Iranian Journal of Chemical Engineering

Journal Homepage: www.ijche.com

pISSN: 1735-5397
eISSN: 2008-2355

Regular Article

Metal-Organic Frameworks in Systems of Drug Delivery: Review

F. Soltani-Tehrani, M. Fattahi*, M. Motevassel

Department of Chemical Engineering, Abadan Faculty of Petroleum Engineering, Petroleum University of Technology, Abadan, Iran.

ARTICLE INFO

Article history:
Received: 2023-03-17
Accepted: 2023-07-24
Available online: 2023-07-25

Keywords:
Metal-organic frameworks,
Drug Delivery System,
UiO-66,
Cancer treatment,
Nanoscale

ABSTRACT

Drug delivery systems (DDSs) have become a crucial aspect of cancer therapy, and researchers are continuously striving to identify the optimal methods for targeted delivery and release of therapeutic agents. Metal-Organic Frameworks (MOFs) have emerged as a promising class of materials for DDSs due to their exceptional storage capacity, unique characteristics, and high durability. This comprehensive review explores the wide-ranging applications of MOFs in various fields, including catalysis, gas separation and storage, fuel purification, water treatment, medication administration, and imaging. The review paper evaluates different approaches to synthesize MOFs, such as the self-assembly of metal ions and clusters and the solvothermal method, to optimize their performance characteristics. The present study aims to shed light on the numerous challenges associated with utilizing MOFs in clinical settings. However, MOF nanocomposites that incorporate reinforcement phases represent a promising strategy for addressing these issues. With the incidence of cancer on the rise, targeted MOFs offer a potential solution to the lack of the selectivity of certain drugs by virtue of their distinctive physical and chemical properties. This investigation delves into how MOFs can be employed to regulate drug release in DDSs and presents research on the key applications of MOFs in the realm of cancer therapy. The application of UiO-66 for drug delivery systems and exploring the different physical characteristics and chemical structures of dicarboxylate ligands incorporated into UiO-66 topology MOFs were investigated. Overall, the review paper provides a comprehensive overview of the diverse applications of MOFs and their potential for drug delivery systems in cancer therapy.

DOI: 10.22034/ijche.2023.390219.1486 URL: https://www.ijche.com/article_176129.html

*Corresponding author: moslem.fattahi@gmail.com; fattahi@put.ac.ir (M. Fattahi)

1. Introduction

Nanotechnology has revolutionized research in numerous sectors, including medicine, biology, the environment, and nutraceuticals (as shown in Figure 1). Nanostructures, such as nanofibers, nanoparticles, nanotubes, and nanocomposites, have enabled the diagnosis and treatment of various ailments. These nanostructures are capable of carrying and transporting medicines, proteins, vaccines, DNAs, and enzymes. Nanomedicine is a rapidly growing field that applies knowledge and techniques from nanoscience to the medical biology, disease prevention, and therapy.

It entails identifying, dispersing, and activating nano-sized substances in living cells, such as nanorobots, nano-vehicles, and nanosensors [1].

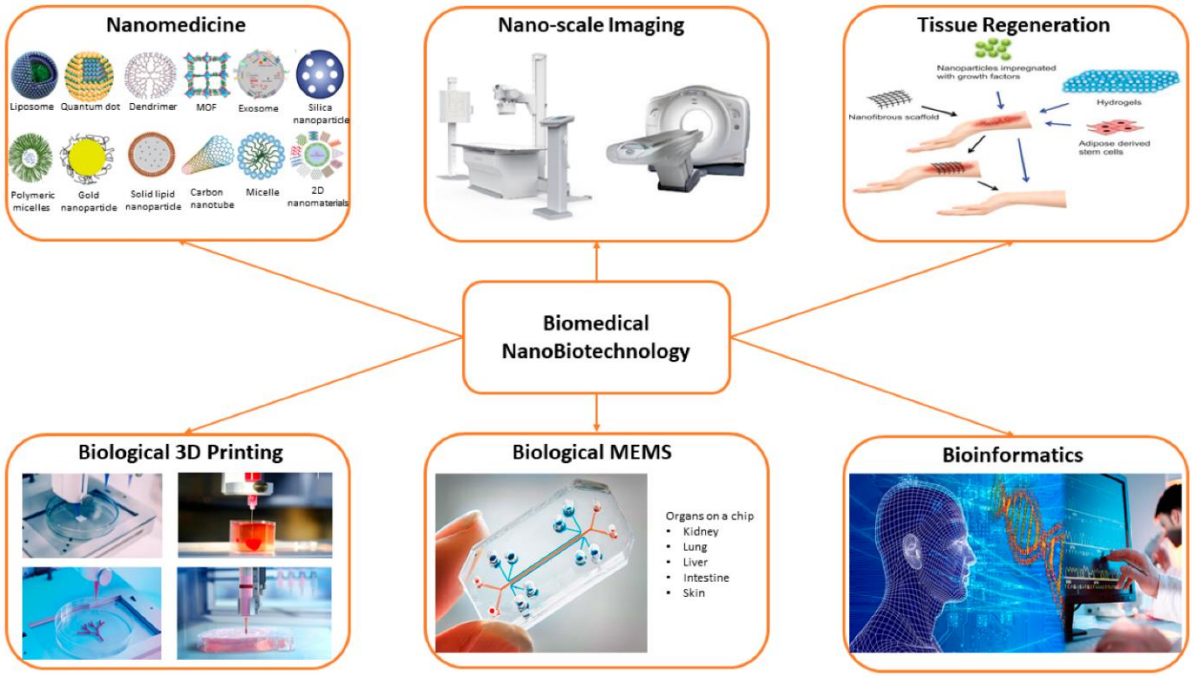

Figure 1. Various applications of nanotechnology in the biomedical field [1].

MOFs are highly organized crystalline porous materials formed by combining metal ion clusters or chains with organic ligands [2]. They are emerging as promising candidates for addressing challenges in nanomedicine since they combine the desirable aspects of both organic and inorganic drug delivery systems (DDSs) [3]. In recent years, MOFs have been extensively researched for biomedical applications, particularly in drug delivery. Designing and composing nanocarriers are crucial in drug delivery as they can modify the hydrophilicity of pharmaceuticals, impact their absorption and excretion, provide targeted distribution, and prevent medications from attaching to unrelated molecules [1]. Furthermore, MOF-based multifunctional platforms that combine the effectiveness of multifunctional components to suit growing needs and treatment operations while achieving specified objectives are also being developed.

Furthermore, MOFs offer greater inherent characteristics than typical nanomaterials such as porous silica do [4]. The vast surface area of MOFs (ranging from 1000 to 10,000 m^2/g) allows for the improved biomolecule loading and encapsulation of various types of

medicines. MOFs also have configurable pore sizes, customizable host-guest interactions, and flexible functionality due to their ability to connect organic ligands into porous materials with metal ions or clusters. These features make MOFs a promising nanomedicine platform [1, 5].

The formation of highly porous macromolecular and coordination polymers known as MOFs is achieved by using multidentate organic bridging ligands to join metal ions or clusters. MOFs are composed of an organic monomer and a metal core [6, 7]. The development of MOFs based on zirconium (Zr-MOF) is a significant breakthrough in the MOF research since they exhibit a high charge density and bond polarization owing to the high oxidation state of Zr (IV). This feature makes them more durable in organic and water-based solvents used in biotechnology, separation, and adsorption [8]. Figure 2 illustrates some of the most extensively studied MOF structures [1].

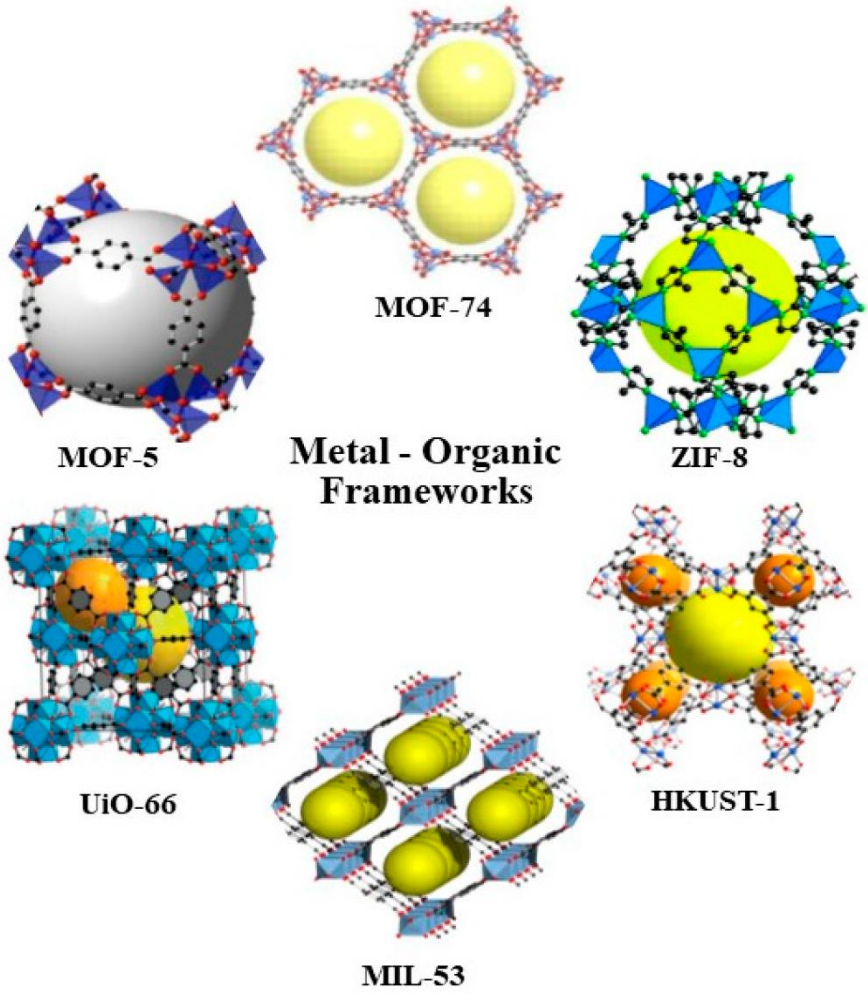

Figure 2. Examples of typical metal-organic frameworks [1].

MOFs offer several advantages over traditional drug delivery systems (DDSs), which are typically either organic or inorganic. While liposomes or polymers have higher biocompatibility, they usually have lower drug payloads. In contrast, gold, iron, and silica nanoparticles, among other inorganic DDSs, may be much more drug-loaded but less biocompatible and may accumulate in the liver

or spleen due to their slow degradation rate, resulting in significant side effects [9].

MOFs are crystalline compounds with porous structures and enormous surface areas that contain unique repeating units consisting of organic ligands and metal ions or clusters [6, 10]. The vast range of metal ions and ligands available for constructing MOFs allows for nearly infinite tunability [7]. However, the stability of certain MOFs in water may be limited by weak coordination bonds, particularly at high pHs. To improve the practical applicability of existing MOFs and address their instability, two key solutions have been recently discovered. The first solution involves introducing hydrophobic functionality to the organic linkers of unstable MOFs. The second approach is to add hydrophobic layers to the external surface of the MOF after synthesis [11]. By carefully controlling the interaction between the MOF host and guest or lightly coating the surface of MOFs with silica, it is possible to enhance the stability and biocompatibility of MOF carriers. This can be achieved by using a responsive polymer or lipid bilayer [4].

As the prevalence of diagnosing cancer is projected to affect at least one-third of individuals in industrialized nations, the scientific community has broadened its research focus to include the development of advanced and effective techniques for the cancer detection and treatment. In this regard, drug delivery has made remarkable progress by utilizing cutting-edge technologies to transport therapeutic payloads to the targeted areas of the body for treatment. By stabilizing and directing medications to affected tissues, DDSs have the potential to minimize adverse side effects and improve therapeutic efficacy, as noted by [9].

The concepts of the "molecular simulation" and "molecular modeling" encompass a diverse set of theoretical and computational methodologies employed to investigate the behavior of individual molecules or systems of molecules. The behavior of a molecule is inherently determined by the behavior of its constituent atoms, which, in turn, is influenced by the behavior of the atomic components. In drug delivery simulations, a range of molecular simulation techniques are typically employed, and Table 1 provides an overview of some commonly utilized methods.

One of the simulation approaches utilized in the drug delivery research is quantum-mechanical (QM) simulation, which accurately solves the Schrödinger equation to depict the molecular behavior. Another commonly employed method is molecular dynamics (MD), which utilizes atoms as the fundamental building blocks of molecules and models their movements based on interatomic forces, known as the "force field", exerted by atoms within the same molecule or other molecules in the system. The MD technology can also be used to study crystallization and drug release from the excipient matrix. Additionally, the atomistic Monte Carlo (MC) technique, which is based on the force field concept and the approximation discussed earlier, differs from MD in terms of methodology. This approach offers a broad range of applications in drug carriage and drug release [12].

Table 1. List of approaches for drug delivery that frequently use the molecular simulation [12].

Simulation method	Variants	Applications
Quantum-mechanical (QM) methods (Merz, 2014; Mucs & Bryce, 2013; Raha et al., 2007)	Density functional theory (DFT); Hartee-Fock (HF) theory; Semiempirical; QM/molecular mechanical (MM) methods	Potential energy, Geometry optimization, Docking, and Force-field parametrization
Monte Carlo (MC)	Atomistic Monte Carlo (Bernini, Fairen-Jimenez, Pasinetti, Ramirez-Pastor, & Snurr, 2014; Meunier, Goupil, & Lienard, 2017);	Free energy, Absorption/binding energy, and Docking Self-assembly, Swelling of gel carriers, and Membrane translocation
	Coarse-graind Monte Carlo (Pogodin, Wemer, Sommer, & Baulin, 2012; Yan & de Pablo, 2003);	Drug release from excipient matrices and crystallization
	Lattice Monte Carlo, Kinetic Monte Carlo (KMC) (Martínez et al., 2009; Vlugt-Wensink et al., 2006; Zeng, Jacob, & Tikare, 2004)	
Molecular dynamics (MD)	Atomistic molecular dynamics (De Vivo, Masetti, Bottegi, & Cavalli, 2016; Zhao & Caflisch, 2015);	Solubility, Hydrogen bonding, Diffusivity, Membrane permeability, Carrier-drug miscibility, Carrier-drug interaction, Glass transition, Drug aggregation, and Crystallization
	Coarse-grained molecular dynamics (Prates Ramalho, Gkeka, & Sarkisov, 2011; Thota, Hu, & Jiang, 2015);	
	Brownian dynamics (BD) (Chen et al., 2009); Dissipative particle dynamics (DPD) (Guo, Zhang, Wu, & Qian, 2010)	Self-assembly, Drug release from excipient matrices, and Membrane translocation

The present review provides an overview of the various applications of MOFs in drug delivery systems, owing to their numerous advantages, such as their high surface area, which facilitates the improved biomolecule loading and encapsulation of various types of drugs, tunable pore size, customizable host-guest interactions, and adaptable functionality. MOFs combine the best properties of both organic (biocompatibility) and inorganic (high loadings) systems.

Initially, a brief introduction to MOFs and their applications as porous coordination polymers is presented. Next, MOFs are discussed as drug delivery systems that can maximize effectiveness while minimizing negative effects. Additionally, the use of MOFs in the cancer treatment is explored, as they can selectively host, transport, and direct therapeutic molecules to tumors, thereby overcoming the lack of selectivity associated with certain medications. Furthermore, nanoscale MOFs are investigated as a

promising drug carrier class, owing to their high porosity, crystalline nature, specific structural information, and potential for the future functionality. Finally, the physical properties of UiO-66, the first Zr(IV)-based MOF, are highlighted, as it has great potential as a drug delivery carrier due to its exceptional thermal and physical properties.

2. Applications of MOFs

Due to their unique characteristics, excellent storage capabilities, durability, and structural tolerability, MOFs offer a wide range of uses. One of their key advantages is the ability to tailor their cytotoxicity and characteristics by carefully selecting metals and linkers [7, 8]. MOFs find applications in various fields, including the catalysis, gas storage separation, water treatment, fuel purification, heat transformation, light emitting, medication administration, and imaging [6, 7, 13].

There are various methods available for synthesizing MOFs, including the one-pot synthesis, reverse microemulsion, rapid microwave-assisted method, solvothermal approach, fast precipitation method, rapid microwave-assisted method, and ultrasonic synthesis [14]. MOFs are synthesized through a self-assembly process of metal ions or clusters that function as coordination centers and organic ligands. Given the distinct characteristics of MOFs, such as their extensive surface area, well-defined channels, low cytotoxicity, and low biodegradability, appropriate modifications are necessary during the synthesis or post-synthesis stages [16].

The solvothermal technique is a traditional method for the MOF synthesis and is often used to produce metal-organic frameworks. For example, Yang et al. synthesized IRMOF-3 using the solvothermal technique and then post-synthetically modified it with folic acid (FA) [17]. Angshuman et al. employed a mixed solvent solvothermal approach to obtain Fe_3O_4@IRMOF3. The material was immersed in a mixture of DMF and pure ethanol containing PVP before being heated at 100 °C to produce dark brown nanomaterials [18]. Nian also used the solvothermal method to create brown $N_3UiO66NH_2$ [14].

MOFs have tremendous potential as nanoscale drug carriers due to their high molecular loading and ease of functionalization. In their early biological uses, MOFs were used as delivery systems for molecular therapies and as effective contrast agents for optical imaging, multimodal imaging, and X-ray computed tomography imaging [5]. As more mature biomedical materials with superior biocompatibility, variable compositions, simple functionalization, and desired loading capacity, MOFs offer significant development potential for MOF-containing nanohybrids for high-performance multimodal treatments [19].

3. MOFs in drug delivery systems

Targeted delivery can be achieved through active or passive methods, and controlled release strategies can be exogenously or endogenously stimulated. Drugs must have acceptable solubility to achieve the required dose at the desired location, as poorly or completely insoluble drugs leave the body through the digestive system before becoming available [20].

DDSs, such as intravenous, oral, and nasal delivery, have been developed to maximize effectiveness while minimizing negative effects. MOFs have been investigated as a drug delivery system to mitigate the negative effects of free drugs by enabling gradual release, targeted delivery, and protection from degradation [21]. Nanomedicine has emerged as a compelling alternative to traditional pharmaceuticals due to its ability to achieve these objectives [22].

Post-synthetic modification is an effective method for developing new capabilities for the

controlled drug release in MOF materials. Zhang et al. developed a multifunctional and biocompatible drug delivery system based on MIL-101-N3(Fe) that demonstrated increased cellular absorption and drug release with a low pH-response. The azide-modified MIL-101(Fe) was first loaded with DOX, and then the strain-promoted [3+2] modification was performed with a bicyclononyne-functionalized-cyclodextrin derivative. It was further functionalized with the v3 integrin-targeting peptide polymer Lys(adamantane)-Arg-Gly-Asp-Ser-bi-PEG1900 (K(ad)RGDS-PEG1900, bi=benzoic imine) through host-guest interaction [4].

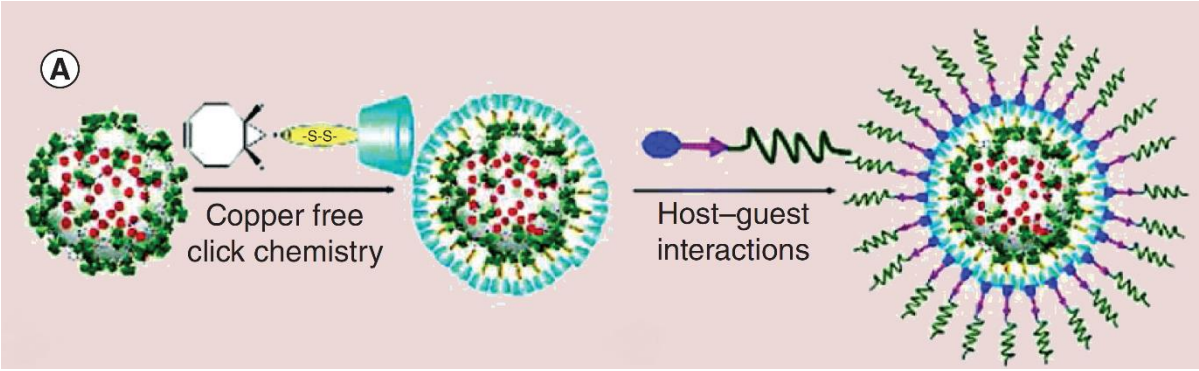

Figure 3. Functional MOF nanocomposites for the multi-stimuli-responsive drug release. Institut Lavoisier (MIL)-101 (Fe) the post-synthetic modification and drug loading schematic [4].

MOFs are becoming increasingly popular as drug delivery vehicles due to their high drug loadings, biocompatibility, storage capacity, low toxicity, and ease of functionalization. These hybrid structures are formed by combining metal clusters with multidivalent organic ligands, resulting in porous crystalline structures. MOFs offer significant advantages over other DDSs, as they combine the best properties of both organic and inorganic systems. However, due to the diversity of MOF materials, it can be challenging to determine which MOF is optimal for a specific drug molecule, and there are few examples of multivariate MOFs for drug delivery applications [7, 8, 21, 23].

MOFs, also known as porous coordination polymers (PCPs), are the specific type of porous crystalline materials that feature extended network topologies. They are formed through the self-assembly of inorganic metal clusters with organic ligands. Currently, there are roughly 99,075 synthesized MOF and MOF-type structures available, according to the Cambridge Structural Database (CSD) (Figure 4a). The exceptional properties of MOFs have led to their increasing popularity in various applications, as evidenced by the rising number of research studies investigating their uses (Figure 4b) [1].

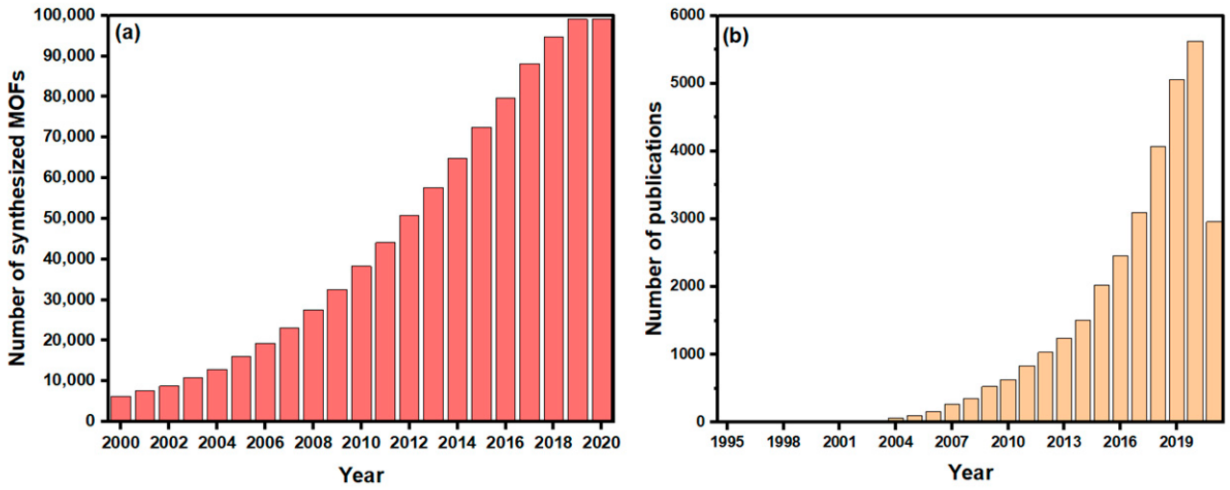

Figure 4. (a) Annually reported total of synthesized MOFs in the Cambridge Structural Database (CSD). (b) Volume of papers using the term "Metal-organic framework(s)" each year [1].

MOFs based on zinc, iron, zirconium, and magnesium are being extensively studied for their potential value as DDS due to their low cytotoxicity, high biodegradability, and excellent biocompatibility [16]. Metal-linker chemistry and post-synthetic modifications offer virtually limitless options for designing desirable structures to improve drug transport capabilities, as seen in Figure 5. MOFs are thus the attractive solution to the challenges currently faced by nanomedicine due to their organic and inorganic natures [9].

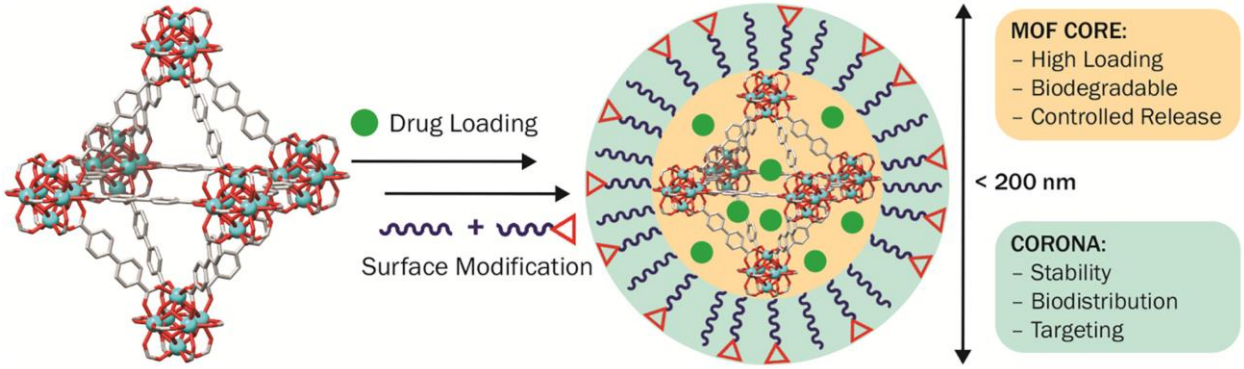

Figure 5. Ideal characteristics of a MOF-based drug delivery system are shown in a schematic, using the structure of UiO-67, $[Zr_6O_4(OH)_4(bpdc)_6]_n$(bpdc=4,40-biphenyldicarboxylate) as an example [9].

MOFs have advantages for industrial applications, but their low chemical stability can be advantageous for drug delivery as they can be quickly biodegraded in the body after drug release. However, there are limitations to their application, such as very quick delivery kinetics of fewer than three days in some MOF-drug systems [15]. Developing universal principles for the particle cellular internalization optimization in DDS is challenging due to various factors such as the material-specific characteristics, cell line-dependent rate, and endocytic route selection [22]. DDSs have drawbacks in clinical settings, including the poor drug loading capacity, rapid drug release kinetics, non-specific biodistribution, and toxicity in rare cases [3]. Researchers have attempted to

improve the water stability, mechanical strength, and biocompatibility of MOFs while maintaining their other advantages by creating MOF nanocomposites using reinforcement phases such as polymers, silica, graphene, and carbon nanotubes [5]. The surface modifications of MOFs can enhance specific carriers, leading to improving stability, dispersion, and the ability to pass physiological barriers [23]. To use MOF systems successfully in DDS, it is necessary to investigate the loading and release of various medicinal chemicals, cellular absorption, and intracellular destiny, as well as to understand the endocytosis process [22]. Molecular simulations, including drug-receptor binding or docking investigations, have been used extensively in recent years for drug delivery applications [12].

Table 2. Representative study using molecular simulations in drug delivery [12].

Reference	System	Simulation software and method	System size	Simulation time	Properties	Comparison/ Correlation to experiment
Bernini et al., (2014)	Ibuprofen on metal-organic frameworks (MOF)	RASPA, GCMC	~3 nm	~2×10^6 MC steps	Drug capacity and drug adsorption	No

The unique pore structures of MOFs allow for easy capture of pharmaceuticals smaller than their pore diameters through a mixing process known as post-encapsulation, which is widely used to incorporate various drugs and proteins into porous MOF materials.

In 2006, Ferey et al. used MOF materials for the first time as drug carriers for controlled delivery. They encapsulated ibuprofen (IBU) in cubic zeotypic metal carboxylates chromium-based MOFs, MIL-100 (3340 m^2/g) and MIL-101 (5510 m^2/g), created from di- or tricarboxylic acids and trimers of metal octahedral. The IBU adsorption was impressive in both MIL-100 and MIL-101, with 0.35 g of IBU/g in MIL-100 and 1.4 g of IBU/g in MIL-101. The total IBUs released from MIL-100 and MIL-101 were achieved in 3 and 6 days respectively, according to kinetic release experiments. The researchers also observed three types of interactions that occurred during the IBU release process: relatively strong electrostatic interaction between the ligands and the IBU molecule, π-π interactions between the ligand and the IBU, and weak IBU-IBU connections [4].

4. MOFs in the cancer treatment

Cancer has become a severe illness affecting human health, with its morbidity continuously increasing. Despite recent advancements in cancer medicines and rising survival rates, the heterogeneity of cancer requires the development of novel therapeutic approaches. The most commonly used cancer therapies include chemotherapy, radiotherapy, and surgery, which often result in the dispersion of nonspecific anticancer agents, inadequate medication concentrations at the tumor site, and uncontrollable toxicity, leading to various side effects. Although immunotherapy has gained popularity as a novel class of cancer treatment procedures, it is more hazardous and only effective for select individuals [14].

Bioactive drugs and other chemicals are frequently utilized as therapeutic agents to improve human health and extend life expectancy. Many of these chemicals have shown promise in the treatment of serious disorders, including cancer. However, they can have substantial drawbacks, such as poor solubility and non-selective biodistribution, which frequently result in harm to healthy tissues and cardiotoxicity, severely limiting their therapeutic potential. These problems can be addressed by utilizing DDS, which increases drug solubility, protects it from degradation, allows for regulated drug release, provides targeted distribution, and reduces harmful side effects [15]. The demand for novel cancer treatments is being driven by an increase in cancer diagnoses, the adverse effects of most present therapies, and tumor resistance to some of them [3].

Targeted MOFs can help overcome the lack of selectivity of certain medications by selectively hosting, transporting, and directing therapeutic molecules to the tumor site. This method allows for a decrease in the amount of the traditional chemotherapy required, resulting in improved therapeutic efficacy and fewer unwanted side effects. Modifying the surface of nanomaterials with antibodies or suitable ligands can potentially target certain cells and organs within the body. For example, Chen et al. reported that Zr-UiO-66 was functionalized with pyrene-derived polyethylene glycol (Py-PGA-PEG) and conjugated to nucleolin using a peptide ligand (F3) for targeting triple-negative breast cancer [14].

Developing effective cancer therapy is one of the most challenging objectives for the scientific community, as most medications lack tumor selectivity, leading to several challenges and side effects. Therefore, DDSs have emerged as one of the most promising healthcare applications. However, DDSs must overcome several challenges, such as the bioavailability, unpredictable drug release (usually due to carrier instability), loading capacities, particle size, nanoparticle cellular internalization routes, and toxicity before they can be used [8]. MOFs are typically characterized by a large specific area, a considerable pore diameter, good biocompatibility, non-toxicity to humans, and easy digestibility, making them useful as medication transporters. To maximize the drug loading capacity, control drug release rate, and safely deliver the medication to its destination, the careful optimization of the pore size, particle size, stability, and other MOFs properties is necessary [14].

Photodynamic therapy is a cancer treatment approach that involves generating reactive oxygen species (ROS) at the tumor location by irradiating photosensitizers. However, porphyrin and its derivatives have been limiting factors as photosensitizers in this method due to their low solubility, self-quenching, and aggregation issues. New research has demonstrated that MOF nanoparticles based on porphyrins hold great promise as drug delivery systems, imaging contrast agents, and for the photodynamic therapy, addressing some of the challenges faced in the cancer treatment. MOFs provide precise spatial controls and a monomeric form, enabling the precise accumulation of medications at tumor locations. Currently, most cancer treatments with nanoscale MOFs rely on the passive targeting (enhanced permeability and retention (EPR) effect) to ensure the targeted delivery of the medication [25].

The use of MOFs in the cancer treatment may face several challenges, including the quality control, toxicity, biocompatibility, and avoiding immune clearance or premature drug release before reaching the target site. To develop a MOFs-based drug delivery system

suitable for the clinical use, significant advancements are still needed, from synthesis to the quality control and in vivo process monitoring. Nonetheless, the MOFs-based drug delivery has demonstrated an unparalleled advantage over traditional cancer therapies [14].

5. Nanoscale Metal-Organic Frameworks (NMOFs)

Scaling-down MOF materials (NMOFs) has resulted in the emergence of a fascinating new class of materials known as nanoscale MOFs. These materials possess the same wide range of architectures, compositions, and properties as bulk MOFs, plus the added benefit of nanomaterials. The morphological aspects of nanomaterials, such as shape, size, and surface characteristics, as well as their chemical structure, have a significant impact on their chemical properties, reactivity, energy qualities, and photocatalytic activities. When a substance gets closer to the nanoscale and has a higher percentage of atoms on its surface, its properties undergo a dramatic shift [1].

MOFs have the potential to serve as drug carrier nano vehicles owing to their capacity to modify the pore size and alter the framework's functional groups. While organic systems have the advantage of biocompatibility, NMOFs can be selected due to their porosity and crystalline characteristics, which allow for the regulated drug delivery [24].

NMOFs have been shown to be a promising drug carrier-class due to their high porosity, crystalline nature, potential for the future functionality, and particular structural information. However, research on MOF-based drug carriers with active tumor targeting activities has been limited up to this point. Over the past decade, NMOFs have garnered significant attention in the field of the particle-mediated drug delivery for the treatment of cancer. NMOF-based drug carriers have several apparent advantages over traditional drug-carrier materials, including a wide range of structures with definite crystal structure information, extremely high surface areas, large pore sizes for drug loading, and intrinsic biodegradability because of their relatively labile coordination bonds. Therefore, several MOFs have been downscaled to the nanoscale and their drug transport capabilities examined [26].

6. UiO-66 and drug delivery system

Lillerud et al. were the first to publish about Zr MOFs in 2008, demonstrating that the Zr-MOF structure can be constructed with longer linkers, and the temperatures required for decomposition are the same as for Zr-MOFs made with BDC linkers and UiO-66 as well as Zr-MOFs made with BPDC linkers and UiO-67 [27]. UiO-66 (UiO for the University of Oslo) $[Zr_6O_4(OH)_4(BDC)_6]$ was the first Zr(IV)-based MOF to be reported, consisting of $ZrCl_4$ and 1,4-benzene dicarboxylic acid (BDC), which has the low toxicity of Zr [22, 27]. The face-centered cubic configuration of the Zr-O clusters in UiO-66 results in a 1:2 ratio of octahedral (B11) and tetrahedral (B8) cages, making zirconium-based MOFs of UiO-66 highly stable and of great interest [28].

UiO-66 is the first MOF in the UiO family. It has a pristine surface area of 1200 m^2/g and a pore volume of 0.5 mL/g, with a 1,4-benzene dicarboxylate (BDC) linker. The octahedral and tetrahedral pores have diameters of 11 and 8 mm respectively, within 3- and 5-mm pore windows. In order to create an isoreticular series, various ligands were tested, with porosity increasing with ligand length until phenylene-bis-ethynylbenzoate linkers caused interpenetration, as shown in Figure 6 [9].

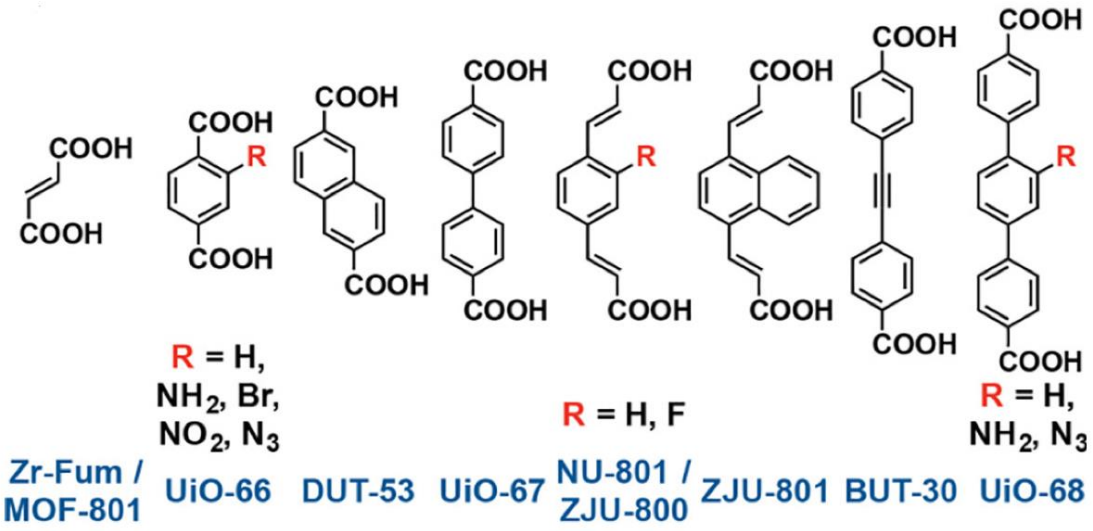

Figure 6. Dicarboxylate ligands used in UiO-66 topological MOFs with specific chemical structures [9].

The zirconium terephthalate MOF UiO-66 is composed of ~200 nm nanoparticles that have been covalently surface modified with PEG chains, loaded with cargo, and coated with functionalized modulators [6]. Due to its excellent thermal and physical properties, large surface area, and flexibility in synthesis and post-synthesis, various zirconium MOFs, including UiO-66, have garnered significant interest for their potential as drug delivery carriers [16]. Zirconium is also a low-toxicity metal, with an LD50 oral lethal dose of 4.1 $g.kg^{-1}$, making it a suitable drug carrier. The drug payload capacity and release in MOFs are influenced by various functional groups, with different MOFs with different functional groups exhibiting varying drug payloads. Altering the hydrogen bonding also affects different aspects of their interaction, resulting in different release rates [29].

7. Conclusion

This review paper focuses on the use of Metal-Organic Frameworks (MOFs) for different applications, particularly for drug delivery systems. The paper discusses the structures of MOFs and their typical applications, including molecular simulation approaches such as QM, MD, and MC, which are used to analyze the behavior of molecules or systems of molecules in the drug delivery research. The review also examines the technique of post-synthetic modification, which expands the capabilities of MOFs and is particularly useful in the context of controlling drug release. The paper acknowledges that MOFs face certain challenges in pharmaceutical applications, but research suggests that modifying the surface and implementing targeted carrier strategies can help overcome these issues.

In modern healthcare, MOFs and NMOFs have become increasingly important, particularly in the cancer treatment. Our review suggests that drug delivery systems have the potential to address several challenges associated with the cancer treatment, and amongst the available options, MOFs are attractive prospects due to their large surface area, sizable pore diameter, and favorable biocompatibility. However, utilizing MOFs for drug delivery may pose challenges, such as ensuring the quality control, managing toxicity, and ensuring compatibility with biological systems. Therefore, it is crucial to explore solutions to

overcome these hurdles, such as optimizing synthesis protocols and implementing rigorous quality control measures. Additionally, the review highlights the physical and chemical structure of UiO-66, which has significant potential as a candidate for drug delivery systems due to its exceptional thermal and physical characteristics, high surface area, and flexibility in synthesis and post-synthesis modifications.

References

[1] Al Sharabati, M.; Sabouni, R.; Husseini, G.A.," Biomedical Applications of Metal−Organic Frameworks for Disease Diagnosis and Drug Delivery: A Review", *Nanomaterials,* 12(277) (2022). https://doi.org/10.3390/nano12020277

[2] P. Tang, R. Wang, and Z. Chen, "In situ growth of Zr-based metal-organic framework UiO-66-NH_2 for open-tubular capillary electrochromatography", *Electrophoresis*, 39(20) (2018), 2619–2625. https://doi.org/10.1002/elps.201800057

[3] I. Abánades Lázaro *et al.*, "Surface-Functionalization of Zr-Fumarate MOF for Selective Cytotoxicity and Immune System Compatibility in Nanoscale Drug Delivery", *ACS Appl. Mater. Interfaces*, 10(37) (2018), 31146–31157. https://doi.org/10.1021/acsami.8b11652

[4] He, Liangcan et al., "Recent progress in nanoscale metal-organic frameworks for drug release and cancer therapy", *Nanomedicine (Lond)*, 14(10) (2019), 1343-1365. https://doi.org/10.2217/nnm-2018-0347

[5] Lu, Liangyu et al," Metal Organic Framework@Polysilsesequioxane Core/Shell-Structured Nanoplatform for Drug Delivery", *Pharmaceutics*, 12(98) (2020). https://doi.org/10.3390/pharmaceutics12020098

[6] El-Shafey, Aziza A M et al. , "Curcumin@metal organic frameworks nano-composite for treatment of chronic toxoplasmosis", *Materials Science Materials in Medicine, 31*(11) (2020), 90. https://doi.org/10.1007/s10856-020-06429-y

[7] Abánades Lázaro, I., Wells, C. J. R., & Forgan, R. S, "Multivariate Modulation of the Zr MOF UiO-66 for Defect-Controlled Combination Anticancer Drug Delivery", *Angewandte Chemie (International ed. in English)*, 59(13) (2020), 5211-5217. https://doi.org/10.1002/anie.201915848

[8] Abánades Lázaro, Isabel et al, "Selective Surface PEGylation of UiO-66 Nanoparticles for Enhanced Stability, Cell Uptake, and pH-Responsive Drug Delivery", *Chem*, 2(4) (2017), 561–578. https://doi.org/10.1016/j.chempr.2017.02.005

[9] Isabel Abánades Lázaro, Ross S. Forgan, "Application of zirconium MOFs in drug delivery and biomedicine", *Coordination Chemistry Reviews*, 380 (2019), 230–259. https://doi.org/10.1016/j.ccr.2018.09.009

[10] Gao, Yan et al., "Novel solid-phase extraction filter based on a zirconium meta-organic framework for determination of non-steroidal anti-inflammatory drugs residues", *Chromatogr. A*, 1652 (2021), 462349. https://doi.org/10.1016/j.chroma.2021.462349

[11] S. Yang et al., "A new post-synthetic polymerization strategy makes metal-organic frameworks more stable", *Chemical Science*, 10(17) (2019), 4542–4549. http://dx.doi.org/10.1039/C9SC00135B

[12] Ratna S. Katiyar, Prateek K. Jha, "Molecular simulations in drug delivery : Opportunities and challenges", *WIREs computational molecular science*, 8(4) (2018), 1–18. https://doi.org/10.1002/wcms.1358

[13] Zhao, Huai-Xin et al., "Theranostic metal-organic framework core-shell composites for magnetic resonance imaging and drug delivery", *Chemical science*, 7(8) (2016), 5294–5301. https://doi.org/10.1039/C6SC01359G

[14] Cai, Mengru et al., "Metal Organic Frameworks as Drug Targeting Delivery Vehicles in the Treatment of Cancer", *Pharmaceutics*, *12*(3) (2020), 232. https://doi.org/10.3390/pharmaceutics12030232.

[15] C. Orellana-Tavra et al., "Amorphous metal-organic frameworks for drug delivery," *Chemical Communicatons*, 51(73) (2015), 13878–13881. http://dx.doi.org/10.1039/C5CC05237H

[16] P. J. Jodłowski et al., "Cracking the Chloroquine Conundrum: The Application of Defective UiO-66 Metal-Organic Framework Materials to Prevent the Onset of Heart Defects: The Vivo and in Vitro", *ACS Applied Materials & Interfaces*, 13(1) (2021), 312–323. https://doi.org/10.1021/acsami.0c21508

[17] B. Yang, M. Shen, J. Liu, and F. Ren, "Post-Synthetic Modification Nanoscale Metal-Organic Frameworks for Targeted Drug Delivery in Cancer Cells", *Pharmaceutical research*, 34(11) (2017), 2440–2450. doi: 10.1007/s11095-017-2253-9

[18] A. Ray Chowdhuri, D. Bhattacharya, and S. K. Sahu, "Magnetic nanoscale metal organic frameworks for potential targeted anticancer drug delivery, imaging and as an MRI contrast agent", *Dalton Transactions*, 45(7) (2016), 2963–2973. https://doi.org/10.1039/C5DT03736K

[19] M. X. Wu et al., "Multifunctional Supramolecular Materials Constructed from Polypyrrole@UiO-66 Nanohybrids and Pillararene Nanovalves for Targeted Chemophotothermal Therapy", *ACS Applied Materials & Interfaces*, 10(40) (2018), 34655–34663. doi: 10.1021/acsami.8b13758.

[20] P. Abasian, S. Khalili, S. Ghanavati, and S. Rahebi, "Polymeric nanocarriers in targeted drug delivery systems : A review", *polymers advanced technologies*, 31(12) (2020), 2939-2954. https://doi.org/10.1002/pat.5031

[21] S. Rojas et al., "Toward Understanding Drug Incorporation and Delivery from Biocompatible Metal-Organic Frameworks in View of Cutaneous Administration", *ACS Omega*, 3(3) (2018), 2994–3003. https://doi.org/10.1021/acsomega.8b00185

[22] Orellana-Tavra, C., Mercado, S. A., & Fairen-Jimenez, D, "Endocytosis Mechanism of Nano Metal-Organic Frameworks for Drug Delivery", *Advanced healthcare materials*, *5*(17) (2016), 2261–2270. https://doi.org/10.1002/adhm.201600296

[23] sabel Abánades Lázaro et al.,

"Mechanistic investigation into the selective anticancer cytotoxicity and immune system nanoparticles", *ACS Applied Materials and Interfaces*, 10(6) (2018), 5255–5268. https://doi.org/10.1021/acsami.7b17756

[24] Filippousi, Maria et al., "Biocompatible Zr-based nanoscale MOFs coated with modified poly (ε-caprolactone) as anticancer drug carriers", *International Journal of Pharmaceutics, 509*(1-2) (2016), 208–218. https://doi.org/10.1016/j.ijpharm.2016.05.048

[25] Y. Liu et al., "ZrMOF nanoparticles as quenchers to conjugate DNA aptamers for target-induced bioimaging and photodynamic therapy", *Chemical Science*, 9(38) (2018), 7505–7509. https://doi.org/10.1039/C8SC02210K

[26] Hong Dong et al., "Folic Acid Functionalized Zirconium-Based Metal–Organic Frameworks as Drug Carriers for Active Tumor-Targeted Drug Delivery", *Chemistry -A Euopean Jornal*, 24(64) (2018), 17148–17154. https://doi.org/10.1002/chem.20180415

[27] Jasmina Hafizovic Cavka et al., "A New Zirconium Inorganic Building Brick Forming Metal Organic Frameworks with Exceptional Stability", *Journal of the American Chemical Society, 130*(42) (2008), 13850–13851. https://doi.org/10.1021/ja8057953

[28] X. Zhu et al., "Inherent anchorages in UiO-66 nanoparticles for efficient capture of alendronate and its mediated release", *Chemical Communications*, 50(63) (2014), 8779–8782. https://doi.org/10.1039/C4CC02570A

[29] Li, Zhen et al. "Functional groups influence and mechanism research of UiO-66-type metal-organic frameworks for ketoprofen delivery", *Colloids and surfaces. B, Biointerfaces*, 178 (2019), 1-7. https://doi.org/10.1016/j.colsurfb.2019.02.027