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METAL–ORGANIC FRAMEWORKS IN BIOMEDICAL APPLICATIONS: ADVANCES IN IMAGING, THERAPY, AND DRUG DELIVERY

Biplab Biswas
Assistant Professor
Department of Chemistry
Hooghly Mohsin College, Chinsurah 712101, India

Abstract: Porous materials are becoming essential building blocks in many various technologies because of their enormous surface areas, functional diversity, and adjustable architectures. Metal–organic frameworks (MOFs), which are crystalline materials composed of metal ions and organic linkers, stand out among them because of their hybrid structure, which combines the advantages of both organic and inorganic porous materials. Due to their adjustable pore diameters, surface functionalizability, biocompatibility, and biodegradability, MOFs have a lot of potential for use in biomedical applications. Theranostics, drug delivery, and diagnostics have all benefited from recent developments in nanoscale MOFs (nMOFs). Recent developments in MOF-based platforms for radiation, photodynamic treatment (PDT), positron emission tomography (PET), magnetic resonance imaging (MRI), computed tomography (CT), and targeted drug delivery are highlighted in this study. Their ability to enhance contrast, their structural flexibility, and their potential for site-specific and regulated therapeutic release are all highlighted. Despite the promise, there are still issues with toxicity, reproducibility, and clinical translation. However, the journey of MOFs from bench to bedside is being accelerated by ongoing developments in synthesis techniques and surface functionalization, underscoring their potential as next-generation multifunctional agents in precision medicine.

Keywords **-** Metal–Organic Frameworks, Biomedical Imaging, Drug Delivery Systems, Theranostics.

1. Introduction

Porous materials have been playing important roles in diverse applications like selective catalysis, gas storage and separation of gases by adsorption based on size and shape, the storage and controlled release of drugs, and serve as templates for producing low-dimensional materials [1–6]. Porous materials are typically classified as either inorganic or organic. Activated carbon is the most often used porous material among the organic alternatives. These materials are usually produced by a process known as pyrolysis from carbon-rich sources. Despite their lack of distinct structures, they display impressive properties like enormous surface areas and improved adsorption efficiencies. Despite inherent disorder, porous carbon materials are used extensively in processes such as solvent extraction and recovery, water purification, and gas separation and storage [7].

Inorganic porous frameworks, such as zeolites, have highly organized structures. Their synthesis usually involves using inorganic or organic templates that interact strongly with the framework during formation. Removing these templates can sometimes cause the structure to collapse. Element-wise, inorganic frameworks generally have limited diversity, predominantly involving Al, Si, and chalcogens. Despite these constraints, inorganic frameworks are effective in separation and catalytic applications [3].

The development and thorough study of metal–organic frameworks (MOFs), which make up porous hybrid materials intended to integrate the useful characteristics of both organic and inorganic porous materials, have received a lot of attention in the last few decades. These materials are made up of coordinated metal ions or ion clusters functioning as nodes and organic ligands acting as struts. It is easy to create MOFs with a variety of properties by adjusting the enormous number of potential pairings between metal nodes and organic ligands.

The properties of the MOFs are significantly affected by their rigid /flexible skeletons, tunable surface affinities, and pore sizes, which range from micropores to mesopores or macropores [8-12]. Applications of MOF heavily depend on the particle morphology, size distribution, and chemical characteristics. Numerous fields, including catalysis, gas adsorption/separation/storage, nonlinear optics, sensing and detection, and biomedical applications, have used MOF-based systems because of their notable physicochemical characteristics, which include easy synthesis and functionalization, variable structures, high surface areas and loading capacities, and good biocompatibility and biodegradability. MOFs, which were first studied for gas storage and separation, have garnered a lot of attention from the biomedical community due to their large surface area, adjustable pore size, and ability to incorporate different functional groups for particular uses. While surface modification enables targeted drug delivery and controlled release,

their intrinsic porosity permits loading of medicines, imaging agents, and other physiologically active molecules to high levels [13].

Drug delivery, combination therapy, and diagnostics are all included in the biomedical use of MOFs. MOFs with high atomic number or paramagnetic metal cores, such as bismuth (Bi), iron (Fe), hafnium (Hf), or gadolinium (Gd), serve as imaging probes and offer contrast for CT and MRI studies [14]. Similarly, MOFs that have been loaded with radionuclides are used as PET scanning tracers. Due to their structural versatility and ability to hold reactive metal centers, MOFs may also be utilized as carriers for photosensitizers in PDT or radiosensitizers in radiotherapy [15]. To further advance MOFs toward clinical application, their pharmacokinetic tunability and biodegradability play important role [13]. In general, medicines used for therapeutic purposes have common drawbacks such as severe side effects, quick clearance from the body, and low bioavailability. Because of their tiny size, high surface area, enhanced drug loading, better pharmacokinetics, and biocompatibility, nanoparticle-based systems offer promising options to solve these issues [16, 17]. Additionally, nanoparticles offer a long-term, non-invasive platform for bioimaging and diagnostic applications [18]. The great sensitivity of nanoparticles and their small size allows them to be used as contrast agents. Additionally, for bioimaging applications, nanoparticles can be integrated with appropriate functional agents or coupled with a targeted ligand [19]. This has led to the development of a variety of nanoparticle forms, including dendrimers, liposomes, magnetic nanoparticles, polymeric nanoparticles, and polymeric micelles. Every nanomaterial exhibits benefits and drawbacks in relation to stability, toxicity, drug loading capacity, and other characteristics [20]. In this context, the intriguing class of crystalline porous materials known as nanoscale metal-organic frameworks (nMOFs) are promising alternative in a wide range of applications [21-23], including gas storage, catalysis, magnetism, sensing, separation, and so forth [24-26]. Their high porosity, high surface area, large pore size, versatility for post-synthetic modifications, biodegradability, and biocompatibility are the reasons for their vast applications. Their biological uses, such as drug delivery and bioimaging, have recently attracted more attention [27]. In biomedical applications, nMOFs have the ability to integrate biomolecules during synthesis or trap them in their cavities [28]. nMOFs can be employed as carriers to target specific body regions and provide controlled release of the drugs due to their vast surface area, high porosity, and tunable properties [21,22]. nMOF development has recently demonstrated efficacy in cancer-targeted therapy [29]. These days, MOFs' inner and outer surfaces have been functionalized to create reliable systems for applications in diagnostics and therapy [30]. Additionally, nMOFs have been the focus of a lot of study in imaging applications [31]; for instance, MOFs could be employed in optical imaging and magnetic resonance imaging (MR) by integrating luminescence-based materials and paramagnetic metal ions, respectively [32]. The nMOFs with improved cellular uptake, biodistribution, and biological compatibility fall under the category of "theranostics" due to their multifunctional character, which includes simultaneous imaging, therapy, and real-time monitoring [14,33]. Key challenges remain, including long-term toxicity, synthesis reproducibility, and regulatory hurdles. Nonetheless, MOFs are gradually moving from the laboratory settings to clinical use thanks to developments in synthesis techniques, biocompatibility, and translational research [34]. In this article, we go over current advancements in MOF-based platforms for various biomedical applications, including drug delivery, radiotherapy, MRI, CT, PET, PDT, and clinical studies.

2. MOFs in Magnetic Resonance Imaging (MRI)

MRI is a powerful non-invasive diagnostic technique that emits no ionizing radiation and has a high spatial resolution. MOFs containing paramagnetic metal ions, such as Gd^{3+} and Fe^{3+}, function as contrast agents as they enhance proton relaxation. For instance, Gd-based MOFs with chelating organic ligands exhibit high longitudinal relaxivity, often outperforming conventional Gd-chelates due to higher Gd payloads and accessibility of coordinated water molecules [2].

MOFs that contain iron, including MIL-88 and MIL-100(Fe), have been studied for their ability to enhance contrast between relaxation times. These substances are both biocompatible and highly biodegradable. Surface functionalization, such as PEGylation, improves circulation time and reduces immunogenicity [15].

3. MOFs in Computed Tomography (CT)

Materials with high-Z elements effectively attenuate X-rays, improving CT imaging. For CT imaging, MOFs based on Hf and Bi are very helpful. High biostability and strong attenuation coefficients are offered by the Hf-MOF-808 and Bi-UiO-66 structures. MOFs can also function as radiosensitizers for synergistic radiation therapy [13,34].

4. MOFs in Positron Emission Tomography (PET)

Radiolabeled Biomaterials with isotopes like ^{64}Cu or ^{89}Zr are required for PET imaging. To bind these isotopes stably, MOFs can be designed with chelators like DOTA (2,2′,2″,2‴-(1,4,7,10-Tetraazacyclododecane-1,4,7,10-tetrayl)tetraacetic acid) or NOTA (1,4,7-Triazacyclononane-1,4,7-triacetic acid). For example, ^{64}Cu-labeled Zr-MOFs have demonstrated tumor-specific uptake and stable radiochemical properties. Drug distribution monitoring and quantitative imaging are made possible by these characteristics [33].

5. MOFs in Photodynamic Therapy (PDT)

Light-activated photosensitizers that generate cytotoxic reactive oxygen species (ROS) are used in photodynamic therapy to kill cancer cells. MOFs incorporating porphyrin or chlorin-based ligands (e.g., PCN-224) act as efficient photosensitizers. Their porosity enables drug encapsulation and oxygen diffusion, both of which enhance PDT's

effectiveness. For synergistic chemo-photodynamic therapy, several MOFs have been co-loaded with chemotherapeutics [14,33].

6. MOFs in Radiotherapy

MOFs can act as radiosensitizers by intensifying radiation-induced damage through high-Z metal centers and oxygen-carrying capacity. By increasing DNA damage in tumor cells, Hf-based MOFs, such as Hf-DBA, have been shown to dramatically increase radiotherapeutic efficacy. These substances are investigated for image-guided and fractionated radiation [34].

7. MOFs for Drug Delivery

MOFs are attractive drug delivery systems because of their ability to encapsulate, adsorb, and release therapeutics upon biological stimulation. In acidic tumor microenvironments, pH-sensitive MOFs like ZIF-8 dissolve, enabling site-specific drug release. MIL-100(Fe), UiO-66, and other materials have been used to transport pharmaceutical compounds such doxorubicin, cisplatin, and paclitaxel efficiently [35]. Additionally, MOFs permit surface functionalization for targeted delivery through the use of ligands like folic acid or antibodies [15].

8. Clinical Trials and Translational Progress

Some MOF-based biomedicinal research is progressing towards clinical translation, although the majority is still in preclinical stages. The safety evaluations of MIL-100(Fe) and UiO-66 derivatives have been performed in large animals. Active efforts are being made to overcome clinical barriers such as scale-up synthesis, standardization, and regulatory approval. To get these materials into human trials, pharmacokinetic, immunogenicity, and excretion profile studies are essential [13,35].

9. Conclusion

MOFs offer unprecedented versatility in biomedical applications due to their tunable structures and multifunctional properties. Their potential as next-generation theranostic agents is only partially realized by their use in drug delivery, therapy (PDT, radiation), and imaging (MRI, CT, PET). MOFs are rapidly approaching useful healthcare applications thanks to ongoing research in synthesis, biocompatibility, and regulatory science, even though there is still much work to be done to get these materials to the clinic.

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