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Biomedical Applications of Nano-Metal-Organic Frameworks

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Abstract

Nanomaterials (NMs) possess extremely small dimensions, which significantly enhance their surface modification capabilities, surface-to-volume ratio, and a range of other unique physicochemical properties. Due to these characteristics, NMs are widely utilized across various research fields. In recent years, the biomedical applications of metal–organic frameworks (MOFs) have attracted considerable attention. MOFs are a class of porous materials composed of metal ions or clusters coordinated to organic ligands, forming hybrid crystalline structures. These materials offer tunable pore sizes, defined active sites, high surface area, and structural versatility, making them particularly suitable for biomedical applications. Based on pore size, MOFs can be categorized into microporous, mesoporous, and nanoporous types. Among their biomedical applications, MOFs are being extensively investigated for drug delivery, cancer treatment, tumor therapy, antiviral therapy, and bioimaging. This review provides an overview of the various types of MOFs employed in biomedical contexts, with a particular focus on their synergistic therapeutic strategies and corresponding efficacy. Finally, we address the current challenges and future prospects in advancing MOF-based systems for drug delivery and cancer therapy.

Keywords: Nanomaterial, Fabrication, Metal Organic Framework, Targeted Drug Delivery, Biomedical Applications.

Introduction

Certain materials exhibit unique properties due to their nanoscale dimensions, typically ranging between 10 and 100 manometers [1]. The intermediate size range, typically between 1 and 100 nanometers, defines the nanoscale, and materials with dimensions within this range are referred to as nanomaterials (NMs). In recent years, nanomaterials have garnered significant attention due to their versatile applications across various scientific and technological fields. Their distinctive features-including high surface area, biocompatibility, biodegradability, and large pore volume-make those particularly suitable for use in biomedical, environmental, and industrial applications [2]. Nanotechnology involves the design, fabrication, and application of functional materials, devices, and systems through the manipulation of nanomaterials. In recent years, it has emerged as a prominent field of study, attracting extensive interest from researchers worldwide. Nanotechnology has made a substantial impact across various industrial sectors by enabling the development of products that are more durable, safer, environmentally cleaner, and more intelligent-particularly in areas such as electronics and communication. Additionally, its applications extend to the medical field, agriculture, and numerous other industries, playing an increasingly vital role in everyday life [3]. Nanomaterial can used to made cosmetics, tyres, electronic and many everyday items [4]. Nanomaterials (NMs) can be classified using two primary approaches: the top-down and bottom-up methods [Fig. 1].

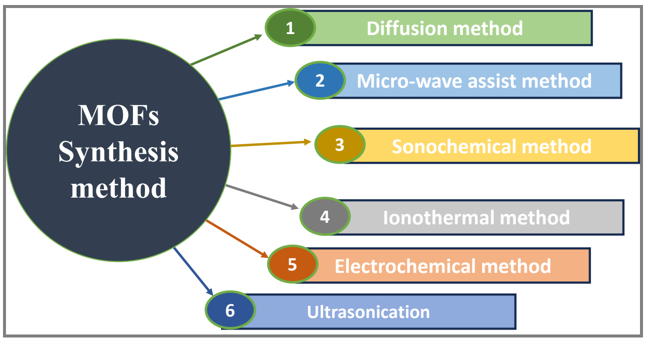

Fig 1: Various synthesis method of MOFs

In recent years, there has been growing interest in Metal-Organic Frameworks (MOFs) for biomedical applications, particularly in drug delivery. Nano-sized MOFs, with their unique properties, serve as efficient nanocarriers for the delivery of therapeutic agents, including those used in bioimaging, biosensing, chemotherapy, photothermal therapy, and antiviral treatments [5-7]. The properties of Nanoparticle-based Metal-Organic Frameworks (NMOFs), such as dendrimers and mesoporous silica nanoparticles, include high structural flexibility, tunable pore sizes, monodispersity or polydispersity, and the presence of open internal cavities [8-11]. Nanoparticle-based Metal-Organic Frameworks (NMOFs) are biodegradable and possess well-defined structures, which are advantageous for facilitating host-guest interactions. Due to these unique properties, MOFs have gained significant attention in biomedical therapies, including drug delivery and cancer treatment. This review focuses on the most recent advancements in the use of nano-Metal-Organic Frameworks (nMOFs) for drug delivery, diagnosis, sensing, and bioimaging in biomedical applications. We summarize the unique properties of NMOFs and their diverse applications in the medical field. Finally, the challenges and future prospects in this area are discussed, offering valuable insights for future researchers and engineers to explore the broader biomedical applications of MOFs.

Applications of Metal Organic Framework in Drug delivery

Hu *et al*. [12] developed a gold nanoparticle (AuNP)-embedded metal-organic framework for highly sensitive SERS detection. AuNPs were in situ grown and encapsulated within the MIL-101 matrix using a solution impregnation method. The resulting AuNPs/MIL-101 nanocomposites leveraged the localized surface plasmon resonance properties of gold nanoparticles and the high adsorption capacity of the MOF, enhancing SERS sensitivity by concentrating analytes near the electromagnetic fields of the SERS-active metal surface. The authors explored the fabrication, physical characterization, and SERS performance of these substrates by analyzing Raman signals from various model analytes. Busulfan, a commonly used alkylating agent in chemotherapy, is associated with severe side effects and poor stability in aqueous media. Traditional nanocarriers have shown low drug loading (≤5 wt%) and rapid release due to weak affinity and drug crystallization during formulation. To overcome these issues, Chalati *et al*. [13] employed iron(III) carboxylate-based nano-MOFs, achieving a significantly higher busulfan loading (up to 25 wt%). This improvement was attributed to the high porosity and amphiphilic internal microenvironment of the MOFs, which favorably interact with the amphiphilic nature of busulfan. Green tea catechins, known for their strong antioxidant and diverse biological activities, require stabilization to prevent degradation. Ke *et al*. [14] developed a nanosized edible γ-cyclodextrin-based metal-organic framework (CD-MOF) via a simple vapor diffusion method for the encapsulation of (-)-epigallocatechin gallate (EGCG). The resulting CD-MOF-EGCG complex significantly enhanced antioxidant activity in alkaline conditions compared to free EGCG. Baa *et al*. [34] highlighted that advance in synthetic methods, post-synthetic modification (PSM), and porosity control continue to drive MOF research. In biological applications, MOFs show strong potential in drug delivery, sensing, imaging, and as BioMOFs. Although not yet commercially available, promising results position MOFs as emerging tools in biomedical science. This review emphasizes recent developments in MOF synthesis, functionalization, and their applications in drug delivery, imaging, sensing, and BioMOFs. Zhang *et al*. [15] developed a biomimetic nanoreactor (TGZ@eM) for enhanced cancer starvation therapy by co-encapsulating glucose oxidase (GOx) and the prodrug tirapazamine (TPZ) within an erythrocyte membrane-coated MOF nanoparticle. This system improves GOx delivery, efficiently depletes glucose and activates TPZ under hypoxic and acidic conditions, enhancing therapeutic efficacy. The erythrocyte membrane coating enables immune evasion and prolonged circulation, resulting in improved tumor targeting and a synergistic cascade effect for effective colon cancer treatment. Tang *et al*. [16] used ZIF-8 nanoparticles as templates to form pH-responsive nanocapsules coated with iron(III)-catechol complexes derived from dopamine-modified alginate and Fe^{3+} ions. Doxorubicin (Dox) was loaded into ZIF-8 by coprecipitation and encapsulated within the nanocapsules after template removal. The pH-sensitive structure of the iron(III)-catechol complex enabled controlled drug release, and *in vitro* studies showed strong cytotoxicity of the Dox@nanocapsules against cancer cells. Al-Ansari *et al*. [17] investigated the cellular uptake of nano MIL-89 in pulmonary artery endothelial and smooth muscle cells using microscopy techniques, revealing its internalization, endosomal packaging, and inheritance during mitosis. Molecular and cellular assays demonstrated its anti-inflammatory activity with minimal cytotoxicity. These findings suggest that nanoMIL-89 holds potential as a therapeutic nanocarrier for cardiovascular diseases and other intractable conditions such as diabetes and cancer. Ding *et al*. [18] reviewed recent advancements in MOF-based nanozymes for combined cancer therapy, highlighting their potential for enhanced synergistic efficacy and reduced side effects. The review outlines representative MOF-based nanozymes and their catalytic mechanisms, construction strategies, and recent progress in dual or triple therapeutic combinations, with a focus on underlying synergistic interactions. It also discusses current challenges and future prospects for translating MOF-based nanozymes into personalized nanomedicine for effective cancer treatment. Kaur *et al*. [19] highlighted the inherent porosity of MOFs as a key feature enabling their application as drug carriers. The physicochemical properties of MOFs have been extensively explored in antibacterial research, where they function either as carriers for antimicrobial agents, exhibit intrinsic antibacterial activity, or form composites with other antimicrobial nanomaterials. This review emphasizes recent developments in MOFs and their composites for antibacterial drug delivery across various biological systems. Chen *et al*. [20] reviewed strategies for constructing porphyrin-based MOFs-such as porphyrin@MOFs, porphyrinic MOFs, and composite porphyrinic MOFs-by incorporating porphyrins as linkers or guest molecules to combine the advantages of both components and overcome the limitations of porphyrins. The review highlights recent advances in their biomedical applications, particularly in tumor therapy and biosensing. Khezri *et al*. [21] reviewed the development of synthetic nano-, micro-, and millimeter-scale machines capable of autonomous motion by harvesting environmental energy. Emphasizing the importance of high surface area for enhanced propellant or cargo loading, the study highlights the integration of porous, tunable metal–organic frameworks (MOFs) into self-propelled devices. This combination significantly advances the design and functionality of such machines, opening new avenues for applications across diverse fields. The review focuses on the unique properties of MOFs that make them ideal components for next-generation micro- and nanomachines. Özsoy *et al.* [22] developed a pH-sensitive ZIF-8-based nanocomposite incorporating bovine serum albumin (BSA) as a core and loaded with 5-sulfosalicylic acid and boswellic acids (BAs). The ZIF-8 shell enables stable drug encapsulation under physiological conditions and triggers release in acidic environments (pH 5.0) due to its pH-dependent stability. Among the tested formulations, 5-sulfosalicylic acid/BSA/BAs@ZIF-8 showed superior biocompatibility and enhanced anticancer efficacy against MCF-7 breast cancer cells with minimal toxicity, suggesting its potential as an effective nanocarrier for targeted cancer therapy. Mohammad *et al.* [23] reviewed the potential of nanoscale metal–organic frameworks (NMOFs) in cancer diagnosis and therapy, highlighting their favorable physicochemical properties for drug design, delivery, and storage. The study covers synthesis methods, applications in drug delivery, imaging, and diagnostics across various cancer types, while also addressing issues of stability and toxicity. Despite promising advancements, further investigation into the *in vivo* stability, clearance, toxicology, and pharmacokinetics of NMOFs is necessary to advance their clinical translation in cancer treatment. Lai *et al.* [24] developed a pH-sensitive nanocomposite by coating ZIF-8 with a hydrated dextran shell via coordination bonds, enhancing particle dispersity and reducing side effects from rapid disintegration. The system demonstrated high loading efficiency and controlled release of doxorubicin hydrochloride. Notably, the drug-loaded nanocomposite (DOX@ZIF-8/Dex) exhibited synergistic anticancer effects against multidrug-resistant human breast carcinoma cells by overcoming drug efflux and downregulating P-glycoprotein expression, highlighting its potential for clinical application in cancer therapy. Daunorubicin was successfully loaded into the MOFs via simple stirring, and an external magnetic field enhanced the anti-tumor activity of the drug-MOF formulation. The results demonstrated the biocompatibility of the MOFs, highlighting their potential for targeted drug delivery with improved therapeutic efficiency. Hatamie *et al.* [25] synthesized a graphene oxide/cobalt metal-organic framework (GO/Co-MOF) using a solvothermal method with cobalt salt and terephthalic acid, targeting biocidal activity against Gram-negative *Escherichia coli* and Gram-positive *Staphylococcus aureus*. Scanning electron microscopy revealed a cornflower-like structure, while transmission electron microscopy confirmed Co-MOF decoration on GO. Cytotoxicity tests using the MTT assay demonstrated biocompatibility with human fibroblast cells over 72 hours. The GO/Co-MOF showed over 99% bacterial growth inhibition at 100 µg/mL. The antibacterial activity was attributed to the synergistic effects of GO sheet edges and the release of toxic cobalt ions (Co^{2+}). Radical scavenging assays confirmed minimal toxicity to bacteria, highlighting GO/Co-MOF as a promising candidate for biological and pharmaceutical applications as a sustained bactericidal material. Cherkosob *et al.* [26] demonstrated the feasibility of targeted drug delivery to specific cancer cells *in vitro* using antibody-functionalized nano-metal-organic frameworks (nMOFs). They developed approximately 120 nm magnetic core/MOF shell nanoagents loaded with doxorubicin/daunorubicin and coupled with an antibody via a hydrophilic carbohydrate interface. The carboxymethyl-dextran coating enabled efficient drug loading (up to 15.7 mg/g), sustained drug release in physiological media, and maintained antibody specificity. The agents successfully targeted and killed HER2/neu-positive breast cancer cells *in vitro* using trastuzumab, showcasing the potential of nMOFs as a platform for theragnostic nanoagent development. Nanotechnology enables the development of delivery vehicles capable of overcoming physiological barriers, enhancing targeting efficiency, and reducing systemic drug delivery side effects, thereby improving therapeutic efficacy. The nanoscale size of metal-organic frameworks (MOFs) is crucial for the advancement of drug delivery systems. Wuttke *et al.* [27] discuss the advantages of MOF nanoparticles over dendrimers and mesoporous silica nanoparticles, while also addressing the challenges that remain in optimizing MOFs for drug delivery applications. Bhardwaj *et al.* [28] investigated the antibacterial efficacy of three Zn-based nano metal-organic frameworks (nMOFs)-IRMOF-3, MOF-5, and ZnBTC-both alone and in combination with ampicillin and kanamycin. When tested against Escherichia coli, Staphylococcus aureus, Staphylococcus lentus, and Listeria monocytogenes, the nMOF/drug mixtures exhibited synergistic effects (IRMOF-3/kanamycin) or additive effects (other nMOF/drug combinations) compared to the individual nMOFs or antibiotics. The study suggests that Zn-based nMOFs could enhance the potency of existing antibiotics, potentially reducing the need for the discovery of new antimicrobial agents. Zhao *et al.* [29] developed a magnetic nanomaterial, Fe-MIL-88B-NH, for encapsulating methylene blue (MB), a tau aggregation inhibitor, and used it as a magnetic resonance contrast agent. To enhance targeting of hyperphosphorylated tau, the targeting reagent Defluorinated MK6240 (DMK6240) was conjugated to the Fe-MIL-88B-NH_2 surface via 1,4,7-triazacyclononane-1,4,7-triacetic acid (NOTA). This resulted in the formation of a drug delivery system, Fe-MIL-88B-NH_2-NOTA-DMK6240/MB, which demonstrated excellent magnetic resonance imaging capability and alleviated Alzheimer's disease symptoms *in vitro* and *in vivo* by inhibiting tau aggregation and preventing neuronal death. El-Bindary *et al.* [30] explored the use of zeolitic imidazolate framework-8 (ZIF-8) as a novel carrier for the anticancer drug doxorubicin (DOX). ZIF-8 nanoparticles effectively encapsulated DOX, preventing premature release before reaching the target site. The DOX@ZIF-8 system was characterized using Fourier transform infrared spectroscopy, scanning electron microscopy, N_2 sorption isotherms, and X-ray diffraction. The drug release rate was faster at pH 5 than at pH 7.4. The system's impact on the viability of human breast and liver cancer cell lines was evaluated, and its antibacterial activity was tested against pathogenic bacteria using the agar well diffusion method. Docking studies predicted the binding interactions of DOX with the breast cancer receptor 3hb5-oxidoreductase and liver cancer 2h80-lipid binding protein. Pandey *et al.* [31] discussed the development of MOFs with stimuli-responsive drug release properties for externally guided cancer therapy. In addition to cellular and subcellular targeting platforms, MOFs have been explored for bioimaging and biosensing applications. Various MOF and nMOF-based biosensing platforms have been proposed for the detection of cancer-related biomolecules, aiding in early diagnosis. MOF-based bioimaging probes have been utilized in multiple diagnostic platforms. The review provides recent advancements in these areas, along with considerations of MOF toxicity for human use, offering a comprehensive overview of MOF-based nanoplatforms for cancer theragnostic. Ali *et al.* [32] reviewed the design and fabrication of MOFs, highlighting their applications in bacterial theranostics and addressing safety considerations.

They identified key challenges and opportunities for advancing research at the interface of nanozymes and MOFs. The authors anticipate that MOF-based nanozymes, with their unique physicochemical and enzyme-mimicking properties, will attract significant interest in both fundamental research and biomedical applications. Rasheed *et al.* [33] summarized recent advancements in MOF-based materials, including pristine MOFs, MOF derivatives, and composites, for electrocatalysis, photocatalysis, and biocatalysis. They first examined the electrocatalytic behavior of various MOFs for oxidation and reduction reactions. The second section focused on the photocatalytic performance of MOFs in light-driven reactions, such as contaminant degradation, CO2 reduction, and water splitting. The biomedical applications of MOF-based materials, including drug delivery, sensing, antibacterial agents, and biomimetic systems, were also discussed. The review concluded with challenges and future prospects for MOFs in catalytic applications. Zhou *et al.* [34] reviewed the recent advancements in nanoscaled MOFs and their composites, focusing on their synthesis, properties, and biomedical applications in biosensing, molecular imaging, and cancer therapy. The review highlights developments over the past three years and discusses the challenges and future opportunities in this field, including processing techniques, optimizing composite properties, and potential clinical applications. Lu *et al.* [35] reviewed the recent advancements in NMOF designs for biomedical applications, emphasizing their role in drug delivery and imaging. The review covers four drug loading strategies for therapeutic applications, followed by NMOF designs for imaging and biosensing. The article concludes by addressing the fundamental challenges faced by NMOF-based agents in these fields. Wen *et al.* [36] reviewed the recent progress of NMOFs in biomedicine, focusing on their classification, synthesis, and drug loading strategies, as well as stimulus-responsive drug release mechanisms. The review also highlights smart NMOF-based platforms for anticancer and antibacterial treatments and discusses the challenges and potential of biomimetic NMOFs. Giménez-Marqués *et al.* [37] reviewed the preparation of nanostructured MOFs and their biomedical applications. The review highlights various synthetic methods and shaping and surface engineering techniques necessary for their use in biomedicine. The miniaturization of MOFs and nMOFs is emphasized for its impact on administration routes, *in vivo* fate, toxicity, and activity. Falahati *et al.* [38] explored the development and applications of nano-/micro-motors based on metal–organic frameworks with nanozyme activity (MOF-NZs) in biomedicine. The study focuses on their catalytic properties and role in cancer treatment, emphasizing the importance of biocompatibility for medical use. The article discusses methods to reduce the toxicity of MOF-NZ nano-/micro-motors, highlighting the benefits and challenges of the required propellants. Liu *et al.* [39] highlited the use of nanoscale MOF particles as drug carriers, bioimaging agents, and therapeutic agents, highlighting their exceptional physicochemical properties. The article covers MOFs as nanocarriers for drug delivery, therapeutic MOF agents, and surface bioengineering techniques to enhance biostability, biocompatibility, and targeted delivery. It concludes with a discussion on the challenges and future prospects of MOF research in biomedical applications. Yang *et al.* [40] explored the preparation and recent advances in nano-MOFs as drug carriers, therapeutic materials, and functionalized materials for drug delivery and tumor therapy. The article emphasizes the use of single/multiple stimulus-responsive drug release for targeted therapy and discusses the hybridization of nano-MOFs with other materials to form composites. Challenges and future prospects are also addressed, providing valuable insights for the design and application of nano-MOFs in biomedical fields. Yalamandala *et al.* [41] summarize the use of various stimuli-responsive MOFs, including MIL, ZIFs, UiO, and others, for tumor suppression. These MOFs enable dual on-demand delivery of therapeutic cargos and energy, which can reduce side effects and support precision medicine. Catalytic therapy, induced by the Fenton reaction utilizing high levels of H2O2 in cancer cells, may also trigger immune responses. The review discusses challenges for clinical translation, such as overcoming tumor heterogeneity and addressing interactions with the immune system. Chedid *et. al*. [42] focused on presenting the recent work achieved in COFs and MOFs for biomedical applications, and to examine some challenges and future directions which the field may take. The paper herein surveys their synthesis, and their use as Drug Delivery Systems (DDS), in non-drug delivery therapeutics and for biosensing and diagnostics. Zhang *et al.* [43] review the recent advancements in nMOFs for biomedical applications, including drug delivery, bioimaging, biosensing, and biocatalysis. They categorize surface modification methods into four types: covalent, coordinative, noncovalent post-synthetic modifications, and modifications to the external surface. The review also addresses the challenges and future perspectives of nMOFs in these fields. Cai *et al.* [44] summarize recent advancements in nanoscale metal–organic frameworks (NMOFs), focusing on synthesis strategies and their applications in drug delivery, molecular imaging, and theranostics. The article also discusses future challenges and opportunities for developing clinically translatable NMOFs in nanomedicine. Simon-Yarza *et al.* [45] provide an overview of preclinical studies evaluating the biomedical applications of MOFs, focusing on *in vivo* pharmacological and toxicity assessments. The article discusses current surface engineering approaches to understand the *in vivo* behavior of nano-MOFs and offers future research directions for their use in drug delivery and biomedical applications. Luo *et al.* [46] discuss the advantages of MOF nanoparticles in biomedicine, comparing their properties to other nanoparticles. The review begins with an overview of MOF biomaterial scaffolds, followed by a detailed analysis of stimuli-responsive mechanisms, categorized into intrinsic (pH, redox) and extrinsic (temperature, light, magnetic field) types. The combination of photothermal and radiation therapies is also addressed. Finally, the article highlights clinical applications, challenges, and future perspectives of MOFs in biomedical systems and bioimaging.

Challenges and Future Perspectives

In this review, we have explored the emerging role of nano-metal-organic frameworks (n-MOFs) and their diverse biomedical applications, including bioimaging, biosensing, drug delivery, biocatalysis, and cancer therapy, among others. The unique characteristics of n-MOFs, such as their well-defined pore sizes and high surface area, make them highly effective in these fields. Firstly, the synthesis of n-MOFs should prioritize the use of non-toxic or low-toxicity raw materials to ensure safety for biomedical applications. Secondly, the selection of suitable n-MOFs depends on their stability, degradability, and their ability to maintain a prolonged circulation half-life in the bloodstream, which is crucial for effective *in vivo* performance. Thirdly, biocompatibility and toxicological considerations play an essential role in evaluating the potential of n-MOFs for medical use, ensuring they do not induce adverse effects upon administration. Moreover, n-MOFs offer distinct advantages as nanocarriers for drug delivery due to their high surface area, tunable porosity, and ability to be functionalized with therapeutic agents. For example, HKUST-1, a nanosized MOF, has demonstrated significant potential as a drug delivery system for cancer treatment, providing a promising approach for targeted and efficient therapeutic interventions. These features make n-MOFs highly valuable in advancing precision medicine and improving therapeutic outcomes.

Conclusion

In summary, this review introduces the development of nano-metal-organic frameworks (n-MOFs) for a wide range of biomedical applications, including drug delivery, biomedical imaging, biosensing, cancer therapy, and tumor treatment. N-MOFs offer distinct advantages due to their unique properties, such as high surface area, tunable pore size, and versatile physical and chemical characteristics. We discuss how n-MOFs interact effectively with body cells, enabling targeted delivery and therapeutic effects. For example, Busulfan is used in chemotherapy, MIL-53 serves as a drug carrier for DOX delivery, and ZIF-8 nanoparticles act as an anticancer agent. As a result, n-MOFs are playing an increasingly important role in the biomedical industry, driving advancements in various therapeutic applications.

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