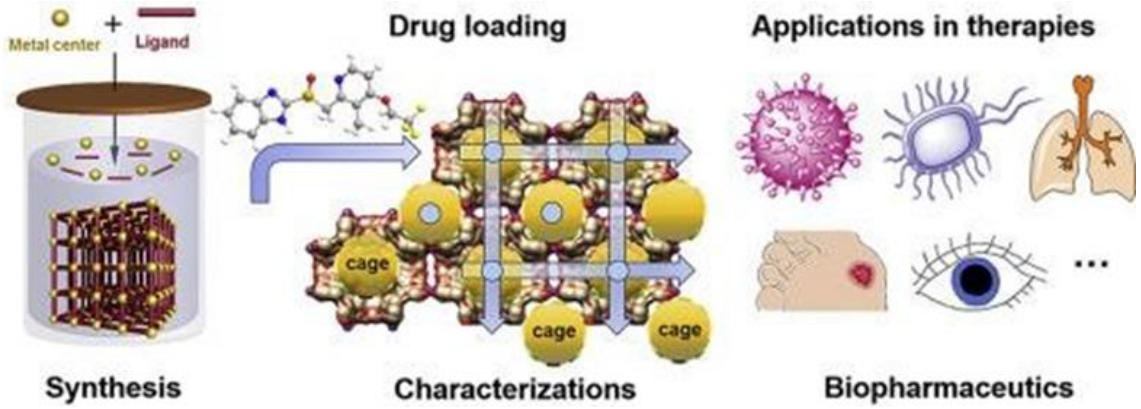


**Figure 1: Basics of MOFs for Drug Delivery Systems [5]**

Research on MOFs as drug transporters has surged during the past ten years, leading to notable improvements in both their design and use. MOFs have a number of clear benefits over conventional nanocarriers such liposomes, polymers, quantum dots, and inorganic nanoparticles.[5] For a wide range of therapeutic agents, including peptides, small pharmacological molecules, and even biomacromolecules, their enormous surface areas allow for remarkable drug-loading capabilities, frequently over 100%. Furthermore, by choosing particular metal nodes and organic linkers, researchers can optimise the characteristics of MOFs and create carriers with effective encapsulation, stimuli-responsive drug release profiles, and regulated biodegradability. Without substantially changing their physicochemical characteristics, MOFs' potential is further increased by the ability to modify their surfaces by post-synthetic functionalisation or pre-synthetic design, allowing for targeted and intelligent drug delivery.[7] For example, surface coatings containing silica, lipids, or polymers enhance stability and biocompatibility while preserving the MOF structure's functional integrity.[8] Because of the weak coordinative connections in their structures, MOFs are naturally biodegradable, which increases their attractiveness for therapeutic applications by guaranteeing their safe breakdown into non-toxic components in biological

contexts.[9] Additionally, certain MOFs have medicinal qualities of their own.[7] For instance, Fe-based MOFs have shown inherent antibacterial activity and the capacity to improve the effectiveness of radiation therapy, providing multiple uses in the treatment of infectious diseases and cancer.[10] These attributes highlight the vast potential of MOFs in advanced therapeutic approaches, such as the ranostics, which integrate diagnostics and therapy into a single platform.[11] Research on MOFs' potential in medication delivery systems has grown in importance as interest in these materials keeps rising. [12] Aspects of MOFs in biomedicine, including as their application in theranostics, stimuli-responsive systems, and cancer treatment, have been covered in a number of reviews. [13] Refer figure1. Their usefulness in bio-applications has increased with the introduction of biological MOFs (BioMOFs), which are made of biomolecular linkers such cyclodextrins, amino acids, and nucleobases.[14] Additionally, MOFs' better adaptability in terms of drug loading, controlled release, and biodegradability has been highlighted by comparisons with other nanocarriers, including dendrimers and mesoporous silica nanoparticles.[7] This review aims to explore the transformative potential of MOFs in DDSs, emphasizing their design, synthesis, characterization, and practical applications in disease treatment. As MOFs continue to evolve, their integration with emerging technologies, such as microrobotics and personalized medicine, promises to revolutionize the field of drug delivery, paving the way for next-generation therapeutic strategies. In figure 2 data indicates the growing interest and research output related to Metal-Organic Frameworks (MOFs) over the years, as reflected in the number of publications or mentions. The significant increase from 2010 to 2025 showcases the rising importance of MOFs in various fields such as catalysis, gas storage, drug delivery, and more.

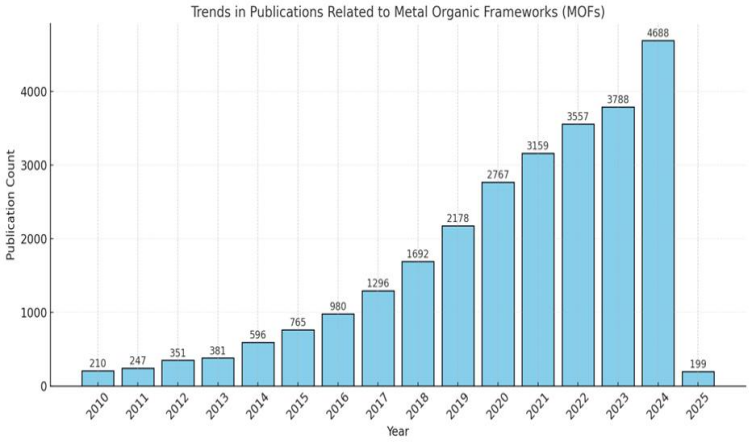


**Figure 2: Annual Trends in Publications on Metal-Organic Frameworks**

## Classification Of MOFS for Drug Delivery Systems (DDS)

Metal-Organic Frameworks (MOFs) have gained significant attention in drug delivery systems (DDS) due to their tunable structures, biocompatibility, and biodegradability.[15] The classification of MOFs for DDS is primarily based on the metal ions used in their synthesis, as these metals influence the framework's stability, drug loading capacity, and release profile. Refer figure 3. Below are some of the commonly studied MOFs based on their metal ions:

### Classification by Metal Ions

### Cr-MOFs (Chromium-based Metal-Organic Frameworks)

Chromium-based MOFs, such as MIL-100(Cr) and MIL-101(Cr), are constructed using chromium (III) ions coordinated with organic carboxylate

linkers like 1,3,5- benzenetricarboxylic acid (BTC) and 1,4-benzenedicarboxylic acid (BDC).[16] The frameworks feature octahedral metal clusters linked by these organic ligands, resulting in highly porous structures.[17] The high surface area and porosity of these MOFs make them suitable for applications like drug delivery, where their ability to encapsulate large quantities of drugs is particularly beneficial. [12] For instance, MIL-101(Cr) has demonstrated a drug-loading capacity of up to 1.4 grams of ibuprofen (IBU) per gram of MOF. This property makes them ideal for delivering hydrophobic drugs in a controlled manner, potentially enhancing therapeutic effects while minimizing side effects. [7] Aside from drug delivery, Cr-MOFs have also been explored for gas storage, catalysis, and water treatment, benefiting from their large surface area and versatility.[15] However, the potential toxicity of chromium, especially in its hexavalent form (Cr(VI)), poses a significant limitation to their use in biomedical applications.[18] While Cr(III) is less toxic, concerns remain About the potential release of chromium ions from the MOF during degradation, which could be harmful to health.[19] This highlights the need for further research on the safety, biodegradability, and biocompatibility of Cr-based MOFs in living systems. Alternative materials or modifications may be necessary to address these toxicity concerns for broader biomedical.

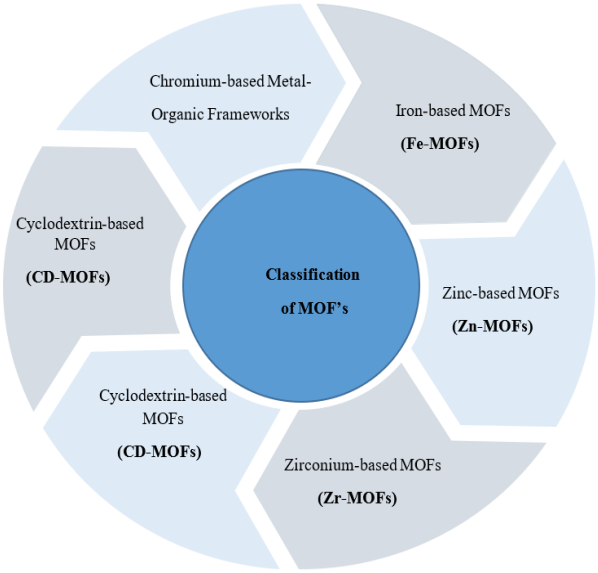


**Figure 3: Classification of MOFs for Drug Delivery Systems**

**Fe-MOFs (Iron-based Metal-Organic Frameworks)**

Iron-based Metal-Organic Frameworks (Fe-MOFs), such as MIL-53(Fe), are highly versatile materials synthesized by coordinating Fe(III) ions with organic carboxylate ligands like terephthalic acid. [20] One of the key features of Fe-MOFs is their unique structural flexibility, which allows these frameworks to undergo reversible changes in response to external stimuli, such as temperature and pressure. [21] This flexibility makes Fe-MOFs ideal candidates for various applications in drug delivery, especially in environments where responsive behavior is crucial. [5]

Fe-MOFs have been shown to successfully load and deliver a variety of drugs, including anticancer agents like oridonin and retroviral drugs, owing to their high surface area and tunable pore structures. [7] Their ability to encapsulate drugs is enhanced by the presence of open metal sites, which facilitate the adsorption of therapeutic molecules. [22] This characteristic is particularly useful in

controlled drug release applications, where the release profile can be tailored according to the needs of specific drugs or disease sites.

In addition to their use in drug delivery, Fe-MOFs also possess significant potential in medical imaging, particularly in magnetic resonance imaging (MRI). This is due to the paramagnetic properties of Fe(III) ions, which can enhance the contrast in MRI scans [23]. This makes Fe-MOFs valuable not only as drug carriers but also as diagnostic tools in medical applications, especially for monitoring the distribution and release of drugs in vivo. [24] One of the most promising aspects of Fe-MOFs in drug delivery is their biodegradability and low toxicity. [25] These properties make them particularly suitable for biomedical applications, where the long-term accumulation of materials in the body could pose risks. Fe-MOFs are designed to degrade safely, which minimizes the chances of harmful side effects. [26] Moreover, they are able to respond to the acidic microenvironment of tumors, a characteristic that is highly advantageous in cancer therapies. The pH-responsive release mechanism allows for more targeted drug delivery, ensuring that the drug is released predominantly at the tumor site, where the environment is more acidic than in normal tissues. [27] The combination of these beneficial properties—flexibility, high drug loading capacity, potential for MRI applications, biodegradability, and pH-responsive release—makes Fe-MOFs an attractive option for use in drug delivery systems (DDS). [7] Their ability to deliver drugs in a controlled, targeted manner, especially in anticancer treatments, has been the focus of extensive research, with promising results in preclinical and clinical settings. [28] Given their biocompatibility and relatively low toxicity, Fe-MOFs are expected to play a significant role in the development of more effective and safer drug delivery systems in the future. [7]

**Zinc-based MOFs (Zn-MOFs)**

Zinc-based Metal-Organic Frameworks (Zn-MOFs), including structures like ZIF-8 and Zn-BDP_X, are composed of Zn(II) ions coordinated with organic ligands such as imidazolate or pyrazolate. These frameworks are highly stable in aqueous environments, which makes them particularly valuable for biomedical applications, especially for drug delivery systems. The inherent stability and tunability of Zn-MOFs allow for the efficient encapsulation and controlled release of therapeutic agents. [7] Zn-MOFs have demonstrated significant success in delivering a range of anticancer drugs, including mitoxantrone, 5-fluorouracil (5-FU), and curcumin. [29] This success can be attributed to their ability to encapsulate both hydrophilic and hydrophobic drugs, overcoming the typical limitations faced by conventional drug delivery systems. Hydrophobic drugs, which are often challenging to deliver, benefit from the ability of Zn-MOFs to improve their solubility, thus enhancing bioavailability. [30]

In addition to their drug encapsulation capabilities, Zn-MOFs exhibit pH-responsive release behavior, which makes them ideal for targeted drug delivery to acidic environments such as tumors.[31] The release of the drug can be triggered under acidic conditions, facilitating the precise delivery of the therapeutic agent to the tumor site, thereby reducing the systemic side effects typically associated with chemotherapy. [32] The stability, biodegradability, and targeted drug delivery potential of Zn-MOFs make them promising candidates for advanced cancer therapies. Their ability to encapsulate a wide range of drugs, improve solubility, and provide pH-responsive release properties positions them as highly effective carriers in the field of drug delivery systems[31]. With ongoing research into their applications, Zn-MOFs hold significant promise in improving the efficacy and safety of drug treatments, particularly for cancer therapy.[33]

**Zirconium-based MOFs (Zr-MOFs)**

Zirconium-based Metal-Organic Frameworks (Zr-MOFs), such as UiO-66, are synthesized using Zr(IV) ions that coordinate with carboxylate ligands, which contribute to their exceptional stability.[34] These frameworks are renowned for their ability to withstand harsh environmental conditions, including high temperatures and acidic environments, making them highly suitable for challenging biomedical applications.[35] The robustness of Zr-MOFs is one of their key advantages, particularly in drug delivery systems that require durability under physiological conditions.[22] Zr-MOFs, including UiO-66, have shown great potential in drug delivery, especially in co- delivery systems where multiple drugs can be delivered simultaneously.[36] This ability to deliver diverse therapeutic agents allows for more comprehensive treatment strategies, such as combination therapies for cancer. For instance, UiO-66 has been utilized to deliver anticancer drugs like 5-fluorouracil (5-FU) and dichloroacetate, demonstrating controlled release profiles.[37] This capability is especially important for improving the efficacy of cancer treatments, as controlled release minimizes side effects and enhances therapeutic outcomes.[28] Another significant advantage of Zr-MOFs is their versatility in drug loading. These frameworks can load both hydrophilic and hydrophobic drugs, which expands their applicability to a broad range of drug types.[5] This makes them particularly useful in targeted cancer therapies, where long-term drug release and precise targeting of tumor cells are crucial.[38] The ability to tailor the release profiles of drugs through the structural properties of Zr-MOFs further enhances their suitability for therapeutic applications.[5] Moreover, the low toxicity, excellent stability, and biodegradability of Zr-MOFs make them strong candidates for therapeutic and diagnostic applications.[39] Their properties enable them to be used not only for delivering cancer drugs but also for potential imaging and diagnostic purposes, where stability and biocompatibility are paramount. As research on Zr-MOFs continues to advance, their role in drug delivery systems, especially for cancer therapy, is expected to expand, offering promising outcomes for improved patient care.[40]

**Cyclodextrin-based MOFs (CD-MOFs)**

Cyclodextrin-based Metal-Organic Frameworks (CD-MOFs) are a subclass of potassium- based MOFs in which potassium ions are coordinated with cyclodextrin (CD) linkers.[41]These frameworks are particularly valued for their water solubility and biodegradability. CD-MOFs are highly effective for the delivery of poorly soluble drugs, such as azilsartan and lansoprazole, because the cyclodextrin units enhance the solubility of hydrophobic drugs. [42] This makes CD-MOFs ideal candidates for facilitating drug delivery through various routes, including oral, intravenous, and pulmonary administration.[7] In addition to improving solubility, CD-MOFs are also beneficial in providing sustained drug release, allowing for the maintenance of therapeutic drug levels over extended periods.[43] This property is especially useful for oral drug delivery, where enhancing the bioavailability of drugs is critical. The non-toxic, biodegradable, and water-soluble nature of CD-MOFs further contributes to their suitability for clinical applications, particularly in drug delivery systems that aim to improve the therapeutic outcomes of poorly soluble drugs.[7] Their ability to enhance drug solubility and release profiles positions CD-MOFs as promising materials for improving the efficacy and safety of drug therapies.[44]

**Copper-based MOFs (Cu-MOFs)**

Copper-based Metal-Organic Frameworks (Cu-MOFs) are an important subclass of MOFs that utilize copper ions as metal centers, typically coordinated with organic carboxylate ligands like benzene-1,4-dicarboxylic acid (BDC).[45] These frameworks can also incorporate functionalized

organic linkers to further enhance their drug-loading capabilities. The high surface areas and uncoordinated metal sites in Cu-MOFs allow for efficient drug adsorption and controlled release, making them highly effective for drug delivery applications. Cu-MOFs have been shown to successfully load a variety of therapeutic agents, including anti- inflammatory drugs like ibuprofen (IBU), anticancer agents such as doxorubicin, and other pharmaceutical compounds. The ability to control the release of these drugs makes Cu-MOFs particularly useful in addressing chronic conditions, where sustained drug delivery is crucial for therapeutic success. In addition to their use in cancer therapies, Cu-MOFs are valuable in antibacterial drug delivery. Their strong binding to drug molecules, coupled with the flexibility to release drugs in a controlled manner, makes them ideal for antibacterial treatments. Cu-MOFs are also being explored in dual-drug delivery systems, where two therapeutic agents can be delivered simultaneously, offering synergistic effects for more effective treatment outcomes. [7] Due to their stability, versatility in loading different drug types, and efficient drug release mechanisms, Cu-MOFs are proving to be highly promising candidates for a broad range of therapeutic applications, including both antibacterial and anticancer treatments. These features position Cu-MOFs as potential game-changers in the development of more effective and targeted drug delivery systems.[46]

**Synthesis Of MOFS**

The synthesis of Metal-Organic Frameworks (MOFs) can be carried out using several methods, each offering distinct advantages for controlling the properties and functionality of the resulting structures.[47] Refer Figure 4. The following are some commonly used methods for synthesizing MOFs, along with detailed explanations:

**Hydrothermal/ solvothermal synthesis**

The hydrothermal or solvothermal synthesis method is one of the most widely employed approaches for the preparation of MOFs due to its versatility and effectiveness. In this technique, metal precursors and organic ligands are dissolved in a solvent or a mixture of solvents. Common solvents include water, alcohols, or other organic solvents like DMF (dimethylformamide) or DEF (diethylformamide).[48] The prepared solution is then transferred to a sealed reaction vessel, typically an autoclave, where it is subjected to high temperatures and pressures for a specified duration. These elevated conditions facilitate the formation and crystallization of MOF structures, driven by the slow reaction kinetics and stable environment provided by the autoclave.[49] The solvent used in this process plays a dual role. It not only dissolves the reactants but also contributes to stabilizing the coordination between metal ions and organic linkers during the crystallization process.[50] Adjusting the temperature, pressure, reaction time, and choice of solvent allows researchers to control critical aspects of the MOF, such as its porosity, particle size, and morphology. For example, variations in temperature can influence the nucleation and growth rate of crystals, which in turn affects their size and uniformity. Similarly, the choice of solvent can dictate the solubility of the precursors and the resulting framework structure.[51] The hydrothermal/solvothermal method is particularly advantageous for producing highly crystalline MOFs with well-defined structures and tunable properties. By carefully optimizing the reaction parameters, it is possible to synthesize MOFs with specific pore sizes, surface areas, and functionalities tailored for various applications, such as gas storage, catalysis, or drug delivery [51]. Moreover, this method is relatively straightforward and does not require highly specialized equipment, making it accessible for both laboratory and industrial-scale production.[52]

A notable example of this method is the synthesis of UiO-66, a zirconium-based MOF known for its exceptional stability and porosity. UiO-66 is typically prepared using zirconium chloride or zirconium oxynitrate as the metal source and terephthalic acid as the organic linker in a solvent mixture of DMF and water.[53] The reaction is conducted at elevated temperatures (120– 200°C) for several hours, resulting in a highly crystalline product. Similarly, MIL-101, an iron or chromium-based MOF, is synthesized using hydrothermal or solvothermal conditions, often employing water or DMF as the solvent. The temperature and solvent conditions can be varied to produce MIL-101 with different particle sizes and morphologies, depending on the intended application.[54]

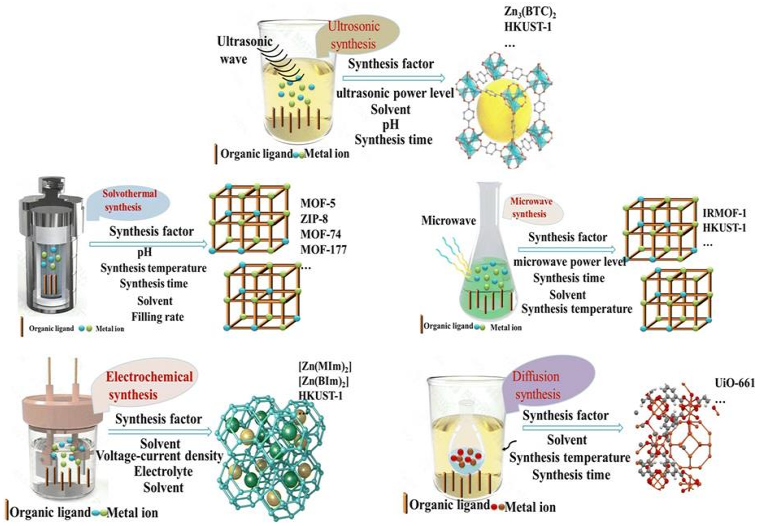


**Figure 4: Different methods of synthesis of MOFs for Drug Delivery Systems [81]**

**Solvent-assisted ligand exchange (SALE)**

The solvent-assisted ligand exchange (SALE) method is a post-synthetic modification approach used to tailor the properties of pre-synthesized MOFs. In this process, an existing MOF is exposed to a solution containing a new ligand that can partially or completely replace the original ligand(s) coordinated to the metal nodes.[55] This exchange occurs under mild conditions, making it possible to modify the functionality of the MOF without compromising its structural integrity. SALE is particularly valuable for enhancing the performance of MOFs by improving their stability, catalytic activity, pore structure, or selectivity toward specific guest molecules.[56] The mechanism of SALE typically involves the new ligand diffusing into the MOF's pores, where it competes with the existing ligand for coordination with the metal centers.[57] The success and extent of ligand exchange depend on several factors, including the affinity of the new ligand for the metal center, the structural flexibility of the MOF, the solvent used, and the reaction time. For instance, solvents that solubilize the new ligand effectively while promoting ligand mobility within the MOF framework are essential for efficient exchange.[58] SALE has been widely applied to modify MOFs like MIL-101, a chromium-based framework. By exchanging its original terephthalate or trimesate linkers with ligands containing functional groups such as amines, sulfonates, or phosphonates, researchers have enhanced MIL-101's stability under acidic or basic conditions. Additionally, SALE has been used to fine-tune the pore size and chemical environment of MIL-101 to improve its capacity for gas storage, drug delivery, or catalysis. For example, replacing some of the original ligands with functionalized ones has resulted in MIL-101 variants with improved guest-host interactions, thereby

increasing their adsorption capacity and selectivity for specific molecules. This method is not limited to MIL-101; SALE has also been employed with other MOFs, including those based on zirconium, iron, and copper, to introduce functionalities such as hydrophobicity, chirality, or catalytic activity. By retaining the MOF's core structure while selectively modifying its properties, SALE has emerged as a versatile and practical approach to expand the application scope of MOFs in various fields, including environmental remediation, drug delivery, and heterogeneous catalysis. [59]

**Mechanochemical synthesis**

Mechanochemical synthesis is an efficient and environmentally friendly method for producing MOFs. This technique involves solid-state reactions where mechanical force—such as grinding or milling—is applied to mixtures of metal salts and organic ligands without the use of solvents. The mechanical energy facilitates bond breaking and formation, leading to the creation of MOF structures. Unlike conventional solution-based methods, mechanochemical synthesis eliminates solvent use, reducing waste and making the process more sustainable. This feature makes it particularly attractive for green chemistry applications.[60] The mechanochemical process can be performed using various devices, such as ball mills, pestles, or automated grinders. When subjected to mechanical stress, the reactants undergo localized heating and pressure, which initiate the reaction between the metal and ligand. This technique is especially beneficial for synthesizing MOFs that are sensitive to solvents or moisture, as the absence of a solvent minimizes potential degradation of the framework during synthesis.[61] A notable example is the synthesis of Cu-MOFs, such as Cu-BTC (also known as HKUST-1). Using a mechanochemical approach, copper salts and trimesic acid (BTC) are mixed and ground together, resulting in the formation of the desired framework without the need for high temperatures or solvents. This method not only simplifies the synthesis process but also improves efficiency by eliminating solvent-related steps like drying and purification.[62] Additionally, the energy consumption of mechanochemical synthesis is relatively low compared to solvothermal methods, further enhancing its appeal for large-scale MOF production. Beyond Cu-MOFs, the mechanochemical approach has been successfully applied to a wide range of MOFs, including those based on zinc, aluminum, and zirconium. It allows for the rapid and scalable production of MOFs while maintaining control over particle size and morphology.[63] Recent advances in mechanochemical synthesis have even enabled the incorporation of functional additives or dopants during grinding, allowing for the customization of MOF properties for specific applications, such as catalysis, gas storage, or drug delivery.[58] This versatility and sustainability position mechanochemical synthesis as a pivotal method in modern MOF research and production.

**Electrochemical synthesis**

Electrochemical synthesis is a method that uses an electric current to drive the formation of MOFs. In this approach, metal ions are generated via anodic dissolution from a metal electrode and subsequently coordinated with organic ligands in the reaction medium to form the MOF framework. This technique is particularly advantageous for producing MOFs with controlled structures, crystal sizes, and morphologies, as the application of the electric current can precisely regulate the reaction kinetics and crystal growth rates.[47] During the process, the electrochemical reaction generates a continuous supply of metal ions, which react with the organic ligands dissolved in the electrolyte solution. The method allows for high yields and often eliminates the need for additional metal salts, making it more sustainable and cost-effective compared to traditional chemical routes. Electrochemical synthesis is particularly suitable

for large-scale MOF production due to its straightforward setup and the ability to fine-tune synthesis parameters like current density, voltage, and reaction time. An example of this method is the synthesis of copper-based MOFs, such as HKUST-1 (Cu- BTC). In this case, copper is electrochemically dissolved from a copper anode in the presence of trimesic acid (BTC) ligands in a solvent system. The copper ions released from the electrode react with the ligands to form the MOF framework. The process is often conducted at room temperature, making it energy-efficient while allowing precise control over the crystal morphology and size. [58] This method has also been employed to synthesize other MOFs, including MIL-53, MIL-100, and ZIF-8, by using different metal electrodes (such as aluminum or zinc) and organic linkers. Electrochemical synthesis has shown promise for producing high-quality MOFs with desirable properties for applications in gas storage, catalysis, and drug delivery.[63] Moreover, the ability to fabricate MOFs directly on conductive substrates through this method opens avenues for developing MOF-based devices, such as sensors and electrodes for energy storage.

**Direct synthesis (one-pot synthesis)**

Direct synthesis, also known as one-pot synthesis, is a straightforward approach for preparing MOFs by mixing metal salts and organic ligands in a single step. This process typically involves dissolving the reactants in an appropriate solvent under ambient or slightly elevated conditions to enable the formation of the MOF framework47. The simplicity of this method makes it highly attractive, as it does not require multiple stages or the isolation of intermediates, thereby reducing the overall time and complexity involved in the synthesis.[64] One of the key benefits of direct synthesis is its efficiency in yielding MOFs with minimal preparation steps. However, achieving high crystallinity and purity can be a challenge, as the conditions may not always favor the controlled growth of the MOF crystals. Compared to more controlled methods such as solvothermal or hydrothermal synthesis, the crystals produced via direct synthesis might exhibit lower uniformity in terms of size and structure. Optimizing reaction parameters like temperature, concentration, solvent type, and pH can improve these outcomes.[58] A notable example of MOF synthesis using this method is ZIF-8, a zinc-based imidazolate framework. In this approach, zinc nitrate or zinc acetate (as the metal source) is mixed with 2- methylimidazole in a solvent such as methanol or water. The reaction leads to the rapid precipitation of ZIF-8 crystals, which can then be collected, washed, and dried. The method has been widely adopted due to its ease of use and scalability, making it suitable for industrial and research applications.[65] Direct synthesis is not limited to ZIF-8 and has been employed for a variety of MOFs, including MIL-53 and HKUST-1, under appropriately chosen reaction conditions. It is particularly suitable for applications requiring high-throughput production or when the focus is on feasibility rather than achieving the highest-quality crystalline frameworks.[58]

**Microwave-assisted synthesis**

Microwave-assisted synthesis leverages microwave radiation to rapidly heat the reactants in a controlled manner, significantly accelerating the synthesis process of MOFs compared to conventional solvothermal methods.[66] In this technique, the reaction mixture—typically comprising metal precursors and organic linkers dissolved in a solvent—is subjected to microwave irradiation, which provides uniform and efficient heating. This localized heating effect enhances reaction kinetics, leading to faster crystallization, reduced reaction times (sometimes within minutes), and improved energy efficiency. One of the significant advantages of microwave-assisted synthesis is the potential to achieve high yields of

MOFs with desirable properties, such as better crystallinity, uniform particle size, and tunable morphology. The ability to precisely control reaction conditions (e.g., temperature and time) makes this method particularly useful for synthesizing temperature- sensitive MOFs or frameworks that require specific heat profiles to form. It also opens pathways to "green" chemistry, as this technique often eliminates the need for prolonged heating and large solvent volumes, reducing environmental impact.[58] An example of a MOF synthesized via this method is MIL-53(Fe), where microwave irradiation at optimized temperatures and durations results in well-crystallized particles with narrow size distributions. Similarly, ZIF-8 has been efficiently synthesized using this approach, demonstrating high yields and exceptional structural properties within short reaction times. These examples highlight the utility of microwave-assisted synthesis for biomedical and industrial applications, where time efficiency and scalability are critical.[58] This approach is increasingly being adopted to prepare MOFs for applications ranging from drug delivery to catalysis, as the rapid and uniform heating ensures the reproducibility and scalability of the synthesis process.

**Liquid-liquid diffusion method**

The liquid-liquid diffusion method is a straightforward and efficient technique for synthesizing metal-organic frameworks (MOFs) in a two-phase liquid system. In this method, two immiscible liquids—one containing a metal precursor and the other containing an organic ligand—are brought into contact. The components diffuse across the liquid-liquid interface, initiating the crystallization of the MOF at this boundary. This process is driven by the gradual interaction and reaction of the metal ions with the organic linkers as diffusion progresses.[47] One of the key advantages of this method is the precise control over the diffusion rates of the reactants, which allows for the fine-tuning of crystal size, morphology, and uniformity. This is particularly useful for synthesizing MOFs with well-defined properties for specific applications. Additionally, because the reaction occurs at the interface, it minimizes the use of excess reactants and solvents, making the method relatively eco-friendly. The liquid-liquid diffusion method has been successfully used to synthesize MOFs such as Cu-BTC (copper-based MOF, also known as HKUST-1) and Co-MOFs (cobalt-based MOFs). For instance, in the synthesis of Cu-BTC, copper salts are dissolved in an aqueous phase while benzene-1,3,5-tricarboxylic acid (BTC) is dissolved in an organic solvent such as ethanol or acetone. When the two solutions are layered or placed in contact, the slow diffusion of BTC into the aqueous layer containing copper ions facilitates the nucleation and growth of MOF crystals at the interface. [58] This method is particularly valued for applications where control over particle size and morphology is critical, such as in drug delivery systems, catalysis, or gas adsorption. By optimizing parameters like diffusion rates, solvent selection, and reaction time, researchers can tailor the properties of the resulting MOFs to meet specific functional requirements.

**Seed-assisted synthesis**

Seed-assisted synthesis is a powerful method used in the preparation of metal-organic frameworks (MOFs), where pre-synthesized MOF crystals, known as "seeds," are introduced into a reaction mixture containing the necessary precursors—metal salts and organic linkers. These seeds serve as nucleation centers, facilitating the orderly growth of new MOF structures on their surfaces. This technique is particularly advantageous for achieving precise control over the morphology, size, and crystallinity of the resulting MOFs.[47]

One of the primary benefits of seed-assisted synthesis is its ability to produce MOF crystals with a uniform size and shape, which can be

challenging with other methods. By adjusting factors such as the quantity of seeds, the composition of the reaction mixture, and the reaction time, researchers can fine-tune the crystal growth process to obtain large and well-defined MOF structures [47]. This method is especially useful for growing large single crystals, which are often required for detailed structural analysis or specific applications like catalysis, separation, and sensing. For example, in the synthesis of ZIF-8, a zinc-based zeolitic imidazolate framework, small seed crystals are prepared initially and added to a fresh reaction solution containing zinc nitrate and 2-methylimidazole. The seeds act as templates, promoting the uniform deposition of additional layers of the MOF structure.[67] This approach enhances the scalability and reproducibility of ZIF-8 production, making it suitable for industrial applications. Seed-assisted synthesis is also utilized for creating hierarchical MOFs, where a secondary MOF grows around or on top of the seed crystals, leading to composite structures with enhanced functionality. This is particularly valuable in applications like drug delivery, where the outer MOF layer can provide controlled release properties, while the inner seed core offers structural stability or additional active sites for interaction with therapeutic molecules.[68] These methods offer a variety of options for synthesizing MOFs with different properties, including size, porosity, and functionality. The choice of synthesis method depends on factors such as the desired application, the metal and ligand used, and the required properties of the final product. Each method has its own advantages and challenges, and in some cases, combinations of these techniques may be used to optimize the MOF structure for specific uses.

**Drug Loading**

Drug loading in metal-organic frameworks (MOFs) involves incorporating therapeutic agents into the porous structure of MOFs for drug delivery applications. The process leverages the high surface area, tunable pore sizes, and chemical functionality of MOFs. Drug loading methods can be categorized into two primary approaches: incorporation during synthesis and post-synthetic drug loading.[5]

**Drug Loading During MOF Synthesis**

Drug loading during MOF synthesis involves incorporating drug molecules into the reaction mixture containing metal precursors and organic ligands. As the MOF crystallizes, the drug molecules become encapsulated within the framework. This method is advantageous because it typically results in high drug-loading capacity and allows for a uniform distribution of the drug throughout the MOF structure. The inclusion of drugs in the synthesis stage also helps to stabilize the drug molecules, as they become trapped within the stable, porous structure of the MOF.[63] However, this method does have some limitations. The harsh conditions required for MOF synthesis, such as high temperatures and the use of organic solvents, can potentially degrade sensitive drugs, limiting the types of drugs that can be incorporated during the synthesis process. Despite this, it remains a highly effective approach for creating drug-loaded MOFs for various therapeutic applications. For example, anticancer drugs like doxorubicin (DOX) have been successfully co-crystallized with MOFs during synthesis, resulting in drug-loaded nanoparticles with controlled release profiles suitable for targeted cancer therapy.[69]

**Post-Synthetic Drug Loading**

This approach involves first synthesizing the MOF, followed by introducing the drug into its pores via diffusion or adsorption. Refer figure 5. There are several variations:

**Incubation/Immersion**

In the incubation or immersion method of post-synthetic drug loading, the MOF is immersed in a solution of the drug, allowing the drug molecules

to diffuse into the framework's pores. This technique is relatively simple and does not require altering the MOF's synthesis process, making it versatile for various drugs. The drug loading occurs as the drug molecules enter the pores by diffusion, where they become adsorbed or trapped within the structure. For instance, MOF-74 has been used for loading ibuprofen (IBU) by immersing it in an ethanol solution of the drug.[70] However, one limitation of this method is the potentially long diffusion times required to achieve high loading efficiency, particularly for larger or more complex drug molecules. The time needed can depend on the porosity and surface area of the MOF, as well as the solubility of the drug in the solvent. As a result, it may be challenging to achieve high drug loading in a short period. Despite this limitation, incubation and immersion remain valuable methods for loading drugs into pre-synthesized MOFs, particularly when post-synthesis modification is desired.[5]

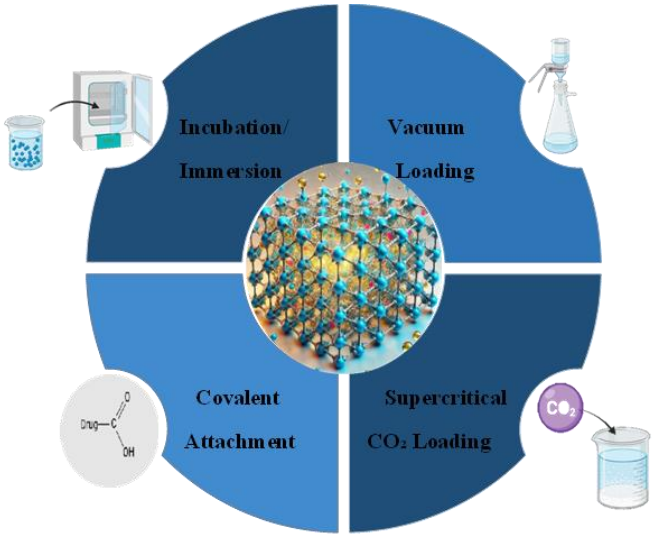


**Figure 5: Post Synthesis Drug Loading Methods in MOF's**

**Vacuum Loading**

In vacuum loading, the MOF is first subjected to a vacuum to remove air from its pores, creating a higher affinity for drug molecules. Once the pores are evacuated, the MOF is exposed to a drug solution, and the vacuum aids in the penetration of the drug molecules into the framework. The reduced pressure enhances the diffusion of drug molecules into the MOF's pores, ensuring that the drug is effectively adsorbed.[63] This technique is particularly useful for loading hydrophobic drugs that may not easily diffuse into the pores under normal conditions. For example, ZIF-8, a well-known MOF, has been successfully loaded with hydrophobic drugs like paclitaxel under vacuum conditions. The vacuum loading method provides a way to load a high quantity of drug molecules, enhancing the drug's therapeutic efficacy by improving its bioavailability.[31]

However, a potential challenge of this method is the difficulty in achieving uniform drug distribution within the MOF if the drug does not diffuse evenly throughout the material. Additionally, the method can be time-consuming, as the duration of vacuum application and drug loading can affect the overall efficiency of the process. Nonetheless, vacuum loading remains a valuable technique for enhancing drug encapsulation in MOFs, especially for poorly soluble or hydrophobic compounds.[71]

**Supercritical $CO_2$ Loading**

Supercritical $CO_2$ loading utilizes supercritical carbon dioxide as a solvent to dissolve the drug, which is then transferred into the MOF pores under

controlled conditions of pressure and temperature. In its supercritical state, $CO_2$ behaves as both a gas and a liquid, allowing it to penetrate the MOF structure and effectively deliver the drug into its porous framework. After the drug is loaded, the pressure is reduced, causing $CO_2$ to evaporate, leaving the drug trapped within the MOF. [72] This technique offers several advantages. First, it is solvent-free, which reduces the environmental impact associated with traditional solvent-based methods. Additionally, supercritical $CO_2$ is particularly effective for loading hydrophobic drugs that are poorly soluble in conventional solvents. The process also provides a high degree of control over the loading conditions, allowing for precise tuning of the drug loading amount. [73] For example, ibuprofen has been successfully loaded into MIL-101(Cr) using supercritical $CO_2$, demonstrating the effectiveness of this method for enhancing the loading of hydrophobic drugs. The use of supercritical $CO_2$ for drug loading is beneficial for improving the bioavailability of poorly soluble drugs, making it a promising technique for pharmaceutical applications. However, the method does require specialized equipment to achieve the supercritical state of $CO_2$, which can make the process more costly compared to other loading methods. Additionally, the process conditions, such as temperature and pressure, must be carefully optimized to prevent damage to the drug or the MOF structure. Despite these challenges, supercritical $CO_2$ loading remains a promising technique, particularly for applications where traditional solvent-based methods are less effective. [74] This technique is particularly useful for loading hydrophobic drugs that may not easily diffuse into the pores under normal conditions. For example, ZIF-8, a well-known MOF, has been successfully loaded with hydrophobic drugs like paclitaxel under vacuum conditions. The vacuum loading method provides a way to load a high quantity of drug molecules, enhancing the drug's therapeutic efficacy by improving its bioavailability. [31]

**Covalent Attachment**

Covalent attachment involves the formation of a strong chemical bond between the drug and the MOF framework, usually through functional groups that are incorporated into the organic linkers of the MOF. This method can enhance the stability of the drug within the MOF structure, preventing premature release and enabling controlled, sustained release over time. The covalent bonding ensures that the drug is tightly held in place, which is particularly beneficial for drugs that are prone to rapid leaching or degradation in aqueous environments.[75] For instance, MOFs with functionalized linkers, such as those incorporating carboxyl or amino groups, can be used to covalently attach small molecules like anti-inflammatory drugs. By chemically attaching the drug, the system improves stability and reduces the likelihood of burst release, making it more suitable for applications requiring prolonged drug release or targeted therapy. Covalent attachment is also advantageous because it can help control the drug release profile, as the drug is slowly released when the bond is broken under specific conditions, such as changes in pH or the presence of specific enzymes. This method is particularly useful for drugs that require a longer duration of action or those that may otherwise be unstable or susceptible to premature release.[7] The covalent attachment approach is highly customizable depending on the nature of both the drug and the MOF. However, it can be more complex and require more sophisticated synthetic strategies compared to other methods like simple adsorption or encapsulation.

**Factors Influencing Drug Loading**

The efficiency of drug loading into Metal-Organic Frameworks (MOFs) is influenced by several key factors:

**Pore Size and Surface Area:**

MOFs with larger pores and higher surface areas can accommodate more drug molecules, leading to higher drug-loading capacities. The larger the available space, the greater the potential to encapsulate or adsorb a larger quantity of the drug. This is one reason why MOFs with high porosity, such as MIL- 101 or ZIF-8, are particularly attractive for drug delivery applications.[7]

**Functional Groups:**

The chemical compatibility between the drug and the MOF structure plays a crucial role in the drug loading process. MOFs with functional groups (e.g., hydroxyl, carboxyl, amine) can interact with drug molecules via hydrogen bonding, π-π stacking, or electrostatic interactions. These interactions can enhance the drug's binding efficiency and stability within the MOF pores, making the loading process more efficient and controlled.

**Solvent Choice:**

The solvent used in the drug-loading process can significantly impact the solubility and stability of the drug during loading. The solvent must dissolve the drug efficiently and also interact favorably with the MOF. A poorly chosen solvent may lead to precipitation or poor distribution of the drug, thus affecting the loading efficiency. Solvents that can create a mild and controlled environment for drug loading are preferred for preserving the stability of both the MOF and the drug.

**Drug Concentration and Loading Time:**

Higher drug concentrations and longer loading times generally result in better drug-loading efficiency. Higher concentrations of the drug can increase the likelihood of more molecules entering the MOF pores. Extended loading times also allow the drug to diffuse more thoroughly into the MOF structure, improving the overall encapsulation or adsorption efficiency. However, the balance must be maintained as excessive drug concentration or time may lead to saturation or premature release.[5] Each of these factors contributes to the overall efficiency and effectiveness of the drug loading process and optimizing them can enhance the therapeutic potential of MOF-based drug delivery systems.

**Characterization Of Metal-Organic Frameworks (MOFS)**

Characterization of Metal-Organic Frameworks (MOFs) involves a variety of techniques to determine their structural, chemical, and physical properties. These methods are crucial for understanding the material's porosity, surface area, crystallinity, morphology, and drug loading capabilities. Included in figure 6. Commonly used characterization techniques for MOFs include:

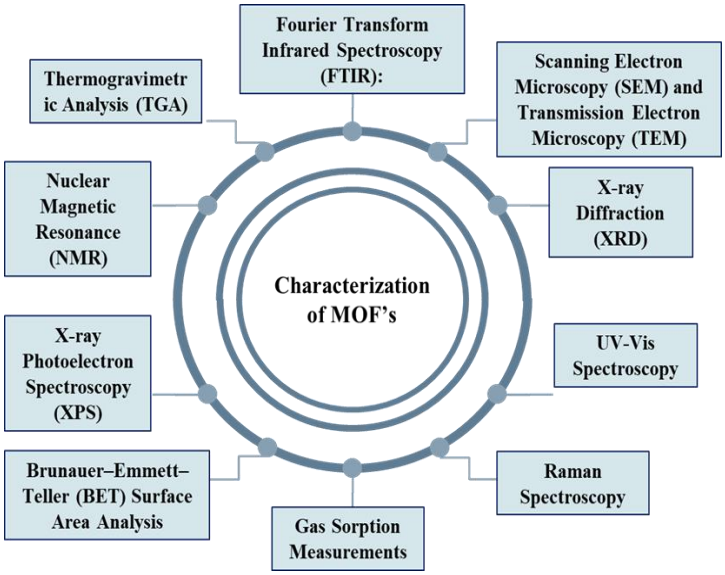


**Figure 6: Characterization Methods of MOF's**

**X-ray Diffraction (XRD):**

XRD is one of the most important techniques for determining the crystallinity and structure of MOFs. It provides information on the framework's symmetry, lattice parameters, and phase purity. High-resolution XRD is used to identify the type of MOF, determine the crystallographic space group, and confirm its structure.[77]

**Brunauer –Emmett–Teller (BET) Surface Area Analysis:**

The BET method is used to measure the surface area of MOFs by determining the amount of nitrogen gas adsorbed onto the surface at liquid nitrogen temperature. This technique provides insights into the porosity of the MOF, including both microporosity and mesoporosity, which is essential for evaluating the material's suitability for applications like drug delivery.[78]

**Scanning Electron Microscopy (SEM) and Transmission Electron Microscopy (TEM):**

SEM and TEM are used to investigate the morphology and particle size of MOFs. SEM provides detailed surface topography and helps determine the particle size and shape, while TEM offers higher resolution for internal structures at the nanometer scale. These methods are crucial for visualizing the MOF's surface and understanding the homogeneity and stability of the framework.

**Fourier Transform Infrared Spectroscopy (FTIR):**

FTIR is employed to study the chemical bonding in MOFs, particularly the functional groups present in the organic linkers and metal nodes. It helps in confirming the presence of the expected ligands and the interaction between the metal centers and organic molecules in the framework.

**X-ray Diffraction (XRD):**

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**Nuclear Magnetic Resonance (NMR):**

NMR is sometimes used to analyze the structure of the organic linkers in MOFs. It provides information on the chemical environment of hydrogen or carbon atoms and is useful for understanding the connectivity and bonding in the framework.

**Gas Sorption Measurements:**

These are used to measure the adsorption of gases such as nitrogen, carbon dioxide, or hydrogen on the MOF surface. This technique helps determine the surface area, pore size distribution, and porosity of the material, which are crucial for applications like gas storage, separation, and drug delivery

**Raman Spectroscopy:**

Raman spectroscopy can provide complementary information to FTIR by offering details on the vibrational modes of the molecules in the MOF structure. It can also be used to identify metal-ligand interactions and assess the structural integrity of the MOF.

**UV-Vis Spectroscopy:**

Raman spectroscopy can provide complementary information to FTIR by offering details on the vibrational modes of the molecules in the MOF structure. It can also be used to identify metal-ligand interactions and assess the structural integrity of the MOF.

**Applications Of MOFS In Therapy and Drug Delivery**

Metal-Organic Frameworks (MOFs) have demonstrated significant potential in various therapeutic and drug delivery fields due to their distinctive characteristics, such as high surface area, adaptable porosity, and chemical flexibility. MOFs are capable of encapsulating diverse therapeutic agents, which include small molecules, peptides, proteins, and nucleic acids, facilitating controlled release and targeted delivery to specific

tissues[79]. A major application of MOFs in therapy is their role in drug delivery systems. Their porous structure enables high drug loading capacities and regulated release profiles, making them suitable for sustained and targeted drug delivery. MOFs can safeguard sensitive medications from degradation, release drugs in response to environmental changes (like pH or temperature), and allow precise targeting by modifying their surfaces with ligands that can identify specific cell types or tissues.[46] In terms of therapeutic applications, MOFs have been utilized for the delivery of anticancer medications (like doxorubicin), antibiotics, and anti-inflammatory agents. Their capacity to target tumor sites or areas of inflammation enhances therapeutic outcomes while reducing side effects. For instance, cancer treatments benefit from MOF-based delivery methods that can encapsulate chemotherapeutic drugs and release them directly at the tumor location, minimizing systemic toxicity.[80] Another exciting application is in the treatment of genetic disorders through gene delivery. MOFs can enclose DNA, RNA, or small interfering RNA (siRNA) for gene therapy purposes. The nanostructured features of MOFs enable efficient transfection and controlled release of genetic material into targeted cells, allowing for the treatment of genetic illnesses at the molecular level. In the realm of pharmaceuticals, MOFs are increasingly recognized for their utility as drug carriers because of their versatility and capacity to encapsulate a wide array of drugs. Their biocompatibility, high surface area, and substantial pore volume make MOFs excellent drug carriers, enhancing the solubility, stability, and bioavailability of poorly soluble medications.

MOFs have particular advantages in the creation of controlled-release systems. By adjusting the properties of the MOF, such as pore size and surface chemistry, drug release can be regulated, enabling more accurate dosing and decreasing the frequency of medication administration. For instance, MOF-74, a zinc-based MOF, has been utilized to encapsulate and release the anti-inflammatory medication ibuprofen in a sustained manner. Moreover, MOFs are being investigated for use in vaccine delivery. Their extensive surface area facilitates the incorporation of antigens, while their surface can be modified with adjuvants to enhance immune responses. MOFs can also be employed to deliver proteins or enzymes, paving the way for potential applications in enzyme replacement therapies or protein-based treatments.[5]

**Functionalization Of MOFS And Design of Advanced Systems Using MOFS**

The adaptability of metal-organic frameworks (MOFs) stems from their capacity to be customized for particular applications in drug delivery. Customization entails altering the structure of the MOF, often by modifying the organic linkers or adding new functional groups to the MOF surface. This process enables precise adjustments of the drug loading and release characteristics, in addition to embedding targeting moieties that can strengthen the MOF's selectivity for cells or tissues.

**Surface Functionalization:**

Surface modification involves the addition of functional groups, such as amino, carboxyl, or thiol groups, to the exterior of the MOF. These groups can engage with drug molecules to enhance loading efficiency or create a suitable environment for drug release. For instance, MOFs can be modified with targeting ligands, including folic acid or antibodies that bind to overexpressed receptors on cancer cells, facilitating targeted drug administration.

**Incorporation of Stimuli-Responsive Elements:**

The incorporation of stimuli- responsive components is one of the most intriguing possibilities for MOFs, allowing them to react to environmental factors like pH, temperature, light,

or magnetic fields. By integrating such responsive elements, MOFs can release their cargo in a regulated fashion, making them suitable for pH-responsive drug delivery systems. For example, some MOFs have been designed to discharge their contents in acidic conditions, which is advantageous for targeting cancer cells that typically exhibit a lower pH than healthy tissues.[5]

**Nanocomposite MOFs:**

Advanced drug delivery systems frequently involve the combination of MOFs with other materials to improve their characteristics. MOF-based nanocomposites can be developed by integrating polymeric substances, lipid nanoparticles, or metal nanoparticles, resulting in hybrid systems that possess enhanced stability, biocompatibility, and drug release capabilities. These composites can offer extra functionalities, such as magnetic targeting or improved mechanical strength, which can aid in systemic drug delivery.

**Multifunctional MOFs:**

Multifunctional MOFs are crafted to execute several tasks at once, such as drug delivery, imaging, and therapy (theranostics). For example, MOFs can be modified to include both imaging agents and therapeutic drugs, enabling concurrent diagnosis and treatment of diseases such as cancer. These systems can be monitored using techniques like magnetic resonance imaging (MRI), fluorescence imaging, or positron emission tomography (PET).[7]

By integrating various functionalization techniques, MOFs can be tailored to address specific challenges in drug delivery, such as achieving substantial drug-loading capacity, enhancing stability, and improving targeting accuracy. Additionally, their application in personalized medicine is on the rise, as MOFs can be customized to align with individual patients' requirements based on the type of illness, drug, or delivery method.

## REFERENCES


1. Patra JK, Das G, Fraceto LF, Campos EVR, Del Pilar Rodriguez-Torres M, Acosta- Torres LS, et al. Nano based drug delivery systems: recent developments and future prospects. Journal of Nanobiotechnology [Internet]. 2018 Sep 19;16(1).
2. Zhang Q, Yan S, Yan X, Lv Y. Recent advances in metal-organic frameworks: Synthesis, application and toxicity. The Science of the Total Environment [Internet]. 2023 Aug 4;902:165944.
3. Kirlikovali KO, Hanna SL, Son FA, Farha OK. Back to the basics: developing advanced Metal–Organic frameworks using fundamental chemistry concepts. ACS Nanoscience Au [Internet]. 2022 Dec 27;3(1):37–45.
4. Majumdar S, Moosavi SM, Jablonka KM, Ongari D, Smit B. Diversifying databases of metal organic Frameworks for High-Throughput Computational Screening. ACS Applied Materials & Interfaces [Internet]. 2021 Dec 15;13(51):61004–14
5. Benny A, Pai SDKR, Pinheiro D, Chundattu SJ. Metal organic frameworks in biomedicine: Innovations in drug delivery. Results in Chemistry [Internet]. 2024 Jan 1;7:101414.
6. Sharabati MA, Sabouni R, Husseini GA. Biomedical Applications of Metal−Organic Frameworks for Disease Diagnosis and Drug Delivery: A review. Nanomaterials [Internet]. 2022 Jan 16;12(2):277.
7. He S, Wu L, Li X, Sun H, Xiong T, Liu J, et al. Metal-organic frameworks for advanced drug delivery. Acta Pharmaceutica Sinica B [Internet]. 2021 Mar 14;11(8):2362–95.
8. Chen X, Argandona SM, Melle F, Rampal N, Fairen-Jimenez D. Advances in surface functionalization of next-generation metal-organic frameworks for biomedical applications: Design, strategies, and prospects. Chem [Internet]. 2023 Oct 16;10(2):504–43.

9. Hubab M, Al-Ghouti MA. Recent advances and potential applications for metal- organic framework (MOFs) and MOFs-derived materials: Characterizations and antimicrobial activities. Biotechnology Reports [Internet]. 2024 Mar 20;42:e00837.
10. Chen Z, Xing F, Yu P, Zhou Y, Luo R, Liu M, et al. Metal-organic framework-based advanced therapeutic tools for antimicrobial applications. Acta Biomaterialia [Internet]. 2023 Dec 17;175:27–54.
11. Khan MU, Alissa M, Inam M, Alsuwat MA, Abdulaziz O, Mostafa YS, et al. Comprehensive overview of utilizing metal-organic frameworks (MOFs) for precise cancer drug delivery. Microchemical Journal [Internet]. 2024 Jun 24;204:111056.
12. Khafaga DSR, El-Morsy MT, Faried H, Diab AH, Shehab S, Saleh AM, et al. Metal– organic frameworks in drug delivery: engineering versatile platforms for therapeutic applications. RSC Advances [Internet]. 2024 Jan 1;14(41):30201–29.
13. Li B, Ashrafizadeh M, Jiao T. Biomedical application of metal-organic frameworks (MOFs) in cancer therapy: Stimuli-responsive and biomimetic nanocomposites in targeted delivery, phototherapy and diagnosis. International Journal of Biological Macromolecules [Internet]. 2024 Jan 20;260:129391.
14. Shahzaib A, Shaily N, Kamran LA, Nishat N. The Biomolecule-MOF Nexus: Recent advancements in biometal-organic frameworks (Bio-MOFs) and their multifaceted applications. Materials Today Chemistry [Internet]. 2023 Nov 6;34:101781.
15. Rabiee N. Sustainable metal-organic frameworks (MOFs) for drug delivy systems. Materials Today Communications [Internet]. 2023 May 18;35:106244.
16. Muñoz-Senmache JC, Cruz-Tato PE, Nicolau E, Hernández-Maldonado AJ. Confined space synthesis of chromium–based metal–organic frameworks in activated carbon: Synergistic effect on the adsorption of contaminants of emerging concern from water. Journal of Environmental Chemical Engineering [Internet]. 2022 Jan 29;10(2):107282.
17. Leus K, Muylaert I, Van Speybroeck V, Marin GB, Van Der Voort P. A coordinative saturated vanadium containing metal organic framework that shows a remarkable catalytic activity. In: Studies in surface science and catalysis [Internet]. 2010. p. 329– 32.
18. Liu S, Zhang L, Kim H, Sun J, Yoon J. Recent advances and challenges in monitoring chromium ions using fluorescent probes. Coordination Chemistry Reviews [Internet]. 2023 Nov 26;501:215575.
19. Mitra S, Chakraborty AJ, Tareq AM, Emran TB, Nainu F, Khusro A, et al. Impact of heavy metals on the environment and human health: Novel therapeutic insights to counter the toxicity. Journal of King Saud University - Science [Internet]. 2022 Jan 29;34(3):101865.
20. Joseph J, Iftekhar S, Srivastava V, Fallah Z, Zare EN, Sillanpää M. Iron-based metal-organic framework: Synthesis, structure and current technologies for water reclamation with deep insight into framework integrity. Chemosphere [Internet]. 2021 Jun 14;284:131171.
21. Elsaidi SK, Mohamed MH, Banerjee D, Thallapally PK. Flexibility in Metal–Organic Frameworks: A fundamental understanding. Coordination Chemistry Reviews [Internet]. 2017 Dec 26;358:125–52.
22. Raza A, Wu W. Metal-organic frameworks in oral drug delivery. Asian Journal of Pharmaceutical Sciences [Internet]. 2024 Aug 23;19(5):100951

23. Bunzen H, Jirák D. Recent advances in Metal–Organic frameworks for applications in magnetic resonance imaging. ACS Applied Materials & Interfaces [Internet]. 2022 Oct 14;14(45):50445–62.
24. Sharabati MA, Sabouni R, Husseini GA. Biomedical Applications of Metal−Organic Frameworks for Disease Diagnosis and Drug Delivery: A review. Nanomaterials [Internet]. 2022 Jan 16;12(2):277.
25. Pham H, Ramos K, Sua A, Acuna J, Slowinska K, Nguyen T, Bui A, Weber MDR, Tian F. Tuning crystal structures of iron-based metal-organic frameworks for drug delivery applications. ACS Omega. 2020;5(7):3418–3427. doi:10.1021/acsomega.9b03696
26. Wiśniewska P, Haponiuk J, Saeb MR, Rabiee N, Bencherif SA. Mitigating metal- organic framework (MOF) toxicity for biomedical applications. Chemical Engineering Journal [Internet]. 2023 Jun 25;471:144400.
27. Chu S, Shi X, Tian Y, Gao F. PH-Responsive Polymer nanomaterials for tumor therapy. Frontiers in Oncology [Internet]. 2022 Mar 22;12.
28. Elumalai K, Srinivasan S, Shanmugam A. Review of the efficacy of nanoparticle- based drug delivery systems for cancer treatment. Biomedical Technology [Internet]. 2023 Sep 29;5:109–22.
29. Li M, Zhang Z, Yu Y, Yuan H, Nezamzadeh-Ejhieh A, Liu J, et al. Recent advances in Zn-MOFs and their derivatives for cancer therapeutic applications. Materials Advances [Internet]. 2023 Jan 1;4(21):5050–93.
30. Hawthorne D, Pannala A, Sandeman S, Lloyd A. Sustained and targeted delivery of hydrophilic drug compounds: A review of existing and novel technologies from bench to bedside. Journal of Drug Delivery Science and Technology [Internet]. 2022 Nov 4;78:103936.
31. Gautam S, Lakhanpal I, Sonowal L, Goyal N. Recent advances in targeted drug delivery using metal-organic frameworks: toxicity and release kinetics. Next Nanotechnology [Internet]. 2023 Sep 1;3–4:100027.
32. Senapati S, Mahanta AK, Kumar S, Maiti P. Controlled drug delivery vehicles for cancer treatment and their performance. Signal Transduction and Targeted Therapy [Internet]. 2018 Mar 14;3(1).
33. Khan MU, Alissa M, Inam M, Alsuwat MA, Abdulaziz O, Mostafa YS, et al. Comprehensive overview of utilizing metal-organic frameworks (MOFs) for precise cancer drug delivery. Microchemical Journal [Internet]. 2024 Jun 24;204:111056.
34. Taddei M. When defects turn into virtues: The curious case of zirconium-based metal-organic frameworks. Coordination Chemistry Reviews [Internet]. 2017 Apr 29;343:1–24.
35. Abdelkareem MA, Abbas Qaisar, Mouselly M, Alawadhi H, Olabi AG. High- performance effective metal–organic frameworks for electrochemical applications. Journal of Science Advanced Materials and Devices [Internet]. 2022 May 10;7(3):100465.
36. Mansouri A, Badivi S, Ghodsi R, Jamshidi E, Jevinani HN, Farahmand F, et al. Folic Acid-Conjugated UIO-66-MOF enhances the targeted Co-Delivery of cisplatin and cyclophosphamide for breast cancer therapy. Journal of Drug Delivery Science and Technology [Internet]. 2024 Dec 1;106510
37. Zhao D, Zhang W, Yu S, Xia SL, Liu YN, Yang GJ. Application of MOF-based nanotherapeutics in light-mediated cancer diagnosis and therapy. Journal of Nanobiotechnology [Internet]. 2022 Sep 24;20(1).

38. Yao Y, Zhou Y, Liu L, Xu Y, Chen Q, Wang Y, et al. Nanoparticle-Based drug delivery in cancer therapy and its role in overcoming drug resistance. Frontiers in Molecular Biosciences [Internet]. 2020 Aug 20;7.
39. Chattopadhyay K, Mandal M, Maiti DK. A review on zirconium-based metal– organic frameworks: synthetic approaches and biomedical applications. Materials Advances [Internet]. 2023 Nov 21;5(1):51–67.
40. Al-Thani AN, Jan AG, Abbas M, Geetha M, Sadasivuni KK. Nanoparticles in cancer theragnostic and drug delivery: A comprehensive review. Life Sciences [Internet]. 2024 Jul 9;352:122899.
41. Han Y, Liu W, Huang J, Qiu S, Zhong H, Liu D, et al. Cyclodextrin-Based Metal- Organic Frameworks (CD-MOFs) in Pharmaceutics and biomedicine. Pharmaceutics [Internet]. 2018 Dec 12;10(4):271.
42. Chen X, Guo T, Zhang K, Chen J, Wang C, Ren X, et al. Simultaneous improvement to solubility and bioavailability of active natural compound isosteviol using cyclodextrin metal-organic frameworks. Acta Pharm Sin B. 2021;11(9):2914-23. doi:10.1016/j.apsb.2021.04.018.
43. Si Y, Luo H, Zhang P, Zhang C, Li J, Jiang P, et al. CD-MOFs: From preparation to drug delivery and therapeutic application. Carbohydrate Polymers [Internet]. 2023 Sep 20;323:121424.
44. Singh P, Feng J, Golla VK, Lotfi A, Tyagi D. Crosslinked and biofunctionalized γ-cyclodextrin metal organic framework to enhance cellular binding efficiency. Materials Chemistry and Physics [Internet]. 2022 Jul 16;289:126496.
45. Singh R, Singh G, George N, Singh G, Gupta S, Singh H, et al. Copper-Based Metal–Organic Frameworks (MOFs) as an emerging catalytic framework for click chemistry. Catalysts [Internet]. 2023 Jan 6;13(1):130.
46. Vikal A, Maurya R, Patel P, Paliwal SR, Narang RK, Gupta GD, et al. Exploring metal-organic frameworks (MOFs) in drug delivery: A concise overview of synthesis approaches, versatile applications, and current challenges. Applied Materials Today [Internet]. 2024 Sep 21;41:102443.
47. Stock N, Biswas S. Synthesis of Metal-Organic Frameworks (MOFs): routes to various MOF topologies, morphologies, and composites. Chemical Reviews [Internet]. 2011 Nov 18;112(2):933–69.
48. Goglio G, Foy D, Demazeau G. State of Art and recent trends in bulk carbon nitrides synthesis. Materials Science and Engineering R Reports [Internet]. 2007 Dec 6;58(6):195–227.
49. Das B, Mohanty S. A comprehensive review on piezoelectric inks: From concept to application. Sensors and Actuators a Physical [Internet]. 2023 Dec 20;366:114939.
50. Li N, Du J, Wu D, Liu J, Li N, Sun Z, et al. Recent advances in facile synthesis and applications of covalent organic framework materials as superior adsorbents in sample pretreatment. TrAC Trends in Analytical Chemistry [Internet]. 2018 Sep 7;108:154–66.
51. Hu Z, Wang Y, Zhao D. Modulated hydrothermal chemistry of Metal–Organic frameworks. Accounts of Materials Research [Internet]. 2022 Oct 27;3(11):1106–14.
52. Xia Y, Shen Z, Wang H, Liu Y, Li W, Liu W, et al. Metal-organic frameworks in drug delivery: An emerging paradigm. Colloids and Interface Science Communications. 2023;61:103010. https://doi.org/10.1016/j.cis.2023.103010
53. Rojas S, Arenas-Vivo A, Horcajada P. Metal–Organic Frameworks: A Novel Platform for Combined Advanced Therapies. Inorg Chem.

2021;60(14):10241–59. doi:10.1021/acs.inorgchem.1c01839

54. Yan Y, Liu C, Zhao X, Zhao L. Metal-Organic Frameworks for Drug Delivery and Biomedicine. Int J Mol Sci. 2022;23(16):9396. doi:10.3390/ijms23169396
55. Chen W-H, Luo G-F, Lei Q, Hong S, Qiu W-X, Liu L-H, et al. Metal-organic framework-based stimuli-responsive systems for drug delivery. Nat Commun. 2020;11(1):714. doi:10.1038/s41467-020-14671-9
56. Viciano-Chumillas M, Liu X, Leyva-Pérez A, Armentano D, Ferrando-Soria J, Pardo E. Mixed component metal-organic frameworks: Heterogeneity and complexity at the service of application performances. Coordination Chemistry Reviews [Internet]. 2021 Oct 28;451:214273.
57. Pullen S, Clever GH. Mixed-Ligand Metal–Organic frameworks and heteroleptic coordination cages as Multifunctional Scaffolds—A comparison. Accounts of Chemical Research [Internet]. 2018 Oct 31;51(12):3052–64.
58. Abdelkareem MA, Abbas Qaisar, Mouselly M, Alawadhi H, Olabi AG. High- performance effective metal–organic frameworks for electrochemical applications. Journal of Science Advanced Materials and Devices [Internet]. 2022 May 10;7(3):100465.
59. Gennari FC, Andrade-Gamboa JJ. A systematic approach to the synthesis, thermal stability and hydrogen storage properties of Rare-Earth borohydrides. In: Elsevier eBooks [Internet]. 2018. p. 429–59.
60. Niknam E, Panahi F, Daneshgar F, Bahrami F, Khalafi-Nezhad A. Metal–Organic Framework MIL-101(CR) as an efficient heterogeneous catalyst for clean synthesis of benzoazoles. ACS Omega [Internet]. 2018 Dec 12;3(12):17135–44.
61. Do JL, Friščić T. Mechanochemistry: a force of synthesis. ACS Central Science [Internet]. 2016 Dec 29;3(1):13–9.
62. Abou-Elyazed AS, Ftooh AI, Sun Y, Ashry AG, Shaban AKF, El-Nahas AM, et al. Solvent-free synthesis of HKUST-1 with abundant defect sites and its catalytic performance in the esterification reaction of oleic acid. ACS Omega. 2024;9(36):37662–71. doi:10.1021/acsomega.4c01852
63. Yusuf VF, Malek NI, Kailasa SK. Review on metal–organic framework classification, synthetic approaches, and influencing factors: Applications in energy, drug delivery, and wastewater treatment. ACS Omega. 2022;7(49):44507–31. doi:10.1021/acsomega.2c05310
64. Zhao X, Zhang R, Liu Y, He M, Su Y, Gao C, et al. Antifouling membrane surface construction: Chemistry plays a critical role. Journal of Membrane Science [Internet]. 2018 Jan 31;551:145–71.
65. Itatani M, Német N, Valletti N, Schuszter G, Prete P, Lo Nostro P, et al. Synthesis of zeolitic imidazolate Framework-8 using glycerol carbonate. ACS Sustainable Chemistry & Engineering [Internet]. 2023 Aug 21;11(35):13043–9.
66. Khan NA, Jhung SH. Synthesis of metal-organic frameworks (MOFs) with microwave or ultrasound: Rapid reaction, phase-selectivity, and size reduction. Coordination Chemistry Reviews [Internet]. 2014 Nov 1;285:11–23.
67. Zhu M, Venna SR, Jasinski JB, Carreon MA. Room-Temperature Synthesis of ZIF- 8: The coexistence of ZNO Nanoneedles. Chemistry of Materials [Internet]. 2011 Jul 29;23(16):3590–2.
68. Feng L, Wang KY, Powell J, Zhou HC. Controllable synthesis of Metal-Organic

frameworks and their hierarchical assemblies. Matter [Internet]. 2019 Oct 1;1(4):801–24.

69. Elmehrath S, Nguyen HL, Karam SM, Amin A, Greish YE. BioMOF-Based Anti- Cancer Drug delivery Systems. Nanomaterials [Internet]. 2023 Mar 6;13(5):953.
70. Sun Y, Zheng L, Yang Y, Qian X, Fu T, Li X, et al. Metal–Organic Framework Nanocarriers for drug delivery in biomedical applications. Nano-Micro Letters [Internet]. 2020 May 2;12(1).
71. Yang S, Karve VV, Justin A, Kochetygov I, Espín J, Asgari M, et al. Enhancing MOF performance through the introduction of polymer guests. Coordination Chemistry Reviews [Internet]. 2020 Sep 17;427:213525.
72. López-Periago A, López-Domínguez P, Barrio JP, Tobias G, Domingo C. Binary supercritical CO 2 solvent mixtures for the synthesis of 3D metal-organic frameworks. Microporous and Mesoporous Materials [Internet]. 2016 Jul 16;234:155–61.
73. Kaur K. Functional nutraceuticals: past, present, and future. In: Elsevier eBooks [Internet]. 2016. p. 41–78.
74. Chakravarty P, Famili A, Nagapudi K, Al-Sayah MA. Using supercritical fluid technology as a green alternative during the preparation of drug delivery systems. Pharmaceutics [Internet]. 2019 Nov 25;11(12):629.
75. Kang MJ, Cho YW, Kim TH. Metal- and covalent-organic framework-based drug delivery systems: Applications to control cell functions. Coordination Chemistry Reviews [Internet]. 2024 Dec 16;527:216400.
76. Aguilar ZP. Targeted drug delivery. In: Elsevier eBooks [Internet]. 2012. p. 181–234.
77. Abid HR, Azhar MR, Iglauer S, Rada ZH, Al-Yaseri A, Keshavarz A. Physicochemical characterization of metal organic framework materials: A mini review. Heliyon [Internet]. 2023 Dec 16;10(1):e23840.
78. Sinha P, Datar A, Jeong C, Deng X, Chung YG, Lin LC. Surface area determination of porous materials using the Brunauer–Emmett–Teller (BET) method: Limitations and improvements. The Journal of Physical Chemistry C [Internet]. 2019 Jul 17;123(33):20195–209.
79. Zheng A, Yin K, Pan R, Zhu M, Xiong Y, Sun L. Research progress on Metal– Organic frameworks by Advanced Transmission Electron Microscopy. Nanomaterials [Internet]. 2023 May 26;13(11):1742.
80. Tran VA, Le VT, Doan VD, Vo GNL. Utilization of Functionalized Metal–Organic Framework Nanoparticle as targeted drug delivery system for cancer therapy. Pharmaceutics [Internet]. 2023 Mar 13;15(3):931.
81. Ko S, Gao F, Yao X, Yi H, Tang X, Wang C, et al. Synthesis of metal–organic frameworks (MOFs) and their application in the selective catalytic reduction of NOx with NH3. New Journal of Chemistry [Internet]. 2022 Jan 1;46(33):15758–75.

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