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# Metal Organic Frameworks- Carriers for Drug Delivery

MadhuryaChavali[1], Sowmya C [2],SuriyaPrakaash K K*[3]
[1]Student, Maharajah's College of Pharmacy, Vizianagaram, Andhra Pradesh, India
[2] Student, Department of Pharmaceutics, Sri Ramachandra Faculty of Pharmacy, Sri Ramachandra Institute of Higher Education and Research (DU), Porur, Chennai, India
[3]Assistant Professor, Department of Pharmaceutics, Sri Ramachandra Faculty of Pharmacy, Sri Ramachandra Institute of Higher Education and Research (DU), Porur, Chennai, India
Corresponding Author: Dr. Soumya C

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**ABSTRACT**: Metal Organic Frameworks (MOFs) are the compounds that are incorporated with metal ions joined with organic ligands with the help of coordination bonds. These compounds have several advantages such as high loading capacity of drugs due to their high surface area and high porosity, have high biodegradability, structure is beneficial for host-guest interaction. The major components of MOFs are Metal ions and Organic ligands. There are various preparation methods involved in the synthesis of MOF. There are various strategies through which drug can be incorporated in MOFs, such as Surface adsorption, Pore encapsulation, Covalent binding, Functional molecule as the building blocks. Different techniques such as X-ray diffraction, SEM and TEM analysis, Zeta potential, FTIR, NMR spectroscopy etc., are employed to identify various parameters to evaluate a MOF. MOFs are identified as promising drug carriers, as they have managed to achieve targeted drug delivery and shown controlled release of drug.

**KEYWORDS:**Metal organic frameworks, drug carriers, components, synthesis, functionalization, characterisation, targeted drug delivery.

## I. INTRODUCTION

Metal-organic frameworks (MOFs) are a class of porous materials that consist of metal ions or clusters coordinated to organic ligands, forming a highly ordered and crystalline network with a well-defined porous structure. [1] These materials exhibit exceptional tunability in terms of pore size, surface area, and functional group modification, making them ideal candidates for various pharmaceutical applications. [2] In the realm of pharmaceutics, MOFs offer several advantages over traditional drug delivery systems. Firstly, their high surface area enables efficient loading and encapsulation of drug molecules, allowing for enhanced drug solubility, stability, and bioavailability. The porous nature of MOFs also enables controlled release of drugs, as the empty pores can accommodate drug molecules and release them gradually, ensuring a sustained and controlled therapeutic effect. The structural versatility of MOFs allows for the incorporation of various functional groups, making them capable of targeted drug delivery. By modifying the organic ligands or adding specific functional moieties, MOFs can be tailored to interact selectively with certain biological receptors or target sites, thus improving drug efficacy while minimizing side effects. [3] This targeted approach reduces off-target interactions and enhances the therapeutic index of drugs.

The history of metal-organic frameworks (MOFs) has its roots in the early 1990s when the first reports of these materials emerged. In the 1960s and 1970s, researchers began exploring the field of coordination polymers. Even though there were reports of the compounds of similar characteristics, the first one to progress was MOF-5 in the year 1992 by Yaghi. In 1992, the groundbreaking work of Omar M. Yaghi and colleagues at the Michigan State University marked a significant milestone in the field of MOFs. They reported the synthesis of a new type of porous material called a pillared-layer structure. The resulting materials exhibited high porosity and accessible cavities [4]. Following the discovery of pillared-layer structures, Yaghi's research group and other scientists made significant contributions to the field. They developed new synthetic methodologies and explored a wide range of metal ions, organic ligands, and reaction conditions to create MOFs with diverse structures and properties. This included the development of more stable MOFs, expansion of pore sizes, and the ability to incorporate functional groups [5].

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Throughout the 2000s, the field of MOFs experienced exponential growth. Researchers from around the world joined in the exploration of MOFs and expanded their applications beyond gas storage and separation. MOFs were investigated for uses in catalysis, sensing, optics, electronics, and, most notably, in the field of pharmaceutics for drug delivery systems. [6] Furthermore, MOFs can protect sensitive drugs from degradation, such as enzymatic degradation or hydrolysis, thereby prolonging their shelf life and maintaining their pharmacological activity. [7] The porous framework of MOFs also enables the co-delivery of multiple drugs or therapeutics with different physicochemical properties, opening up opportunities for combination therapies and synergistic effects.

The synthesis and fabrication of MOFs can be tailored to meet specific pharmaceutical requirements. Various methods, such as solvothermal, hydrothermal, or microwave-assisted synthesis, can be employed to achieve precise control over the size, morphology, and porosity of MOFs. [8] Additionally, surface modification techniques can be applied to enhance MOF stability, biocompatibility, and to introduce functionalities for specific applications.Moreover, MOFs can serve as carriers for imaging agents, allowing simultaneous diagnosis and therapy. By incorporating imaging probes or contrast agents into the MOF structure, it becomes possible to monitor drug release, distribution, and accumulation in real-time using non-invasive imaging techniques. [9] This capability provides valuable insights into the pharmacokinetics and pharmacodynamics of drugs, enabling personalized medicine and optimizing treatment regimens. By providing an overview of the recent advancements, design strategies, and applications of MOFs in drug delivery, this review aims to provide valuable insights and highlight the potential of MOFs as carriers for drug delivery, thus fostering further research and development in this emerging field.

## II. COMPONENTS

MOFs consist of two primary components: metal nodes (or clusters) and organic ligands. These components work together to form the highly ordered and crystalline structure characteristic of MOFs.

### METAL NODES

The metal nodes in MOFs are typically transition metals or metal clusters. These metal atoms serve as the central coordination centers within the framework. They provide the connectivity and stability to the overall structure. Commonly used metal ions include zinc (Zn), copper (Cu), iron (Fe), and chromium (Cr), among others. The choice of metal nodes depends on the desired properties and applications of the MOF. [10]

### ORGANIC LIGANDS

Organic ligands are organic molecules that coordinate to the metal nodes in MOFs. These ligands form coordination bonds with the metal atoms, connecting them together to generate the framework. Ligands can vary in size, shape, and functionality, contributing to the tunability and diversity of MOFs. Examples of organic ligands include carboxylates, imidazoles, pyridines, and various aromatic and aliphatic compounds. The organic ligands play several critical roles in MOFs. They not only connect the metal nodes, but also contribute to the overall stability of the structure. The functional groups present in the ligands can impart specific properties to the MOFs, such as porosity, hydrophilicity, or selectivity towards certain guest molecules. The choice and design of ligands are crucial for tailoring the properties and functionalities of MOFs to suit specific applications. [11]

In addition to the metal nodes and organic ligands, MOFs may contain secondary linkers or modulators. These molecules can be incorporated within the MOF structure, either covalently or through non-covalent interactions, to introduce additional functionalities or enhance the structural stability. Secondary linkers can further tune the properties of MOFs, such as pore size, surface area, or guest molecule interactions. [12]The combination of metal nodes, organic ligands, and potential secondary linkers results in the formation of a crystalline, porous framework with well-defined structural features. The precise choice of metal nodes, ligands, and their coordination geometries governs the overall architecture, porosity, and properties of the MOF. It is worth noting that the concept of MOFs also extends to "post-synthetic modification" (PSM) and "guest-induced formation" (GIF), where the framework can be further modified or decorated with additional functional groups, guest molecules, or nanoparticles. These modifications enable fine-

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tuning of the MOF properties and expand their applications in areas such as catalysis, sensing, and drugdelivery. [13]

## III. PREPARATION TECHNIQUES

There are various methods involved in the synthesis of MOFs such as, Solvothermal method, Microwave assisted method,Electrochemical method,Mechanochemical method, Sonochemical method. [14, 15]

### SOLVOTHERMAL METHOD

In this method, the MOF crystals are formed by taking, metal salts and organic ligand in a suitable solvent. This reaction mixture placed in autoclave whose inner cavity is lined with Teflon to prevent corrosion. The reaction takes place at temperature between 80-220ºC and at high pressure of 3MPa. If the solvent used is water, then this method is called as Hydrothermal Synthesis. This major drawback associated with this method is that reaction time may range from 3-4 days. [14]

Sha J et al., 2017 utilized this method for the synthesis of Na-α-CD MOF. As name suggests sodium is the metal ion sourced from NaOH, whereas α-cyclodextrin is the organic ligand. The solvent involved is tetramethyl ammonium hydroxide solution dissolved in water along with source of metal ion and organic ligand. [16] The MOF's with cyclodextrin as an organic ligand is considered to be most advantageous as they are biocompatible given that metal ion is also biocompatible.

Another example is the synthesis of ZIF-8 by Zhuang J et al., 2014. It is a Zn-MOF, where Zinc nitrate is the source of metal ions and has two organic ligands, 2-nitroimidazolate and 5-nitrobenzimidazolate. These reaction mixtures are dissolved in the solvent mixture of dimethylformamide and triethylamine. [17]

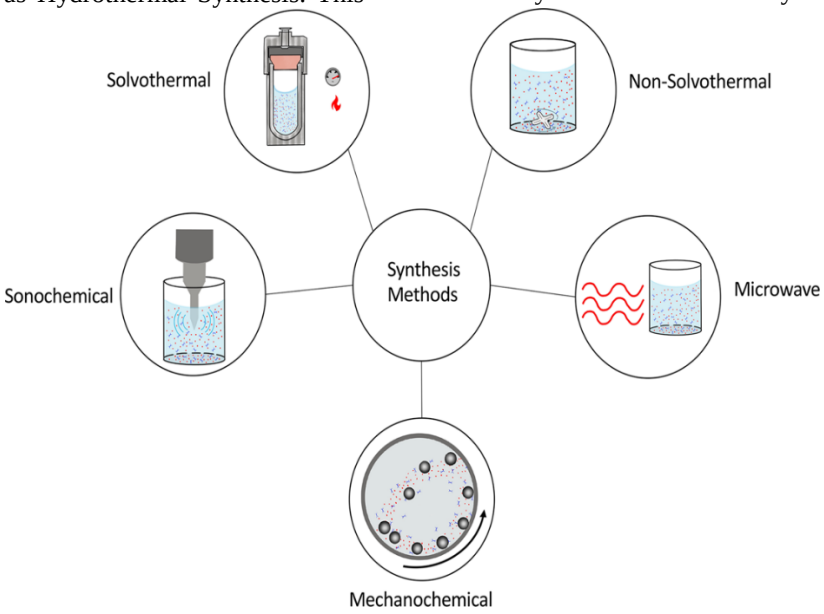


**Figure 1: Various methods of metal organic framework synthesis**

### MICROWAVE ASSISTED METHOD

In this method, unlike solvothermal synthesis there is no utilization of external heating. The reaction mixture present in suitable solvent is exposed to microwave radiation. There occurs interaction between the waves of radiation and ions present in the reaction mixture, this results in direct and uniform heating. Due to this, there induction of crystal growth. This method is advantageous over the solvothermal synthesis as the reaction time is less. [14]

Zhao Z et al., 2011 utilized this method for the synthesis of MIL-101, which is Chromium based metal organic framework. The reaction mixture consists of Chromium (III) nitrate nonahydrate which is a source of metal ion and 1,4-benzene dicarboxylic acid as organic ligand in the DMF which acts as solvent. This mixture was exposed to microwave irradiation at 300 W, at 493K for 60 min. [18]

Wu X et al., 2013 utilized this method for the synthesis of two MOF-74, with two metal ions

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respectively. One being Mg-MOF-74, where magnesium nitrate is source of metal ion, and other being Ni-MOF-74, where nickel nitrate is source of metal ion. The organic ligand used is 2,5-dihydroxyterephthalic acid whereas dimethylformamide, ethanol and water are used in different ratios for solvent. The reaction temperatures for Mg-MOF-74 and Ni-MOF-74 are 398K and 373K respectively. [19]

**ELECTROCHEMICAL METHOD**

In this method, there is involvement of anode and cathode in reaction medium containing organic ligand and conducting solvent, connected to power supply. The source of metal ion is anode, whereas discharge of ions from cathode is prevented by utilizing protic solvents.Van AsscheTR et al., 2012 utilized this method for the synthesis of HKUST-1, which is a Cu-MOF. The organic ligand employed was benzene-1,3,5-tricarboxylic acid. The reaction medium along with organic ligand consists of mixture of water and ethanol and the electrolyte methyltributylammonium methyl sulfate (MTBS). [20]

Wei JZ et al., 2019 utilized this method for the synthesis of Uio-66-NH2, a Zirconium based MOF. The organic ligand employed was 2-aminoteraphthalic acid. The reaction mixture along with organic ligand consists of dimethylformamide, acetic acid and tetrabutylammonium bromide. [21]

**Table 1: Methods involved in the synthesis of MOFs**

| Method of Synthesis | MOFs | Components |
|---|---|---|
| Solvothermal synthesis | Na-α-CD | Sodium ions and Cyclodextrin |
| | ZIF-8 | Zinc ions and 2-nitroimidazolate and 5-nitrobenzimidazolate |
| Microwave assisted synthesis | MIL-101 | Chromium ions and 1,2-dicarboxylic acid |
| | Mg-MOF-74 | Magnesium ions and 2,5-dihydroxyterephthalic acid |
| | Ni-MOF-74 | Nickel ions and 2,5-dihydroxyterephthalic acid |
| Electrochemical method | HKUST-1 | Copper ions and Benzene-1,3,5-tricarboxylic acid |
| | Uio-66-NH2 | Zirconium ions and 2-aminoteraphthalic acid |
| Mechanochemical method | Cu-MOF | Copper ions and Isonicotinic acid |
| Sonochemical method | MOF-5 | Zinc ions and 1-methyl-2-pyrrolidone |
| | HKUST-1 | Copper ions and Benzene-1,3,5-tricarboxylate |

**MECHANOCHEMICAL METHOD**

In this method, there is no utilization of solvent to carry out the reaction, whereas mechanical stress is applied on to the reaction mixture containing metal salts and organic ligand. The stress created breaks the intramolecular bonds and chemical transformation. This reaction takes place at room temperature in a ball mill. The synthesis time for this method may take 10-60 min.

Pichon A et al., 2006 were the first to

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utilize this method. They synthesized a Cu-MOF by employing copper acetate monohydrate as a source of metal ion and isonicotinic acid as an organic ligand. It took about 10 min for the production of MOFs. [22]

**SONOCHEMICAL METHOD**

In this method, reaction mixture is exposed to ultrasonic waves (20kHz-10MHz). Upon exposure, there is occurrence of acoustic cavitation, which is production, raise and collapse of the bubbles formed in the medium. Due to repeated cavitation, there is generation of high pressure up to 1000bars and temperature up to 5000K. This results in the formation of crystals of MOFs.

Jiang H et al., 2013 utilized this method for the synthesis MOF-5, which is a Zn-MOF. The source of metal ion was Zinc nitrate hexahydrate and organic ligand was terephthalic acid whereas solvent utilized was 1-methyl-2-pyrrolidone.It took 10-75 min for the synthesis of MOF-5 after exposing the reaction mixture to sonication. [23]

Li ZQ et al., 2009 utilized this method for the synthesis of HKUST-1, a Copper based metal organic framework. The reaction mixture included Cupric acetate as a source of metal ion and benzene-1,3,5-tricarboxylate as organic ligand in the solvent mixture of dimethylformamide, ethanol and water. The MOFs were produced in high yield at reaction time 5-60min. [24]

## IV. FUNCTIONALIZATION

Due to their high porosity, large surface area and structural framework, it is possible to incorporate therapeutic agents into these structures, hence helpful in drug delivery. There are various strategies through which drug can be incorporated in MOFs, such as Surface adsorption, Pore encapsulation, Covalent binding, Functional molecule as the building blocks.

**SURFACE ADSORPTION**

In this method, as discussed due to MOFs high porosity and large surface area, drugs can be adsorbed onto their surface. Synthesized MOFs are placed in the solution containing active component. There is involvement hydrogen bonding and Van der Waal interactions. The major drawback associated with this technique is due to the weak interaction forces in between the molecules and MOFs, hence it may lead to leaching.

Pisklak TJ et al., 2006 developed a Cu-MOF from solvothermal synthesis, with copper acetate and 4,4`-diphenylcarboxylic acid as a metal source and organic ligand respectively. Into the synthesized MOFs micro peroxidase-11 (MP-11) was incorporated. 3.5mg of MP-11 was dissolved in 100 ml solution of dimethylformamide. 10ml of this solution was dissolved in 10mg of MOF and stirred for 3 hours at room temperature. MP-11 incorporated MOFs were isolated by centrifugation. [2]

**PORE ENCAPSULATION**

In this technique, the incorporation of active moiety takes place during the synthesis of MOFs. In this, the drug is encapsulated in the pore of the MOF, such that MOF act as a host molecule and prevent leaching as seen in surface adsorption technique.

Zhuang J et al., 2014 developed ZIF-8 encapsulated with camptothecin, an anti-cancer agent. These nanoparticles were identified to be pH triggered drug delivery systems, these released the drug in acidic compartment of targeted site and have shown cytotoxic activity against cancer cells. [17]

**COVALENT BINDING**

In this technique, the functional groups present on the MOFs are utilized and active moiety is bonded covalently to it. This method is considered more advantageous because it offers strong interactive forces between the active compound and MOF when compared to the other two methods discussed above.

Nucleic acids functionalized MOFs were synthesized by Morris W et al., 2014 Zirconium based frameworks Uio-66-N3 were first prepared, and combined with DNA functionalized with dibenzyl cyclooctane. [26]

**FUNCTIONAL MOLECULES AS THE BUILDING BLOCKS**

In this strategy, various biomolecules such as amino acids, saccharides, nucleobases, peptides are used as organic ligands as they contain various functional groups which are coordinatively bonded with metal ion forming structural frameworks. Such MOFs are named as Bio-MOFs. These have better biocompatibility compared to others.

Alves RC et al., 2021 have utilized N3-bio-MOF-100 and loaded anticancer drug curcumin, by placing MOFs in drug solution. Later, this drug loaded MOFs are covalently bonded to the Folic acid on their surface. The resulted drug

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delivery systems have shown enhanced drug release against cancer cells. [27]

## V. CHARACTERIZATION

Generally various methods are utilized for the evaluation or characterize various attributes of MOFs. Different techniques such as X-ray diffraction, SEM and TEM analysis, Zeta potential, FTIR, NMR spectroscopy etc., are employed to identify various parameters to evaluate a MOF. [1]

To determine the crystalline structure and crystalline parameters of a MOF, X-ray diffraction technique is employed. SEM and TEM analysis of the MOFs determine the size and morphology. [1]For example, when ZIF-78 was analysed by Ban Y et al., 2013 the MOFs were present as hexagonal microrods and discs. [28] Similarly, when Zhuang J et al., 2014 subjected ZIF-8 for SEM and TEM analysis, they were identified as monodispersed spherical structures with 70nm in size. [17]

Fourier-transform infrared spectroscopy (FTIR), it is utilized to determine modifications in structure and if any degradation that occurred. [1] Upon FTIR analysis of synthesized Uio-66-NH2 and comparing it with spectrum of organic ligand 2-aminoteraphthalic acid, Wei JZ et al., 2019 identified the coordination reaction occurred between Zirconium metal ions and deprotonation of -COOH group of organic ligands due to shift in peak from 1686cm-1 to 1572cm-1. [21]

Zeta potential gives information about the surface charge. Zhuang J et al., 2014 measured zeta potential of synthesized ZIF-8 using zetasizer and the value was found to be 31.4mV. [17]

**Table 2: Characterization techniques of MOFs**

| Characterization technique | Quality |
|---|---|
| X-ray diffraction (XRD) | Structure and Crystalline parameters |
| Scanning Electron Microscopy (SEM) | Size and Morphology |
| Transmission Electron Microscopy (TEM) | Size and Morphology |
| Zeta potential | Surface charge |
| Nuclear Magnetic Resonance (NMR) spectroscopy | Binding between MOFs and drug and Metal ion and organic linker |
| Thermogravimetric Analysis | Thermal decomposition of MOFs |

NMR spectroscopy helps in examining the metal ions and their binding with the organic linkers and as well as centre of drug in the MOFs. Leflunomide, a prodrug of teriflunomide was loaded into γ-CD-MOF byKritskiy I et al., 2019 and was subjected to 1H-NMR, and are compared to free drug. The results obtained shown that drug loaded sample MOFs have similar peak characteristics as that of free drug, indicating that drug is successfully loaded into MOFs. [29] Thermogravimetric analysis (TGA) generally used to describe about the thermal decomposition of the MOFs. [1]

Evaluating the loading and encapsulation efficiency place an important factor for selecting MOFs as drug carriers, these can be calculated by following equations:

Loading efficiency (%) = Mass of loaded drug / Mass of loaded drug MOFs X 100

Encapsulation efficiency (%) = Mass of loaded drug / Mass of total drug X 100

## VI. CURRENT APPLICATIONS

MOFs are identified as promising drug carriers, as they have managed to achieve targeted drug delivery and shown controlled release of drug. MOF's can be utilized in anti-bacterial, cancer and diabetes therapies and as well as in enhancement of solubility and stability.

Controlled drug release can be achieved by the MOFs, which was shown by Jiang K*et al.*, 2016 taking Diclofenac sodium as the model drug. The drug was loaded into ZJU-800, which is a zirconium-based MOF. The system has shown

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release of drug for 2-8 days with a high drug loading capacity up to 58.80%. [30]Vancomycin, an anti-bacterial drug was incorporated into MOF-53(Fe) by Lin S*et al*., the resulted MOF nanoparticles has shown high drug loading capacity due to their large surface area and it was also found to be stable in the acidic environment. MOF-53(Fe)@Van has shown 91.7% of anti-bacterial activity against *Staphylococcus aureus.* The drug loaded MOFs were found to be highly biocompatible. [31]

Ceftazidime, a third-generation cephalosporin was incorporated into ZIF-8 by Sava Gallis DF*et al*., 2019 the drug loaded MOFs have shown sustained drug release for a week. The antibacterial activity was tested against gram-negative *E. coli* and it has shown complete growth inhibition at 100µg/mL after 72 hrs of incubation in media. [32]

Hu X*et al*., 2019 modified γ-CD-MOF with cholesterol and leucine poloxamer, to improve its flowability and particle aerodynamic behaviour. The modified MOFs were loaded with budesonide, formulating dry powder for inhalation that can be utilized in the treatment of asthma. When tested for *in vivo*, the modified MOFs have shown better bioavailability, making them a promising drug delivery system to target lungs. [33]

Wyszogrodzka-Gaweł G*et al*., 2019 loaded isoniazid into Fe-MIL-101-$NH_2$, to form an inhalable system for local treatment of tuberculosis. These MOFs are optimized by spray drying with poly (lactide-co-glycolide) and also packed with leucine. These modified MOFs have better aerodynamic behaviour when compared to drug loaded MOFs. [34]

Yang XX*et al*., 2020 synthesized multi-enzyme loaded MOFs, Co-ZIF-8 MOFs are loaded with Insulin and as well as Glucose oxidase (GOx). These are designed as microneedles for glucose-mediated transdermal insulin delivery. Glucose in the presence of GOx forms into gluconic acid along with $H_2O_2$. The formed $H_2O_2$ changes local pH, as a result MOFs are degraded and insulin is released. This strategy offers a promising novel technique for the treatment of diabetes through transdermal route. [35]

One of the major drawbacks in treatment of cancer is multidrug resistance, to overcome such a drawback, Zhang H*et al*., synthesized multidrug loaded MOFs. Doxorubicin hydrochloride an anticancer drug and Verapamil hydrochloride, a P-glycoprotein inhibitor which helps in controlling multi-drug resistance, are both loaded into ZIF-8 nanoparticles. The multidrug loaded are stabilized with the help of methoxy poly (ethylene glycol)-folate. These stabilized MOFs have increased safety when compared to free Doxorubicin. The MOFs increased accumulation of drug near the tumour there by increasing the therapeutic efficacy. [36]

Xiaogang W *et al*., loaded Doxorubicin into MIL-101, and they further modified the surface of MOF. The resultant MOF have prevented pre-mature release of drug. The cellular uptake has also found to be increased. *In vitro* and *in vivo* test results have shown that the drug loaded MOF have decreased cytotoxic activity against normal cells and effectively inhibited the tumour growth. [37]

Dichloroacetate was loaded into UiO-66 and conjugated it with triphenyl phosphonium, which helps in localization of mitochondria by F Haddad S*et al*., 2020. The resultant MOFs obtained were tested on MCF-7 cells of human breast carcinoma under super-resolution microscopy for any mitochondrial morphological changes, which was consequently achieved and caused cell death. Due to mitochondrial targeting dose required for the therapy can be decreased. [38]

For the HIV treatment therapy, azidothymidine triphosphate and lamivudine triphosphate were incorporated into MIL-100(Fe). These multidrug loaded MOFs have shown increased anti-retroviral activity when tested *in vitro* on monocyte derived macrophages which are infected with HIV. With the help of MOFs as the carriers, these drugs can overcome their drawback of poor cellular uptake and resulting increased therapeutic efficacy. [39]

Leflunomide, it is a prodrug of teriflunomide. It is used as an anti-rheumatoid, also has the action of anti-cancer and can be used in the treatment of sclerosis when administered orally. It is a poorly aqueous soluble drug, hence has poor oral bioavailability. This drug was loaded into γ-CD-MOF by Kritskiy I*et al*., 2019 to increase its solubility and. The drug loaded MOFs have shown 80-fold increase in their solubility, hence making them a novel drug carrier system. [29]

Curcumin, has anti-cancer pharmacological activity, but the drawback associated is, it is unstable in neutral and alkaline conditions and hence undergoes degradation. Moussa Z*et al*., 2016 loaded curcumin in γ-CD-MOFs and found that interaction between curcumin and MOF is strong due to the formation of hydrogen bond. The resultant loaded MOF crystals,

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have shown increased chemical stability of curcumin in both water and alkaline mediums, making the MOFs a suitable carrier. [40]

## VII. CHALLENGES AND FUTURE ASPECTS

One of the major challenges is to ensure the biocompatibility and safety of MOFs for pharmaceutical applications. Comprehensive studies are required to understand the potential toxicity and long-term effects of MOFs in biological systems. It is essential to address concerns related to biodegradation, immune response, and potential interactions with living tissues.

MOFs can be sensitive to environmental conditions, such as moisture, pH, and temperature, which may affect their stability. Ensuring the stability of MOFs under physiological conditions is crucial for their use in drug delivery. Moreover, there is a need to develop scalable and cost-effective synthesis methods to produce MOFs in large quantities without compromising their structural integrity.Achieving precise control over drug release kinetics from MOFs is a challenge. While MOFs offer the potential for controlled and sustained drug release, fine-tuning the release rate and duration to match therapeutic requirements remains a complex task. Factors such as pore size, functionalization, and interactions between the drug and MOF surface need to be optimized to achieve controlled release profiles.

MOFs have the potential to enable targeted drug delivery by incorporating specific ligands or functional groups that interact selectively with target sites or receptors. However, challenges persist in designing MOFs that exhibit high specificity and selectivity towards the target site, ensuring efficient drug accumulation and minimizing off-target effects.The regulatory landscape for MOFs in the pharmaceutical industry is still evolving. The approval process for MOF-based drug delivery systems involves addressing safety concerns, demonstrating efficacy, and establishing consistent manufacturing processes. Bridging the gap between academic research and industrial applications while meeting regulatory requirements is a significant challenge.

Continued research and development efforts are focused on designing MOFs with tailored properties and functionalities for advanced drug delivery systems. This includes the development of stimuli-responsive MOFs that can release drugs in response to specific triggers such as pH, temperature, enzymes, or light. Additionally, the incorporation of targeting ligands or antibodies within MOFs can further enhance site-specific drug delivery.

MOFs offer opportunities for combination therapies by co-loading multiple drugs with different mechanisms of action. This approach can lead to synergistic effects, improved treatment outcomes, and reduced drug resistance. Further exploration is needed to optimize co-delivery strategies, achieve controlled release of multiple drugs, and understand the interactions between different drugs within MOFs.

MOFs can be integrated with imaging agents or therapeutics to create theranostic platforms. These systems enable simultaneous diagnosis and therapy, allowing real-time monitoring of drug distribution, release kinetics, and therapeutic efficacy. Developing MOFs that combine imaging capabilities with controlled drug release properties holds great promise for personalized medicine and treatment optimization.The potential of MOFs extends beyond drug delivery. MOFs can be explored for other pharmaceutical applications such as biosensing, enzyme immobilization, tissue engineering scaffolds, and controlled release of growth factors or biomolecules. The multifunctionality and tunability of MOFs make them versatile platforms for various biomedical applications.

As the field of MOFs progresses, there is an increasing emphasis on developing sustainable and environmentally friendly synthesis methods. Green synthesis routes, such as solvent-free or aqueous-based synthesis, are being explored to reduce the use of organic solvents and minimize environmental impact. Developing sustainable MOFs with reduced energy requirements and eco-friendly processes will be a focus in the future.

## VIII. CONCLUSION

In conclusion, this review article has provided an in-depth exploration of metal-organic frameworks (MOFs) as carriers for drug delivery. MOFs, with their unique structural properties and tunability, offer immense potential in overcoming the limitations of traditional drug delivery systems. By summarizing the recent advancements, design strategies, and applications of MOFs in drug delivery, this review has highlighted the promising

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opportunities for targeted and controlled drug release. Despite current challenges related to biocompatibility, stability, and regulatory considerations, the future of MOFs in the pharmaceutical industry appears bright. With ongoing research efforts and advancements in MOF synthesis, characterization, and functionalization, MOFs hold the promise of revolutionizing drug delivery, enabling personalized medicine, and enhancing therapeutic outcomes. The insights provided in this review lay the foundation for further exploration and development of MOFs as innovative carriers for drug delivery in the quest for improved healthcare solutions.

## REFERENCES

[1]. Sun Y, Zheng L, Yang Y, Qian X, Fu T, Li X, Yang Z, Yan H, Cui C, Tan W. Metal–organic framework nanocarriers for drug delivery in biomedical applications. *Nano-Micro Letters*. 2020 Dec;12:1-29.

[2]. Pisklak TJ, Macías M, Coutinho DH, Huang RS, Balkus KJ. Hybrid materials for immobilization of MP-11 catalyst. *Topics in catalysis*. 2006 Aug;38:269-78.

[3]. Masoudifar R, Pouyanfar N, Liu D, Ahmadi M, Landi B, Akbari M, Moayeri-Jolandan S, Ghorbani-Bidkorpeh F, Asadian E, Shahbazi MA. Surface engineered metal-organic frameworks as active targeting nanomedicines for mono-and multi-therapy. Applied Materials Today. 2022 Dec 1;29:101646.

[4]. Zhou HC, Long JR, Yaghi OM. Introduction to metal–organic frameworks. Chemical reviews. 2012 Feb 8;112(2):673-4.

[5]. Hiroyasu Furukawa et al. ,The Chemistry and Applications of Metal-Organic Frameworks.Science341,1230444(2013).

[6]. Maranescu B, Visa A. Applications of metal-organic frameworks as drug delivery systems. International Journal of Molecular Sciences. 2022 Apr 18;23(8):4458.

[7]. Chen S, Lu J, You T, Sun D. Metal-organic frameworks for improving wound healing. Coordination Chemistry Reviews. 2021 Jul 15;439:213929.

[8]. Remya VR, Kurian M. Synthesis and catalytic applications of metal–organic frameworks: a review on recent literature. International Nano Letters. 2019 Mar;9:17-29.

[9]. Wu Y, Zeng F, Zhao Y, Wu S. Emerging contrast agents for multispectral optoacoustic imaging and their biomedical applications. Chemical Society Reviews. 2021;50(14):7924-40.

[10]. Masoomi MY, Morsali A, Dhakshinamoorthy A, Garcia H. Mixed- metal MOFs: unique opportunities in metal–organic framework (MOF) functionality and design. AngewandteChemie. 2019 Oct 21;131(43):15330-47.

[11]. Freund R, Zaremba O, Arnauts G, Ameloot R, Skorupskii G, Dincă M, Bavykina A, Gascon J, Ejsmont A, Goscianska J, Kalmutzki M. The current status of MOF and COF applications. AngewandteChemie International Edition. 2021 Nov 2;60(45):23975-4001.

[12]. Haldar R, Maji TK. Metal–organic frameworks (MOFs) based on mixed linker systems: structural diversities towards functional materials. CrystEngComm. 2013;15(45):9276-95.

[13]. Mandal S, Natarajan S, Mani P, Pankajakshan A. Post- synthetic modification of metal–organic frameworks toward applications. Advanced Functional Materials. 2021 Jan;31(4):2006291.

[14]. Sud D, Kaur G. A comprehensive review on synthetic approaches for metal-organic frameworks: From traditional solvothermal to greener protocols. *Polyhedron*. 2021 Jan 1;193:114897.

[15]. Lee YR, Kim J, Ahn WS. Synthesis of metal-organic frameworks: A mini review. *Korean Journal of Chemical Engineering*. 2013Sep;30:1667-80.

[16]. Sha J, Yang X, Sun L, Zhang X, Li S, Li J, Sheng N. Unprecedented α-cyclodextrin metal-organic frameworks with chirality: Structure and drug adsorptions. *Polyhedron*. 2017 May 8;127:396-402.

[17]. Zhuang J, Kuo CH, Chou LY, Liu DY, Weerapana E, Tsung CK. Optimized metal–organic-framework nanospheres for drug delivery: evaluation of small-molecule encapsulation. *ACS nano*. 2014 Mar 25;8(3):2812-9.

[18]. Zhao Z, Li X, Huang S, Xia Q, Li Z. Zhao Z, Li X, Huang S, Xia Q, Li Z. Adsorption and diffusion of benzene on chromium-based metal organic framework MIL-101 synthesized by microwave irradiation.

*Industrial & Engineering Chemistry Research*. 2011 Feb 16;50(4):2254-61.

[19]. Wu X, Bao Z, Yuan B, Wang J, Sun Y, Luo H, Deng S. Microwave synthesis and characterization of MOF-74 (M= Ni, Mg) for gas separation. *Microporous and mesoporous materials*. 2013 Nov 1;180:114-22.

[20]. Van Assche TR, Desmet G, Ameloot R, De Vos DE, Terryn H, Denayer JF. Electrochemical synthesis of thin HKUST-1 layers on copper mesh. *Microporous and Mesoporous Materials*. 2012 Aug 1;158:209-13.

[21]. Wei JZ, Gong FX, Sun XJ, Li Y, Zhang T, Zhao XJ, Zhang FM. Rapid and low-cost electrochemical synthesis of UiO-66-NH2 with enhanced fluorescence detection performance. *Inorganic chemistry*. 2019 Apr 26;58(10):6742-7.

[22]. Pichon A, Lazuen-Garay A, James SL. Solvent-free synthesis of a microporous metal–organic framework. CrystEngComm. 2006;8(3):211-4.

[23]. Jiang H, Feng Y, Chen M, Wang Y. Synthesis and hydrogen-storage performance of interpenetrated MOF-5/MWCNTs hybrid composite with high mesoporosity. International journal of hydrogen energy. 2013 Aug 21;38(25):10950-5.

[24]. Li ZQ, Qiu LG, Xu T, Wu Y, Wang W, Wu ZY, Jiang X. Ultrasonic synthesis of the microporous metal–organic framework Cu3 (BTC) 2 at ambient temperature and pressure: an efficient and environmentally friendly method. *Materials Letters*. 2009 Jan 15;63(1):78-80.

[25]. Lawson HD, Walton SP, Chan C. Metal–organic frameworks for drug delivery: a design perspective. *ACS applied materials & interfaces*. 2021 Feb 7;13(6):7004-20.

[26]. Morris W, Briley WE, Auyeung E, Cabezas MD, Mirkin CA. Nucleic acid–metal organic framework (MOF) nanoparticle conjugates. *Journal of the American Chemical Society*. 2014 May 21;136(20):7261-4.

[27]. Alves RC, Schulte ZM, Luiz MT, Bento da Silva P, Frem RC, Rosi NL, Chorilli M. Breast cancer targeting of a drug delivery system through postsynthetic modification of curcumin@ N3-bio-MOF-100 via click chemistry. *Inorganic Chemistry*. 2021 Jun 8;60(16):11739-44.

[28]. Ban Y, Li Y, Liu X, Peng Y, Yang W. Solvothermal synthesis of mixed-ligand metal–organic framework ZIF-78 with controllable size and morphology. Microporous and mesoporous materials. 2013 Jun 1;173:29-36.

[29]. Kritskiy I, Volkova T, Surov A, Terekhova I. γ-Cyclodextrin-metal organic frameworks as efficient microcontainers for encapsulation of leflunomide and acceleration of its transformation into teriflunomide. *Carbohydrate polymers*. 2019 Jul15;216:224-30.

[30]. Jiang K, Zhang L, Hu Q, Zhao D, Xia T, Lin W, Yang Y, Cui Y, Yang Y, Qian G. Pressure controlled drug release in a Zr-cluster-based MOF. Journal of Materials Chemistry B. 2016;4(39):6398-401.

[31]. Lin S, Liu X, Tan L, Cui Z, Yang X, Yeung KW, Pan H, Wu S. Porous iron-carboxylate metal–organic framework: a novel bioplatform with sustained antibacterial efficacy and nontoxicity. ACS applied materials & interfaces. 2017 Jun 7;9(22):19248-57.

[32]. Sava Gallis DF, Butler KS, Agola JO, Pearce CJ, McBride AA. Antibacterial countermeasures via metal–organic framework-supported sustained therapeutic release. *ACS applied materials & interfaces*. 2019 Jan 25;11(8):7782-91.

[33]. Hu X, Wang C, Wang L, Liu Z, Wu L, Zhang G, Yu L, Ren X, York P, Sun L, Zhang J. Nanoporous CD-MOF particles with uniform and inhalable size for pulmonary delivery of budesonide. *International journal of pharmaceutics*. 2019Jun10;564:153-61.

[34]. Wyszogrodzka-Gaweł G, Dorożyński P, Giovagnoli S, Strzempek W, Pesta E, Węglarz WP, Gil B, Menaszek E, Kulinowski P. An inhalable theranostic system for local tuberculosis treatment containing an isoniazid loaded metal organic framework fe-mil-101-NH2—from raw MOF to drug delivery system. *Pharmaceutics*. 2019 Dec 17;11(12):687.

[35]. Yang XX, Feng P, Cao J, Liu W, Tang Y. Composition-engineered metal–organic framework-based microneedles for glucose-mediated transdermal insulin delivery. *ACS applied materials & interfaces*. 2020 Mar 6;12(12):13613-21.

[36]. Zhang H, Jiang W, Liu R, Zhang J, Zhang D, Li Z, et al. Zhang H, Jiang W, Liu R, Zhang J, Zhang D, Li Z, Luan Y. Rational design of MOF nanocarrier-based co-delivery system of doxorubicin hydrochloride/verapamil hydrochloride for overcoming multidrug resistance with efficient targeted cancer therapy. *ACS Applied Materials & Interfaces*. 2017;9:19687-97.

[37]. Li H, Zhang Y, Liang L, Song J, Wei Z, Yang S, Ma Y, Chen WR, Lu C, Wen L. Doxorubicin-loadedmetal-organic framework nanoparticles as acid-activatable hydroxyl radical nanogenerators for enhanced chemo/chemodynamic synergistic therapy. Materials. 2022 Jan 30;15(3):1096.

[38]. FHaddad S, AbánadesLázaro I, Fantham M, Mishra A, Silvestre-Albero J, Osterrieth JW, Kaminski Schierle GS, Kaminski CF, Forgan RS, Fairen-Jimenez D. Design of a functionalized metal–organic framework system for enhanced targeted delivery to mitochondria. *Journal of the American Chemical Society*. 2020 Mar 17;142(14):6661-74.

[39]. Marcos-Almaraz MT, Gref R, Agostoni V, Kreuz C, Clayette P, Serre C, Couvreur P, Horcajada P. Towards improved HIV-microbicide activity through the co-encapsulation of NRTI drugs in biocompatible metal organic framework nanocarriers. Journal of Materials Chemistry B. 2017;5(43):8563-9.

[40]. Moussa Z, Hmadeh M, Abiad MG, Dib OH, Patra D. Encapsulation of curcumin in cyclodextrin-metal organic frameworks: Dissociation of loaded CD-MOFs enhances stability of curcumin. *Food chemistry*. 2016 Dec1;212:485-94.