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Synthesis and Application of Metal-Organic Frameworks (MOFs) in Biosensing and Drug Delivery

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ABSTRACT

Metal-organic frameworks (MOFs) have emerged as versatile materials with promising applications in various fields owing to their tunable structures, high surface areas, and diverse functionalities. In this review, we delve into the synthesis methodologies and recent advancements in the application of MOFs in biosensing and drug delivery. The synthesis of MOFs involves the coordination of metal ions or clusters with organic ligands, leading to a wide range of structures with tailored properties. Various synthesis approaches including solvothermal, hydrothermal, microwave-assisted, and mechanochemical methods have been developed to control the size, shape, and pore characteristics of MOFs, thus enabling fine-tuning of their properties for specific applications. In biosensing, MOFs exhibit exceptional performance due to their large surface areas, high porosity, and ability to incorporate functional groups for selective analyte recognition. By immobilizing biomolecules or nanomaterials within MOF matrices, biosensors with enhanced sensitivity, selectivity, and stability have been developed for the detection of biomolecules, pathogens, and environmental pollutants. Moreover, MOFs have shown great potential in drug delivery systems owing to their ability to encapsulate and protect drug molecules, control release kinetics, and target specific sites. The tunable pore sizes and surface chemistries of MOFs enable efficient loading and delivery of various therapeutic agents, including small molecules, proteins, nucleic acids, and imaging agents. Additionally, the biocompatibility and degradability of certain MOFs make them attractive candidates for in vivo applications. This review provides insights into the recent progress, challenges, and future perspectives in utilizing MOFs for biosensing and drug delivery applications. With continued advancements in synthesis techniques and a deeper understanding of MOF properties, the integration of MOFs into biomedical technologies holds great promise for addressing critical healthcare challenges and advancing personalized medicine.

1. INTRODUCTION

The journey of metal-organic frameworks (MOFs) began with the pioneering work by Yaghi and colleagues in the late 1990s, who demonstrated the concept of utilizing metal ions or clusters as nodes interconnected by organic linkers to create porous crystalline materials [1,2]. Since then, the landscape of MOF research has rapidly evolved as a vibrant research field at the intersection of chemistry, materials science, and biomedical engineering; offering unparalleled opportunities for diverse applications, including catalysis, adsorption, gas storage, energy and fuel storage, and sensing [3-5]. Compared with other high-class materials such as carbon nanotubes (CNTs), graphene, graphene oxides (GO), magnetic nanoparticles, and gold nanoparticles, MOFs have displayed more attractive properties (See Fig. 1). With the precisely tailored structures, high surface areas, and versatile functionalities, MOFs have caught the attention of many researchers worldwide [6-9].

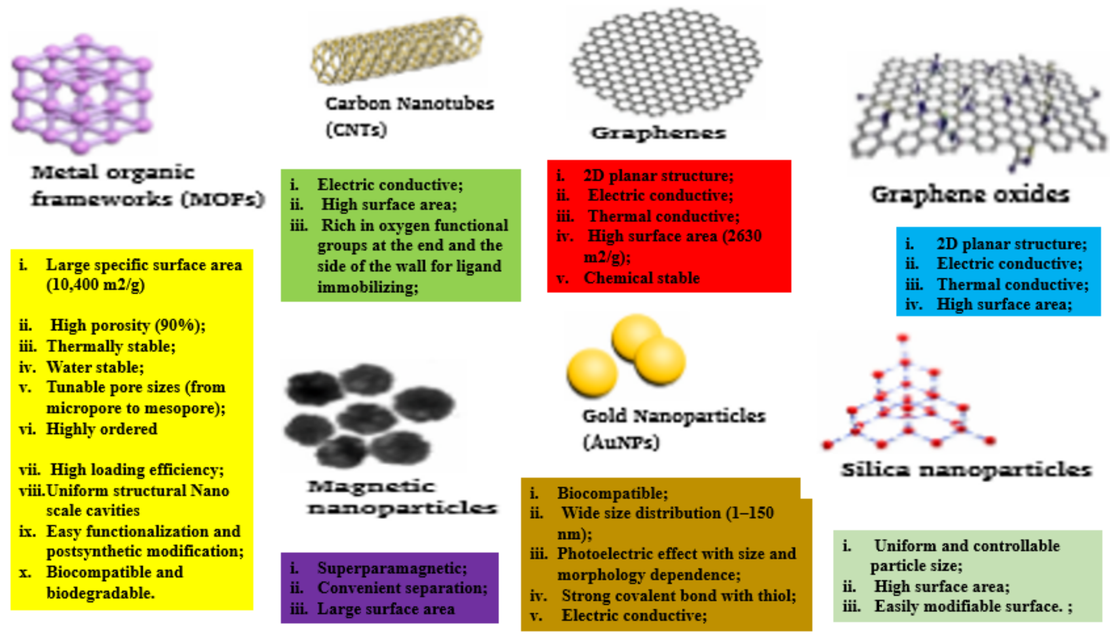

Figure 1 Stunning Properties of MOF Compared to other high-class materials

MOFs have undergone various synthesis techniques, ranging from traditional solvothermal and hydrothermal methods to innovative approaches such as microwave-assisted and mechanochemical synthesis [10,11]. The choice of the right synthesis method is an essential first step to obtaining the MOF that suits the desired application.

In recent years, the application of MOFs in biosensing and drug delivery has garnered significant interest due to their unique characteristics. In biosensing, MOFs offer an ideal platform for the development of sensitive and selective sensors [12,13]. Their large surface areas provide ample sites for biomolecule immobilization, while their tunable porosities and functional groups facilitate the recognition of target analytes [12,13]. By integrating MOFs with biological molecules or nanomaterials, biosensors with enhanced performance characteristics have been realized, enabling the detection of biomolecules, pathogens, and environmental pollutants with high sensitivity and specificity [14]. Moreover, MOFs exhibit great potential in drug delivery applications, offering opportunities for controlled release and targeted delivery of therapeutics [15,16]. The ability to encapsulate drug molecules within their porous structures, along with the capability to modulate release kinetics, enables precise control over drug delivery profiles. Additionally, the biocompatibility and degradability of certain MOFs make them promising candidates for in vivo applications, opening avenues for the development of next-generation drug delivery systems with improved efficacy and reduced side effects [17,18].

This study seeks to examine the synthesis methodologies and recent advancements in the application of MOFs in biosensing and drug delivery. It elucidates the underlying principles and challenges associated with harnessing the potential of MOFs in biomedicine. By highlighting the current state-of-the-art and future directions in this rapidly evolving field, we aim to inspire further research efforts aimed at exploiting the unique properties of MOFs for addressing critical healthcare challenges and advancing personalized medicine.

2. CHEMICAL COMPOSITION OF MOFs

Metal-organic frameworks (MOFs) are crystalline materials composed of metal ions or clusters coordinated with organic ligands, forming extended porous networks. The chemical composition of MOFs comprises metal nodes, organic linkers, guest molecules, defects, and functional groups, (Fig. 2) which play a pivotal role in determining their structural diversity, properties, and functionalities [19-21].

2.1 Metal Nodes

The metal nodes in MOFs serve as the central building blocks, providing structural integrity and imparting specific properties to the framework. These metal nodes typically consist of transition metal ions such as zinc (Zn), copper (Cu), nickel (Ni), chromium (Cr), and cobalt (Co), among others. The choice of metal ion governs key characteristics of the MOF, including its stability, catalytic activity, and magnetic properties. Moreover, the coordination geometry and oxidation state of the metal ion influence the structural diversity and porosity of the resulting MOF framework [19,20].

2.2 Organic Linkers

Organic linkers, also known as ligands, play a pivotal role in connecting the metal nodes to form the three-dimensional structure of MOFs. These organic ligands are typically aromatic or polydentate molecules containing carboxylate, imidazolate, pyrazolate, or other functional groups capable of coordinating with metal ions. The chemical nature and geometry of the organic linker dictate the topology and pore characteristics of the MOF framework. Furthermore, the functional groups present in the organic ligands can be tailored to introduce specific functionalities such as hydrophobicity, hydrophilicity, or chemical reactivity, thereby expanding the applicability of MOFs in various domains [19, 20].

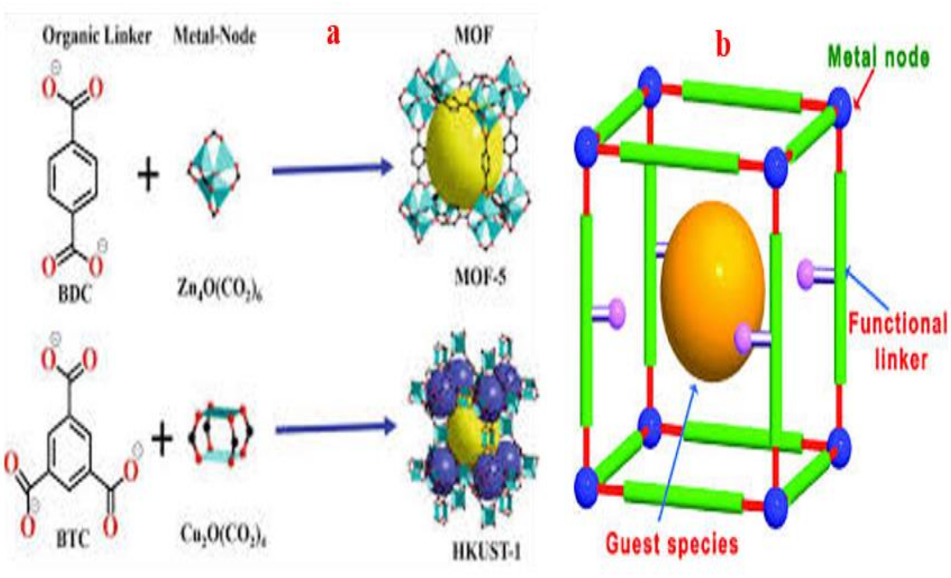

Figure 2: MOF Composition (a) Linkers reacting with metal nodes to give MOFs (b) MOF structure

showing guest species, functional linker, and Metal nodes

2.3 Guest Molecules

In addition to the metal nodes and organic linkers, MOFs can incorporate guest molecules within their porous structures. These guest molecules can be small molecules, solvents, gases, or even biomolecules, depending on the pore size and properties of the MOF framework. The encapsulation of guest molecules within MOFs enables applications such as gas storage, separation, catalysis, and drug delivery. Moreover, the interactions between the guest molecules and the MOF framework can influence the stability, reactivity, and performance of MOFs in different environments [22].

2.4 Defects and Functionalization

Furthermore, MOFs may exhibit defects or vacancies in their structures, which can arise during synthesis or post-synthetic modifications. These defects can significantly impact the properties and functionalities of MOFs, affecting their stability, porosity, and catalytic activity. Additionally, MOFs can be functionalized through post-synthetic modifications to introduce specific functionalities or enhance their performance for targeted applications. Functionalization strategies include surface modification, incorporation of guest molecules, and covalent attachment of functional groups, offering tailored solutions for diverse applications [24].

3.SYNTHESIS OF MOFs FOR BIOSENSING AND DRUG DELIVERY PURPOSES

The synthesis of MOFs involves the coordination of metal ions or clusters with organic ligands, resulting in crystalline frameworks with well-defined structures. Various synthetic routes, such as solvothermal, hydrothermal, microwave-assisted, and mechanochemical methods, offer precise control over MOF morphology, pore size, and surface chemistry. These synthetic strategies have enabled the design and fabrication of MOFs tailored to specific applications, including biosensing and drug delivery. The various methods of MOF synthesis are presented in Fig.3. Several reviews have already been presented on the different methods of MOF synthesis [10,11].

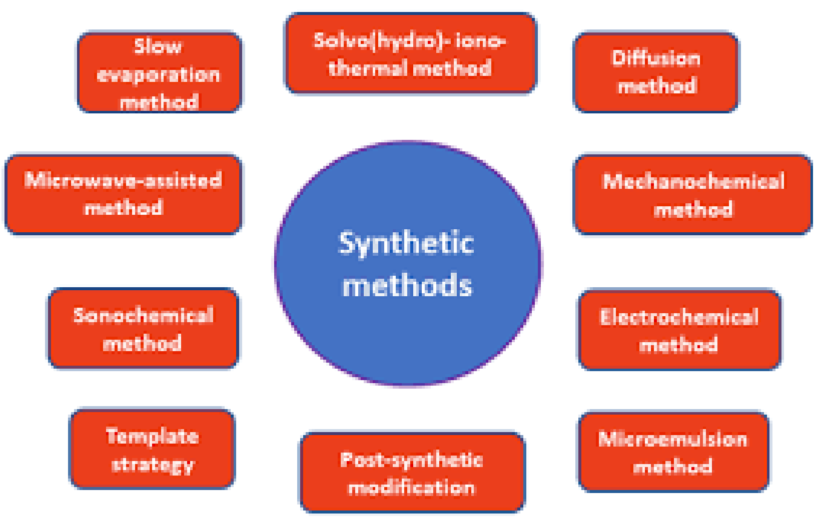

Figure 3: Various Methods of MOF Synthesis

MOF synthesis for biosensing and drug delivery purposes involves careful consideration of various parameters to tailor the properties of MOFs toward the desired use. Key strategies and considerations for designing MOFs optimized for biosensing and drug delivery applications are highlighted below:

3.1 Choice of Metal Nodes and Organic Linkers

Selecting appropriate metal nodes and organic linkers is crucial for controlling the structure, porosity, and functionality of MOFs. The choice of metal ions determines the coordination geometry and properties of MOFs, while the selection of organic ligands influences the pore size, surface chemistry, and stability. For biosensing applications, functionalized organic ligands capable of selectively recognizing target analytes or biomolecules are often preferred. These ligands can be tailored with specific functional groups for enhanced sensitivity and selectivity. In drug delivery applications, biocompatible metal nodes and degradable organic linkers are desirable to ensure compatibility with biological systems and facilitate controlled drug release [24,25].

3.2 *Synthetic Methods*

Various synthetic methods, including solvothermal, hydrothermal, microwave-assisted, and mechanochemical approaches, can be employed to fabricate MOFs with desired properties. Solvothermal and hydrothermal methods are commonly used for the synthesis of MOFs under controlled temperature and pressure conditions, leading to well-defined crystalline structures. Microwave-assisted synthesis offers rapid and efficient MOF fabrication by utilizing microwave irradiation to accelerate reaction kinetics. Mechanochemical synthesis involves the milling or grinding of reactants to promote solid-state reactions, offering advantages such as reduced reaction times and simplified purification procedures [10, 24, 25].

3.3 Post-Synthetic Modifications

Post-synthetic modifications allow for the introduction of additional functionalities or properties to pre-synthesized MOFs, expanding their utility in biosensing and drug delivery. Surface functionalization of MOFs with biomolecules, polymers, or nanoparticles can enhance their biocompatibility, targeting specificity, and stability in biological environments. The incorporation of guest molecules or therapeutic agents into MOF frameworks via post-synthetic encapsulation or exchange processes enables controlled drug loading and release [26,27].

3.4 Scale-up and Reproducibility

Scaling up MOF synthesis while maintaining reproducibility and batch-to-batch consistency is essential for practical applications in biosensing and drug delivery. Process optimization, reactor design, and automation of synthesis protocols are critical for achieving large-scale production of MOFs with consistent properties and performance [24, 28].

3.5 *Characterization and Quality Control*

Comprehensive characterization techniques such as X-ray diffraction (XRD), scanning electron microscopy (SEM), transmission electron microscopy (TEM), and nitrogen adsorption-desorption analysis are essential for evaluating the structural, morphological, and textural properties of MOFs. Quality control measures, including purity assessments, chemical stability tests, and biocompatibility evaluations, ensure the reliability and safety of MOFs for biomedical applications [11].

4. RECENT ADVANCES IN THE APPLICATION OF MOFs IN BIOSENSING

Biosensing refers to the process of detecting and measuring biological molecules or entities, such as proteins, nucleic acids, enzymes, hormones, pathogens, and toxins, using biochemical or biophysical techniques [29, 30]. Biosensors are analytical devices that incorporate a biological sensing element, such as enzymes, antibodies, DNA, or cells, coupled with a physicochemical transducer to convert the biological recognition event into a measurable signal [31]. Metal Organic Frameworks (MOFs) have emerged as promising platforms for biosensing applications, owing to their unique properties such as high surface areas, tunable porosities, and versatile chemical functionalities. A MOF biosensor is a type of biosensor that incorporates Metal Organic Frameworks (MOFs) as the sensing element. In recent years, significant advancements have been made in harnessing the potential of MOFs for developing highly sensitive and selective biosensors. The recent breakthroughs and innovations in the application of MOFs in biosensing are hereby highlighted [32, 33].

4.1 Enhanced Sensitivity and Selectivity

Recent studies have demonstrated the use of MOFs with tailored pore sizes and functional groups to enhance the sensitivity and selectivity of biosensors [34,35]. By fine-tuning the pore dimensions and incorporating specific functional groups, MOFs can selectively capture target analytes, leading to improved detection limits and reduced interference from non-specific binding [34, 35]. The large surface area of MOF provides ample sites for biomolecule immobilization and interaction.

4.2 Integration with Nanomaterials and Biomolecules

Another notable trend in recent research involves the integration of MOFs with nanomaterials and biomolecules to enhance biosensor performance [36-38]. For instance, hybrid nanostructures composed of MOFs and plasmonic nanoparticles have been developed for surface-enhanced Raman scattering (SERS) detection of biomolecules with ultrahigh sensitivity [36-38]. Additionally, the immobilization of enzymes, antibodies, or DNA probes within MOF matrices enables the construction of enzyme-based, immunosensors, or DNA biosensors with enhanced specificity and stability [36-38].

4.3 Multiplexed Detection and Portable Devices

Recent efforts have also focused on the development of multiplexed biosensors based on MOFs, enabling the simultaneous detection of multiple analytes in complex biological samples. By functionalizing MOFs with different recognition elements or integrating them into microfluidic devices, researchers have achieved multiplexed detection of biomolecules with high throughput and sensitivity. Moreover, advancements in miniaturization and integration have led to the development of portable biosensing devices based on MOFs, facilitating point-of-care diagnostics and on-site monitoring in resource-limited settings [39, 40].

4.4 Biocompatibility and Biodegradability

Biocompatible MOFs have been explored for real-time monitoring of cellular processes, intracellular imaging, and in vivo biosensing. The biocompatibility and biodegradability of certain MOFs have made them attractive candidates for biosensing applications in biological environments.

5 RECENT ADVANCES IN THE APPLICATION OF MOFs IN DRUG DELIVERY

Drug delivery refers to the process of administering therapeutic agents, such as medications or biologics, to patients to achieve desired therapeutic effects. The goal of drug delivery is to deliver drugs to the target site in the body at the appropriate concentration and rate while minimizing side effects and maximizing therapeutic efficacy [41]. Drug delivery systems can vary in complexity, ranging from simple oral tablets to sophisticated nanotechnology-based carriers. Drug delivery systems often utilize carriers or vehicles to transport drugs to the target site in the body. These carriers can be made from various materials, including lipids, polymers, nanoparticles, micelles, and hydrogels. Carriers can protect drugs from degradation, enhance their solubility, and facilitate targeted delivery to specific tissues or cells [41-43]. Metal Organic Frameworks (MOFs) have garnered considerable attention as promising candidates for drug delivery applications due to their high surface areas, tunable porosities, and versatile functionalities. Recent advances in MOF-based drug delivery systems have showcased their potential to address key challenges in drug delivery, including controlled release, targeted delivery, and improved therapeutic efficacy [44-49].

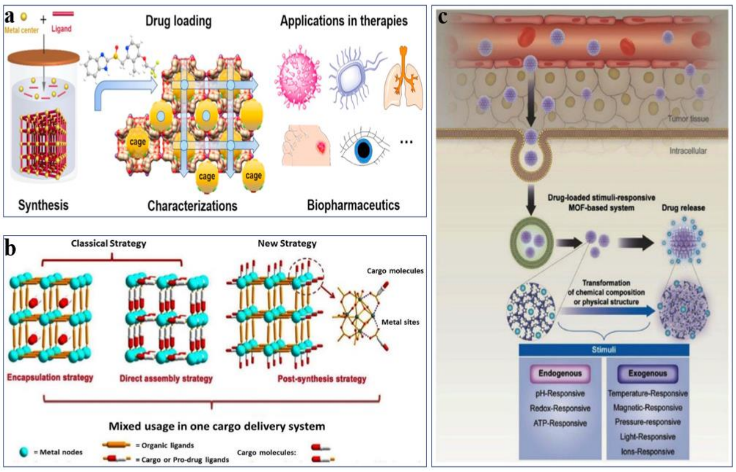

Figure 4: Schematic illustration of metal-organic frameworks (MOFs) Drug Delivery Strategies: (a) MOF Synthesis and Drug loading approach (b) Encapsulation, direct assembly, and post-synthesis of cargo-loading (c) MOFs-based stimuli-responsive system for drug delivery. *Reproduced with Permission from ref [15]. Copyright © 2022 by the Authors MDPI.*

5.1 Controlled Release Kinetics

Recent studies have demonstrated the use of MOFs with tailored pore sizes, surface chemistries, and functional groups to achieve controlled and sustained release of various therapeutic agents, including small molecules, proteins, and nucleic acids [17, 45]. By fine-tuning parameters such as pore size, pore geometry, and guest-host interactions, researchers have been able to design MOF-based delivery systems with precise control over drug release profiles, thereby optimizing therapeutic outcomes and minimizing side effects. The ability to encapsulate drug molecules within MOF porous structures and modulate release kinetics is indeed one of the primary advantages of MOFs in drug delivery [44, 45]. Figure 5 shows a typical example of controlled-released process [50].

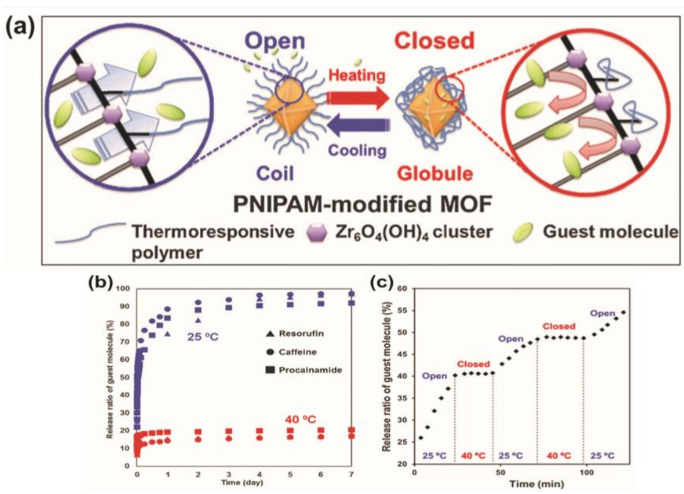

Figure 5: Controlled release profiles of UiO-66-PNIPAM. b) Release behavior of drug-loaded UiO-66-PNIPAM in water at 25 °C and 40 °C for seven days. c) Temperature-responsive release behavior of resorufin from UiO-66-PNIPAM in water at 572 nm [50].

5.2 Targeted Delivery and Site-Specific Accumulation

Another promising aspect of MOF-based drug delivery is their potential for targeted delivery and site-specific accumulation of therapeutic agents. By functionalizing MOFs with targeting ligands such as antibodies, peptides, or aptamers, researchers have successfully engineered targeted drug delivery systems capable of selectively recognizing and binding to specific cells or tissues [51, 52]. This targeted approach not only enhances the therapeutic efficacy of drugs but also reduces off-target effects and systemic toxicity [51, 52]. Moreover, the porous nature of MOFs enables the loading of multiple drugs or imaging agents within the same carrier, facilitating combination therapy and theragnostic applications [46]. Fig. 6 shows example of specific site drug delivery platform with MOF.

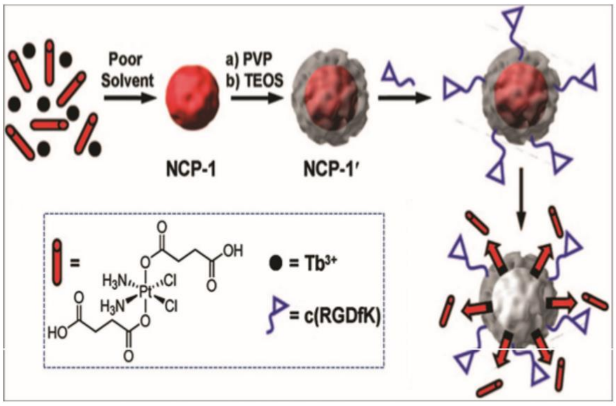

Figure 6: Schematic fabrication process of the silica-coated MOF for drug delivery at specific site of cancer cells [53].

5.3 Biocompatibility and Biodegradability

Recent efforts have focused on the development of biocompatible and biodegradable MOFs for drug delivery applications, aiming at minimizing potential cytotoxicity and promoting safe clearance from the body. Biocompatible MOFs derived from biocompatible metal ions and biodegradable organic linkers have been explored for in vivo drug delivery, showing promising results in terms of biocompatibility, biodistribution, and pharmacokinetics [44,54]. Additionally, bioresponsive MOFs capable of undergoing controlled degradation or triggered release in response to specific biological stimuli offer opportunities for on-demand drug delivery and personalized medicine [55].

5.4 Multifunctional Platforms and Therapeutic Synergy

Furthermore, recent advances in MOF-based drug delivery have focused on developing multifunctional platforms capable of integrating therapeutic, diagnostic, and imaging functionalities within a single carrier [48, 49]. By incorporating imaging agents, stimuli-responsive moieties, and therapeutic payloads into MOFs, researchers have created multifunctional nanocomposites for theragnostic applications, enabling real-time monitoring of drug release, disease progression, and treatment response. Moreover, the synergistic combination of MOFs with other nanomaterials such as liposomes, polymers, or nanoparticles has led to the development of hybrid drug delivery systems with enhanced stability, bioavailability, and therapeutic efficacy [48, 49]. Fig. 7 present a typical multifunctional drug delivery platform.

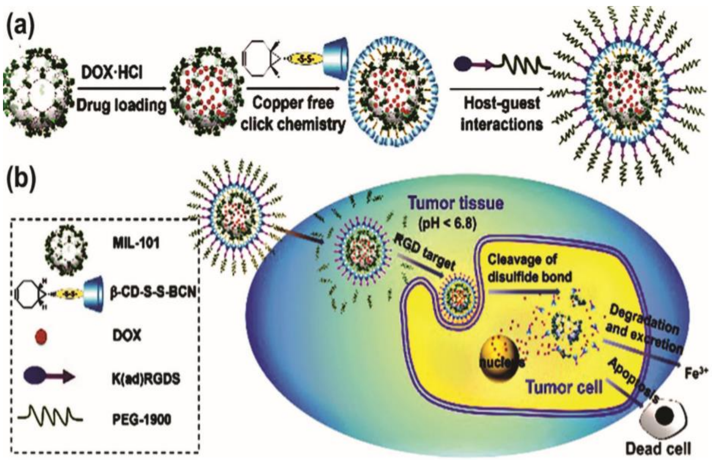

Figure 7: Schematic fabrication process of the multifunctional drug delivery platform (a) DDS based on MIL-101 and (b) its cancer therapy procedure [56].

6. PROSPECTS, CHALLENGES, AND FUTURE DIRECTION OF MOFs AS BIOSENSING AND DRUG DELIVERY MATERIALS

Through precise control over the chemical composition, structure, and functionality, MOFs offer unique opportunities for the development of innovative technologies with applications ranging from healthcare to environmental monitoring.

In biosensing, recent advancements in MOF-based sensors have demonstrated their ability to achieve high sensitivity, selectivity, and multiplexed detection capabilities. By harnessing the large surface areas and tunable porosities of MOFs, researchers have engineered biosensors capable of detecting a wide range of biomolecules with exceptional precision and efficiency. Moreover, the integration of MOFs with nanomaterials and biomolecules has further enhanced biosensor performance, paving the way for applications in diagnostics, therapeutics, and point-of-care testing.

Similarly, in drug delivery, MOFs offer unparalleled advantages such as controlled release kinetics, targeted delivery, and multifunctionality. Recent developments in MOF-based drug delivery systems have shown promising results in improving drug solubility, bioavailability, and therapeutic efficacy. By exploiting the biocompatibility, biodegradability, and stimuli-responsive properties of MOFs, researchers have developed novel drug carriers capable of delivering therapeutic agents to specific sites within the body, thereby minimizing side effects and maximizing therapeutic outcomes.

However, despite the significant progress made in the application of MOFs in biosensing and drug delivery, some challenges remain to be addressed. The stability and reproducibility of MOF-based biosensors, enhanced biocompatibility and biostability for in vivo applications, optimized integration with signal transduction mechanisms for robust and reliable sensing, optimized drug loading and released kinetics, ensured long-term stability and safety, remain some challenges.

Future research directions may involve exploring novel MOF architectures, functionalization strategies, and synergistic therapeutic combinations with other materials to further advance the field of biosensing towards practical applications in healthcare, environmental monitoring, and beyond as well as the field of drug delivery towards clinical translation and commercialization.

7. CONCLUSION

Metal-Organic Frameworks (MOFs) have emerged as versatile materials with tremendous potential in the fields of biosensing and drug delivery.

Although challenges such as scalability, reproducibility, biocompatibility, and long-term stability still need to be addressed to fully realize the potential of MOFs in practical applications, the remarkable progress made in harnessing the unique properties of MOFs for biosensing and drug delivery underscores their importance in advancing healthcare, environmental monitoring, and beyond. By continuing to innovate and collaborate across disciplines, we can unlock the full potential of MOFs and usher in a new era of transformative technologies for the benefit of man.

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