

Metal–Organic Frameworks in Advanced Drug Delivery: Design Principles, Functionalization Strategies and Translational Prospects

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Abstract

Metal–organic frameworks (MOFs) are crystalline coordination networks assembled from metal nodes and multitopic organic linkers. Their modular chemistry, tunable pore environments, high internal surface area and stimuli-responsive degradation make them attractive carriers for small molecules, proteins, nucleic acids and combination therapeutics. This review discusses a design-to-translation framework for MOF drug delivery, linking node/linker selection and particle engineering to loading, release, targeting, biocompatibility and manufacturing. We compare one-pot encapsulation, biomimetic mineralization, post-synthetic loading, surface adsorption and covalent conjugation, and examine polymer, lipid, biomolecule and cell-membrane functionalization. Representative performance data include insulin loading near 39.7 wt% in NU-1000, 5-fluorouracil release exceeding 45% within 1 h at pH 5 versus approximately 17% at pH 7.4 in a ZIF-8 system, and targeted ZIF-90 systems releasing more than 95% payload in under 16 h at acidic pH. The field remains predominantly preclinical: long-term safety, metal/linker fate, colloidal stability, scale-up, batch reproducibility, sterile processing and clinically relevant pharmacokinetics require systematic resolution. Translation will depend less on record loading than on robust quality-by-design, physiologically realistic testing and a clearly justified clinical use case.

Keywords: metal–organic frameworks; nano-MOFs; drug delivery; stimuli-responsive release; surface functionalization; nanomedicine; translational pharmaceuticals.

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Introduction

Conventional dosage forms frequently provide limited control over exposure, particularly for poorly soluble drugs, labile biomolecules and therapeutics requiring intracellular delivery. MOFs offer an unusually broad design space because the inorganic node, organic linker, secondary building unit, pore size, defect density, particle morphology and external surface can be tuned semi-independently. This architecture enables high loading, protection

from degradation, controlled release and co-delivery within one platform [1–3]. MOFs are not a single material class with a universal safety profile. The biological response depends on metal identity, linker chemistry, particle size, morphology, surface charge, aggregation, degradation rate, dose and route of administration. Accordingly, a clinically meaningful formulation must be designed as a

complete drug product rather than as a high-surface-area powder alone [1,4].

Design principles for drug-delivery MOFs

A rational MOF begins with the therapeutic and route of administration.

Small hydrophobic drugs may benefit from hydrophobic aromatic pores and π - π interactions, whereas proteins and nucleic acids require larger mesopores, electrostatic anchoring or biomimetic mineralization.

The framework must remain sufficiently intact during formulation and circulation but degrade or open at the intended site. For intravenous use, nanoscale dimensions, narrow size distribution, low aggregation and controlled

protein-corona formation are especially important.

Node selection determines coordination strength and degradation. Zr(IV)-based UiO frameworks are generally valued for strong metal-oxygen clusters; Fe-based MIL systems offer biodegradation and possible iron handling advantages; Zn-based ZIFs can be useful for acid-triggered intracellular release but require attention to zinc exposure and buffer-dependent instability. Linker functional groups determine charge, hydrophilicity, ligand exchange, targeting chemistry and host-guest affinity.

Defects can increase pore volume and reactivity, but excessive defects may accelerate collapse or metal release [1,2].

Table 1. Design variables and their pharmaceutical implications

Design variable	Desired control	Drug-delivery implication
Metal node/SBU	Coordination strength and degradation	Controls physiological stability, ion release and stimulus response.
Organic linker	Charge, polarity, aromaticity, reactive groups	Tunes drug affinity, water dispersibility and post-synthetic chemistry.
Pore size/volume	Molecular fit and diffusion path	Determines loading of small molecules versus proteins/nucleic acids and release rate.
Particle size/morphology	Biodistribution and uptake	Affects clearance, tissue penetration, cellular internalization and route compatibility.
Defect density	Additional voids and reactive sites	May improve loading but can reduce stability and reproducibility.
Surface chemistry	Charge, hydration and ligand display	Controls colloidal stability, corona formation, targeting and immunological interactions.

Synthesis and characterization

Solvothermal and hydrothermal routes remain useful for phase-pure crystalline materials and precise morphology control, but their high solvent use, long reaction times and scale-up constraints are unfavorable for pharmaceutical manufacturing. Microwave, sonochemical, electrochemical, microfluidic and mechanochemical approaches can shorten processing or reduce solvent demand.

A translational process should specify critical material attributes such as particle size, crystallinity, surface area, residual solvent, endotoxin, elemental impurities, drug content, release profile and sterility. Characterization must combine structure, composition, porosity, surface and biological performance. PXRD confirms phase identity and structural retention; SEM/TEM define morphology and size; BET analysis evaluates accessible surface

area and pore volume; FTIR/Raman and XPS probe bonding and surface chemistry; TGA supports solvent, guest and framework-composition assessment; ICP-MS or ICP-OES quantifies metal content and release.

DLS and zeta potential should be measured in the actual formulation medium, serum-containing media and infusion diluents rather than only in purified water.

Table 2. Core characterization package for nano-MOF drug products

Attribute	Technique	Pharmaceutical question
Phase/crystallinity	PXRD; optionally SXRD	Is the intended framework formed and retained after loading, storage and release?
Size and morphology	TEM/SEM; DLS; nanoparticle tracking	Are size, shape and aggregation compatible with the route?
Porosity	N ₂ /Ar adsorption; BET; pore distribution	Are pores accessible and occupied by the therapeutic?
Composition	ICP-MS/OES; elemental analysis; XPS/EDS	What are total and leachable metal/linker levels?
Drug state/content	HPLC/UPLC; TGA; DSC; NMR	How much active is present and is it chemically intact?

Loading and functionalization strategies

One-pot loading and co-crystallization integrate the drug during framework formation and can provide high, relatively homogeneous payload distribution. They may expose labile drugs to heat, coordinating solvents, extreme pH or reactive metal precursors. Biomimetic mineralization is particularly useful for proteins, enzymes, nucleic acids and virus-like cargos because the biomolecule can nucleate a protective MOF shell under mild conditions. The trade-off is that release may depend strongly on framework degradation and therefore be delayed or incomplete.

Post-synthetic pore impregnation is versatile for small molecules and allows the framework to be synthesized and characterized before drug loading. Surface adsorption is operationally simple and useful for anionic nucleic acids or secondary payloads, although

it commonly increases burst release. Covalent or cleavable conjugation offers stronger retention and can introduce pH-, redox- or enzyme-cleavable bonds, but it must preserve drug activity and avoid generating an undesirable linker-drug impurity profile [1,3]. Functionalization is used to solve specific formulation problems. PEG, PVP, chitosan, albumin, lipid layers and cell membranes can reduce aggregation and improve circulation. Folic acid, RGD peptides, hyaluronic acid, antibodies and aptamers can support receptor-mediated targeting. Calcium phosphate or polymer shells can gate pores, while porphyrinic linkers and magnetic components can provide photodynamic or magnetic functions. Every added layer increases molecular complexity and must therefore be justified by a measurable benefit in stability, targeting, therapeutic index or manufacturability.

Table 3. Representative MOF drug-delivery performance data

System/example	Reported performance	Interpretation
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NU-1000–insulin	Approximately 39.7 wt% insulin loading; acid-resistant behavior and phosphate-triggered release were reported.	Illustrates macromolecule loading with environment-dependent release.
ZIF-8–doxorubicin	Approximately 14–20 wt% with one-pot loading; about 4.9 wt% for a surface-loading example.	Loading route strongly affects payload and release.
ZIF-8–5-fluorouracil	Up to 60% loading reported in one study; >45% released at pH 5 in 1 h versus about 17% at pH 7.4.	Supports acid-responsive release, but assay conditions must be standardized.
ZIF-90 co-delivery	5-FU loading about 36.35%; doxorubicin about 11–13.5 wt%; >95% release under acidic conditions in <16 h in one report.	Demonstrates co-loading and tumor-microenvironment-responsive release.
Ni-IRMOF-74-II–ssDNA	Approximately 6.9 wt% ssDNA; reported protection from nuclease degradation and efficient transfection in several cell types.	Shows pore-size matching for nucleic-acid delivery.
Fe ₃ O ₄ @Fe-MOF@HAp–doxorubicin	Reported DOX loading of 75.38 mg/g versus 12.3 mg/g for a mesoporous-silica comparator in one study.	Combines magnetic targeting, pH sensitivity and composite architecture.

Values in this table are representative literature reports rather than directly comparable benchmarks. Differences in drug-to-MOF ratio, solvent, pH, dialysis membrane, sink conditions, particle size and analytical method can substantially alter apparent loading and release [1–4].

Stimuli-responsive and advanced delivery

Internal stimuli include acidic pH, redox gradients, enzymes, ATP, hypoxia and ionic composition. Acid-responsive ZIF and MIL systems can exploit endosomal or tumor-associated acidity, whereas disulfide- or diselenide-containing linkers can respond to intracellular glutathione. Enzyme-cleavable gates may provide greater biological specificity but require validation in human-relevant matrices. External stimuli such as light, ultrasound, heat and magnetic fields offer temporal control, yet tissue penetration, equipment requirements and safety limits can restrict clinical use.

MOFs can also function as combination and theranostic platforms. A single particle may carry a cytotoxic drug, siRNA and imaging or photodynamic component, while the framework or released metal contributes catalytic activity.

These designs are scientifically attractive but introduce multidimensional pharmacology: each component requires separate identity, potency, degradation, biodistribution and safety assessment. The most translatable designs are likely to use a limited number of well-characterized components and a clinically meaningful therapeutic advantage.

Translational prospects and barriers

The major gap is between proof-of-concept efficacy and a reproducible, clinically acceptable product. Many studies report cytotoxicity in cancer cell lines or tumor growth inhibition in small-animal models, but fewer establish full pharmacokinetics, tissue

metal burdens, immune activation, complement effects, repeated-dose toxicity, reproductive risk, degradation products and long-term clearance. Biological media can alter framework structure, generate aggregates or produce a protein corona that changes uptake and biodistribution. Therefore, stability and release should be studied in serum, whole blood, relevant mucosal fluids, infusion diluents and disease-relevant tissues.

Manufacturing requires control of nucleation, particle size distribution, defect density, residual solvent, endotoxin, microbial burden, drug content and surface ligand density. Scale-up from batch synthesis to continuous or intensified processes may change mixing, heat transfer and crystallization kinetics. A design-of-experiments and quality-by-design strategy should connect process parameters to critical

quality attributes, with validated analytical methods and reference standards.

For parenteral products, sterile filtration may be impossible for larger particles, making aseptic processing or terminal sterilization decisions central early in development [4,5].

As of the literature reviewed for this article, MOF drug delivery remains largely preclinical. A notable clinical translation example is the nanoscale hafnium-based MOF candidate RiMO-301, reported as entering a phase 1 trial for radiotherapy enhancement; this should not be confused with an approved MOF drug. The field should distinguish framework-enabled delivery from therapeutic metal-organic products and should report trial status, route, dose, formulation and endpoint transparently.

Table 4. Translation-readiness checklist

Domain	Minimum evidence before clinical development
Material identity	Reproducible PXRD, composition, morphology, surface chemistry and defect profile across multiple batches.
Pharmaceutical quality	Validated assay, impurities, residual solvents, endotoxin, sterility strategy, stability-indicating methods and release specification.
Biological stability	Colloidal stability, aggregation, protein-corona behavior, metal/linker release and drug leakage in clinically relevant media.
Pharmacology	Exposure–response relationship, tissue distribution, intracellular delivery, active-drug release and comparison with an approved or clinically relevant control.
Safety	Single- and repeat-dose toxicity, immunotoxicity, complement activation, genotoxicity where relevant, organ accumulation and clearance.
Manufacturing	Scalable synthesis, process capability, batch-to-batch reproducibility, formulation robustness and container compatibility.
Clinical rationale	A defined unmet need where MOF-specific control improves therapeutic index, adherence, administration or outcome.

Future directions

Future work should prioritize clinically relevant endpoints over maximum loading. Standardized reporting of particle size in formulation medium, drug loading by validated chromatographic methods, release

under sink and nonsink conditions, metal mass balance, and pharmacokinetics will improve cross-study comparison. Human-relevant models—including organoids, disease-on-chip systems, primary immune cells and patient-derived xenografts—can reveal corona

formation, uptake and toxicity mechanisms missed by simple cell lines. Machine learning and computational reticular chemistry may accelerate selection of nodes, linkers and surface chemistries, but predictions must be linked to experimentally measured biocompatibility and manufacturability. Green synthesis, continuous processing, low-solvent activation and degradable or nutritionally familiar components may improve regulatory acceptability. The strongest candidates will likely be simple, scalable and purpose-built: a MOF should be selected when its structural control produces a clear benefit that conventional liposomes, polymers, lipid nanoparticles or hydrogels cannot reliably provide.

Conclusion

MOFs provide a powerful platform for advanced drug delivery because their composition, porosity, degradation and surface can be engineered together. Their demonstrated ability to load small molecules, proteins and nucleic acids; respond to pathological stimuli; and support targeted or combination therapy makes them important research materials. Translation, however, depends on solving stability, toxicity, scale-up,

reproducibility and regulatory characterization as integrated product-development problems.

A design framework that begins with the clinical use case and ends with quality-by-design and human-relevant safety testing offers the most credible route from laboratory MOF to pharmaceutical product.

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