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Metal-organic frameworks towards bio-medical applications

Xin Ma,^a Mathilde Lepoitevin,^{*a} and Christian Serre^{*a}

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This mini review summarises the progress in the field of MOFs and their use in biomedical applications, from their early discovery and conception, to more recent achievements including promising *in vivo* applications. It looks to identify in detail the main advantages and current limitations of MOFs, with emphasis on their synthesis, stability (chemical, colloidal) and toxicity issues, as well as proposing guidelines to circumvent these challenges in the near future, in order to meet the demanding criteria of clinical stage trials.

1. MOFs and biomedical applications

1.1. Introduction of MOFs

Metal-organic frameworks (MOFs) are synthetic crystalline hybrid porous compounds,¹ which since their discovery at the end of the 80's,² have emerged as one of the most attractive classes of porous solids. This is largely due to their unique structural and chemical diversity. Their pore geometry can vary from channels, cages, or even multi-modal pore systems, with pore size ranging from ultra-micropores to the mesoporous domain. These solids can also bear a specific and unprecedented variety of functionalities (acid-base, redox, polar or non-polar groups), associated with the quasi-infinite combination of ligands (carboxylates, phosphonates, azolates)³ and inorganic moieties (clusters, chains or layers of transition metals, 3p, lanthanides). This leads to thousands of architectures that in some cases can be predicted based on the building blocks and the directionality of the coordination.⁴

These attractive features, once combined with good biocompatibility and biodegradability,¹ following a careful choice of the metal and organic linkers, are suitable to meet the practical demands for several potential applications such as gas separation,^{5–7} transport⁸ and storage,^{9,10} catalysis,^{11–13} sensing,¹⁴ energy,^{15,16} and bioapplications.^{3,17}

1.2. Why MOFs in biomedical applications

Research in biomedicine is aiming to discover more effective treatments of diseases. This calls for a continuous multidisciplinary effort from research scientists, including chemists, pharmacists and biologists as well as physicists.

1.2.1. Pre-requisites for bioapplications

Requirements of materials in biomedical fields depend on the application in play, from *in vitro* diagnosis to clinical tests. If *in vivo* and drug delivery is considered, the biocompatibility of the carrier is the primary criterion. The lowest possible toxicity is desired. This calls for the use of non-toxic constitutive elements, as well as a need for the carrier to degrade once administered in the body or alternatively a lack of accumulation. Thus for any new nanocarrier, it is important to assess first the chemical and colloidal stability, and secondly, once an administration route has been selected, the biodistribution and pharmacokinetics. The efficacy of the treatment also requires the nanocarrier to reach its target; the particle shall (i) be stealth to escape from the immune system and (ii) reach the targeted zone or lesion. In both cases, this requires an adequate engineering of the outer surface of the carrier as well as a particle size control. Finally, the carrier should possess a drug loading as high as possible along with a controlled drug release depend upon the selected disease.

1.2.2. Advantages of MOFs in biomedical applications

MOFs are among the most promising classes of materials for bioapplications reported within the past two decades. Some of these solids are biodegradable and biocompatible, with a structure and composition that can be easily tuned to optimize the loading capacities (drugs, gases) and release properties to meet the requirements for drug delivery systems (DDS),^{18,19} imaging,^{19–22} sensing^{23–28} and tissue engineering.²⁹

1.3. Drug delivery systems (DDS)

One of the primary concerns with conventional chemotherapy is the need for a high dose of drugs due to inadequate biodistribution, resulting in multiple dose-related side effects.³⁰ This calls for the emergence of innovative and effective drug delivery systems (DDS).³¹ DDS consists of delivering drugs or other active compounds to a target with a controlled drug release. This allows for more effective therapy

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with minimal side effects. The materials selected to deliver drugs are called drug carriers, and to meet the requirements for an efficient therapy, the drug carriers are expected to: (1) entrap drugs efficiently with high payloads, (2) control the drug release and avoid the 'burst effect' (main release within the first minutes), (3) control matrix degradation, (4) offer the possibility to easily engineer its surface to control *in vivo* fate and (5) be detectable by imaging techniques.¹⁹

Beyond the traditional DDS carriers (liposomes, polymers...), an increasing number of possible nanocarriers have been established in recent years (mesoporous silica, zeolites, dendrimers, cages...). This includes MOFs, which have been used in preclinical studies for enhanced treatment for numerous diseases that are still challenges in modern society, such as tumor therapy,³² antibacterial,^{33,34} diabetes.³⁵

1.4. Biosensing and bioimaging

Biosensing and bioimaging are promising tools for achieving rapid, sensitive, and selective analysis in clinical diagnosis applications. The increasing demand for accurate sensing has boosted the design and manufacturing of functional materials. A variety of materials such as metallic nanoparticles,^{36,37} graphene Oxide (GO),³⁸ silica nanoparticles,³⁹ quantum dots⁴⁰ or metal-organic frameworks,^{41,42} have been used as platforms for the design of biosensors. Among them, MOFs with specific functional sites have sparked a lot of interest because of their diverse structures and multifunctionalities, allowing for specific molecular recognition and fluorescence generation and/or change. When it deals with sensing and imaging, apart from encapsulation, MOFs have been investigated as new imaging probes following mainly two strategies: (1) as fluorescence quenchers toward the fluorophores of analytes based on charge transfer,⁴³ fluorescence resonance energy transfer (FRET),⁴⁴ or photoinduced electron transfer (PET);⁴⁵ (2) fluorescence or luminescence properties that can react sensitively to their local environment or guest species are intentionally prepared

When it comes to *in vivo* diagnosis applications, the MOF particles shall be in the nanoscale regime, non toxic and biodegradable to enable a clearance with little side-effects after completing the desired task.^{46,47} Some MOFs exhibit such properties, which together with the above mentioned properties, make them an ideal platform for biosensing and bioimaging, paving the way for their use MOFs in clinical laboratory diagnostics in a near future.

2. MOFs' main limitations

Even though MOFs possess numerous advantages for biomedical applications, most current reports focus on the *in vivo* efficiency, and often neglect the fate of MOFs once administered inside the body and the possible longer-term side effects of this. In addition, there are still some important limitations, which means that MOFs do not meet yet all the

requirements of clinical biomedical applications, and researchers shall better address these requirements in a near future. In addition to the above-mentioned toxicity issues, main limitations include the stability in body fluids, control of particle size distribution, formulation stability, as well as *in vivo* efficient stealth and targeting properties.⁴⁸

To address these main limitations, several strategies are proposed as advanced surface modification routes. They typically associate nanoMOFs with polymers, supramolecular, lipids or other substances, to improve the MOFs' features for practical use in biomedicine. Surface modification of MOFs can be categorised into coordinative ligand or metal exchange, covalent and non-covalent surface modification.⁴⁹ When dealing with coordination surface modification, which has been extensively utilized to post-synthetically modify MOFs, ligands can be partially or completely exchanged by soaking/heating MOF crystals in appropriate solutions of the exchanging species. The covalent surface modification involves the selective unmasking of functionality at the outer surface of MOF crystals.⁵⁰ non-covalent surface modification relies on other interactions - such as electrostatic ones.

2.1. Toxicity

2.1.1. Limitations

Toxicity is one of the most significant issues in biomedicine. Even if MOFs can be predominantly considered safe for a wide range of potential applications, the toxicity of MOFs, and related composites, is still a critical challenge for a future translation of these nanocarriers to the clinical stage.

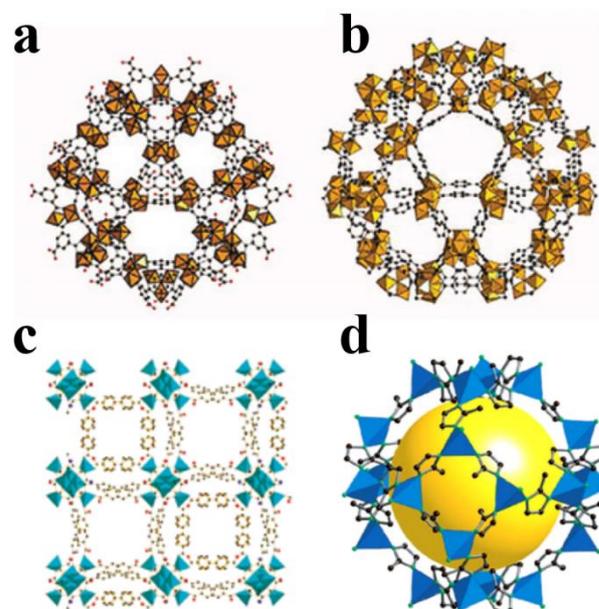


Figure 1 schematic diagram of (a) MIL-100(Fe), (b) MIL-101(Fe), (c) Bio MOF-1 and (d) ZIF-8. Reproduced with permission.^{19,53,60} Copyright 2014, Royal Society of Chemistry. Copyright 2011, American Chemical Society. Copyright 2020, Higher Education Press and Springer-Verlag GmbH Germany, part of Springer Nature.

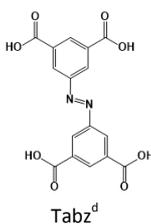
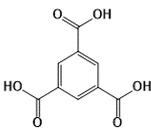
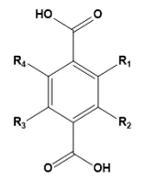
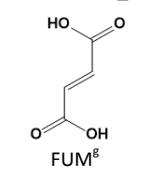
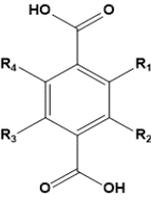
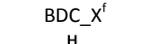
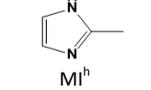
MOF NPs	M ^a	L ^b	R _n ^c	Size (nm)	ζ-potential (mV)	IC ₅₀ (mg/mL)			
						Hela		J774	
						MOF NPs	L ^b	MOF NPs	L ^b
MIL-127	Fe		-	476 ± 82	-38.5 ± 2.0	> 2.00	0.80 ± 0.02	0.44 ± 0.02	0.82 ± 0.17
MIL-100	Fe		-	120 ± 40	-18.3 ± 0.6	1.10 ± 0.15	2.00 ± 0.06	0.70 ± 0.02	> 1.00
MIL-101_2CH ₃	Fe		(CH ₃) _{1,3} (H) _{2,4}	120 ± 15	-24.2 ± 2.1	> 2.50	> 1.70	0.17 ± 0.01	0.80 ± 0.01
MIL-101_NH ₂	Fe		(NH ₂) ₁ (H) ₂₋₄	100 ± 18	-27.4 ± 1.5	> 1.00	0.60 ± 0.01	0.07 ± 0.002	0.02 ± 0.004
MIL-88A	Fe		-	105 ± 15	-25.0 ± 4.3	0.015 ± 0.005	0.03 ± 0.003	0.05 ± 0.002	0.40 ± 0.01
MIL-88B	Fe		(H) ₁₋₄	100 ± 20	-23.5 ± 1.8	1.26 ± 0.08	0.80 ± 0.02	0.37 ± 0.08	0.43 ± 0.03
MIL-88B_CH ₃	Fe		(CH ₃) ₁ (H) ₂₋₄	75 ± 20	-22.8 ± 2.2	> 2.00	1.05 ± 0.03	0.37 ± 0.01	0.24 ± 0.02
MIL-88B_2CH ₃	Fe		(CH ₃) _{1,3} (H) _{2,4}	100 ± 20	-26.0 ± 0.4	2.10 ± 0.08	> 1.70	0.36 ± 0.03	0.80 ± 0.01
MIL-88B_4CH ₃	Fe		(CH ₃) ₁₋₄	120 ± 20	-41.3 ± 0.6	0.69 ± 0.02	> 2.00	0.80 ± 0.01	0.42 ± 0.01
MIL-88B_2CF ₃	Fe		(CF ₃) _{1,3} (H) _{2,4}	105 ± 30	-53.2 ± 7.3	> 2.00	1.12 ± 0.08	0.41 ± 0.01	0.57 ± 0.01
MIL-88B_NH ₂	Fe		(NH ₂) ₁ (H) ₂₋₄	115 ± 20	-25.7 ± 1.6	1.10 ± 0.02	0.60 ± 0.01	0.45 ± 0.03	0.02 ± 0.004
MIL-88B_NO ₂	Fe		(NO ₂) ₁ (H) ₂₋₄	130 ± 15	-28.4 ± 0.7	> 2.00	> 2.00	0.03 ± 0.001	0.17 ± 0.01
UIO-66	Zr		(H) ₁₋₄	100 ± 20	-26.3 ± 1.5	0.40 ± 0.01	0.80 ± 0.02	0.06 ± 0.001	0.43 ± 0.03
ZIF-8	Zn		-	90 ± 15	-11.0 ± 0.6	0.10 ± 0.01	1.40 ± 0.02	0.025 ± 0.001	> 1.00

Table 1: Physico-chemical characterization of MOFs nanoparticles (size and ζ-potential), and their IC₅₀ at 24 h in J774 and Hela cells. a M: metal. b L: linker. c R_n: functionalisation. d Tabz: azobenzene-tetracarboxylic acid. e BTC: 1,3,5-benzenetricarboxylic acid. f BDC-X: 1,4-dicarboxylic acid or terephthalic acid. g FUM: fumaric acid. h MI: 2-methylimidazolate. Reproduced with permission.⁵² Copyright 2014, Royal Society of Chemistry.

Due to their versatility, a comprehensive evaluation of the toxicity of MOFs and related composites is therefore a prerequisite. Their toxicity is strongly influenced not only by their physicochemical properties, but also through the difference in tolerance of living tissues.¹ However, so far, most MOFs studies in biomedicine lack acute and/or short-term *in vivo*

toxicity studies, and only very few explore long-term toxicity of MOFs in human internal environment.⁵¹

Previous studies have successfully prepared a large series of nanoscale MOFs and evaluated their cytotoxicity using two different cell lines: human epithelial cells from foetal cervical carcinoma (HeLa) and murine macrophage cell line (J774). The cytotoxicity depends on the chosen MOF's composition,

particularly the nature of metal - where lower toxicity of Fe-based MOFs is expected in comparison with Zn- or Cu- based ones. The nature of the organic ligand, and in particular its solubility (usually related to its hydrophobic character) is also an important parameter. Aside from the composition, a faster internalization of MOFs in the (macrophage) cell line can also result in higher toxicity.⁵²

2.1.1.1. Toxicity of metal

The lethal dose 50 (LD50) and the daily dose of metals have a dominant impact on the toxicity of MOFs. The cytotoxicity of MOFs has indeed proven to be highly dependent on the nature of the metal.⁵² From Table S1, Fe and Ti stand out due to their excellent LD50, with Mg, Zr, Mn and Ca closely following. The most toxic metals considered for MOF biomedical applications are Zn and Cu. Higher LD50 will be associated with lower acute toxicity. On the other hand, Mg, Ca, Na and K are macro-elements in the human body while Fe, Zn, Cu, Mn, Cr, etc., are called trace metal elements. The daily need for Ca and Mg is the highest, followed by Zn and Fe, while the less needed metals are Ti and Zr. Metals required in higher doses by the body are also considered more friendly to the internal body environment. Metals required in lower quantities are barely absorbed by oral and dermal administration. This makes them more suitable for external body applications, for example in cosmetics.⁵³

2.1.1.2. Toxicity from linker

The toxicity of the ligand also plays a significant role in the toxicity of MOFs. In a recent review, the toxicity of benchmark MOFs, as well as their constitutive linkers, was evaluated by lethal concentration 50 (LC50) after 24 hours, using a Mouse BALB/c monocyte macrophages (J774) cell line and a human cervix epithelioid carcinoma (Hela) cell line, as shown in Table 1.

MOF's ligands can be either exogenous or endogenous, and synthetic or bioderived. The exogenous ligands usually do not interfere much with the human cycle.⁵⁴ In most cases linkers are simple polycarboxylate-based ligands such as terephthalic

acid (1,4 BDC), 1,3,5 benzenetricarboxylic acid (BTC) (LD50 of 1.13 and 5.5 g/kg respectively) or alternatively imidazole ligands

such as 2-methylimidazole (LD50 of 8.5 g/kg).⁵⁵ Benchmark MOFs in biomedicine, made from exogenous linkers, are iron(III) carboxylates such as MIL-100(Fe) (Figure 1a), MIL-101(Fe) (Figure 1b)^{56,57} (MIL for Material from Institut Lavoisier), zinc adeninate-4,40 biphenyldicarboxylate BioMOF-1 (Figure 1c),⁵⁸ or Zeolitic Imidazolate Frameworks such as ZIF-8 (Figure 1d).^{59,60} Some MOFs exhibit open metal sites, enabling direct binding to drug molecules. A recent example deals with a titanium(IV) tetracarboxylate, denoted MIP-177, which upon contact with the biologically active NO molecule, led to the formation of nitrites on its inorganic building unit,⁶¹ in turn leading to an unprecedented slow release in body fluid suitable for wound healing. For exogenous linkers, it is required that they do not accumulate once inside the body and thus are expected to be excreted out of the body after treatment. Previous toxicity studies indicated that exogenous polycarboxylic or imidazolate linkers exhibit low LD50s due to their high polarity and easy removal under physiological conditions.⁵³ For instance, in the toxicity study of MIL-100(Fe) and MIL-88B-4CH₃,⁵⁴ BTC and tetramethyl terephthalic acid (BDC-4CH₃) were proven to be fully excreted through urines and feces without any further biotransformation.

Biocompatible MOFs with endogenous bio-ligands or active ingredients have been designed. Endogenous ligands are expected to decrease MOF toxicity by reducing non-active undesirable compounds in the human body. So far, many endogenous ligands have been proposed to produce bioMOFs, such as peptides,⁶² nucleobases,⁶³ carbohydrates,^{64,65} porphyrins,⁶⁶ as well as some active ingredients.^{54,67,68} Unfortunately, most of these bioMOFs are still in the initial stages of development, sometimes non-porous or water-unstable and only a few have undergone *in vivo* preclinical evaluation.

2.1.1.3. Impact of the synthesis route

Apart from their composition, the synthetic route of MOFs

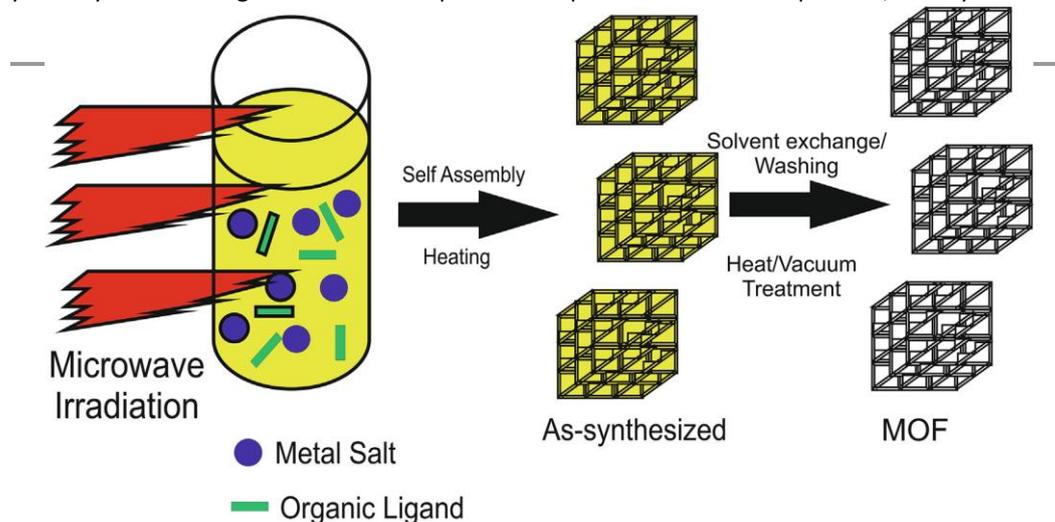


Figure 2 Microwave method for synthesis of MOFs. Reproduced with permission.⁷³ Copyright 2020, Elsevier B.V.

may also impact their toxicity. In this section, we will describe different MOFs synthesis techniques, their advantages and limitations with regards to biomedical applications.

Solvothermal synthesis

Conventional solvothermal synthesis is an efficient, archetypal method for the preparation of MOFs. It involves the use of metal salts, organic linkers and organic solvents.⁶⁹ Polar solvents with a high boiling point such as methanol, acetonitrile, dimethyl sulfoxide, dimethylformamide (DMF), and some of their mixed solutions, are preferred to obtain faster and uniform nucleation during crystal growth.⁵³ However, most of these solvents are highly toxic; short-term exposure to DMF or chloroform could lead to abdominal pain, nausea, vomiting,..., whereas long-term exposure is likely to cause liver damage.⁷⁰ Moreover, the use of toxic solvents enhance MOF toxicity due to traces of solvent molecule that remain in the pores. Unfortunately, these solvents are still commonly used, even in biomedical research. In the latter case, extensive washing is needed to remove solvent before using MOFs. This is not only time-consuming and labor-intensive, but also difficult to gauge when all solvent has been successfully removed. For example, zirconium-based NU-1000 with large channel diameters was synthesized in DMF,^{35,71,72} for the application of gene⁷¹ and oral insulin delivery,³⁵ and the removal of the DMF was verified by H NMR.⁷¹

Microwave-assisted synthesis

Microwave irradiation solvothermal synthesis is one of the best methods in terms of both controlling the particle size and obtaining rapidly high yields. It also reduces the time required for MOF crystallization at different temperatures without causing structural deformation to the MOF.⁶⁹ Polar solvents are also favored based on the microwave absorption capacity of solvents (Figure 2).⁷³ This method allows control over the face morphology and particle size distribution. Typical MOFs including IRMOF1 (zinc oxide with 1,4-benzenedicarboxylate),

IRMOF2 (zinc oxide with 2-bromoterephthalic acid), IRMOF3 (zinc oxide with 2-aminoterephthalic acid),⁷⁴ MIL-100(Fe),^{75,76} MIL-101(Fe)-NH₂⁷⁷ and HKUST-1⁷⁸ can be synthesized using this method.

Sonochemical synthesis

Another synthesis method, selected for the preparation of micro and nano-sized MOFs, is sonochemistry. This is a rapid and environmental-friendly route. Sonication enables the obtention of smaller particles using milder conditions.⁷⁹ The synthetic rate was higher than microwave-assisted synthesis for both MIL-53(Fe)^{80,81} and MOF-74.⁸² The sonochemical technique has been applied for the construction of sundry MOF networks like HKUST-1,⁷⁸ MOF-5,⁸³ MIL-53 (Fe).⁸⁰

In summary, microwave- and sonochemical-assisted syntheses are both efficient routes for MOF, and allow the control of size distribution at mild conditions, especially for nano and micro-particles. Nevertheless, the choice of the solvent for MOF synthesis for use in biomedical applications is primordial. Up to now, most have considered the use of toxic solvents. The LD50 of DMF,⁸⁴ methanol,⁸⁵ acetonitrile,⁸⁶ pyridine⁸⁷ and dimethyl sulfoxide⁸⁸ are 2800, 5628, 3800, 1580 mg/kg and 17.9 ml/kg, (oral for mice) respectively. The development of greener methods and the use of greener solvents such as in the hydrothermal route should be utilized where possible to reduce hazardous reagents or by-products and to maximize yields.⁸⁹

2.1.2. How to reduce the toxicity of MOFs

To minimise the toxicity effects of MOFs, the nanoparticles can be coated by biomolecules. As for coordination modification, Gu *et al.* shielded Zr-based MOFs, e.g., PCN-223, with DOPC phospholipid bilayers (PBLs) through the formation of metal-phosphate coordination. The lipid bilayer coating led to a decrease of the cytotoxicity. (Figure 3)

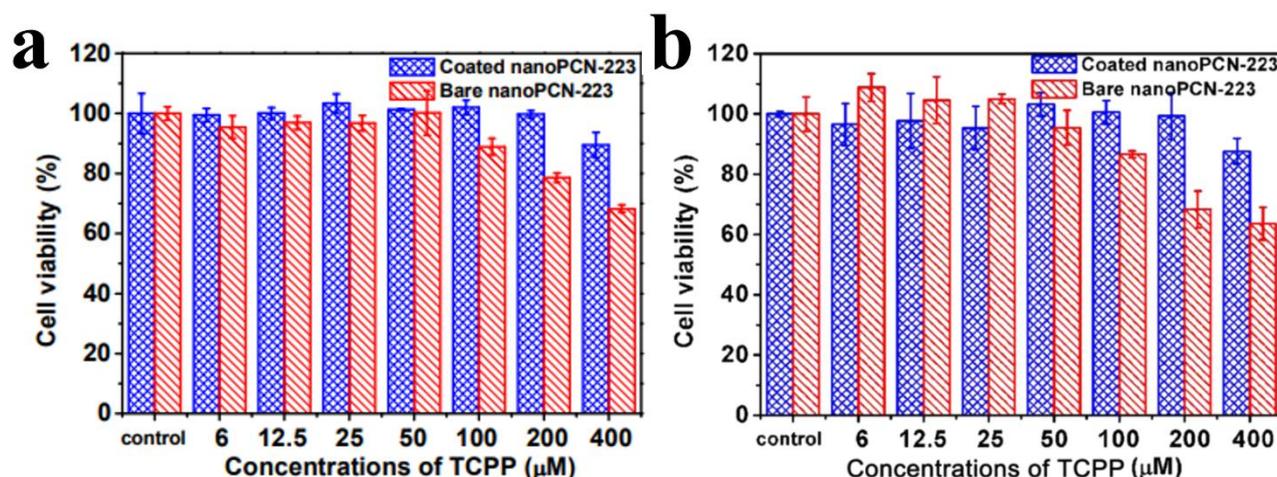


Figure 3 Viability test of HeLa (a) and SMMC-7721 (b) cells with different concentrations (0–400 μM) of bare and coated nanoPCN-223 after 24 h of incubation. Reproduced with permission.⁹⁷ Copyright 2017, American Chemical Society.

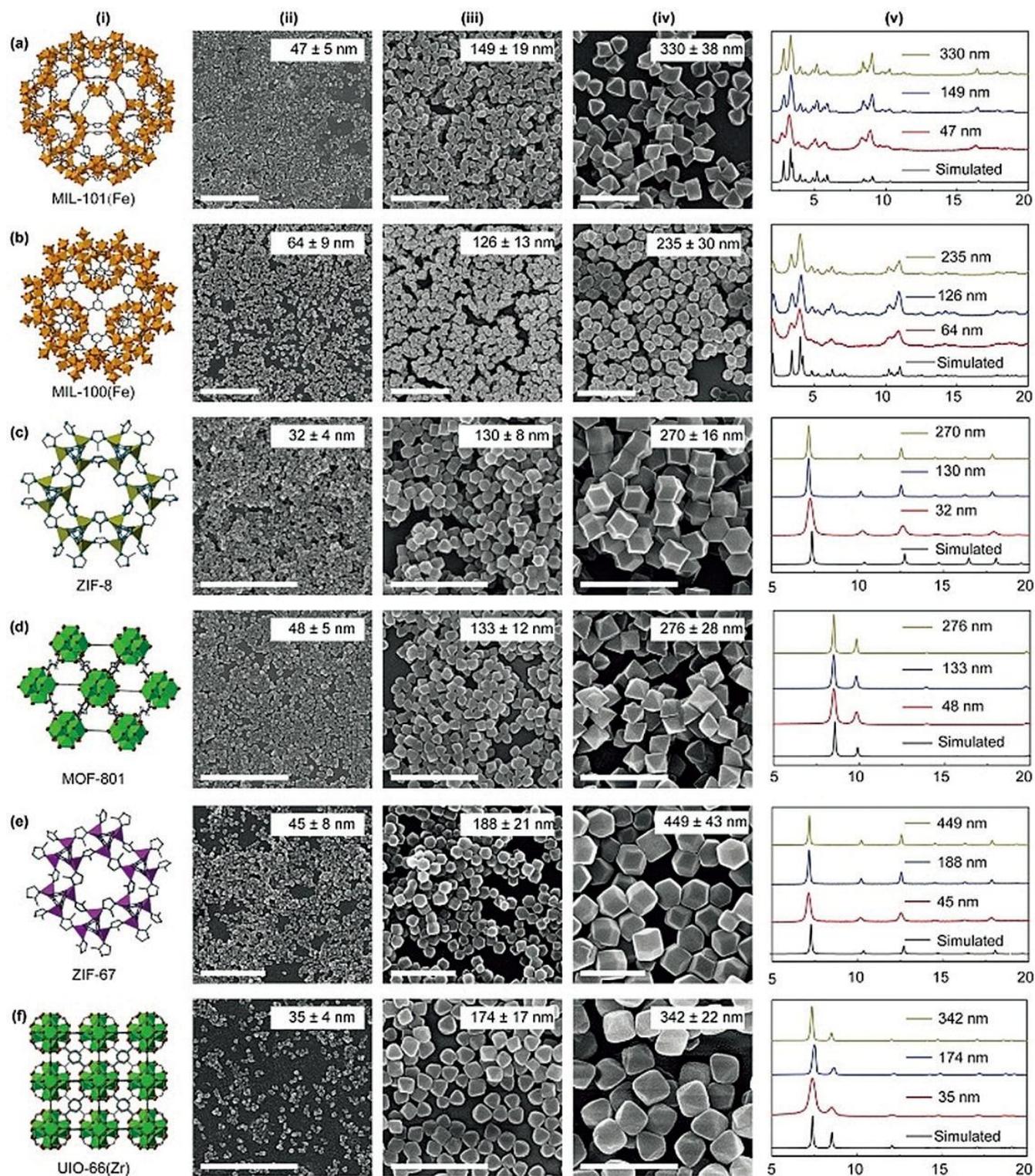


Figure 4 : crystal structures of (a) MIL-101(Fe). (b) MIL-100(Fe). (c) ZIF-8. (d) MOF-801. (e) ZIF-67. (f) UIO-66-(Zr). (ii)–(iv) FEMSEM images of representative nanoMOFs of different sizes. Scale bar: 1 μ m. (v) Simulated and experimental PXRD patterns of different sized nanoMOFs. Reproduced with permission.⁹⁶ Copyright 2018, Wiley-VCH Verlag GmbH & Co. KGaA, Weinheim

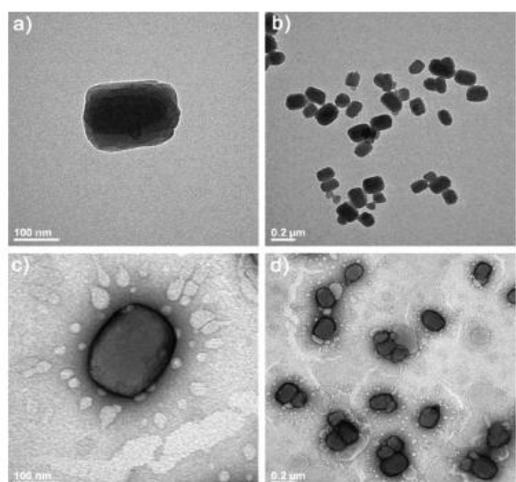


Figure 5 Negative-stained TEM images of (a, b) the bare nanoPCN-223 and (c, d) the coated nanoPCN-223@DOPC/DOPC particles. Reproduced with permission.⁹⁷ Copyright 2017, American Chemical Society.

Covalent modification is also utilized to decrease toxicity side effects. In 2020, Cong *et al.* coated MIL-53(Fe) nanoparticles with PEG then folic acid (FA). The MTT cytotoxicity tests carried out on HeLa cells showed an 80% cell viability for a dose of 25 $\mu\text{g}/\text{mL}$ for the bare MIL-53 against 100 $\mu\text{g}/\text{mL}$ for the coated nanoparticles.⁹⁰ A similar effect was observed by Ren *et al.* upon the PEG coating of ZIF-8 nanoparticles.⁹¹

In the numerous following attempts to minimize the toxicity of MOFs, most *in vitro* studies have shown only a slight decrease in toxicity, including the use of surface modification. Among the different strategies proposed to date, it is important to consider developing systems without increasing their complexity, as this can not only cause scale-up, cost and lower drug loadings issues, but could lead to additional long-term toxicity issues, reducing the likelihood of their use in biomedicine.

2.2. Size dispersity

2.2.1. Limitations

Particle size and polydispersity influence the physicochemical properties of MOFs (rheology, external surface, reactivity, packing, etc.). In biomedical fields, well-defined MOFs with mono-dispersity are needed. Particle size limitations vary depending on the administration route. Nanoparticles typically below 200 nm are required in parenteral routes to (i) freely circulate in the smallest capillaries, (ii) exhibit an enhanced permeability and retention (EPR) effect, associated with longer blood circulation times, (iii) reach higher cellular uptake for target tumor therapy together and (iv) with higher drug viability and fewer side-effects. Cell uptake happens through either endocytosis for particles smaller than 0.5 μm , or phagocytosis for particles larger than 0.5 μm . In the case of inorganic composites, particles within 5-10 nm can be easily filtered by kidneys or trapped in the hepatic parenchyma. Particles larger than 200 nm, are filtered in the liver or spleen, and particles larger than 4 μm will remain in the lungs until

degradation.^{92,93} In addition, the smaller the particle is, the faster the kinetics of drug release and the higher the penetration ability into cellular membranes will be.^{48,89,94} However, the size and mono-dispersity control is still a major challenge that needs to be addressed, and surface functionalization is a common solution to this.

2.2.2. Routes to improve the stability

MOFs size and mono-dispersity influence the physicochemical properties of MOFs. Many studies have focused on controlling MOF particle size and dispersity. The particle size depends strongly on the selected synthetic route. Even though a large number of synthesis routes have been reported to date, see part 2.1.1.3, producing nanoparticles of MOFs with a controlled particle size distribution following green and scalable protocols is still in its infancy.⁹⁵ Low-dispersity and size-controlled particles can be synthesized only if rapid homogeneous nucleation occurs followed by a separate growth. In 2018, Wang *et al.* proposed a protocol for MOFs, from nano to sub-micrometer size, through the control of supersaturation as well as a high control of the reaction conditions, for series of benchmark MOFs: HKUST-1, MIL-101(Fe), MIL-101-NH₂(Fe), MIL-100(Fe), ZIF-8, MOF-801, ZIF-90, ZIF-67, and UiO-66(Zr) (Figure 4). However, in most cases, a toxic solvent was used such as DMF. Thus developing new solvent-free synthesis routes will increase chances for these nanomaterials to reach bioapplication.⁹⁶

Surface coated nanoMOFs with a size around 100 nm and a rather low polydispersity have been reported. For example, bare PCN-223 and PCN-223 with phospholipid bilayers (PLBs),⁹⁷ (Figure 5a-d). The uranium ions accumulated uniformly around the nanosized coated PCN-223, and evidenced the formation of PLBs on PCN-223. Moreover, the supported PLBs on PCN-223 showed little aggregation, and the particle size remained around 200 nm. Nanosized PCN-333 (nPCN-333) around 100 nm (Figure 10a) with a low polydispersity, was proposed for

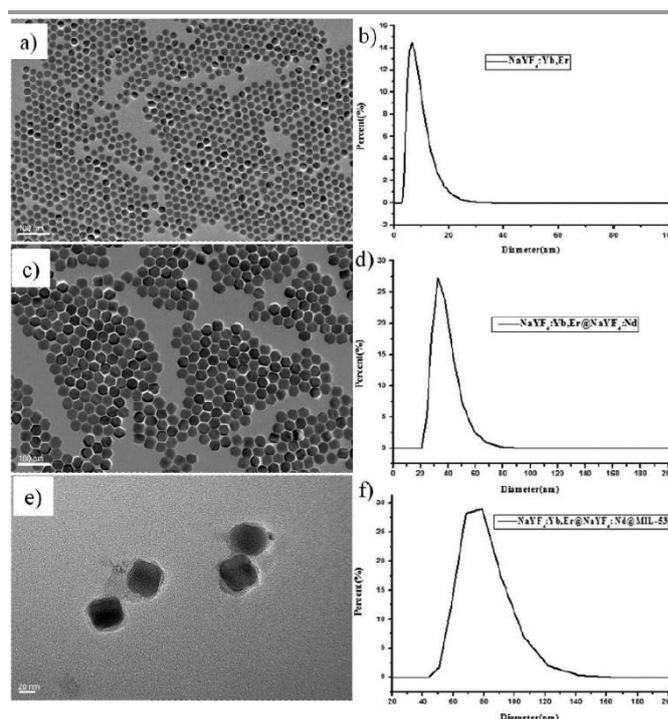


Figure 6 TEM images of (a) oleate-stabilized NaYF₄:Yb,Er, (c) oleate-stabilized NaYF₄:Yb,Er @ NaYF₄:NdUCNPs, (e) core-shell UCNPs@Fe-MIL-53-NH₂ as well as corresponding DLS spectra of (b) oleate-stabilized NaYF₄:Yb,Er, (d) oleate-stabilized UCNPs, (f) core-shell UCNPs@Fe-MIL-53-NH₂. Reproduced with permission.³⁰ Copyright 2020, Taylor & Francis Group, LLC.

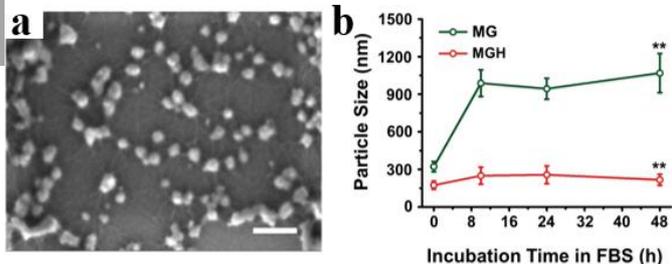


Figure 7 (a) The SEM image of MGH nanoamplifier. (Scale bar: 200 nm); (b) The particle size of MG and MGH nanoamplifiers during incubating in the medium containing FBS. Reproduced with permission.¹⁰⁵ Copyright 2019, Elsevier Ltd.

cancer therapy by Zhou's group in 2018.⁹⁸

Covalent surface modification to control the particle size has also been investigated to develop MOF nanoplatfoms for multi-functional bio-applications. In 2020, Zhu and his team made a platform for synergistic chemotherapy and photodynamic therapy with ZIF-67 and ZIF-8.⁹¹ 130 nm nanoMOFs were prepared and covalently coated with PEG, leading to particles of 150 nm with a low polydispersity index (< 0.2). Concomitantly, Cong and co-workers designed nanoparticles of *ca.* 80 nm, by upconverting nanoparticle (UCNPs)@MIL-53, but DLS analysis (Figure 6) revealed this led to an increase in polydispersity.⁹⁰ Nanoparticles of *ca.* 100 nm of UiO-68-NH₂@UCNP, non-covalently coated, were also utilized by Li. *et al.* for photodynamic theranostics through electrostatic interaction.⁹⁹

Although 100 nm MOFs with polydispersity indexes lower than 0.2 can be obtained, their synthetic routes using toxic solvents are still imperfect and it is hard to decrease the polydispersity after surface modification. Moreover, even though MOF size control and mono-dispersity can be achieved after synthesis, their long-term control, especially in biological conditions, is still a considerable issue. So how can MOF stability be improved?

2.3. Stability

MOFs in biomedicine require both good chemical and colloidal stability - an even greater challenge in body fluids (i.e., pH 7.4, phosphate and salt concentrated, biomolecules...). The aggregation of MOF particles induced by a lack of colloidal stability results in formulation issues and administration limitations; too fast degradation of the MOF might cause undesirable drug delivery effects, while the absence of degradation might cause long-term toxicity effects.

2.3.1. Colloidal stability

2.3.1.1. Limitations

Colloidal aggregation of MOF nanoparticles is one of the most critical challenges to be addressed. After the preparation of the particles, one shall first consider potential aggregation issues upon long-term storage, and subsequently, the re-dispersion of the particles in solution prior to the administration.¹⁰⁰

Lyophilization is one of the most widely-used methods to handle and stabilize drug nanocarriers and prevent undesirable changes during storage. The eviction of water by lyophilization could help to overcome the degradation of MOFs in aqueous conditions. Nevertheless, lyophilization could

adjust margins

also affect the robustness and size of the MOFs, ultimately leading to consequences in the colloidal or mechanical stability.¹⁰¹ Cryoprotectants may be selected to improve the stability of MOFs upon lyophilizing, in order to protect them from the mechanical stress of ice crystals.¹⁰²

Secondly, it is necessary to evaluate the aggregation of MOFs once they have been incubated in physiological conditions.⁵⁵

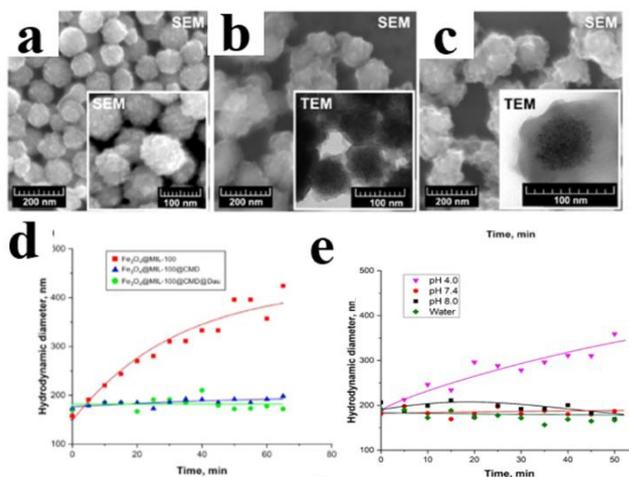


Figure 8 (a-c) Scanning electron microscopy (SEM) and transmission electron microscopy (TEM) images of: (a) initial magnetite nanoparticles (Fe₃O₄); (b) magnetic core-shell nMOFs (Fe₃O₄@MIL-100); (c) magnetic core-shell nMOFs coated with carboxymethyl-dextran (Fe₃O₄@MIL-100@CMD); (d) Time evolution of the hydrodynamic diameter of Fe₃O₄@MIL-100 (red), without daunorubicin (Fe₃O₄@MIL-100@CMD (blue)) and daunorubicin-loaded (Fe₃O₄@MIL-100@CMD@Dau (green)) nMOFs in physiological solution (0.15 M NaCl, pH = 7.4); (e) Time evolution of the hydrodynamic diameter of MMOF@CMD@Mab@Dau nMOFs in water and phosphate-containing buffers with different pH (0.15 M, RT). Reproduced with permission.⁷⁵ Copyright 2019, Acta Materialia Inc. Published by Elsevier Ltd.

solution (0.15 M NaCl, pH = 7.4); (e) Time evolution of the hydrodynamic diameter of MMOF@CMD@Mab@Dau nMOFs in water and phosphate-containing buffers with different pH (0.15 M, RT). Reproduced with permission.⁷⁵ Copyright 2019, Acta Materialia Inc. Published by Elsevier Ltd.

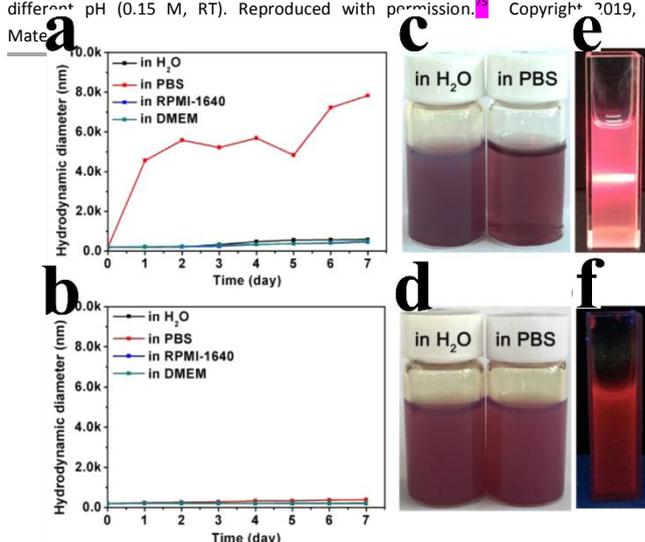


Figure 9 (a) Time evolution of the hydrodynamic diameter of nanoPCN-223 in H₂O, PBS, RPMI-1640 and DMEM media, respectively. The corresponding photographs of (c) bare and (d) coated nanoPCN-223 in H₂O and PBS for 7 days, indicating a serious aggregation and precipitation for bare nanoPCN-223 in PBS. (e) Tyndall phenomenon of coated nanoPCN-223 after 7-day aging in PBS solution. (f). A digital picture of coated nanoPCN-223 in PBS solution under UV illumination. Reproduced with permission.⁹⁷ Copyright 2017, American Chemical Society.

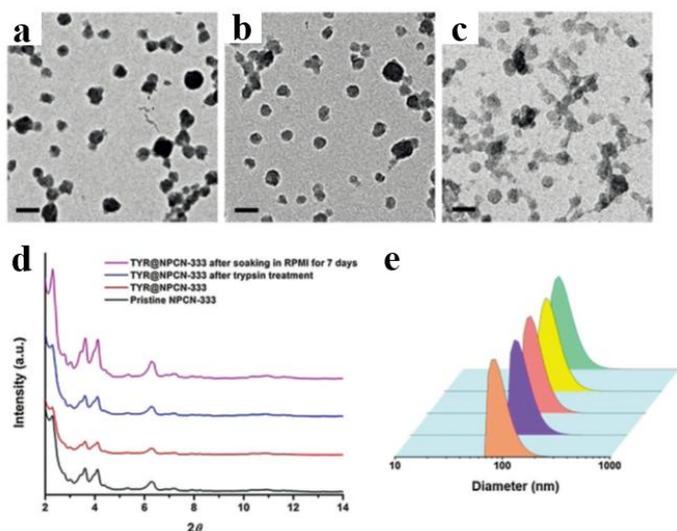


Figure 10 Structural characterization of NPCN-333. TEM images of NPCN-333 (a), TYR@NPCN-333 (b), and TYR@NPCN-333 after soaking in RPMI-1640 for 7 days (c). Scale bar: 200 nm. d) Powder X-ray diffraction (PXRD) patterns of pristine NPCN-333 (black), TYR@NPCN-333 (red), TYR@NPCN-333 after trypsin treatment (blue), and TYR@NPCN-333 after soaking in RPMI 1640 media for 0 and 7 days. Reproduced with permission.⁹⁸ Copyright 2018, Wiley-VCH Verlag GmbH & Co. KGaA, Weinheim.

issues also need to be addressed, as for any type of nanocarriers. The colloidal stability of nanoMIL-100(Fe) in physiological conditions was systematically studied by some of us within the past few years, through the monitoring of the size and surface charge of MOFs.¹⁰³ It has been indicated that MIL-100(Fe) nanoparticles are rather unstable and aggregate at 37 °C even in pure water. Moreover, if one reduces electrostatic repulsion between nanoparticles, this decreases the stability of the MOF particles. Nevertheless, under intravenous administration, the presence of a protein corona was shown to hamper the degradation of the nanoMOFs and promote their colloidal stability. On the contrary, when nanoMIL-100(Fe) was exposed in oral conditions, the pancreatin corona formation provoked a faster degradation. The glycosylated coating after incubation with mucin possesses bioadhesive properties, and prevented rapid degradation and aggregation of MIL-100(Fe).

2.3.1.2. Improving the formulation

Within the past few years, several strategies have been proposed to improve colloidal stability - one of the major limitations of MOFs in biomedicine. Surface modification is one of the most common strategies to overcome this.

Several recent approaches for the covalent modification of MOFs have mainly reported improved colloidal stability.¹⁰⁴ For example, polydopamine modified hyaluronic acid (HA-PDA) was covalently grafted on the surface of nanoparticles of MIL-100(Fe), and the enhanced dispersibility and remarkable stability of the HA-PDA coated MIL-100 (MGH) was compared with the bare MIL-100 (MG), and was confirmed even after 2 days of incubation in FBS (Figure 7).¹⁰⁵

Coordinative modification methods were also used for the enhancement of MOF stability. For instance, Nikiton *et al.* coordinatively coated carboxymethyl-dextran (CMD) on the

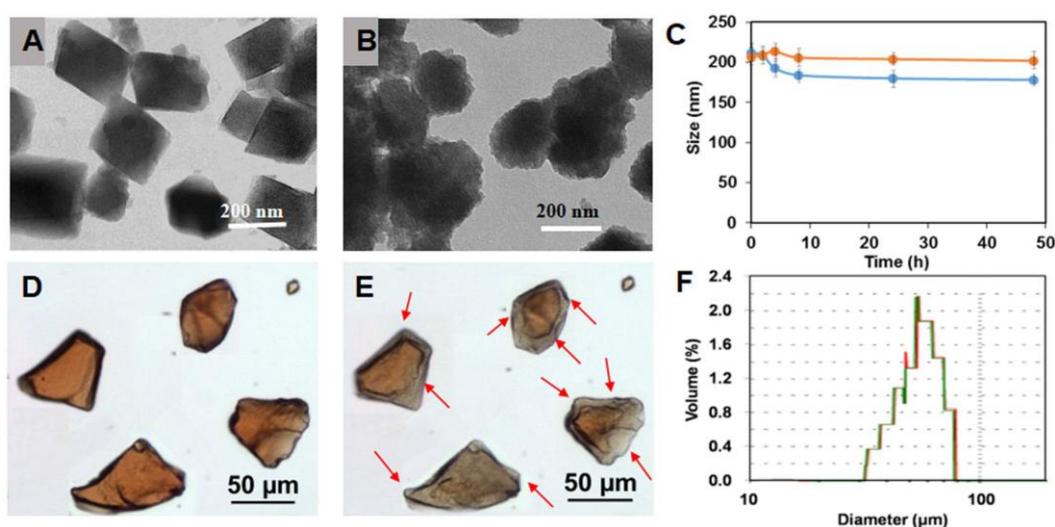


Figure 11 Morphology of MIL-100(Fe) nano- and microMOFs and size variations after incubation in water or PBS. TEM images of nanoMOFs before (A) and after (B) degradation in PBS (1.19 mM) for 6 h. Size variation (C) of nanoMOFs (100 µg/mL) in MilliQ water (orange) and PBS (0.12 mM, blue) for 2 days. Images of microMOFs observed by Raman-microscopy before (D) and after (E) degradation in PBS (11.9 mM) for 8 days; size distribution (F) of microMOFs before (green) and after (red) degradation. Reproduced with permission.¹¹² Copyright 2017, Scientific Reports.

This is critical for biomedical applications, although storage

surface of *ca.* 100 nm nanoMIL-100(Fe), leading to enhanced stability in physiological conditions while maintaining a high drug loading capacity (15.7 mg/g).⁷⁵ SEM and TEM images of the nanoparticles in Figure 8a-c showed a lower aggregation of the nanoparticles after CMD coating, leading to enhanced colloidal stability of the coated Fe₃O₄@MIL-100 particles in physiological solution (Figure 8d,e), further loaded with Daunorubicin (Dau). Gu's work evaluated the phospholipid coating capacity to improve the colloidal stability of Zr carboxylate nanoMOFs. Increased colloidal stability of PCN-223 in water, PBS and cell culture medium was achieved by shielding these Zr-based MOFs with DOPC phospholipid bilayers (PLBs).⁹⁷ Colloidal stability of the bare nanoPCN-223 and PLBs coated PCN-223 was evaluated by long-term size and dispersity of the particles in water, PBS, and cell culture media (Figure 9). It was proven that the hydrodynamic size of the bare MOFs increases as a function of the incubation time, and the size of MOFs incubated in PBS increased the most. After coating with PLBs, the hydrodynamic size of the MOFs did however not change in water, PBS or cell culture medium over a 7-day incubation. PLBs coating on nanoPCN-223 enhanced their colloidal stability in PBS and other cell culture media. Other lipid coating strategies such as DSPE-PEG were used on UiO-66(Zr)-(COOH)₂. DSPE-PEG coated UiO-66(Zr)-(COOH)₂ could sustain their hydrodynamic size around 110 nm and PDI around 0.3 even after 3 days in PBS buffer.¹⁰⁶

Non-covalent surface modification could also improve the colloidal stability of MOFs. For example, cell membranes have been studied as a coating layer for MOFs to improve their stability through physical and electrostatic interactions.¹⁰⁷ Liangfang Zhang and his team proposed a platelet-membrane-coated ZIF-8 for siRNA delivery,¹⁰⁸ the size of ZIF-8 after coating could remain around 100 nm in PBS and serum environment for a week, indicating the apparent enhancement of the colloidal stability of ZIF-8 with the platelet membrane coating.

Even though most MOFs for biomedicine need to be coated, few new MOFs exhibit intrinsic colloidal stability even in cell culture media. In 2018, Zhou's group proposed an enzyme loaded Al-MOF nanoreactor tyrosinase-PCN-333 for prodrug activation in cancer cells.⁹⁸ After incubation in a cell culture medium for 7 days, the morphology and crystallinity were preserved as TEM (Figure 10b,c) and nearly unchanged PXRD results demonstrated (Figure 10d). Furthermore, (Figure 10e) the mono-dispersity of the nanoMOFs was confirmed by dynamic light scattering (DLS) analysis. However, there was no detailed explanation related to this unusual stability.

In conclusion, to reach better colloidal stability for MOFs nanoparticles in a physiological environment, several successful surface engineering strategies have been recently proposed. However, many problems still result, such as the need of understanding the improved stability in some cases, or the use of toxic solvents for the coating. Not mentioning the impact of the coating on the *in vivo* fate of the particles.

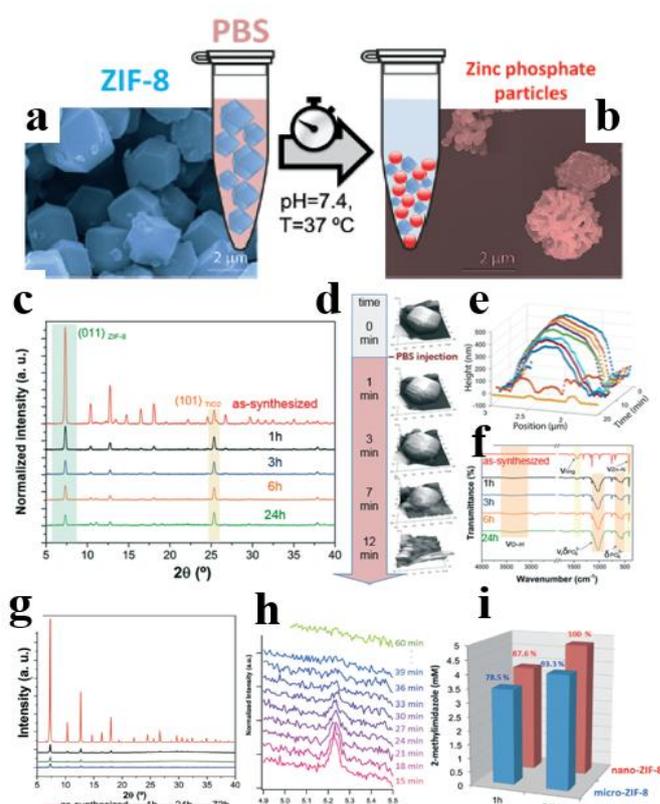


Figure 12 Incubation process of ZIF-8 particles in phosphate buffered saline media (PBS) under physiological conditions of pH (7.4) and temperature (37 °C). (a) SEM image of as-synthesized micro-ZIF-8 particles. (b) SEM image of micro-ZIF-8 particles after being soaked in PBS for 24 h. (c) PXRD patterns illustrating the structural evolution of micro-ZIF-8 particles before and after the incubation process in PBS. (d) Evaluation of the degradation process followed by *in situ* AFM experiments. (e) Height profiles extracted from (d), showing the morphological evolution of a single micrometric ZIF-8 particle upon the incubation in PBS (the first 6 min the measurements were performed in deionized (DI) water as incubation media). (f) Comparative FTIR spectroscopic analysis of the micro-ZIF-8 particles before and after the treatment with PBS. (g) PXRD diffractograms of nano-ZIF-8 particles before and after the incubation process in PBS (1 h, 24 h, and 72 h). (h) Time-resolved SAXS of nano-ZIF-8 particles dispersed in PBS (1X) solution. The reported *q* range (4.9–5.5 nm⁻¹) highlights the time-evolution of the intensity of the (011) diffraction peak of sod-ZIF-8. (i) Quantitative comparison of the degradation process suffered by nano- and micro-ZIF-8 particles by the determination of the concentration of 2-methylimidazole in the mother liquors. Reproduced with permission.¹¹³ Copyright 2019, Royal Society of Chemistry.

Furthermore, there is not study that has analysed the long-term continuous monitoring of the colloidal stability of MOFs which is a pre-requisite to reach industrial production and utilization of nanocarriers in biomedicine.

2.3.2. Chemical stability

2.3.2.1. Limitation

The ideal chemical stability of MOFs refers to the synchronisation of its *in vivo* degradation and the functional therapy effect expected for a given biomedical application. Most of the MOFs exhibit un-expected more serious intrinsic biodegradable behavior when in aqueous media, especially in the presence of phosphate, resulting from the relatively labile metal-ligand bonds of the MOFs structure, as well as the strong driving force between metal clusters and phosphate

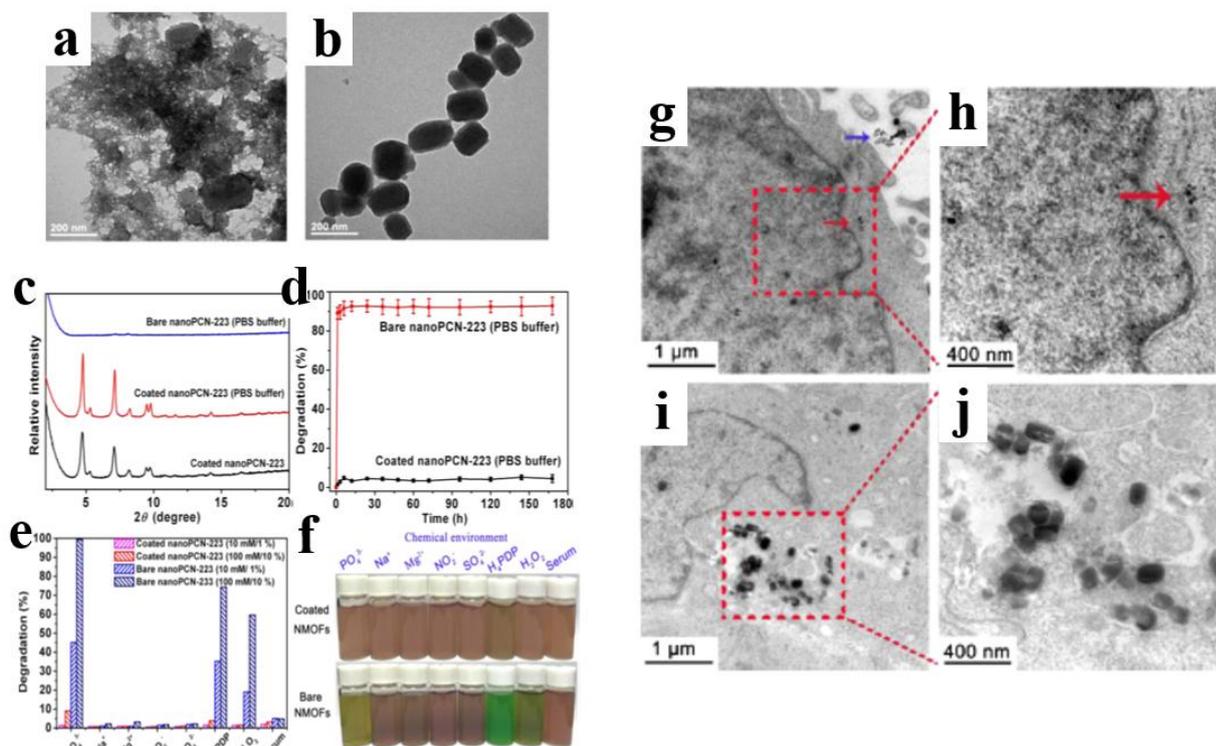


Figure 5 TEM images of (a) bare nanoPCN-223 and (b) PBLs coated nanoPCN-223 particles in PBS solution with 2-day incubation time. (c) Powder XRD patterns for coated nanoPCN-223 (Black), coated nanoPCN-223 in PBS (Red) and bare nanoPCN-223 in PBS (Blue). (d) Degradation rate of the bare and coated nanoPCN-223 in PBS for a 7-day incubation period. (e) Displacement of TCPP ligands from the bare and coated nanoPCN-223 by potentially coexistent ions (e.g., phosphate, Na^+ , Mg^{2+} , NO_2^- and SO_4^{2-} ; 10 mM and 100 mM each), H_4PDP (10 mM and 100 mM), reactive oxygen species (H_2O_2 , 1% and 10%) and serum (1% and 10%) in 2-day incubation time. (f) The corresponding photographs illustrating the changes of bare and coated nanoPCN-223 suspensions under various chemical environments (100 mM or 10% of the above compounds). (g, h) bare nanoPCN-223 and (i, j) coated nanoPCN-223. (h) and (j) are the enlarged images correspond to the rectangle sections in images g) and i). The red arrows in the images indicate the degraded fragment of bare nanoPCN-223 in the cytoplasm, whereas the blue one shows the presence of partially degraded nanoPCN-223 before endocytosis. Reproduced with permission.⁹⁷ Copyright 2017, American Chemical Society.

species.^{55,97,109} The opportune degradability velocity of the MOFs gives them the possibility to degrade slowly and to be eliminated out from the body to prevent endogenous accumulation and additional toxic effects. To complete the designed therapy assignment, a controllable slow degradation of MOFs is preferable to start the drug release to maximize the therapeutic effect.¹ The degradation of MOFs should not happen before reaching the target site.⁸⁹ MOFs are unstable in aqueous environments since protonated linkers or hydroxide metal nodes would be produced by hydrolysis at metal-ligand bonds or nodes of MOFs, which lead to selectivity loss along with deconstruction and degradation of MOFs.¹¹⁰ Over and above, the pH value in aqueous solutions influenced the hydrolysis pace, for example, an acidic solution could accelerate the construction of protonated linkers and the basic ones could generate metal nodes.¹¹¹

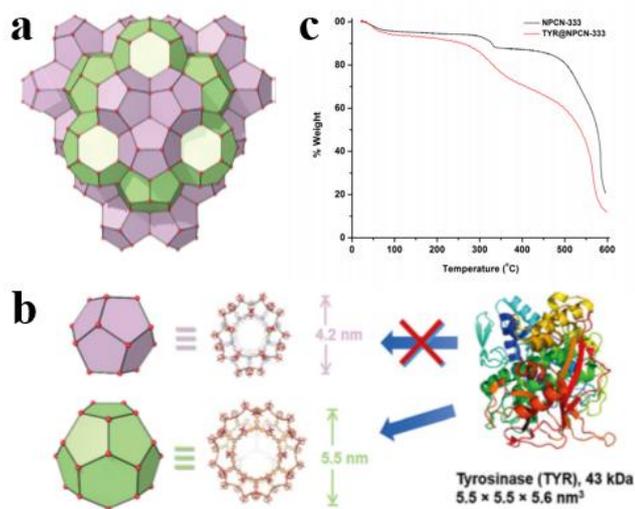
The degradation behavior of MOFs is still an important challenge in aqueous conditions, with the presence of phosphate, serum, and/or other biomolecules *in vitro*, as well as *in vivo*.⁸⁹ Some of us detected the degradation behavior of MIL-100(Fe) in the PBS environment for 8-day aging and lack of chemical stability of MIL-100(Fe) was shown.¹¹² (Figure 11) Falcaro's team reported the chemical and structural changes of ZIF-8 (particle size: 2 μm and 250 nm) incubated in

phosphate-buffered saline (PBS) solutions.¹¹³ In their works, the rapid deconstruction of ZIF-8 in PBS (10 mM) and the formation of zinc-phosphate particles were demonstrated. The nanoZIF-8 of 250 nm degraded faster than the micro one. As shown in Figure 12, 0.5 mg/mL of micro ZIF-8 was incubated in PBS buffer at pH 7.4, 37°C. After incubation, the framework changes were evaluated. From SEM, the rhombic dodecahedron structure becomes spherical-shaped zinc-phosphate nanoparticles (Figure 12a, b). PXRD results showed the peak intensity of the (011) plane of the crystal micro-ZIF-8 decreased after incubation in PBS (Figure 12c). It is noticeable that there is an intensity drop of 74% from its original value in 1 h, and after 24 h incubation, an 89% drop of its original value, suggesting that long-range order was lost during the degradation of ZIF-8 along with the amorphization of the by-products. A real-time in-situ AFM analysis along with other characterization was performed to monitor morphology changes (Figure 12d, e, f). A clear change of morphology appears in 3 min, and the crystal was γ dissolved in less than 15 min. Same trends were observed in nano-ZIF-8 degradation (Figure 12g, h, i).

2.3.2.2. Recent progress in chemical stability

Polymers,^{114,115} polysaccharides,^{116,117} phospholipids^{97,118} have been utilized as surface modification methods for improving

the chemical stability of MOFs in the physiological environment (PBS buffer, cell culture medium). Lipids and polysaccharides coatings led to better stability (chemical and colloidal) in PBS and cell culture media (DMEM and HPMI 1640), since the hydrophobic region of the lipids or polymers could provide a continuous shield around MOFs, which is particularly impermeable to ions, and could then protect vulnerable coordination bonds in MOFs from phosphate attacks.¹¹⁰ Since the degradation of carriers is one of the main causes of the burst effect, the improved stability of the MOFs could help avoid the burst effect of the loaded molecules within MOFs.



Like for colloidal stability, coordination modification is an important strategy to improve the chemical stability of MOFs. In 2017, Gu *et al.* shielded Zr-based MOFs, PCN-223, with DOPC phospholipid bilayers (PLBs) to protect coordination bonds in MOFs (PCN-223) from phosphate attack.⁹⁷ As shown in **Erreur ! Source du renvoi introuvable.**, the PLBs coating on nanoMOF PCN-223 could effectively protect nanoPCN-223 from the attack of phosphate, destructive cations, H₄PDP, reactive oxygen species, serum and intracellular environment, thereby ensuring that the nanoMOFs remain whole for a long enough time to complete their functions.

The covalent modification was also utilized for the improvement of the chemical stability of MOFs. Forgan *et al.* covalently modified PEG chains on the surface of UiO-66 by click modulation¹¹⁹. Bare UiO-66 showed an exponential degradation profile reaching a plateau of around 85% ligand release after 6 hours of PBS exposure. While the PEGylated UiO-66 showed sigmoidal degradation patterns reaching an 85% ligand release plateau after incubation in PBS for 24 h with a much slower degradation rate. The crystallinity of the MOFs after PBS incubation was retained from less than 18 min to 1 hour after PEGylated modification. The enhanced chemical stability of PEGylated UiO-66 might be because the phosphate attack onto the Zr₆ clusters was hindered by the surface corona of the attached PEG chains.

However, systematic research on the stability of materials is still rare, and deeper stability tests of MOFs in blood, PBS and cell culture media for further incubation aging (more than a week) are still needed.

3. Bioapplication process of MOFs

3.1. Drug loading and release

3.1.1. Limitations

Past investigations have depicted the application of MOF nanocarriers to achieve targeted drug delivery, increased cellular uptake, and controlled drug release, making MOFs a promising class of DDS, which includes anticancer drugs,³² antimicrobial agents,^{120,121} metabolic coding molecules,¹²⁰ antiglaucoma drugs,¹²² and hormone delivery.³⁵ MOFs are considered a promising emerging material in biomedicine as they combine the well-defined porosity of inorganic porous materials, with tuneable organic groups or metal nodes within the structure. The high porosity with a large surface area is a pivotal trait for high drug loading and controllable release. The organic linker and/or metal site yields encapsulation of diverse and large amounts of drugs, both of which mean an enhancement of drug viability and smarter design of DDS strategies.⁸⁹ Nonetheless, the loading capacities of distinguished MOFs with different drugs/molecules are different, for example, the doxorubicin (DOX) encapsulation in MIL-100(Fe) is 9.1%,^{53,123} while the urea loading in MIL-100(Fe) is 69.2%.³⁸ And the DOX encapsulation in CD-MOF is 6-8%,¹²⁴ while in ZIF-8, it is 20%.¹²⁵ In general, a higher drug loading capacity, as well as a controllable release without “burst effect”, remains to be enhanced.

3.1.2. Recent progress in drug delivery systems

3.1.2.1. Drug loading

To date, amounts of molecules have been selected to assess MOFs for drug delivery applications as therapeutic agents. For example, for intracellular delivery and cancer treatment, anticancer drugs like doxorubicin,¹²⁶⁻¹²⁸ cisplatin,¹²⁹ topotecan,¹³⁰ camptothecin,¹³¹ and 5-fluorouracil³² have been integrated into MOFs. Some photosensitizer^{132,133} and organic dyes^{32,134,135} from the near-infrared region (NIR) have been used for photodynamic therapy (PDT) and photothermal therapy. In recent years, the delivery of several biomolecules by MOF nanocarriers has also been studied, macromolecules, such as nucleic acids,^{71,136,137} proteins,^{35,138,139} carbohydrates, and small molecules, such as amino acids and fatty acids included. The drug loading process is governed by the accessibility of the MOFs cages and the loading capacity is influenced by the hydrophilicity/ hydrophobicity of the MOFs and the encapsulated molecule.¹⁴⁰ In general, drugs are loaded into MOFs by in situ encapsulation or post-synthetic modification. The former is a relatively straightforward approach for thermostable drugs to resolve the premature release of drugs. While the latter one, even though more

Carriers	DOX loading (wt%)	DOX encapsulation ratio (%)
F	11.0	38.7
M	10.7	37.6
F50M	18.0	65.0
F100M	18.2	67.3
F125M	19.4	70.2
F150M	18.7	65.9
F200M	14.7	51.8
F400M	13.4	49.7

complex and time-consuming, offers a milder atmosphere to prevent the destruction of drug molecules.

The *in-situ* encapsulation method (one-pot synthesis) allows the encapsulation of large molecules inside the cage of MOFs with small window openings, improves the drug loading capacity, and further alleviates the problem of premature drug release.³¹ *In-situ* encapsulation is the method of choice for the encapsulation of macromolecules, such as nucleic acids and proteins. Cas9 protein and sgRNA were co-encapsulated in ZIF-8 by one-pot synthesis and 1.2 wt% of Cas9 protein loading was confirmed by fluorescence labelling.¹⁴¹ Similar methods were used when loading siRNA in ZIF-8.¹⁰⁸

Drug loading through the post-synthetic strategy has been widely used. In Zhou's work in 2018, they loaded tyrosinase after synthesis of PCN-333 for prodrug activation in cancer cells,⁹⁸ the enzyme, tyrosinase (TYR) is a polypeptide (43 kDa) with size at 5.5 * 5.5 * 5.6 nm, so the TYR can be stacked in the larger cage with a diameter as 5.5 nm(see

a,b), the TYR loading efficiency was estimated as 0.80 g.g⁻¹, which was consistent with their theoretical value (1.08 g.g⁻¹). The high enzyme loading capacity was confirmed by TGA analysis (

c).

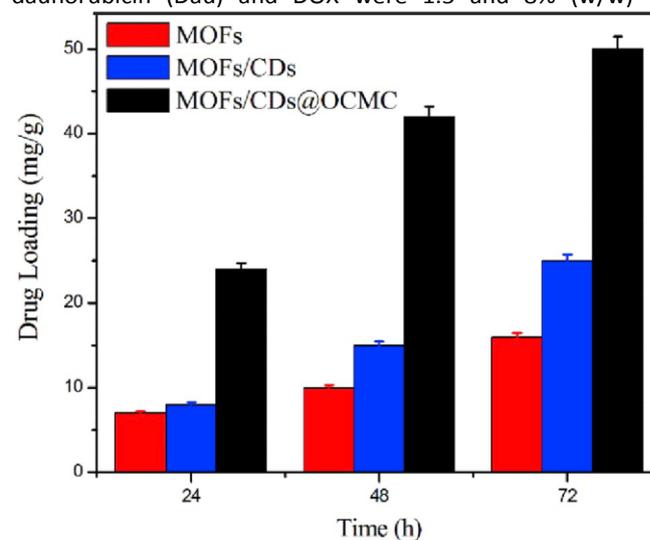
In addition, the drug loading capacity of MOFs might be influenced by nanoparticle surface modification methods. Purkait and his group investigated Fe₃O₄@MIL-100 as drug delivery agents for DOX.¹⁴² Different amounts of Fe₃O₄ were added to a series of synthesized MIL-100, DOX was loaded subsequently and the drug loading capacity of different Fe₃O₄@MIL-100 carriers (FxM), evaluated (

). The DOX drug loading efficiency of Fe₃O₄ and MIL-100 were similar (11 and 10.7 wt%, respectively). The presence of Fe₃O₄ in the MIL-100 composites, notably increased the DOX payloads from 10.7 wt% (for MIL-100) to 18 wt% (for F50M), as more Fe₃O₄ introduced in the MIL-100, the DOX loading capacity increased further. The maximum loading efficiency and encapsulation ratio (%) observed were 19.4% and 70.2%, respectively, for F125M. This enhancement of DOX loading

capacity of MIL-100 might be ascribed to the synergistic effect of the Fe₃O₄ nanoparticles as they augmented the interaction between DOX and MIL-100 framework. Further increase of Fe₃O₄ in MIL-100 framework (from composites F150M to F400M) provoked a decreased DOX loading efficiency, probably due to the blocking of MOF pores by Fe₃O₄.

Table 2 DOX loading capacity of Fe₃O₄ (F), MIL-100 (M) and Fe₃O₄@MIL-100 (FxM) composites. Reproduced with permission.¹⁴² Copyright 2017, Elsevier Inc.

As for surface modification methods, coating layers such as polysaccharides could improve the drug loading efficiency of MOFs, by the interaction between drugs and induced coating layers. For example, the carboxymethyl-dextran coating layer on the surface of MIL-100 was proposed by Nikitin and his team, the maximum payload for the studied drugs daunorubicin (Dau) and DOX were 1.5 and 8% (w/w) for



Fe₃O₄@MIL-100@CMD@Dau and Fe₃O₄@MIL-100@CMD@DOX nMOFs, respectively.⁷⁵ Another polysaccharide used was O-carboxymethyl chitosan (OCMC), OCMC was also proposed for modification of MIL-100,²¹ and Figure 15 Drug loading capacities of MOFs, MOFs/CDs and MOFs/CDs@OCMC. Reproduced with permission.²¹ Copyright 2019, Elsevier Inc..

DOX loading capacities results of the particles were shown in **Erreur ! Source du renvoi introuvable.** The drug loading efficiency of OCMC coated MIL-100 (MOFs/CDs@OCMC) was 50 mg/g, much higher than that of bare MIL-100 (15 mg/g). The -NH₂ and -OH of the OCMC and -NH₂ of DOX can form hydrogen bonds, therefore increasing the drug loading capacity of the particle.

Nonetheless, there are still challenges for drug loading in MOFs. For example, molecules embedded by surface adsorption and pore encapsulation tend to leak gradually due to poor interaction forces. Stronger interactions could be provided by covalent binding, but complex synthetic procedures are needed and the behavior of functional molecules might be changed.³¹ On the other hand, the organic ligands suitable for MOF synthesis are always rigid and highly symmetrical, which makes it difficult to use biomolecules directly as the building block. Besides, the encapsulation of

large molecules is another issue. The post-synthetic method could provide a milder environment for molecules, but the access of molecules is prone to be hindered by small windows. On the contrary, one-pot synthesis could improve the drug loading amount but the synthetic conditions might not be suitable for every macromolecule. Therefore, strategies to achieve high encapsulation of macromolecules without losing structural integrity remain to be studied.

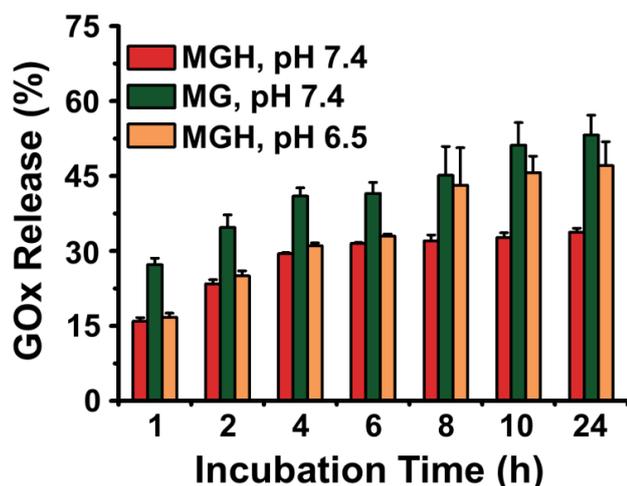


Figure 16 The cumulative GOx release from MG and MGH nanoamplifiers at pH 7.4 or pH 6.5. Reproduced with permission.¹⁰⁵ Copyright 2019, Elsevier Ltd.

3.1.2.2. Drug release

A few strategies to achieve better control of the drug release from MOFs were proposed recently to overcome the “burst effect”. This includes surface engineering of MOFs and triggered drug release.³¹

Stimuli-triggered materials have also been proposed to control the kinetics of drug delivery with MOFs.¹²³ These stimuli-responsive porous solids are capable of releasing their drug cargo upon application of various stimuli, e.g pH, ions, magnetic field, temperature, pressure and light with the combination of other functional materials. This is of particular interest when the kinetics of delivery is slow and thus can be triggered upon application of the stimulus when the drug-loaded particles have reached their target. However, there are numerous examples of drug-loaded MOFs that release their cargo too rapidly thus requiring alternative strategies to slowdown the drug release. This is the case of surface engineering. Functional nanoparticles encapsulated can be associated with slowing down the drug release. Purkait *et al*, in 2018,¹⁴² investigated the core-shell Fe_3O_4 @MIL-100 nanoparticles as DDS using DOX; the kinetics of drug release was significantly slowed down for up to 30 days in PBS (pH 7.4) with only a slipped “burst effect”, which was attributed to the Fe_3O_4 nanoparticles stuck in the pore of the nanoMOFs.

The surface coating can lead to a slowdown of the drug release by slowing down the rate of MOF degradation. Polydopamine-

modified hyaluronic acid (HA-PDA) coating led to the slower release in PBS (pH 7.4) of glucose oxidase (GOx) from MIL-100@GOx/HA-PDA (MGH) nanoparticles as compared to that of the bare MIL-100@GOx (MG) nanoparticles as shown in **Erreur ! Source du renvoi introuvable.**¹⁰⁵ There could be two reasons that cause the decreased GOx release. First, the coating layer around the surface of MOFs could obstruct the surface pore. A slight decrease of the surface charge of the particle after HA-PDA coating, associated with the grafting of HA-PDA on the surface of MIL-100, occurred, possibly due to coordination of HA-PDA through $-\text{NH}_2$ groups on the Fe metal sites. Such modification of the MOF outer surface could protect the MOF from the attack in physiological conditions and then reduce the drug release rate, owing to the slower degradation rate of the MOFs. Moreover, at lower pH (6.5) GOx release from MGH was accelerated, probably due to a partial detachment of HA-PDA from the MOF surface under more acidic conditions.

Despite these promises, the control of the kinetics of drug release is still far from being systematically achieved, depending on the application and the selected drug. Furthermore, there is still a strong lack of understanding of the complex interplay between all the parameters that drive such release. This calls for a continuous strong effort to develop new generations of controllable drug release MOF systems that are able to release their cargo at specific spatial and temporal manners, with a minimal pre-mature release, especially with long-term *in vivo* monitoring.⁸⁹

3.2. Biosensing and bioimaging

3.2.1. Limitation

Due to its diverse structures and multifunctionalities, a considerable effort has been devoted to the development of MOF-based biosensing and bioimaging applications.^{41,42} Main strategies consist of tuning the MOF (structure, composition) while adding new functionalities, in a view of molecular recognition. In addition, since the fluorescence can be issued from the metal and ligand moieties, as well as tuned by the interplay/interactions among the building components,^{143,144} MOFs are promising candidates for designing new fluorescent or luminescent sensors. Organic ligands with aromatic or conjugated *p* moieties, for example, can emit fluorescent light upon irradiation, while metal cations (lanthanides, transition metals, etc.) can also contribute to the photoluminescence.^{145,146} It has also been demonstrated that guest molecules can induce alterations in fluorescence or luminescence intensity through interactions with the framework. Recent studies have mainly been focused on the development of MOFs as Magnetic Resonance Imaging (MRI) or Computed Tomography (CT) contrast agents. MOFs are an efficient way to introduce metal centers into organisms. In MRI, Gd^{3+} - and Mn^{2+} - containing MOFs have been proposed, despite toxicity concerns, as T_1 -weighted contrast agents,^{106,147,148} and Fe^{3+} - containing MOFs have shown good T_2 -weighted contrast enhancement.¹⁴⁹ For CT imaging, high-Z elements (e.g., Hf and

Zr) have also acted as viable CT contrast agents.¹⁵⁰ However, the current research on MOF-based sensors and imaging agents, is still at its early stage; several issues must be addressed prior to translate MOFs into the realm of practical diagnosis as biosensors and/or bioimaging.^{151 152} MOFs and related composites shall : (1) exhibit emission and absorption bands that fall within the biological windows (650–950 nm and 1000–1350 nm) where tissue scattering and absorption are minimized, (2) be optically active in biological media, (3) be biocompatible with an easy uptake by cells. There shall also be reliable methods to integrate MOFs into other devices to facilitate signal transduction and readout as well.¹⁵³

3.2.2. Routes to improve MOF-based diagnosis

3.2.2.1. Near-infrared (NIR) emissive MOFs

The biological windows lie in the Near-infrared (NIR) and consist of either NIR-I: 650–950 nm or NIR-II: 1000–1700 nm. In order to promote the development of biological diagnosis research, fluorescent NIR emissive materials have been paid an increasing attention in nanomedicine. One of the most promising strategies is to use lanthanide ions (Yb^{III}, Nd^{III}, Er^{III}), which have long luminescence lifetimes and are resistant to photobleaching. However, when Ln^{III} compounds are directly excited, the molar extinction coefficients and forbidden nature of the *f-f* transitions of Ln^{III} ions can result in low luminescence intensity. The most efficient way to sort out this issue is to introduce an auxiliary chromophore. This molecule will be converted to the accepting electronic levels of the Ln^{III} ions after absorbing the light and energy via the "antenna effect."¹⁵⁴

Very recently, Yu and his co-workers designed a near-infrared emission Nd-based MOF (Nd-MOF-Y) by selecting 1,10-phenanthroline (L-N) and 2,3,5,6-tetrafluoroterephthalic acid (L-F4) with weaker vibration bonds and high energy level into the framework. The Nd-MOF-Y could detect explosives (cyclotetramethylene tetranitramine, HMX) with high sensitivity, selectivity, cyclicity, and low detection limit in the near-infrared range.¹⁵⁴

3.2.2.2. Facilitate signal transmission

The current non-invasive imaging or sensing strategies (e.g., MRI, CT, and Positron Emission Tomography (PET)) lead to important side effects/limitations due to radioactivity, long usage intervals, and/or low resolution.^{155–158} The next-generation of materials, including MOFs, shall overcome these limitations through the design of a more sensitive and safe preclinical diagnosis platform, facilitating transduction and readout of signals.

A FRET MOF-based near-infrared (NIR) excited nanosensors was developed by Li *et al.*¹⁵⁹ The BMU-Ru(bio-MOF-100-UCNPS@[Ru(dpp)₃]²⁺Cl₂) nanostructures exhibit unprecedented NIR-induced FRET efficiency, due to the integration of multiple UCNP donors and [Ru(dpp)₃]²⁺Cl₂ acceptors in close proximity, as well as the limited aggregation and steric restriction of [Ru(dpp)₃]²⁺Cl₂ inside the porous bio-

MOF-100. When used as hypoxia sensors, BMU-Ru nanostructures showed high sensitivity, reversible response, high selectivity, and robust stability, allowing them to detect low concentrations of O₂ under NIR excitation. In addition, *in vivo* non-small-cell lung cancer (NSCLC) lesion tracking was evaluated at the preclinical level using an engineered murine model (GEMM) for the first time without any apparent long-term toxicity. The optimization of energy transfer in MOFs, while not raising toxicity issues among other limitations, is still an important challenge in order to develop next-generation optical sensors to detect for instance tumor lesion progression in a non-invasive manner.

Conclusion and perspective

MOFs in biomedical applications are now well studied drug nanocarriers at the pre-clinical level but still suffer from many drawbacks such as toxicity issues, lack of systematic controlled release or targeting, lack of 'pharmaceutical quality' formulations, etc... Several recent approaches have been proposed to overcome these limitations such as smart surface engineering or multiple-stimuli-responsive systems, among others. These are however still stumped in the "proof-of-concept" stage. Most significantly, further systematic research into their toxicity after long-term use, as well as *in vivo* evaluation, should be carried out to further assess potential side effects previous to their clinical translation. Furthermore, If there is still an interest to propose new pre-clinical concepts, researchers in this field shall therefore better address all the requested parameters, and not only a few of them, for a given application. This encompasses not only chemical or colloidal stability, size dispersity, toxicity, control of drug loading and release or targeting properties that shall be evaluated *in vivo* but one shall bear in mind that the final formulation shall be easy to scale-up and be reproducible for clinicians, not only chemists, if one aims to transfer MOFs at the clinical stage in the near future.

Eventually, designing a MOF-based biomedicine platform from structural design to preclinical evaluation is an interdisciplinary target. Thus this requires a continuous trans-disciplinary effort from the early stage that gathers chemists, physicists, pharmacologists, biologists and finally clinicians, to overcome issues and fully exploit the potential of MOFs in biomedicine and reach clinical practice.

Conflicts of interest

There are no conflicts to declare.

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