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Review Article

Metal-Organic Framework as Emerging Platform for Pharmaceutical Drug Delivery: A Review

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ABSTRACT

Metal–organic frameworks (MOFs) are crystalline, highly porous hybrid materials constructed from metal ions or metal-oxo clusters coordinated to organic linkers. Their exceptionally high surface area, tunable pore chemistry, and structural programmability have driven rapid growth in pharmaceutical research on MOFs over the past decade. This review summarises the structure and classification of pharmaceutically relevant MOFs, the synthesis strategies used to prepare drug-loaded frameworks, and the mechanisms by which drugs are loaded and released, with particular attention to stimuli-responsive (pH-, redox-, and X-ray-triggered) systems. Applications are discussed across cancer chemotherapy and immunotherapy, oral and mucosal delivery, antibacterial therapy, wound healing and tissue engineering, and biosensing. The review also addresses how MOF nanoparticles are taken up and processed by cells, the biocompatibility and toxicity data available for widely studied framework families, and the principal challenges limiting clinical translation. It concludes with emerging directions, including covalent organic frameworks, cyclodextrin-based MOFs, and hybrid nanocomposite carriers.

INTRODUCTION

Conventional oral and parenteral dosage forms are frequently limited by poor aqueous solubility, chemical instability, low membrane permeability, and lack of site-specificity, all of which reduce therapeutic efficacy and increase systemic toxicity. Nanocarrier platforms such as liposomes, polymeric nanoparticles, and mesoporous silica have partly addressed these problems, but each involves trade-offs in drug loading capacity, reproducibility, or biodegradability. Metal–organic frameworks (MOFs) have emerged as a structurally distinct class of hybrid porous nanomaterials that can, in principle, combine the high loading capacity of porous inorganic hosts with the chemical tunability of organic scaffolds.

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A scientometric analysis of the MOF literature shows the field expanding rapidly across chemistry, materials science, and increasingly biomedicine, with drug delivery emerging as one of its fastest-growing sub-domains [1]. A MOF is formed when metal ions or metal-oxo clusters self-assemble with multidentate organic linkers into an ordered, permanently porous crystalline lattice; changing the metal node, the linker, or applying post-synthetic modification allows pore size and surface chemistry to be tailored for a specific therapeutic application [2,3].

This review approaches MOF-based drug delivery from a pharmaceutics standpoint, focusing on synthesis strategies compatible with drug stability, drug loading and release mechanisms, therapeutic applications, and the safety data needed to support eventual clinical translation.

2. STRUCTURE, PROPERTIES AND CLASSIFICATION OF MOFS

MOFs are distinguished from purely inorganic porous materials by the presence of organic linkers, which allows near-limitless structural diversity. Properties of pharmaceutical relevance include exceptionally high surface area, tunable and uniform pore size that can be matched to a specific drug molecule, high pore volume enabling large payloads, and the ability to introduce targeting or stimuli-responsive functionality through post-synthetic surface modification [2,3].

Framework families frequently investigated for drug delivery include zirconium-based UiO frameworks (noted for hydrolytic and chemical stability) [4], zeolitic imidazolate frameworks such as ZIF-8, which are pH-responsive because their imidazolate linkers protonate and the framework disassembles under mildly acidic conditions [5,6], copper-based MOFs, which combine intrinsic antibacterial activity with catalytic and biomedical utility [7,8], iron-based frameworks used in thin-film and nanoparticle form [9], and lanthanide-based frameworks such as La-MOF, explored using natural-product-derived linkers for cancer therapy [10]. Related porous crystalline materials, covalent organic frameworks (COFs), which are held together entirely by covalent rather than coordinate bonds, are increasingly discussed alongside MOFs for pharmacy and biomedical applications, offering an alternative route to tunable porosity with different stability and degradation profiles [11].

Beyond pharmaceutical use, the same porous architecture underpins MOF applications in energy storage devices such as supercapacitors and in environmental remediation, including pollutant dye adsorption, illustrating the broad versatility of this materials class beyond biomedicine [12,13].

3. SYNTHESIS METHODS

The method used to prepare a MOF strongly influences its crystallinity, particle size, and compatibility with the drug to be incorporated. Conventional solvothermal synthesis remains widely used, but a range of tailored approaches have been developed for pharmaceutical MOFs. Hybrid nanocomposite strategies combine MOFs with polymeric or metal nanoparticle components in a core-shell architecture; for example, styrene-acrylonitrile (SAN) based polymer shells combined with zinc and aluminium MOF cores to improve mechanical stability and processability [14]. Gold nanoparticles have similarly been encapsulated within hybrid MOF architectures to enable co-delivery of two drugs from a single carrier [15].

At the same time, porphyrinic MOFs have served as a scaffold for the controlled growth of a second, drug-encapsulated MOF layer for combined photodynamic and chemotherapy [16]. Composite

MOFs grown on polydopamine-modified cellulose nanofibril hydrogels have been used to construct carriers suited to hydrophobic drug delivery [17], and MOFs nucleated directly on silk fibroin scaffolds have been functionalised with tumour-targeting peptides for multimodal cancer therapy [18].

4. DRUG LOADING AND STIMULI-RESPONSIVE RELEASE

Drugs associate with the MOF pore surface through physical adsorption, hydrogen bonding, coordinate bonding to open metal sites, or electrostatic interaction, with the dominant mechanism depending on both the drug and the framework chemistry [19]. A central advantage of MOFs for pharmaceutics is the possibility of engineering release to respond to a physiological trigger rather than occurring passively.

Redox-responsive systems exploit the elevated glutathione (GSH) concentration inside tumour cells; a GSH-responsive MOF has been used to achieve intratumoral co-release of nitric oxide and an IDO inhibitor to enhance antitumour immunotherapy [20]. Other frameworks have been engineered to be acid-degradable while simultaneously generating hydrogen gas in situ, a strategy used to overcome drug resistance and limit off-target effects [21]. External-stimulus systems have also been developed, including a nanoscale MOF carrying an X-ray-triggerable prodrug that enables spatially and temporally controlled release synchronised with radiotherapy [22]. Broader reviews of environment-responsive MOFs highlight pH, redox, enzyme, and combinations of these triggers as the principal design strategies for tumour-selective release [23,24].

5. APPLICATIONS IN PHARMACEUTICAL DRUG DELIVERY

5.1 Cancer Therapy and Immunotherapy

Oncology remains the most extensively studied application of MOF-based drug delivery. Reported strategies include co-loading complementary agents within a single degradable framework such as doxorubicin and indocyanine green for combined targeted release and photothermal ablation [25] and functionalising frameworks with natural-product-derived linkers, as in a lanthanum-based MOF incorporating a caffeic-acid derivative for breast cancer therapy [10]. Mixed-ligand MOFs have been designed for all-in-one theranostics, combining controlled drug release with enhanced photodynamic therapy in a single platform [26].

Targeting strategies feature prominently: surface-engineered MOFs functionalised with targeting moieties have been developed for both mono- and multi-drug active targeting [27], gold-nanoparticle-hybrid MOFs have enabled co-delivery of 5-fluorouracil and curcumin and autonomous MOF-based nanorobots have been designed to actively navigate toward mitochondria for organelle-targeted cancer therapy [28]. Immune-modulating approaches include immunoadjuvant-functionalised MOFs for tumour immune modulation [29]. Frameworks have also been engineered to trigger ferroptosis via controlled structural defects as a route to overcome drug resistance [30]. Electrospun nanofiber membranes incorporating chitosan, polycaprolactone, and MOF particles have been optimised (via Box–Behnken design) for doxorubicin delivery with combined anticancer and antimicrobial activity [31], and functionalised MOF nanoparticles engineered specifically as targeted drug delivery carriers for cancer therapy have also been described as a generalisable platform strategy [32].

5.2 Oral and Mucosal Delivery

MOF-based carriers have also been investigated for oral and local mucosal delivery of both small molecules and biologics. Hydrogel–MOF hybrid systems have been used for efficient oral delivery of siRNA in the treatment of ulcerative colitis, aiming to improve local gastrointestinal bioavailability while limiting systemic exposure [33]. HKUST-1, a copper-based MOF, has been investigated as a carrier for paracetamol using an improvised synthesis route intended to optimise drug loading and release behaviour [34].

5.3 Antibacterial Applications

Several MOF systems combine drug delivery with intrinsic or delivered antibacterial activity. Core-shell ZIF-8@ZIF-67 nanocomposites have been synthesised for antibiotic decomposition alongside antibacterial activity [6], and copper-based MOFs have shown antibacterial efficacy against both Escherichia coli and Lactobacillus, reflecting the inherent antimicrobial properties of copper ions released from the framework [8]. The electrospun MOF-nanofiber membrane developed for doxorubicin delivery was also reported to show antimicrobial activity in addition to its anticancer effect, illustrating the potential for dual-function pharmaceutical dressings [31].

5.4 Wound Healing and Tissue Engineering

MOF-based nanomaterials have been reviewed for applications in bone tissue engineering and wound healing, reflecting interest in frameworks that can combine mechanical scaffolding functions with sustained release of therapeutic ions or drugs [35]. An aluminium-based MOF encapsulating umbelliferone showed sustained release alongside antioxidant, anti-inflammatory, and wound-healing activity in an invertebrate (earthworm) model, supporting the feasibility of MOF carriers in topical and regenerative applications [36].

5.5 Biosensing and Emerging Applications

Beyond therapeutic delivery, MOF-based sensors have been developed for food safety applications, exploiting the same high surface area and tunable pore chemistry that make MOFs effective drug carriers to achieve sensitive analyte detection [37]. This cross-over illustrates how the structural properties central to pharmaceutical MOF design-porosity, surface functionality, and framework responsiveness is broadly transferable to diagnostic and analytical applications.

6. CELLULAR UPTAKE AND BIOLOGICAL INTERACTIONS

The therapeutic performance of a MOF nanocarrier depends not only on drug loading and release but on how the particle is taken up and processed by cells. A detailed review of MOF nanoparticle uptake describes the pathways by which MOFs enter cells (including endocytic routes), their subsequent intracellular trafficking, and the factors — particle size, surface charge, and shape — that govern uptake efficiency and intracellular fate [38]. Understanding these processes is essential for rational design of MOF carriers intended for intracellular drug release or organelle-targeted therapy, such as the mitochondria-targeted nanorobots described above [28].

7. BIOCOMPATIBILITY AND TOXICITY

Clinical translation of any MOF-based product requires evidence that both the intact framework and its degradation products (the metal ion and organic linker) are safe at therapeutically relevant doses. A comprehensive review of MOF nanoparticle toxicity highlights that biocompatibility depends heavily on the specific metal node, linker chemistry, particle size, and dose, and that toxicity profiles vary substantially

even within families of chemically related frameworks; the review calls for more standardised toxicological analyses to support translation toward clinical and other real-world applications [39]. A related review of MOF biocompatibility and biodegradability similarly emphasises that degradation behaviour in physiological media is a key determinant of long-term safety, since incomplete or uncontrolled breakdown can generate reactive intermediates or cause off-target accumulation [40].

8. CHALLENGES AND LIMITATIONS

Several obstacles continue to limit the clinical translation of MOF-based drug delivery systems. Reproducible, scalable synthesis remains difficult, particularly for hybrid and core-shell architectures that require multiple sequential synthesis steps [4,14]. Structural stability in biological fluids is a persistent concern: frameworks designed to be stimuli-responsive can also be prone to premature or uncontrolled degradation, complicating efforts to achieve a defined sustained-release profile [23,24]. Toxicological data remain incomplete for the great majority of reported MOF structures, and standardised protocols for evaluating MOF biocompatibility are still evolving [39,40]. No MOF-based pharmaceutical product has yet reached regulatory approval, so the regulatory pathway for this class of carrier remains undefined.

9. FUTURE PERSPECTIVES

Several directions are likely to shape the next phase of MOF-based pharmaceutics research. Covalent organic frameworks are gaining attention as a structurally related but chemically distinct alternative, with a growing evidence base for pharmacy and biomedical applications that may complement MOF-based strategies [11]. Hybrid nanocomposite carriers — combining MOFs with polymers, magnetic nanoparticles, hydrogels, or nanofibers — are being explored to improve mechanical stability, enable magnetically guided theragnostic applications, and support new administration routes such as topical nanofiber dressings [14,17]. Continued development of surface-engineering and post-synthetic modification techniques is expected to further improve targeting precision [27], while more systematic toxicological profiling will be needed to build the safety datasets regulators will require before clinical development can proceed [39,40].Cyclodextrin-based MOFs, which combine the inclusion-complex chemistry of cyclodextrins with framework porosity, offer another promising direction, particularly for improving the solubility of poorly soluble drugs [41].

10. CONCLUSION

Metal–organic frameworks provide a structurally versatile and highly tunable platform for pharmaceutical drug delivery, with demonstrated potential across cancer therapy, oral and mucosal delivery, antibacterial treatment, wound healing, and biosensing. Stimuli-responsive frameworks in particular offer a route to more precise, tumour- or site-selective therapy than many conventional carriers, and hybrid MOF-nanocomposite architectures are expanding the range of achievable functions. Realising this potential in the clinic will require continued progress in reproducible and scalable synthesis, a stronger and more standardised evidence base for biocompatibility and toxicity, and closer engagement with regulators to establish an approval pathway for this emerging class of pharmaceutical carrier.

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