**Metal-Organc Framework (MOFs) for Drug Delivery Applications**

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**Abstract.** The idea of Metal-Organc Framework (MOF) materials was first introduced and developed back in 1959, for other applications. The first application of MOFs in drug delivery is carried by Fére and co-workers in 2006. From then on, MOFs are believed to be very efficient drug carriers as they solve the problem for traditional drug delivery methods of, for instance, having low drug loading capacity, unstable structure and composition as well as uncontrolled drug releasing processes. MOF materials generally have extremely high porosity and surface area, some also have flexibility properties. This review outlines some of the most used and studied MOFs for drug delivery applications including the MIL family (MIL-100/101, MIL-125(Ti), MIL-53), HKUST-1, ZIF-8 and UIO-66. Specifically, the structures, drug loading and drug releasing performances of the materials are summarized. The comparisons and outlooks for the future application of MOF materials in drug delivery are also concluded in this review.

**Keywords:** Metal-Organic Framework, Drug Delivery, Drug Loading, Controlled Release.

1. **Introduction**

Drug delivery is a very important field for mankind. While the challenges for the field of drug delivery, or to be specific, for Drug Delivery Systems (DDSs) including how to carry more drugs in a relatively small volume to lower the cost and reduce wasted materials, how to make sure the structure of the carriers are stable and could prevent unwanted degradations, etc.

For traditional DDS, there are two options: the organic route and the inorganic route. For Organic DDS, there are for example, Liposome based systems polymeric systems, dendrimers and so on. These materials usually have very good biocompatibility but they usually could not achieve a very stable and controlled releasing rate as a result of not having well-defined porosity. On the other hand, for inorganic DDS, there are examples like microporous silicon, mesoporous zeolites, layered double hydroxide and so on. Interestingly, these materials solve the problem of having uncontrolled releasing rate but unfortunately, they usually have very limited loading capacity.

By considering that both organic drug delivery systems and inorganic delivery systems have fatal disadvantages but do also have some really useful advantages, a combination of them might be a good option. This is where Metal Organic Framework (MOF) was introduced to the field. MOFs have a rich history spanning over 60 years. The first recorded report on MOFs dates back to 1959, where the focus was on a material known as Bis(adiponitrilo)copper(I) Nitrate and its crystal structures [1]. However, it was not until 1995, approximately 36 years later, that MOFs with adsorption isomers were discovered by Professor Omar Yaghi and his colleagues [2]. Subsequently, in the early 2000s, MOFs began to be utilized as drug carriers. This groundbreaking development was first implemented by Fére and his colleagues [3]. The innovative approach of using MOFs for drug delivery has opened up numerous possibilities in the field of medicine and has paved the way for further research and advancements. This paper will cover some specific materials that had been used for drug delivery as well as their structures and performances.
2. The Material Institute Lavoisier (MIL) Family

2.1. MIL-101

2.1.1. Structure and Drug Loading

In 2006, Férey et al. first reported a mesoporous chromium terephthalate, Cr-MIL-101, which has high porosity, large surface area and performs well resistance to air, water and heat, thus was expected to give good performance in applications in drug delivery.

MIL-101 shows a stiff zeotype (MTN type) crystal construction with the diameter (2~3 µm) and is built by octahedral chains of metals as secondary building units (SBUs) and terephthalic acid (BDC) linkers [4]. It consists of large spherical mesoporous cages of two modes (29 and 34 Å and large windows of 12 and 16 Å, which are pentagonal and hexagonal respectively, hence the huge cages allow the loading of the drug easily [4]. Ibuprofen adsorption by MIL-101(Cr) would be taken as an example. The result shows that MIL-101 had significant amount of adsorption which is up to 140% w/w in simulated bodily fluid (SBF) at 37°C which is extremely high and makes MIL-101 a competitive candidate in drug delivery [4].

2.1.2. Releasing Kinetics

To explain the release kinetics of MIL-101 containing two stages, ibuprofen would be still taken as an example.

At the first stage, there was a ‘burst effect’ that great proportion of ibuprofen was released rapidly, followed by a steady and persistent release governed by diffusion. After several hours, the release of ibuprofen from MIL-101 had exceeded 90% [5]. Many analytical techniques showed that MIL-101 successfully loaded all the medicines into the pores, it is possible that the rapid release was brought on by rapid dissolution followed by a rapid diffusion from the massive mesopores. It is important to note that continual stirring prevents the external diffusion process; as a result, the only cause of diffusion is the passage of the drug through the cages [3]. Moreover, it is very possible that fraction of ibuprofen that does not contact with the surface of the mesopores directly, would dissolve once it is immersed within the release medium. As the mesopores have relatively large diameter, obstruction to any diffusion beyond the pores is very small, which is the main reason caused the rapid diffusion [6]. Furthermore, there are restrictions on rate of delivery caused by dissolution and diffusion process, as the amount of ibuprofen entering the pores in the physiological fluid is near to the saturated state [3]. The drug release needs to be spread out over a few days because ibuprofen and the aromatic rings on the surface of MIL-101 interact more often at the second stage [3]. Research has demonstrated that there was no apparent decomposition of skeletal structure or loss of crystal of MIL-101, even it is under high loading level (1.4 g ibuprofen/1g MIL-101), which makes MIL-101 an important and promising drug carrier [6].

2.2. MIL-100

2.2.1. Structure and Drug Loading

Férey et al. reported the Fe-MIL-100 later on. MIL-100, represented by [Fe₃(OH₂)₂OH(BTC)₂]·nH₂O (BTC stands for 1,3,5-benzenetricarboxylic acid) is built from BTC based on octahedral trimers of Fe (III) with a large porosity (~1.2 cm³g⁻¹) and high surface area (~2000 m²g⁻¹) [7, 8]. Also, it consists of two kinds of mesoporous cages with 25 and 29 Å, containing microporous window (4.8 and 8.6 Å) [7].

To find the drug loading capacity of MIL-100, ibuprofen and aspirin are taken as example. The result indicates that the total drug loading for ibuprofen and aspirin are ~26.8 wt% and ~22.4 wt% respectively. The relative low adsorption ability of MIL-100 compared with MIL-101 could be explained by occupancy volume of the pore and small cages. It was deduced that the drug adsorption only occurred in larger cages of MIL-100, since the smaller cages (pentagonal windows of ca. 4.8~5.8 Å) might avoid both loading of ibuprofen (11.0 × 5.0 × 4.3 Å³) and aspirin (7.8 × 5.8 × 2.3 Å³). Moreover, there is no obvious difference between Cr based MIL-100 and Fe based MIL-100 on drug
loading level (35 vs. 31 wt%), indicating that there is slight impact of species of metal on drug loading [7].

2.2.2. Releasing Kinetics

The release procedure is carried out at 37 degree Celsius with continuous stirring in distilled water, in order to simulate the hydration under specific environment. The experiment shows that in the first two hours, the drug release follows the zero-order kinetics [8]. Furthermore, MIL-100 release ~99% ibuprofen and ~85% aspirin within one day, which is really fast no matter the cargo is hydrophilic or hydrophobic. This could be attributed to the structure of large cages and windows of MIL-100 that governing the delivery process [7].

2.3. Comparison in Drug Loading of MIL-100 and MIL-101

Although the linker of MIL-101 were just altered from BDC for 1,3,5- benzenetricarboxylate (BTC) that could directly form MIL-100, the ibuprofen loading is significantly different between MIL-101 and MIL-100 [4]. Indeed, this phenomenon is resulted from disparate porosity of these two MIL families. Even does MIL-100 have larger pore volume, it contains smaller cages which have similar size with the drug that would prevent loading. In other words, all the cages of MIL-101 have been used because of the high porosity, while the drug only occupied larger cages in MIL-100 selectively, and hence there must be pores that loads no drug [2].

2.4. MIL-88B (Fe)

Due to their non-toxic and extremely flexible characteristics, iron-based MOFs, particularly MIL-88B, have drawn a lot of attention. A member of the MIL-88 series, MIL-88B (Fe) is made up of terephthalic acid and oxygen-centered trimeric iron carboxylate (III) molecular building blocks (1,4-BDC). In order to compare the crystal structure of MIL-88B (Fe) before and after being loaded with ibuprofen, Tian and his colleagues used powder X-ray diffraction [9]. The results show that the diffraction angle increases, indicating that the crystal unit is contracting according to Bragg’s law. The flexibility of Mil-88B (Fe) is shown in the experiment, which is the result of the "respiratory effect" that enables nanomaterials to capture guest molecules using a stretchable framework. This increase in angle supports the discovery that the volume of the MIL-88B (Fe) cage trapped in the crystal decreases after the dimethylformamide (DMF) solvent is replaced and eliminated. In addition, according to calculations, the drug loading capacity of MIL-88B (Fe) for ibuprofen is about 194.6 mg/g [9]. This indicates that Mil-88B is significantly superior to other porous materials in terms of drug delivery, although its value is not as high as reported by other MOFs such as MIL-100/101. Fe-MIL-88B exhibits long and controlled releasing process because of its porous structure. MIL-88B (Fe) particles were also introduced into the culture medium to test their cytotoxicity to NIH3T3 Swiss mouse fibroblasts. (After sterilization) [9]. After 48 hours of incubation, the particles exhibited no detrimental effects on cell viability, according to the results of the CellTier 96 activity test [9]. Moreover, the cell activity did not fall below 40% even at the highest measured dose of 2.5 mg/mL. As an applicable drug carrier, amine terminated Fe-MIL-88B-NH2-NP may be employed to deliver anticancer drug in tumor settings in a pH-responsive way and the maximal release amount if carrying doxorubicin in an acidic tumor environment may reach a considerable degree [10]. In 2022, a Mil-88B (Fe) thin film for releasing medicinal compounds was manufactured. When ibuprofen is a delivery drug, the drug loading of this method is 8.7% higher than other polymer based thin film drug delivery technologies [11]. In summary, MIL-88B (Fe) has great development potential as a drug delivery system due to all its good characteristics mentioned.

2.5. MIL-125 (Ti)

In 2009, Serre, Sanchez, and colleagues announced the construction of the first titanium-based MOF using BDC ligands with titanium oxide clusters [12]. MIL-125 (Ti) represents titanium-based MOFs that have minimal toxicity and are easy to synthesize. Synthesis can be accomplished using
the starting reagent 1,4-benzoic acid and isopropoxytitanium (IV), which are dissolved in a solvent mixture consisting of DMF and methanol [12]. If the mixture is further heated to 140 degrees Celsius in a solvothermal oven, a crystalline powder can be obtained [12]. In addition, the tetragonal cavity and the octahedral cavity of MIL-125 have structural advantages that can be used for drug packaging. MIL-125 and its amino functionalized MOF MIL-125-NH2 have been used as drug carriers for a variety of drugs, including doxorubicin (DOX) and etc [13]. In 2017, Yun Suk Huh and his colleagues studied the combination of porous Mil-125-NH2 and polyethylene glycol (PEG) as an effective nanomaterial. In 2021, Wang Fei and her colleagues revealed that MIL-125 and Mil-125-NH2 may be drug carriers of chloroquine (CQ) [13]. Chloroquine is widely recognized as an antimalarial drug and has been widely used in clinical practice. It is expected to become a potential autophagy inhibitor and anticancer agent. Both nanomaterials have shown high CQ loading capacities in experiments (MIL-125 460 mg/g and MIL-125-NH2 400 mg/g, respectively) [13]. In addition, after 14 days in a phosphate buffer solution, the sustained release of CQ may reach about 70%, indicating that Mil-125 and Mil-125-NH2 loaded with CQ may be able to reduce the negative impact of CQ [13].

2.6. MIL-53

2.6.1. Structure

MIL-53, also known as chromium terephthalate, has been extensively studied for its potential use in various fields, especially drug delivery. Starting from the structure, MIL-53 has a pore diameter of about 1.3 nm flexible structure that can undergo a reversible phase transition in response to changes in temperature, pressure, or guest molecules [10,14]. MIL-53 is being researched for its possible use as a stimuli-responsive medication delivery system as a result of this special characteristic. Using neutron powder diffraction and inelastic neutron scattering techniques, it was discovered and shown that MIL-53 materials performs a reversible structural shift as a function of temperature between a close-pore and open-pore structure without the presence of any guest molecules [15].

2.6.2. Drug Loading

Ibuprofen was absorbed into Iron and Chromium based MIL-53 solids by impregnating the solids with hexane solutions that contained Ibuprofen while they were being agitated to determine the drug loading capacity. Chemical investigation reveals that Iron and Chromium based MIL-53 solids both adsorb about 20 weight percent of Ibuprofen drug. This result showed that the metal used would not affect the drug loading of the materials for MIL-53 [10].

2.6.3. Releasing Kinetics

Investigations into the Cr and Fe based MIL-53’s releasing kinetics were conducted in simulated bodily fluid (SBF), which produced an environment that was similar to the human body. The fact that MIL-53 is finished after 3 weeks demonstrates a very slow delivery which also showed a zero-order kinetics. While the utilization of two different metals revealed various delivery patterns. The delivery of MIL-53-Cr is almost linear, whereas MIL-53-Fe delivery plateaus after a stage of very quick pace. The releasing rate then returned to being linear following the plateau [10].

2.6.4. Future Perspectives

The application of MIL-53 in drug delivery still needs further researches. Under some circumstances, MIL-53’s structural alterations can affect the stability and release of the medication. Limited biodegradability in some MIL-53 formulations might result in buildup in the body and probable toxicity. There are also concerns on the metal ions used might be toxic to human body cells.

3. The Hong Kong University of Science and Technology (HKUST) Family

The 1,3,5-benzenetricarboxylic acid (BTC) ligands and copper ions that make up the MOF known as HKUST-1 give it its distinctive properties and structures, such as its enormous pore volume, high
surface area, and great chemical stability. These characteristics gave it a significant potential for uses in gas separation, hydrogen storage, and other areas.

3.1. Structure and Preparation

A 3D porous framework and a cubic crystal structure are both present in HKUST-1. The structure consists of cages and channels measuring 9 by 9 inches, together with paddlewheel units constructed of copper ions and BTC ligands. HKUST-1 is believed to be useful materials in applications including catalysis, drug delivery and gas separation due to its high pore volume and high surface area supplied by cages and channels in the framework [16].

3.2. Drug Loading and Releasing

With HKUST-1, the medication loading and releasing performance was likewise impressive. Ibuprofen, guaiacol, and anethole were used by Chen and colleagues to study the drug loading and releasing capabilities of HKUST-1 [17]. These three medicines could have entered through the HKUST-1 building's windows due to their size. Ibuprofen, guaiacol, and anethole each had a drug loading dose of 0.34 g*g⁻¹, 0.38 g*g⁻¹, and 0.40 g*g⁻¹, respectively. Ibuprofen's specific drug loading is thought to be higher than MIL-53(Fe) and very similar to MIL-100(Fe), developed by Ferey and colleagues [3, 18, 19]. While the drug release times for HKUST-1 are 16 hours for ibuprofen, 22 hours for anethole, and 10 hours for guaiacol, respectively, the timing of the drug releases follows the pattern of drug loading capacity [17].

3.3. Future Prospectives

Overall, HKUST-1 has a high potential in uses in the delivery of pharmaceuticals, and current research is investigating these possible uses in a number of therapeutic contexts, including the delivery of vaccines, combination therapies, and targeted pharmaceuticals. Before HKUST-1 may be employed as a common medication delivery method, there are still issues that must be resolved. For instance, extensive research into its possible toxicity and biocompatibility in vivo is required, and manufacturing processes must be streamlined for large-scale production. Notwithstanding these difficulties, HKUST-1 has bright possibilities for the future in the field of medication delivery, and further research and development are believed to result in even more intriguing applications in the future.

4. Zeolitic Imidazolate Frameworks (ZIF) Family

4.1. ZIF-8

4.1.1. Structure

ZIFs are porous substances with crystalline structures that develop as a result of the association of metal ions with organic ligands. They are composed of Zn ions and the sodalite-like compound 2-methylimidazole (MIM). The configuration of these structures is M-IM-M, where M stands for the imidazolate ligands and IM for the tetrahedrally coordinated metal ions, such as the cations of Cu, Zn, and Co. The M-IM-M structure has a bond angle of roughly 145 degrees. The remarkable thermal and chemical stability, enormous surface area (BET: 1630 m²/g), tunable big pore size (11.6 Å), and high loading capacity of ZIFs are all characteristics shared with MOFs and zeolites.

The most extensively researched ZIF of the different ZIF varieties for drug delivery systems is ZIF-8. ZIF-8 are used in many different applications, including catalysts, medication delivery, adsorbents, and more [19].

4.1.2. Drug Loading

The amount of drug that ZIF-8 can hold depends on the size of its pores, which can be changed by altering the reaction conditions during synthesis. The porosity design of ZIF-8 can be modified to accommodate therapeutic compounds with different lengths and shapes. ZIF-8 allows for the
adsorptive attachment of larger molecules like proteins and peptides as well as the encapsulation of smaller therapeutic compounds like methotrexate and doxorubicin inside the framework's holes. ZIF-8's high surface area also allows for the adsorption of many drug molecules, increasing its capacity for drug loading [20].

The capacity of drug loading of ZIF-8 can be further improved by functionalizing the framework with specific functional groups. For example, carboxylic acid groups can be introduced onto the surface of ZIF-8, which can form coordination bonds with metal ions in the drug molecules, resulting in enhanced drug loading capacity. Other functional groups such as amino groups and hydroxyl groups could also be introduced onto the surface of ZIF-8, which can increase the affinity of the framework towards certain types of drugs [20].

4.1.3. Releasing Kinetics

The releasing kinetics of ZIF-8 can be greatly affected by one of its properties which is being a stimuli-responsive MOF. Stimuli-responsive MOFs are MOFs that require activation by specific stimuli. Upon activation, the chemical composition or physical structure of these systems undergoes a given transformation, triggering the release of drugs at the intended site. ZIF-8 is a type of stimuli-responsive MOF because the Zn ions in ZIF-8 are pH-sensitive which means that it can be activated by pH-responsive stimuli [19, 21].

ZIF-8's drug release procedure consists of three phases. The ZIF-8 framework is first swollen and degraded. The ZIF-8 framework in this phase expands and degrades in response to stimuli that are external, such as a change in pH or temperature, allowing the drug molecules to diffuse out of the pores. The second step entails the drug molecules diffusing out of the pores. The drug molecules spread through the pores of ZIF-8 once the framework begins to break down. Several factors, including the size of the drug molecules, the porosity of the ZIF-8 framework, and the gradient of the drug molecules' concentrations can influence the rate of diffusion. Finally, during the third step, the drug molecules interact with the release medium such as body fluid, buffer solution as they diffuse out of the pores of ZIF-8. The temperature and pH of the release medium can affect the solubility and stability of the drug molecules, which can further affect the release rate.

5. University of Oslo (UIO) Family

Another family of MOFs that has seen substantial research is the UIO MOFs. A group of academics at the University of Oslo under the direction of Karl Petter Lillerud synthesized and published the first UIO MOF in 2008. The UIO MOFs have a highly porous and ordered structure because they are made of metal ions like Zn, Cu, and Fe that are coordinated to organic ligands like terephthalic acid and 2-methylimidazole [22].

5.1. Structure

One of the most well-known UIO MOFs is UIO-66, which consists of a ZnO₆ octahedra structure with terephthalic acid (H₂BDC) as the organic ligand and zinc ions as the metal ions. The structure ZnO₆ octahedra are six-coordinated and are linked by the terephthalic acid ligands creating a 3D framework. Each ZnO₆ octahedron is connected to six terephthalic acid ligands, and each ligand is connected to four ZnO₆ octahedra. This results in a highly ordered and interconnected network of metal ions and organic ligands. The formula for UIO-66 is [Zn(BDC)₂], where BDC represents the terephthalic acid ligands [22].

The structure of UIO-66 gives rise to its unique properties, including high surface area (usually in a range of 1200 to 2200 m²/g), high porosity (the pore volume can range of 0.6 ~ 1.2 cm³/g), and high thermal stability. The large void areas that are present in the structure are the cause of UIO-66's high porosity. Gases and other tiny molecules can be adsorbed in these empty areas. Small channels and pores inside the structure are what give UIO-66 its large surface area. UIO-66 has strong covalent connections throughout its structure, which contribute to its thermal stability.
5.2. Drug Loading

The drug loading of UIO-66 involves the encapsulation of drugs within the pores of the MOF. This process can be achieved through several methods, including solvent evaporation, impregnation, and covalent functionalization. UIO-66 can carry drugs such as anticancer drugs and anti-inflammatory drugs. For anticancer drugs like doxorubicin, UIO-66 can reach a loading capacity of 450 mg/g. Whereas for anti-inflammatory drug like ibuprofen, it reaches a loading capacity of 67 mg/g. This huge contrast in loading capacity can be explained using the sizes of these two drugs. Doxorubicin is a larger molecule than ibuprofen, with an approximately 544 g/mol of molecular weight compared to ibuprofen's molecular weight of approximately 206 g/mol. This means that the larger size of doxorubicin can occupy more of the available space inside the pores of UIO-66, this leads to a higher loading capacity [23].

5.3. Releasing Kinetics

UIO-66 normally releases its drugs in two stages: an initial burst release and a sustained release. For the first few hours or days after the drug-loaded UIO-66 material is ingested, an initial burst release occurs. At this stage, a significant amount of drug is rapidly released from the surface of the UIO-66 material due to the difference in drug concentration between the interior and exterior of the MOF structure. After the first burst release, the drug is released slowly and under more control over a period of days, weeks, or even months. This stage is known as sustained release. The drug molecules' diffusion through the UIO-66 structure's pores primarily controls the sustained release.

Multiple factors can impact the drug release dynamics from UIO-66. These include the characteristics of the drug molecules, the pore shape and size, and the surface area and morphology of the UIO-66 particles. Additionally, UIO-66 is also a stimuli-responsive MOF that can respond to various stimuli such as temperature and pH. This ability allows for more precise control over drug release at particular times and locations [23, 24].

6. Conclusion

For MIL-100 and 101, they have two volumes of mesoporous cages, high surface area and stable releasing kinetics that contribute to considerable drug loading efficient release, which makes them possible drug carriers. Furthermore, MIL-101 has much more significant drug capacity than MIL-100 due to its complete utilization of all cages rather than empty smaller cages in MIL-100. For Fe-MIL-88B, the material exhibits high drug loading capacity, high flexibility, cytotoxicity and general adaptability. MIL-125(Ti) is characterized by low toxicity and easy synthesis. It also showed great biocompatibility and therefore has been designed as carriers of different types of drugs like ibuprofen. It also showed comparatively high drug loading capacity and potential drug carrier for chloroquine. MIL-53 is another example of flexible MOF with high surface area, tunable pore size and flexible structure. It also has potential for being a stimuli responsive drug delivery systems as the structure alternates as the temperature changes. Similarly, UiO-66 and ZIF-8 also have tunable pore sizes and flexible structure, that allows them to change the structure under the changes of temperature and pH value of the environment. While HKUST-1 does have advantages like other MOF materials but the efficiency is dependent on the size of the drug molecule.

Overall, there are still serveral problems and challenges that MOF materials are facing now including the toxicity of the transition metal used, the stability of the sturture in different delivery environment, as well as how to scale up the production of these materials to be used more in the industry, which means the produccion process must be highly cost-effective, simple and green.

References


