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Review

Advances in metal-organic framework-based drug delivery systems

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ABSTRACT

Metal-organic frameworks (MOFs) are emerging crystalline porous materials with significant potential in biomedical applications, particularly as drug delivery systems (DDS). MOFs, composed of metal ions or clusters linked by organic ligands, feature large surface areas, adjustable pores, and diverse functionalities. This review comprehensively examines MOFs as advanced DDS, detailing their structures, synthesis, and drug loading mechanisms. We highlight high drug loading capacity and controlled release capabilities of MOF. Developments of design strategies for MOF-based DDS, namely, surface functionalization for targeted delivery and stimuli-responsive MOFs for controlled release, have been discussed and explored. The use of MOFs for delivering therapeutic agents such as small molecules, peptides, proteins, nucleic acids, and cancer drugs is discussed. Challenges addressed include stability, degradation in biological environments, potential toxicity, and scalability. Advances in hybrid MOF-based DDS, integrating MOFs with polymers, lipids, or nanoparticles for improved delivery, are also examined.

1. Introduction

Drug delivery systems (DDS) optimize therapeutic efficacy and safety by controlling release rate, timing, and location enhancing pharmacological efficacy, addressing solubility and bioavailability issues, and mitigating adverse effects (Chahibi, 2017; Hamzy et al., 2021; Li et al., 2019). Various administration routes present distinct advantages and challenges (Hamzy et al., 2021; Jain, 2020, 2008). Nanoparticles (NPs) are crucial vehicles for drugs and diagnostics (Jain, 2020), with molecular communication conceptualizing drug delivery as analogous to data transmission (Chahibi, 2017). Nanotechnology, advanced carriers, and controlled release mechanisms allow targeted delivery while increasing precision and efficacy (Djorovic and Amler, 2021; Hamzy et al., 2022). Modern DDS combines nanoparticles, stimuli-responsive biomaterials, and self-regulating devices, all to create improved patient outcomes, improved treatment efficacy, and contribute towards

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Abbreviations: DDS, drug delivery systems; NPs, nanoparticles; MOFs, metal-organic frameworks; CD-MOFs, cyclodextrin- based MOFs; MOF- 74, MOF variant made up of divalent metallic cations; MIL-101- Fe, Iron based MOF; HKUST- 1, MOF variant made up of Cu2 and benzene tricarboxylate ligands; MIL-100, Iron (III) based MOF variant; MOF- 808, a Zr-based MOF variant; MIL- 88B, MOF variant made up of trivalent metal cations; NU- 901, a zirconium based MOF variant; MIL-125, a titanium-based MOF variant; Uio- 66, Uio- 67 and Uio- 68, zirconium based MOF variants; ZIF- 8, zeolitic imidazolate framework-8; PP, peptide- based Drugs; PDT, photodynamic therapy; PTT, photothermal therapy; DNA, deoxyribonucleic acid; RNA, ribonucleic acid; siRNA, small interfering RNA; mRNA, messenger RNA; miRNA, microRNA; ROS, reactive oxygen species; MRSA, methicillin- resistant staphylococcus aureus; IL, interleukin; PLK1, polo-like kinase 1; siPDL1, siRNA targeting programmed cell death protein ligand-1; TLR, toll- like receptor; BBB, blood- brain barrier; CD-44, cell surface adhesion receptor; MMM, mixed matrix membranes; GSH, glutathione; STING, stimulator of interferon genes; SR717, a non-nucleotide STING agonist; ALP, alkaline phosphatase; MRI, magnetic resonance imaging; N3-PEG-PO3, azide-functionalised clickable PEG phosphate ligand; PXR, powder X-ray; BET, Brunauer Emmett Teller; TGA, thermogravimetric analysis; PET, positron emission tomography; T1, longitudinal relaxation time; R1, relaxivity; DTPA, diethylenetriamine pentaacetate; NaErF4:Yb@NaLuF4, sodium erbium fluoride doped with ytterbium and sodium lutetium fluoride nanoparticles; 4T1, breast cancer cell line; T cell, T lymphocyte; H2O2, hydrogen peroxide; Gd, gadolinium; PEG, polyethylene glycol; 19F MRI, fluorine- 19 MRI; NIR, near-infrared; MBG, mesoporous bioactive glass; AI, artificial intelligence; ML, machine learning; TEM, transmission electron microscopy; FFT, fast Fourier transform.

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personalized medicine (Hamzy et al., 2022; Jain, 2020, 2014).

Metal-organic frameworks (MOFs) may be defined as porous crystalline frameworks composed of metal clusters or ions coordinated with organic ligands. They have thus attracted tremendous attention because of their high surface area, tunable porosity, and considerable diversity in composition (Yan, 2022; Yang and Yang, 2020). MOFs are synthesized by coordination of metal-containing nodes with organic linkers giving rise to either a 2D or a 3D structure (Sikma et al., 2022; Yan, 2022). A large number of various combinations of metal nodes and organic linkers allows for designs tailored to particular applications (Fordham et al., 2014; Haldar et al., 2020). Although the vast majority of MOFs employ high-oxidation-state metal ions, there is a steady trend toward low-valent MOFs that have potential applications in catalysis and luminescence (Sikma et al., 2022). The exploration of MOFs encompasses gas storage, catalysis, sensing, drug delivery, and environmental applications (Nemiwal et al., 2021; Yang and Yang, 2020). Their high efficiency and selectivity in binding to certain guest molecules make them excellent sensors in which detection occurs upon structural change after guest-molecule interaction (Sacchetti et al., 2021).

MOFs present significant advantages as DDS for advanced therapeutic applications owing to their unique structure and properties, surpassing traditional drug carriers (Safdar Ali et al., 2021; Vikal et al., 2024). The impressive drug loading capacity, thanks to their enhanced surface area with considerable porosity, makes it possible for effective entrapment of the drug and enhancement of its stability and solubility (Khafaga et al., 2024; Sun et al., 2013; Yang et al., 2024c). The MOFs allow for controlled and targeted drug delivery, increasing therapeutic efficacy and minimizing adverse effects (Khafaga et al., 2024; Sun et al., 2013). The tunable composition and structure of MOFs allow precise engineering of tailored drug delivery systems (Karki et al., 2020; Srivastava et al., 2024). Such stimuli might include pH, glutathione, or specific cations, which allow smart drug-release mechanisms. Cyclodextrin-MOFs, especially, improve drug delivery through a variety of interactions (Yang et al., 2024c). MOFs provide a versatile drug delivery platform with high loading capacity, improved stability and solubility, controlled release, and stimulus responsiveness, promising personalized medicine and better patient outcomes due to their tunability and functionalization capabilities (Khafaga et al., 2024; Rao et al., 2022).

The review presents a thorough assessment of the biomedical potential of MOFs and their place as advanced DDS. It introduces the drug delivery systems and unique advantages of MOFs to their structure, composition, and encapsulation mechanisms. The review explores the MOF-based delivery strategies for delivering against such a category of therapeutic agents as small molecules, peptides, nucleic acids, and cancer drugs, and discusses design strategies such as functionalization and stimuli-responsiveness. The review also discusses integrating the MOFs with other materials (polymers, lipids) to enhance delivery efficiency and explores the possibilities of stimuli-responsive MOFs for precise drug release. It describes MOFs' stability and degradation in biological environments in regard to their use as theranostic agents. It further discusses the challenges relating to MOF-based drug delivery, such as scalabilities and their possible toxicities. Future research directions are personalized medicine, smart MOFs for gaining control over drug release whenever needed, and AI-assisted optimization in drug delivery.

2. Fundamentals of MOF-based drug delivery

Nanoscale size and capability to protect sensitive drugs during transport enhance the potential of MOFs as drug delivery vehicles. They offer high drug loading capacity, controlled release mechanisms, and the ability to incorporate additional functionalities. MOFs also address specific therapeutic needs with pH-responsive, redox-responsive, and zero-order drug delivery systems. Both the method of synthesis and the synthesis conditions influence the geometrical skeleton of the framework, along with other physical properties of the material, such as crystal structure, morphology, dimensions, porosity, and surface area. Various synthetic approaches have been applied to prepare MOFs and MOF-based materials by attributing different characteristics to the obtained systems. Hydrothermal and solvothermal techniques, microwave-assisted synthesis, sonochemical methods, mechanochemical approaches, and electrochemical synthesis are typically used (Zhang et al., 2023). The summary of different methods of synthesis is shown in Table 1.

2.1. Structure and composition of MOFs

MOFs consist of inorganic metal-containing nodes connected by organic linkers (Bon et al., 2019; Yang et al., 2022a). Synthesis of such a hybrid organic–inorganic combination has given rise to over 90,000 developed varieties (Yang et al., 2022a). Being modular, they enable a delicate control of pore size, surface functionality, and specific surface areas (Bon et al., 2019). MOFs present structural transformations and stepwise adsorption behavior absent in rigid porous materials (Bon et al., 2019), enabling "smart" adsorbent designs. Derivable nanomaterials and multifunctional nanocomposites include carbons, metal oxides, and metal phosphides (Kaneti et al., 2017). Their tunable structures and compositions enable the fabrication of materials for specific applications. MOFs having crystallinity, modularity, high specific surface area, and pore volume find good applications in gas storage, catalysis, energy storage and conversion, sensors, and environmental remediation (Bon et al., 2019; Kaneti et al., 2017). Phase-engineering techniques provide the additional enhancement of their application potential by allowing the control of the crystal phases (Ma et al., 2022a). Further, MOFs may be discovered under different morphological forms such as spheres, cubes, cuboctahedra, octahedra, rods, filaments, sheets, and sophisticated hierarchical structures (Łuczak et al., 2023).

Table 1
A summary of different methods of MOF synthesis.

Synthesis method	Benefits	Example of study	Ref.
Solvothermal	Simple method. High crystallinity, controlled morphology	Zinc-isonicotinic acid MOF ZIF- 8	(Kouser et al., 2025; Zhang et al., 2025)
Hydrothermal	Environmentally friendly, aqueous medium	MIL-88B	(Zhang et al., 2025)
Microwave-assisted	Rapid synthesis, uniform heating	MOF-801, a Zr based MOF	(Mahmoud, 2025)
Physical grinding	Solvent-free, energy-efficient	Mixed-metal copper–ruthenium HKUST-1 MOFs	(Sondermann et al., 2024; Wang et al., 2023b)
Electrochemical	Scalable, mild conditions	Cu based MOF	(Araújo-Cordero et al., 2024; Ghoorchian et al., 2020)
Sonochemical	Fast synthesis, reduced particle size	Cu based MOF	(Abaszadeh et al., 2024)
Spray-drying	Continuous fabrication, high yield, low moisture content, reduced reaction time.	Uio-66-NH$_2$	(Albadarin et al., 2024)
Template-assisted	Synthesis of MOF with tunable morphology, size and composition	CoFe bimetallic MOF using cobalt hydroxide as template	(Shen et al., 2024b; Zhao et al., 2020)
Simple solution	Relaxed way, no interference	ZIF-8 by mixing 2-methylimidazole and zinc carbonate	(Gugin et al., 2022)

2.2. Mechanisms of drug loading/encapsulation in MOFs

The high porosity, large surface area, and tunable structures of the MOFs contribute towards the prospects of drug delivery. Any drug loading in the MOFs might be based on physical entrapment, covalent bonding, and host-gust interactions (Benny et al., 2024a). Physical encapsulation involves either adsorption or capillary action, utilizing porosity and surface area of MOFs for constructive drug loading while optimized pore size and shape increases the carrying capacity (Benny et al., 2024a). It is a two-fold increase in loading capacity of defect-engineered MOFs with a well-established mesoporosity compared to the perfect analogues (Xu et al., 2024c). Moreover, it includes covalent bonding, which chemically anchors the drug molecules onto the MOF structure for better retaining and controlling. Host-guest interactions occur via non-covalent interactions that can be modulated by stimuli such as pH or temperature among others (Benny et al., 2024a; Bhat and Lee, 2022). Depending on the drug and MOF properties-including pore size, surface functionalization, and desired release kinetics-various loading mechanisms might be chosen in their design. Multiple load mechanisms render them more exciting and efficacious candidates for DDS (Benny et al., 2024a; Khafaga et al., 2024).

2.3. Mof-drug interactions and release mechanisms

MOFs are distinguished by high porosity, tunability, and substantial drug uptake capacity (Ernst and Gryn'ova, 2023; Kim et al., 2019). Drug-MOF interactions, involving non-covalent host–guest interactions, are crucial for drug binding strength and release kinetics. Interaction energy is important for screening and designing MOFs for drug delivery (Ernst and Gryn'ova, 2023). Defects in MOFs can significantly influence the loading of the drug, especially those with phosphate or phosphonate groups, by generating Coulombic attractions that enhance capacity (Durymanov et al., 2019). The degradation of MOFs in physiological environments influences drug release, for example MIL-88A and MIL-88B-NH2 show only 10 %−15 % degradation over 24 h in Kupffer cells (Wang et al., 2020). Stimuli-responsive drug release mechanisms for MOFs are affected by pH, glutathione, ATP, enzymes, light, temperature, and pressure (Wang et al., 2020; Xing et al., 2024). A hyaluronic acid-coated MOF targets the overexpressing cancer cells of CD44 and hence the drug release from the MOFs engendered responses of enzymes in the local environment of the cancer cells (Kim et al., 2019). It is important to comprehend these interactions and mechanisms in order to set the basis for an efficient MOF-based DDS with controlled-release kinetics for better therapeutic outcomes.

3. Design strategies for MOF-based drug delivery

Formulation strategies for MOF-based drug delivery systems include drug loading optimization, release kinetics, and targeted delivery. Modifying the MOFs makes for a better drug-loading capacity and control of release. The choice of metal cation and organic ligand has a marked influence on the pore size, shape, and chemical properties of the MOFs (Benny et al., 2024a; He et al., 2021). Examples of post-synthesis modifications, such as surface functionalization, that improve the drug-MOF interactions whereby stimuli enable these responsive drug releases include pH, temperature, or specific molecules. Cyclodextrin-based MOFs (CD-MOFs) have proved to increase drug solubility and bioavailability involved in host–guest interactions (Yang et al., 2024c). CD-MOFs can be customized via co-crystallization with functional components or surface modification to achieve controlled release and targeted delivery. Hence, MOF-designing in drug delivery systems involves selection of MOF components, structural optimization, and surface modifications.

3.1. Functionalization of MOFs for targeted delivery

Surface alteration of MOFs is critical to enhancing their role as carriers for drug molecules. Functionalization enables specific drug targeting through surface chemistry, coupling specific ligands to enhance drug loading, control release profiles, and improve targeting efficiencies (Karki et al., 2020; Uthappa et al., 2019). Also, resulting functionalized MOFs can react to various stimuli including pH, temperature control, redox conditions, magnetic fields, enzymes, and light, thereby causing a clearer advance in tumor therapy and diagnosis (Bhat and Lee, 2022). Post-synthetic modification to introduce targeting ligands is an interesting approach. For instance, those nanoscale zinc MOFs that were functionalized with folate target folate receptors on tumor cells that are more or less cytotoxic toward malignant cells, and selecting between folate receptor-positive and negative cells compared to free drugs (Lin et al., 2022).

3.2. MOF surface modification techniques

There exist varieties of surface technique modifications on the MOFs for the enhancement of properties and applications. Post-synthetic modification is a powerful strategy for the introduction of functionalities within the parent frameworks, which can be generally classified into covalent modification, coordinative transformation, encapsulation, and hybridization with other compounds (Lin et al., 2022). One technique is the modification of nanoscale MOFs by 1,2-dioleoyl-*sn*-glycero-3-phosphate (DOPA) to create stable colloids while with porosity retained (Wang et al., 2015). This synthesis method leads to stable colloidal nanoscale MOFs. The second one is two-fold: in-situ alteration, fabrication, and post-synthetic modification to prepare such MOFs possessing increased properties. Usually used methods of surface modification are dispersion of other compounds on the surface of the former or pore impregnation with some other active materials (Gangu and Jonnalagadda, 2020). The selection of a modification method depends on the particular properties and related applications, these being for example catalysis, drug delivery, sensor, or energy storage fields (Abdelkareem et al., 2022; Jain et al., 2024; Liu et al., 2024; Yang and Yang, 2020).

3.3. Stimuli-responsive MOFs

Stimuli-responsive MOFs attract significant interest for biomedical applications due to their high surface area, biocompatibility, and customizable structures. These nanoplatforms can respond to stimuli like pH, temperature, light, magnetic fields, and redox reactions, making them ideal for controlled DDS and cancer therapy (Cai et al., 2019; Oroojalian et al., 2022). pH-responsive MOFs like ZIF-8 show low stability in physiological conditions but decompose under acidic environments, thus allowing pH-sensitive drug responses. Stimuli-responsive MOFs often rely on materials with temperature responsiveness, such as phase-changing materials, that melt just above body temperature, thus facilitating thermally responsive drug release (Wei and Lu, 2024). Redox-responsive MOFs perform reversible oxidation–reduction, changing material flexibility and breathing behavior, which can ease development of stimuli-responsive DDS (Liu et al., 2020; Su et al., 2017). Combining multiple stimuli-responsive mechanisms, like pH and temperature, allows creating complex structures for precise drug release (Wei and Lu, 2024). These MOFs have potential in cancer therapy, including photothermal therapy with chemotherapy and integrated platforms for magnetic resonance imaging (Moharramnejad et al., 2023).

3.4. Size and porosity optimization of MOFs for drug loading

Optimizing the size and porosity of MOFs is essential for efficient drug loading and controlled release. The production of MOFs is fundamentally decided by the synthesis method, which, in turn, influences their morphology and structure and affects their porosity and surface area. Hydrothermal synthesis produces the most crystalline MOFs, whereas solvothermal synthesis serves to broaden the pores, ideal for drug adsorption (Chiñas-Rojas et al., 2024). Microporous MOFs with pore widths under 2 nm are endowed with high porosity and surface area that allows efficient loading of drugs. Strategies for synthesizing microporous MOFs include modulator, defect formation, structure-directing agents, and pillared-layer assemblies (Ahmadi et al., 2022). A one-pot approach for loading active molecules during MOF synthesis has shown a high encapsulation efficiency (~96 %) for benzimidazole molecules in Cu-MOFs, surpassing post-functionalization methods (Nehra et al., 2019). Incorporating metal NPs into MOFs can further enhance their drug delivery properties (Meilikhov et al., 2010). The optimization of drug loading onto MOFs requires careful synthesis method selection, making them promising candidates for targeted and controlled DDSs (Karki et al., 2020).

Table 2 gives a brief account of the different MOF-based drug delivery strategies elaborated in this section and highlights their mechanisms, strengths, limitations, and specific remarks.

4. MOF-based delivery for different classes of therapeutics

MOFs came out as innovative materials for DDS because of their highly distinctive structural properties, like high porosity, large surface area, and tunable chemical functionalities. Taking advantage of these unique characteristics, MOFs encapsulate a wide variety of guest molecules, thus improving their therapeutic effects while minimizing side effects.

4.1. Small molecule drugs

Recent studies have highlighted the prospective of MOFs for small-molecule drug delivery, showing both *in vitro* and *in vivo* applications. These studies demonstrated the versatility of MOFs in enhancing drug loading, release kinetics, and therapeutic efficacy in various diseases. MOFs can serve as DDS in the treatment of cancer, diabetes, pulmonary disease, wound healing, etc. (Ding et al., 2022). Various strategies are available for small-drug-molecule loading into MOFs by encapsulation, that is, by incorporating drug molecules within the porous structure of the MOF. The drugs are held inside the pores through noncovalent interactions, like hydrogen-bonding, π-π stacking, and van der-Waals forces. The other methods include direct assembly in which the drug acts as a ligand that coordinates with metal ions during the formation of the MOF. This method allows for a more uniform distribution of the drug within the framework, but requires careful control over the synthesis conditions to avoid damaging sensitive drug molecules and post-synthesis modification where drugs can be loaded onto its surface or into its pores through adsorption or covalent bonding. This strategy is advantageous for the modification of existing MOFs in order to change their cargo-loading capacity or their release profile. One of the best advantages of the use of MOFs for drug delivery systems is their ability to be triggered by specific stimuli within biosystems. These stimuli can be endogenous (e.g., pH changes or temperature variations at tumor sites) or exogenous (e.g., light or magnetic fields). By designing stimuli-responsive MOFs, researchers can achieve the targeted and controlled release of small-molecule drugs at desired locations within the body (Maranescu and Visa, 2022a). Many factors affect the efficiency of MOF for drug delivery. Research on Mg-MOF-74 revealed that the solubility and molecular weight of drugs such as ibuprofen and 5-fluorouracil significantly affect their release rates, with higher solubility leading to improved pharmacokinetics (Pederneira et al., 2023).

4.2. Peptides and proteins

MOFs are ideal candidates for encapsulating biologically active

Table 2
A concise summary of MOF-based drug delivery design strategies.

Design Strategy	Mechanisms	Strengths	Limitations	Remarks
Targeted functionalization	Modifying the MOF surface by incorporating specific ligands. This can involve covalent modification, coordinative transformation, encapsulation, or hybridization.	Enhanced specificity and reduced off-target effects, improved drug delivery to diseased tissues. Can improve drug loading, control release, and enhance targeting.	Requires careful selection of targeting ligands and can be complex to implement. May involve altering the MOF structure.	Functionalization is often used to create stimuli-responsive MOFs and can be combined with surface modifications. It can involve altering the MOF structure itself to incorporate targeting ligands.
Surface modification	Altering the outer layer of MOFs through methods such as covalent modification, coordinative transformation, encapsulation, and hybridization. Can include coating with polymers or lipids. Can involve dispersing substances or impregnating pores.	Improved drug loading, controlled release, enhanced stability, and reduced toxicity. Can enhance drug-MOF interactions and targeting efficiency.	May alter the inherent properties of the MOF and can be complex.	Surface modification is a specific way to achieve targeted functionalization and can also create stimuli-responsive MOFs.
Stimuli-responsive MOFs	Designing MOFs to release drugs in response to specific environmental triggers such as pH, temperature, light, or magnetic fields. Can be achieved by incorporating functional groups or surface modifications. Phase change materials can also be used.	Precise and controlled drug release at the target site, especially useful for cancer therapy and other diseases with localized conditions.	Requires careful selection of stimuli and can be difficult to design for complex biological environments.	Stimuli-responsiveness often involves functionalization and/or surface modification with molecules that are sensitive to specific triggers.
Size and porosity optimization	Controlling the physical dimensions and pore structure of MOFs during synthesis. The choice of metal ions and organic ligands influences pore size, shape, and chemical properties.	Improved drug loading capacity, controlled release kinetics, and enhanced bioavailability. Important for entry into the bloodstream and reaching target cells.	May require precise synthesis methods and can be challenging to achieve the desired pore size and distribution.	The size and porosity affect drug loading, which is also an output of targeted functionalization, surface modification, and stimuli-responsive design.

molecules. The ability to maintain the bioactivity of sensitive biomolecules during delivery is crucial, particularly given that peptides and proteins is often large and environmentally sensitive. Peptide-based drugs (PPs) are widely used in medical treatments, especially for conditions such as diabetes. However, their oral delivery presents unique challenges owing to their chemical structure, such as instability in the gastrointestinal tract, reduced bioavailability, and limited permeability. To tackle these issues, studies are exploring alternate delivery methods for PPs that can enable enteral administration, while maintaining bioavailability and stability (Duan et al., 2018). In an attempt to fabricate an efficient oral insulin delivery system based on the UiO-68-NH_2 MOF through a two-step solvo-thermal method, substantial drug loading while providing protection from any degradation was attained. Through receptor-mediated transcellular pathways, transferrin-coated NPs show efficient transport across the intestinal epithelium and controlled insulin release. Since MOFs can be designed as stimuli responsive carriers, leading to targeted release at specific locations, an MOF developed from a single-step synthesis for intelligent glucose-responsive insulin delivery was also found to be feasible (Nicze et al., 2024).

The delivery mechanism of PPs involves loading, transporting them to the target site, and releasing them in a controlled manner. The porous nature of MOFs allows for high loading capacities; PPs can be encapsulated within their pores or attached to their surface. For hypoxia mitigation, catalase enzyme that converts intracellular H_2O_2 to O_2 attached to the outer surface of MOF NPs realized effective cellular entry of catalase, whose applicability is very much limited owing to the intrinsic membrane impermeability; otherwise, it results in the enhancement of photodynamic therapy (PDT) (Sim et al., 2023). In another study regarding functionalization, a UiO-66-based double enzyme nano drug delivery system, decorated with Au NPs with excellent photothermal conversion performance, enhanced anti-cervical tumor proliferation and migration by combining PTT and starvation therapy. The system, loaded with glucose oxidase, breaks the hydrophilic binding chain and releases enzymes and Au NPs into cancer cells, leading to cell death and H_2O_2 release (Gong et al., 2024). The development of non-toxic, biocompatible materials for MOF is also a topic of interest in biomedicine. The linker 5,5′-((pyridine-2,6-diylbis(methylene)) bis(oxy)) diisophthalic acid in synthesizing a new Cu-MOF were studied and found to be stable over a wide range of biological fluids. The framework was exploited for insulin delivery by covering the MOF with gelatin, thereby opening up a new route for controlled oral insulin delivery. The fact that PPs can be used as organic ligands for framework generation (Benny et al., 2024b) owing to their inherent biocompatibility and targeting capabilities could also be exploited for their delivery.

4.3. Nucleic acid delivery (siRNA, DNA, mRNA)

Delivering nucleic acids such as DNA and RNA into cells presents several challenges. Due to the negative charge on nucleic acids, they encounter barriers towards passive transport via the lipid bilayer of the cell membrane due to charge repulsive forces with the negatively charged lipid bilayer of the cell membrane, in addition to their high molecular weight. As a result, nucleic acids should be delivered via effective delivery systems that would overcome such barriers, yet stability and bioavailability are highly encouraged (Lin and Qi, 2023). On the basis of more current research, it appears that metal–organic frameworks can be composed into nanocarriers administering therapeutic nucleic acid molecules. Nanoscale MOFs include those that encapsulate and deliver short interference RNAs, messenger RNAs, and DNA. The main advantage of MOFs is that they provide protection against nucleic acid degradation by enzymes. Studies have shown that when DNA duplexes are associated with nano-MOFs, they exhibit enhanced stability against nuclease degradation compared with unprotected nucleic acids. This protective capability is crucial for maintaining the integrity of therapeutic nucleotides during delivery (Li et al., 2023e). In studies involving UIO-66 and NH2-UIO-66 MOFs, researchers have explored different strategies for encapsulating mRNA. Incorporating polyethyleneimine into the matrix can be considered an effective functionalization method for plasmid delivery (Khosrojerdi et al., 2024). A study demonstrated that the magnetic properties of Iron nanoparticles for *in vivo* tracking can be combined with the functionalization of PEI to achieve a successful delivery system for functional genes (Ringaci et al., 2021). Another innovation that promises many advantageous applications in nucleic acid studies is the growing development of lanthanide metal–organic frameworks for improved extraction and interaction analysis. These materials possess unique properties that allow high-affinity binding, selective extraction, and advanced analyses based on luminescence (Yu et al., 2024).

5. MOF-based drug delivery for biomedical applications

The primary mechanism by which MOFs deliver drugs is by encapsulating them in the pores of the MOF, preserving the structural integrity of the MOF framework while allowing controlled release. Other methods involve letting the drugs participate in the synthesis process as ligands that contribute to constructing the MOF structure through coordination bonds or carrying out post-synthesis strategies where drugs are attached to pre-synthesized MOFs either by covalent bonding or adsorption on the surfaces without altering their core structure. MOFs can be of profound applications in drug delivery particularly cancer therapy, wound healing, immunotherapy etc. (Fig. 1). Despite their potential benefits, several challenges hinder the widespread adoption of MOF-based DDS, such as toxicity concerns, scalability issues, and regulatory hurdles (Liu et al., 2024).

5.1. Cancer treatment

The integration of controlled release mechanisms and stimuli-responsive behaviors into nano-MOFs represents a significant advancement in cancer treatment. By leveraging the unique properties of these materials alongside external stimuli, such as pH changes (Shen et al., 2024a), temperature fluctuations, and enzymatic activity (Xiao et al., 2023), researchers are developing innovative approaches for precise and effective DDS aimed at improving therapeutic outcomes while minimizing the side effects associated with conventional treatments. Metal-based nanomaterials are utilized in new tumor therapy by changing intracellular osmotic pressure, breaking cell redox balance or other homeostasis, or modulating T cell and macrophage phenotypes to enhance anti-tumor immune responses (Lei et al., 2023). Ongoing research into optimizing these systems continues to hold promise for enhancing cancer therapies through personalized medical approaches tailored specifically for individual patient needs (Shano et al., 2024). Tumor-targeting strategies are essential in cancer therapy, aiming to deliver therapeutic agents specifically to tumor cells while sparing the healthy tissues, including passive targeting based on enhanced permeability and retention effects, active targeting based on modifying MOF with ligands, or functionalization with post-synthetic strategies that bind specifically to receptors overexpressed on tumor cells; the choice depends on the enhancement of selectivity of drug delivery, allowing for higher concentrations of drugs at the tumor site while reducing systemic toxicity. Common ligands include antibodies, peptides, and small molecules that target specific biomarkers associated with tumors. For example, attaching folic acid molecules onto MOFs is an effective method to build an active targeting drug-delivery system due to the overexpression of folic acid receptors in tumor tissues (Mansouri et al., 2025).

Another critical challenge concerning bioavailability can be tackled through enhanced solubility, protection from degradation, and prolonged circulation time using larger particles or modifying surface properties. MOFs can evade rapid clearance by the immune system. MOFs can also be used in combination with other treatment modalities,

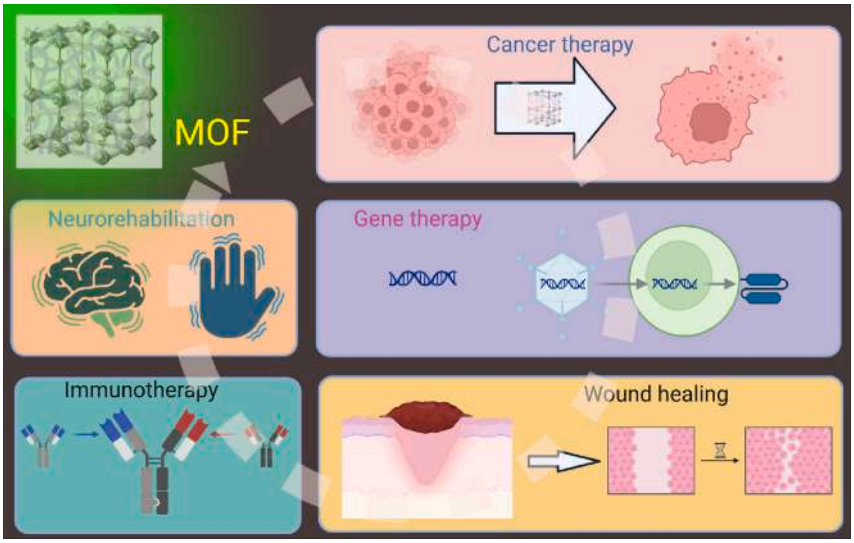

Fig. 1. Schematic illustration of MOFs in biomedical applications.

such as photothermal therapy or radiotherapy, providing a synergistic effect that enhances overall therapeutic outcomes (Liu et al., 2024). A previous study demonstrated that MIL-101-Fe, a carrier for delivering anticancer drug methotrexate, effectively caused death of HeLa cells from human cervical cancer and spared healthy Vero cells. Drug release was supposedly pH dependent and caused apoptosis (Yunus et al., 2024).

MOFs can encapsulate chemotherapeutic drugs such as doxorubicin and release them in response to specific stimuli present in the tumor microenvironment, enhancing their efficacy while minimizing systemic side effects. MOFs can enhance the effectiveness of radiotherapy by acting as radiosensitizers (Neufeld et al., 2021), can be utilized as carriers for photosensitizers in PDT that generate ROS when exposed to light (Zhang et al., 2023a), and can even find their way in combination therapies that utilize multiple treatment modalities simultaneously, including theranostic applications. MOFs can be engineered for targeted delivery by modifying their surfaces with targeting ligands that bind specifically to cancer cell markers (Deng et al., 2024). A porous biodegradable Iron-MOF equipped with the anticancer drug doxorubicin, biocompatibility imparted with a coating of polyethylene glycol, and a colorectal cancer-specific aptamer was developed for targeted colorectal cancer theranostics; this is an example of how functionalization can enhance the internalization of MOF into cancer cells, sparing normal cells (Babaei et al., 2024).

MOFs broaden the concept of tumor targeting by considering nucleic acid delivery aims at combating tumor heterogeneity and resistance mechanisms, thereby ensuring better therapeutic outcomes. In the context of gene therapy, nucleic acid (DNA or RNA) delivery into target cells poses a challenge in doing so without causing toxicity or immune over-reaction. The mechanism of gene delivery using MOFs involves several critical steps that ensure the effective transport of genetic material into target cells. Nucleic acids are also demonstrated to be encapsulated inside the MOF pores. This affords protection to the genetic material from degradation and allows for controlled release within the target cells. The combined use of MOFs, such as ZIF-8, with advanced strategies for delivery, such as tumor cell membrane coating and lysosomal release mechanisms, is a promising way to enhance siRNA-based cancer therapy targeting genes such as PLK1. This combined approach will surmount the mechanisms of specificity to also increase anti-tumor efficacy (Mishra et al., 2024). Functionalizing MOFs allows these carriers targeted delivery of nucleic acids such as DNA, RNA, and plasmids specifically to the target cells that have more specific affinities with their functionalized carriers. For instance, MOFs conjugated with folate or transferrin could therefore enable targeted delivery toward cancer cells bearing their respective receptors (Li et al., 2024a). A novel functional framework of the conjugation of photosensitizer porphyrin with siPDL1 and masked by hyaluronic acid works as an effective model for tumor treatment, combining phototherapy and gene therapy (Li et al., 2024b). In gene therapy, the carrier' s efficiency in encapsulating genetic materials is among the important determinants of success. Among the plethora of MOFs, ZIF-8 displayed commendably increased gene loading capacity over UiO-66 and MIL-88B, which apparently showed little or no gene loading capacity. Further issues in gene therapy applications center about the interactions between MOFs and the immune system. ZIF-8 has been reported to inhibit proinflammatory cytokines like IL8 while keeping normal levels of anti-inflammatory cytokines such as IL10 (Poddar et al., 2022). The findings emphasize the urge to condone the salient aspects in developing MOFs for gene delivery-based therapies.

5.2. *Antibacterial and wound healing applications*

The potential of MOFs for antimicrobial delivery has different aspects, such as serving as reservoirs for antibacterial metal ions, allowing controlled degradation in biological fluids, encapsulating antibiotics in the framework, incorporating bioactive linkers with antibacterial properties, incorporating photosensitizers in MOFs for photodynamic therapy, allowing targeted destruction of bacteria, or even facilitating the simultaneous delivery of multiple therapeutic agents, enhancing overall antibacterial efficacy (Guo et al., 2024). Multidrug-resistant bacteria have emerged as a worldwide health problem, requiring immediate attention to development of novel and potent antimicrobial treatments. Copper being a metal ion with inherent antibacterial activity, Cu-MOF and Cu-Gallic acid MOF substituting conventional antibiotics was synthesized and compared for antibacterial activity (Elmehrath et al., 2024). Another popular metal with antibacterial activity is zinc, because of its low toxicity, accessibility, and affordability. A study examined three MOFs with zinc as the central metal: ZIF-4, ZIF-7, and ZIF-8, among which ZIF-8 showed the highest antibacterial activity, whereas ZIF-7 showed the lowest (Khattami Kermanshahi and Akhbari, 2024). A photo-responsive MOFs hydrogel with antibacterial and anti-inflammatory effects to improve wound healing has been developed against *Staphylococcus aureus* and MRSA, supporting berberine as an anti-inflammatory drug as a promising approach for designing MOFs materials with enhanced antibacterial and anti-inflammatory functions (He et al., 2024).

MOFs play a multifaceted role in promoting skin repair through direct involvement in various stages of wound healing, and their cargo loading and hance can be used, particularly for treating diabetic wounds and for antimicrobial drug delivery. MOF can promote wound healing through different mechanisms, among which the release of antimicrobial metal ions and bioactive ligands upon degradation is well-versed. Metal ions, with well-documented bactericidal effects against a range of pathogens commonly found in infected wounds, are used as metal nodes in MOF. These ions play critical roles in cellular functions related to wound repair. For example, zinc has been shown to reduces oxidative stress and inflammation, whereas copper promotes angiogenesis and collagen synthesis (Wang et al., 2021a). MOFs and their nanocomposites can be used to load and deliver antibacterial ions or drugs. The antibacterial effects of Fucoidan and ZIF have already been established, and fucoidan-encapsulated ZIF-8 coated with hyaluronic acid has been applied to the tips of microneedles for MRSA-infected wound healing, (Jiang et al., 2024) serving both courses of release. Hybrid MOFs and hydrogels provide another direction for wound healing, which can not only make the MOFs disperse more uniformly but also endow the hydrogel with more bioactivity (Xing et al., 2023). Studies with Cu-MOF-cryogel composite (Fig. 2) (Singh et al., 2024), photodynamic alginate Zn-MOF thermosensitive hydrogel loaded with Chlorin- e6 (Zhang et al., 2023d) etc. are examples of antibacterial delivery.

5.3. Tissue engineering

MOFs are becoming increasingly promising materials for tissue engineering and regenerative medicine due to unique properties such as intrinsic bioactivity, drug delivery capabilities, and tunable structures. In the context of tissue engineering, MOFs can liberate bioactive metal ions, foster bone regeneration, and serve as drug carriers with a sustained therapeutic effect. In orthopedic applications, they can be incorporated into implants and coating to enhance bone healing and to avoid infections. In cardiovascular implants, copper-based MOFs can generate nitric oxide that acts as an anti-thrombotic agent. Furthermore, MOFs hold potential in neuronal tissue engineering via nerve regeneration and targeted drug delivery (Shyngys et al., 2021). MOFs can be structural components in scaffolds that support cell adhesion and growth. The physical, chemical and biological properties of the scaffolds had subsequently been investigated by incorporation of MOFs. The findings show that introduction of the MOF into polylactic acid and gelatin scaffolds increased mechanical properties, promoted bioactivity and supported bone formation (Ansari-Asl et al., 2025). The estimated amount of new bone formation was approximately 41 %, substantially surpassing the control groups. An iron-based metal–organic framework, which was loaded with the pro-angiogenic small-molecular drug dimethyloxallyl glycine and embedded into the PLGA scaffold, profoundly improved vascularization as well as bone regeneration *in vivo* when used for cranial defects in rats (Xu et al., 2023a). Also, a scaffold made of immobilizing exosomes from human bone mesenchymal stem cells onto polymer meshes developed by PLGA and Cu-based MOF resulted in controlled release of copper ions and exosomes that promote osteogenesis and angiogenesis (Xu et al., 2023a). These studies point to the promise of nanocomposite scaffolds in the application of bone regeneration and tissue engineering (Moris et al., 2024). The fabrication method chosen not only governs the final structure, morphology, and properties of the MOF-based scaffold but also consequently determines its interface and interactions with cells and tissues, guiding its overall performance in promoting tissue regeneration. For example, when melt electrowriting is used to incorporate MOFs into polycaprolactone scaffolds, an ordered microfibrous PCL scaffold embedded with MOFs is created (Kong et al., 2024a; Mansi et al., 2024). Although the preliminary findings are promising, it is vital that any forthcoming studies focuses on assessing the safety of MOFs, clarifying mechanisms of dose-

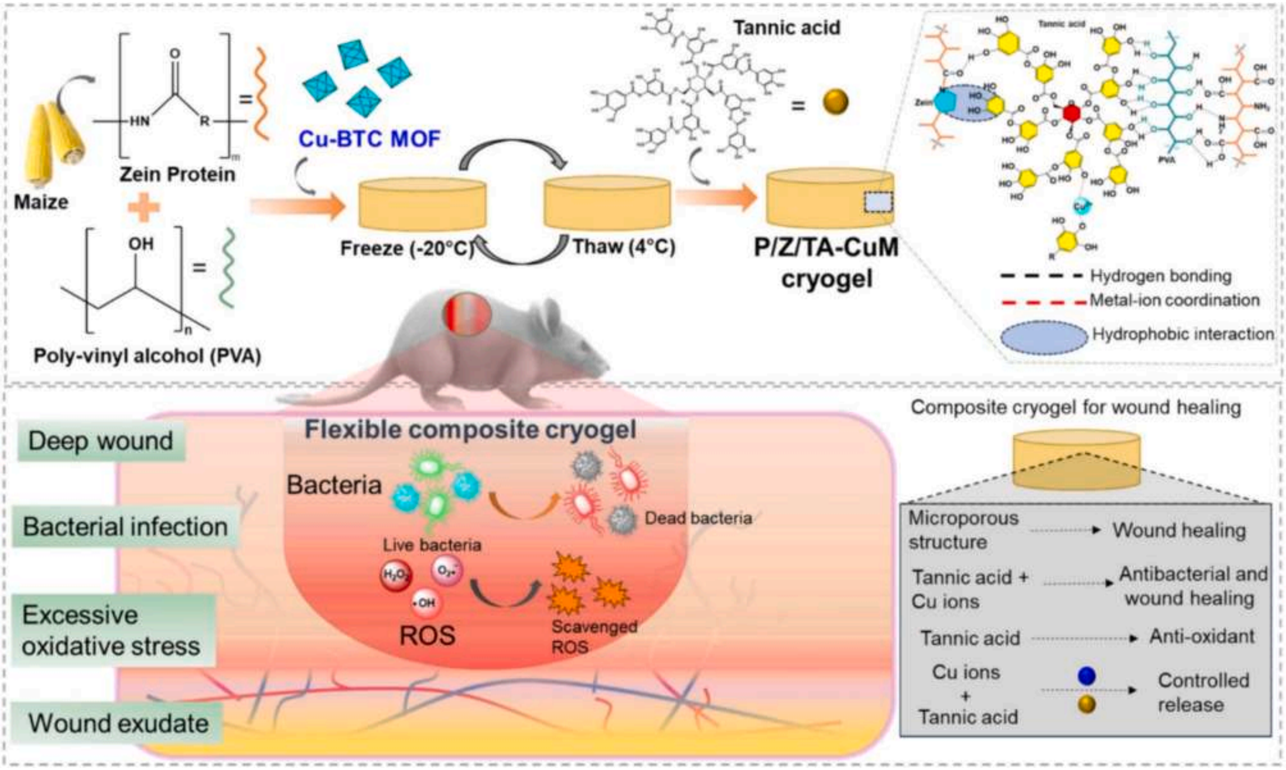

Fig. 2. Illustrations of the fabrication of composite cryogels containing MOF, properties, and their potentials for wound healing. A multifunctional composite cryogel based on Cu-MOF, tannic acid, polyvinyl alcohol, and zein protein was developed demonstrating powerful antimicrobial, antioxidant, and biodegradable properties, high biocompatibility, controlled ion release, and ability to accelerate wound healing, suggesting an advanced wound dressing that has many potentials to expedite its clinical applications. “Reprinted with permission from (Singh et al., 2024). Copyright (2024) Elsevier B.V.”

dependent responses, and accelerating the translation of these findings into clinical applications, thereby confidently unleashing their potential to tissue engineering.

5.4. MOFs in immunotherapy

The application of MOFs in immunotherapy primarily revolves around their ability to effectively deliver immune-modulating agents, particularly in cancer. One significant aspect is their capacity to co-deliver enzymes such as glucose oxidase and inhibitors such as indoleamine 2,3-dioxygenase inhibitors. The combination of these agents can amplify the immune response against tumors by addressing metabolic needs and inhibiting the pathways that suppress immune activity. By combining starvation therapy with immune checkpoint blockade strategies through indoleamine 2,3,dioxygenase inhibition, studies aim to create a synergistic effect that enhances anti-tumor immunity while simultaneously targeting tumor metabolism (Dai et al., 2022). MOFs have significant potential to improve therapeutic outcomes in cancer therapeutics through enhanced immunogenic cell death mechanisms. MOFs can serve as intelligent nanoadjuvants by delivering therapeutic agents that promote immunogenic cell death, while also modulating the tumor microenvironment by lactic acid metabolism and relieving the immunosuppressive tumor microenvironment (Hu et al., 2024a). In a study, a pH-responsive MOF nanosystem with iron and manganese was developed to combine pyroptosis with augmented immunotherapy. The system disintegrates and releases metal ions, thereby initiating Fenton-like reactions for reactive oxygen species (ROS)-mediated pyroptosis. This release induces proinflammatory cytokines and immunogenic constituents, promoting anti-tumor immune responses, and activates the TLR7/8 pathway. An acid-responsive Fe/Mn bimetal-organic framework nanosystem (FeMn@R@H) based on pyroptosis-mediated programmed cell death and enhanced immunotherapy was reported. Upon release of metal ions and immune adjuvant R848 in the acidic tumor microenvironment, the pyroptosis induction, ROS-mediated immunogenic cell death, and TLR7/8 activation orchestrated a rich complementary antitumor immune response (Fig. 3) (Feng et al., 2023). In addition, immune cell membrane-coated MOFs exhibit immune cell-like behaviors such as stealth, targeting, and immunomodulation (Ding et al., 2023). An MOF-based nanoplatform for atherosclerosis, combination therapy with rapamycin and IL-1Ra, is another example of the use of MOF in inflammatory conditions (Xu et al., 2023c).

5.5. MOFs in neurological disorders

Neurotherapeutics face several critical obstacles, including limitations in diagnosis, crossing of the BBB, off-target treatment effects, inflammatory responses coupled with oxidative stress, and irreversible nerve cell death. Recent research has highlighted the potential of MOFs to address several neurological conditions, particularly stroke and neurodegenerative diseases. MOFs can be engineered to be sufficiently small to facilitate passive diffusion through the BBB. Additionally, surface modifications with targeting ligands can enhance their ability to bind to receptors on endothelial cells, thereby promoting receptor-mediated endocytosis (Nabipour and Rohani, 2024a). Through the receptor-mediated transcellular pathway, the transferrin-coated MOF NPs achieved efficient transport across the BBB and targeted accumulation at the cerebral ischemic injury site in mice, wherein the nanocarrier exhibited catalytic activities for ROS scavenging (Chen et al., 2024a). High boron content MOF nano-co-crystals were engineered for precise boron neutron capture therapy of brain gliomas, offering excellent stability, biocompatibility, blood–brain barrier penetration, and selective tumor targeting (Fig. 4). These MOF nano-co-crystals also exhibited intrinsic fluorescence and PET imaging capabilities, enabling precise localization and high antitumor efficacy in glioma-bearing mice

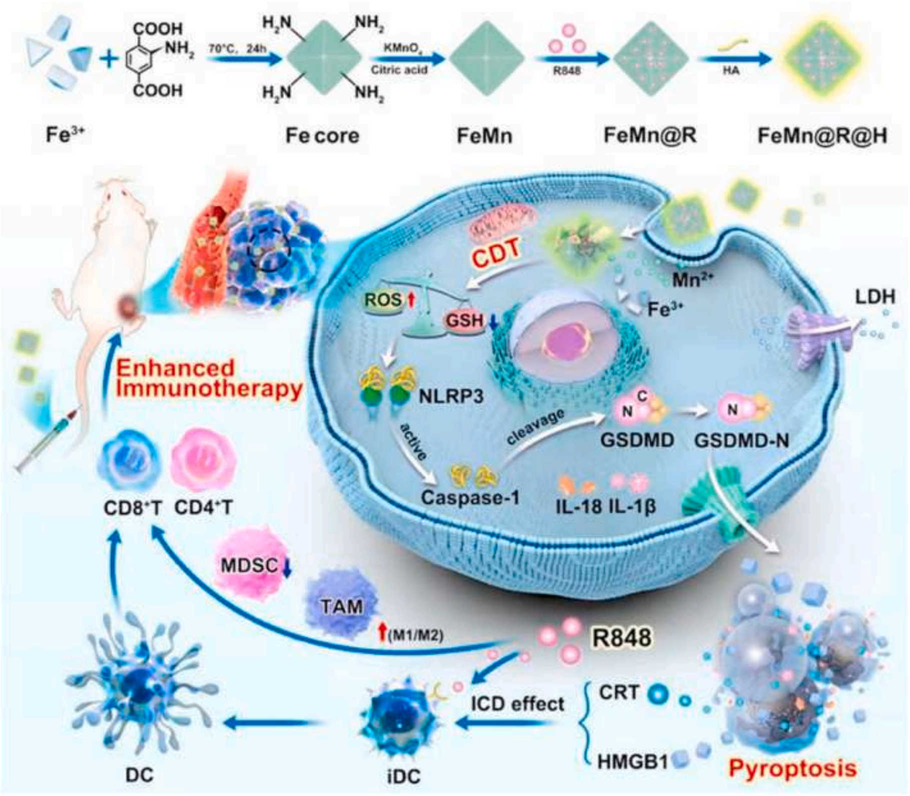

Fig. 3. Illustrations on the synthesis and molecular mechanism of an acid-responsive Fe/Mn bimetal-organic framework nanosystem (FeMn@R@H) against tumors, showing its dual function of inducing pyroptosis by ROS-mediated therapy and activating caspase-1, while further enhancing immune-regulation by ICD-triggered DC maturation alongside R848-mediated immunosuppressive cell downregulation. "Reprinted with permission from (Feng et al., 2023). Copyright (2023) Elsevier Ltd.".

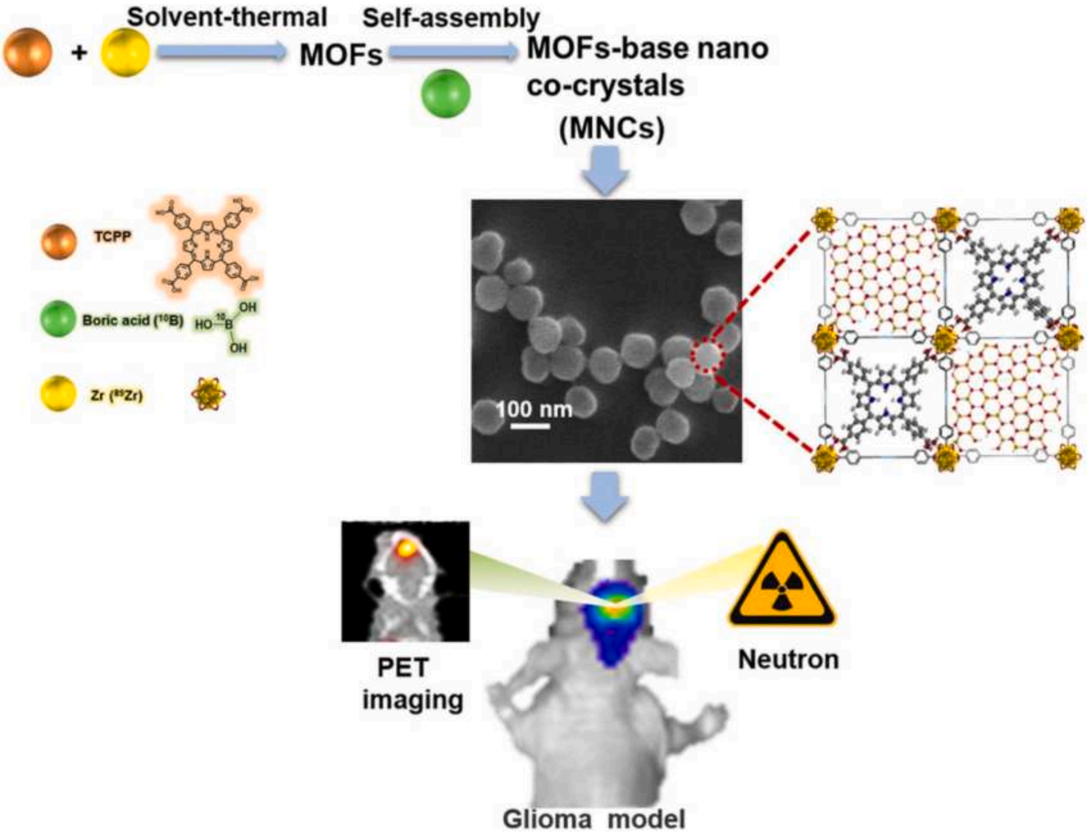

Fig. 4. Illustrations on the design strategy, function, and brain glioma therapeutic mechanism of high boron content MOF nano-co-crystals. "Reprinted with permission from (Z. Wang et al., 2022). Copyright (2022) Elsevier Ltd.".

(Wang et al., 2022b).

In another example, a neutrophil membrane-coated MOF nanozyme offers a promising avenue for disrupting the malignant cycle associated with Alzheimer's disease through the targeted modulation of amyloid β deposition and inflammation (Liu et al., 2024). MOF-based nanozymes can effectively scavenge ROS and alleviate oxidative stress in patients with stroke. Some studies demonstrated that cerium oxide nanoparticles, embedded in a ZIF-8 framework, can significantly enhance antioxidant activity and reduce the neuronal cells' damage during ischemic insults (He et al., 2020). MOFs were also shown to be useful for diagnosis of neurological disorders. MOF-based sensors have been designed for use in the diagnosis of Alzheimer's, Parkinson's, and other amyloid diseases (Leite et al., 2023). MOFs can be employed as contrast agents for neuroimaging because of their ability to encapsulate imaging agents (Niu et al., 2023).

6. Hybrid MOF-based DDS

The trend of combining functional materials has been driven by the growing need for improved features and functions. When different functional materials are combined with MOFs, they often exhibit synergistic effects that enhance the overall performance beyond what each component can achieve individually, as well as surpass the limitations of the individual components (Table 3). A composite material of MOF may show improved catalytic activity owing to interactions between the active sites in both components that facilitate reaction pathways more efficiently than either component alone (Zhu and Xu, 2014). Techniques for covalent post-synthetic modification and coordinative post-synthetic modification, in which organic molecules are bound to unsaturated metal sites and organic linkers are assigned functional groups, respectively, can be used to tailor MOFs to accommodate polymers or biomacromolecules, such as lipids or nucleic acids, to the surface of MOF crystallites.

6.1. MOF-polymer composites

The integration of polymers with MOFs that leverage the unique properties of both components and can be achieved primarily through different approaches such as polymer coating, encapsulation, and dispersion in the matrix (Hosono and Uemura, 2021a). A biocompatible polymer coating on the drug-physisorbed MOF attains a core–shell architecture that can impart stability, add targeting functionalities, or introduce a stimuli-responsive release, imparting improved drug delivery and sustained release of the drug (Yadav et al., 2023). Polymer encapsulation inside MOF pores is based on *in situ* polymerization of monomers in MOF nanochannels (Hosono and Uemura, 2021b). The formation of polymer-MOF composite gels is also influenced by both the physical trapping of polymers within MOF pores and chemical interactions between polymers and metal clusters, which could be based on covalent interactions or involving end-functionalized polymers reacting with MOF functional groups. Concurrent gelation and MOF synthesis were made possible by the selection of polymers with functional groups that engage the metal nodes of MOFs without rivaling the organic linkers and without degrading the porosity. It is possible to synthesize these materials using either top-down or bottom-up methods (Verma et al., 2024). Blending MOFs into a polymer matrix permits the structuring of MOFs and enhances the performance of mixed matrix membranes (MMM) formed by resolving the inherent permeability-selectivity paradox. However, there are problems with void formation and uneven dispersion in polymer matrices. In the composite, the primary functional element that controls the overall performance of the membrane is the MOF filler in the MMM; thus, it is desirable to increase the loading amount of MOF crystals in the MMM. In addition, excessive MOF loading can cause brittleness and agglomeration, making handling

Table 3
Applications of some important hybrid metal organic framework (MOF) composites.

MOF	Non-MOF component	Obtained results	[Ref.]
UiO-67	Polyurethane	Improved adsorption capacity of the polymer matrix, prolonged release of ocular drug	(Gandara-Loe et al., 2020)
ZIF-8	Poly (styrene-maleic anhydride-N,N-dimethylaminoethyl methacrylate-spiropyran); Bacterial cellulose-based hydrogel; Copper NPs; 1,2-dipalmitoyl-*sn*-glycero-3-galloy	Encapsulation of enzyme, stability and high catalytic performance; Favorable mechanical properties and swelling ability for antibacterial wounds; Enhanced antibacterial activity; Structural integrity and porosity retained	(Jabeen et al., 2024) (Deng et al., 2023) (Kumar et al., 2021) (Zhu et al., 2018)
HKUST-1, ZIF-8, MIL-100, ZIF-67	Alginate	Improvement of absorbent properties and tunability of macroscopic shape of the composite	(Zhu et al., 2016)
ZIF-8-Glucose Oxidase	Poloxamer 407 Poloxamer 188 HPMC	In situ gel formation, glucose-sensitive insulin delivery	(Liu et al., 2022)
UiO-66 and UiO-67	Poly(ε-caprolactone) with d-α-tocopheryl polyethylene glycol succinate polymeric matrix	Better anticancer activity compared to free drug alternatives	(Filippousi et al., 2016)
MOF 808	poly(acrylic acid-mannose acrylamide) glycopolymer	Increased and selective uptake of the NPs in cancer cells Dual drug delivery	(Demir Duman et al., 2022)
MIL-100	Chitosan 1,2-dioleoyl-*sn*-glycero-3-phosphocholine	Enhanced cellular penetration in breast cancer cells facilitates stealth endolysosomal uptake	(Quijia et al., 2024; (Ploetz et al., 2020))
Magnesium-Gallic acid MOF	Poly(lactic-co-glycolic acid)	Slow-release of components	(Kang et al., 2022)
Ag-MOF	Sodium Alginate	Reduced biotoxicity and slower release of Ag^+ ions	(Xu et al., 2024a)
Ce-MOF	Polydopamine	Nanozyme activity	(Duan et al., 2023)
Ti-MOF	Silver NPs	increased ROS production, improved antibacterial efficiency through synergistic chemical-PDT	(Zhan et al., 2024)
Cu-MOF	Silver NPs	Improved antibacterial effects	(Gao et al., 2024)
Zr-MOF	Iron oxide-platinum nanospheres	Potential drug loading and cell penetration, tumor microenvironment-triggered drug release in breast cancer cells	(Li et al., 2023)
Dual MOFs (ZIF-8/ZIF-67)	Superparamagnetic iron oxide NPs	Specific targeting of folate receptor overexpressed in tumor cells	(Pandit et al., 2022)

the composite membrane challenging (Ma et al., 2022b). Ultra-high molecular weight polyethylene was successfully used as the polymer matrix in an attempt to address these polymer issues, as was the case with other innovative methods that achieved uniform dispersion of MOF particles in the matrix (Alshurafa et al., 2024; Hussain et al., 2020).

6.2. *MOF-lipid nanocarriers*

When MOFs and lipid NPs are combined, a flexible platform is produced that improves drug loading capability, offers controlled release, boosts stability, improves cellular uptake, lowers cytotoxicity, and permits therapeutic functionalization. On NU-901 MOFs, a bilayer coating of lipids and surfactants has delayed drug release, causing a delayed cytotoxic effect in cancer cell models and possibly allowing for less frequent drug dosing (X. Liu et al., 2024a). In addition, extracellular vesicles and erythrocyte membranes, which possess a lipid bilayer with inherent biocompatibility, can convert MOFs into biomimetic ones that would help the carrier, especially when dealing with the BBB and other physiological barriers (Wang et al., 2024b). Compared to liposomes, which have an aqueous core rather than a porous MOF core, they are theoretically expected to be substantially more stable. MOFs with a lipid bilayer coating enhance drug delivery efficacy by increasing uptake by cells or even by crossing the blood–brain barrier, opening new avenues for drug delivery (X. Liu et al., 2024b; Nabipour and Rohani, 2024b).

6.3. *MOF-metal nanoparticle conjugates*

The advantages of MOF-metal nanoparticle composites, where MOFs act as supports for uniformly dispersed metal NPs, include enhanced surface area and porosity, improved catalytic activity, versatile functionalization options, increased stability and durability, enhanced electrical conductivity, synergistic effects in energy applications, and potential for advanced applications across various fields. MOF incorporating metal and metal oxide NPs exhibiting a variety of nanozyme activities that render them advantageous for a wide range of scientific and industrial applications have been of interest (Sen et al., 2024). Researchers have successfully enhanced the control over the spatial distribution of metal NPs within MOFs by employing strategies such as optimizing ligand concentrations during crystallization and utilizing sacrificial templates. This control is pivotal for effectively exploiting synergistic effects, leading to improved performance in various applications (Qin et al., 2022).

6.4. *MOF-hydrogel systems*

Hydrogels are pliable, soft polymers with high water content that are ideal for use in biomedical processes such as wound healing; hence, MOF-hydrogel composites have been extensively explored for this purpose (Fan et al., 2024; Lian et al., 2024; Yang et al., 2024b; Zhang et al., 2023b). The water absorption and penetrability of hydrogels are due to their polar groups because of the construction of a flexible polymer network thus focusing on metal-ion adsorption due to interaction with functional groups provided. It functions as nucleation and growth anchoring sites to MOF proving its well-thought-out architecture of an effective wound dressing system (Li et al., 2023a,b,c). The mechanical strength, swelling behavior control, thermal stability, structural integrity, release profiles, porosity, diffusion properties, and compatibility with biological systems were improved by MOF-based hydrogels. Studies have discovered that instead of external crosslinking agents, MOF NPs can serve as strong crosslinks, serving as templates around which polymer chains grow during polymerization and toughen the physical hydrogels, highlighting the importance of cross-linking agents in preparing MOF hydrogels for stable network structure formation (Wang et al., 2022a). Nevertheless, MOFs frequently suffer from hydrolytic instability that can cause disintegration, which in turn hinders their combination with hydrogels. To overcome this, water-stable MOFs such as those containing robust metal–ligand linkages derived from high-valent metals have also been developed (Lim et al., 2023). A three-dimensional zeolitic imidazolate framework-8 (ZIF-8)/polysaccharide (sodium alginate-kappa-carrageenan, SC) hydrogel beads, prepared via phase inversion based on an in situ one-pot method demonstrated excellent mechanical performance which grant the feasibility of development of cargo delivery in biomedical applications as well (Fig. 5) (Chai et al., 2022).

7. Stimuli-responsive MOFs in drug delivery

Stimuli-responsive MOFs encoded with structural information respond dynamically to specific environmental triggers, including chemical stimuli such as pH changes, ions, redox conditions, and physical stimuli such as light, heat, or magnetic fields, which trigger drug release (Shen et al., 2024c). Fig. 6 illustrates the mechanisms of stimuli-responsive MOFs in drug delivery systems.

7.1. pH-responsive MOFs

While cancer therapy (Yang et al., 2024a) remains a prominent application area for pH-responsive MOFs in DDS, there is a growing research interest in exploring their utility across various medical fields, including antibiotic therapy (Wang et al., 2024a), anti-inflammatory treatments, gene therapy (Zhang et al., 2023e), vaccine delivery, enzyme stabilization, and hormonal therapies. Upon exposure to an acidic environment (typically around pH 5.0 or lower), certain functional groups within the MOF may become protonated, and leaching of metal ions from the MOF at acidic pH can also add to the structural breakdown of the MOF, which can be exploited wisely by using a proper choice of metal ions and organic linkers to develop a pH-responsive drug delivery system. Acidic pH levels increase the hydrogen ion concentration, leading to protonation of the functional groups on the MOF structures. Typically, MOFs contain carboxylate or amine groups that can be protonated, causing them to change from a neutral to a positively charged state, affecting the overall charge balance (Raza and Wu, 2024a).

7.2. Light-responsive MOF

Photo-responsive MOFs, with their unique structural characteristics and photoelectronic properties, are being used in various applications, such as tumor bioimaging, photothermal therapy, and photodynamic therapy. The development of these MOFs requires a solid understanding of the structure–property links and crystal engineering. These MOFs, which are typically made from Mn and Au, can produce toxic ROS when irradiated, leading to cell death and tissue lesions. Stimuli-responsive MOFs can be created by selecting appropriate metal ions with inherent photochemical properties and integrating them into framework design. Plasmonic metals such as gold and silver can provide dual functionality: structural integrity and the photothermal effect induced by the metal. When irradiated with light at specific wavelengths, these composites absorb energy and generate localized heat, which can induce changes in the MOF structure or disrupt the interactions between drug molecules and the framework, accelerating the release of therapeutic agents (Kong et al., 2024b; Lelouche et al., 2022; Shelonchik et al., 2024). Methods such as the use of organic ligands bearing photoactive units or post-synthetic modifications of MOF with photoresponsive agents have also been applied for the preparation of photoresponsive MOFs. MOFs incorporating spiropyrans at controlled positions can modulate ionic conductivity and hydrophilicity in response to light stimuli, opening new avenues for smart DDS (Greussing et al., 2022).

7.3. Redox-responsive MOFs

Redox activity, develops through the insertion of redox active sites into the MOFs, which then utilizes the differences in redox potential between normal and pathological environments, particularly in cancerous tissues for drug release, usually owe it to the higher GSH concentrations compared to normal tissues (Razavi et al., 2024). The redox-responsive mechanism typically involves the incorporation of

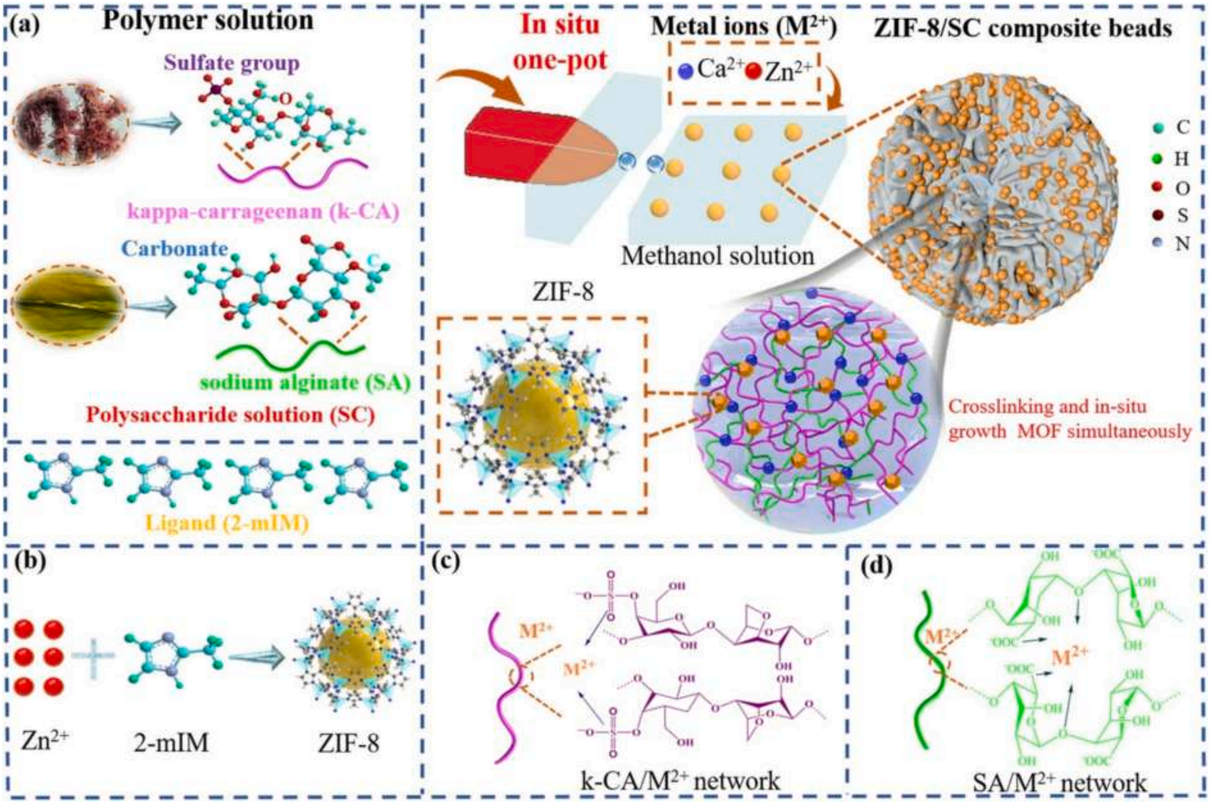

Fig. 5. Illustrations on the preparation of (a) ZIF/ sodium alginate-kappa-carrageenan composite beads, (b) ZIF-8, (c) kappa-carrageenan /M^{2+} network, and (d) sodium alginate /M^{2+} network. “Reprinted with permission from (Chai et al., 2022) Copyright (2022) Elsevier B.V.”.

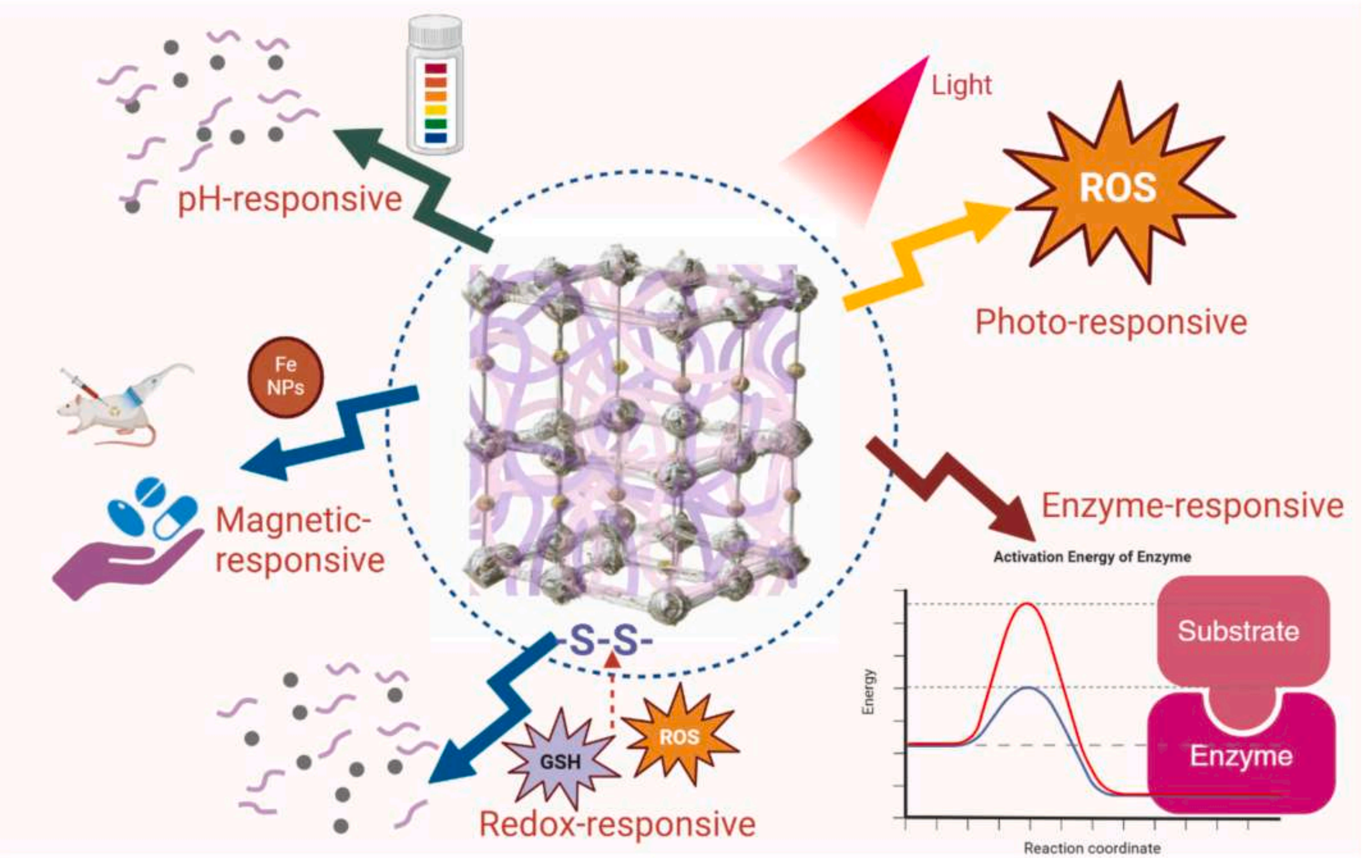

Fig. 6. Illustration depicting the mechanisms of stimuli-responsive MOFs in drug delivery systems, highlighting their adaptability to various stimuli such as pH, temperature, light etc. for controlled release of therapeutic agents.

disulfide linkages into the framework or on the MOF surface. For example, 4,4-dithiobisbenzoic acid can be used as an organic ligand because of its disulfide bond, which is susceptible to reduction by GSH via a thiol-disulfide exchange reaction, leading to structural changes that facilitate drug release (Meng et al., 2024a). A study developed a self-sufficient chemodynamic anticancer agent, CaO2-DOX-CuMOF/PEG, which disintegrates in response to GSH and releases doxorubicin, promoting H_2O_2 formation and reactive oxygen species generation in cancer cells (Chatterjee et al., 2024). Oxidation-responsive immunotherapy strategy of polymeric MOF NPs for combination photodynamic and immunotherapy with enhanced activation of STING (Stimulator of interferon genes), by STING agonists (SR-717) (Zhou et al., 2023a), BRAP, a hydrogen peroxide-activatable antioxidant prodrug, was used in a novel H_2O_2 responsive covalent cyclodextrin framework for effective inflammatory bowel disease therapy (Huang et al., 2022) adds to the attempts to develop a redox-responsive MOF. Redox-responsive DDS are a promising strategy for treating Alzheimer's disease and other neurodegenerative disorders.

7.4. Enzyme-responsive MOFs

Enzyme-responsive MOFs function by integrating the framework with particular ligands that can interact with the kinds of enzymes found in biological environments or post-synthetic modifications with enzyme-susceptible groups. Despite the exploration of enzyme-responsive MOF, little is known about their potential for drug administration. A study on MOF-based micronutrient supply for crops and pesticide delivery found that zein, a protease-susceptible peptide, can be utilized as a protease response system, suggesting that functionalized MOFs can improve therapeutic outcomes (Ma et al., 2022c).

Employing a lipase-sensitive crosslinker in the polypeptide outer shell of the nanocomposite integrated with a ZIF-containing antibiotic resulted in the degradation of the MOF in response to lipase (Xiang et al., 2023). For the PDT-based elimination of MRSA, photosensitizer indocyanine green delivery in ZIF-8 coated with hyaluronic acid was attempted as a targeted delivery mechanism because it combines with CD44, which is overexpressed on the surface of many types of macrophages. Hyaluronic acid chains can be degraded by hyaluronidase, which is present in the infection microenvironment, thus exposing the wrapped indocyanine green for bacterial infection treatment (Xu et al., 2024b). Another study demonstrated the controlled drug-release capability of nanosized UiO-66 functionalized with N3–PEG–PO3 ligands. It has the potential to integrate any additional functionalities and render the framework susceptible to intracellular ALP, cleaving the phosphate ester bond between the PEG ligand and the MOF surface (Carrillo-Carrión et al., 2023). In an attempt to develop a smart drug delivery system for cancer drug delivery, based on the principle of conjugating drug with enzyme sensitive peptide, different MOFs as a drug carrier was assessed utilizing computational analysis. Among the three MOFs were investigated using an optimized prodrug concentration in microfluidic and bulk systems, ZIF indicate the best condition for microfluidics loading of doxorubicin peptide prodrug (Fig. 7) (Dahri et al., 2022).

7.5. Magnetic- responsive MOFs

Magnetic responsive MOFs integrating magnetic NPs, such as magnetite (Fe_3O_4), maghemite (γ-Fe_2O_3), and some ferrite colloids in the matrix are promising frontiers in materials science, offering advanced structural properties and functional versatility. Their physicochemical properties are tuned for various applications including drug delivery, magnetic hyperthermia, MRI etc. Combining these properties with those of MOFs makes them suitable for advanced drug delivery,

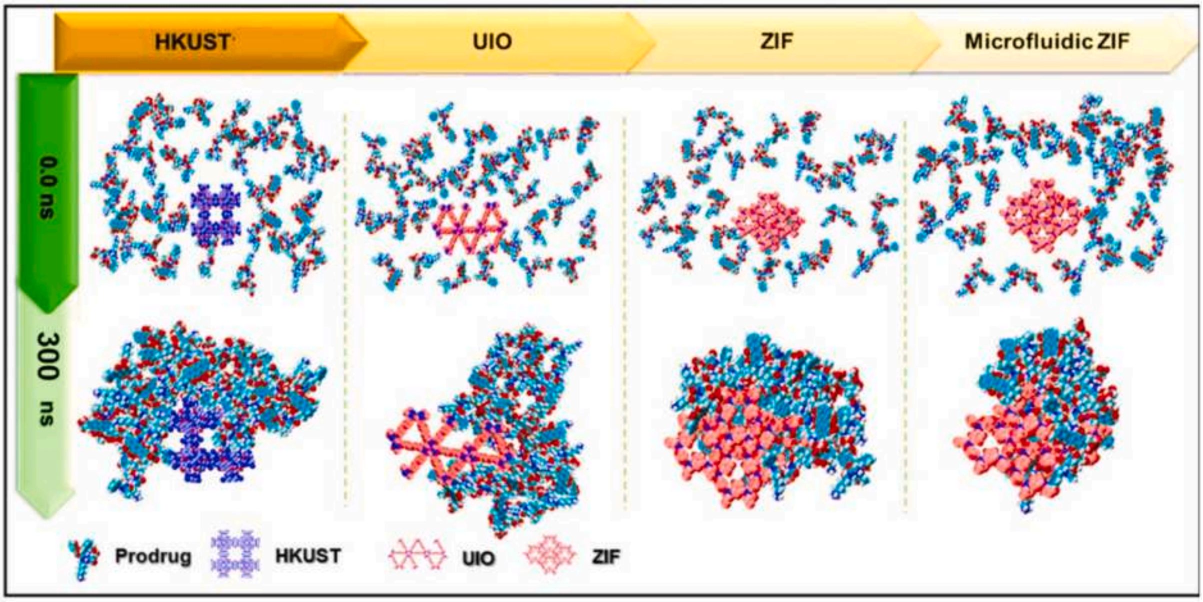

Fig. 7. Illustrations on the in silico interactions of doxorubicin-short peptide conjugates for enzyme-responsive delivery with various MOF carriers. "Reprinted with permission from (Dahri et al., 2022). Copyright (2022) Elsevier Ltd.".

biosensing, bioimaging, and MRI contrast agents (Picchi et al., 2024). The design of the MOF topology is crucial for achieving the desired magnetic properties. This involves considering how the selected metal ions and organic linkers assemble into a three-dimensional structure. An example is MOF-decorated iron-gold alloy NPs encapsulating doxorubicin, which generates hyperthermia upon magnetic field stimulation, triggering oral cancer cell apoptosis (Dhawan et al., 2023). While different types of stimuli may induce independent responses in MOFs, there is evidence suggesting that multi-stimuli-responsive MOF can show interactive synergism (Chen et al., 2023a).

8. MOF stability and degradation in biological environments

The stability of MOFs is paramount when considering their use in biological systems because they may encounter various conditions such as pH changes, enzymatic activity, and the presence of different ions or

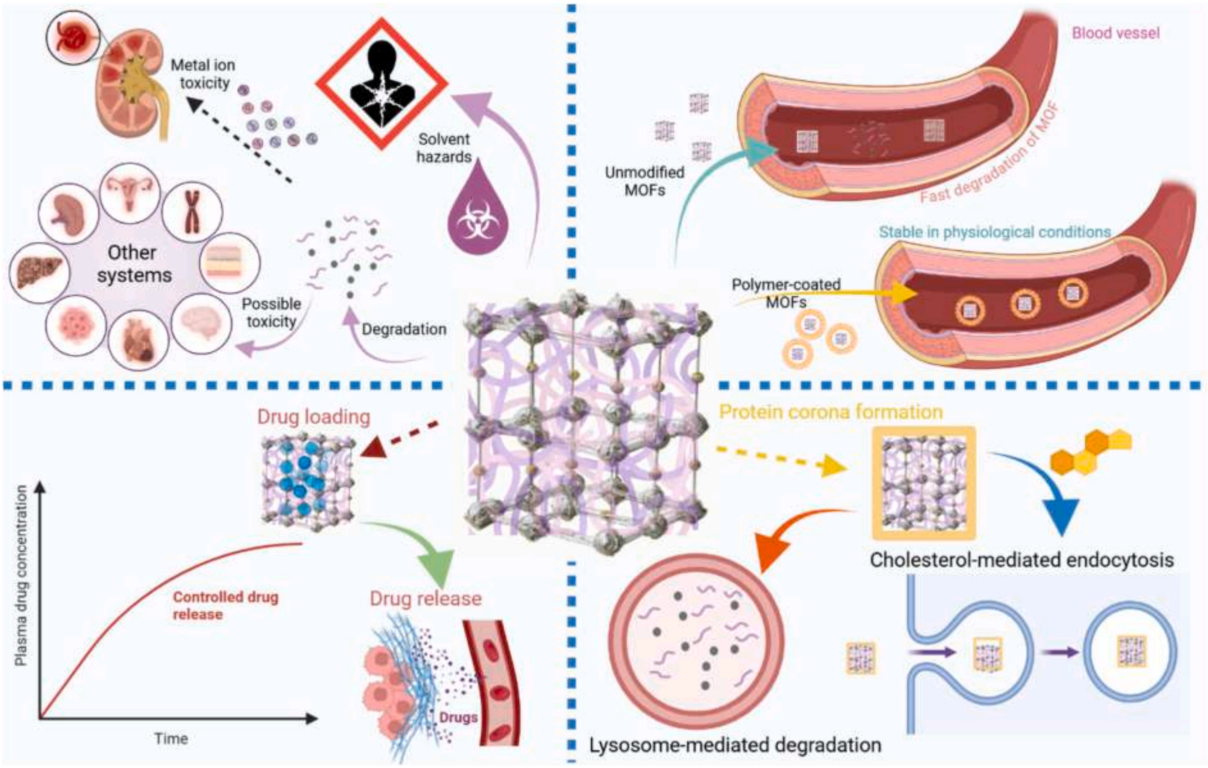

Fig. 8. Illustration depicting the mechanisms of stability and degradation of MOFs in biological environments, highlighting factors influencing structural integrity and functional performance.

biomolecules. Owing to the comparatively weak coordination bonds, degradation of the framework structure and release of toxic metal ions into the surrounding environment occur, which significantly limits their practical applicability. As depicted in Fig. 8, the knowledge of the subtle balance of stability and degradation of MOFs in biological settings plays an important role for developing effective biomaterials for drug delivery. Since divalent metal ions with carboxylate bonds are inherently unstable in aqueous solutions or humid air, the early studies on MOF utilizing Cu^{2+} and Zn^{2+} subsequently shifted towards the design of stable MOFs, employing reagents with a higher valency (Kulkarni et al., 2024). The stability of MOFs relies chiefly on the strength of their coordination bonds with protective groups providing surrounding strength. The incorporation of certain organic linkers can enhance the chemical stability of the MOFs against hydrolysis and other chemical reactions that can occur in biological fluids. Recent research has indicated that a judicious modification of the ligand structure can significantly enhance the stability of these frameworks under biological conditions (Mosca et al., 2023). Thermal stability is another important aspect to consider when evaluating the performance of MOFs in biological settings. Many biological processes operate within a specific temperature range; therefore, it is essential for MOFs to maintain their structural integrity at these temperatures. Some studies have demonstrated that certain Zr-based MOFs possess excellent thermal stability (Lai et al., 2024), a benefit for applications that generate heat or expose materials to higher temperatures.

8.1. *Stability in physiological conditions*

Experimentally, the stability of MOFs can be deduced from PXR, BET, and TGA. MOFs with high coordination numbers are highly stable (Abid et al., 2024). The Corrosive effect of water molecules on coordination bonds is related to thermodynamic factors such as the oxidation state of metals and metal properties. It can be reduced by providing some steric hindrance by rendering it hydrophobic and functionalizing with groups such as alkyl and methyl groups (An et al., 2024). A method to thermally stabilize MOF-808 via post-synthetic modification by adding benzoate functional group into its framework was also developed (Aunan et al., 2021). The creation of interpenetrated structures can provide additional mechanical strength and resistance to collapse under stress or environmental changes (Zhao et al., 2024b). For instance, as an approach for the controlled and sustained release of ciprofloxacin, a study was conducted using porous Zr-based MOF- polycaprolactone composite (Aden et al., 2023). Further, *in situ* polymerization on MOF NPs forms a protective polymer coating, preventing decomposition by phosphate ions or acid and stopping cargo leakage. According to PET imaging studies, polymer-coated MOFs have prolonged circulation time and higher tumor accumulation than unmodified MOF NPs (Liu et al., 2019). Another strategy comprises embedding luminescent dyes within ionic MOFs via dimensional confinement and electrostatic interaction. This combination has generated composites with extraordinary aqueous stability and biocompatibility proper for biological applications (Wan et al., 2018).

8.2. *MOF degradation mechanisms*

MOFs with a crucial size of less than 200 nm can enter the bloodstream through various routes. They interact with biological fluids, forming a "protein corona" that influences cell recognition and internalization. MOFs must penetrate target cells via endocytosis, which is a cholesterol-dependent process. The specific pathway is dictated by the particle size and shape, surface chemistry as well as cell type. MOFs are transported in vesicles upon fusion with organelles, and their fate thereafter depends on their ability to escape before degradation in the lysosomes. The degradation rate of MOFs is paramount for their activity as DDS. Once degraded and emptied from active circulation, fragments might be removed via renal filtration or by macrophages and excreted via urine or feces (Chen et al., 2024b; Linnane et al., 2022; Oh et al., 2024).

8.3. *Controlled release kinetics*

The kinetics of drug release from MOFs are described using mathematical models such as zero-order kinetics, first-order kinetics, and Higuchi kinetics. Factors such as structure, drug-MOF interactions, and complex release mechanisms can influence kinetics. The control of drug release is primarily determined by the properties of the framework, such as pore size, chemical composition, stability, and environmental factors. The design can be tailored for specific controlled delivery using functionalization, stimuli-responsive systems, composite materials, and drug-loading methods (Gautam et al., 2023; Mhettar et al., 2023). In most cases, the pore size of the MOFs plays the key role in drug release by affecting its loading capacity, release kinetics, and characteristics of surface area. The University of Miami produced nanoscopic DDS by minor modification of the methodology of synthesis of an already existent chromium-containing MOF with acetic acid to yield enlarged pores. This, in turn, provided an enhanced surface area and the availability of pores for faster drug loading and release so as to allow more efficient absorption of ibuprofen and 5-fluorouracil molecules. Such is the way by which slight alterations in pore size may help us achieve the kinetics of interest in drug release (Pederneira et al., 2024).

The way in which MOFs were characterized is based on the effect of their chemical composition on drug release mechanisms. This is also influenced by hydrophilicity/hydrophobicity; pore structure; chemical stability; and the most preferred factor, drug-MOF interactions. The various organic ligands have each their own advantages and disadvantages, and consequently, such effect on drug release is well reported (Yan et al., 2024). Stimulus responsiveness of MOF is another method for the controlled release of drugs. An MOF-based magnetic microrobot swarm for targeted therapy has been developed using ZIF-8 as a pH-responsive drug vehicle. Incorporating the magnetically responsive components allows this design to be immediately transformed under the influence of an external magnetic field. Entailing an assembly of magnetic microrobots entering the tumor site, degrading automatically, and releasing the drug, these are capable of minimizing the tumor *in vivo* (Cao et al., 2024). The effect of MOF composites on controlled drug release kinetics is multifaceted, involving structural characteristics, chemical interactions with drugs, environmental conditions, and composite properties, which together determine the effective delivery of drugs over time. A composite of a sodium alginate hydrogel matrix and curcumin-loaded ZIF-8 MOFs was constructed for extended drug release and antimicrobial activity in wound healing (Li et al., 2023a,b,c). The introduction of functional groups into MOFs significantly affects controlled drug release kinetics by enhancing the drug loading capacity through improved interactions, altering diffusion rates via changes in hydrophilicity/hydrophobicity, facilitating degradation processes that promote faster release, and enabling tailored responses to environmental stimuli. Using oridonin as a model drug, the same MOF with the introduction of different functional groups and its effect on the drug delivery performance of isoreticular MOFs were compared (Cai et al., 2020). The choice of drug loading method in MOFs has profound implications for drug release behavior; hydrothermal synthesis yields MOFs with high crystallinity, while solvothermal synthesis results in MOFs with increased porosity (Chiñas-Rojas et al., 2024b), all of which in turn affect overall stability.

8.4. *Toxicity and clearance mechanisms*

MOFs, despite their promising drug delivery mechanisms, face some potential challenges and limitations, specifically concerning their toxicity. The toxicity of MOFs is mostly due to the degradation of metal ions and functional groups in the organic ligands and is influenced by several factors such as the proportion of materials used, physicochemical properties etc. Smaller MOFs can bypass physiological barriers and reach in specific tissues or organs, leading to toxicity. Some MOFs can undergo degradation into metal ions and organic linkers within the body, which can then be cleared by renal or hepatobiliary systems or metabolized. The rate of degradation depends on the stability of the MOF in biological environments. MOFs with bio-responsive properties (e.g., pH-sensitive or enzymatically degradable linkers) may degrade faster, and their byproducts can be more easily excreted (Ettlinger et al., 2022; Raza and Wu, 2024b). In this context, the safety of MOFs can be improved by properly controlling their size, assessing the toxicity of metals based on lethal and daily doses, modifying ligands through functionalization, and using a biocompatible solvent system. The use of endogenous molecules as organic linkers and the selection of important elements such as iron, zinc, and magnesium, all of which are vital to the organism as metal nodes, could improve the overall safety of MOF building provided that stability and porosity are maintained (Singh et al., 2021). Replacing the methods of synthesis of MOFs with toxic organic solvents, we can use solvent-free synthesis methods or polar solvents such as water (Binaeian et al., 2023).

The cytotoxicity of the MOFs is governed by such factors as size, surface charge, and the specific types of interactions between themselves and the cells, particularly via the release of metal ions or organic ligands. In order for MOFs to become useful for cancer treatment, they ought to selectively target cancer cells while sparing normal cells and include controlled drug release mechanisms, biocompatibility, and comprehensive *in vivo* studies exploring potential combination therapies. These actions are essentially favorable to the development of safe and effective treatments that enhance the good while minimizing the toxicity (Farasati Far et al., 2023; Khan et al., 2023). For example, the topical gel formulation incorporated ZIF-8 loaded with 5-FU and sonidegib for skin cancer therapy (Padya et al., 2023). In addition, molecular dynamics simulations were also utilized to design MOFs as nanocarriers for chemotherapeutic drugs such as cisplatin to facilitate a drug delivery mechanism directed toward tumors (Mashayekh et al., 2024).

9. MOFs as theranostic agents

The ability of MOFs to integrate various functionalities makes them highly suitable for theranostic purposes by enabling simultaneous diagnosis and treatment through advanced DDS and imaging capabilities. This integration can involve the encapsulation of therapeutic agents, imaging agents (contrast agents), or even targeting moieties that allow specific delivery to diseased tissues (Petrovic et al., 2024). Certain MOFs can be designed for the triggered release of cargo in the pathological microenvironment, thus enhancing drug delivery specificity by functionalizing their surface with targeting ligands. Such MOFs can be designed to also incorporate imaging agents, like dyes or radionuclides, for real-time monitoring of drug distribution and efficacy. This combination of therapeutic activity and diagnostics is a key aspect of theranostics, employing intra-therapeutic imaging techniques like CT, MRI, and PET (Bigham et al., 2024). Moreover, MOFs have been made even more appealing theranostic agents via their application in combination therapies, where several drugs are loaded onto the same framework, as well as in their use in biosensing to detect certain biomarkers associated with diseases (Chai et al., 2024).

For instance, cerium-based MOF nanoenzyme hydrogels mark a significant advancement in theranostics dealing with diabetic wound care. This innovative material combines the properties of MOFs with the capabilities of 3D printing technology to create a hydrogel that not only serves as a wound dressing, but also provides real-time monitoring of glucose levels in wounds (Chen et al., 2023b). Zr-based MOFs also present a promising avenue for advancements in biomedical applications owing to their effective DDS, bioimaging potential, stability, and biocompatibility (Gupta et al., 2024). Amorphous MOFs, owing to their superior porosity, increased thermal conductivity, and enhanced catalytic activity compared to their crystalline counterparts, have also been studied for their theranostic potential (Zhao et al., 2024a). In a study, zinc-based MOF using antitumor drug curcumin as organic ligand further loaded with doxorubicin and modified as theranostic system for synergistic multi-drug chemo-photothermal therapy was also developed as a Bio-MOF (Fig. 9) (Yang et al., 2022b).

9.1. MOFs for magnetic resonance imaging (MRI)

Among the various contrasting agents for MRI, Gadolinium (Gd)(III)-based agents have shown significant development in the past decades and are widely used (Lv et al., 2023). These compounds enhance the contrast of images by shortening the longitudinal relaxation time (T1) of nearby protons in tissues, which leads to brighter signals in T1-weighted images. However, traditional Gd(III) chelates have relatively low longitudinal relaxivity (r1), which limits their effectiveness and efficiency in clinical imaging. Recent studies have explored innovative combinations of materials to improve the performance of high-relaxation-rate Gd (III)-based contrast agents for theranostic applications. One promising approach involves combining Gd(III) with diethylenetriamine pentaacetate (DTPA), MOFs, specifically MOF-808, and polyaniline for the bioimaging of 4T1 breast cancer cells. DTPA serves as a chelating agent that stabilizes Gd(III) ions, MOF-808 is a versatile material known for its high surface area and tunable properties, which can facilitate better interaction with water molecules, thus enhancing relaxivity, and is a conductive polymer that can further modify the electronic environment around Gd(III), potentially increasing its relaxivity (Jia et al., 2021).

Another promising nanosytem with Gd-MOF, which acts as a platform for cancer combination immunotherapy owing to its multifunctional capabilities, was designed. The Gd-MOF nanosystem operates through microwave thermal responsiveness, tumor microenvironment improvement, enhanced T cell anti-tumor ability, controlled drug release via phase-change materials, and serves as a contrast agent for MRI, enhancing treatment outcomes and minimizing systemic exposure and potential side effects (Cui et al., 2024). However, despite the safety issues raised about gadolinium over the past decade, researchers have been working on other paramagnetic metal ion alternatives for the development of contrast agents such as high-spin $Mn^{2\ +}$, $Mn^{3\ +}$,$Fe^{2\ +}$ and Fe^{3+} (Du et al., 2023; Lacerda et al., 2021). Mn-MOF-74, with 2,5-dihydroxyterephthalic acid as a ligand modified with PEG and characterized by a safe paramagnetic center endowing high relaxivity, is an example of a Mn-based MOFs as a contrast agent, leading to better image quality (Iki et al., 2023).

The integration of fluorinated stimuli-responsive polymers into 19F MRI is a significant advancement in medical imaging technology that offers detailed insights into biological processes. Studies in this topic area show promising potential for improving the accuracy of diagnosis and patient outcomes, hence advancing research in clinical diagnostics (Tunca Arın and Sedlacek, 2024). A promising recent development includes hybrid theranostic agents that combine water-soluble fluoropolymers with pH-responsive ZIF-8 nanoparticles specifically designed to interact with the tumor microenvironment. These fluoropolymers permit the controlled release of the anticancer drug doxorubicin from the MOF, thus increasing blood flow, imaging, tumor uptake, and treatment efficiency (Wang et al., 2023a).

MOFs substantially improve CT imaging quality by enhancing contrast, resolution, and functionalization capabilities. Hafnium-based MOFs have an enhanced contrast because of high atomic numbers and superior X-ray absorption, which results in better images at lower radiation doses (Zhou et al., 2022). It is possible to develop these frameworks to accommodate multiple imaging modalities, thus facilitating multimodal procedures integrating CT with other techniques such as MRI or OI (Lai et al., 2021).

9.2. MOF-based fluorescent imaging

Functionalization of MOFs for fluorescent imaging in theranostic

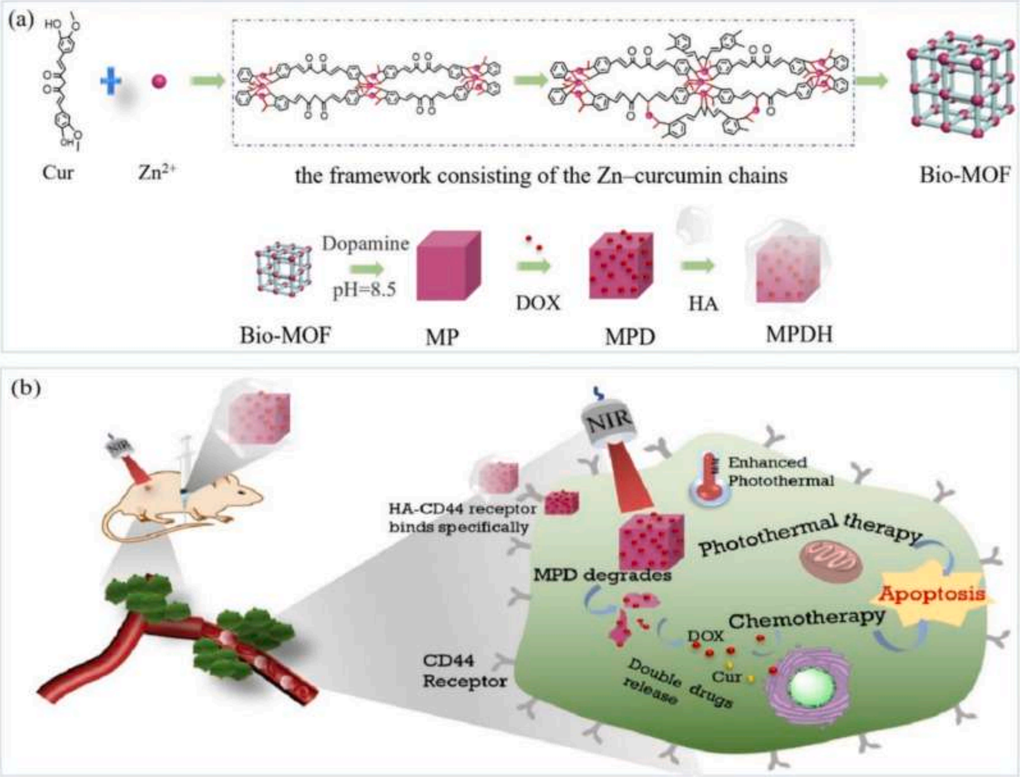

Fig. 9. Illustrations on (**a**) fabrication of biodegradable multifunctional photothermal drug delivery nanoparticles (NPs) with curcumin (Cur) as the ligand coated with hyaluronic acid (HA). These NPs can deliver Cur and doxorubicin hydrochloride (DOX) at the same time to help cancer cells overcome common drug resistance (**b**) Schematic illustration of chemo-/photothermal combinational tumor therapy. "Reprinted with permission from (S. Yang et al., 2022). Copyright (2022) Elsevier B.V."

applications is a promising avenue to further develop biomedical diagnostics and therapeutics using new nanotechnology strategies. Functionalization of MOFs involves incorporation of fluorescent dyes or photosensitizers in their structures via encapsulation, post-synthetic modification and covalent attachment (Xu et al., 2023c). An example is a theranostic nanoplatform based on photosensitizing MOFs, which was loaded with DNA via coordination bonds to metal nodes, altogether furnishing theranostic capabilities via imaging abnormally expressed miRNA in human cancers and treatment (Yang et al., 2023). Porous MOFs can encapsulate therapeutic agents along with fluorescent probes, such as doxorubicin, for simultaneous cancer therapy and imaging. Targeted delivery can enhance therapeutic efficacy and provide real-time imaging. Lanthanide-based MOFs are particularly attractive for fluorescence imaging because of their sharp and stable emissions. They enhance luminescence properties owing to the antenna effect and long fluorescence lifetimes (Meng et al., 2024b). Amino-functionalized MOFs also represent a promising avenue for advancing cell imaging techniques and enhancing the detection and delivery of chemotherapeutic agents, such as doxorubicin (Hu et al., 2024b). As another possible functionalization, a fluorescent system fabricated out of graphene quantum dots merged with magnetic hydroxyapatite-MIL-100 MOFs for the pH-responsive and controlled release of doxorubicin was developed. The proposed drug delivery system exhibited fluorescent and controlled pH drug release properties (Karimi et al., 2023). Another study investigated the theranostic ability of MOF as a meso-tetra (4-carboxyphenyl) porphine porphyrin MOF as a porous shell, containing the chemotherapeutic sorafenib to inhibit GSH synthesis. In a study, sodium erbium fluoride doped with ytterbium and sodium lutetium fluoride nanoparticles with inherent optical properties that can provide tumor microenvironment-responsive NIR IIb luminescence was incorporated for precise optical imaging of the sonodynamic therapy for brain glioma treatment (Jia et al., 2024). Future development of biodegradable and responsive MOFs may lead to safer and more efficient theranostic applications.

10. Challenges and limitations in MOF-based drug delivery

MOFs show potential in drug delivery but face challenges like toxicity from released metal ions during degradation, raising concerns about long-term biocompatibility and safety (Ghareeb and Nasr, 2021; Raza and Wu, 2024c). Stability in biological environments, reproducibility in body fluids, and pharmacokinetics of drug-loaded MOFs need thorough investigation and improvement (Ghareeb and Nasr, 2021). Scale-up production for clinical use is also a significant hurdle (Khafaga et al., 2024). Ongoing studies aim to develop sustainable MOFs by incorporating biodegradable linkers and using less toxic metals to enhance safety (Rabiee, 2023a). Additionally, stimuli-responsive MOFs and their integration into combination therapies are promising for overcoming drug resistance and reducing side effects (Maranescu and Visa, 2022b; Moharramnejad et al., 2023).

10.1. Scalability and manufacturing challenges

MOFs face significant challenges in scalability and manufacturing for clinical applications. Transitioning from laboratory-scale synthesis to industrial-scale production is problematic (Khafaga et al., 2024; Vikal et al., 2024). It is important to combine large-scale reproducibility of MOF synthetic processes while maintaining uniformity in their quality and properties for pharmaceutical purposes (Ghareeb and Nasr, 2021). The synthesis and functionalization of MOFs are quite rather cumbersome. Thus, successful industrial MOF manufacturing requires much modification or changes (Oh et al., 2023; Shen et al., 2020). Consistently replicating these processes on a larger scale may hinder commercial viability.

10.2. In vivo stability, biodistribution, and biocompatibility

MOFs offer high surface area, tunable pore size, and excellent drug-loading capacity, but biocompatibility and safety are vital for clinical applications (Rabiee, 2023a; Raza and Wu, 2024c). MOFs can degrade significantly in biological environments, leading to uncontrolled drug release and reduced therapeutic efficacy. Some MOFs remain stable at various pH levels but may start decomposing in intracellular environments (Jarai et al., 2020). This property could be useful for targeted drug release but requires careful design to ensure stability during circulation and regulated degradation at the site of action. Biodistribution also remains a challenge for MOF-based drug delivery systems because the MOFs can accumulate in different organs, creating the potential for off-target effects. For instance, it was reported that UiO-66 NPs after pulmonary delivery localized within the lungs for over a week before clearance (Jarai et al., 2020). This localization is, however, favorable for the treatment of lung diseases but sets a window of limit on the use of MOFs for systemic drug delivery. Research is needed to improve the stability of MOFs in the biological environment and for the ability to control biodistribution.

The degradation of MOF contributes to the release of toxic metal ions that endanger safety. Thus, studies are exploiting biodegradable linkers and less toxic metals for developing sustainable MOFs exhibiting a balance of biocompatibility and controlled drug release (Bhat and Lee, 2022; Rabiee, 2023a). Despite progress, toxicity concerns persist and require further *in vivo* studies to evaluate MOF behavior in biological systems (Biswal, 2023). Engineering pore size and surface properties may serve to enhance biocompatibility through permitting controlled release of cargo thereby inhibiting burst release. For instance, the introduction of hyaluronic acid into MOFs can target and control drug delivery release in response to certain enzymes. These strategies are, therefore, very crucial in developing MOFs that are safer for drug delivery and biosensing. One study, focused on a synthesis of a biocompatible zinc-based MOF with isophthalic acid as a linker, indicated a minimal adverse effect on normal human lung cell lines, demonstrated by a high IC_{50} value signifying that the compound has low cytotoxicity (Ismail et al., 2024). While MOFs greatly hold to it potential for drug delivery, one has to consider biocompatibility and safety, as ongoing studies focus on carrying out *in vivo* studies, optimizing the designs, and using sustainable materials.

10.3. Toxicity issues and immune response

Toxicity problems concerned with MOFs can only be circumvented through a multifaceted process concentrating on the systematic selection of the materials, structural design, and extensive safety assessments. The concern related to the toxicity of MOFs stems from potential MOF dissolution and release of metal ions, inherent toxic properties of various organic linkers, and influence of particle morphology and the respective size attributes on biological interactions. Excess ROS can be generated by MOFs, e.g., O^{2-}, –OH•, and –OOH, which could damage the mitochondrial membranes, proteins, DNAs, and lipids. Nanoparticles may be found freely moving in the cells; therefore, the toxic effect of endocytosis is due to their interaction with DNA and organelles and, ultimately, leading to cell death. The size and morphology of the MOF particles also matter because nanoscale MOFs are generally more toxic compared to other larger micron-sized ones since they exhibit more surface area for cellular uptake. Also, surface interactions governed by the zeta potential might also have some impact on toxicity. A neutral zeta potential may lead to MOF aggregations, which could subsequently result in membrane damage and cell death. Taken together, assessing the toxicity of a certain MOF emerges as a continuous examination when the chemical, physical, and surface interaction variables are appraised (Wiśniewska et al., 2023). The reduction of MOF toxicity in biological applications means reducing toxic solvents and precursor use and selecting biocompatible building blocks. To arrive at the desired results, methods of green synthesis can be implemented using microwave synthesis. Focus can be on metals such as zinc and iron which are less toxic and integrated bioactive ligands such as amino acids, peptides, and carbohydrates.

Some studies report minimal toxicity to living cells (Akbar et al., 2022; Carrillo-Carrión, 2020), whereas others call for more research. FeMn-MIL-88B MOFs showed no harmful effects on human embryonic kidney cells up to 100 μg/mL due to the low toxicity of their structural components (Akbar et al., 2022). Nonetheless, biocompatibility and toxicity remain significant challenges in MOF research (Sun, 2023). Extensive toxicity tests are required to ensure the long-term safety of MOF-based DDS (Benny et al., 2024a; Raza and Wu, 2024c). The immune response to MOFs can be both problematic and advantageous. One study found that MOF nanoparticles can enhance immune responses in vaccine delivery, inducing strong cellular immunity and a cytotoxic T lymphocyte response in mice (Yang et al., 2018). This indicates that while immune response is a concern for some uses, it could be beneficial in vaccine development.

10.4. Drug loading efficiency and release profile control

One major challenge is achieving high drug-loading efficiency with controlled release. While some MOFs, like UiO-66-NH2, show a 50.3 % loading of tetracycline hydrochloride (Hanafi et al., 2022), others have lower efficiencies. Drug-loading capacity varies significantly with MOF structure, pore size, and drug compatibility. Fe-MOF-based microcapsules reached a 77 % drug loading rate (Cui et al., 2021), and CD- MOF with silica coating exhibited a 166.78 % loading efficiency for folic acid (Liu et al., 2024). Many MOF-based systems experience a burst effect, releasing drugs rapidly within the first 48 h, posing a significant challenge (X. Liu et al., 2024b). Uncontrolled release can lead to suboptimal therapeutic outcomes or adverse effects. Strategies to address this include stimuli-responsive DDS (Xing et al., 2024) and surface modifications. For example, a bilayer coating on MOF NU-901 slowed pemetrexed release from 48 h to 7 days (X. Liu et al., 2024b). Table 4 summarises key biomedical studies involving MOFs, presenting the MOF type, therapeutic agents, application areas, experimental settings, and significant findings.

11. Future directions and opportunities

The future of MOFs in drug delivery is promising, with several key opportunities and directions identified as depicted in Fig. 10. Designing stimuli-responsive MOFs for controlled and targeted drug release is crucial for addressing current challenges and exploring opportunities in MOF-based DDS (Cai et al., 2019; Wang et al., 2020). MOFs like MIL-125 provide drug release in acidic tumor environments with no complicated modifications (Jiang et al., 2018). The integration of nanotechnology is promising for use with MOFs, since nano-MOFs have shown topical efficiency both *in vivo* and *in vitro* while possessing greater surface areas and bioavailability (Batool et al., 2023). Redox-sensitive MOFs such as zirconium-based MOFs complexed with 4,4-dithiobisbenzoic acid show potential for drug delivery to the tumor cells since these tumor cells contain high levels of glutathione (Patil et al., 2024). Biocompatibility, biodegradability, and low toxicity need to be considered for designing any material for clinical applications (Jiaxun Li et al., 2023; Mhettar et al., 2023). Design of experiments will provide better optimization for synthesis and performance of the MOFs (Mhettar et al., 2023). Combining MOFs with other advanced drug delivery technologies may lead to innovative hybrid systems with superior therapeutic outcomes (Hamzy et al., 2021; Wang et al., 2021b).

MOFs show immense promise in personalized medicine on account of their tunable porosity, intrinsic large surface area, and a plethora of synthesis options (Benny et al., 2024a; Khafaga et al., 2024). Their tunable characteristics, like surface area and pore size, enable the design of specialized drug carriers suitable for enhancing therapeutic efficacy

Table 4
Summary of key biomedical applications involving metal–organic framework (MOF).

MOF type	Therapeutic agent	Application	*In vitro/ in vivo*	Key results	Ref.
Biotin decorated ZIF-8	Celastrol	Cancer therapy	*In vivo*	improved water solubility and anti-tumor efficacy of celastrol.	(Zhou et al., 2023b)
Folic acid conjugated UiO-66	Cisplatin and cyclophosphamide	Breast cancer therapy	*In vitro*	Improved targeted drug delivery	(Mansouri et al., 2025)
Zinc-Based MOF	Curcumin, Doxorubicin	Chemo-photothermal therapy	*In vivo*	Synergistic anti-cancer activity with reduced drug resistance	(Yang et al., 2022b)
MIL101-Fe	Methotrexate	Cervical cancer therapy	*In vitro*	pH-dependent drug release causing apoptosis in HeLa cells while sparing healthy Vero cells	(Yunus et al., 2024)
Iron-MOF	Doxorubicin	Colorectal cancer therapy	*In vivo*	Specific targeting using aptamer modification, sparing normal cells	(Babaei et al., 2024)
Cu-MOF, Cu-Gallic Acid MOF	Copper ions	Antibacterial applications	*In vitro*	Cu-GA showed higher sensitivity against E. coli While Cu-MOF against Lactobacillus	(Elmehrath et al., 2024)
Zinc based MOF ZIF-4, ZIF-7, ZIF-8	Zinc ions	Antibacterial applications	*In vitro*	ZIF-8 exhibited the highest antibacterial effect, and ZIF-7 was the weakest among them.	(Khattami Kermanshahi and Akhbari, 2024)
Photo-Responsive MOF Hydrogel with boric acid attached	Berberine Ag ions	Wound healing	*In vivo*	Effective against *Staphylococcus aureus* and MRSA with antibacterial and anti-inflammatory effects	(He et al., 2024)
Zinc-MOF thermosensitive hydrogel	Chlorin e6	Antibacterial applications in PDT	*In vitro*	Destroyed the integrity of bacterial cell membranes and enhanced the production of bacterial ROS	(Zhang et al., 2023)
Cerium based MOF Hydrogel	Glucose Monitoring System	Diabetic wound care	*In vivo*	Combines theranostics with 3D printing for real-time glucose level monitoring in wounds	(Chen et al., 2023b)
Amine-functionalized silver-based metal–organic framework, oxidized alginate and borax hydrogel	Silver	Antibacterial applications	*In vitro*	Reduced biotoxicity and enhanced antibacterial activity. Structural stability	(Javanbakht and Mohammadi, 2025)
sodium alginate hydrogel matrix loaded ZIF-8 MOFs	curcumin	Antibacterial for wound healing	*In vitro*	flexible and tough composite hydrogel that adapt to the mechanical behaviors of human skin. Extended drug release	(Li et al., 2023)
ZIF-8 coated with hyaluronic acid	Fucoidan	MRSA-infected wound healing	*In vitro*	NPs targeted against subcellular MRSA and the lysosomes	(Jiang et al., 2024)
Cu-MOF in PVA/Zein/Tannic acid composed composite cryogels	Streptomycin sulphate	antibacterial activity	*In vivo*	enhanced mechanical properties and increased antibacterial activity	(Singh et al., 2024)
Ca-based metal–organic framework in polylactic acid and gelatine mixture.	As obtained scaffold	Tissue engineering	*In vivo*	Enhanced bone formation	
Iron-based MOF embedded in PLGA Scaffold	Dimethyloxallyl glycine	Bone regeneration	*In vivo*	Enhanced vascularization and bone regeneration in cranial defect models	(Xu et al., 2023b)
Cu-Based MOF embedded in PLGA Scaffold	Copper ions and exosomes	Tissue engineering	*In vivo*	Controlled release of copper ions and exosomes promoting osteogenesis and angiogenesis	(Xu et al., 2023a)
NH$_2$-MIL-88B(Fe) embedded in polycaprolactone scaffold	Ag ions	Tissue engineering	*In vitro*	Multifunctional Scaffolds with Controlled Microarchitecture was attained	(Mansi et al., 2024)
ROS-responsive Mn-based MOF	Glucose oxidase and indoleamine 2,3-dioxygenase inhibitor 1-methyltryptophan	Immunotherapy	*In vivo*	Synergistic effect targeting tumor metabolism and amplifying anti-tumor immunity	(Dai et al., 2022)
Fe based MOF and coated with liposomes	Lactate oxidase and monocarboxylate transporter 4 (MCT4)-inhibiting siRNA	Immunotherapy	*In vivo*	Tumor immunotherapy by enhanced ICD and LA metabolism blockade.	(Hu et al., 2024a)
UiO-66-NH2 IL-1Ra for cellular targeting, and 5-FAM for fluorescence imaging.	Rapamycin IL-1 for cellular targeting, and 5-FAM for fluorescence imaging.	Immunotherapy	*In vivo*	Targeted and reduced atherosclerosis plaques in coronary arteries, carotid arteries, and aorta.	(Xu et al., 2023d)
MIL-101-NH$_2$(Fe/Cu) decorated with transferrin	rapamycin	Neurological applications	*In vivo*	Crossed BBB enhanced drug retention and controlled release within ischemic lesions	(Chen et al., 2024b)
High boron content Zr based MOF nano-co-crystals	Boric acid	Neurological applications	*In vivo*	crossed BBB, boron neutron capture therapy of brain glioma.	(Wang et al., 2022b)
Neutrophil Membrane-Coated MOF	Carbon monoxide	Neurological applications	*In vivo*	Targeted modulation of amyloid β deposition and inflammation, disrupting the disease cycle of Alzhiemers disease	(Liu et al., 2024)
ZIF-8	CeO$_2$ NPs	Neurological applications	*In vivo*	enhanced catalytic and antioxidative activities in ischemic stroke	(He et al., 2020)

and reducing toxic effects (Khafaga et al., 2024). Probably one of the most interesting properties of MOFs is the behavior that permits their communication with several stimuli-pH, temperature, light, and redox state. These stimuli allow for efficient and controlled release of drugs (Cai et al., 2019). The future of MOF-based DDS shall be focused in the creation of intelligent systems, capable of responding dynamically to polysensory intelligence stimuli according to release on demand-enhanced scientific efficacy while reducing adverse effects. Smart

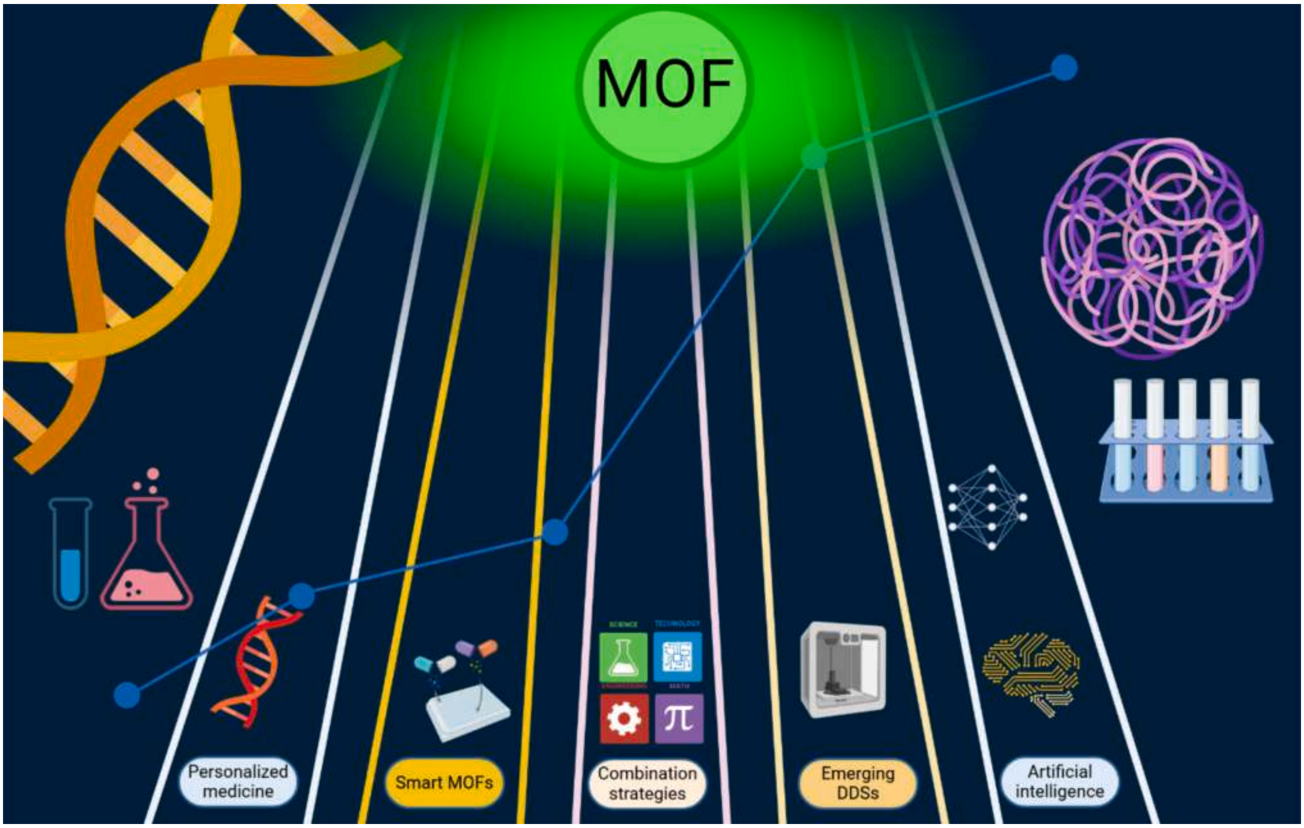

Fig. 10. Illustration highlighting emerging directions and potential opportunities for advancing MOF applications in biomedical research, showcasing key areas for future exploration and innovation.

MOF-based DDS respond to one or more stimuli like pH, temperature, light, and ions-causing controlled drug release (Fatima et al., 2023; Xing et al., 2024). pH-responsive MOFs release drugs in acidic tumor environments while external heat can trigger temperature-responsive MOFs to guide the localized delivery (Fatima et al., 2023). Multi-stimuli-responsive systems allow for more control in drug distribution (Xing et al., 2024). MOFs combined with imaging agents allow for theranostic applications for both diagnosis and treatment. The use of MOFs in combination therapies could bring more effective treatments for complex diseases such as cancer (Benny et al., 2024b). The design of combination therapies may use the peculiar characteristics of MOF-based DDS so that synergism may occur in different pathology scenarios (Benny et al., 2024b; Vikal et al., 2024). One of the promising directions would be multi-biomimetic MOF nanocarriers for multimodal treatments. A study has introduced a 'Trojan Horse' vehicle, a cancer cell membrane camouflaged MOF nano-drug carrier called "FeTPt", which integrates ferroptosis-PDT-chemotherapy for cancer treatment (Zhang et al., 2023c). The example illustrates the multifaceted use of MOFs towards combining therapeutic modalities.

The integration of MOFs into the realms of 3D printing and microfluidics proposes several advances in pharmaceutics. Combined with micro scale 3D printing, MOFs may ease the formulation of patient-specific dosage forms thereby furthering precision medicine and improving therapeutic outcomes (Ankur Patel et al., 2023). 3D printed MBG/MOF scaffolds have proven useful in treating osteoarticular tuberculosis (Pei et al., 2018). Further, the integration of MOFs with microfluidics has shown immense potential, wherein a 'Trojan Horse'-like vehicle for cancer treatment has recently been developed (Zhang et al., 2023c). This approach couples MOFs with advanced systems for greater drug delivery targeting and efficacy. Such integrations could provide the ground for a furtherance towards more precise individualized and effective treatments, paving the way for ground-breaking future therapeutic approaches (Salla et al., 2024). Artificial intelligence (AI) is becoming instrumental in the design and optimization of MOFs in drug delivery. Various Machine Learning (ML) algorithms are applied on a variety of MOF data sets. These help in extraction of trends and correlations, permitting the predictions and optimizations of properties of newer MOFs for specified applications (Rabiee, 2023b). This method greatly reduces the time and cost of exploring various MOFs in drug delivery. ML classifiers can predict various MOF properties that will enhance MOF-based DDS in in-silico design by predicting their applications as a drug carrier (Pouyanfar et al., 2024). The countless prospects of AI in MOF optimization are accompanied by the ongoing challenges posed by the sophistication linked with MOF synthesis and a multiplicity of performance determinants in DDS. Due to the exceedingly complex interrelations between MOF structure, properties, and drug delivery performance, enhanced AI models are needed. Some datasets require improvement and revalidation to assure the continued credibility and precision of AI predictions for real-life applications (Pouyanfar et al., 2024; Rabiee, 2023b).

12. Conclusions

MOFs represent an exceptionally promising category of materials for advanced DDS owing to their porosity coupled with surface area that enables maximum drug loading and controlled release kinetics. The modular design of MOFs allows for precision-control over structural properties like pore size, shape, and surface functionality post-synthesis. These structural and functional modifications allow requisite action in response to environmental factors like pH, temperature, or enzymes for precise dosage and control over drug absorption. MOF-based DDS can cater to small-molecule loading, encapsulation of peptides, proteins, and nucleic acids.

The practical uses of MOFs are subject to many challenges which will affect their safety and efficacy. The toxicity of a MOF represents one major point of concern since toxic metal ions that are liberated through MOFs degradation pose safety and efficacy hazards. Smaller MOFs may also avoid the physiological barriers, making them deposit in some tissues or organs, causing toxicity dependent on the material used, their physicochemical properties, and degradation kinetics. Stability and degradation, on the other hand, present several challenges. Premature degradation of MOFs in the biological environments becomes spontaneous in the sense of uncontrolled drug release and reduced therapeutic efficiency because of weak coordination bonds. The aforementioned disordering of these frameworks can also be facilitated by pH changes, enzymatic activity, and the presence of ions or biomolecules, with some structures having shown to decompose in intracellular environments. Transitioning from laboratory synthesis to industrial scale poses another set of challenges associated with scaling and manufacturing, wherein achieving reproducibility without compromising the quality still remains very crucial for applications in pharmaceuticals. The complexity of the synthesis and functionalization of MOFs usually implies complex manufacturing techniques for effective delivery or response to stimuli. In addition, biodistribution can lead to accumulation in different organs, producing off-target effects. The immune response to MOFs seems to have two sides. Some reports indicate that this might have led to enhanced immune responses, while others suggest require more studies. Such systems also struggle with achieving high loading efficiency with controlled release, and many MOF-based systems have an early burst release within the first 48 h.

To tackle such challenges, studies are trying out several strategies. Improving biocompatibility and reducing toxicity of the materials used are given priority. The use of less toxic metals for biodegradable linkers can yield safer and more sustainable MOFs. Control of size, assessment of metal toxicity, functionalization of ligands, and the incorporation of biocompatible solvent systems could enhance safety. Surface modification and functionalization techniques can further improve targeted drug delivery, drug loading potential, control of release profiles, and increase targeting efficiency. Hybrid MOF systems that combine MOFs with polymers, lipids, or nanoparticles could also improve delivery mechanisms. Stimuli-responsive MOFs are being designed to enable smart drug-release mechanisms tailored for controlled and targeted applications. Structural modifications and synthesis optimization are equally vital. The choice of synthesis method greatly influences the properties of MOFs. Hydrothermal synthesis has produced highly crystalline structures while solvothermal methods have enhanced porosity. Modulator-induced defect formation and pillared layer assemblies have been developed for the synthesis of microporous MOFs. The use of AI to optimize performance contributes to the modeling of huge datasets in order to identify trends and predict the properties of new MOFs for specific applications. Interpenetrated structures involving stabilization add strength against collapse, even as in situ polymerization on MOF nanoparticles builds protective coatings to prevent decomposition.

In summary, MOFs have great prospects in advanced drug delivery systems. But their further practical application needs to deal with challenges regarding toxicity, stability, and scalability while exploiting their high porosity and modularity to effect effective and targeted drug delivery.

CRediT authorship contribution statement

M.T. Khulood: Writing – review & editing, Writing – original draft, Resources, Funding acquisition, Conceptualization. **U.S. Jijith:** Writing – review & editing, Writing – original draft, Supervision. **P.P. Naseef:** Writing – review & editing, Writing – original draft, Supervision. **Sirajudheen M. Kallungal:** Writing – review & editing, Writing – original draft, Supervision. **V.S. Geetha:** Writing – review & editing, Writing – original draft, Supervision. **K. Pramod:** Writing – review & editing, Writing – original draft, Supervision, Conceptualization.

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Declaration of competing interest

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Data availability

No data was used for the research described in the article.

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