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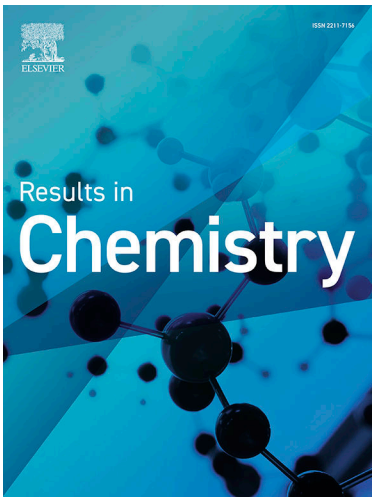

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Metal Organic Frameworks in Biomedicine: Innovations in Drug Delivery

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Abstract

Metal-organic frameworks (MOFs) have emerged as a class of versatile materials, finding extensive applications in drug delivery because of their unique properties and flexible design. This comprehensive review aims to give a broad perspective on the recent advancements in the area of drug delivery applications using MOFs. The fundamental characteristics of MOFs, highlighting their exceptional porosity, high surface area, and tuneable framework structures, enable MOFs to serve as ideal drug carriers, allowing efficient drug loading and controlled release. The review delves into the various ligands and metal ions employed for drug encapsulation. These include physical encapsulation, covalent bonding, and host-guest interactions, each offering distinct advantages for diverse types of drugs and therapeutic applications. The importance of tailoring MOF properties to optimize drug loading capacity, stability, and release kinetics has been emphasized. Additionally, the explorations involve delving into the mechanisms of drug release from MOFs, with factors such as pH, temperature, and external stimuli that can be harnessed to trigger controlled drug release. The utilization of MOFs in combination therapies, such as co-delivery of multiple drugs or integrating imaging agents, has also been examined. Numerous examples of MOFs used for drug delivery, encompassing both in-vitro and in-vivo studies, covering a wide range of therapeutic areas, including cancer treatment, antimicrobial therapy, and targeted drug delivery, are included. Additionally, the review addresses the challenges and future perspectives in the development of MOFs for drug delivery. Strategies to improve MOF stability, biocompatibility, and scalability are discussed, along with the understanding of MOF-drug interaction and potential toxicity concerns. With their tuneable properties, high loading capacities, and controlled

release capabilities, MOFs hold exceptional capabilities that promise to enhance the efficacy of therapeutic interventions. Continued research and development in this area can pave way for the translation of MOFs into clinical applications in the near future.

Keywords: Metal organic frameworks; biomedicine; drug delivery; therapeutic agents; dual stimuli response.

Abbreviations

Sl. No.	Abbreviations	Full form
1.	3T(-Tp)	Amivudine triphosphate
2.	4,4'-bby	4,4' bipyridine
3.	5-FAM	5-carboxyfluorescein
4.	5-FU	5-Fluorouracil
5.	ALP	Alkaline phosphatase
6.	ASCPC	Human pancreatic adenocarcinoma cell line
7.	Azi-Tp	Azidothymidine triphosphate
8.	BPDC	Biphenyl-4,4'-dicarboxylic acid
9.	Br	Brimonidine
10.	BTC	1,3,5 benzene tricarboxylic acid
11.	CHO	Cholesterol
12.	CT-26	Colon Tumor #26 cell line
13.	DA	Dopamine
14.	DABCO	1,4 diazobicyclo [2,2,2] octane
15.	DBCO	Dibenzylcylcooctyne
16.	DCA	Dichloroacetate
17.	DDS	Drug Delivery System
18.	DEF	N,N diethylformamide
19.	dmbpy	2,2'-dimethyl-4.4'-bipyridine
20.	dmcapz	3,5-dimethyl-4-carboxypyrazolato
21.	DMF	N, N dimethylformamide
22.	DOPA	1,2-dioleoyl-sn-glycerol-3-phosphate
23.	DOX	Doxorubicin
24.	DS	Diclofenac sodium

25.	DSCP	Di succinic cisplatin
26.	DSPE-PEG	1,2-disteroyl-sn-glycerol-3-phosphoethanolamine-N-(polyethyleneglycol)
27.	DTBA	4,4,0-dithiobisbenzoic acid
28.	FA	Folic acid
29.	FUGY	FE304@UiO-66-NH2/graphidiyne
30.	GDY	Graphidiyne
31.	GEM	Gemcitabine monophosphate
32.	GOx	Glucose oxidase
33.	GRGDS Pepetide	Gly-Arg-Gly-Asp-Ser peptide
34.	GSH	Glutathione
35.	GSN	Bioflavonoid genistein
36.	H_2BDC	1,4- benzene dicarboxylic acid
37.	H2cpon	5-(4- carboxy phenoxy) nicotinic acid
38.	H_3BTCTB	4,4',4"-[1,3,5-benzene triyltris(carbonylimino) trisbenzoic acid
39.	H460	Human non-small cell lung cancer cell line
40.	HEK293	Immortalized human embryonic kidney cells.
41.	HeLa	Henrietta Lacks cell line
42.	HNK	Honokiol
43.	HRP	Horseradish peroxidase
44.	IBU	Ibuprofen
45.	INA	Isonicotinate
46.	INH	Isoniazid
47.	LC	Leucine
48.	MCF-7 Cell line	Michigan Cancer Foundation-7
49.	MOFs	Metal Organic Frameworks
50.	MTT assay	3-[4,5-dimethylthiazol-2-yl]-2,5 diphenyl tetrazolium bromide) assay
51.	MXT	Methotrexate
52.	NADPH	Nicotinamide-adenine dinucleotide phosphate

53.	Nd-SPME Method	Negligible-depletion solid-phase microextraction method
54.	NIPAM	N-isopropyl acrylamide
55.	NIR	Near-infrared photo responsive
56.	NO	Nitric oxide
57.	NTRI	Nucleoside reverse transcriptase inhibitor
58.	NV	Nivolumab
59.	OPEs	Organophosphate esters
60.	PCM	Phase changing material
61.	PCPs	Porous Coordination Polymers
62.	PDA	Polydopamine
63.	PDT	Photodynamic treatment
64.	PEG-FA	Poly(ethylene glycol)-folate
65.	PEGMA	Poly(ethylene glycol)dimethyl acrylate
66.	PLGA	Hydrophobic poly(lactic-co-glycolide)
67.	PNIPAM	Poly(N-isopropyl acrylamide)
68.	RISC	RNA induced silencing complex
69.	RNAi	Interfering RNA
70.	SBF	Simulated bodily fluid
71.	SEH	Soybean epoxide hydrolase
72.	SIF	Simulated intestinal fluid
73.	SQ-20B	Human squamous cell carcinoma cell line
74.	SS	Disulfide bridges
75.	STEM-EDS	Scanning transmission electron microscope-Energy Dispersive Spectroscopy
76.	TATAT	5,5’5”-(1,3,5-triazine-2,4,6-triyl)tris(azonediyl) triphospahte
77.	TB	Tuberculosis
78.	TOS	Tocopherol succinate
79.	TPP	Triphenyl phosphonium
80.	VCl_3	Vanadium (III) Chloride
81.	VER	Verapamil hydrochloride

1. Introduction

Metal-organic frameworks (MOFs), also known as porous coordination polymers (PCPs), represent a class of crystalline substances formed by organic ligands coordinated to metal ions or clusters [1,2]. These materials possess customizable properties and stand out as a remarkable advancement in modern materials science. Due to their unique structure, MOFs boast exceptionally high specific surface areas of up to 8000 m^2g^{-1}, variable surface chemistries, and pore sizes ranging from micro (2 nm) to mesoporous (2 to 50 nm) structures [3,4]. Additionally, MOFs provide accessible Lewis acidic metal sites and amphiphilic environments within their porosity, enabling additional functionalization, cargo protection, or attachment of components like targeting agents onto their external surfaces. Their versatile applications, encompassing gas adsorption [5], separation [6], catalysis [7], and sensing [8], stem from their adaptable characteristics. However, in recent years, MOFs have garnered significant interest as promising candidates for drug delivery applications. They have been employed to encapsulate various cargos, including drugs, through biomineralization and physisorption, either internally or on the outer surface of MOFs via covalent bonding [9,10]. As they degrade in-vivo upon releasing their cargo, this process effectively impedes their accumulation, thus mitigating potential side effects and toxicity in the body. Many challenges associated with the reduced long-term stability of MOFs in energy applications actually prove advantageous for drug delivery purposes [11,12].

Present investigations in drug delivery aim to develop biocompatible MOFs and improve their efficacy in formulating therapeutic agents [13]. Numerous MOFs and its composites are excellent candidates for the treatment of renal, cardiovascular, microbiological, and acute disorders, including cancer and diabetes [14]. However, substantial limitations, such as poor body absorption, low solubility, unselective biodistribution, and poor bioavailability, restrict their usage in biomedical applications. They can also result in burst release [15], damage to healthy tissues [16], and cardiotoxicity [17]. Examples of traditional drug delivery systems (DDS) encompass tablets, capsules, granules, ointments, oral syrups, as well as solutions for intravenous administration and suppositories [18]. Traditional DDSs have several limitations and drawbacks that prevent them from achieving sustained release. These limitations and drawbacks include pure absorption for target sites, multiple daily dosages, an increased dose requirement, variations in plasma drug levels, difficulty in monitoring, poor

bioavailability problems, serious toxicities, side effects, and premature excretion from the body [19]. In this regard, new DDSs are necessary and are being looked upon.

Horcajada et al. originally proposed MOF nanoparticles (MOF-NPs) for drug administration in proof-of-concept research in 2006 utilizing MIL-100 and MIL-101, which Cr-based MOFs [20]. These two MOFs showed regulated drug release with 1.4 g of ibuprofen/g (IBU/g) of MOF over three and six days. This was one of the first cases wherein MOFs were used for drug delivery. Maji et al. and colleagues synthesized ZIF-8/laponite clay hydrogel nanocomposite with pH-controlled release of the nanocomposite's components [21]. This was effectively used for the delivery of a drug molecule 5-flurouracil (5-FU). Within 24 h, FU@ZIF-8 demonstrated more than 60% release of the encapsulated 5-FU in a phosphate buffer (pH 7.4). A MOF coated with a polyacrylamide/DNA hydrogel was utilized to control the release of DOX. Changing the concentration of adenosine triphosphate (ATP) allows one to regulate the release of DOX. With the NMOFs/hydrogel hybrid, it was discovered that the DOX loading amounted to 79.1 nmol mg^{-1}. Moreover, the release is steadily enhanced as the ATP concentration rises [22]. Figure 1 schematically shows the drug loading on MOFs, which is further used in biopharmaceutics [23].

MOFs have surfaced as hopeful contenders for drug delivery applications because of their distinct properties and meticulously structured crystalline form. This combination allows the new model and synthesis of MOFs with tailored structures and properties, making them versatile platforms for drug encapsulation and release [23]. The biomedical applications of MOFs, spanning from theragnostic sensing applications [24] to the transport of biological gases for wound healing, have gained pace, demonstrating a broad and diversified range for these materials. The prospect of including guest materials, including inorganic NPs, within MOFs has also been made possible by new breakthroughs in synthesis. The resultant MOF-NP composites have made it possible to create more sophisticated materials with more features. These composites have been researched for a variety of uses, including imaging and drug administration. Other applications include environmental adsorption, catalysis, and electrochemical sensing. MOF-NPs composites are used to produce multifunctional materials that are capable of carrying several treatment models and also their use in imaging and therapeutic agents [1,25].

Recent investigations into MOFs as drug delivery agents have concentrated on tackling pivotal challenges such as controlled release, stability, biocompatibility, and targeting.

Scientists have devised diverse approaches to augment the capabilities of MOFs as drug carriers, encompassing surface modifications, integration of stimuli-responsive elements, and combination with other materials like hydrogels or nanoparticles. These advancements have led to refined control over drug release kinetics, heightened stability in biological contexts, and heightened specificity towards target locales. This review centers on the drug delivery potential of MOFs owing to their extraordinary properties and adaptability.

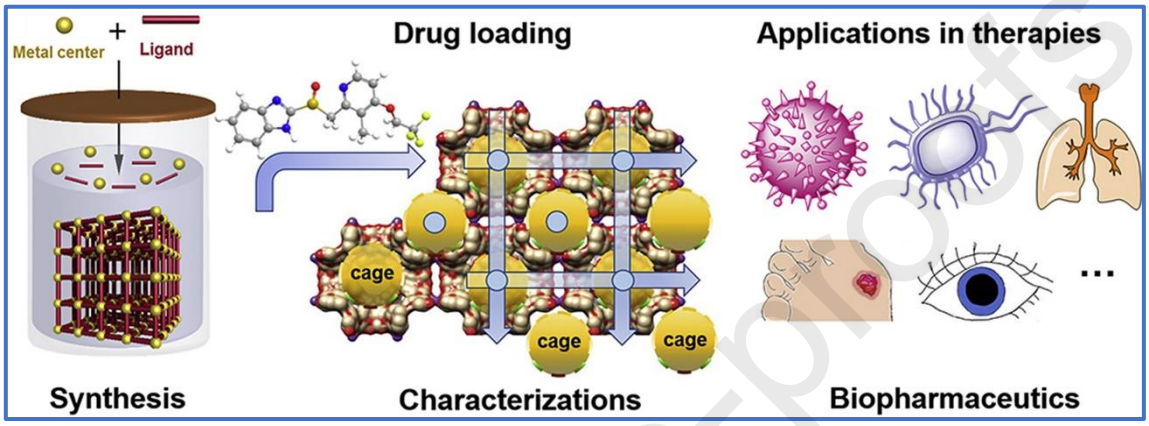

Fig. 1. Metal organic frameworks based material as a drug delivery system [23]. Reproduced with permission from [23], Copyright 2021, Elsevier.

2. Methods of Synthesis

Metal-organic frameworks (MOFs) consist of metal ions or clusters bonded by organic ligands. Achieving the desired structure and properties during MOF synthesis necessitates precise assembly of these metal ions and organic ligands. Two fundamental methods for synthesizing MOFs are top-down and bottom-up techniques. Top-down approaches involve dismantling an existing MOF structure into smaller components and subsequently reassembling them to form a new structure [26,27]. With bottom-up methods, coordination compounds or complex structures are established by self-assembly of organic ligands and individual metal ions/clusters [28]. The final structure and characteristics of the MOFs may be more precisely controlled using this technique. The intended qualities and the amount of control needed over its assembly will determine the appropriate synthesis process to be chosen [29,30]. Figure 2 elaborates on different synthetic routes involved in the formation of MOFs.

2.1.1 Conventional Methods

The conventional approach to synthesizing MOFs is the bottom-up strategy, which entails the controlled interaction of metal ions or clusters with organic ligands in a solvent to form the desired MOF structure. This method typically involves reactions conducted at high temperatures and pressures. Due to its ability to provide precise control over the content, size, and shape of the MOF, the traditional technique is commonly employed for MOF synthesis [31]. The advantages of traditional MOF synthesis are found in its widely used and well-established processes. Utilizing standard methods, researchers can create a variety of MOFs with varying characteristics and experiment with various metal ions and organic ligands. However, the complexity and length of the reaction steps used in these techniques make them less suitable for high-throughput and large-scale manufacturing.

2.1.2 Non solvothermal methods

Non-solvothermal methods of MOF synthesis is those that do not rely on solvents for their fabrication and take place at room temperature or temperatures higher than the boiling temperature of the solvent. This synthesis method includes a precipitation reaction, which could be followed by recrystallization or vapour diffusion. MOF-177, MOF-74, MOF-5, ZIF-8, and HKUST-1 have been prepared by using non-solvothermal technique, wherein the starting materials for the preparation of these MOFs are simply mixed, and the products are obtained by direct precipitation at room temperatures [32].

ZIF-8 synthesized via this method proved to show improved thermal and chemical stabilities. According to Cravillon et al. [33], ZIF-8 has been synthesized by altering the component ratio of $Zn(NO_3)_2$, 2-Methylimidazole, and methanol, and the pure product was obtained without heating, excessive pressure, or ultrasonic and microwave processing. Huang et al. [34] were able to synthesize ZIF-8 structures with a concentration gradient. Imidazole derivatives dissolved in methanol were carefully poured into $Zn(OH)_2$ solution in 25% aqueous ammonia. For pure and highly crystalline ZIF-8 having surface area =1860 $m^2 g^{-1}$, an efficient and dependable microwave-aided non-solvothermal synthesis technique was used. An open system was used for the studies, which resulted in much faster reaction times (7.5 min) [35]. Compared to solvothermal techniques of MOF synthesis, non-solvothermal approaches have greater scalability and less environmental effect.

2.1.3 Vapour Diffusion

A liquid-assisted technique for the synthesis of MOFs is an inexpensive and ecologically friendly substitute for other techniques. It is facile and can be carried out under ambient settings. In this process, vapor-phase reactants are carefully dripped into a solvent or solution that contains metal ions/clusters and organic ligands. This then leads to the formation of MOFs [36]. Vapour diffusion is one of the main synthetic methods used to prepare cyclodextrin (CD-MOFs) [37].

Stoddart et al. and his group prepared a number of γ-CD-MOFs by using various combinations of metal ions like K^+, Rb^+, Cs^+, $Na^{+,}$ and Sr^+ [37]. It was observed that higher yields and better crystalline nature of the γ-CD-MOFs were attained when using temperatures of about 50°C higher than that of room temperature, which significantly reduced the synthesis time from several days to 6 h [39]. The effective use of a combination of ultrasound-vapour phase diffusion approach to synthesize $[Tb(1,3,5\text{-}BTC)]_n$ nanocrystals helped to get higher yields and smaller crystal sizes of 20 μm within a short period of time. The sensitive and selective detection of paracetamol is made possible by the nanoscale Tb-based MOFs, without any interference from nitroaromatic chemicals like nitrobenzene, 2-nitro toluene, 4-nitrotoluene, 2,4 and 2,6-dinitrotoluene, or common organic solvents [40].

Chen et al. [36] designed $Zn(INA)_2(H_2O)_4$ MOF by reacting with an ammonia solution of metal and ligand isonicotinate (INA) to quickly result in single crystals. The diffusion of ammonia to the liquid from the gas phase paved way for a pH gradient from 3 to 5 at the surface of the solution. This resulted in the synthesis of $Zn(INA)_2(H_2O)_4$, which could capture 6 mmol g^{-1} of ammonia in both dry and wet circumstances. $Zn(INA)_2$ was used below 120°C and reused (3 times) in dry conditions without any loss in performance. Overall, the simplicity, scalability, and flexibility to fabricate MOFs with specific features make the vapour diffusion approach a desirable choice for MOF synthesis.

2.1.4 Solvothermal method

Solvothermal methods entail the interaction of metal ions or clusters with organic ligands in a solvent under elevated temperatures and pressures to produce MOFs. Various solvents, such as polar and nonpolar organic solvents, water, and aqueous solutions can be used in solvothermal synthesis, with the selection of solvent influencing the properties of the

resulting MOFs. Vanadium (III) chloride (VCl_3), a rich source of metal ions, has been described as one of the metal precursors used in the synthesis of MIL-47, where the synthesis was carried out using solvothermal techniques. A solution of methanol in water, which contained β-CD and sodium oxalate ($Na_2C_2O_4$) was heated at 160°C for 3 days for the synthesis of β-CD-MOFs and used for the delivery of 5-FU [41]. Na-a-CD-MOF was prepared via solvothermal technique by Sha et al. [42] by mixing α-CD and KOH, heating this mixture at 160°C for 4 days. Similarly, MOF-5 was synthesized using the same principles at 105°C, which produced higher yields in comparison to preparation done at room temperature [43]. The production of a 3D double diffusing framework microporous material, Zn_3(bibenzene-dicarboxylic acid)3(4,4'-bipyridine), was reported by Qianrong's research team [44]. By utilizing a combination of solvents, such as ethanol, N, N-dimethylformamide (DMF), and water, Zn^{2+} was coordinated with 4,4'-bibenzene-dicarboxylic acid (H_2bbdc) and 4,4'-bipyridine (4,4'-bpy) [44]. In an autoclave with an acidic solution, Férey [45] and Biemmi et al. [45] produced MIL-101 and $(H_2NEt_2)_2[Zn_3(BDC)_4]_3$DEF using 1,4-benzenedicarboxylate (H_2BDC), and N,N-diethylformamide (DEF) as organic linkers. In the former work, using sorption measurements, it was shown that the framework contains free holes and is stable up to 400°C in the crystalline phase that results from temperature treatment over 250°C. In the latter work, the MOF was a great candidate for the adsorption of gas and nano-objects in a regular and monodisperse mode with characteristics for drug delivery.

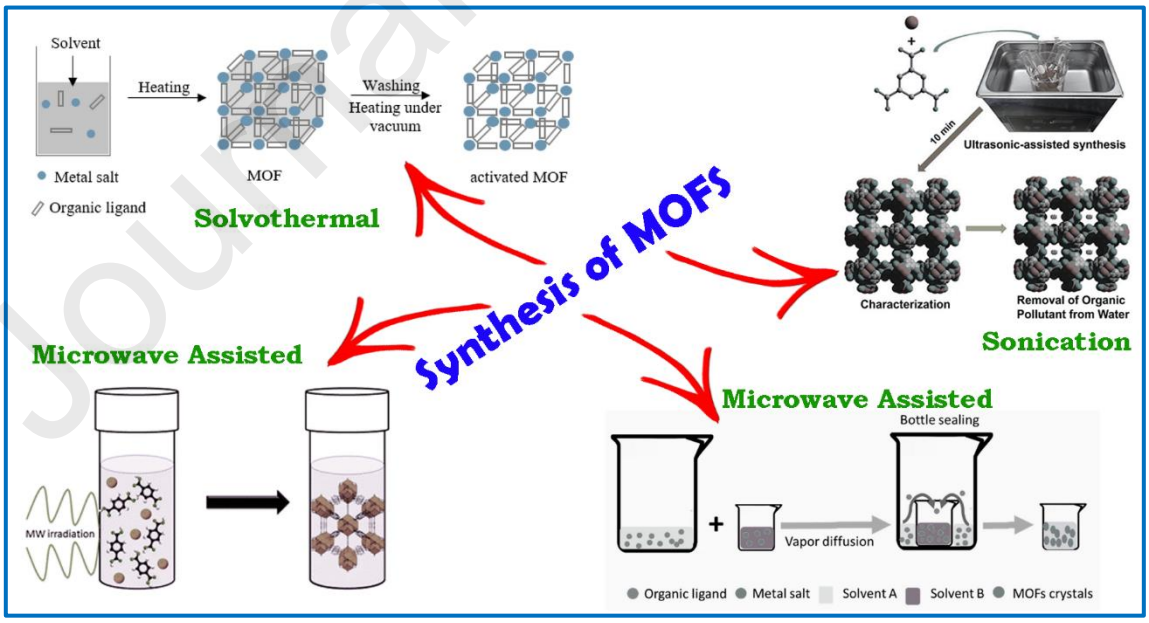

Fig. 2. Synthetic routes involved in MOFs synthesis.

2.1.5 Microwave assisted method

In the fields of nanotechnology and pharmaceutical research, the microwave technique of synthesizing nanoparticles for applications based on drug delivery is an area that is expanding quickly. The microwave approach enables the production of nanoparticles with desired characteristics for drug delivery applications by providing precise control over reaction parameters such as temperature, heating rate, and reaction time [47]. In order to enable the production of MOFs with regulated size, shape, and surface features, microwave irradiation is used as a heating source. In comparison to traditional synthesis methods, this approach has several benefits, such as quicker reaction time, greater reaction yields, and enhanced product homogeneity. The nanoparticles' size, shape, and surface properties can be modified to boost their drug loading capacity, improve targeted drug delivery to certain tissues or cells, and improve their interaction with biological systems [48]. The first nanoparticle synthesized by microwave method was MIL-100(Cr), which was synthesized at 22°C for 4 h rather than 4 days using a conventional heating method [49]. This synthesis method provided narrow particle size and high porosity [50]. The microwave method is especially advantageous in preparing monodispersed MOFs in high yield with a size less than 100 nm [51] and also in synthesizing MOFs on a large scale for biomedical applications [50]. Researchers have synthesized Zr, Zn, and Ca based MOFs for drug delivery applications using this method [52–55]. Liu et al. [56] synthesized γ-Cd-MOF micro and nano sized crystals after optimizing the temperature, time, and ratio of the solvents used. The microwave method is widely used and preferred in the synthesis of HKUST-1, MIL-53, MIL-101-NH2, MIL-100, and ZIF-8 [57–61].

2.1.6 Sonochemical Methods

Sonochemical is a rapid and environmental method for the preparation of nanoparticles and MOFs. The acoustic activation process involves the sound waves interacting with the liquid, which will collapse with the bubble and thus produce elevated temperature and pressures, which aids in the synthesis. The rapid heating and cooling process provides the condition for good crystal growth [62]. The synthesis of HKUST-1 resulted in the formation of nanoparticles after 5 min of sonication and, on further sonication, particle sizes of up to 200 nm [63]. PCN-6, IRMOF-9, IRMOF-10, MOF-5, MOF-74 were synthesized using this technique [64]. By employing the tritopic extended organic linker benzenetribenzoate to synthesize the Zn-based MOF, MOF-177, high-quality crystals with sizes ranging from 5 to 10 m were produced in 40 min with a 95.6% yield while using the cost-effective solvent 1-methyl-

2-pyrrolidone. At 30 atm and 298 K, MOF-177 had the highest CO_2 adsorption capacity (1315 mg g^{-1}) and BET surface area (4898 m^2g^{-1}) [65]. With Triethylamine acting as a deprotonating agent to hasten the deprotonation of the organic linker, an ultrasonic irradiation approach was used to produce a spherical uniform Mg-MOF-74 crystal with a surface area of 1640 m^2g^{-1} and particle size of 0.6 m in 1 h. The creation of intriguing mesoporous structure with a volume of 0.31 cm^3g^{-1} was caused by the competitive binding of triethylamine to the metallic sites [66]. Seoane and his colleagues investigated the dynamics of the sonochemically produced MOFs such as ZIF-7, ZIF-8, ZIF-11, and ZIF-20, which are members of the ZIF family. High quality MOF crystals were made using ultrasonic irradiation of 100 W with a frequency of 47 kHz within a less reaction time that required low temperatures (45-60°C), as opposed to the standard heating approach [67].

2.1.7 Mechanochemical Method

A new technique for creating MOFs called mechanochemical synthesis uses mechanical energy to trigger the interaction between metal ions/clusters and organic ligands. In order to facilitate the mixing and reactivity of the reactants and the creation of MOF crystals, this technique employs a ball milling process. This is a solvent free, environmentally friendly, and low-cost method that uses mechanical force to induce chemical transformations [68,69]. A technique for the manufacture of nanoparticles that aids in avoiding significant energy and material costs was devised by Friscic et al. [69]. With the use of oxide-based chemistry, this technique facilitates the creation of nanoparticles at room temperature. The mechanochemical preparation of a Zn-based MOF known as SPCP-Zn was reported by Zhang et al. [70] using potassium carbonate or sodium hydroxide as a metal precursor and zinc acetate as a phenolic ligand. A pure blue product with a 90% yield was produced in 20 min of reaction time. By pulverizing the precursors In(OAc)36H2O and 3,3',5,5' biphenyltetracarboxylic acid (H_4bptc) for 20 minutes with 0.4 ml CH_3CN, Chen et al. [71] created the water-stable indium metal-organic frameworks ($InOF_{-1}$) $In_2(OH)_2(BPTC)]6H_2O$. $InOF_{-1}$ has a 4.03 mmol g^{-1} CO_2 intake capacity at 273 K and 100 kPa, and selectivity up to 45% and 7%, respectively, have been recorded in the presence of gases like nitrogen and methane.

2.2 Green synthesis

The term "green synthesis" of MOFs describes the creation of MOFs using sustainable and eco-friendly practices. This procedure often uses less energy, less hazardous chemicals,

and produces little trash. Due to the rising need for ecologically friendly and sustainable technology, green synthesis techniques are becoming increasingly popular. The normal synthesis methods of MOFs require the use of very high temperatures and pressure with the use of solvents, which make them potentially harmful [72]. This is shown in Zn-MOF, which was synthesized to take up and release binuclear gold-based dithiocarbamato complexes, which were used in anticancer studies. This particular MOF showed an increased biodegradability [73]. Recently a sub-class of Zn MOFs, zeolite imidazole frameworks (ZIF-8), has also become important in drug delivery studies because of the many properties that it possesses like large pore size, and its ease in tunability, easy functionalization, drug adsorbing capacity, high drug loading and release capabilities, thermal stability, and low cytotoxicity [74]. The main problem with ZIF based drug delivery systems is their instability in relatively higher pH, which can lead to low biostability; thus, more research needs to be done to improve this property [75]. A solvent-free mechanochemical synthesis route was proposed for the synthesis of the ZIF by Vahed et al. [76]. In this method, he proposed to coat the ZIF with alginate to improve its biostability. This study proved that the ZIF can then successfully be used to delivery drugs at higher pH, and it also showed that the alginate coating provided a lesser cytotoxicity when used in cells. Indocyanine green was used in another study to encapsulate ZIF-8, and was used for chemical and photothermal treatment of tumours. The proposed mechanism involves the use of laser which would disintegrate the ICG and thus help in release of the drug from ZIF-8.

Adenine based bio-MOF has been reported [77] for the treatment of hypotension by the targeted release of a cardiac stimulant etilefrine hydrochloride. For the treatment of HIV/AIDS, the use of natural and non-toxic ligands such as fumarate and galactarate were used. This prepared biodegradable Fe-MOF showed a sustained drug loading efficiency of 59% when using multiple metal systems [78]. Glutamic acid has also been in preparation of a 3D-MOF $Zn_3(BTC)_2$ that is used to treat cancer by release of methotrexate induced thermally [79]. Ethanol and water mixture was used to encapsulate ibuprofen by a green electrosynthesis method as studies of the release mechanism is being studied [80]. Nitric oxide has great therapeutic properties which can be used to treat immune, cardiovascular, nervous and many other diseases. This can only be achieved by the controlled release of NO and its targeted delivery. Most porous materials readily adsorb NO, but their slow release is rarely found [81]. Vitamin B_3 and niacin-based MOFs have been used for the slow release of NO. The niacin-based MOF provided a reversible release of NO in both gas and liquid phases [82].

In conclusion, the synthesis methods of MOFs are diverse and continually evolving, driven by the quest for tuning its properties and customizing it for different applications. In this section, we have explored the various synthesis approaches, including solvothermal, hydrothermal, microwave-assisted, and mechanochemical methods, each offering unique advantages and challenges. Solvothermal and hydrothermal methods remain widely employed for their versatility and scalability, enabling the synthesis of MOFs with precise control over particle size, morphology, and crystallinity. Microwave-assisted synthesis has emerged as a rapid and energy-efficient alternative, accelerating reaction kinetics and facilitating the production of MOFs with tailored properties. Despite significant progress, challenges persist in the synthesis of MOFs, including reproducibility issues, scalability constraints, and the need for sustainable and eco-friendly synthesis routes. Future research endeavors will likely focus on addressing these challenges through the development of novel synthesis strategies, leveraging advances in green chemistry, catalysis, and automation. Overall, the synthesis methods of MOFs play a pivotal role in dictating their properties and performance in various applications, including drug delivery, gas storage, catalysis, and sensing. By advancing our understanding of MOF synthesis and harnessing innovative approaches, researchers can unlock new opportunities for the design and fabrication of tailor-made MOFs with enhanced functionalities and applicability, paving the way for transformative advancements in materials science and beyond. The various methods followed for the synthesis of MOFs are given in Table 1.

Table 1. Various methods for the synthesis of MOFs

MOF	**Synthetic method**	**Precursors**	**Ref**
ZIF-8	Non solvothermal	$Zn(NO_3)_2 \cdot 6H_2O$ to a methanol solution of 2-methylimidazole	[33]
[{Zn-(mim)2·2H_2O}1]	Non solvothermal	$Zn(OH)_2$ (0.1 mmol, 0.010 g) in aqueous ammonia, Hmim	[34]
HKUST-1	Non solvothermal	The reaction mixture was microwaved for up to 10 min, resulting in HKUST-1. The product yield is 90%.	[35]

$Zn(INA)_2$ $(H_2O)_4$ (INA = isonicotinate)	Vapour Diffusion	Isonicotinic acid, distilled water, and $Zn(NO_3)_2 \cdot 6H_2O$.	[36]
CD-MOF-1	Vapour diffusion	g-CD and KOH	[37]
CD-MOFs	Vapour Diffusion	γ-CD and alkali metal salt	[38]
sized γ-CD -MOFs	Vapour Diffusion	Micron-sized γ-CD -MOFs were created in less than 6 h at a high temperature (50 °C).	[39]
[Tb(1,3,5-BTC)]n	Vapour Diffusion	$Tb(NO_3)_3.6H_2O$, H_3BTC, N,N-dimethylformamide.	[40]
Na-α-CD-MOF	Solvothermal	α-CD, NaOH, and tetramethylammonium hydroxide solution.	[42]
MOF-5	Solvothermal	1,4-benzenedicarboxylate (BDC) and N,N'-diethylformamide (DEF), $Zn(NO_3).24H_2O$	[43]
$Zn_3(bbdc)_3(4,40$ -bpy)	Solvothermal	H_2bbdc, $Zn(NO_3)_2.6H_2O$, bipyridine, N,N-dimethylformamide (DMF)	[44]
MIL-101	Solvothermal	H_2BDC, $Cr(NO_3)_3.9H_2O$, fluorhydric acid	[45]
MIL-100	Microwave assisted hydrothermal	mesoporous metal(III) trimesates MIL-100(Al, Cr, and Fe) by microwave-assisted hydrothermal method, using water as the solvent.	[83]
MIL-100	Microwave	8 mmol of iron, 5·3 mmol of 1,3,5-benzenetricarboxylic acid, and 4 mmol of HF.	[50]
MIL-88A	Microwave	$FeCl_3.6H_2O$ and fumaric acid	[51]
Hf-UiO-66 and Zr-UiO-66	Microwave	N,Ndimethylformamide (DMF), 1,4-benzenedicarboxylic acid (H_2BDC), and $HfCl_4$ or $ZrCl_4$.	[52]
MOF-5	Sonochemical	Zinc nitrate hexahydrate ($Zn(NO_3)26H_2O$) and terephthalic acid (H_2BDC)	[52]
MOF-177	Sonochemical	$Zn_4O(BTB)_2$	[65]
Mg-MOF-74	Sonochemical	$Mg(NO)_3$, N,N-dimethylformamide (DMF).	[66]

ZIF- MOFs	Sonochemical	Purine and zinc (NO_3).$26H_2O$, dimethylformamide (DMF), ZIF-8, $Zn(NO_3).26H_2O$, 2-methylimidazole (MeIM), and DMF	[67]

3. Ligands used for Drug Delivery

MOFs are favoured for drug delivery due to the diverse range of metal precursors and organic linkers they offer. The organic linkers act as supramolecular organizers and also significantly influence the physicochemical properties. The utilization of ligands such as carboxylate, phosphate, sulfate, and various heterocyclic compounds hold great significance due to their diverse functional groups and chemical properties, enabling the design and synthesis of MOFs with tailored characteristics [84,85]. Their presence imparts specific functionalities and interactions within the MOF structure, leading to enhanced stability, tuneable porosity, and improved performance in various fields such as drug delivery, catalysis, and gas storage [86]. Therefore, the careful selection and incorporation of these ligands contribute to the overall effectiveness and versatility of MOFs [87]. The first amino-acid based biocompatible 3D MOFs was synthesized by Gramaccioli et al. using Zn (II) and glutamate in 1966 [88]. The first study on bio-MOF based drug delivery was done in 2010 by Miller et al. [89], where iron and therapeutic active vitamins B_3 were used for the treatment of pellagra, vasodilation and possessed anti-lipid properties. Olsalazine is a therapeutic agent that is used in the treatment of ulcerative colitis and other gastrointestinal disorders [90].

K. Sun et al. [91], synthesized MOF-2, MOF-3, and MOF-4 for the drug delivery of IBU. The linker used for the study is 1,3,5 benzene tricarboxylic acid (BTC) which had an excellent coordinating ability with metal ions and aided in excellent drug-carrier behaviour. The loading capacity of the IBU also increased due to the similarity in the functional groups of BTC and IBU . The release rate of IBU was found to be 90% which can be attributed to the strong adsorption of the MOFs with BTC ligand (Fig. 3). The same principles were used in releasing IBU molecules from the HKUST-1 with BTC ligand channel. The maximum release of the loaded drug IBU was obtained after 25 h, indicating a delayed molecular release mechanism. For IBU, guaiacol, and anethole, the drug loading amounts were 0.34, 0.38, and 0.40 g^{-1}, respectively. IBU's release time was quicker than that of the Zn-MOF (96 h) and Cu-MOF (72 h) when using HKUST-1. Unexpectedly, the guaiacol release time was clearly longer

than the Cu-MOF release period (3.5 h). A 20 h release rate of guaiacol was discovered. Another MOF of the MIL family, MIL-53, possesses features that make it an attractive long-acting (3 weeks) drug release moiety. It adsorbed around 20 weight percent of IBU [92,93].

The use of 1,4-Benzene dicarboxylic acid (BDC) in the drug delivery of IBU using a Cu- MOF was synthesized via solvent free mechanochemical method [94]. The high surface area of BDC helps to entrap larger molecules of drugs in the framework and increases the loading capacity of the drug [94]. The anion- cation interaction and π-π interaction between the aromatic ring of BDC and IBU determined the size of the pore and channel. The $[Zn_2(BDC)_2(DABCO)]$ MOF was employed as the drug delivery system's carriers, and nalidixic acid was utilized as a test medication. Here, BDC serves as a chelating ligand, 1,4 diazabicyclo[2.2.2]octane (DABCO) serves as a bridging ligand, and Zn as a metal ion connector. The drug release was not observed for a course period of 120 h, but after the influence of pH, release percentages of 96% and 62%, respectively were observed at pH values of 5.0 and 7.4 [95]. By utilizing a technique of incorporating hydrophobic groups to the linkers, a hydro stable MOF $[Zn(NO_2{-}BDC)(dmbpy)_{0.5}]\cdot(C_2H_6O)\cdot(H_2O)$ with BDC functioning as an organic linker was created using 5-nitroisophthalate and 2,2′-dimethyl-4,4′-bipyridine (dmbpy) as co-ligands. As a result of the pore surface being occupied by methyl and nitryl groups, the framework induces a high busulfan payload with an encapsulation efficacy of 21.5% [96].

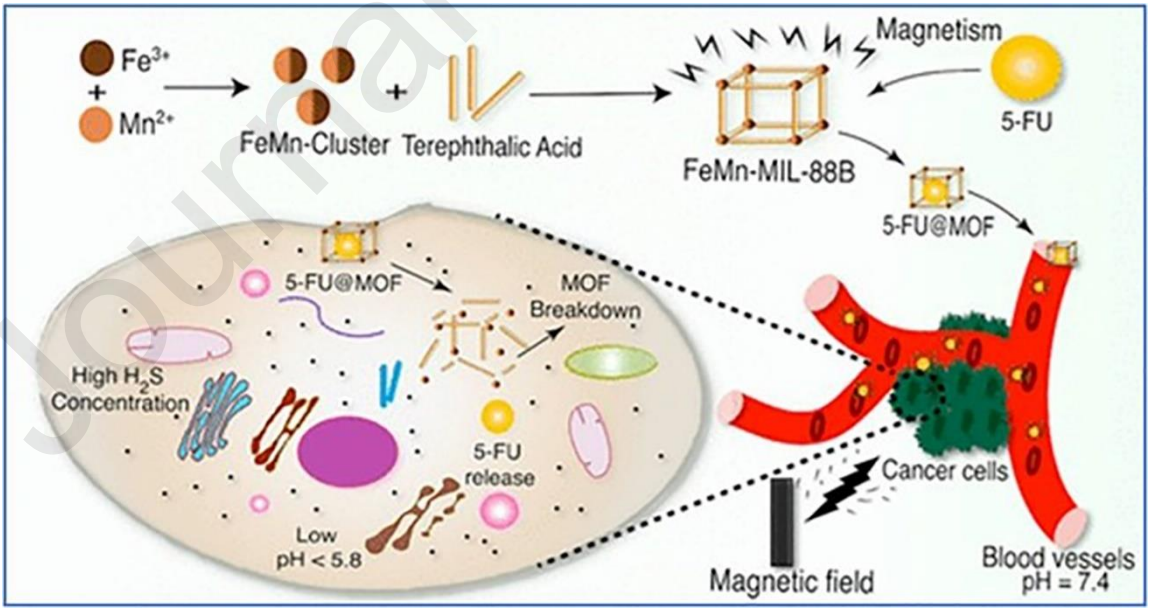

Fig. 3. FeMn-MIL-88B MOFs utilized in drug delivery applications [91]. Reproduced with permission from [91], Copyright 2022, American Chemical Society.

Sun et al. [97] used 5,5 ′,5 ″ -(1,3,5-triazine-2,4,6-triyl)tris(azanediyl)triisophthalate (TATAT) for the drug delivery of 5-FU using a chiral nano porous MOF $[(CH_3)_2NH_2]_2[Zn(TATAT)_{2/3}]\cdot 3DMF\cdot H_2O$. The TATAT offers the possibility for the formation of larger pores, metal binding node, and in host-guest interactions. The loading of 5-FU drug molecule into Zn MOF was achieved due to the bonding present between the carbonyl group of 5-FU and the amino group of the linker. The hydrogen bonding and the π-π interaction of the 5-FU and the organic linker help in increased and sustained drug release. No "burst effect" was seen, only a gradual release. Within a week, 5-FU was delivered, and 86.5% of the loaded medicine was discharged. There are three distinct drug release phases that can be identified. In the first stage (8 h), 42% of the loaded medication was released, and 43% was released in the next two stages. TATAT also helps in the formation of nanoscale cages of different sizes, which helps in the drug release rate based on the size of the cages and thus increases the ability for prolonged and sustained drug release [98–100].

Biphenyl-4,4’-dicarboxylic acid (BPDC) was used as a linker in the drug delivery of Etilefrine hydrochloride using adenine-based MOFs [77]. The BPDC ligand helps in the formation of negatively charged framework with the potential to attract the positively charged molecules into its pores. This structure helps load drug molecules into the pores with less, which helps in definite and prolonged drug release from the framework in comparison to the burst release [101–103]. Abazari et al. [104] synthesized a Zn(II)-based MOF(DUT-32) via a sonochemical method using extremely flexible organic 4,4′,4″-[1,3,5-benzenetriyltris (carbonylimino)]trisbenzoic acid (H_3BTCTB), ditopic 4,4′-BPDC ligand, and modulators as acetic acid and pyridine. The MOF was used for the release of DOX. It demonstrated and enhanced release efficiency of DOX from 54% to 98% (after 100 h) in pH of 7.4 and 4.5, respectively, in addition to maintaining its structure under physiological circumstances. Furthermore, it was shown that the inclusion of DOX in DUT-32-K resulted in the effective elimination of malignant cells, comparable to the efficacy of free DOX. Additionally, a viability assessment indicated that DUT-32-K alone exhibited minimal cytotoxic effects on healthy cells. Table 2 summarizes different organic linkers used for MOFs synthesis.

The advantages of using CD-based MOFs are the size, morphology, and perfection in cubic morphologies with monodispersed distribution [105]. The CDs form inclusion complexes with a variety of DOX drug molecules. CDs also avoid drug degradation and crystallization over long term storage also showed high affinity in binding to Lansoprazole. A

focused and pH-responsive DDS might be created using the AS1411@ poly(ethyleneglycol)dimethacrylate (PEGMA)@GQD@-CD-MOF nanostructure. The DOX loading efficacy of the AS1411@PEGMA@GQD@-CD-MOF carrier was 89.1%, and it also showed good targeting and minimal cytotoxicity. When combined with fewer side effects compared to free DOX, the CD-based medication formulations effectively suppressed tumour development. In vivo fluorescence imaging demonstrated its increased accumulation in cancer locations [106].

Table 2. Summary of organic linkers used in MOFs for drug-delivery

Sl. no	**Organic linker**	**MOFs**	**Synthetic route**	**Drug loaded**	**Ref**
1	1,3,5-Benzenetricarboxylate acid	Cu-MOF (MOFs-3, MOFs-2 and MOFs-4)	Hydrothermal	Doxorubic and Ibuprofen	[91]
2.	1,4-Benzene tricarboxylic acid	{Cu_2(1,4-bdc)2(dabco)}n	Solvent free-mechano chemical	Ibuprofen	[94]
3.	5,5′,5″-(1,3,5-triazine-2,4,6-triyl)tris(azanediyl)triisophthalate	Zn -MOF	Hydrothermal	5-Fluorouracil	[97]
4.	biphenyl-4,4'-dicarboxylic acid	bMOF-1, bMOF-4, bMOF-100, and bMOF-102	Hydrothermal	Etilefrine hydrochloride	[77]
5.	Cyclodextrin	CD-MOF	Modified methanol diffusion	Lansoprazole	[105]
6.	Nicotinic acid	LD50	Hydrothermal	Vitamin B_3	[89]

7.	Succinic acid	NCP-1, NCP-1',NCP-1'-a, NCP-1'-b	Hydrothermal	Cisplatin	[9]

Hartlieb et al. [91] used in vivo and in vitro tests to evaluate the IBU integrated CD-MOF-1 pharmaceutically. Studies on the vitality of cells in vitro showed that at concentrations of 100 M, the CD-MOF-1 had very little impact on the viability of the cells. These experiments led researchers to the conclusion that cocrystals of CD-MOF-1 and IBU had comparable bioavailability and quick absorption in blood plasma after oral administration. An added advantage of the cocrystal over the pure salt form in blood plasma samples was that it had a 100% longer half-life. Miller et al. [89], used nicotinic acid as an active linker to load and deliver vitamin B_3 using nanoscale coordination polymers. The use of active linker CD avoids the necessity for large pore size and volumes required to achieve high drug loading of 50% while the release was 36%, which led to the degradation of the biomolecules without any side effects. The small cavities formed by nicotinic acid help in drug loading and release.

In this section, we have explored the diverse array of ligands employed in MOF-based drug delivery systems, ranging from small molecules to complex biomolecules, each offering unique advantages in terms of encapsulation, targeting, and controlled release of therapeutic agents. The choice of ligands plays a pivotal role in determining the physicochemical properties of MOFs, including porosity, surface area, and chemical stability, thereby influencing their drug loading capacity and release kinetics. Small molecule ligands, such as carboxylates and nitrogen-based ligands, provide flexibility in structural design and functionalization, enabling precise tuning of MOF properties for specific drug delivery applications. Biomolecular ligands, including peptides, proteins, and nucleic acids, offer inherent biocompatibility and targeting capabilities, facilitating site-specific delivery and minimizing off-target effects. Furthermore, the functionalization of MOFs with ligands enables the incorporation of stimuli-responsive elements, such as pH-sensitive groups or enzyme substrates, allowing for triggered drug release in response to specific biological cues. This dynamic responsiveness enhances the spatiotemporal control of drug delivery, maximizing therapeutic efficacy while minimizing systemic toxicity. Despite significant advancements, challenges remain in the design and optimization of ligands for MOF-based drug delivery, including issues related to ligand stability, biocompatibility, and scalability. Future research efforts will likely focus on addressing these challenges through the development of novel ligand scaffolds, rational design

strategies, and innovative functionalization techniques. Overall, the selection and incorporation of ligands in MOF-based drug delivery systems represent a promising avenue for advancing the field of nanomedicine, offering tailored solutions for targeted and controlled drug delivery across a spectrum of diseases. By harnessing the versatility and tunability of ligands, researchers can unlock new opportunities for precision medicine and personalized therapeutics, ultimately improving patient outcomes and quality of life.

4. Metal ions used in MOFs for drug delivery

The most important aspect for a material to function as a drug carrier is that it should possess low toxicity and high biocompatibility. MOFs are one among them where the surface area can be tuned accordingly. MOFs are synthesized using various metal ions like Fe, Zn, Zr, Cr, and Cu with the linkers, which shows good results as a drug carrier [107,108]. In drug delivery applications, metal ions play a crucial role in enhancing the therapeutic efficacy and targeting capabilities of drug delivery systems. Metal ions such as iron, gold, silver, platinum, and gadolinium have been extensively explored for their unique properties and interactions with biological systems [109]. These metal ions can be incorporated into drug carriers, nanoparticles, or complexes to improve stability, drug loading capacity, controlled release, and specific targeting to disease sites. Additionally, metal ions can facilitate imaging and diagnostic applications through their ability to interact with various imaging modalities [110]. The versatility and tunability of metal ions make them promising candidates in the field of drug delivery, offering opportunities for improved treatment outcomes and personalized medicine approaches.

The MOFs used in drug delivery should have high porosity, which helps in increasing the drug loading and releasing capacity [111]. The multiple loading of drugs on Fe-MOFs are used for the imaging properties and high ligand tunability. High-performance liquid chromatography was used to determine the loading capacity of Fe-MOF, which was 56.25 wt%. According to the results of 3-(4,5-dimethylthiazol-2-yl)-2,5-diphenyltetrazolium bromide tests, lactate dehydrogenase assays, and Annexin V-fluoresce isothiocyanate/ propidium iodide double-staining assays of the MOF carrier was found to be safe and nontoxic with cell viability lesser than 95.27% [107]. After loading oridonin into MIL-53 its structural integrity was preserved. Results from an examination of the oridonin release profile indicate that it persists in vitro for more than seven days. On the seventh day, the cumulative release rate of oridonin was approximately 91.75% in phosphate buffer saline solution at 37^{o}C under

pH 7.2 and pH 5.5 [33]. Li et al. [112] in 2017 synthesized Fe-MOF hybrids, which were used to load IBU, and exhibited a high loading and storage capacity of 20% with complete controlled release of the drug. Fe MOF has an extremely high drug storage capacity of 1.4 g of drug/g of porous solid and a fully regulated drug release period of 3 to 6 days under physiological circumstances.

Gao et al. [113] used a hollow Fe-MOF that incorporated drug loading and had capabilities for bioimaging into one single-MOF thus expanding their application in drug delivery. The studies were also carried out using hollow Fe-MOFs to distinguish between normal and cancer cells by functionalizing with folic acid. Its hollow constructions allow for a high medication loading capacity of up to 35%. In vitro tests show that Fe-MOF-5-NH_2-FA-5-FAM/5-FU may target cancer cells HepG-2 and exhibit good magnetic resonance/fluorescence imaging due to post-modification with folic acid (FA), the fluorescent reagent, 5-carboxyfluorescein (5-FAM), and the presence of Fe (III). Fe-MOF was again used also to load nucleoside reverse transcriptase inhibitor (NRTI) drugs, which are used in the treatment of HIV. These NRTI drugs were not only successfully loaded onto Fe-MOF but also stored for 2 months after freeze drying, even after which they retained their physicochemical properties. With over 80% of the loaded medication released during the first 8 h and a full release occurring after 24 h, amivudine triphosphate(3TC-Tp) has the quickest release. On the other hand, azidothymidine triphosphate(AZT-Tp)releases more gradually over the course of three days, maybe as a result of its greater affinity for the nano MOFs.

Certain drugs like 5-FU are particularly used for loading in areas related to applications in treating breast, stomach, pancreatic, and skin cancers. One example of this was the use of Zn-cpon-1. The Weibull release profile of the drug 5-FU is shown in Fig. 4a [114]. To check the loading efficiency, initially 5-FU was loaded onto Cu based MOFs. It was observed that the loading efficiency of 5-FU was reduced by 15% due to structural difficulties. Later, the loading was successful on Zn-MOFs due to V-shape of the ligands 5-(4'-carboxyphenoxy) nicotinic acid (H_2cpon) used and the porous, rigid structure. These investigations demonstrated that the large channel and open N-H site, when employed as a material for the adsorption and delivery of the anticancer medicine 5-FU, displays significant drug loading (53.3%), delayed release of the loaded drug part, and a delivery duration of around three days. After 12 h of incubation with MOF, Zn-cpon-1, the MTT test (3-[4,5-dimethylthiazol-2-yl]-2,5 diphenyl tetrazolium bromide) was done in order to measure mitochondrial activity. The MTT test relies

on the transformation of MTT into formazan crystals by living cells [115]. The successful delivery of the drug molecule, 5-FU into the environment of human body was achieved by using Zn-cpon-1, controlled by a dual stimulus. This caused the Zn-cpon-1 to be flexible in administration of the drug molecule, and the drug releases could be quantitatively estimated as well. The optically and chemically stable Zn-cpon-1 was found to be an excellent drug delivery vehicle and pH-responsive dual-emission platform, with higher 5-FU loading behaviour due to the influence of size and shape matching 4.79 wt% [116]. Zheng et al. [117] synthesized ZIF-8, which helped in the encapsulation of large DOX molecules onto ZIF-8 framework, led to the increase in drug release efficiency. To improve the clinical application of DOX drug, incorporation of Polydopamine (PDA), here PCM (phase-changing material, tetradecanol) PDA-PCM@ZIF-8 MOFs onto DOX was important as the drug was thermally released using a thermally responsive switch which would release the drugs only affecting cancerous cells.

The synthesis and PDA drug loading on ZIF-8 are accomplished in one pot with high loading of 37.86% and encapsulation rate of 78.76%. In the meantime, PDA functions as a photothermal transfer agent to initiate the phase change materials' thermal responsiveness switch for near infrared photo responsive (NIR) controlled drug release. Just 21% of the medication is released in the absence of radiation stimulus, demonstrating a remarkable impact of control release, while as much as 78% of the drug is released in response to simultaneous stimulation of NIR and acid environment. The high tumour suppression rate of the photothermal-chemotherapy group with a substantial synergistic effect is shown by in vivo anti-tumor tests. A switch mechanism was present in HA/α- Tocopherol succinate (TOS)@ZIF-8, here the hyaluronic acid shell acted as a smart switch which guided the MOFs towards tumours, in acidic environments of α-TOS is released to the tumour cells after hyaluronidase disintegrates the HA shells. There was a considerable loading rate up to 43.03 wt%. The study showed that HA shell, which might act as a smart switch and tumour-targeted guider, can stimulate blood flow, which in turn promotes the accumulation of DDS in tumours via CD-44-mediated pathway [118].

Zr based MOFs have received attention since the discovery of $Zr_6(m_3\text{-}OH)_4(BDC)_6$(UiO-66) [119] and $Zr_6(m_3\text{-}OH)_4(CO_2)_{12}$ clusters [120]. Due to their high oxidation state and intensive coordination with ligands like carboxylate, these MOFs provide better stability, particularly hydrothermal stability [121]. This causes Zr MOFs to have great stability in many solvents like water and even in acidic media. The delivery of dichloroacetate

and 5-FU from Zr-MOFs has been demonstrated to boost the cytotoxicity of cancer cells in vivo [122]. Two factors—pit-mediated endocytosis and cytoplasmic drug delivery—depend on the cytotoxicity activity of MOFs and both can be enhanced by adjusting the particle size and surface chemistry. UiO-66-NH_2 had maximum drug loading capacity (Fig. 4b) when loaded with ketoprofen on account of its strong hydrogen bonding ability and alkaline characteristics of eNH_2. According to the HPLC data, ketoprofen was successfully loaded onto the MOFs carriers, with UiO-66-NH_2 having the highest loading percentage 38%. In the experiment on the release of ketoprofen over 72 h, UiO-66-NH_2 had the lowest release rate and partial release of ketoprofen at around 65% due to its high capacity for hydrogen bonding and alkaline characteristics [119]. Zr-MOF consists of Zr-fum with endogenous fumarate linker has a structure similar to that of UiO-66. This remained stable in aqueous solutions, which shows good potential for it to function as a drug delivery system [123]. Dichloroacetate (DCA) molecule, which has anticancer abilities, was loaded on to the Zr-fum as a size-controlled modulator during the fabrication process.

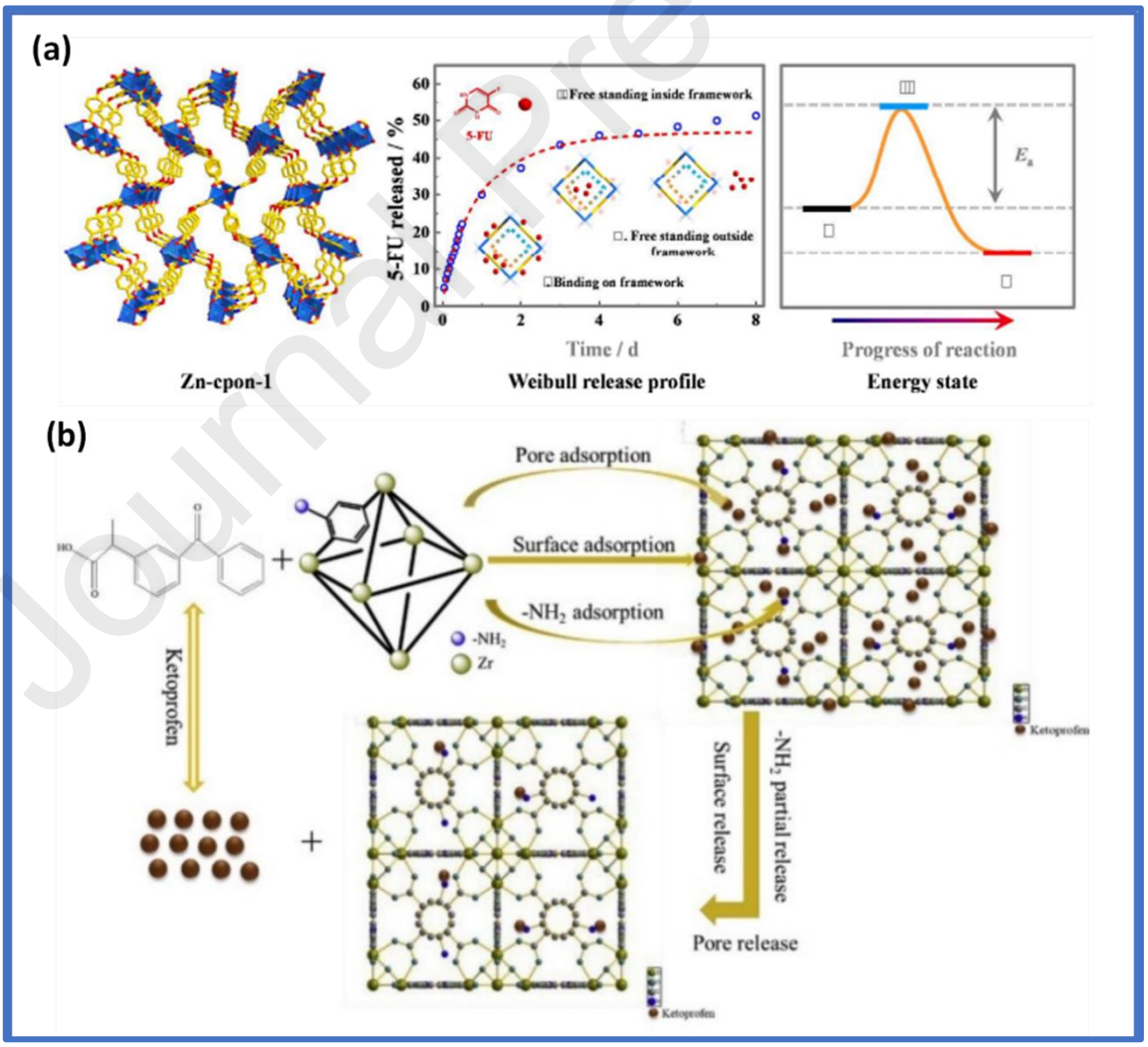

Fig. 4. (a) The release profile of 5-FU using Zn-cpon-1 MOF [114]. Reproduced with permission from [114], Copyright 2018, American Chemical Society. (b) Zr-MOF used for persulfate loading and its activity on bacteria [119]. Reproduced with permission from [119], Copyright 2019, Elsevier.

Zr-fum was given the anticancer probe chemical DCA as a modulator during manufacture, with payloads of 20 wt% stored at defect sites. The samples could also have their surfaces altered without experiencing significant DCA leakage [123]. The Zr-fum showed increase biocompatibility and efficiency in comparison to UiO-66. Two model systems such based on chromium such as MIL-100(Cr) and MIL-101(Cr), which were made up of metal octahedra and di or tricarboxylic acids have been successfully used for drug loading applications [20,124,125]. MIL-100 and its IBU drug release profile are shown in Fig. 5. MIL-100(Cr) and MIL-101(Cr) were made up of Cr (III) ions and BTC/ trimesic acid and BDC/ terephthalic acid, respectively. IBU, a typical model medication, was loaded onto the Cr-MOFs and displayed a high IBU loading capability of 1.4 g while only loading 0.35g with the MIL-100(Cr) [126].

Cu-MOFs are important in treating chronic non-healing wounds. Cu-MOFs stimulate angiogenesis, collagen deposition, and re-epithelization of wounds, which are ideal for wound healing. The concerns related to the high toxicity of Cu-MOFs were overcome with HKUST-1 modified with folic acid. This new framework improved stability, hydrophilicity, and surface area of the Cu-MOFs. The use of folic acid helped in slow release of Cu ions, and also folic acid aided in imaging or acted as a switch to target and kill tumour cells [127]. Sun et al. [91] used a hydrothermal method and prepared Cu-MOFs, MOF-2, and MOF-3 and employed them for delivery of IBU and DOX. Based on the experiments, mixed ligand MOF-2 with 40% BTC and 60% IPA performed the best for drug loading and release. Alkaline phosphatase (ALP) is a crucial biomarker for many disorders, including diabetes, bone diseases, prostatic malignancies, and liver dysfunction. To detect ALP, an amine functionalized NH_2-Cu-MOF was created. A ratio metric multicolour sensing platform that could be detected by a smartphone was built in order to detect ALP. As fictitious point-of-care tools, a hydrogel test kit and a smartphone app for ALP detection were also developed. The LODs of the fluorescent sensing platform were discovered to be 0.078 mU mL^{-1} and 0.35 mU mL^{-1}, respectively, using solution analysis and hydrogel test kit analysis. Cu-MOF could also be used for antibacterial studies as seen in the examples of usage of Cu-MOF containing glutaric acid and pyridine

derivatives which produced a high amount of antibacterial activity against bacteria of very low bactericidal concentrations [128].

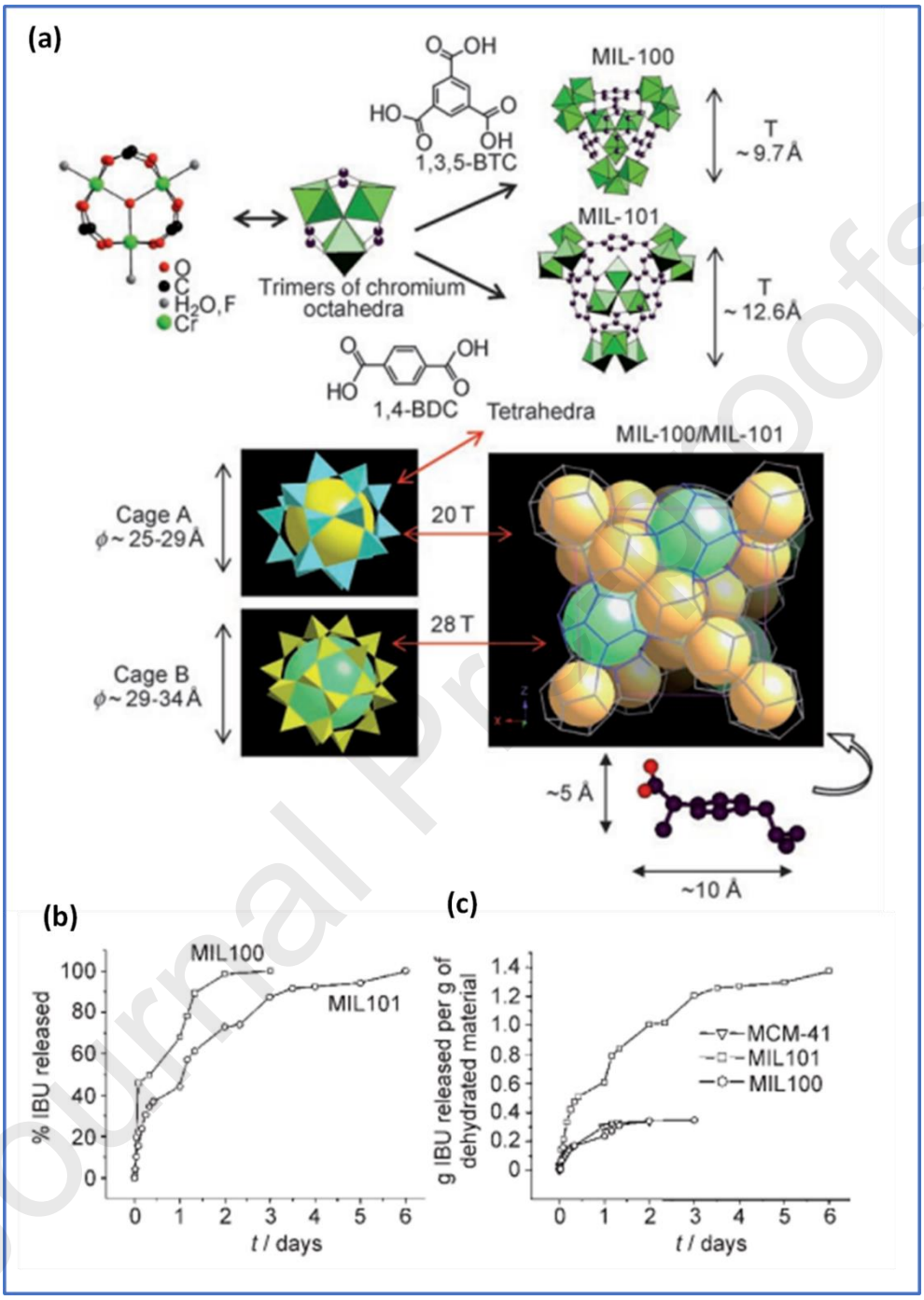

Fig. 5. (a) Structure (b-c) IBU drug release profile of MIL-100 and MIL-101 [126]. Reproduced with permission from [126], Copyright 2006, Elsevier.

The selection of metal ions profoundly influences MOFs characteristics such as porosity, stability, and biocompatibility, thus governing crucial aspects of drug encapsulation,

release kinetics, and targeting efficiency. Transition metals, owing to their versatile coordination chemistry and redox activity, are commonly utilized to impart MOFs with tunable pore sizes, enhanced drug loading capacities, and stimuli-responsive functionalities. Lanthanide ions, on the other hand, offer unique optical and magnetic properties that enable MOFs to serve as imaging contrast agents or theragnostic platforms, facilitating real-time monitoring of drug delivery and disease progression. Moreover, the integration of metal ions with specific biological functions, such as enzyme cofactors or metalloenzymes, further expands the biomedical applications of MOFs, enabling synergistic interactions with therapeutic payloads or catalytic activities within biological environments.

5. MOFs Based Composites

In recent years, there have been notable strides in the realm of drug delivery, showcasing remarkable progress aimed at enhancing therapeutic outcomes while minimizing potential side effects [129]. Among these innovations, MOFs have become an important class of materials due to their unique physicochemical properties [130,131]. This has paved the way for the development of MOFs-based composites, where the integration of MOFs with various functional components has opened up new avenues for precise and controlled drug delivery systems. This introduction delves into the fascinating realm of MOFs-based composites for drug delivery applications, exploring their underlying principles, design strategies, and the remarkable potential they hold in revolutionizing the landscape of therapeutic interventions [132,133]. By harnessing the synergistic capabilities of MOFs and complementary materials, researchers are forging ahead to unlock novel solutions that address the challenges of conventional drug delivery, ushering in a new era of targeted, efficient, and personalized treatments. Figure 6 illustrates different MOFs based composites for DDS.

5.1 Magnetic NPs

The use of magnetic nanoparticles (MNPs) inside MOFs is primarily involved in the magnetophoretic treatment [134]. This therapeutic approach involves the targeted delivery of magnetic NPs by means of an external magnetic field in Magnetic Resonance Imaging (MRI), where supra-magnetic NPs help in the reduction of spin-spin T_2*-relaxation time [135]. In majority of the cases, Fe has been utilized as MNPs for drug delivery applications. Ke et al. [136] in 2011 synthesized the first Fe_3O_4 MNPs and composited it with HKUST MOF for the drug delivery application. The drug Nimesulide was loaded onto this Fe_3O_4MNPs@HKUST

and used to treat pancreatic cancer. The Fe_3O_4@HKUST produced magnetization, and the drug molecule was released completely in 11 days.

Yang et al. [137] synthesized a Fe_3O_4@MIL-100 (Fe) composite where the core-shell magnetic microspheres have a substantial surface area available for interaction with analytes present in the aqueous phase, leading to a notable reduction in diffusion distance. The variables encompassing this phenomenon consist of a diminutive pore size measuring 4.81 nm, a substantial surface area amounting to 141 m^2g^{-1}, a notable pore volume of 0.17 m^3g^{-1}, and the presence of very thin layers of MOFs. Also, by using a magnetic field following the extraction procedure, the microspheres may be simply collected. In contrast to the Negligible-depletion solid-phase microextraction (nd-SPME) method, which needs 35 h (t90%) of equilibration time, the recommended strategy for these investigated Organophosphate esters (OPEs) achieves equilibration in just 24 min. From the results, it is observed that utilizing polyacrylate-coated fibre and polydimethylsiloxane-coated fibre with nd-SPME were very consistent with the sorption coefficients of the OPEs to humic acid, which varied from 3.85 to 4.28. The method is based on the volume exclusive effect of MOFs for the selective extraction of freely dissolved analytes, which is different from nd-SPME. OPEs linked to DOM were prevented from entering MOF pores, while OPEs that are freely dissolved can do so and thereafter be removed. Additionally, because the sorbent layer was thin, OPEs diffused more quickly from the aqueous phase to the MOFs. The suggested approach yielded sorption coefficient values that were in agreement with nd-SPME, although the equilibrium period was significantly shortened.

Using the same Fe MNPs Wu et al. [138], synthesized Fe MNPs@ ZIF-8. Here, Wu and co-workers loaded IBU, and the release of the drug molecule was observed within 7 days. In a recent study, polymeric MNPs containing Fe_3O_4 were successfully encapsulated inside MIL-88A, and the composite MIL-88A (Fe) was used for the purpose of magnetophoretic administration of Dopamine (DA) in the treatment of Parkinson's disease. A rapid drug release of DA. The highest DA concentration recorded for MIL-88A was 0.56 mg mL^{-1} [139]. By loading DOX into Fe MNPs, the composite formed is Fe_3O_4@UiO-66-NH_2 MOF used as MRI contrasting agents [140]. The sensitivity of Fe_3O_4@UiO-66-DOX to an acidic tumour microenvironment was evident from the release of 36.1 and 21.6% of DOX, respectively, during a period of 41 days at pH 4.0 and 5.0. In contrast, the release of DOX at pH 6.0 and 7.4 was much lower, with only 17.1% and 13.8% being released, respectively. Thus, the rate of

release would provide a stable drug concentration, allowing for sufficient accumulation of Fe_3O_4@UiO-66-DOX at the cancer site. Similar MOF composites Fe_3O_4@UiO-66@WP6 were reported by Wu et al. [141] in which 5-FU loaded was released after 2 h. The released rate rose as pH decreased, and after 2 h, 5-FU was released at a rate that was about two times quicker at pH 5.0 than at pH 7.0.

The drug-loaded nano platform discussed above had desirable super-paramagnetism and transverse relaxivity of 72.23 $x10^{-3}$ m, making it a potential T_2 contrast agent that can be used with T_2-weighted MRI. Chowdhuri et al. [142] synthesized Fe_3O_4@IRMOF-3/FA nano MOFs with a PTX load of 10 g mL^{-1}. The result of drug loading resulted in the killing of 60% HeLa cells. For comparison, the same group synthesized Fe_3O_4@IRMOF-3 NMOFs, and exhibited enhanced negative contrast enrichment (signal darkening) in the phantom pictures. This study demonstrated that, unlike the Fe_3O_4@IRMOF-3/FA, the folate targeted NMOFs significantly improved the negative contrast. Bio MOF composite MOF- Fe_3O_4@Bio-MOF-FC was loaded into 5-FU, and the drug release profile was seen at pH 7.4 with a release percentage of 30 [143]. Initially, 40% burst release of 5-FU was seen after 10 h followed by a steady release up to 87% after 78 h. For MRI imaging process, another research group synthesized Fe_3O_4@MOF-FC NCs had the ability to generate a negative contrast, resulting in darkening. The spin-spin relaxation time (T_2 and T_2^*) of Fe_3O_4@MOF-FC NCs and Fe_3O_4 samples exhibited a notable reduction in magnetic resonance signals, which may be attributed to an elevated concentration of Fe^{3+}. Consequently, when the concentration was increased from 0.04 to 1.28 mM, there was a corresponding drop in the T_2 relaxation period from 0.15 to 0.04 ms. The transverse relaxivity of Fe_3O_4@MOF-FC NCs was measured to be 114.74 mM^{-1} s^{-1}, while Fe_3O_4 NPs exhibited a relaxivity of 83.93 mM^{-1} s^{-1}. As a result, this process yielded a high-quality magnetic resonance imaging (MRI) contrast picture.

5.2 Lipid-MOF Composites

NPs are usually coated with a layer of lipid around them, which helps to improve cellular uptake and colloidal stability [144–148]. Huxford-Phillips [149] and colleagues successfully fabricated a nanoscale coordination polymer based on lanthanum (La) that incorporated disuccino cisplatin (DSCP), resulting in La-DSCP, a material known for its cisplatin-producing properties. The substance was applied onto a lipid bilayer composed of 1,2-dioleoyl-sn-glycerol-3-phosphate (DOPA) forming the outer layer, and afterwards coated with 1,2-disteroyl-sn-glycerol-3-phosphoethanolamine-N-(Polyethyleneglycol) (DSPE-PEG),

cholesterol, and DOPA. The composite was made target specific sigma-receptor by addition of anisamide conjugate.

Lie et al. [150] successfully synthesized a biocompatible Zn-based nanoporous coordination polymer, Zn(II) bisphosphonate, and then coated it with a bilipid layer. The Zn(II) bisphosphonate demonstrated significantly heightened effectiveness against CT26 colon cancer, H460 non-small-cell lung cancer, and AsPC-1 pancreatic cancer compared to the standalone drug component. The polymer incorporated a combination of Zn bisphosphonate with 45.5% oxaliplatin prodrug and 48.3% cisplatin prodrug. In pharmacokinetic assessments conducted in vivo, mice exhibited favorable blood circulation half-lives of 16.4±2.9 h and 12.0±3.9 h for coordination polymers containing cisplatin and oxaliplatin, respectively. Additionally, in vivo pharmacokinetic studies in mice indicated minimal uptake of pegylated coordination polymers by the mononuclear phagocyte system, with exceptional blood circulation half-lives of 16.4±2.9 h and 12.0±3.9 h for polymers carrying cisplatin and oxaliplatin, respectively. Across all assessed tumor xenograft models, including CT26 colon cancer, H460 lung cancer, and AsPC-1 pancreatic cancer, pegylated NCPs exhibited superior potency and efficacy compared to free drugs.

He et al. [151] helped in acquiring an added photodynamic treatment (PDT) function, which helped in treatment of head and neck cancers. In the mouse model of cisplatin-resistant human head and neck cancer, SQ20B xenograft showed that coordination polymers with pyrolipids enhanced potency and efficacy in inducing tumour regression. Notably, even at modest treatment doses, the pyrolipid composite achieved a substantial reduction in tumour volume, amounting to 83% decrease. The same method had been used to stabilize the surfaces of Fe- [145], Cr-[145], Zr-[146], and Zn [147] based MOFs. The direct coordination of phenolic-lipid to metal clusters has also induced versatile chemical functions [148]. The conjugation of lipophilic cation triphenylphosphonium (TPP) to UiO-66 was used to target the mitochondrial cells [25]. This was used to deliver dichloroacetate to MCF-7 breast cancer cells for intracellular targeting.

5.3 Protein-MOF Composites

The formation of protein MOF composites involves the encapsulating of proteins on the surface of MOF materials, like a bottle-around-ship configuration [152,153]. Liang and colleagues [154] have shown evidence for nature-inspired biomineralization by the

encapsulation of bovine serum albumin in ZIF-8, resulting in enhanced chemical and thermostabilities of the MOF. The pH-induced release profiles demonstrated that the encapsulated proteins could be released by changing the pH from 7.4 to 6. This strategy helped in delivering biologically sensitive proteins preventing their degradation. The synthesis of tyrosine@PCN-33 composite by infiltration was used to oxidise a prodrug paracetamol into 4-acetoamido-o-benzoquinone which in turn helped in producing Reactive oxygen species. The oxidative stress induced the tumour suppression in HeLa cancer bearing mice in 7 days [155].

5.4 Nucleotide-MOF Composites

Nucleic acid -based macromolecule delivery, such as in the case of interfering RNA (RNAi) gives an opportunity for selective inhibition by gene-targeting therapies [156]. Small interfering RNA (siRNA) induces gene silencing by targeting the mRNA through incorporation of RNA induced silencing complex (RISC) by utilizing the catalytic activity of this complex, which inhibits protein expression by binding to RNA during the gene expression step [157]. siRNA cannot cross the cellular membrane because of its high molecular weight and negative charge and thus requires a delivery system. The siRNA was loaded onto a mesoporous NU-1000(Zr) by impregnation [158]. With siRNA-MOF complexation, in vitro tests showed up to 27% consistent knockdown. The integration of MOF and siRNA was proved by enzymatic degradation studies and fluorescence lifetime imaging. The invitro efficiency of the siRNA@NU-1000(Zr) was demonstrated by masking the expression of proteins in HEK293-mC cells. The above experiment produced different results, showing the integration of siRNA in some and no integration in others.

Based on earlier research, it was deduced that siRNA integration into the MOF did take place but that endosomes destroy siRNA before it reaches the cytoplasm [159]. Using the large pore capacity, the MOFs obtained amazing model drug loading percentages greater than 35 wt% [158]. Alphacyano-4-hydroxycinnamic acid (-CHC), an anticancer therapeutic agent, was encapsulated in NU-901 and NU-1000, and subsequent thermal treatment led to loadings upto 81 wt% and showed effectiveness in killing cells beyond the burst release effect [160]. When proton-sponge cofactor was added to the HeLa cells, there was successful delivery of the siRNA into the cytoplasm, thus proving the effect of the degradation effect of endosomes/lysosomes. Other nucleotide based composites have been developed for delivery in gene-editing tool CRISPR/CAS9 [161], siRNNA@NCP [162], sDNA@IRMOF-74(Ni) [163], mRNA using UiO-66 [164], and in MIL-100 [165]. Due to the biocompatibility and stability

in phosphate-containing solutions, the delivery of mRNA using MIL-100(Fe) is rather promising. Figure 6 explains the targetted drug delivery applications of different MOF composites.

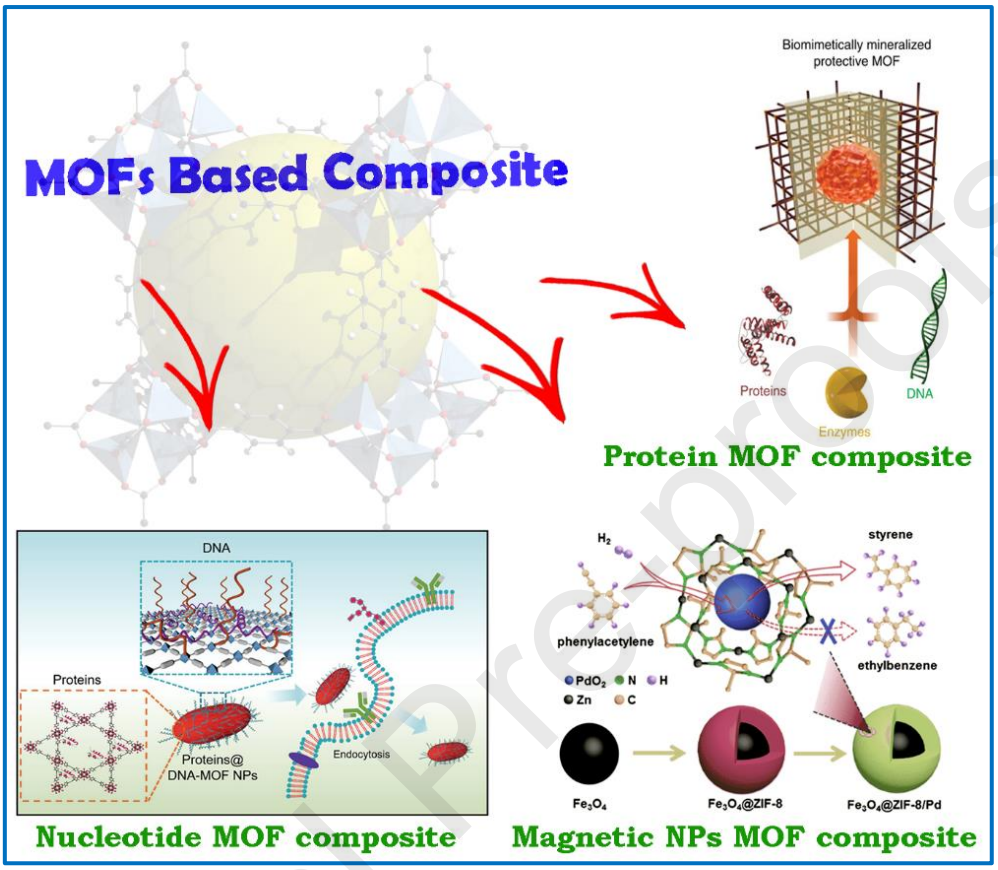

Fig. 6. Different MOFs based composites for the targeted drug delivery applications.

In this section, we have delved into the diverse landscape of MOF-based composites, encompassing hybrid materials, nanocomposites, and bio-inspired constructs, each offering unique advantages in terms of drug encapsulation, delivery kinetics, and biocompatibility. The synergy between MOFs and other nanomaterials, such as polymers, nanoparticles, and biomolecules, enables the creation of multifunctional composites with tailored properties and functionalities. Hybrid MOF-polymer composites, for instance, combine the high drug loading capacities of MOFs with the tunable mechanical properties and biodegradability of polymers, facilitating sustained drug release and enhanced biocompatibility. Similarly, the integration of MOFs with nanoparticles or biomolecules imparts additional functionalities, such as imaging capabilities, targeting ligands, or stimuli-responsive behavior, further expanding the utility of MOF-based composites in drug delivery applications.

6. Surface Modifications

Surface modification of MOFs for drug delivery applications is an area of research that focuses on enhancing the performance and capabilities of MOFs as carriers for delivering therapeutic agents, such as drugs or biomolecules, to specific targets within the body [166]. Surface modification techniques involve altering the outer layer of MOFs to achieve specific properties or functionalities that are advantageous for drug delivery. These modifications can improve the stability of MOFs in physiological conditions, enhance their biocompatibility, and enable controlled release of drugs [167].

6.1 Polymer-functionalization

The process of polymer functionalization involves the application of a silica coating onto a MOF, or, alternatively, the incorporation of silica particles into the framework of the MOF [168]. The silica coatings exhibit many notable characteristics, including favourable biocompatibility, enhanced water dispersion, and convenient potential for further functionalization owing to the existence of silyl groups on the surface of the silica [169]. Water dispersion was enhanced by surface changes using polyvinyl pyrrolidone. Polymers often exhibit binding to the terminal groups of MOFs by means of electrostatic interaction with the surface or by covalent bridging ligands, hence offering shielding effects [170]. Conjugation methods are used to coat MOF surfaces with silica or polymers during MOF synthesis or post MOF synthesis. Polysaccharides such as dextran, biotin, and chitosan have been used to enhance the effectiveness of other MOF structures. This utilization leads to improvements in solubility, adhesion, and contrast imaging capabilities [171]. Polymer functionalization involving polyvinyl pyrrolidone uses thiol end group conjugation with Gd MOFs. This type of polymer coating provides controlled drug release from the MOF [170]. An alternative method involves using the combination of silica and polymer functionalization, which contributes to the enhancement of water solubility and dispersibility. The use of silica coated iron terephthalate MIL-101 MOF showed enhanced drug encapsulation and improved tumour targeting capabilities upon cisplatin loading [172].

6.2 Polyethylene glycol (PEG) and Peptides functionalization

Functionalization of MOF with PEG moiety has varied applications in enhancement of solubility, diagnostic imaging, and tumour targeting. The use of PEG moiety as a surface

coating on iron-carboxylate micro MOFs facilitates a regulated interaction between the MOF and biological surfaces, resulting in an extended half-life of the encapsulated medication ranging from several hours to days [173]. The functionalization of nano MOFs with PEG moiety leads to enhanced stealth properties, hence promoting increased absorption by the reticuloendothelial system [174]. Functionalization of MOF by peptide functionalization has been done with fluorescence dyes which were used for in vitro imaging and tumour targeting [175]. Rhodamine, RGDfK, and angiogenic coated MOF functionalization are recent examples of the functionalization of MOFs used for targeting cancer cells [176]. Table 3 gives details of various MOFs composites and their applications.

Table 3. Comparison of Various MOFs composites.

MOF based Composites	**Composite type**	**Synthetic method**	**Ligand used**	**Application**	**Ref.**
$Fe_3O_4/Cu_3(BTC)_2$	Magnetic	Solvothermal	BTC	Anti cancer medication	[136]
Fe_3O_4@MIL-100 (Fe)	Magnetic	Solvothermal	BTC	Sorption studies of toxic materials	[137]
γ-Fe_2O_3 @MOFs	Magnetic	Solvothermal	H_2BDC, 2MI	Drug delivery	[177]
PMP@MIL-88A	Magnetic	Solvothermal	Fumaric acid	Drug delivery	[139]
NCPs	Lipid	Solvothermal	DSCP	Cisplatin loading	[149]
Zn(II) bisphosphonate NCP	Lipid	Solvothermal	DOPA	Anti Cancer activity	[150]
NCP@Pyrolipid	Lipid	Solvothermal	DOPA	Tumour regression	[151]
ZIF-8/BSA biocomposite	Protein	Solvothermal	2-MI	Bioactivity	[154]
TYR@NPCN-333	Protein	Solvothermal	TATB	Anti cancer activity	[178]
siRNA-MOF	Nucleotide	Solvothermal	Pyrene	Gene knockdown	
cal@MOF	Nucleotide	Ultrasonic	pyrene	Drug release	[160]
CC-ZIFs	Nucleotide	Solvothermal	2-MI	Gene editing	[161]

7. Drug loading on MOFs

Drug loading of MOF refers to the process of incorporating therapeutic agents into the pores or channels of MOFs for controlled and targeted drug delivery. This approach offers several advantages, such as protection of the drug from degradation, controlled release, and enhanced therapeutic efficacy [179,180]. There are different methods like one step and two step methods, which are used for loading drugs into MOFs and used for various therapeutic purposes.

7.1 One step method

The one-step method of drug loading on MOFs represents a streamlined approach in which drugs are seamlessly incorporated into the MOF structure during the initial process of MOF synthesis [31,181]. This innovative technique offers notable advantages by simplifying the drug-loading process and creating drug-MOF composites in a single operation. In this method, the drug of interest is introduced into the reaction mixture containing the precursors for MOF formation. As the MOF crystals grow, they effectively encapsulate the drug molecules within their porous framework [182]. This integration occurs simultaneously with MOF crystallization, eliminating the need for separate drug-loading steps post-MOF synthesis. The one-step drug loading process not only enhances efficiency but also allows for the precise tuning of drug release kinetics. By controlling the synthesis conditions, researchers can influence the size, structure, and porosity of the MOF, thereby tailoring the drug release profile to meet specific therapeutic requirements [129]. In this technique, there are various sub-methods used for drug loading.

7.1.1 Co-crystallization technique

In the co-crystallization technique, the drugs are loaded into MOFs by incorporating the drug molecules directly into the MOF crystal lattice during the synthesis process. This approach involves the simultaneous crystallization of the MOF and the drug, resulting in a composite material where the drug molecules are distributed within the MOF's porous framework [105,183]. During co-crystallization, the drug molecules and the MOF precursors are combined in a reaction mixture under specific conditions, such as temperature, solvent, and reaction time. As the MOF crystals form, the drug molecules become embedded within the MOF's cavities and channels, creating a drug-loaded MOF composite. Poorly soluble drugs

such as IBU [184], lansoprazole [105], leflunomide [185], and methotrexate (MTX) [186] have been effectively integrated into g-CD-MOFs by the co-crystallization technique. The loading capacity done this way was found to be equal to or higher than when done by impregnation method. Lansoprazole had an increased loading capacity of 23.2 ± 2.1% (wt). Leflunomide, IBU, and methotrexate possessed loading capacities of 37 80 wt.% and ~6 wt%, respectively, in 2 h.

7.1.2 Drug molecules as an organic linker

Using the drug molecule itself as a linker for drug loading in MOFs is an intriguing and innovative approach that combines the drug's therapeutic properties with the MOF's porous structure. In this technique, the drug molecule serves a dual purpose: it acts as both a therapeutic agent and a building block for the MOF framework, effectively becoming a linker that contributes to the MOF's structural integrity [187]. The process involves incorporating the drug molecule into the MOF synthesis alongside traditional metal ions and organic ligands. As the MOF crystals form, the drug molecules become integral parts of the MOF structure, occupying specific sites within the pores and channels [187]. In a drug delivery system composed of phosphonate ligands, different MOFs were synthesized. The MOF was constructed utilizing biologically-compatible calcium (II) and magnesium (II) ions as the metal ions, while etidronate, pamidronate, alendronate, and neridronate were used as model medicines for anti-osteoporosis bisphosphonates. After a duration of 192 h, it was observed that the release rates of Mg(II) ions displayed a variability of 8%, whereas the release rates of Ca(II) ions exhibited a variability of 24% [188].

7.1.3 One pot technique

The "one-pot" technique for drug loading in MOFs is an efficient and straightforward approach that involves combining all necessary components—such as metal ions, organic ligands, solvents, and drug molecules—into a single reaction vessel or "pot" to synthesize a composite material where the drug is incorporated within the MOF structure. This method offers the advantage of integrating drug loading with MOF synthesis in a single step, streamlining the process and simplifying subsequent drug delivery applications [31].

Various drugs, such as DOX [189], camptothecin [190], and 3-methyladenine [191], have been successfully incorporated into the ZIF-8 MOF using one-pot synthesis techniques.

The loading capabilities of DOX were shown to be 20%, and its release occurred at a consistent pace, with over 95% being released within the time frame of 7-9 days. The highest loading quantity for DOX was discovered to be 2 wt %. Similarly, camptothecin exhibited a loading capacity of 30%, while 3-methyladenine showed a loading capacity of 19.798%. The formation of Gox-HRP@ZIF-8 occurred through the interaction between Glucose oxidase (Gox) and horseradish peroxidase (HRP), which were then combined with a solution of zinc nitrate. This result showed an increase in catalytic efficiency when compared to Gox@ZIF-8 and HRP@ZIF-8.

7.2 Two-step method

The two-step synthesis approach for drug loading on MOFs involves a sequential process where the MOF framework is first synthesized separately, followed by the subsequent incorporation of drug molecules into the pre-formed MOF structure [192]. This method provides a controlled and targeted way to load drugs into MOFs, allowing for precise tuning of drug loading and release characteristics. In the first step of this approach, the MOF is synthesized by combining metal ions and organic ligands under specific conditions. This leads to the formation of MOF crystals with well-defined pores and channels, creating a porous architecture that can later encapsulate drug molecules [193]. The second step focuses on loading the desired drug into the pre-formed MOF structure. The drug molecules diffuse into the MOF pores and cavities, becoming entrapped within the MOF's porous network. The resulting drug-loaded MOF composite retains the original MOF's structural integrity while gaining the ability to deliver therapeutic agents in a controlled manner.

7.2.1 Mechanochemical method

This drug loading technique mixes drugs with the MOFs mechanically in the solid state. This is an economical, green, and solvent free loading technique [194]. The sturdy 3D MOF [Zn_4O(3,5-dimethyl-4-carboxypyrazolato)$_3$] ([Zn_4O(dmcapz)$_3$]) is investigated as a promising platform for the regulated release of bioactive compounds. This is accomplished by effectively encapsulating the model pharmaceuticals 5-fluorouracil, caffeine, para-aminobenzoic acid, and benzocaine using a straightforward ball milling approach. The suitability of [Zn_4O(dmcapz)$_3$] to integrate high loadings of the investigated bioactive compounds is confirmed by computational and experimental tests. The findings demonstrate that the bioactive molecules' physicochemical characteristics have an impact on the MOF structure's loading effectiveness.

The controlled discharge of bioactive compounds from drug@[Zn4O(dmcapz)3] is investigated in simulated skin conditions to showcase its potential as a topical drug delivery system (Benzocoa). The Drug@MOF systems released 98.7 ±1.5% and 97.8 ±1.7% of the total hydrophilic 5FU and Caff medications. Within 6-7 days, PABA@MOF and Benzoca@MOF released 92.1 ± 2.5% and 86.2 ± 1.7% of the cargo, respectively [59].

7.2.2 Impregnation technique

In this method, the MOFs are immersed in a drug solution, which helps the drugs to diffuse into MOFs due to their porosity. The typical mode of interaction between drugs and MOFs mostly involves Van der Waals forces, π-π interactions, and hydrogen bonding. The critical factors required for effective drug loading include the pore size, window dimension, and chemical composition of the MOFs [111]. Caffeine loading was done on MOF via impregnation. In the amino-functionalized and bare UiO-66(Zr), the caffeine loading varied from 2 to 3.4 molecules per unit cell, for amino groups, respectively. When functionalized with the Br- and 2OH groups, the solids had intermediate loadings of 2.5 and 2.2 caffeine molecules per unit cell, respectively [195]. IBU was embedded into Cu-MOF via impregnation and showed a rapid drug release of 95% at pH 1.2 [196]. The IBU, caffeine and honokiol loading are done here to show the comparison for two of the molecules. The integration of poorly soluble drug honokiol (HNK) into CD-MOFs was done using supercritical carbon dioxide assisted impregnation, which increased the efficiency of the loaded drug molecule in comparison to the other molecules. Within 24 h, the cumulative release percentage of HNK@CD-MOF reached around 94% [197].

When using the same strategy for phosphate drugs, the efficiency increased to an extremely high extent due to greater coordination between the phosphate group and Fe. Gemcitabine monophosphate (GEM) was loaded on MIL-100(Fe), which increased its efficiency. MIL-100(Fe)-GMP NPs showed only 22:8 metastasis/lungs 29 days after metastasis induction, whereas 58:8 metastasis was still present in the lungs of the mice receiving GMP treatment when the number of metastases was 65:21 and 60:14 for MIL-100(Fe) NPs [198].

7.2.3 Covalent Binding

Due to the low contact force between the medication and MOF, leaching issues often arise. Thus, it is important to devise a method that involves the immobilization of drug

molecules on MOF via covalent binding. Covalent bonding is possible on MOFs due to various groups that are present on the surface, such as carboxyl, hydroxyl, and amino groups [199]. The formation of a DNA-MOF conjugate was achieved using a click reaction involving the azide-functionalized UiO-66 and dibenzylcyclooctyne (DBCO) functionalized DNA. For MOF nanoparticle-DNA conjugates functionalized with (3′T_{20}T- (DBCO)5′), loadings of 12.3(6) and 13.0 (1) pmol cm^{-2} correspond to 5 x 10^{-10} ng of DNA/nanoparticle and $1x10^{-9}$ ng of DNA/nanoparticle, respectively, for 14 and 19 nm MOF nanoparticle-DNA conjugates [200]. This conjugate was reported to have increased cellular transfection and stability in comparison to normal non functionalized UiO-66. The immobilization of soybean epoxide hydrolase (SEH) onto the surface of UiO-66-NH_2 MOF by cross-linking has shown the feasibility of covalently attaching enzymes to MOF surfaces. Compared to free SEH this new composite showed higher loading capacity, binding efficiency, and catalytic efficiency. The SEH@UiO-66-NH_2 composite exhibited a high SEH loading of 87.3 mg g^{-1} and a notable enzyme activity recovery of 88.0%. After a storage period of 4 weeks at a temperature of 4ºC, the SEH@UiO-66-NH_2 sample exhibited a retention of around 97.5% of its initial activity. Table 4 gives details about the methods of drug loading in MOFs.

In this section, we have explored the various methods and factors influencing drug loading efficiency, encapsulation capacity, and release kinetics within MOFs. The selection of appropriate loading methods, including impregnation, covalent binding, and mechanochemical synthesis, play a pivotal role in determining the loading efficiency and distribution of therapeutic agents within MOFs pores. Additionally, factors such as drug physicochemical properties, MOFs structure, and pore size significantly impact the loading capacity and release behavior of encapsulated drugs. Impressive advancements have been made in enhancing drug loading efficiency through the design of functionalized MOFs, tailored pore architectures, and surface modifications. Using these strategies, researchers can optimize drug-MOF interactions, improve loading capacities, and achieve controlled release profiles tailored to specific therapeutic needs.

Table 4. Various methods of drug loading in MOFs.

MOF	Drug loading Mechanism	Synthetic method	Conditions	Ref.

CD-MOFs	Co-crystallization	Solvothermal	CD-MOF microcrystals in EtOH, MeOH, and CH_2Cl_2, results greatest impregnation.	[184]
γCD-MOF-2	Co-crystallization	Solvothermal	Aqueous solution of γ-CD, KOH, and LEF.	[185]
γCD - MOF/MTX composite	Co-crystallization	Solvothermal	Aqueous solution γ-CD, KOH (1:8), and MTX (0.05 M) were used for crystallization.	[186]
DOX@ZIF-8	One pot	Solvothermal	Particles of DOX@ZIF-8 were obtained with loadings as high as 20%.	[189]
ZIF-8	One pot	Solvothermal	With a loading efficiency of 10%, the maximum loading quantity is 1 wt %.	[190]
Cu-MOF/IBU@GM	Impregenation	Solvothermal	Drug solution containing 300 mg of IBU in 10 mL of n-hexane, 100 mg of Cu-MOF	[196]
HNK@CDMOF	Impregnation	Solvothermal	600 mg of CD-MOF crystals were distributed into 10 mL of HNK ethanolic solution	[197]

8. Drug Delivery Mechanism

8.1 Single Stimuli Response of MOFs

Single stimuli response in MOFs refers to the behaviour of these materials to a specific external stimulus, such as changes in temperature, pressure, or the presence of a particular molecule or gas. Unlike multi-stimuli response, where MOFs react to multiple external factors, single stimuli response focuses on a single triggering condition that induces a specific change in the MOF's properties. MOFs are known for their tuneable structures and properties, which makes them excellent candidates for various applications, including sensing, drug delivery, gas storage, and separation. When a MOF exhibits single stimuli response, it means that it can undergo significant changes in its structure, porosity, or properties in response to a particular stimulus.

8.1.1 Temperature Responsiveness

Temperature sensitive MOFs have been developed using both organic and inorganic materials [201]. The drug molecule is absorbed onto the surface of the MOF by physical adsorption if they have comparable pore sizes [202]. The interactions which are based on dipoles, hydrogen bonds, or charges are not very stable when compared to chemical bonds. When heated, these interactions are lost as a result of entropy [13,202]. Thus, drugs can be released much faster by triggering the weakening of these interactions between the host and guest at higher temperatures. The use of this can be seen in ZJU-801, a Zr-based MOF, which released the encapsulated drug at higher temperatures. The release was found to have a 10-fold increase at 60°C when compared to 25°C [109]. This release was done by weakening the π-π interactions between the MOF and the drug molecule.

8.1.2 Thermo-responsive

Thermo-responsive polymers can also be used to modify the porous surface, which can act as temperature responsive MOFs. Poly(N-isopropylacrylamide)(PNIPAM) exhibits a reversible phase transition characterized by a lower critical solution temperature, whereby it undergoes a transformation from a hydroswollen state to a shrunken dehydrated state [203]. The polymer that is used for thermal responsiveness is usually hydrophobic, dissolves in water at a temperature below 32°C, and forms aggregates [204–206]. Karmer et al. [207] reported a MOF using this above mentioned principle (MIL-101 modified with PNIPAM), which exhibited thermo-responsive water capture and release. MIL-101/polymer composite with 38 wt% PNIPAM could hold a remarkable 440 wt% of water at 25 °C with a relative humidity of 96%. This increased as the hydrophobic and hydrophilic conditions were transitioning in PNIPAM. Smart PNIPAM-modified Uio-66, which, when loaded with caffeine, procainamide, and resorufin, showed temperature responsive drug release at certain temperatures.

In phosphate buffered saline with a neutral pH value of 7.4, Methotrexate (MTX) release from MTX-loaded ZJU-64 and ZJU-64-CH_3 was assessed at two distinct temperatures (37 and 60.8^{o}C). MTX, an anticancer medication, is effectively loaded into MOFs using a straightforward impregnation process. The drug payloads for ZJU-64 and ZJU-64-CH_3 are around 13.45 and 10.63 wt%, respectively [208]. Temperature control is a critical problem in tissues as there can be other side effects due to this increase and decrease in temperature. The synthesis of MOFs at room temperature holds significant promise, particularly due to its

facilitation of biomolecule incorporation, enabling applications in the biomedical field. A notable instance of this approach was demonstrated by Dai et al. [209], who achieved the synthesis of a highly porous metal (IV) carboxylate MOF through a one-pot reaction conducted at room temperature. This MOF-801 comprised five 12-connected and two 8-connected M-6 oxo-clusters functionalized with diverse organic ligands. Remarkably, this marked the first successful instance of room-temperature Zr-MOF synthesis. Unlike lab-scale methods, this procedure consistently produced an exceptionally crystalline solid with an impressive water adsorption capacity of 41 wt% H_2O/MOF. Furthermore, this synthesis method was effectively scaled up, resulting in a high yield of Zr-based MOFs at room temperature. Noteworthy achievements include the development of an ultra-stable titanium carboxylate MOF, exhibiting an increase in electrical conductivity from 1.5 x 10^{-10} S cm^{-1} to 5.2 x 10^{-14} S cm^{-1} at 1 Hz.

The substantial increase in the stability of STAM-17-OEt compared to HKUST-1 when subjected to cycling relative humidity between 0 and 90% at 298 K over 120 h has also been explored. STAM-17-OEt had a Cu-based MOF with a structure and chemical make-up similar to those of HKUST-1 but improved hydrolytic stability due to a novel mechanism [210]. During these trials, STAM-17-OEt maintained a constant maximal water uptake capacity, whereas HKUST-1's capacity diminished with each cycle. In the context of toxic gas adsorption, the ammonia capacity of STAM-17-OEt exhibited sustained enhancement even after prolonged exposure to 90% humidity over five days, demonstrating superior performance compared to HKUST-1. Innovative techniques like ionothermal synthesis have introduced novel avenues for the production of MOFs. This method, using ionic liquids as both templates and solvents, facilitated the creation of zeolites and inorganic-organic hybrids like MOFs.

Leveraging the unique properties of MOFs, there have been significant advancements in gas delivery and catalytic reactions for modulating tumour microenvironments. For instance, MCM@PEG-CO NPs exhibited temperature elevation upon NIR laser irradiation, with concentration-dependent effects on temperature increase. Photothermal studies demonstrated the efficient conversion of NIR energy into heat by MCM@PEG-CO NPs, indicating their potential for CO and DOX release under NIR conditions. However, complete tumour cell eradication was not achieved even with maximal temperature (46.0°C) and short illumination times [211]. In the realm of nucleic acid delivery, MOFs like MIL-100 and UiO-66 have shown promise in maintaining the integrity of nucleic acids during cytoplasmic delivery. Notably,

mitochondria-targeted MOFs exhibited enhanced gene expression and cell death outcomes, underscoring their potential in therapeutic applications.

8.1.3 Magnetic Responsiveness

The integration of magnetic materials into MOFs allows for the manifestation of magnetic targeting capabilities, hence enabling their use as contrast agents in MRI. Magento-hypothermia effects of tumour can be remotely actuated with alternating magnetic field, with the potential to be used in tumour therapies, whereby the temperature may be elevated to levels above 43°C. The dissipation of magnetic energy, which is damaging to crystals, may be ascribed to this particular function [212]. A study reported the development of a composite material, Fe_3O_4@C, which exhibited both hyperthermia and chemotherapeutic functionalities that could be activated by magnetic fields, achieved via harnessing the magnetothermal effect [213]. When the Fe_3O_4@C were loaded with DOX, they exhibited an increased efficiency of 75% in magnetic heating, along with a release mechanism activated by strong magnetic fields. These effects have greatly inhibited tumour growth, the high amount of apoptosis, and necrosis of the cell.

An induced magnetic field may have negative effects if a significant number of magnetic MOFs build up in a particular target organ. Thus, the focusing method used is of great relevance when using magnetothermal effects. The magnetic responsive MOFs have been receiving a great deal of interest because it incorporate both magnetic and MOF properties in one molecule [214]. Many examples can be cited for the varied application of MOFs as stated above, one of them is a Fe_3O_4 decorated MOF that is loaded with the drug nimesulide, which showed magnetic resonance imaging and controlled drug release for pancreatic cancer. After just 24 h, MTT tests showed 14% drug release of nimesulide at pH 7.2. Additionally, the Raman signature of lysosomes and lipid vesicles in cells varies between the two pH levels 7.2 and 6.5, confirming changes in the chemical composition, which includes a greater cysteine concentration and related reductive potential at lower pH. The spectra displayed a greater signal in the aliphatic C-S stretch vibration band at pH 7.2 [215].

The natural amino acid was used to create the Zr-MOF and MIP-202(Zr), which exhibit a high and stable proton conductivity of 0.011 S cm^{-1} at 95% relative humidity [216]. This MOF had a preparation that was affordable, environmentally friendly, and scalable with an exceedingly high space-time yield exceeding 7000 kg m^3 day^{-1}. The proton conduction

mechanism was clarified using a thorough molecular simulation. MIP-202(Zr) is one of the most promising possibilities to reach the commercial benchmark due to all of these characteristics. The usage of an external magnetic field greatly yielded particle accumulation, and thus, therapeutic effects were found to be increased. MOF showed increased efficiency in delivering drugs to the tumour target site via magnetic targeting. Figure 7 explains different drug loaded NPs and their different stimuli response-mediated drug release for tumour treatment [217].

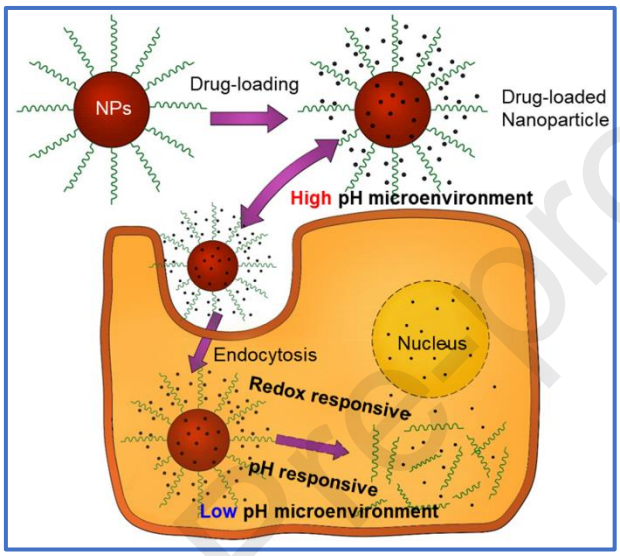

Fig. 7. Schematic illustration of stimuli response-mediated drug release for tumour treatment [217]. Reproduced with permission from [217], Copyright 2020, MDPI.

A new two-dimensional material, graphdiyne (GDY), was combined with a MOF structure, Fe_3O_4@UiO-66-NH_2 (FU), to create Fe_3O_4@UiO-66-NH_2/graphdiyne (FUGY). The FU MOF structure, which was created via an in situ growing technique and which functions as a delivery system for anticancer medications, had excellent magnetic targeting capabilities. DOX, an anticancer medication used to treat tumours, was placed onto FUGY and used as both a fluorescent probe and an anticancer agent to locate the tumour. The findings demonstrate that at pH 5.0, FUGY has a high drug loading content of 43.8% and an efficient drug release surrounding the tumour cells [218].

8.1.4 Redox- responsiveness

Redox responsiveness can be utilized effectively in studying tumour environments. The different oxidation and reduction states of glutathione (GSH) and nicotinamide-adenine

dinucleotide phosphate (NADPH) can be monitored in order to understand tumour environments. The concentration of GSH is higher than that of NADPH thus, GSH plays a key role in regulating tumour environments. GSH concentration in cells is an important marker for the studies of tumours, which helps in the formation and breaking of the disulfide bonds. Thus, the concentration of GSH will be more intracellular than extracellular and can be utilized as a drug delivery agent to cells that have a reduced environment due to broken disulfide bonds [219,220]. Surface modifications and ligand design are the areas in MOFs that can utilize the above mechanism for drug delivery [221].

Zhao et al. [222] created a novel type of coordination polymers sensitive to redox reactions using manganese ions (Mn^{2+}) and dithiodiglycolic acid, forming disulfide (SS) bridges. This Mn-SS MOF, with mesoporous structures, was effectively loaded with the chemotherapy drug DOX. The resulting Mn-SS/DOX nanoparticles were coated with polydopamine (PDA) and modified with PEG. This structure allowed the SS to be cleaved in the presence of GSH, triggering the release of DOX. Mn^{2+} within the Mn-SS/DOX@PDA-PEG framework offered strong T1 contrast in MRI. Intravenously injected Mn-SS/DOX@PDA-PEG exhibited efficient tumour homing and significantly improved in vivo therapeutic outcomes compared to free DOX. The disulfide linkers enabled controlled drug release upon GSH exposure, and the presence of Mn^{2+} facilitated MRI imaging for accurate tracking.

Lei et al. [223] reported a MOF using Zr, Fe and Al as the metal centers and 4,4 0-dithiobisbenzoic acid (DTBA) as the organic linker. The composite exhibited faster release of the encapsulated drug due to the increased rate of disulfide bond cleavage by GSH in DTBA in tumour cells compared to normal cells. The active drug component uses redox responsiveness, which is mainly based on the disintegration of the disulfide bonds by redox active species. UiO-66-NH_2 MOFs functionalized with disulfide anhydride and folic acid studies were carried out by Liu et al. [224]. The cancer cells with overexpressed GSH attacked the thiolate moiety and cleaved the disulfide bonds, which caused the release of the encapsulated drug. The redox response was observed by measuring GOx in diabetic patients. Another application of redox response was done by inducing the release of insulin by GOx. The concentration of GOx that ranges from 1 to 10 U mL^{-1} will convert glucose to gluconic acid and H_2O_2, thereby causing acidification of the local environment.

Chen et al. [69] synthesized a ZIF-8 for the controlled release of drugs using glucose responsiveness. ZIF-8 was degraded by the aerobic oxidation of glucose, resulting in the drug

release, followed by the release of insulin after treatment with glucose. Additionally, for angiogenic regeneration of blood vessels for muscular diseases in diabetic patients, the MOF could be loaded with vascular endothelial growth factor aptamer, which could then be released after treatment with glucose. Intracellular drug delivery can be achieved by enzyme responsiveness. Hyaluronic acid, proteases, and pectinases can be used to attain this responsiveness for drug delivery [225]. The delivery mechanism involves the degradation of MOF by enzymes by redox reactions. High loading and low leaching properties are attained when using mesoporous MOFs.

Kim et al. [226] fabricated a MOF consisting of Zr-based porphyrinic MOF (PCN) and hyaluronic acid. Multivalent coordination bonding between Zr and carboxylic acids of HA helped in coating the MOF with enzyme responsive hyaluronic acid. DOX could also be loaded into MOFs and could be degraded using the above enzyme responsive mechanism. This catalytic approach has one disadvantage, which is autophagy of cells. The release kinetics of HA-DOX-PCN were assessed, and the nanoparticles were dispersed in pH 7.4 phosphate-buffered saline. Subsequently, the fluorescence intensity of DOX was measured at an excitation wavelength of 480 nm. To examine the drug release profile, hyaluronidase (400 U ml^{-1}) was introduced to the nanoparticle solution after 4 h, and the release pattern was then studied using fluorescence analysis.

8.1.5 pH responsiveness

MOFs can be used to transport drugs to tumour cells by utilizing the pH environment present in tumour cells [227]. The pH in extracellular environment is higher (6.5-6.7) due to the abnormal growth of these cells, which leads to rapid nutrient consumption, and this higher pH can be used to target MOFs at these sites where they can breakdown, size transition, or even undergo changes in their morphology or surface charges which helps in delivery the drug moiety to the cells [118,228]. To utilize MOFs effectively in drug delivery using pH conditions, it is necessary to control the method of synthesis of the MOFs. The coordination bonds in the MOFs are highly affected by the conditions (acidic or basic) [106,229]. These coordination bonds are thus highly sensitive to pH [230]. Oligohistadine tags can be done at these coordination bonds, which can anchor different moieties, and then these can be released effectively in acid medium of the cancer cells [231].

MIL-100 an iron based MOF was used to load the drug DOX using the ligand 1,10-(1,4-butanediyl)bis(imidazole) with a coating of polypyrrole. It was observed that this MOF had an increase in the surface area, that helped to load more amount of the drug. This MOF, when loaded with drug molecules, showed a pH response at 5.0 and possessed a release rate of 80%. The mechanism of the drug release was ascribed to the weakening of the interaction between DOX and the MOF due to the protonation of the amine group on DOX, which causes its release from the MIL-100 shell. Similarly, MOF MIL-100 is coated with hyaluronic acid on its surface to generate hydroxyl radicals by Fenton reaction and the DOX was efficiently delivered. This new modification of MIL-100 is less toxic and also improves drug delivery [232].

Lajevardi et al. [233] synthesized a porous MOF MIL-100@Fe_3O_4@SiO_2 for the delivery of the drug celecoxib. This MOF produced drug release of ± 80% at a pH of 3 and showed a high drug release rate at pH 7.4. This MOF was found to be biocompatible and also possessed control drug release properties. This pH response MOF was also used to load a hydrophobic antioxidant and antigiogenic molecule (bioflavonoid genistein) [GSN]. This study was done to improve the oral availability of the GSN [234]. It was found that the MIL-100 produced controlled release of the GSN, which was sustained for 3 days. There was also high bioavailability of the drug when tests were conducted using the MIL-100 loaded with GSN in mouse models.

The Zn-based MOF system found extensive use in a pH-sensitive drug delivery system (DDS) MOF featuring protonated compounds. ZIF-8 represents a pH-responsive DDS MOF incorporating Zn and 2-methylimidazole. These MOFs possess significant pore size and drug loading capability due to their heightened sensitivity to acids [189]. Modifying ZIF synthesis and encapsulating DOX in ZIF-8 in a single pot procedure resulted in a 20% DOX loading in ZIF-8. After 7 days, the nanosystem remained stable without releasing DOX at 60°C in a phosphate buffered saline solution (pH 7.4), however at pH 5.5, 90% of the DOX was released from the nanocarrier due to dissolution of the nanocarrier structure in an acidic environment. The nanosystem demonstrated great effectiveness against breast cancer cell lines in the MTT test.

Zhang et al. [235] synthesized ZIF-8 gold coated nanocluster loaded with DOX, and these nanoprobes were extremely successful in chemotherapy and PDT in acidic circumstances when the ZIF-8 structure crumbled and enhanced DOX release. Furthermore, the separation of

AuNCs from AuNCs@MOF-DOX produced the synergistic impact of chemo/PDT treatment. The combined chemo/PDT therapy fully reduced the 4T1 tumour (mammary carcinoma) after treatment with the nanoprobes in vivo, highlighting the relevance of AuNCs@MOF-DOX as a bifunctional pH-responsive nanoprobe for efficient chemo/PDT in human therapy for breast cancer. In another work, a pH-sensitive MOF, ZIF-8/DOX-PD-FA achieved DOX release through swelling in an acidic tumour microenvironment. The cytotoxicity data revealed that nanocarriers combined with NIR radiation produced more MCF-7 tumour cell death than other nanocarriers [212]. Duan and coworkers [236] produced a MOF self-assembled by Eu ions, guanosine monophosphate and loaded with an antigen for cancer treatment. The technique demonstrated high loading capacity and antigen release efficiency of 55%; moreover, the MOF-loaded antigen demonstrated pH-dependent drug delivery behaviour. Furthermore, a pH responsive co-delivery method improved antitumor results. Because of the dissociation of MOFs in the acidic environment, antigen was released over 48 h at pH 7.4, whereas 60% of the antigen was released at pH 5.0. The researchers stated that antigen and immunostimulatory molecule administration was simple, appropriate, and successful, with no harm in vivo or in vitro.

Zirconium MOF MIP-202 synthesized with natural amino acids, showed proton conduction properties, high chemical stability, and a broad pH range [216]. The Zr-based MOF displayed a variety of photoluminescence properties after the linker molecules were modified with intrinsic fluorophores. The as-prepared MOF demonstrated strong colloidal stability and showed promise for use in biological applications. Surprisingly, the precise MOF design with several functional groups for the regulation of guest release profiles allowed for the prediction and programming of the release of guest molecules. Even if the tumour tissue has a local pH (6.5–6.7) lower than that of the milieu, the difference in acidity can be too small to effectively activate the pH responses of the MOF. This is a key concern for tumour therapy despite the many benefits of pH-responsive MOFs.

8.2 Multi Stimuli Response of MOFs

Multi-stimuli response in MOFs refers to the ability of these materials to exhibit distinct changes in their properties or behaviours when exposed to multiple external stimuli. The multi-stimuli response of MOFs (Fig. 8) involves their sensitivity to different external factors, such as changes in temperature, pressure, light, or the presence of specific molecules [237]. When subjected to these stimuli, MOFs can exhibit various responses, including changes in their

crystal structure, pore size, surface area, and interactions with guest molecules. This dynamic behaviour is rooted in the reversible nature of the coordination bonds between metal ions and organic ligands in MOFs, allowing for structural rearrangements in response to environmental changes [109]. The ability to harness and manipulate the multi-stimuli response of MOFs holds promise for designing functional materials with applications in diverse fields. These could include sensors capable of detecting multiple analytes, smart drug delivery systems that release cargo in response to specific triggers, and materials for controlled gas storage and release [238]. By understanding and engineering the multi-stimuli response in MOFs, researchers aim to create innovative materials that can respond dynamically to their environment for targeted and controlled applications.

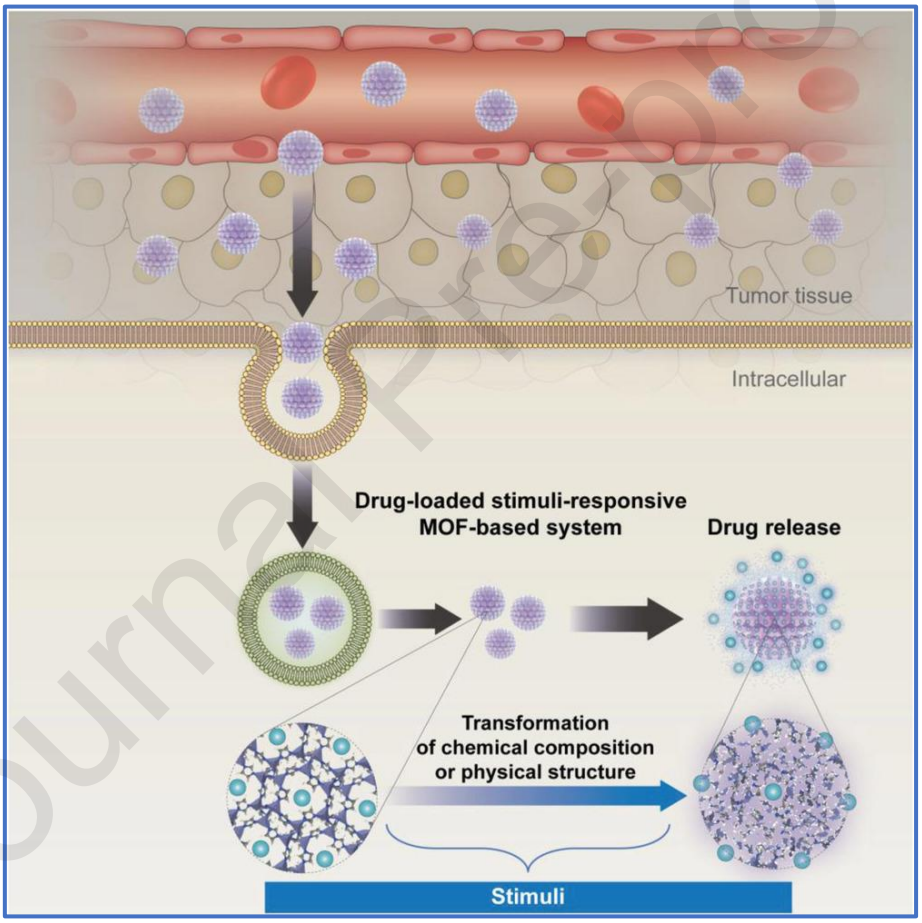

Fig. 8. Depicts the multi- stimuli responsive on the MOF as a drug delivery agent [237]. Reproduced with permission from [237], Copyright 2018, Wiley.

Nagata and co-workers developed a UiO-66 MOF in a post-synthetic process by utilizing copolymerization of N-isopropyl acrylamide (NIPAM) and acrylic acid [239].UiO-66-P(NIPAM-AA) used two stimuli- pH and temperature for the controlled release of the drug

molecules. This new polymer allowed the quick release of the guest molecule (procainamide) in an on-off manner at a pH of 6.8 and with a temperature lower than 25°C. The pH and thermosensitive MOF suppressed the release of the drug molecule at pH 4 or a temperature above 40°C. This dual stimuli MOF demonstrated a strategy for controlled drug delivery and can be potentially used for applications in cell imaging.

Jing et al. [225] reported a dual MOF, ZIF-90 and ZIF-8, in which ZIF-90 had a good targeting ability compared to ZIF-8 for mitochondria and good cell biocompatibility. ZIF-90 was synthesized via a fast assembly process and used to target tumour cells. By loading ZIF-90 with DOX conjugated to Y1 receptor ligand, it was observed that the release of the drug inside the cancer cells increased and also decreased any premature release of DOX by utilizing low pH and high adenosine triphosphate levels. Studies after treatment showed high efficacy of the DOX loaded ZIF-90 in cancer cells with 80% survival rate, which promises the utility of this system for the treatment of triple-negative breast cancer.

Jiang et al. [240] used quercetin and NPs for combinational therapy. This system exhibited high loading capacity of quercetin and NIR induced release with pH responsiveness. A folic acid- bovine serum (FA-BSA)/CuS@ZIF-8 DDS was used to overcome drawbacks like drug chemical instability, low solubility in water, and low bioavailability. This new BSA-modified MOF demonstrated tumor cell uptake in invivo and in vitro studies. The quercetin chemical showed an improved drug-carrying capacity. This was safely administered intravenously and displayed low toxicity and hemolysis ratio. This system also had a better radiation-induced anticancer effect in comparison to PPT or chemotherapy. Thus, this combination of pH and NIR proves to be an efficient treatment strategy in cancer cells using dual stimuli for drug release and manipulated cell death at a targeted site.

8.3 Cellular Uptake

Endocytosis is the name given to the highly conserved and strictly controlled energy-dependent process that brings extracellular ligands, membrane proteins, and lipids into the cell. Cell processes include signaling, motility, and nutrition absorption, which depend on endocytosis. Endocytosis produces tiny, membrane-bound vesicles that range in size from 50 to 150 nm and are capable of moving cargo across the cell to various locations. Naturally, this is especially important for applications involving drug administration and nanoMOF internalization. Depending on the kind of cell, the biological environment, and the material

being transported, the absorption happens through a variety of processes, some of which are designated for internal cell destruction and others for recycling [241]. Proteins belonging to the Rab GTPase family facilitate the mobility of these vesicular structures. These proteins, when activated, control the processes of membrane fusion, movement, and creation necessary for effective membrane trafficking. Various organelles in the cell, such as the Golgi bodies, autophagosomes, lysosomes, early, late, and recycling endosomes, are often involved in vesicle trafficking [242,243]. The processes involved in endocytosis are complex and highly controlled, encompassing both cellular signaling routes and spatiotemporal coordination. Significantly, it is well known that the primary channels for the absorption of nanomaterials into cells are these endocytic pathways [244,245]. While several distinct endocytic routes have been identified in eukaryotic cells, the endocytosis mechanisms that are well understood are those that are mediated by clathrin and caveolae, those that are independent of clathrin and caveolin, macropinocytosis, and phagocytosis.

Clathrin-mediated endocytosis is called after the protein clathrin, a tri-skeleton protein structure consisting of heavy and light protein chains, but, in addition to clathrin, there are over fifty additional proteins implicated in this mechanism of trafficking [246]. Molecules like iron-bound transferrin are transported throughout cells by clathrin-mediated endocytosis. The cytoplasmic proteins that assemble at the cell membrane to create clathrin-coated pits—which are made up of adaptor proteins like the AP2 complex—then attract additional protein components to initiate this process. After being put together, the actin module, which is made up of actin filaments and regulatory elements, develops. The vesicle is subsequently created by a process called scission that constricts the membrane. The vesicle is subsequently freed during the uncoating procedure, enabling further trafficking to the endosome [247]. The lipid raft membrane region of the plasma membrane has a cholesterol-dependent route called caveolin-mediated transport, which is in charge of absorbing poisons and viruses in addition to albumin. Caveolin proteins have the ability to oligomerize on the cell membrane, resulting in the formation of caveolae, which are membrane invaginations. These caveolae can travel to endosomes by budding off from the membrane. Nevertheless, other routes have also been documented via which caveolae bypass the endolysosomal pathway and instead go to caveosomes or caveolin-1 positive endosomes [241].

There are also various endocytic routes identified termed clathrin- and caveolin-independent pathways. Such routes include glycosylphosphatidylinositol-anchored proteins (GPI-AP)-enriched early endosomal compartments (GEECs). It is suggested that uncoated

tubulovesicular clathrin-independent carriers (CLICs) fuse to form GEECs. Cell-surface proteins such as MHC I and Tac, the interleukin-2 (IL-2) receptor a-subunit, are internalized in a dynamin- (and clathrin)-independent way into an ARF6- positive tubular endosomal system, which is separate from the clathrin-dependent cargo-containing endosomes. It has also been demonstrated that flotillin proteins work differently. They are confined to tiny puncta in separate membrane domains and are necessary for the induction of membrane invaginations [248].

Other well-established mechanisms of endocytosis include phagocytosis, which involves the receptor-mediated engulfment of big particles like bacteria and cell detritus, and macropinocytosis, a non-receptor-mediated mechanism by which the cell internalizes soluble materials. Macropinocytosis, which is also referred to as "cell drinking," is the process by which extracellular substances, including fluids, solutes, and tiny particles, are taken up by the fluid phase. Signaling molecules, including growth factors, kinases, and integrins, can cause membrane alterations that result in the creation of actin ruffles, which subsequently form protrusions to ingest extracellular materials [249]. The internalized material is then integrated into macropinosomes, which are large vesicles that can enter the cytosol. They typically measure between 200 nm and 5 mm. Phagocytosis, often known as "cell eating," is the process by which big components are engulfed by a cell in order to degrade them within. Immune cells most frequently employ this route to eliminate undesirable infections and cell debris [241]. Different from other endocytosis processes is phagocytosis. The items to be ingested are surrounded by membrane protrusions in this location, and the internalized materials are transferred into the phagosome for eventual destruction. Opsonization, a process by which serum proteins designate a material to be removed by immune cells, is linked to phagocytosis. This process leads to the internalization and degradation of nanomaterials, which is caused via opsonization [12,250].

9. Applications

9.1 Treatment of diabetes

Globally, diabetes mellitus remains a significant health concern. For type 1 diabetes management, maintaining stable euglycemia necessitates continuous insulin injections. Developing a reliable and advanced insulin delivery system is imperative [251]. An effective example of the PEG-Au/FeMOF@CPT is represented in Fig. 9 [252]. An enhanced glucose-

responsive insulin delivery system was examined by Duan et al. [253] synthesized ZIF-8 using a straightforward one-pot method in which insulin-GOx/ZIF-8 was self-assembled. When blood glucose levels were elevated, GOx catalyzed the conversion of glucose to gluconic acid, which was then converted to insulin by ZIF-8 after a local pH adjustment. By adding a fluorescent pH-sensitive sensor (pyranine), the pH shift in the microenvironment was monitored since it could affect the stability of ZIF-8 and the release of insulin. The excitation wavelength at 405 nm decreases with increasing pH, but the excitation wavelength at 450 nm rises with increasing pH when the emission wavelength of pyranine was 513 nm. An indication of pH may be made using the ratio of fluorescence intensity at 450 and 405 nm excitation wavelengths (F450/F405), where a lower value denotes a lower pH. Additionally, insulin release from the ZIF-8 slowed when the glycaemic level approached normoglycemic circumstances, preventing hypoglycaemia.

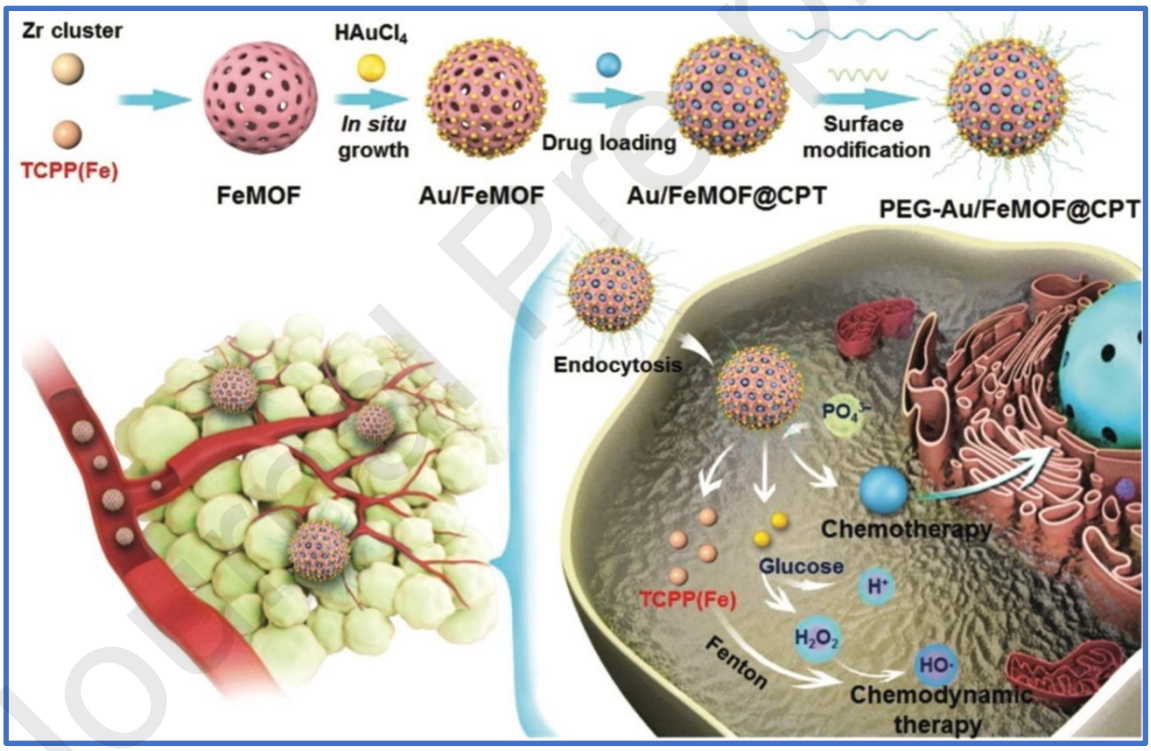

Fig. 9. Polymer composite MOF used as a drug delivery agent for the treatment of diabetes [252]. Reproduced with permission from [252], Copyright 2020, Wiley.

Yang et al. [254] introduced a novel approach for transdermal insulin delivery, combining multi-enzyme Co-ZIF-8 with insulin and GOx as reservoirs. Co-ZIF-8 MOFs, utilizing Co (II) ions as a biomimetic catalase, were designed to degrade excessive H_2O_2, preventing potential damage to healthy tissue. Simultaneously, ethylene diamine tetra acetic

acid-modified SiO_2 NPs within microneedles could chelate free Co(I) ions, allowing their subsequent removal upon peeling off the microneedles. The resulting MOF-based microneedles demonstrated effective insulin release tied to glucose concentration without H_2O_2 and Co leakage, as indicated by the findings. The insulin release patterns were assessed in a phosphate buffer saline solution with various pH values and a glucose solution. It was shown that in neutral and acidic circumstances, time-dependent insulin release curves were observed. For a period of 1.5 h, almost 80% of the insulin loaded in the MOF has been released at pH 5.0. Diabetes patients have a major issue with diabetic foot ulcers, and there is no cure. Cu-MOFs with FA modifications (F-HKUST-1) were created by Xiao et al. for the treatment of persistent nonhealing wounds. Incorporating FA into the HKUST-1 synthesis resulted in a decelerated release of Cu (II) ions, leading to improved wound healing and reduced toxicity. In vivo experiments demonstrated that FA-modified HKUST-1 accelerated wound healing, promoted collagen deposition and re-epithelialization, and induced angiogenesis [127].

MOFs in drug delivery hold enormous potential for the treatment of diabetes. These unique properties like drug loading capacity and tuneable pore size, enhance the efficient encapsulation and controlled release of therapeutic agents, specifically tailored to address the challenges associated with diabetes management. By encapsulating anti-diabetic drugs within MOFs, targeted delivery to specific tissues or cells can be achieved, enhancing the drug's efficacy while minimizing side effects. Furthermore, MOFs can protect the encapsulated drugs from degradation and enhance their stability, ensuring their prolonged release and sustained therapeutic effect. Overall, the utilization of MOFs in drug delivery systems presents a promising approach for improving the treatment outcomes of diabetes, offering new possibilities for personalized and precise therapeutic interventions in the future.

9.2 Ocular Disease Treatment

The ocular bioavailability of ophthalmic drugs intended as eye drops is often less than 5% since they are immediately removed from the eyes. With topical drop delivery, the bioavailability for the eyes is quite low [255]. Several anatomical and physiological constraints, such as tear turnover, nasolacrimal drainage, reflex blinking, and static and dynamic ocular barriers, impede the deeper absorption of ocular medications [256].

Kim et al. [257] used NH_2-MIL-88 (Fe) for brimonidine's prolonged release to increase its ocular bioavailability. A metal ion (Fe) and an organic ligand (2-aminoterephthalic acid)

made up this particular MOF, and they have been shown to be biocompatible. Brimonidine (Br) was physically absorbed into the NH_2-MIL-88's vast interior pores (Fe). Additionally, the amino groups and organic ligands in this NH_2-MIL-88 (Fe) form hydrogen bonds with the hydroxyl groups and intrinsic carboxyl of mucin chains, leading to mucoadhesive characteristics and enhancing drug retention in the preocular (Fig. 10).

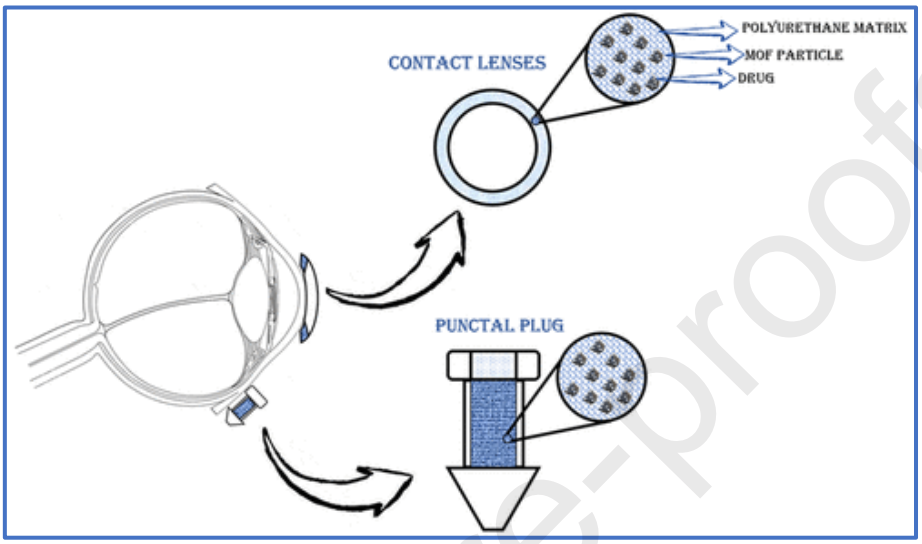

Fig. 10. Amine functionalized MIL-88 MOF used for the treatment of ocular disease [257]. Reproduced with permission from [257], Copyright 2020, American Chemical Society.

An in vitro investigation of the medication encapsulated in NH_2-MIL-88 (Fe) revealed a sustained release mechanism. The NH_2-MIL-88(Fe)/Br showed a persistent drug release pattern for 12 h with an average release rate of 5.2% h^{-1}, which could be maintained in vivo as the volume of tear fluid increases. This pattern followed an initial burst release of around 40% brimonidine within the first 30 min. Additionally, in an in vivo test using NH_2-MIL-88 (Fe), brimonidine's bioavailability was increased compared to the commercially available form (Alphagan-P). By 1 h, Alphagan P had a peak drug concentration of 0.76 lg/mL, which subsequently dropped and was undetectable by 6 h. In comparison, the peak drug level for NH_2-MIL-88(Fe)/Br was 0.73 lg mL^{-1} at 2 h, and it continued to be detectable until 10 h. Gandara-Loe et al. [255] conducted another study using Zr-based UiO-67 loaded brimonidine tartrate and polyurethane nanocomposite films for new ocular treatments. Due to the massive tetrahedral and octahedral cages of UiO-67, this functional MOF-based ocular polymeric device demonstrated good absorption and release performance for brimonidine tartrate in glaucoma treatment. MOFs are remarkably well-suited for efficient drug encapsulation and

controlled release in ocular tissues due to their huge surface area, tuneable pore size, and biocompatibility, among other exceptional qualities. This novel method opens up new possibilities for the targeted treatment of diseases, including glaucoma, macular degeneration, and ocular infections, by both protecting medications against degradation and improving their absorption.

9.3 Treatment of Lung Diseases

Targeted medication therapy for lung diseases such as lung cancer, chronic obstructive pulmonary disease, and respiratory tract infections can be achieved with great efficiency using pulmonary drug delivery. The adjustable structure, porosity, and inhalable size of MOFs make them suitable pulmonary drug delivery vehicles (Fig. 11) [258]. Recently, Hu et al. [259] used g-CD-MOF to load budesonide for dry powder inhalers that had been modified with leucine poloxamer and cholesterol (CHO). More than 90% of the particles in the sample had an appropriate diameter of 1 to 5 μm, according to the particle size distribution. Additionally, in vitro modification with CHO was successful in enhancing the fluidity and aerodynamic characteristics of g-CD-MOF. The CHO-CD-MOF based dry powder inhaler may be a suitable pulmonary delivery carrier, according to in vivo animal tests. Mohamed et al. [260] reported another study using MIL-89 and PEGylated MIL-89 (MIL-89 PEG) as delivery vehicles for the treatment of pulmonary arterial hypertension. Both possessed particles that ranged in size from 50 to 150 nm, with a preponderance of 100 ± 38 nm. MIL-89 PEG showed better stability and homogeneity after PEGylation. Both MIL-89 and MIL-89 PEG were shown through cell tests to be harmless to endothelial cells and had an anti-inflammatory impact. Additionally, in vivo tests showed that the MOF was quickly well tolerated and accumulated in the lungs, which may make them acceptable delivery systems for medications to treat pulmonary arterial hypertension.

To achieve better management and personalized treatment for tuberculosis (TB), a combination of medication administration and imaging is necessary. The optimal approach involves administering anti-tuberculosis medication directly into the lungs, ensuring locally effective concentrations while minimizing systemic exposure and associated adverse effects [261]. As a result, Wyszogrodzka et al. [262] employed Fe-MIL-101-NH_2 NPs as carriers to regulate the release of isoniazid (INH) as an MRI contrast agent. Fe MIL-101-NH_2 was found to be safe in invitro cytotoxicity tests, and cell internalization research supported its potential use in the treatment of TB. To enhance the aerodynamic properties of INH-loaded MOF (INH-

MOF), hydrophobic poly (lactide-co-glycolide) (PLGA) microparticles were loaded onto INH-MOF via spray drying, and they were then mixed with leucine (LC) microparticles. The resulting INH-MOF-loaded PLGA/LC also demonstrated efficient uptake of INH into macrophages, and outstanding aerodynamic characteristics were observed. About 55.0% of the INH content in the composite powder was released into the cell during the first 6 h of dissolution, and it increased 94.2% after 48 h. Therefore, INH MOFs can also be employed as an MRI contrast agent to track inhaled particles. Additionally, Simon-Yarza et al. [198] found that the pH-sensitiveness and reversible aggregation characteristics of Fe(III) polycarboxylate based nano MOFs to target lung tissue against lung cancer. The conclusion that can be drawn from the above is that intravenously delivered nano MOFs collect in lung capillaries, dissolve over the course of 24 h, and may reduce metastasis while improving medication release and therapeutic efficacy.

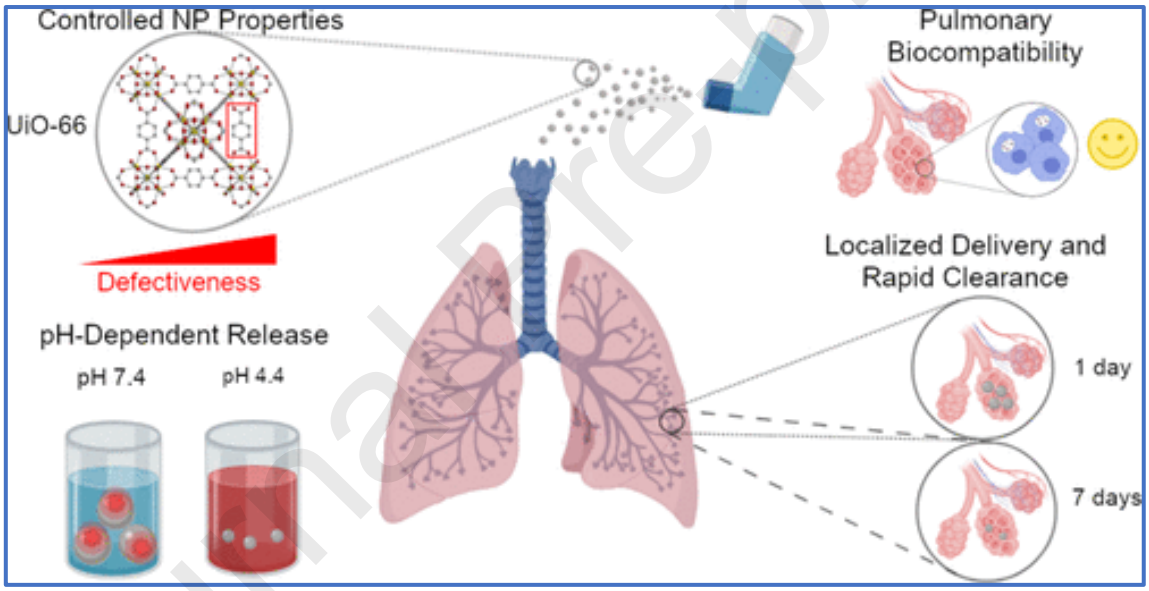

Fig. 11. UiO-66 as acid-sensitive carriers for Pulmonary Drug Delivery applications [258]. Reproduced with permission from [258], Copyright 2020, American Chemical Society.

In particular, the timing of reversible aggregation and disaggregation was suitable and consistent with tissue function, minimizing toxicity problems. The utilization of MOFs as drug vehicles for the treatment of lung diseases offers enhanced drug delivery, targeted therapy, and controlled release, thereby improving treatment effectiveness and minimizing side effects. Further research and development in this field hold promise for revolutionizing lung disease treatments in the future.

9.4 Antibacterial disease treatments

Given the bacterial resistance and bacterial infection in wounds and surgical procedures, smart antibacterial agent administration is of considerable interest. Targeting antibacterial DDSs has been suggested for both inorganic and organic polymer carriers, however, their use is constrained by their instability, poor biocompatibility, and uncontrolled release characteristics [263,264]. Recently, hybrid organic-inorganic MOFs have been investigated for anti-bacterial treatment. Lin et al. [265] investigated MOF-53(Fe) comprised of iron ions and BDC, as a carrier for antibacterial drugs due to its strong chemical stability in acidic environments. Vancomycin, a glycopeptide macromolecule antibiotic, was physically absorbed into MOF-53(Fe) NPs, and the drug loading was as high as 20 wt%. Additionally, under conditions of bacterial infection, MOF-53(Fe) demonstrated a slower and more predictable drug release profile with 99.3% antibacterial efficacy against *Staphylococcus aureus* (pH 5.5). In addition to the above release, MOF-53 (Fe)@vancomycin demonstrated exceptional in vitro chemical stability and outstanding biocompatibility.

Gallis et al. [266] to load the third-generation wide spectrum antibiotic ceftazidime. High resolution STEM-EDS elemental mapping was used to check if ceftazidime was successfully loaded into ZIF-8. The effectiveness of pristine ZIF-8 and ceftazidime@ZIF-8 particles against Gram-negative *E. coli* was evaluated. Even though there was no difference in their activity after 24 h, ceftazidime@ZIF-8 showed nearly complete growth inhibition of *E. coli* at 50 mg $mL^{-1,}$ while pristine ZIF-8 showed no antibacterial effect after 72 h, indicating the antibacterial effectiveness was dependent on ceftazidime@ZIF-8's degradation. Additionally, cell internalization of particles was directly seen by confocal microscopy, proving that this technology is suitable for killing bacteria inside cells. Additionally, tetracycline@ZIF-8 coated with hyaluronic acid has been reported for active targeting against *S.aureus* and *Salmonella* inside the cell [267].

Guo et al. [268] investigated MIL-88 (A) and MIL-100 (Fe) particles with rod-like and spherical morphologies, respectively. They were combined with mannose for a viable bacteria-mimicking delivery approach for intramacrophage-based infections. Orthopedics has two key objectives: preventing infection and fostering osseointegration. Mineralized collagen was coated with naringin loaded MOF NPs synthesized by Yu et al. [269] that promoted osseointegration and prevented bacterial infection. The coating for mesenchymal stem cells demonstrated remarkable performance in terms of adhesion, proliferation, osteogenic

differentiation, and mineralization, according to the results. The antibacterial efficiency against *S. aureus* was also improved, confirming the antibacterial coating's potential use for orthopedic implants.

By using g-CD-MOFs' mesoporosity, Shakya et al. [270] reported a template-assisted synthesis of ultrafine Ag NPs with a size of around 2 nm, enabling stability improvement of Ag NPs. For better haemostasias in the wound region, the Ag@CD-MOFs were further cross-linked and surface modified with Gly-Arg-Gly-Asp-Ser(GRGDS) peptide. By reacting the surface hydroxyl groups of the cross-linked Ag@CD-MOF (CL-Ag@CD-MOF) with the C-terminus of the GRGDS peptide, the surface of the CL-Ag@CD-MOF was further modified. The acquired GS5-CL-Ag@CD-MOFs was an excellent method to combine haemostasis with antibiosis, as shown by the anti-bacteria test and the haemostasis test. It is crucial to develop a dual bactericidal system due to the low antibacterial efficacy, high dose utilization, and slow sterilizing rate of the single-model bactericidal approach. In another work, Ag-doped carbonized ZIF nanocomposites (C-Zn/Ag) had a carbon framework that resembled graphite [271]. The nanocomposite had the best metal-ion-releasing capacity as well as the strongest photothermal conversion potential for synergistic sterilization.

9.5 Antitumour Studies

Developing innovative DDSs to increase the efficiency of chemotherapy and minimize unpleasant responses is of importance for the treatment of malignancies. MOFs have been used as nanocarriers with high drug loadings and ease of modification to improve the accumulation of medicines into malignancies. Zhang et al. [272] used ZIF-8 to co-deliver chemotherapeutic medication DOX and P-glycoprotein inhibitor verapamil hydrochloride (VER), achieving higher drug concentrations in multidrug resistant tumour cells, in order to overcome the multidrug resistance impact. In order to achieve prolonged circulation and active targeting, DOX and VER were co-incorporated into ZIF-8 using a one-pot strategy. (DOX VER)@ZIF-8 was then functionalized with poly (ethylene glycol)-folate (PEG-FA) by coordination bond, which demonstrated improved therapeutic efficacy and safer properties than free DOX. ZIF-8 demonstrated a pH-triggered release behaviour and a high drug loading content of up to around 40.9%. Figure 12 shows the efficiency of IRMOF as a drug delivery agent for antitumour studies [273].

A potential approach to treating tumours is GOx-based cancer starvation therapy. However, its use has been constrained by the self-limiting curative effect and limited GOx delivery effectiveness. Zhang et al. [274] developed the biomimetic nanoreactor tirapazamine-GOx-ZIF-8@erythrocyte membrane by utilizing ZIF-8 as the carrier to incorporate GOx and the prodrug tirapazamine. Large ZIF-8 cavities could enable high GOx loading efficiencies while shielding the metal from leaching, aggregation, and loss of catalytic activity. Erythrocyte membrane also aided in immune system evasion and prolongation of blood flow, which helped supply GOx to tumour cells and deplete intracellular glucose and oxygen levels.

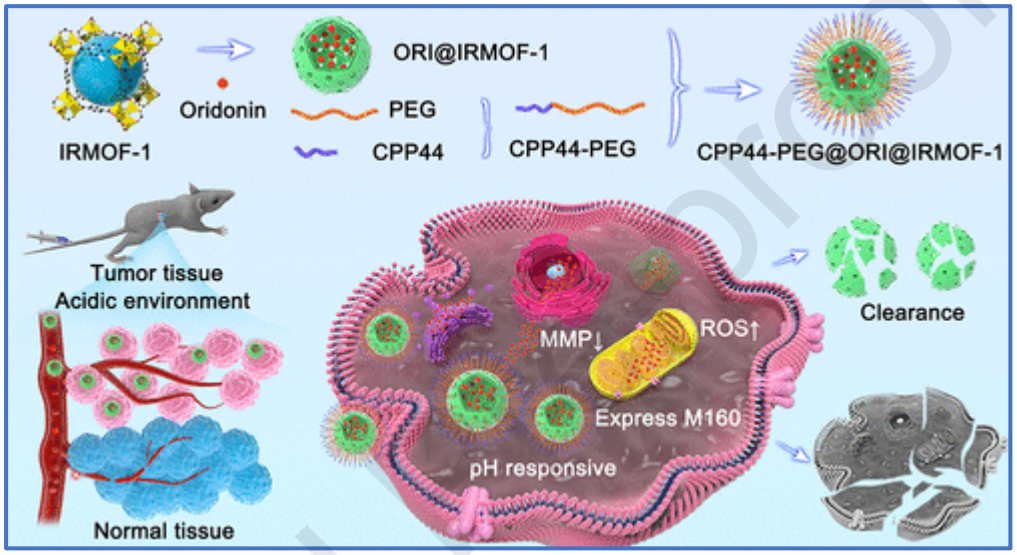

Fig. 12. IRMOF used for antitumour studies [273]. Reproduced with permission from [273], Copyright 2022, American Chemical Society.

Huang et al. [275] investigated the in situ synthesis of MIL-53 (Fe) nanocomposites by using the oxidation of the pyrrole monomer in the cage to produce polypyrrole NPs. MIL-53 was able to load DOX for chemotherapy due to its vast surface area, and porosity. The original structure remained unaltered after polymerization, pointing towards a strong framework. As a T_2 MRI contrast agent, the Fe ions in MIL-53 would be used to monitor the distribution of the composites. The produced PPy@MIL-53/DOX with excellent drug loading capability and photothermal action showed good therapeutic synergism.

A biomimetic O_2-evolving PDT nano platform (O_2@UiO-66@ICG@RBC) was synthesized by Gao et al. [276] employed UiO-66 as a depot for O_2 storage and conjugated it with indocyanine green. Red blood cell membrane coating was finally accomplished to enable immunologic escape. When subjected to 808 nm laser light produced from indocyanine green

PDT effects were increased by weakening the RBC membrane and promoting O_2 release from UiO-66. GSH concentration, an essential intracellular antioxidant for preserving redox equilibrium, dropped in response to the intracellular damage brought on by singlet oxygen. It was interesting to discover that GSH consumption was important for ferroptosis, a Fe-dependent cell death that is often distinct from other types of cell death. Min et al. [277] reported another study combining PDT with anti-angiogenesis therapy, utilizing porphyrinic MOF nanostructure as antiangiogenic drug delivery carrier and PDT agent, which was decorated with MnO_2 layer to neutralize excessive GSH in tumour for enhancement of PDT therapy, then endowed with mouse breast cancer cells ($4T_1$) membrane to achieve tumour targeting ability. Following intravenous treatment, the multifunctionalized porphyrin Zr-MOF would selectively accumulate in tumour via homologous targeting mediated by tumour cell membrane camouflage, followed by better PDT via GSH consumption and release of antiangiogenic medication apatinib. Furthermore, because of its MRI contrast quality, the liberated Mn(II) from MnO_2 might be employed for in vivo tumour imaging.

A recent study demonstrated the first use of radio-enhanced fabrication of MIL-100 in combination with a radio-sensitizing anticancer medication, GEM [278]. The MIL-100 regular porous framework with oxo centered Fe trimers separated by approximately 5 A° (trimesate linkers) was able to scatter electrons produced from nano-MOFs due to gamma radiation activation. As a result, water radiolysis occurred, resulting in the formation of hydroxyl radicals, which harmed cancer cells. Furthermore, MIL-100 transported its GEM within cancer cells. MIL-100 and GEM both contributed to the synergistic enhancement of radiation impact by demonstrating separate modes of action.

Through their tunable structures, high surface areas, and customizable functionalities, MOFs offer a versatile platform for various biomedical applications. In drug delivery, they enable targeted and controlled release of therapeutics, enhancing efficacy while minimizing side effects. Moreover, MOFs show great potential in imaging modalities, allowing for precise diagnosis and monitoring of diseases. Their biocompatibility and ability to encapsulate biomolecules further expand their utility in biosensing and bioimaging applications. However, challenges such as stability, biodegradability, and scalability need to be addressed for widespread clinical translation. Continued research efforts in optimizing MOF properties and addressing these challenges will undoubtedly pave the way for their integration into clinical

practice, revolutionizing diagnostics, therapeutics, and personalized medicine. Table 5 gives details on various applications of MOFs.

Table 5. Different applications of MOFs

MOF	Ligand	Cell lines /solutions used to mimic human body	Methos of synthesis	Application	Ref.
HKUST-1	H_3BTC	PBS	Solvothermal	Diabetic wound healing	[127]
PEG-Au/Fe-MOF@CPT NPs	PEG	PBS	Solvothermal	Chemo dynamic cancer therapy	[252]
Insulin-GOx/ZIF-8	2-MI	PBS	One pot	pH-sensitive insulin delivery system	[253]
Ins/GOx@ Co-ZIF-8	2-MI	PBS	One pot	pH sensitive insulin delivery system	[254]
Uio-67@PU	BPDC	PBS	Solvothermal	Ocular drug delivery of brimonidine	[255]
NH_2-MIL-88(Fe)	BDC	Male New Zealand and white rabbits	Solvothermal	Ocular drug delivery of brimonidine	[257]
MIL-100(Fe)	BDC	LLC-1 Cell line	Hydrothermal microwave assisted	pH-sensitive drug release for lung diseases	[198]
UiO-66 NPs	BDC	PBS; A549	Solvothermal	pH-sensitive drug release	[258]
Nanoporous CD-MOF		A549	Solvothermal	pulmonary delivery of budesonide	[259]

MIL-89-PEG	BDC	A549;J774; HASMCs	Solvothermal	Pulmonary arterial hypertension therapy	[279]
Fe-MIL-101-NH_2	BDC	Wistar rat lung cells	Solvothermal	Drug delivery	[262]
MOF-53(Fe)/Van	BDC	MC3T3-E1 cell line	Solvothermal	Drug delivery	[265]
Ceftazidime @ZIF-8	2-MI	A549	Solvothermal	Antibacterial application, sustained drug release	[266]
(Tet)@ZIF-8@hyaluronic acid (TZH)	2-MIM	LT2, ATCC 29213	One pot water phase	pH-responsive antibiotic synergistic system	[267]
MIL-88 A(Fe)		3D4/21(ATCC, CRL-2843)	Solvothermal	Chlorpromazine loaded for antibacterial action by cellular internalization.	[268]
COL/MOF/NG	Porphyrin	SD rats (MCSs)	Hydrothermal	Osseointegration and antibacterial activity.	[269]
CIL-Ag@CD-MOF		CMCC(B) 44102, CMCC(B) 26112 strain	Solvothermal	Antibacterial and wound healing.	[269]
C-Zn/Ag Nanocomposite	2-MI	Rabbit skin	Solvothermal	Antibacterial activity	[271]

10. Stability and Toxicity

Drug application, storage, and development are all hampered by stability problems. Many drugs are susceptible to oxidation, polymerization, deterioration, and crystallization due to exposure to acids, alkalis, heat, light, oxygen, and moisture. Numerous literatures have indicated that MOFs may be utilized to increase medication stability (Fig. 13) [280]. Curcumin generally unstable in neutral and alkaline environments. Curcumin was added into the cavity

of γ-CD-MOFs to alleviate this issue. In comparison to free curcumin and the curcumin/γ-CD inclusion complex, γ-CD-MOFs enhanced curcumin stability at pH 11.5 at least three times. γ-CD-MOFs, on the other hand, might be utilized as carriers to avoid drug degradation and crystallization during long-term storage [281].

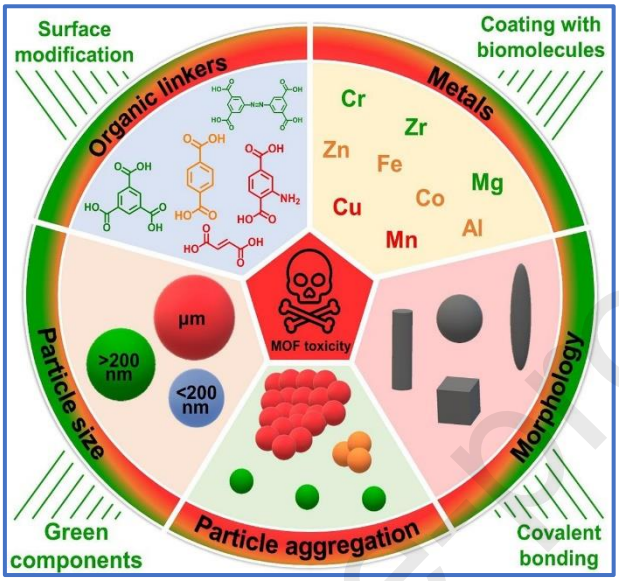

Fig. 13. Different strategies which reduce the inherent toxicity of MOFs [280]. Reproduced with permission from [280], Copyright 2023, Elsevier.

Lansoprazole degrades quickly in humid settings and has a significant crystallization propensity. He et al. [282] used a self-assembly technique to encapsulate thermophilic lipase within ZIF-8, which increased the chemical stability and preserved lipase's enzymatic activity. Lipase@ZIF-8 retained 91% of catalytic activity following trypsin treatment as compared to same MOF without trypsin treatment. Liang et al. [283] investigated the stability of urease embedded in ZIF-8, which was prepared via one-pot method. The results revealed that urease@ZIF-8 significantly improved the reaction rate in a temperature range of 23-80°C compared to free enzyme.

10.1 Controlled Drug Release

MOFs regulate drug release by preventing the "burst effect" and extending the drug retention period. Diclofenac sodium (DS) encapsulated with MOFs demonstrated sustained release of DS. Drug delivery candidates such as DS@ZJU-800 produced the release of drugs in response to variations in pressures. In comparison to the 2-day release kinetics of DS@ZJU-

800 in PBS (pH 7.4), the drug release could be prolonged to 5 and 8 days when the pressure was increased to 10 and 30 MPa, respectively. This work showed that pressure changes could act as stimuli for a prolonged drug release from MOFs [284]. In another work, γ-CD MOFs were used to modulate DS release in simulated gastrointestinal tract, making use of physiological settings such as pH. In the first 2 h, DS@γ-CD MOF discharged around 20% of its DS at pH 1.2. Free DS, on the other hand, demonstrated burst release, with more than 70% of the medication released during the first 30 min [285]. This proved that making use of different physiological conditions in the body can help improve sustained release of drugs.

MOFs acted as ideal carriers for the controlled release of IBU. The release behaviour of Fe_2O_3@MIL-53(Al) encapsulated IBU in saline was separated into three stages: first, 30% of IBU was released in the first 3 h; next, followed by 50% and 20% within 2 and 5 days; respectively. Another family of MOFs MIL-100, MIL-101, and MIL-53, also demonstrated improved controlled release to IBU [138]. According to the release kinetics, the whole release of IBU from MIL-100 occurred after 3 days, 6 days for MIL-101, and 21 days for MIL-53 [112]. From the above studies, it was understood that the non-toxic Fe(III)-based MOFs offer the potential for regulated medication release [116,286]. Thus, comparing diverse types of MOFs and studying the release patterns of these MOFs towards similar drugs can help select the best type of MOF that needs to be used for a specific type of prolonged drug release mechanism, which can then be applied based on different applications of the said MOF.

10.2 Biocompatibility

The coordination metal, organic linker, size, shape, and surface charge are some of the elements that affect the biocompatibility of MOFs [287]. The most promising properties so far are determined by analyzing the degradability of MOFs using in vivo and in vitro data. Studying the degradation of MOFs from a biosafety perspective is essential before studying them as carriers in various bio-applications [13]. MOFs are routinely examined in various aquatic environments, including water, phosphate buffer saline, and cell culture medium, at various pH levels and temperatures as part of degradation investigations [124]. However it is advised to carry out in vitro studies utilizing various biological fluids that resemble the route of administration, such as simulated bodily fluid (SBF) for parenteral administration and simulated intestinal fluid (SIF) for oral administration [288]. This method offers insightful information on the influence of carrier degradation and the transport to target cells. The pH of the body fluid must be taken into consideration since it has a significant impact on MOF

degradation and cargo release, making MOFs an excellent choice for applications involving the transport of drugs [289]. To quickly translate these intelligent materials into useful pharmacological and biological applications, new ways to develop these materials must be explored [290,291].

MOF breakdown and cargo release are strongly influenced by the pH of the body fluid, which makes MOFs ideal for medication delivery. Micron/nanoscale Mg-MOF74's in vitro cytotoxicity was assessed against HeLa cells at concentrations ranging from 50 to 2000 g mL^{-1} [292]. Below 200 g mL^{-1}, Mg-MOF74 at the micron and nanoscales demonstrated no discernible toxicity to cells. However, the cytotoxicity of n-Mg-MOF74 rose beyond 1000 g $mL^{-1,}$ whereas that of -Mg-MOF74 increased above 500 g mL^{-1}. On HeLa cells, the in vitro cytotoxicity of CAU-7, a biocompatible MOF based on bismuth, was also assessed in the range of 0-1.5 mg mL^{-1}. The biocompatibility of CAU-7 MOF was demonstrated by the MTS viability values, and there was no appreciable difference between the treated and untreated cells.

Numerous factors need to be considered for in vivo biocompatibility, including bio-distribution, pharmacokinetics, organ toxicity, and immune response. It is essential to research these aspects in order to create a system that is reliable and has few adverse effects. The first parameter is pharmacokinetics, which aids in understanding the identification, metabolism, and clearance of MOFs as they enter the body until they are eliminated. The pattern of MOF accumulation in the body's various organs, known as bio-distribution, is also essential for evaluating the delivery system. As the primary organs for elimination, the liver [293] and kidneys [294], MOFs often tend to accumulate in these tissues. Few have documented significant MOF accumulations in the spleen and lungs [295].

Zhu and colleagues [292] investigated the biosafety of Mg-MOF74 in vivo. The rat model was used to evaluate the in vivo biocompatibility of Mg-MOFs by intraperitoneal injection administration. Except for the highest dose, no significant difference between treated and untreated rats was seen when the doses were calculated based on body weight, confirming the concentration dependence of the in vivo toxicity of m/n-Mg-MOF74. Excellent biosafety and great in vivo clearance efficiency were also demonstrated by Mg-MOF74, with myocardial toxicity being minimal and only occurring at extremely high dosages. By analyzing their bio-distribution, metabolism, and excretion, three distinct porous iron (III) carboxylate MOF NPs—MIL-88A, MIL-88B-4CH_3, and MIL-100—were tested intravenously for their in vivo

toxicity. Animal behaviour, water/food consumption, biochemical parameters, changes in body/organ weights, macro/microscopic histological observations, oxidative stress/ metabolism, as well as some insights into NP bio-distribution and elimination, were all used to evaluate the toxicity of the MOFs. No fatality, toxicity, or changes in body weight were seen throughout these tests up to 30 days following dosing. No signs of serious toxicity were found during the histological examination of the kidneys, liver, brain, spleen, lungs, and other organs.

Innovative techniques have been developed by researchers to strengthen these MOFs while reducing their in vivo cytotoxicity. Functionalizing MOFs' surface and covering it with a biocompatible material improved the stability and target ability. One of the cutting-edge methods for giving MOFs cell-like features is cell membrane coating [296]. Men et al. [277] wrapped Zr-MOFs in MnO_2 to combine photodynamic treatment with antiangiogenic medications. To improve the bio-distribution, a cancer membrane was additionally coated on this device. Few papers have been published about the immunological response of MOFs in vivo since most metal-based MOFs do not affect the immune system. Therefore, other immunogenic elements like adjuvants or antigens must be added to the system in order to employ MOFs for immunotherapy applications. For instance, aluminium-based MOFs and MOFs with aluminium incorporation have been described for use in vaccine-related applications since aluminium has long been utilized as a vaccine adjuvant. Additionally, employing a tumour antigen has yielded good outcomes.

A biocompatible and biodegradable immunotherapeutic delivery system for the regulated distribution of the monoclonal antibody checkpoint inhibitor nivolumab (NV) was created by Alsaiari et al. utilizing ZIF-8 [297]. In haematological malignancies, the NV-ZIF activated T cells more effectively than the naked NV did. To facilitate the tumour-specific targeted administration, we further improved the device by coating the NV-ZIF with the breast cancer cell membrane (MCF-7). In mice, NV-ZIF_{MCF} demonstrated a higher reduction of tumour growth and protracted retention of NV-ZIF_{MCF} in the tumour microenvironment, which led to effective NV delivery.

10.3 Biodegradation

It is commonly recognized that when exposed to water molecules, the majority of MOFs exhibit poor stability. Even though a number of water-stable MOFs have been discovered and proposed to get around this restriction, there is still a significant barrier to

expanding their application [298]. For instance, using first-principles molecular dynamics, the early phases of MOF degradation in liquid water were investigated [299]. Through Born-Oppenheimer molecular dynamics in liquid water, the function of the metal ions and secondary building unit (SBU) has been explored against IRMOF-1- (e.g., structures with the three metals Zn, Mg, and Be) in order to provide insight into the underlying process of disruption. According to Bellarosa et al., hydrated Be (metal ions) based MOFs remained stable up to 500 K, but comparable structures containing Mg or Zn disintegrated at 300 K. It was attributed to the strength of the M-O bond and the metal atom's propensity to form penta- (and hexa-) coordination spheres.

We have discussed the importance of these issues in terms of biological applications in this review. MOFs have been proposed for many different biomedical technologies (e.g., therapeutic and diagnostic reasons) throughout the last ten years. However, in the majority of biological applications, the main cause for worry is the deterioration of MOFs. The material's desired qualities may noticeably decline if MOFs are broken down by physical, chemical, or biological processes [20,300–304]. Because MOF deterioration correlates with changes in the shape and chemical composition of individual crystals, MOFs frequently exhibit exceptional heat stability. A steep erosion front is probably the mechanism via which MOF crystals deteriorate. According to Raman microscopy and Mössbauer spectroscopy, this front shelters the inorganic network and keeps the material from eroding the crystalline core [303,304]. Through the visualization of the separation of cores from the eroded zones, Raman microscopy sheds light on the degradation process. However, a number of chemical characteristics, including oxidation state, species type, the presence of phases other than MOFs, and the ensuing oxide production, may be probed using Mössbauer spectroscopy [303]

Li et al. [304] looked at the degradation of Fe-MOFs, or MIL-100 and MIL-101. Fe-MOFs' large pore widths and, in some situations, low toxicity have allowed them to demonstrate remarkable efficiency towards drug loading. Ibuprofen, for instance, may be loaded at up to 35 weight percent and 140 weight percent on MIL-100 and MIL-101, respectively [20]. On the other hand, biocompatible NMOFs break down quickly in phosphate buffer saline (PBS), like MIL-101. The use of MOFs for regulated medication release is hampered by this breakdown since phosphate molecules are already present in living things. According to Horcajada et al., the strong interactions between phosphates and MOFs result in fast breakdown and drug release. Therefore, a better comprehension of MOFs' degrading processes in the presence of phosphates is necessary for the creation of MOFs for drug delivery

[301,302,305]. However, in addition to the deterioration of MOFs in biological applications, there is also worry about some other uses, such as water purification and heat pumps [306,307]. Owing to thermal and hydrolytic instability, applications that are undertaken in aqueous environments or at high temperatures and moisture levels should generally be done with extreme caution. For many typical MOFs, exposure to heat and moisture will result in a loss of structural integrity. Lastly, it should be mentioned that there are MOFs that are sufficiently stable to be used in water purification, heat pumps, and other applications [308,309].

10.4 Colloidal stability

In the realm of biomedical applications, ensuring the colloidal stability of MOFs is paramount for their successful implementation. Colloidal stability refers to the ability of MOF nanoparticles or colloids to remain dispersed in a solvent or biological medium without aggregation or precipitation. This property is crucial for applications such as drug delivery, imaging, and biosensing, where uniform distribution and long-term stability are essential [310]. Several factors influence the colloidal stability of MOFs in biomedical applications. One key consideration is the choice of MOF synthesis method and surface modification techniques [311]. Strategies such as ligand functionalization, coating with biocompatible polymers, or encapsulation within liposomes can enhance the stability of MOF colloids in physiological environments by preventing interactions with proteins or other biomolecules that may lead to aggregation [312].

Additionally, the configuration of MOF structures can influence their colloidal stability. Modulating the size, morphology, and surface charge of MOF nanoparticles can impact how they disperse and interact within their environment. For example, smaller nanoparticles typically demonstrate enhanced colloidal stability due to decreased gravitational settling and a reduced propensity for aggregation. Furthermore, the choice of dispersants or stabilizing agents is crucial for maintaining colloidal stability. Surface modifications involving hydrophilic ligands or surfactants can enhance the dispersibility of MOFs in aqueous solutions while providing steric hindrance against particle aggregation [313]. Nonetheless, challenges persist in achieving optimal colloidal stability for MOFs in biomedical applications. Variables such as pH, temperature, and the presence of ions or biomolecules in physiological fluids can affect the stability of MOF colloids, often necessitating tailored solutions for specific applications [314].

In summary, ensuring the colloidal stability of MOFs is essential for their successful utilization in biomedical applications. By carefully designing MOF structures, selecting appropriate surface modification strategies, and optimizing dispersants, researchers can enhance the stability and functionality of MOF colloids for a wide range of biomedical applications, including drug delivery, imaging, and biosensing. Continued efforts in this area will be instrumental in unlocking the full potential of MOFs in biomedicine.

11. Conclusions and Future Perspective

In summary, MOFs have emerged as a promising framework for drug delivery applications, leveraging their unique characteristics such as significant porosity, expansive surface area, and customizable structures. These attributes facilitate efficient encapsulation, targeted delivery, and controlled release of pharmaceuticals, thereby potentially improving drug solubility, stability, and bioavailability for better therapeutic outcomes across various diseases. Functionalizing MOFs with specific ligands enables precise targeting, minimizing systemic exposure and side effects. Moreover, the controlled release capability ensures sustained drug concentrations, prolonging therapeutic effects. While further research and development are necessary, MOFs offer immense potential as versatile drug delivery systems, paving the way for personalized and efficacious medical treatments.

Research interest in MOFs has surged due to their remarkable chemical and physical attributes, finding utility across diverse applications. Notably, their exploration as drug delivery systems and biological sensing platforms has gained significant traction in recent research. This article provides a fundamental overview of MOFs and their synthesis techniques, along with the associated benefits and drawbacks. Furthermore, it introduces the latest MOF-based platforms utilized as viable candidates for diagnosis and treatment across a spectrum of ailments, including bacterial and viral infections, cancer, diabetes, neurological and ophthalmic disorders, as well as lung disorders. Despite the substantial progress made in employing MOFs for biomedical applications, further work is necessary before they can be effectively utilized as diagnostic and therapeutic tools. As we gaze into the horizon of biomedical research, the role of MOFs in drug delivery stands as a beacon of innovation. As evidenced by recent advancements, the future holds immense promise for the integration of MOFs into the therapeutic landscape.

Future research endeavours will likely focus on refining the targeting capabilities of MOFs to achieve unprecedented precision in drug delivery. By engineering MOFs with highly specific ligands, researchers can direct therapeutic payloads to diseased tissues with pinpoint accuracy, minimizing off-target effects and maximizing therapeutic efficacy. The integration of multiple functionalities within MOF-based drug delivery systems is poised to revolutionize treatment paradigms. Future MOFs may be designed to not only encapsulate and deliver drugs but also possess diagnostic capabilities, allowing for real-time monitoring of therapeutic responses and disease progression. The development of stimuli-responsive MOFs holds immense potential for achieving on-demand drug release kinetics. By incorporating stimuli-responsive elements such as pH, temperature, or external triggers, researchers can design MOFs that release therapeutic payloads in response to specific environmental cues, thereby optimizing drug delivery efficiency. As MOFs transition from the laboratory bench to clinical applications, comprehensive studies on biocompatibility and toxicity will be imperative. Future research will likely focus on elucidating the long-term effects of MOF exposure on biological systems and optimizing MOF formulations to ensure minimal adverse effects in vivo. The advent of personalized medicine heralds a new era in healthcare, wherein treatments are tailored to individual patient profiles. MOF-based theragnostic platforms, capable of simultaneous drug delivery and disease imaging, hold immense promise for advancing personalized medicine initiatives and revolutionizing patient care. The future of MOFs in biomedicine is rife with possibilities. By harnessing the inherent versatility and tunability of MOFs, researchers can usher in a new era of precision medicine, where targeted drug delivery holds the key to unlocking enhanced therapeutic outcomes and improving patient well-being.

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References

[1] B. Maranescu, A. Visa, Applications of Metal-Organic Frameworks as Drug Delivery Systems, Int. J. Mol. Sci. 23 (2022) 4458. https://doi.org/10.3390/ijms23084458.

[2] M. Al Sharabati, R. Sabouni, G.A. Husseini, Biomedical Applications of Metal−Organic Frameworks for Disease Diagnosis and Drug Delivery: A Review, Nanomaterials. 12 (2022) 277. https://doi.org/10.3390/nano12020277.

[3] O.M. Yaghi, M. O'Keeffe, N.W. Ockwig, H.K. Chae, M. Eddaoudi, J. Kim, Reticular synthesis and the design of new materials, Nature. 423 (2003) 705–714. https://doi.org/10.1038/nature01650.

[4] H.-C. Zhou, J.R. Long, O.M. Yaghi, Introduction to Metal–Organic Frameworks, Chem. Rev. 112 (2012) 673–674. https://doi.org/10.1021/cr300014x.

[5] L. Wang, H. Xu, J. Gao, J. Yao, Q. Zhang, Recent progress in metal-organic frameworks-based hydrogels and aerogels and their applications, Coord. Chem. Rev. 398 (2019) 213016. https://doi.org/10.1016/j.ccr.2019.213016.

[6] D. Wu, P.-F. Zhang, G.-P. Yang, L. Hou, W.-Y. Zhang, Y.-F. Han, P. Liu, Y.-Y. Wang, Supramolecular control of MOF pore properties for the tailored guest adsorption/separation applications, Coord. Chem. Rev. 434 (2021) 213709. https://doi.org/10.1016/j.ccr.2020.213709.

[7] H. Konnerth, B.M. Matsagar, S.S. Chen, M.H.G. Prechtl, F.-K. Shieh, K.C.W. Wu, Metal-organic framework (MOF)-derived catalysts for fine chemical production, Coord. Chem. Rev. 416 (2020) 213319. https://doi.org/10.1016/j.ccr.2020.213319.

[8] Q. Qiu, H. Chen, Y. Wang, Y. Ying, Recent advances in the rational synthesis and sensing applications of metal-organic framework biocomposites, Coord. Chem. Rev. 387 (2019) 60–78. https://doi.org/10.1016/j.ccr.2019.02.009.

[9] W.J. Rieter, K.M. Pott, K.M.L. Taylor, W. Lin, Nanoscale Coordination Polymers for Platinum-Based Anticancer Drug Delivery, J. Am. Chem. Soc. 130 (2008) 11584–11585. https://doi.org/10.1021/ja803383k.

[10] P. Horcajada, R. Gref, T. Baati, P.K. Allan, G. Maurin, P. Couvreur, G. Férey, R.E. Morris, C. Serre, Metal–Organic Frameworks in Biomedicine, Chem. Rev. 112 (2012) 1232–1268. https://doi.org/10.1021/cr200256v.

[11] Z. Ma, B. Moulton, Recent advances of discrete coordination complexes and coordination polymers in drug delivery, Coord. Chem. Rev. 255 (2011) 1623–1641. https://doi.org/10.1016/j.ccr.2011.01.031.

[12] E. Linnane, S. Haddad, F. Melle, Z. Mei, D. Fairen-Jimenez, The uptake of metal–organic frameworks: a journey into the cell, Chem. Soc. Rev. 51 (2022) 6065–6086. https://doi.org/10.1039/D0CS01414A.

[13] M. Cai, G. Chen, L. Qin, C. Qu, X. Dong, J. Ni, X. Yin, Metal Organic Frameworks as

Drug Targeting Delivery Vehicles in the Treatment of Cancer, Pharmaceutics. 12 (2020) 232. https://doi.org/10.3390/pharmaceutics12030232.

[14] J.K. Patra, G. Das, L.F. Fraceto, E.V.R. Campos, M.D.P. Rodriguez-Torres, L.S. Acosta-Torres, L.A. Diaz-Torres, R. Grillo, M.K. Swamy, S. Sharma, S. Habtemariam, H.-S. Shin, Nano based drug delivery systems: recent developments and future prospects, J. Nanobiotechnology. 16 (2018) 71. https://doi.org/10.1186/s12951-018-0392-8.

[15] M. Chamundeeswari, J. Jeslin, M.L. Verma, Nanocarriers for drug delivery applications, Environ. Chem. Lett. 17 (2019) 849–865. https://doi.org/10.1007/s10311-018-00841-1.

[16] L. Meng, X. Zhang, Q. Lu, Z. Fei, P.J. Dyson, Single walled carbon nanotubes as drug delivery vehicles: Targeting doxorubicin to tumors, Biomaterials. 33 (2012) 1689–1698. https://doi.org/10.1016/j.biomaterials.2011.11.004.

[17] K. Shan, Anthracycline-Induced Cardiotoxicity, Ann. Intern. Med. 125 (1996) 47. https://doi.org/10.7326/0003-4819-125-1-199607010-00008.

[18] A. Mathew, A. Varghese, S. Devi K.R., D. Pinheiro, Comprehensive understanding of biomedical usages of metal and non metal doped carbon dots, Mater. Today Commun. 37 (2023) 106991. https://doi.org/10.1016/j.mtcomm.2023.106991.

[19] S. Adepu, S. Ramakrishna, Controlled Drug Delivery Systems: Current Status and Future Directions, Molecules. 26 (2021) 5905. https://doi.org/10.3390/molecules26195905.

[20] P. Horcajada, C. Serre, M. Vallet-Regí, M. Sebban, F. Taulelle, G. Férey, Metal–Organic Frameworks as Efficient Materials for Drug Delivery, Angew. Chemie. 118 (2006) 6120–6124. https://doi.org/10.1002/ange.200601878.

[21] W.-H. Chen, W.-C. Liao, Y.S. Sohn, M. Fadeev, A. Cecconello, R. Nechushtai, I. Willner, Stimuli-Responsive Nucleic Acid-Based Polyacrylamide Hydrogel-Coated Metal-Organic Framework Nanoparticles for Controlled Drug Release, Adv. Funct. Mater. 28 (2018) 1705137. https://doi.org/10.1002/adfm.201705137.

[22] A. Chakraborty, P. Sutar, P. Yadav, M. Eswaramoorthy, T.K. Maji, Charge-Assisted Self-Assembly of ZIF-8 and Laponite Clay toward a Functional Hydrogel Nanocomposite, Inorg. Chem. 57 (2018) 14480–14483.

https://doi.org/10.1021/acs.inorgchem.8b02545.

[23] S. He, L. Wu, X. Li, H. Sun, T. Xiong, J. Liu, Metal-organic frameworks for advanced drug delivery, 11 (2021). https://doi.org/10.1016/j.apsb.2021.03.019.

[24] C. Nam, Y. Jang, K.-S. Lee, J. Shim, B.K. Cho, Insertion of a Specular Reflective and Transmissive Nano-Oxide Layer into Giant Magnetoresistance Spin-Valve Structure, J. Nanosci. Nanotechnol. 6 (2006) 3483–3486. https://doi.org/10.1166/jnn.2006.039.

[25] S. Haddad, I. Abánades Lázaro, M. Fantham, A. Mishra, J. Silvestre-Albero, J.W.M. Osterrieth, G.S. Kaminski Schierle, C.F. Kaminski, R.S. Forgan, D. Fairen-Jimenez, Design of a Functionalized Metal–Organic Framework System for Enhanced Targeted Delivery to Mitochondria, J. Am. Chem. Soc. 142 (2020) 6661–6674. https://doi.org/10.1021/jacs.0c00188.

[26] J.-L. Zhuang, A. Terfort, C. Wöll, Formation of oriented and patterned films of metal–organic frameworks by liquid phase epitaxy: A review, Coord. Chem. Rev. 307 (2016) 391–424. https://doi.org/10.1016/j.ccr.2015.09.013.

[27] I. Stassen, N. Burtch, A. Talin, P. Falcaro, M. Allendorf, R. Ameloot, An updated roadmap for the integration of metal–organic frameworks with electronic devices and chemical sensors, Chem. Soc. Rev. 46 (2017) 3185–3241. https://doi.org/10.1039/C7CS00122C.

[28] P. Falcaro, R. Ricco, C.M. Doherty, K. Liang, A.J. Hill, M.J. Styles, MOF positioning technology and device fabrication, Chem. Soc. Rev. 43 (2014) 5513–5560. https://doi.org/10.1039/C4CS00089G.

[29] C.L. Ruiz-Zambrana, M. Malankowska, J. Coronas, Metal organic framework top-down and bottom-up patterning techniques, Dalt. Trans. 49 (2020) 15139–15148. https://doi.org/10.1039/D0DT02207A.

[30] K.A.S. Usman, J.W. Maina, S. Seyedin, M.T. Conato, L.M. Payawan, L.F. Dumée, J.M. Razal, Downsizing metal–organic frameworks by bottom-up and top-down methods, NPG Asia Mater. 12 (2020) 58. https://doi.org/10.1038/s41427-020-00240-5.

[31] S. He, L. Wu, X. Li, H. Sun, T. Xiong, J. Liu, C. Huang, H. Xu, H. Sun, W. Chen, R. Gref, J. Zhang, Metal-organic frameworks for advanced drug delivery, Acta Pharm. Sin. B. 11 (2021) 2362–2395. https://doi.org/10.1016/j.apsb.2021.03.019.

[32] M. Moharramnejad, A. Ehsani, M. Shahi, S. Gharanli, H. Saremi, R.E. Malekshah,

Z.S. Basmenj, S. Salmani, M. Mohammadi, MOF as nanoscale drug delivery devices: Synthesis and recent progress in biomedical applications, J. Drug Deliv. Sci. Technol. 81 (2023) 104285. https://doi.org/10.1016/j.jddst.2023.104285.

[33] J. Cravillon, S. Münzer, S.-J. Lohmeier, A. Feldhoff, K. Huber, M. Wiebcke, Rapid Room-Temperature Synthesis and Characterization of Nanocrystals of a Prototypical Zeolitic Imidazolate Framework, Chem. Mater. 21 (2009) 1410–1412. https://doi.org/10.1021/cm900166h.

[34] X.-C. Huang, Y.-Y. Lin, J.-P. Zhang, X.-M. Chen, Ligand-Directed Strategy for Zeolite-Type Metal–Organic Frameworks: Zinc(II) Imidazolates with Unusual Zeolitic Topologies, Angew. Chemie Int. Ed. 45 (2006) 1557–1559. https://doi.org/10.1002/anie.200503778.

[35] G. Blanita, G. Borodi, M.D. Lazar, A.-R. Biris, L. Barbu-Tudoran, I. Coldea, D. Lupu, Microwave assisted non-solvothermal synthesis of metal–organic frameworks, RSC Adv. 6 (2016) 25967–25974. https://doi.org/10.1039/C5RA26097C.

[36] Y. Chen, C. Yang, X. Wang, J. Yang, K. Ouyang, J. Li, Kinetically controlled ammonia vapor diffusion synthesis of a Zn(II) MOF and its H2O/NH3 adsorption properties, J. Mater. Chem. A. 4 (2016) 10345–10351. https://doi.org/10.1039/C6TA03314H.

[37] R.A. Smaldone, R.S. Forgan, H. Furukawa, J.J. Gassensmith, A.M.Z. Slawin, O.M. Yaghi, J.F. Stoddart, Metal-Organic Frameworks from Edible Natural Products, Angew. Chemie Int. Ed. 49 (2010) 8630–8634. https://doi.org/10.1002/anie.201002343.

[38] R.S. Forgan, R.A. Smaldone, J.J. Gassensmith, H. Furukawa, D.B. Cordes, Q. Li, C.E. Wilmer, Y.Y. Botros, R.Q. Snurr, A.M.Z. Slawin, J.F. Stoddart, Nanoporous Carbohydrate Metal–Organic Frameworks, J. Am. Chem. Soc. 134 (2012) 406–417. https://doi.org/10.1021/ja208224f.

[39] B. Liu, H. Li, X. Xu, X. Li, N. Lv, V. Singh, J.F. Stoddart, P. York, X. Xu, R. Gref, J. Zhang, Optimized synthesis and crystalline stability of γ-cyclodextrin metal-organic frameworks for drug adsorption, Int. J. Pharm. 514 (2016) 212–219. https://doi.org/10.1016/j.ijpharm.2016.09.029.

[40] J.-D. Xiao, L.-G. Qiu, F. Ke, Y.-P. Yuan, G.-S. Xu, Y.-M. Wang, X. Jiang, Rapid synthesis of nanoscale terbium-based metal–organic frameworks by a combined

ultrasound-vapour phase diffusion method for highly selective sensing of picric acid, J. Mater. Chem. A. 1 (2013) 8745. https://doi.org/10.1039/c3ta11517h.

[41] H. Lu, X. Yang, S. Li, Y. Zhang, J. Sha, C. Li, J. Sun, Study on a new cyclodextrin based metal–organic framework with chiral helices, Inorg. Chem. Commun. 61 (2015) 48–52. https://doi.org/10.1016/j.inoche.2015.08.015.

[42] J. Sha, X. Yang, L. Sun, X. Zhang, S. Li, J. Li, N. Sheng, Unprecedented α-cyclodextrin metal-organic frameworks with chirality: Structure and drug adsorptions, Polyhedron. 127 (2017) 396–402. https://doi.org/10.1016/j.poly.2016.10.012.

[43] M. Eddaoudi, J. Kim, N. Rosi, D. Vodak, J. Wachter, M. O'Keeffe, O.M. Yaghi, Systematic Design of Pore Size and Functionality in Isoreticular MOFs and Their Application in Methane Storage, Science (80-.). 295 (2002) 469–472. https://doi.org/10.1126/science.1067208.

[44] Q. Fang, X. Shi, G. Wu, G. Tian, G. Zhu, R. Wang, S. Qiu, The synthesis and characterization of a new 3-D inorganic–organic hybrid framework porous material Zn3(bbdc)3(4,4′-bpy)·2(DMF)·4(H2O), J. Solid State Chem. 176 (2003) 1–4. https://doi.org/10.1016/S0022-4596(03)00141-5.

[45] G. Férey, C. Mellot-Draznieks, C. Serre, F. Millange, J. Dutour, S. Surblé, I. Margiolaki, A Chromium Terephthalate-Based Solid with Unusually Large Pore Volumes and Surface Area, Science (80-.). 309 (2005) 2040–2042. https://doi.org/10.1126/science.1116275.

[46] E. Biemmi, T. Bein, N. Stock, Synthesis and characterization of a new metal organic framework structure with a 2D porous system: (H2NEt2)2[Zn3(BDC)4]·3DEF, Solid State Sci. 8 (2006) 363–370. https://doi.org/10.1016/j.solidstatesciences.2006.02.025.

[47] I. Thomas-Hillman, A. Laybourn, C. Dodds, S.W. Kingman, Realising the environmental benefits of metal–organic frameworks: recent advances in microwave synthesis, J. Mater. Chem. A. 6 (2018) 11564–11581. https://doi.org/10.1039/C8TA02919A.

[48] N.S. John, C. Scherb, M. Shöâeè, M.W. Anderson, M.P. Attfield, T. Bein, Single layer growth of sub-micron metal–organic framework crystals observed by in situ atomic force microscopy, Chem. Commun. 2 (2009) 6294. https://doi.org/10.1039/b908299a.

[49] A. García Márquez, A. Demessence, A.E. Platero-Prats, D. Heurtaux, P. Horcajada, C.

Serre, J. Chang, G. Férey, V.A. de la Peña-O'Shea, C. Boissière, D. Grosso, C. Sanchez, Green Microwave Synthesis of MIL-100(Al, Cr, Fe) Nanoparticles for Thin-Film Elaboration, Eur. J. Inorg. Chem. 2012 (2012) 5165–5174. https://doi.org/10.1002/ejic.201200710.

[50] V. Agostoni, P. Horcajada, V. Rodriguez-Ruiz, H. Willaime, P. Couvreur, C. Serre, R. Gref, 'Green' fluorine-free mesoporous iron(III) trimesate nanoparticles for drug delivery, Green Mater. 1 (2013) 209–217. https://doi.org/10.1680/gmat.13.00001.

[51] T. Chalati, P. Horcajada, R. Gref, P. Couvreur, C. Serre, Optimisation of the synthesis of MOF nanoparticles made of flexible porous iron fumarate MIL-88A, J. Mater. Chem. 21 (2011) 2220–2227. https://doi.org/10.1039/C0JM03563G.

[52] Y. Thi Dang, H.T. Hoang, H.C. Dong, K.-B.T. Bui, L.H.T. Nguyen, T.B. Phan, Y. Kawazoe, T.L.H. Doan, Microwave-assisted synthesis of nano Hf- and Zr-based metal-organic frameworks for enhancement of curcumin adsorption, Microporous Mesoporous Mater. 298 (2020) 110064. https://doi.org/10.1016/j.micromeso.2020.110064.

[53] C. Fu, H. Zhou, L. Tan, Z. Huang, Q. Wu, X. Ren, J. Ren, X. Meng, Microwave-Activated Mn-Doped Zirconium Metal–Organic Framework Nanocubes for Highly Effective Combination of Microwave Dynamic and Thermal Therapies Against Cancer, ACS Nano. 12 (2018) 2201–2210. https://doi.org/10.1021/acsnano.7b08868.

[54] M. Ranjbar, A. Pardakhty, A. Amanatfard, A. Asadipour, Efficient drug delivery of β-estradiol encapsulated in Zn-metal–organic framework nanostructures by microwave-assisted coprecipitation method, Drug Des. Devel. Ther. Volume 12 (2018) 2635–2643. https://doi.org/10.2147/DDDT.S173324.

[55] P. George, R.K. Das, P. Chowdhury, Facile microwave synthesis of Ca-BDC metal organic framework for adsorption and controlled release of Curcumin, Microporous Mesoporous Mater. 281 (2019) 161–171. https://doi.org/10.1016/j.micromeso.2019.02.028.

[56] B. Liu, Y. He, L. Han, V. Singh, X. Xu, T. Guo, F. Meng, X. Xu, P. York, Z. Liu, J. Zhang, Microwave-Assisted Rapid Synthesis of γ-Cyclodextrin Metal–Organic Frameworks for Size Control and Efficient Drug Loading, Cryst. Growth Des. 17 (2017) 1654–1660. https://doi.org/10.1021/acs.cgd.6b01658.

[57] M. Schlesinger, S. Schulze, M. Hietschold, M. Mehring, Evaluation of synthetic

methods for microporous metal–organic frameworks exemplified by the competitive formation of [Cu2(btc)3(H2O)3] and [Cu2(btc)(OH)(H2O)], Microporous Mesoporous Mater. 132 (2010) 121–127. https://doi.org/10.1016/j.micromeso.2010.02.008.

[58] H.-J. Park, D.-H. Jeong, S.-G. Noh, H.-J. Lim, J.-Y. Han, J.-Y. Park, Identification of Secondary Chemistry Teachers' Ability to Carry-out Experimentation, J. Korean Chem. Soc. 53 (2009) 765–773. https://doi.org/10.5012/jkcs.2009.53.6.765.

[59] L.W. Aguiar, G.P. Otto, V.L. Kupfer, S.L. Fávaro, C.T.P. Silva, M.P. Moisés, L. de Almeida, M.R. Guilherme, E. Radovanovic, E.M. Girotto, A.W. Rinaldi, Simple, fast, and low-cost synthesis of MIL-100 and MIL-88B in a modified domestic microwave oven, Mater. Lett. 276 (2020) 128127. https://doi.org/10.1016/j.matlet.2020.128127.

[60] K.M.L. Taylor-Pashow, J. Della Rocca, Z. Xie, S. Tran, W. Lin, Postsynthetic Modifications of Iron-Carboxylate Nanoscale Metal−Organic Frameworks for Imaging and Drug Delivery, J. Am. Chem. Soc. 131 (2009) 14261–14263. https://doi.org/10.1021/ja906198y.

[61] Z. Ni, R.I. Masel, Rapid Production of Metal−Organic Frameworks via Microwave-Assisted Solvothermal Synthesis, J. Am. Chem. Soc. 128 (2006) 12394–12395. https://doi.org/10.1021/ja0635231.

[62] S. Głowniak, B. Szczęśniak, J. Choma, M. Jaroniec, Recent Developments in Sonochemical Synthesis of Nanoporous Materials, Molecules. 28 (2023) 2639. https://doi.org/10.3390/molecules28062639.

[63] Z.-Q. Li, L.-G. Qiu, T. Xu, Y. Wu, W. Wang, Z.-Y. Wu, X. Jiang, Ultrasonic synthesis of the microporous metal–organic framework Cu3(BTC)2 at ambient temperature and pressure: An efficient and environmentally friendly method, Mater. Lett. 63 (2009) 78–80. https://doi.org/10.1016/j.matlet.2008.09.010.

[64] W.-J. Son, J. Kim, J. Kim, W.-S. Ahn, Sonochemical synthesis of MOF-5, Chem. Commun. (2008) 6336. https://doi.org/10.1039/b814740j.

[65] D.-W. Jung, D.-A. Yang, J. Kim, J. Kim, W.-S. Ahn, Facile synthesis of MOF-177 by a sonochemical method using 1-methyl-2-pyrrolidinone as a solvent, Dalt. Trans. 39 (2010) 2883. https://doi.org/10.1039/b925088c.

[66] D.-A. Yang, H.-Y. Cho, J. Kim, S.-T. Yang, W.-S. Ahn, CO 2 capture and conversion using Mg-MOF-74 prepared by a sonochemical method, Energy Environ. Sci. 5 (2012)

6465–6473. https://doi.org/10.1039/C1EE02234B.

[67] B. Seoane, J.M. Zamaro, C. Tellez, J. Coronas, Sonocrystallization of zeolitic imidazolate frameworks (ZIF-7, ZIF-8, ZIF-11 and ZIF-20), CrystEngComm. 14 (2012) 3103. https://doi.org/10.1039/c2ce06382d.

[68] J.G. Hernández, T. Friščić, Metal-catalyzed organic reactions using mechanochemistry, Tetrahedron Lett. 56 (2015) 4253–4265. https://doi.org/10.1016/j.tetlet.2015.03.135.

[69] T. Friščić, I. Halasz, V. Štrukil, M. Eckert-Maksić, R.E. Dinnebier, Clean and Efficient Synthesis Using Mechanochemistry: Coordination Polymers, Metal-Organic Frameworks and Metallodrugs, Croat. Chem. Acta. 85 (2012) 367–378. https://doi.org/10.5562/cca2014.

[70] P. Zhang, H. Li, G.M. Veith, S. Dai, Soluble Porous Coordination Polymers by Mechanochemistry: From Metal-Containing Films/Membranes to Active Catalysts for Aerobic Oxidation, Adv. Mater. 27 (2015) 234–239. https://doi.org/10.1002/adma.201403299.

[71] D. Sud, G. Kaur, A comprehensive review on synthetic approaches for metal-organic frameworks: From traditional solvothermal to greener protocols, Polyhedron. 193 (2021) 114897. https://doi.org/10.1016/j.poly.2020.114897.

[72] S. Kumar, N. Dilbaghi, R. Saharan, G. Bhanjana, Nanotechnology as Emerging Tool for Enhancing Solubility of Poorly Water-Soluble Drugs, Bionanoscience. 2 (2012) 227–250. https://doi.org/10.1007/s12668-012-0060-7.

[73] R.W.-Y. Sun, M. Zhang, D. Li, Z.-F. Zhang, H. Cai, M. Li, Y.-J. Xian, S.W. Ng, A.S.-T. Wong, Dinuclear Gold(I) Pyrrolidinedithiocarbamato Complex: Cytotoxic and Antimigratory Activities on Cancer Cells and the Use of Metal-Organic Framework, Chem. - A Eur. J. 21 (2015) 18534–18538. https://doi.org/10.1002/chem.201503656.

[74] J.Y.R. Silva, Y.G. Proenza, L.L. da Luz, S. de Sousa Araújo, M.A.G. Filho, S.A. Junior, T.A. Soares, R.L. Longo, A thermo-responsive adsorbent-heater-thermometer nanomaterial for controlled drug release: (ZIF-8,EuxTby)@AuNP core-shell, Mater. Sci. Eng. C. 102 (2019) 578–588. https://doi.org/10.1016/j.msec.2019.04.078.

[75] T. Azizi Vahed, M.R. Naimi-Jamal, L. Panahi, Alginate-coated ZIF-8 metal-organic framework as a green and bioactive platform for controlled drug release, J. Drug Deliv.

Sci. Technol. 49 (2019) 570–576. https://doi.org/10.1016/j.jddst.2018.12.022.

[76] C. Yang, J. Xu, D. Yang, X. Wang, B. Liu, N. He, Z. Wang, ICG@ZIF-8: One-step encapsulation of indocyanine green in ZIF-8 and use as a therapeutic nanoplatform, Chinese Chem. Lett. 29 (2018) 1421–1424. https://doi.org/10.1016/j.cclet.2018.02.014.

[77] H. Oh, T. Li, J. An, Drug Release Properties of a Series of Adenine-Based Metal-Organic Frameworks, Chem. - A Eur. J. 21 (2015) 17010–17015. https://doi.org/10.1002/chem.201501560.

[78] M. Al Haydar, H.R. Abid, B. Sunderland, S. Wang, Multimetal organic frameworks as drug carriers: aceclofenac as a drug candidate, Drug Des. Devel. Ther. Volume 13 (2018) 23–35. https://doi.org/10.2147/DDDT.S182983.

[79] W. Lin, Y. Cui, Y. Yang, Q. Hu, G. Qian, A biocompatible metal–organic framework as a pH and temperature dual-responsive drug carrier, Dalt. Trans. 47 (2018) 15882–15887. https://doi.org/10.1039/C8DT03202E.

[80] W.W. Lestari, M. Arvinawati, R. Martien, T. Kusumaningsih, Green and facile synthesis of MOF and nano MOF containing zinc(II) and benzen 1,3,5-tri carboxylate and its study in ibuprofen slow-release, Mater. Chem. Phys. 204 (2018) 141–146. https://doi.org/10.1016/j.matchemphys.2017.10.034.

[81] N.J. Hinks, A.C. McKinlay, B. Xiao, P.S. Wheatley, R.E. Morris, Metal organic frameworks as NO delivery materials for biological applications, Microporous Mesoporous Mater. 129 (2010) 330–334. https://doi.org/10.1016/j.micromeso.2009.04.031.

[82] R. V. Pinto, F. Antunes, J. Pires, V. Graça, P. Brandão, M.L. Pinto, Vitamin B3 metal-organic frameworks as potential delivery vehicles for therapeutic nitric oxide, Acta Biomater. 51 (2017) 66–74. https://doi.org/10.1016/j.actbio.2017.01.039.

[83] A. García Márquez, A. Demessence, A.E. Platero-Prats, D. Heurtaux, P. Horcajada, C. Serre, J. Chang, G. Férey, V.A. de la Peña-O'Shea, C. Boissière, D. Grosso, C. Sanchez, Green Microwave Synthesis of MIL-100(Al, Cr, Fe) Nanoparticles for Thin-Film Elaboration, Eur. J. Inorg. Chem. 2012 (2012) 5165–5174. https://doi.org/10.1002/ejic.201200710.

[84] W. Lu, Z. Wei, Z.-Y. Gu, T.-F. Liu, J. Park, J. Park, J. Tian, M. Zhang, Q. Zhang, T.

Gentle III, M. Bosch, H.-C. Zhou, Tuning the structure and function of metal–organic frameworks via linker design, Chem. Soc. Rev. 43 (2014) 5561–5593. https://doi.org/10.1039/C4CS00003J.

[85] T. Simon-Yarza, A. Mielcarek, P. Couvreur, C. Serre, Nanoparticles of Metal-Organic Frameworks: On the Road to In Vivo Efficacy in Biomedicine, Adv. Mater. 30 (2018) 1707365. https://doi.org/10.1002/adma.201707365.

[86] S. Bala, S. Bhattacharya, A. Goswami, A. Adhikary, S. Konar, R. Mondal, Designing Functional Metal–Organic Frameworks by Imparting a Hexanuclear Copper-Based Secondary Building Unit Specific Properties: Structural Correlation With Magnetic and Photocatalytic Activity, Cryst. Growth Des. 14 (2014) 6391–6398. https://doi.org/10.1021/cg501226v.

[87] M. Giménez-Marqués, T. Hidalgo, C. Serre, P. Horcajada, Nanostructured metal–organic frameworks and their bio-related applications, Coord. Chem. Rev. 307 (2016) 342–360. https://doi.org/10.1016/j.ccr.2015.08.008.

[88] C.M. Gramaccioli, R.E. Marsh, The crystal structure of copper glutamate dihydrate, Acta Crystallogr. 21 (1966) 594–600. https://doi.org/10.1107/S0365110X66003517.

[89] S.R. Miller, D. Heurtaux, T. Baati, P. Horcajada, J.-M. Grenèche, C. Serre, Biodegradable therapeutic MOFs for the delivery of bioactive molecules, Chem. Commun. 46 (2010) 4526. https://doi.org/10.1039/c001181a.

[90] D.J. Levine, T. Runčevski, M.T. Kapelewski, B.K. Keitz, J. Oktawiec, D.A. Reed, J.A. Mason, H.Z.H. Jiang, K.A. Colwell, C.M. Legendre, S.A. FitzGerald, J.R. Long, Olsalazine-Based Metal–Organic Frameworks as Biocompatible Platforms for H 2 Adsorption and Drug Delivery, J. Am. Chem. Soc. 138 (2016) 10143–10150. https://doi.org/10.1021/jacs.6b03523.

[91] K. Sun, L. Li, X. Yu, L. Liu, Q. Meng, F. Wang, R. Zhang, Functionalization of mixed ligand metal-organic frameworks as the transport vehicles for drugs, J. Colloid Interface Sci. 486 (2017) 128–135. https://doi.org/10.1016/j.jcis.2016.09.068.

[92] M. Kotzabasaki, G.E. Froudakis, Review of computer simulations on anti-cancer drug delivery in MOFs, Inorg. Chem. Front. 5 (2018) 1255–1272. https://doi.org/10.1039/C7QI00645D.

[93] Q. Chen, Q.-W. Chen, C. Zhuang, P.-P. Tang, N. Lin, L.-Q. Wei, Controlled release of

drug molecules in metal–organic framework material HKUST-1, Inorg. Chem. Commun. 79 (2017) 78–81. https://doi.org/10.1016/j.inoche.2017.03.027.

[94] Z. Nadizadeh, M.R. Naimi-Jamal, L. Panahi, Mechanochemical solvent-free in situ synthesis of drug-loaded {Cu2(1,4-bdc)2(dabco)}n MOFs for controlled drug delivery, J. Solid State Chem. 259 (2018) 35–42. https://doi.org/10.1016/j.jssc.2017.12.027.

[95] H. Nabipour, M. Hossaini Sadr, G. Rezanejade Bardajee, Release behavior, kinetic and antimicrobial study of nalidixic acid from [Zn 2 (bdc) 2 (dabco)] metal-organic frameworks, J. Coord. Chem. 70 (2017) 2771–2784. https://doi.org/10.1080/00958972.2017.1363391.

[96] D.-Y. Ma, Z. Li, J.-X. Xiao, R. Deng, P.-F. Lin, R.-Q. Chen, Y.-Q. Liang, H.-F. Guo, B. Liu, J.-Q. Liu, Hydrostable and Nitryl/Methyl-Functionalized Metal–Organic Framework for Drug Delivery and Highly Selective CO 2 Adsorption, Inorg. Chem. 54 (2015) 6719–6726. https://doi.org/10.1021/acs.inorgchem.5b00335.

[97] C.-Y. Sun, C. Qin, C.-G. Wang, Z.-M. Su, S. Wang, X.-L. Wang, G.-S. Yang, K.-Z. Shao, Y.-Q. Lan, E.-B. Wang, Chiral Nanoporous Metal-Organic Frameworks with High Porosity as Materials for Drug Delivery, Adv. Mater. 23 (2011) 5629–5632. https://doi.org/10.1002/adma.201102538.

[98] Q. Li, J. Wang, W. Liu, X. Zhuang, J. Liu, G. Fan, B. Li, W. Lin, J. Man, A new (4 , 8) -connected topological MOF as potential drug delivery, INOCHE. 55 (2015) 8–10. https://doi.org/10.1016/j.inoche.2015.02.023.

[99] W. Liu, Y. Zhong, X. Wang, C. Zhuang, J. Chen, D. Liu, W. Xiao, Y. Pan, J. Huang, J. Liu, A porous Cu(II)-based metal-organic framework carrier for pH-controlled anticancer drug delivery, Inorg. Chem. Commun. 111 (2020) 107675. https://doi.org/10.1016/j.inoche.2019.107675.

[100] R. Cui, P. Zhao, Y. Yan, G. Bao, A. Damirin, Z. Liu, Outstanding Drug-Loading/Release Capacity of Hollow Fe-Metal–Organic Framework-Based Microcapsules: A Potential Multifunctional Drug-Delivery Platform, Inorg. Chem. 60 (2021) 1664–1671. https://doi.org/10.1021/acs.inorgchem.0c03156.

[101] C. Larabi, E.A. Quadrelli, Titration of Zr3(μ-OH) Hydroxy Groups at the Cornerstones of Bulk MOF UiO-67, [Zr6O4(OH)4(biphenyldicarboxylate)6], and Their Reaction with [AuMe(PMe3)], Eur. J. Inorg. Chem. 2012 (2012) 3014–3022. https://doi.org/10.1002/ejic.201200033.

[102] C. Larabi, E.A. Quadrelli, Titration of Zr 3 (μ-OH) Hydroxy Groups at the Cornerstones of Bulk MOF UiO-67, [Zr 6 O 4 (OH) 4 (biphenyldicarboxylate) 6], and Their Reaction with [AuMe(PMe 3)], Eur. J. Inorg. Chem. 2012 (2012) 3014–3022. https://doi.org/10.1002/ejic.201200033.

[103] R. Huang, Y. Peng, C. Wang, Z. Shi, W. Lin, A Rhenium-Functionalized Metal–Organic Framework as a Single-Site Catalyst for Photochemical Reduction of Carbon Dioxide, Eur. J. Inorg. Chem. 2016 (2016) 4358–4362. https://doi.org/10.1002/ejic.201600064.

[104] R. Abazari, A. Reza Mahjoub, A.M.Z. Slawin, C.L. Carpenter-Warren, Morphology- and size-controlled synthesis of a metal-organic framework under ultrasound irradiation: An efficient carrier for pH responsive release of anti-cancer drugs and their applicability for adsorption of amoxicillin from aqueous solution, Ultrason. Sonochem. 42 (2018) 594–608. https://doi.org/10.1016/j.ultsonch.2017.12.032.

[105] X. Li, T. Guo, L. Lachmanski, F. Manoli, M. Menendez-Miranda, I. Manet, Z. Guo, L. Wu, J. Zhang, R. Gref, Cyclodextrin-based metal-organic frameworks particles as efficient carriers for lansoprazole: Study of morphology and chemical composition of individual particles, Int. J. Pharm. 531 (2017) 424–432. https://doi.org/10.1016/j.ijpharm.2017.05.056.

[106] Q. Jia, Z. Li, C. Guo, X. Huang, Y. Song, N. Zhou, M. Wang, Z. Zhang, L. He, M. Du, A γ-cyclodextrin-based metal–organic framework embedded with graphene quantum dots and modified with PEGMA via SI-ATRP for anticancer drug delivery and therapy, Nanoscale. 11 (2019) 20956–20967. https://doi.org/10.1039/C9NR06195A.

[107] X. Leng, X. Dong, W. Wang, N. Sai, C. Yang, L. You, H. Huang, X. Yin, J. Ni, Biocompatible Fe-Based Micropore Metal-Organic Frameworks as Sustained-Release Anticancer Drug Carriers, Molecules. 23 (2018) 2490. https://doi.org/10.3390/molecules23102490.

[108] J. Schnabel, R. Ettlinger, H. Bunzen, Zn-MOF-74 as pH-Responsive Drug-Delivery System of Arsenic Trioxide, ChemNanoMat. 6 (2020) 1229–1236. https://doi.org/10.1002/cnma.202000221.

[109] W. Cai, J. Wang, C. Chu, W. Chen, C. Wu, G. Liu, Metal-Organic Framework-Based Stimuli-Responsive Systems for Drug Delivery, Adv. Sci. 6 (2019) 1801526. https://doi.org/10.1002/advs.201801526.

[110] J.Q. Liu, Z.D. Luo, Y. Pan, A. Kumar Singh, M. Trivedi, A. Kumar, Recent developments in luminescent coordination polymers: Designing strategies, sensing application and theoretical evidences, Coord. Chem. Rev. 406 (2020) 213145. https://doi.org/10.1016/j.ccr.2019.213145.

[111] P. Horcajada, T. Chalati, C. Serre, B. Gillet, C. Sebrie, T. Baati, J.F. Eubank, D. Heurtaux, P. Clayette, C. Kreuz, J.-S. Chang, Y.K. Hwang, V. Marsaud, P.-N. Bories, L. Cynober, S. Gil, G. Férey, P. Couvreur, R. Gref, Porous metal–organic-framework nanoscale carriers as a potential platform for drug delivery and imaging, Nat. Mater. 9 (2010) 172–178. https://doi.org/10.1038/nmat2608.

[112] P. Horcajada, C. Serre, G. Maurin, N.A. Ramsahye, F. Balas, M. Vallet-Regí, M. Sebban, F. Taulelle, G. Férey, Flexible Porous Metal-Organic Frameworks for a Controlled Drug Delivery, J. Am. Chem. Soc. 130 (2008) 6774–6780. https://doi.org/10.1021/ja710973k.

[113] X. Gao, R. Cui, L. Song, Z. Liu, Hollow structural metal–organic frameworks exhibit high drug loading capacity, targeted delivery and magnetic resonance/optical multimodal imaging, Dalt. Trans. 48 (2019) 17291–17297. https://doi.org/10.1039/C9DT03287H.

[114] K. Xing, R. Fan, F. Wang, H. Nie, X. Du, S. Gai, P. Wang, Y. Yang, Dual-Stimulus-Triggered Programmable Drug Release and Luminescent Ratiometric pH Sensing from Chemically Stable Biocompatible Zinc Metal–Organic Framework, ACS Appl. Mater. Interfaces. 10 (2018) 22746–22756. https://doi.org/10.1021/acsami.8b06270.

[115] P.P. Bag, D. Wang, Z. Chen, R. Cao, Outstanding drug loading capacity by water stable microporous MOF: a potential drug carrier, Chem. Commun. 52 (2016) 3669–3672. https://doi.org/10.1039/C5CC09925K.

[116] M.T. Marcos-Almaraz, R. Gref, V. Agostoni, C. Kreuz, P. Clayette, C. Serre, P. Couvreur, P. Horcajada, Towards improved HIV-microbicide activity through the co-encapsulation of NRTI drugs in biocompatible metal organic framework nanocarriers, J. Mater. Chem. B. 5 (2017) 8563–8569. https://doi.org/10.1039/C7TB01933E.

[117] Q. Wu, M. Niu, X. Chen, L. Tan, C. Fu, X. Ren, J. Ren, L. Li, K. Xu, H. Zhong, X. Meng, Biocompatible and biodegradable zeolitic imidazolate framework/polydopamine nanocarriers for dual stimulus triggered tumor thermo-chemotherapy, Biomaterials. 162 (2018) 132–143.

https://doi.org/10.1016/j.biomaterials.2018.02.022.

[118] Q. Sun, H. Bi, Z. Wang, C. Li, X. Wang, J. Xu, H. Zhu, R. Zhao, F. He, S. Gai, P. Yang, Hyaluronic acid-targeted and pH-responsive drug delivery system based on metal-organic frameworks for efficient antitumor therapy, Biomaterials. 223 (2019) 119473. https://doi.org/10.1016/j.biomaterials.2019.119473.

[119] Z. Li, S. Zhao, H. Wang, Y. Peng, Z. Tan, B. Tang, Functional groups influence and mechanism research of UiO-66-type metal-organic frameworks for ketoprofen delivery, Colloids Surfaces B Biointerfaces. 178 (2019) 1–7. https://doi.org/10.1016/j.colsurfb.2019.02.027.

[120] J.H. Cavka, S. Jakobsen, U. Olsbye, N. Guillou, C. Lamberti, S. Bordiga, K.P. Lillerud, A New Zirconium Inorganic Building Brick Forming Metal Organic Frameworks with Exceptional Stability, J. Am. Chem. Soc. 130 (2008) 13850–13851. https://doi.org/10.1021/ja8057953.

[121] M. Zhang, Y.-P. Chen, M. Bosch, T. Gentle, K. Wang, D. Feng, Z.U. Wang, H.-C. Zhou, Symmetry-Guided Synthesis of Highly Porous Metal-Organic Frameworks with Fluorite Topology, Angew. Chemie. 126 (2014) 834–837. https://doi.org/10.1002/ange.201307340.

[122] I. Abánades Lázaro, S. Abánades Lázaro, R.S. Forgan, Enhancing anticancer cytotoxicity through bimodal drug delivery from ultrasmall Zr MOF nanoparticles, Chem. Commun. 54 (2018) 2792–2795. https://doi.org/10.1039/C7CC09739E.

[123] I. Abánades Lázaro, S. Haddad, J.M. Rodrigo-Muñoz, R.J. Marshall, B. Sastre, V. del Pozo, D. Fairen-Jimenez, R.S. Forgan, Surface-Functionalization of Zr-Fumarate MOF for Selective Cytotoxicity and Immune System Compatibility in Nanoscale Drug Delivery, ACS Appl. Mater. Interfaces. 10 (2018) 31146–31157. https://doi.org/10.1021/acsami.8b11652.

[124] D. Giliopoulos, A. Zamboulis, D. Giannakoudakis, D. Bikiaris, K. Triantafyllidis, Polymer/Metal Organic Framework (MOF) Nanocomposites for Biomedical Applications, Molecules. 25 (2020) 185. https://doi.org/10.3390/molecules25010185.

[125] G. Férey, C. Mellot-Draznieks, C. Serre, F. Millange, Crystallized frameworks with giant pores: Are there limits to the possible?, Acc. Chem. Res. 38 (2005) 217–225. https://doi.org/10.1021/ar040163i.

[126] P. Horcajada, C. Serre, M. Vallet-Regí, M. Sebban, F. Taulelle, G. Férey, Metal–Organic Frameworks as Efficient Materials for Drug Delivery, Angew. Chemie Int. Ed. 45 (2006) 5974–5978. https://doi.org/10.1002/anie.200601878.

[127] J. Xiao, Y. Zhu, S. Huddleston, P. Li, B. Xiao, O.K. Farha, G.A. Ameer, Copper Metal–Organic Framework Nanoparticles Stabilized with Folic Acid Improve Wound Healing in Diabetes, ACS Nano. 12 (2018) 1023–1032. https://doi.org/10.1021/acsnano.7b01850.

[128] J.H. Jo, H.-C. Kim, S. Huh, Y. Kim, D.N. Lee, Antibacterial activities of Cu-MOFs containing glutarates and bipyridyl ligands, Dalt. Trans. 48 (2019) 8084–8093. https://doi.org/10.1039/C9DT00791A.

[129] M. Moharramnejad, A. Ehsani, M. Shahi, S. Gharanli, H. Saremi, R.E. Malekshah, Z.S. Basmenj, S. Salmani, M. Mohammadi, MOF as nanoscale drug delivery devices: Synthesis and recent progress in biomedical applications, J. Drug Deliv. Sci. Technol. 81 (2023) 104285. https://doi.org/10.1016/j.jddst.2023.104285.

[130] S. Rajasekaran, B.S. Reghunath, K.R. Sunaja Devi, D. Pinheiro, Designing coordinatively unsaturated metal sites in bimetallic organic frameworks for oxygen evolution reaction, Mater. Today Chem. 31 (2023) 101616. https://doi.org/10.1016/j.mtchem.2023.101616.

[131] S. Rajasekaran, B.S. Reghunath, S. Devi K. R., B. Saravanakumar, J.J. William, D. Pinheiro, Bi Functional Manganese-Pyridine 2,6 Dicarboxylic Acid Metal Organic Frameworks with Reduced Graphene Oxide as an Electroactive Material for Energy Storage and Water Splitting Applications, J. Electrochem. Soc. 170 (2023) 036505. https://doi.org/10.1149/1945-7111/acbfe3.

[132] S. Rajasekaran, B.S. Reghunath, S.D. R, B. Saravanakumar, J.J. William, D. Pinheiro, Facile synthesis of Mn - Ni bimetal organic framework decorated with amine as an electrode for a high - performance supercapacitor, J. Solid State Electrochem. 27 (2023) 911–925. https://doi.org/10.1007/s10008-023-05382-4.

[133] S. Rajasekaran, K.R.S. Devi, D. Pinheiro, M.K. Mohan, P. Iyyappa Rajan, Metal Organic Frameworks to Remove Arsenic Adsorption from Wastewater, Springer Singapore, 2022. https://doi.org/10.1007/978-981-16-5928-7_1.

[134] A. Kumar, P.K. Jena, S. Behera, R.F. Lockey, S. Mohapatra, S. Mohapatra, Multifunctional magnetic nanoparticles for targeted delivery, Nanomedicine

Nanotechnology, Biol. Med. 6 (2010) 64–69. https://doi.org/10.1016/j.nano.2009.04.002.

[135] M. Jadav, D. Pooja, D.J. Adams, H. Kulhari, Advances in Xanthan Gum-Based Systems for the Delivery of Therapeutic Agents, Pharmaceutics. 15 (2023) 402. https://doi.org/10.3390/pharmaceutics15020402.

[136] F. Ke, Y.-P. Yuan, L.-G. Qiu, Y.-H. Shen, A.-J. Xie, J.-F. Zhu, X.-Y. Tian, L.-D. Zhang, Facile fabrication of magnetic metal–organic framework nanocomposites for potential targeted drug delivery, J. Mater. Chem. 21 (2011) 3843. https://doi.org/10.1039/c0jm01770a.

[137] L. Pang, P. Yang, H. Yang, L. Ge, J. Xiao, Y. Zhou, Application of Fe3O4@MIL-100 (Fe) core-shell magnetic microspheres for evaluating the sorption of organophosphate esters to dissolved organic matter (DOM), Sci. Total Environ. 626 (2018) 42–47. https://doi.org/10.1016/j.scitotenv.2018.01.089.

[138] Y. Wu, M. Zhou, S. Li, Z. Li, J. Li, B. Wu, G. Li, F. Li, X. Guan, Magnetic Metal-Organic Frameworks: γ-Fe 2 O 3 @MOFs via Confined In Situ Pyrolysis Method for Drug Delivery, Small. 10 (2014) 2927–2936. https://doi.org/10.1002/smll.201400362.

[139] A. Pinna, R. Ricco', R. Migheli, G. Rocchitta, P.A. Serra, P. Falcaro, L. Malfatti, P. Innocenzi, A MOF-based carrier for in situ dopamine delivery, RSC Adv. 8 (2018) 25664–25672. https://doi.org/10.1039/C8RA04969F.

[140] H.-X. Zhao, Q. Zou, S.-K. Sun, C. Yu, X. Zhang, R.-J. Li, Y.-Y. Fu, Theranostic metal–organic framework core–shell composites for magnetic resonance imaging and drug delivery, Chem. Sci. 7 (2016) 5294–5301. https://doi.org/10.1039/C6SC01359G.

[141] M.-X. Wu, J. Gao, F. Wang, J. Yang, N. Song, X. Jin, P. Mi, J. Tian, J. Luo, F. Liang, Y.-W. Yang, Multistimuli Responsive Core-Shell Nanoplatform Constructed from Fe 3 O 4 @MOF Equipped with Pillar[6]arene Nanovalves, Small. 14 (2018) 1704440. https://doi.org/10.1002/smll.201704440.

[142] A. Ray Chowdhuri, D. Bhattacharya, S.K. Sahu, Magnetic nanoscale metal organic frameworks for potential targeted anticancer drug delivery, imaging and as an MRI contrast agent, Dalt. Trans. 45 (2016) 2963–2973. https://doi.org/10.1039/C5DT03736K.

[143] V. Nejadshafiee, H. Naeimi, B. Goliaei, B. Bigdeli, A. Sadighi, S. Dehghani, A.

Lotfabadi, M. Hosseini, M.S. Nezamtaheri, M. Amanlou, M. Sharifzadeh, M. Khoobi, Magnetic bio-metal–organic framework nanocomposites decorated with folic acid conjugated chitosan as a promising biocompatible targeted theranostic system for cancer treatment, Mater. Sci. Eng. C. 99 (2019) 805–815. https://doi.org/10.1016/j.msec.2019.02.017.

[144] R. Langer, Drug Delivery Systems, MRS Bull. 16 (1991) 47–49. https://doi.org/10.1557/S0883769400056050.

[145] S. Wuttke, S. Braig, T. Preiß, A. Zimpel, J. Sicklinger, C. Bellomo, J.O. Rädler, A.M. Vollmar, T. Bein, MOF nanoparticles coated by lipid bilayers and their uptake by cancer cells, Chem. Commun. 51 (2015) 15752–15755. https://doi.org/10.1039/C5CC06767G.

[146] S. Wang, W. Morris, Y. Liu, C.M. McGuirk, Y. Zhou, J.T. Hupp, O.K. Farha, C.A. Mirkin, Surface-Specific Functionalization of Nanoscale Metal–Organic Frameworks, Angew. Chemie Int. Ed. 54 (2015) 14738–14742. https://doi.org/10.1002/anie.201506888.

[147] N. Nasihat Sheno, S. Farhadi, A. Maleki, M. Hamidi, A novel approach for the synthesis of phospholipid bilayer-coated zeolitic imidazolate frameworks: preparation and characterization as a pH-responsive drug delivery system, New J. Chem. 43 (2019) 1956–1963. https://doi.org/10.1039/C8NJ04715D.

[148] W. Zhu, G. Xiang, J. Shang, J. Guo, B. Motevalli, P. Durfee, J.O. Agola, E.N. Coker, C.J. Brinker, Versatile Surface Functionalization of Metal–Organic Frameworks through Direct Metal Coordination with a Phenolic Lipid Enables Diverse Applications, Adv. Funct. Mater. 28 (2018) 1705274. https://doi.org/10.1002/adfm.201705274.

[149] R.C. Huxford-Phillips, S.R. Russell, D. Liu, W. Lin, Lipid-coated nanoscale coordination polymers for targeted cisplatin delivery, RSC Adv. 3 (2013) 14438. https://doi.org/10.1039/c3ra42033g.

[150] D. Liu, C. Poon, K. Lu, C. He, W. Lin, Self-assembled nanoscale coordination polymers with trigger release properties for effective anticancer therapy, Nat. Commun. 5 (2014) 4182. https://doi.org/10.1038/ncomms5182.

[151] C. He, D. Liu, W. Lin, Self-Assembled Core–Shell Nanoparticles for Combined Chemotherapy and Photodynamic Therapy of Resistant Head and Neck Cancers, ACS

Nano. 9 (2015) 991–1003. https://doi.org/10.1021/nn506963h.

[152] M.A. Elgadir, M.S. Uddin, S. Ferdosh, A. Adam, A.J.K. Chowdhury, M.Z.I. Sarker, Impact of chitosan composites and chitosan nanoparticle composites on various drug delivery systems: A review, J. Food Drug Anal. 23 (2015) 619–629. https://doi.org/10.1016/j.jfda.2014.10.008.

[153] A. Ali, S. Ahmed, A review on chitosan and its nanocomposites in drug delivery, Int. J. Biol. Macromol. 109 (2018) 273–286. https://doi.org/10.1016/j.ijbiomac.2017.12.078.

[154] K. Liang, R. Ricco, C.M. Doherty, M.J. Styles, S. Bell, N. Kirby, S. Mudie, D. Haylock, A.J. Hill, C.J. Doonan, P. Falcaro, Biomimetic mineralization of metal-organic frameworks as protective coatings for biomacromolecules, Nat. Commun. 6 (2015) 7240. https://doi.org/10.1038/ncomms8240.

[155] X. Lian, Y. Huang, Y. Zhu, Y. Fang, R. Zhao, E. Joseph, J. Li, J.-P. Pellois, H.-C. Zhou, Enzyme-MOF Nanoreactor Activates Nontoxic Paracetamol for Cancer Therapy, Angew. Chemie. 130 (2018) 5827–5832. https://doi.org/10.1002/ange.201801378.

[156] S. Jayrajsinh, G. Shankar, Y.K. Agrawal, L. Bakre, Montmorillonite nanoclay as a multifaceted drug-delivery carrier: A review, J. Drug Deliv. Sci. Technol. 39 (2017) 200–209. https://doi.org/10.1016/j.jddst.2017.03.023.

[157] J.K. Watts, D.R. Corey, Silencing disease genes in the laboratory and the clinic, J. Pathol. 226 (2012) 365–379. https://doi.org/10.1002/path.2993.

[158] M.H. Teplensky, M. Fantham, C. Poudel, C. Hockings, M. Lu, A. Guna, M. Aragones-Anglada, P.Z. Moghadam, P. Li, O.K. Farha, S. Bernaldo de Quirós Fernández, F.M. Richards, D.I. Jodrell, G. Kaminski Schierle, C.F. Kaminski, D. Fairen-Jimenez, A Highly Porous Metal-Organic Framework System to Deliver Payloads for Gene Knockdown, Chem. 5 (2019) 2926–2941. https://doi.org/10.1016/j.chempr.2019.08.015.

[159] M. Chen, C. Dong, S. Shi, Nanoparticle-Mediated siRNA Delivery and Multifunctional Modification Strategies for Effective Cancer Therapy, Adv. Mater. Technol. 6 (2021). https://doi.org/10.1002/admt.202001236.

[160] M.H. Teplensky, M. Fantham, P. Li, T.C. Wang, J.P. Mehta, L.J. Young, P.Z.

Moghadam, J.T. Hupp, O.K. Farha, C.F. Kaminski, D. Fairen-Jimenez, Temperature Treatment of Highly Porous Zirconium-Containing Metal–Organic Frameworks Extends Drug Delivery Release, J. Am. Chem. Soc. 139 (2017) 7522–7532. https://doi.org/10.1021/jacs.7b01451.

[161] S.K. Alsaiari, S. Patil, M. Alyami, K.O. Alamoudi, F.A. Aleisa, J.S. Merzaban, M. Li, N.M. Khashab, Endosomal Escape and Delivery of CRISPR/Cas9 Genome Editing Machinery Enabled by Nanoscale Zeolitic Imidazolate Framework, J. Am. Chem. Soc. 140 (2018) 143–146. https://doi.org/10.1021/jacs.7b11754.

[162] C. He, C. Poon, C. Chan, S.D. Yamada, W. Lin, Nanoscale Coordination Polymers Codeliver Chemotherapeutics and siRNAs to Eradicate Tumors of Cisplatin-Resistant Ovarian Cancer, J. Am. Chem. Soc. 138 (2016) 6010–6019. https://doi.org/10.1021/jacs.6b02486.

[163] S. Peng, B. Bie, Y. Sun, M. Liu, H. Cong, W. Zhou, Y. Xia, H. Tang, H. Deng, X. Zhou, Metal-organic frameworks for precise inclusion of single-stranded DNA and transfection in immune cells, Nat. Commun. 9 (2018) 1293. https://doi.org/10.1038/s41467-018-03650-w.

[164] P. Sun, Z. Li, J. Wang, H. Gao, X. Yang, S. Wu, D. Liu, Q. Chen, Transcellular delivery of messenger RNA payloads by a cationic supramolecular MOF platform, Chem. Commun. 54 (2018) 11304–11307. https://doi.org/10.1039/C8CC07047D.

[165] T. Hidalgo, M. Alonso-Nocelo, B.L. Bouzo, S. Reimondez-Troitiño, C. Abuin-Redondo, M. de la Fuente, P. Horcajada, Biocompatible iron(<scp>iii</scp>) carboxylate metal–organic frameworks as promising RNA nanocarriers, Nanoscale. 12 (2020) 4839–4845. https://doi.org/10.1039/C9NR08127E.

[166] S. Porrang, N. Rahemi, S. Davaran, M. Mahdavi, B. Hassanzadeh, A.M. Gholipour, Direct surface modification of mesoporous silica nanoparticles by DBD plasma as a green approach to prepare dual-responsive drug delivery system, J. Taiwan Inst. Chem. Eng. 123 (2021) 47–58. https://doi.org/10.1016/j.jtice.2021.05.024.

[167] Y. Cu, C.J. Booth, W.M. Saltzman, In vivo distribution of surface-modified PLGA nanoparticles following intravaginal delivery, J. Control. Release. 156 (2011) 258–264. https://doi.org/10.1016/j.jconrel.2011.06.036.

[168] J. Della Rocca, D. Liu, W. Lin, Nanoscale Metal–Organic Frameworks for Biomedical Imaging and Drug Delivery, Acc. Chem. Res. 44 (2011) 957–968.

https://doi.org/10.1021/ar200028a.

[169] W.J. Rieter, K.M.L. Taylor, W. Lin, Surface Modification and Functionalization of Nanoscale Metal-Organic Frameworks for Controlled Release and Luminescence Sensing, J. Am. Chem. Soc. 129 (2007) 9852–9853. https://doi.org/10.1021/ja073506r.

[170] G. Lu, S. Li, Z. Guo, O.K. Farha, B.G. Hauser, X. Qi, Y. Wang, X. Wang, S. Han, X. Liu, J.S. DuChene, H. Zhang, Q. Zhang, X. Chen, J. Ma, S.C.J. Loo, W.D. Wei, Y. Yang, J.T. Hupp, F. Huo, Imparting functionality to a metal–organic framework material by controlled nanoparticle encapsulation, Nat. Chem. 4 (2012) 310–316. https://doi.org/10.1038/nchem.1272.

[171] K.K. Tanabe, Z. Wang, S.M. Cohen, Systematic Functionalization of a Metal−Organic Framework via a Postsynthetic Modification Approach, J. Am. Chem. Soc. 130 (2008) 8508–8517. https://doi.org/10.1021/ja801848j.

[172] K.A. Mocniak, I. Kubajewska, D.E.M. Spillane, G.R. Williams, R.E. Morris, Incorporation of cisplatin into the metal–organic frameworks UiO66-NH 2 and UiO66 – encapsulation vs. conjugation, RSC Adv. 5 (2015) 83648–83656. https://doi.org/10.1039/C5RA14011K.

[173] L.G. Harris, S. Tosatti, M. Wieland, M. Textor, R.G. Richards, Staphylococcus aureus adhesion to titanium oxide surfaces coated with non-functionalized and peptide-functionalized poly(L-lysine)-grafted- poly(ethylene glycol) copolymers, Biomaterials. 25 (2004) 4135–4148. https://doi.org/10.1016/j.biomaterials.2003.11.033.

[174] S. Beg, M. Rahman, A. Jain, S. Saini, P. Midoux, C. Pichon, F.J. Ahmad, S. Akhter, Nanoporous metal organic frameworks as hybrid polymer–metal composites for drug delivery and biomedical applications, Drug Discov. Today. 22 (2017) 625–637. https://doi.org/10.1016/j.drudis.2016.10.001.

[175] S. Jung, Y. Kim, S.-J. Kim, T.-H. Kwon, S. Huh, S. Park, Bio-functionalization of metal–organic frameworks by covalent protein conjugation, Chem. Commun. 47 (2011) 2904. https://doi.org/10.1039/c0cc03288c.

[176] C. V. McGuire, R.S. Forgan, The surface chemistry of metal–organic frameworks, Chem. Commun. 51 (2015) 5199–5217. https://doi.org/10.1039/C4CC04458D.

[177] Y. Wu, M. Zhou, S. Li, Z. Li, J. Li, B. Wu, G. Li, F. Li, X. Guan, Magnetic Metal–Organic Frameworks: γ-Fe 2 O 3 @MOFs via Confined In Situ Pyrolysis Method for

Drug Delivery, Small. 10 (2014) 2927–2936. https://doi.org/10.1002/smll.201400362.

[178] X. Lian, Y. Huang, Y. Zhu, Y. Fang, R. Zhao, E. Joseph, J. Li, J.-P. Pellois, H.-C. Zhou, Enzyme-MOF Nanoreactor Activates Nontoxic Paracetamol for Cancer Therapy, Angew. Chemie. 130 (2018) 5827–5832. https://doi.org/10.1002/ange.201801378.

[179] N. Motakef-Kazemi, S.A. Shojaosadati, A. Morsali, In situ synthesis of a drug-loaded MOF at room temperature, Microporous Mesoporous Mater. 186 (2014) 73–79. https://doi.org/10.1016/j.micromeso.2013.11.036.

[180] L. Li, Y.Q. Wu, K.K. Sun, R. Zhang, L. Fan, K.K. Liang, L.B. Mao, Controllable preparation and drug loading properties of core-shell microspheres Fe3O4@MOFs/GO, Mater. Lett. 162 (2016) 207–210. https://doi.org/10.1016/j.matlet.2015.09.096.

[181] M.X. Wu, Y.W. Yang, Metal–Organic Framework (MOF)-Based Drug/Cargo Delivery and Cancer Therapy, Adv. Mater. 29 (2017) 1–20. https://doi.org/10.1002/adma.201606134.

[182] B. Kabak, E. Kendüzler, Europium metal-organic frameworks: Synthesis, characterization, and application as fluorescence sensors for the detection of Cu2+, Ni2+ cations and T3, T4 hormones, Talanta. 266 (2024) 124944. https://doi.org/10.1016/j.talanta.2023.124944.

[183] J. Rodríguez-Martínez, M.J. Sánchez-Martín, O. López-Patarroyo, M. Valiente, Novel cannabinoid release system: Encapsulation of a cannabidiol precursor into γ-cyclodextrin metal-organic frameworks, J. Drug Deliv. Sci. Technol. 79 (2023). https://doi.org/10.1016/j.jddst.2022.104085.

[184] H. Li, N. Lv, X. Li, B. Liu, J. Feng, X. Ren, T. Guo, D. Chen, J. Fraser Stoddart, R. Gref, J. Zhang, Composite CD-MOF nanocrystals-containing microspheres for sustained drug delivery, Nanoscale. 9 (2017) 7454–7463. https://doi.org/10.1039/C6NR07593B.

[185] I. Kritskiy, T. Volkova, A. Surov, I. Terekhova, γ-Cyclodextrin-metal organic frameworks as efficient microcontainers for encapsulation of leflunomide and acceleration of its transformation into teriflunomide, Carbohydr. Polym. 216 (2019) 224–230. https://doi.org/10.1016/j.carbpol.2019.04.037.

[186] I. Kritskiy, T. Volkova, T. Sapozhnikova, A. Mazur, P. Tolstoy, I. Terekhova, Methotrexate-loaded metal-organic frameworks on the basis of γ-cyclodextrin: Design, characterization, in vitro and in vivo investigation, Mater. Sci. Eng. C. 111 (2020) 110774. https://doi.org/10.1016/j.msec.2020.110774.

[187] A. Carneiro, L. Santana, M.J. Matos, Oxidation-labile linkers for controlled drug delivery, Bioorganic Med. Chem. Lett. 87 (2023). https://doi.org/10.1016/j.bmcl.2023.129264.

[188] M. Vassaki, K.E. Papathanasiou, C. Hadjicharalambous, D. Chandrinou, P. Turhanen, D. Choquesillo-Lazarte, K.D. Demadis, Self-sacrificial MOFs for ultra-long controlled release of bisphosphonate anti-osteoporotic drugs, Chem. Commun. 56 (2020) 5166–5169. https://doi.org/10.1039/D0CC00439A.

[189] H. Zheng, Y. Zhang, L. Liu, W. Wan, P. Guo, A.M. Nyström, X. Zou, One-pot Synthesis of Metal–Organic Frameworks with Encapsulated Target Molecules and Their Applications for Controlled Drug Delivery, J. Am. Chem. Soc. 138 (2016) 962–968. https://doi.org/10.1021/jacs.5b11720.

[190] J. Zhuang, C. Kuo, L. Chou, D. Liu, E. Weerapana, C. Tsung, Optimized Metal–Organic-Framework Nanospheres for Drug Delivery: Evaluation of Small-Molecule Encapsulation, ACS Nano. 8 (2014) 2812–2819. https://doi.org/10.1021/nn406590q.

[191] X. Chen, R. Tong, Z. Shi, B. Yang, H. Liu, S. Ding, X. Wang, Q. Lei, J. Wu, W. Fang, MOF Nanoparticles with Encapsulated Autophagy Inhibitor in Controlled Drug Delivery System for Antitumor, ACS Appl. Mater. Interfaces. 10 (2018) 2328–2337. https://doi.org/10.1021/acsami.7b16522.

[192] E. Nazarzadeh Zare, D. Khorsandi, A. Zarepour, H. Yilmaz, T. Agarwal, S. Hooshmand, R. Mohammadinejad, F. Ozdemir, O. Sahin, S. Adiguzel, H. Khan, A. Zarrabi, E. Sharifi, A. Kumar, E. Mostafavi, N.H. Kouchehbaghi, V. Mattoli, F. Zhang, V. Jucaud, A.H. Najafabadi, A. Khademhosseini, Biomedical applications of engineered heparin-based materials, Bioact. Mater. 31 (2024) 87–118. https://doi.org/10.1016/j.bioactmat.2023.08.002.

[193] G. Altun, Z. Tu, Food Hydrocolloids Synthesizing mechanically robust natural pea protein hydrogels via deep cryogenic treatment : State of the art in bioactive compound delivery system, 146 (2024). https://doi.org/10.1016/j.foodhyd.2023.109202.

[194] M. Szabados, A. Gácsi, Y. Gulyás, Z. Kónya, Á. Kukovecz, E. Csányi, I. Pálinkó, P.

Sipos, Conventional or mechanochemically-aided intercalation of diclofenac and naproxen anions into the interlamellar space of CaFe-layered double hydroxides and their application as dermal drug delivery systems, Appl. Clay Sci. 212 (2021). https://doi.org/10.1016/j.clay.2021.106233.

[195] S. Devautour-Vinot, C. Martineau, S. Diaby, M. Ben-Yahia, S. Miller, C. Serre, P. Horcajada, D. Cunha, F. Taulelle, G. Maurin, Caffeine Confinement into a Series of Functionalized Porous Zirconium MOFs: A Joint Experimental/Modeling Exploration, J. Phys. Chem. C. 117 (2013) 11694–11704. https://doi.org/10.1021/jp402916y.

[196] S. Javanbakht, P. Nezhad-Mokhtari, A. Shaabani, N. Arsalani, M. Ghorbani, Incorporating Cu-based metal-organic framework/drug nanohybrids into gelatin microsphere for ibuprofen oral delivery, Mater. Sci. Eng. C. 96 (2019) 302–309. https://doi.org/10.1016/j.msec.2018.11.028.

[197] Y. He, X. Hou, J. Guo, Z. He, T. Guo, Y. Liu, Y. Zhang, J. Zhang, N. Feng, Activation of a gamma–cyclodextrin–based metal–organic framework using supercritical carbon dioxide for high–efficient delivery of honokiol, Carbohydr. Polym. 235 (2020) 115935. https://doi.org/10.1016/j.carbpol.2020.115935.

[198] T. Simon-Yarza, M. Giménez-Marqués, R. Mrimi, A. Mielcarek, R. Gref, P. Horcajada, C. Serre, P. Couvreur, A Smart Metal-Organic Framework Nanomaterial for Lung Targeting, Angew. Chemie Int. Ed. 56 (2017) 15565–15569. https://doi.org/10.1002/anie.201707346.

[199] Z. Wang, S.M. Cohen, Postsynthetic modification of metal–organic frameworks, Chem. Soc. Rev. 38 (2009) 1315. https://doi.org/10.1039/b802258p.

[200] W. Morris, W.E. Briley, E. Auyeung, M.D. Cabezas, C.A. Mirkin, Nucleic Acid–Metal Organic Framework (MOF) Nanoparticle Conjugates, J. Am. Chem. Soc. 136 (2014) 7261–7264. https://doi.org/10.1021/ja503215w.

[201] A. Karmakar, P.G.M. Mileo, I. Bok, S.B. Peh, J. Zhang, H. Yuan, G. Maurin, D. Zhao, Thermo-Responsive MOF/Polymer Composites for Temperature-Mediated Water Capture and Release, Angew. Chemie. 132 (2020) 11096–11102. https://doi.org/10.1002/ange.202002384.

[202] H. Furukawa, K.E. Cordova, M. O'Keeffe, O.M. Yaghi, The Chemistry and Applications of Metal-Organic Frameworks, Science (80-.). 341 (2013). https://doi.org/10.1126/science.1230444.

[203] D. Zheng, P. Yu, Z. Wei, C. Zhong, M. Wu, RBC Membrane Camouflaged Semiconducting Polymer Nanoparticles for Near - Infrared Photoacoustic Imaging and Photothermal Therapy, Nano-Micro Lett. 12 (2020) 94. https://doi.org/10.1007/s40820-020-00429-x.

[204] M. Wang, G. Gong, J. Feng, T. Wang, Dual pH-Mediated Mechanized Hollow Zirconia Nanospheres, ACS Appl. Mater. Interfaces. 8 (2016) 23289–23301. https://doi.org/10.1021/acsami.6b07603.

[205] F. Jin, C. Zhao, G. Chen, Y. Dong, Homochiral BINAPDA-Zr-MOF for Heterogeneous Asymmetric Cyanosilylation of Aldehydes, Inorg. Chem. 58 (2019) 9253–9259. https://doi.org/10.1021/acs.inorgchem.9b00963.

[206] G. Tan, Y. Zhong, L. Yang, Y. Jiang, J. Liu, F. Ren, A multifunctional MOF-based nanohybrid as injectable implant platform for drug synergistic oral cancer therapy, Chem. Eng. J. 390 (2020) 124446. https://doi.org/10.1016/j.cej.2020.124446.

[207] A.A. Karmakar, P.G.M. Mileo, I. Bok, S. Bo, J. Zhang, H. Yuan, G. Maurin, Thermo-Responsive MOF/Polymer Composites for Temperature Mediated Water Capture and Release, Angew. Chemie Int. Ed. 59 (n.d.) 11003–11009. https://doi.org/10.1002/anie.202002384.

[208] W. Lin, Q. Hu, J. Yu, K. Jiang, Y. Yang, S. Xiang, Low Cytotoxic Metal – Organic Frameworks as Temperature- Responsive Drug Carriers, Chempluschem. 81 (2016) 804–810. https://doi.org/10.1002/cplu.201600142.

[209] S. Dai, F. Nouar, S. Zhang, A. Tissot, C. Serre, One-Step Room-Temperature Synthesis of Metal(IV) Carboxylate Metal—Organic Frameworks, Angew. Chemie. 133 (2021) 4328–4334. https://doi.org/10.1002/ange.202014184.

[210] L.N. McHugh, M.J. McPherson, L.J. McCormick, S.A. Morris, P.S. Wheatley, S.J. Teat, D. McKay, D.M. Dawson, C.E.F. Sansome, S.E. Ashbrook, C.A. Stone, M.W. Smith, R.E. Morris, Hydrolytic stability in hemilabile metal–organic frameworks, Nat. Chem. 10 (2018) 1096–1102. https://doi.org/10.1038/s41557-018-0104-x.

[211] J. Yao, Y. Liu, J. Wang, Q. Jiang, D. She, H. Guo, N. Sun, Z. Pang, C. Deng, W. Yang, S. Shen, On-demand CO release for amplification of chemotherapy by MOF functionalized magnetic carbon nanoparticles with NIR irradiation, Biomaterials. 195 (2019) 51–62. https://doi.org/10.1016/j.biomaterials.2018.12.029.

[212] Y.-T. Qin, H. Peng, X.-W. He, W.-Y. Li, Y.-K. Zhang, pH-Responsive Polymer-Stabilized ZIF-8 Nanocomposites for Fluorescence and Magnetic Resonance Dual-Modal Imaging-Guided Chemo-/Photodynamic Combinational Cancer Therapy, ACS Appl. Mater. Interfaces. 11 (2019) 34268–34281. https://doi.org/10.1021/acsami.9b12641.

[213] Z. Xiang, Y. Qi, Y. Lu, Z. Hu, X. Wang, W. Jia, J. Hu, J. Ji, W. Lu, MOF-derived novel porous Fe 3 O 4 @C nanocomposites as smart nanomedical platforms for combined cancer therapy: magnetic-triggered synergistic hyperthermia and chemotherapy, J. Mater. Chem. B. 8 (2020) 8671–8683. https://doi.org/10.1039/D0TB01021A.

[214] A. Cadiau, N. Kolobov, S. Srinivasan, M.G. Goesten, H. Haspel, A. V. Bavykina, M.R. Tchalala, P. Maity, A. Goryachev, A.S. Poryvaev, M. Eddaoudi, M. V. Fedin, O.F. Mohammed, J. Gascon, A Titanium Metal–Organic Framework with Visible-Light-Responsive Photocatalytic Activity, Angew. Chemie. 132 (2020) 13570–13574. https://doi.org/10.1002/ange.202000158.

[215] E. Ploetz, A. Zimpel, V. Cauda, D. Bauer, D.C. Lamb, C. Haisch, S. Zahler, A.M. Vollmar, S. Wuttke, H. Engelke, Metal–Organic Framework Nanoparticles Induce Pyroptosis in Cells Controlled by the Extracellular pH, Adv. Mater. 32 (2020) 1907267. https://doi.org/10.1002/adma.201907267.

[216] S. Wang, M. Wahiduzzaman, L. Davis, A. Tissot, W. Shepard, J. Marrot, C. Martineau-Corcos, D. Hamdane, G. Maurin, S. Devautour-Vinot, C. Serre, A robust zirconium amino acid metal-organic framework for proton conduction, Nat. Commun. 9 (2018) 4937. https://doi.org/10.1038/s41467-018-07414-4.

[217] S.H. Pham, Y. Choi, J. Choi, Stimuli-Responsive Nanomaterials for Application in Antitumor Therapy and Drug Delivery, (2020).

[218] Z. Xue, M. Zhu, Y. Dong, T. Feng, Z. Chen, Y. Feng, Z. Shan, J. Xu, S. Meng, An integrated targeting drug delivery system based on the hybridization of graphdiyne and MOFs for visualized cancer therapy, Nanoscale. 11 (2019) 11709–11718. https://doi.org/10.1039/C9NR02017A.

[219] Y. Qin, J. Fan, W. Yang, B. Shen, Y. Yang, Q. Zhou, W. Chen, M. Daniyal, F. Xiao, W.-B. Sheng, H. Yu, J. Zhou, W. Wang, C. Tong, B. Liu, Endogenous Cys-Assisted GSH@AgNCs-rGO Nanoprobe for Real-Time Monitoring of Dynamic Change in

GSH Levels Regulated by Natural Drug, Anal. Chem. 92 (2020) 1988–1996. https://doi.org/10.1021/acs.analchem.9b04374.

[220] X. Guo, Y. Cheng, X. Zhao, Y. Luo, J. Chen, W.-E. Yuan, Advances in redox-responsive drug delivery systems of tumor microenvironment, J. Nanobiotechnology. 16 (2018) 74. https://doi.org/10.1186/s12951-018-0398-2.

[221] Y. Miao, X. Zhao, Y. Qiu, Z. Liu, W. Yang, X. Jia, Metal–Organic Framework-Assisted Nanoplatform with Hydrogen Peroxide/Glutathione Dual-Sensitive On-Demand Drug Release for Targeting Tumors and Their Microenvironment, ACS Appl. Bio Mater. 2 (2019) 895–905. https://doi.org/10.1021/acsabm.8b00741.

[222] J. Zhao, Y. Yang, X. Han, C. Liang, J. Liu, X. Song, Z. Ge, Z. Liu, Redox-Sensitive Nanoscale Coordination Polymers for Drug Delivery and Cancer Theranostics, ACS Appl. Mater. Interfaces. 9 (2017) 23555–23563. https://doi.org/10.1021/acsami.7b07535.

[223] B. Lei, M. Wang, Z. Jiang, W. Qi, R. Su, Z. He, Constructing Redox-Responsive Metal–Organic Framework Nanocarriers for Anticancer Drug Delivery, ACS Appl. Mater. Interfaces. 10 (2018) 16698–16706. https://doi.org/10.1021/acsami.7b19693.

[224] C. Liu, X. Xu, J. Zhou, J. Yan, D. Wang, H. Zhang, Redox-responsive tumor targeted dual-drug loaded biocompatible metal–organic frameworks nanoparticles for enhancing anticancer effects, BMC Mater. 2 (2020) 7. https://doi.org/10.1186/s42833-020-00013-y.

[225] B. Nirosha Yalamandala, W. Shen, S. Min, W. Chiang, S. Chang, S. Hu, Advances in Functional Metal-Organic Frameworks Based On-Demand Drug Delivery Systems for Tumor Therapeutics, Adv. NanoBiomed Res. 1 (2021). https://doi.org/10.1002/anbr.202100014.

[226] K. Kim, S. Lee, E. Jin, L. Palanikumar, J.H. Lee, J.C. Kim, J.S. Nam, B. Jana, T.-H. Kwon, S.K. Kwak, W. Choe, J.-H. Ryu, MOF × Biopolymer: Collaborative Combination of Metal–Organic Framework and Biopolymer for Advanced Anticancer Therapy, ACS Appl. Mater. Interfaces. 11 (2019) 27512–27520. https://doi.org/10.1021/acsami.9b05736.

[227] Y.-D. Zhu, S.-P. Chen, H. Zhao, Y. Yang, X.-Q. Chen, J. Sun, H.-S. Fan, X.-D. Zhang, PPy@MIL-100 Nanoparticles as a pH- and Near-IR-Irradiation-Responsive Drug Carrier for Simultaneous Photothermal Therapy and Chemotherapy of Cancer Cells,

ACS Appl. Mater. Interfaces. 8 (2016) 34209–34217. https://doi.org/10.1021/acsami.6b11378.

[228] H. Ding, P. Tan, S. Fu, X. Tian, H. Zhang, X. Ma, Z. Gu, K. Luo, Preparation and application of pH-responsive drug delivery systems, J. Control. Release. 348 (2022) 206–238. https://doi.org/10.1016/j.jconrel.2022.05.056.

[229] D. Wang, J. Zhou, R. Chen, R. Shi, G. Zhao, G. Xia, R. Li, Z. Liu, J. Tian, H. Wang, Z. Guo, H. Wang, Q. Chen, Controllable synthesis of dual-MOFs nanostructures for pH-responsive artemisinin delivery, magnetic resonance and optical dual-model imaging-guided chemo/photothermal combinational cancer therapy, Biomaterials. 100 (2016) 27–40. https://doi.org/10.1016/j.biomaterials.2016.05.027.

[230] M. Pooresmaeil, H. Namazi, Facile preparation of pH-sensitive chitosan microspheres for delivery of curcumin; characterization, drug release kinetics and evaluation of anticancer activity, Int. J. Biol. Macromol. 162 (2020) 501–511. https://doi.org/10.1016/j.ijbiomac.2020.06.183.

[231] R. Röder, T. Preiß, P. Hirschle, B. Steinborn, A. Zimpel, M. Höhn, J.O. Rädler, T. Bein, E. Wagner, S. Wuttke, U. Lächelt, Multifunctional Nanoparticles by Coordinative Self-Assembly of His-Tagged Units with Metal–Organic Frameworks, J. Am. Chem. Soc. 139 (2017) 2359–2368. https://doi.org/10.1021/jacs.6b11934.

[232] T. Xue, C. Xu, Y. Wang, Y. Wang, H. Tian, Y. Zhang, Doxorubicin-loaded nanoscale metal–organic framework for tumor-targeting combined chemotherapy and chemodynamic therapy, Biomater. Sci. 7 (2019) 4615–4623. https://doi.org/10.1039/C9BM01044K.

[233] A. Lajevardi, M. Hossaini Sadr, A. Badiei, M. Armaghan, Synthesis and characterization of Fe3O4@SiO2@MIL-100(Fe) nanocomposite: A nanocarrier for loading and release of celecoxib, J. Mol. Liq. 307 (2020) 112996. https://doi.org/10.1016/j.molliq.2020.112996.

[234] A. Botet-Carreras, C. Tamames-Tabar, F. Salles, S. Rojas, E. Imbuluzqueta, H. Lana, M.J. Blanco-Prieto, P. Horcajada, Improving the genistein oral bioavailability via its formulation into the metal–organic framework MIL-100(Fe), J. Mater. Chem. B. 9 (2021) 2233–2239. https://doi.org/10.1039/D0TB02804E.

[235] L. Zhang, Y. Gao, S. Sun, Z. Li, A. Wu, L. Zeng, pH-Responsive metal–organic framework encapsulated gold nanoclusters with modulated release to enhance

photodynamic therapy/chemotherapy in breast cancer, J. Mater. Chem. B. 8 (2020) 1739–1747. https://doi.org/10.1039/C9TB02621E.

[236] F. Duan, X. Feng, X. Yang, W. Sun, Y. Jin, H. Liu, K. Ge, Z. Li, J. Zhang, A simple and powerful co-delivery system based on pH-responsive metal-organic frameworks for enhanced cancer immunotherapy, Biomaterials. 122 (2017) 23–33. https://doi.org/10.1016/j.biomaterials.2017.01.017.

[237] W. Cai, J. Wang, C. Chu, W. Chen, C. Wu, G. Liu, Metal–Organic Framework-Based Stimuli-Responsive Systems for Drug Delivery, Adv. Sci. 6 (2019). https://doi.org/10.1002/advs.201801526.

[238] R. Huo, C. Wang, F. Xu, Y.H. Xing, Y.F. Wang, F.Y. Bai, Multistimuli-responsive pyrene-based lanthanide (III)-MOF construction and applied as dual-function fluorescent chemosensors for trace water and vitamins molecules, Mater. Today Chem. 27 (2023). https://doi.org/10.1016/j.mtchem.2022.101292.

[239] S. Nagata, K. Kokado, K. Sada, Metal–organic framework tethering pH- and thermo-responsive polymer for ON–OFF controlled release of guest molecules, CrystEngComm. 22 (2020) 1106–1111. https://doi.org/10.1039/C9CE01731C.

[240] W. Jiang, H. Zhang, J. Wu, G. Zhai, Z. Li, Y. Luan, S. Garg, CuS@MOF-Based Well-Designed Quercetin Delivery System for Chemo–Photothermal Therapy, ACS Appl. Mater. Interfaces. 10 (2018) 34513–34523. https://doi.org/10.1021/acsami.8b13487.

[241] G.J. Doherty, H.T. McMahon, Mechanisms of Endocytosis, Annu. Rev. Biochem. 78 (2009) 857–902. https://doi.org/10.1146/annurev.biochem.78.081307.110540.

[242] J.S. Rodman, A. Wandinger-ness, Rab-GTPases, in: Encycl. Mol. Pharmacol., Springer Berlin Heidelberg, Berlin, Heidelberg, 2008: pp. 1059–1059. https://doi.org/10.1007/978-3-540-38918-7_6574.

[243] H. Stenmark, V.M. Olkkonen, The Rab GTPase family, Genome Biol. 2 (2001) 1–7. https://doi.org/https://doi.org/10.1186/gb-2001-2-5-reviews3007.

[244] S. Behzadi, V. Serpooshan, W. Tao, M.A. Hamaly, M.Y. Alkawareek, E.C. Dreaden, D. Brown, A.M. Alkilany, O.C. Farokhzad, M. Mahmoudi, Cellular uptake of nanoparticles: journey inside the cell, Chem. Soc. Rev. 46 (2017) 4218–4244. https://doi.org/10.1039/C6CS00636A.

[245] E. V. Munsell, N. L. Ross, M. O. Sullivan, Journey to the Center of the Cell: Current

Nanocarrier Design Strategies Targeting Biopharmaceuticals to the Cytoplasm and Nucleus, Curr. Pharm. Des. 22 (2016) 1227–1244. https://doi.org/10.2174/1381612822666151216151420.

[246] L.M. Traub, Regarding the Amazing Choreography of Clathrin Coats, PLoS Biol. 9 (2011) e1001037. https://doi.org/10.1371/journal.pbio.1001037.

[247] M. Kaksonen, A. Roux, Mechanisms of clathrin-mediated endocytosis, Nat. Rev. Mol. Cell Biol. 19 (2018) 313–326. https://doi.org/10.1038/nrm.2017.132.

[248] S. Kumari, S. MG, S. Mayor, Endocytosis unplugged: multiple ways to enter the cell, Cell Res. 20 (2010) 256–275. https://doi.org/10.1038/cr.2010.19.

[249] J. Mercer, A. Helenius, Gulping rather than sipping: macropinocytosis as a way of virus entry, Curr. Opin. Microbiol. 15 (2012) 490–499. https://doi.org/10.1016/j.mib.2012.05.016.

[250] S. Nie, Understanding and overcoming major barriers in cancer nanomedicine, Nanomedicine. 5 (2010) 523–528. https://doi.org/10.2217/nnm.10.23.

[251] A.L. McCall, L.S. Farhy, Treating type 1 diabetes: from strategies for insulin delivery to dual hormonal control., Minerva Endocrinol. 38 (2013) 145–63.

[252] Y. Ding, H. Xu, C. Xu, Z. Tong, S. Zhang, Y. Bai, Y. Chen, Q. Xu, L. Zhou, H. Ding, Z. Sun, S. Yan, Z. Mao, W. Wang, A Nanomedicine Fabricated from Gold Nanoparticles-Decorated Metal–Organic Framework for Cascade Chemo/Chemodynamic Cancer Therapy, Adv. Sci. 7 (2020). https://doi.org/10.1002/advs.202001060.

[253] Y. Duan, F. Ye, Y. Huang, Y. Qin, C. He, S. Zhao, One-pot synthesis of a metal–organic framework-based drug carrier for intelligent glucose-responsive insulin delivery, Chem. Commun. 54 (2018) 5377–5380. https://doi.org/10.1039/C8CC02708K.

[254] X.-X. Yang, P. Feng, J. Cao, W. Liu, Y. Tang, Composition-Engineered Metal–Organic Framework-Based Microneedles for Glucose-Mediated Transdermal Insulin Delivery, ACS Appl. Mater. Interfaces. 12 (2020) 13613–13621. https://doi.org/10.1021/acsami.9b20774.

[255] J. Gandara-Loe, B.E. Souza, A. Missyul, G. Giraldo, J.-C. Tan, J. Silvestre-Albero, MOF-Based Polymeric Nanocomposite Films as Potential Materials for Drug Delivery

Devices in Ocular Therapeutics, ACS Appl. Mater. Interfaces. 12 (2020) 30189–30197. https://doi.org/10.1021/acsami.0c07517.

[256] A. Patel, Ocular drug delivery systems: An overview, World J. Pharmacol. 2 (2013) 47. https://doi.org/10.5497/wjp.v2.i2.47.

[257] S.N. Kim, C.G. Park, B.K. Huh, S.H. Lee, C.H. Min, Y.Y. Lee, Y.K. Kim, K.H. Park, Y. Bin Choy, Metal-organic frameworks, NH2-MIL-88(Fe), as carriers for ophthalmic delivery of brimonidine, Acta Biomater. 79 (2018) 344–353. https://doi.org/10.1016/j.actbio.2018.08.023.

[258] B.M. Jarai, Z. Stillman, L. Attia, G.E. Decker, E.D. Bloch, C.A. Fromen, Evaluating UiO-66 Metal–Organic Framework Nanoparticles as Acid-Sensitive Carriers for Pulmonary Drug Delivery Applications, ACS Appl. Mater. Interfaces. 12 (2020) 38989–39004. https://doi.org/10.1021/acsami.0c10900.

[259] X. Hu, C. Wang, L. Wang, Z. Liu, L. Wu, G. Zhang, L. Yu, X. Ren, P. York, L. Sun, J. Zhang, H. Li, Nanoporous CD-MOF particles with uniform and inhalable size for pulmonary delivery of budesonide, Int. J. Pharm. 564 (2019) 153–161. https://doi.org/10.1016/j.ijpharm.2019.04.030.

[260] N.A. Mohamed, R.P. Davies, P.D. Lickiss, B. Ahmetaj-Shala, D.M. Reed, H.H. Gashaw, H. Saleem, G.R. Freeman, P.M. George, S.J. Wort, D. Morales-Cano, B. Barreira, T.D. Tetley, A.H. Chester, M.H. Yacoub, N.S. Kirkby, L. Moreno, J.A. Mitchell, Chemical and biological assessment of metal organic frameworks (MOFs) in pulmonary cells and in an acute in vivo model: relevance to pulmonary arterial hypertension therapy, Pulm. Circ. 7 (2017) 643–653. https://doi.org/10.1177/2045893217710224.

[261] G. Sotgiu, R. Centis, L. D'ambrosio, G.B. Migliori, Tuberculosis Treatment and Drug Regimens, Cold Spring Harb. Perspect. Med. 5 (2015) a017822–a017822. https://doi.org/10.1101/cshperspect.a017822.

[262] G. Wyszogrodzka-Gaweł, P. Dorożyński, S. Giovagnoli, W. Strzempek, E. Pesta, W.P. Węglarz, B. Gil, E. Menaszek, P. Kulinowski, An Inhalable Theranostic System for Local Tuberculosis Treatment Containing an Isoniazid Loaded Metal Organic Framework Fe-MIL-101-NH2—From Raw MOF to Drug Delivery System, Pharmaceutics. 11 (2019) 687. https://doi.org/10.3390/pharmaceutics11120687.

[263] F. Paladini, M. Pollini, Antimicrobial Silver Nanoparticles for Wound Healing

Application: Progress and Future Trends, Materials (Basel). 12 (2019) 2540. https://doi.org/10.3390/ma12162540.

[264] K.M. Ismayil, A. Varghese, R. Antony, Silver-doped polyaniline–polyvinyl chloride nanocomposite films for photocatalytic and antibacterial applications, J. Elastomers Plast. 52 (2020) 103–116. https://doi.org/10.1177/0095244318819238.

[265] S. Lin, X. Liu, L. Tan, Z. Cui, X. Yang, K.W.K. Yeung, H. Pan, S. Wu, Porous Iron-Carboxylate Metal–Organic Framework: A Novel Bioplatform with Sustained Antibacterial Efficacy and Nontoxicity, ACS Appl. Mater. Interfaces. 9 (2017) 19248–19257. https://doi.org/10.1021/acsami.7b04810.

[266] D.F. Sava Gallis, K.S. Butler, J.O. Agola, C.J. Pearce, A.A. McBride, Antibacterial Countermeasures via Metal–Organic Framework-Supported Sustained Therapeutic Release, ACS Appl. Mater. Interfaces. 11 (2019) 7782–7791. https://doi.org/10.1021/acsami.8b21698.

[267] X. Zhang, L. Liu, L. Huang, W. Zhang, R. Wang, T. Yue, J. Sun, G. Li, J. Wang, The highly efficient elimination of intracellular bacteria via a metal organic framework (MOF)-based three-in-one delivery system, Nanoscale. 11 (2019) 9468–9477. https://doi.org/10.1039/C9NR01284B.

[268] A. Guo, M. Durymanov, A. Permyakova, S. Sene, C. Serre, J. Reineke, Metal Organic Framework (MOF) Particles as Potential Bacteria-Mimicking Delivery Systems for Infectious Diseases: Characterization and Cellular Internalization in Alveolar Macrophages, Pharm. Res. 36 (2019) 53. https://doi.org/10.1007/s11095-019-2589-4.

[269] M. Yu, D. You, J. Zhuang, S. Lin, L. Dong, S. Weng, B. Zhang, K. Cheng, W. Weng, H. Wang, Controlled Release of Naringin in Metal-Organic Framework-Loaded Mineralized Collagen Coating to Simultaneously Enhance Osseointegration and Antibacterial Activity, ACS Appl. Mater. Interfaces. 9 (2017) 19698–19705. https://doi.org/10.1021/acsami.7b05296.

[270] S. Shakya, Y. He, X. Ren, T. Guo, A. Maharjan, T. Luo, T. Wang, R. Dhakhwa, B. Regmi, H. Li, R. Gref, J. Zhang, Ultrafine Silver Nanoparticles Embedded in Cyclodextrin Metal-Organic Frameworks with GRGDS Functionalization to Promote Antibacterial and Wound Healing Application, Small. 15 (2019) 1901065. https://doi.org/10.1002/smll.201901065.

[271] Y. Yang, X. Wu, C. He, J. Huang, S. Yin, M. Zhou, L. Ma, W. Zhao, L. Qiu, C.

Cheng, C. Zhao, Metal–Organic Framework/Ag-Based Hybrid Nanoagents for Rapid and Synergistic Bacterial Eradication, ACS Appl. Mater. Interfaces. 12 (2020) 13698–13708. https://doi.org/10.1021/acsami.0c01666.

[272] H. Zhang, W. Jiang, R. Liu, J. Zhang, D. Zhang, Z. Li, Y. Luan, Rational Design of Metal Organic Framework Nanocarrier-Based Codelivery System of Doxorubicin Hydrochloride/Verapamil Hydrochloride for Overcoming Multidrug Resistance with Efficient Targeted Cancer Therapy, ACS Appl. Mater. Interfaces. 9 (2017) 19687–19697. https://doi.org/10.1021/acsami.7b05142.

[273] M. Cai, W. Liang, K. Wang, D. Yin, T. Fu, R. Zhu, C. Qu, X. Dong, J. Ni, X. Yin, Aperture Modulation of Isoreticular Metal Organic Frameworks for Targeted Antitumor Drug Delivery, ACS Appl. Mater. Interfaces. 14 (2022) 36366–36378. https://doi.org/10.1021/acsami.2c07450.

[274] L. Zhang, Z. Wang, Y. Zhang, F. Cao, K. Dong, J. Ren, X. Qu, Erythrocyte Membrane Cloaked Metal–Organic Framework Nanoparticle as Biomimetic Nanoreactor for Starvation-Activated Colon Cancer Therapy, ACS Nano. 12 (2018) 10201–10211. https://doi.org/10.1021/acsnano.8b05200.

[275] J. Huang, N. Li, C. Zhang, Z. Meng, Metal–Organic Framework as a Microreactor for in Situ Fabrication of Multifunctional Nanocomposites for Photothermal–Chemotherapy of Tumors in Vivo, ACS Appl. Mater. Interfaces. 10 (2018) 38729–38738. https://doi.org/10.1021/acsami.8b12394.

[276] S. Gao, P. Zheng, Z. Li, X. Feng, W. Yan, S. Chen, W. Guo, D. Liu, X. Yang, S. Wang, X.-J. Liang, J. Zhang, Biomimetic O2-Evolving metal-organic framework nanoplatform for highly efficient photodynamic therapy against hypoxic tumor, Biomaterials. 178 (2018) 83–94. https://doi.org/10.1016/j.biomaterials.2018.06.007.

[277] H. Min, J. Wang, Y. Qi, Y. Zhang, X. Han, Y. Xu, J. Xu, Y. Li, L. Chen, K. Cheng, G. Liu, N. Yang, Y. Li, G. Nie, Biomimetic Metal–Organic Framework Nanoparticles for Cooperative Combination of Antiangiogenesis and Photodynamic Therapy for Enhanced Efficacy, Adv. Mater. 31 (2019) 1808200. https://doi.org/10.1002/adma.201808200.

[278] X. Li, S. Sun, G. Wu, X. Che, J. Zhang, Effect of Hydroxyethyl Starch Loading on Glycocalyx Shedding and Cerebral Metabolism During Surgery, J. Surg. Res. 246 (2020) 274–283. https://doi.org/10.1016/j.jss.2019.09.030.

[279] N.A. Mohamed, R.P. Davies, P.D. Lickiss, B. Ahmetaj-Shala, D.M. Reed, H.H. Gashaw, H. Saleem, G.R. Freeman, P.M. George, S.J. Wort, D. Morales-Cano, B. Barreira, T.D. Tetley, A.H. Chester, M.H. Yacoub, N.S. Kirkby, L. Moreno, J.A. Mitchell, Chemical and biological assessment of metal organic frameworks (MOFs) in pulmonary cells and in an acute in vivo model: relevance to pulmonary arterial hypertension therapy, Pulm. Circ. 7 (2017) 643–653. https://doi.org/10.1177/2045893217710224.

[280] P. Wiśniewska, J. Haponiuk, M.R. Saeb, N. Rabiee, S.A. Bencherif, Mitigating metal-organic framework (MOF) toxicity for biomedical applications, Chem. Eng. J. 471 (2023) 144400. https://doi.org/10.1016/j.cej.2023.144400.

[281] Y. JIANG, L. MA, R. LIN, Y. XIONG, S. JIANG, B. LIU, Z.-J. LIU, S. CHEN, Cymbidium codonanthum (Orchidaceae; Epidendroideae; Cymbidiinae), a new species from China: evidence from morphological and molecular analyses , Phytotaxa. 453 (2020) 275–283. https://doi.org/10.11646/phytotaxa.453.3.9.

[282] H. He, H. Han, H. Shi, Y. Tian, F. Sun, Y. Song, Q. Li, G. Zhu, Construction of Thermophilic Lipase-Embedded Metal–Organic Frameworks via Biomimetic Mineralization: A Biocatalyst for Ester Hydrolysis and Kinetic Resolution, ACS Appl. Mater. Interfaces. 8 (2016) 24517–24524. https://doi.org/10.1021/acsami.6b05538.

[283] K. Liang, C.J. Coghlan, S.G. Bell, C. Doonan, P. Falcaro, Enzyme encapsulation in zeolitic imidazolate frameworks: a comparison between controlled co-precipitation and biomimetic mineralisation, Chem. Commun. 52 (2016) 473–476. https://doi.org/10.1039/C5CC07577G.

[284] K. Jiang, L. Zhang, Q. Hu, D. Zhao, T. Xia, W. Lin, Y. Yang, Y. Cui, Y. Yang, G. Qian, Pressure controlled drug release in a Zr-cluster-based MOF, J. Mater. Chem. B. 4 (2016) 6398–6401. https://doi.org/10.1039/C6TB01756H.

[285] M.P. Abuçafy, B.L. Caetano, B.G. Chiari-Andréo, B. Fonseca-Santos, A.M. do Santos, M. Chorilli, L.A. Chiavacci, Supramolecular cyclodextrin-based metal-organic frameworks as efficient carrier for anti-inflammatory drugs, Eur. J. Pharm. Biopharm. 127 (2018) 112–119. https://doi.org/10.1016/j.ejpb.2018.02.009.

[286] V. Agostoni, R. Anand, S. Monti, S. Hall, G. Maurin, P. Horcajada, C. Serre, K. Bouchemal, R. Gref, Impact of phosphorylation on the encapsulation of nucleoside

analogues within porous iron(iii) metal–organic framework MIL-100(Fe) nanoparticles, J. Mater. Chem. B. 1 (2013) 4231. https://doi.org/10.1039/c3tb20653j.

[287] A.S. Spitsyna, A.S. Poryvaev, N.E. Sannikova, A.A. Yazikova, I.A. Kirilyuk, S.A. Dobrynin, O.A. Chinak, M. V. Fedin, O.A. Krumkacheva, Stability of ZIF-8 Nanoparticles in Most Common Cell Culture Media, Molecules. 27 (2022) 3240. https://doi.org/10.3390/molecules27103240.

[288] Y. Liu, C.S. Gong, Y. Dai, Z. Yang, G. Yu, Y. Liu, M. Zhang, L. Lin, W. Tang, Z. Zhou, G. Zhu, J. Chen, O. Jacobson, D.O. Kiesewetter, Z. Wang, X. Chen, In situ polymerization on nanoscale metal-organic frameworks for enhanced physiological stability and stimulus-responsive intracellular drug delivery, Biomaterials. 218 (2019) 119365. https://doi.org/10.1016/j.biomaterials.2019.119365.

[289] M. Ahmadi, S.M. Ayyoubzadeh, F. Ghorbani-Bidkorbeh, S. Shahhosseini, S. Dadashzadeh, E. Asadian, M. Mosayebnia, S. Siavashy, An investigation of affecting factors on MOF characteristics for biomedical applications: A systematic review, Heliyon. 7 (2021) e06914. https://doi.org/10.1016/j.heliyon.2021.e06914.

[290] N. Singh, S. Qutub, N.M. Khashab, Biocompatibility and biodegradability of metal organic frameworks for biomedical applications, J. Mater. Chem. B. 9 (2021) 5925–5934. https://doi.org/10.1039/D1TB01044A.

[291] M.J. Neufeld, B.R. Ware, A. Lutzke, S.R. Khetani, M.M. Reynolds, Water-Stable Metal–Organic Framework/Polymer Composites Compatible with Human Hepatocytes, ACS Appl. Mater. Interfaces. 8 (2016) 19343–19352. https://doi.org/10.1021/acsami.6b05948.

[292] Z. Zhu, S. Jiang, Y. Liu, X. Gao, S. Hu, X. Zhang, C. Huang, Q. Wan, J. Wang, X. Pei, Micro or nano: Evaluation of biosafety and biopotency of magnesium metal organic framework-74 with different particle sizes, Nano Res. 13 (2020) 511–526. https://doi.org/10.1007/s12274-020-2642-y.

[293] S. Liu, L. Kang, J. Zhang, E. Jung, S. Lee, S.C. Jun, Structural engineering and surface modification of MOF-derived cobalt-based hybrid nanosheets for flexible solid-state supercapacitors, Energy Storage Mater. 32 (2020) 167–177. https://doi.org/10.1016/j.ensm.2020.07.017.

[294] J. Zhuang, Y. Duan, Q. Zhang, W. Gao, S. Li, R.H. Fang, L. Zhang, Multimodal Enzyme Delivery and Therapy Enabled by Cell Membrane-Coated Metal–Organic

Framework Nanoparticles, Nano Lett. 20 (2020) 4051–4058. https://doi.org/10.1021/acs.nanolett.0c01654.

[295] Z. Xue, L. Jia, R.R. Zhu, L. Du, Q.H. Zhao, High-performance non-enzymatic glucose electrochemical sensor constructed by transition nickel modified Ni@Cu-MOF, J. Electroanal. Chem. 858 (2020) 113783. https://doi.org/10.1016/j.jelechem.2019.113783.

[296] W. Liu, M. Zou, S. Qin, Y. Cheng, Y. Ma, Y. Sun, X. Zhang, Recent Advances of Cell Membrane-Coated Nanomaterials for Biomedical Applications, Adv. Funct. Mater. 30 (2020) 2003559. https://doi.org/10.1002/adfm.202003559.

[297] S.K. Alsaiari, S.S. Qutub, S. Sun, W. Baslyman, M. Aldehaiman, M. Alyami, A. Almalik, R. Halwani, J. Merzaban, Z. Mao, N.M. Khashab, Sustained and targeted delivery of checkpoint inhibitors by metal-organic frameworks for cancer immunotherapy, Sci. Adv. 7 (2021) 1–11. https://doi.org/10.1126/sciadv.abe7174.

[298] N.C. Burtch, H. Jasuja, K.S. Walton, Water Stability and Adsorption in Metal–Organic Frameworks, Chem. Rev. 114 (2014) 10575–10612. https://doi.org/10.1021/cr5002589.

[299] L. Bellarosa, S. Calero, N. López, Early stages in the degradation of metal–organic frameworks in liquid water from first-principles molecular dynamics, Phys. Chem. Chem. Phys. 14 (2012) 7240. https://doi.org/10.1039/c2cp40339k.

[300] E. Bellido, M. Guillevic, T. Hidalgo, M.J. Santander-Ortega, C. Serre, P. Horcajada, Understanding the Colloidal Stability of the Mesoporous MIL-100(Fe) Nanoparticles in Physiological Media, Langmuir. 30 (2014) 5911–5920. https://doi.org/10.1021/la5012555.

[301] T. Faust, MOFs deliver, Nat. Chem. 7 (2015) 270–271. https://doi.org/10.1038/nchem.2229.

[302] M. Wu, Y. Yang, Metal–Organic Framework (MOF)-Based Drug/Cargo Delivery and Cancer Therapy, Adv. Mater. 29 (2017) 1–20. https://doi.org/10.1002/adma.201606134.

[303] V.P. Santos, T.A. Wezendonk, J.J.D. Jaén, A.I. Dugulan, M.A. Nasalevich, H.-U. Islam, A. Chojecki, S. Sartipi, X. Sun, A.A. Hakeem, A.C.J. Koeken, M. Ruitenbeek, T. Davidian, G.R. Meima, G. Sankar, F. Kapteijn, M. Makkee, J. Gascon, Metal

organic framework-mediated synthesis of highly active and stable Fischer-Tropsch catalysts, Nat. Commun. 6 (2015) 6451. https://doi.org/10.1038/ncomms7451.

[304] X. Li, L. Lachmanski, S. Safi, S. Sene, C. Serre, J.M. Grenèche, J. Zhang, R. Gref, New insights into the degradation mechanism of metal-organic frameworks drug carriers, Sci. Rep. 7 (2017) 13142. https://doi.org/10.1038/s41598-017-13323-1.

[305] E. Bellido, T. Hidalgo, M.V. Lozano, M. Guillevic, R. Simón-Vázquez, M.J. Santander-Ortega, Á. González-Fernández, C. Serre, M.J. Alonso, P. Horcajada, Heparin-Engineered Mesoporous Iron Metal-Organic Framework Nanoparticles: Toward Stealth Drug Nanocarriers, Adv. Healthc. Mater. 4 (2015) 1246–1257. https://doi.org/10.1002/adhm.201400755.

[306] S. Li, Y. Chen, X. Pei, S. Zhang, X. Feng, J. Zhou, B. Wang, Water Purification: Adsorption over Metal-Organic Frameworks, Chinese J. Chem. 34 (2016) 175–185. https://doi.org/10.1002/cjoc.201500761.

[307] W. Li, X. Xia, M. Cao, S. Li, Structure–property relationship of metal–organic frameworks for alcohol-based adsorption-driven heat pumps via high-throughput computational screening, J. Mater. Chem. A. 7 (2019) 7470–7479. https://doi.org/10.1039/C8TA07909A.

[308] M.F. de Lange, K.J.F.M. Verouden, T.J.H. Vlugt, J. Gascon, F. Kapteijn, Adsorption-Driven Heat Pumps: The Potential of Metal–Organic Frameworks, Chem. Rev. 115 (2015) 12205–12250. https://doi.org/10.1021/acs.chemrev.5b00059.

[309] P. Kumar, B. Anand, Y.F. Tsang, K.-H. Kim, S. Khullar, B. Wang, Regeneration, degradation, and toxicity effect of MOFs: Opportunities and challenges, Environ. Res. 176 (2019) 108488. https://doi.org/10.1016/j.envres.2019.05.019.

[310] X. Chen, Y. Zhuang, N. Rampal, R. Hewitt, G. Divitini, C.A. O'Keefe, X. Liu, D.J. Whitaker, J.W. Wills, R. Jugdaohsingh, J.J. Powell, H. Yu, C.P. Grey, O.A. Scherman, D. Fairen-Jimenez, Formulation of Metal–Organic Framework-Based Drug Carriers by Controlled Coordination of Methoxy PEG Phosphate: Boosting Colloidal Stability and Redispersibility, J. Am. Chem. Soc. 143 (2021) 13557–13572. https://doi.org/10.1021/jacs.1c03943.

[311] W. Morris, S. Wang, D. Cho, E. Auyeung, P. Li, O.K. Farha, C.A. Mirkin, Role of Modulators in Controlling the Colloidal Stability and Polydispersity of the UiO-66 Metal–Organic Framework, ACS Appl. Mater. Interfaces. 9 (2017) 33413–33418.

https://doi.org/10.1021/acsami.7b01040.

[312] J. Schubert, M. Chanana, Coating Matters: Review on Colloidal Stability of Nanoparticles with Biocompatible Coatings in Biological Media, Living Cells and Organisms, Curr. Med. Chem. 25 (2018) 4553–4586. https://doi.org/10.2174/0929867325666180601101859.

[313] N. Yanai, S. Granick, Directional Self-Assembly of a Colloidal Metal–Organic Framework, Angew. Chemie Int. Ed. 51 (2012) 5638–5641. https://doi.org/10.1002/anie.201109132.

[314] M. Sindoro, N. Yanai, A.-Y. Jee, S. Granick, Colloidal-Sized Metal–Organic Frameworks: Synthesis and Applications, Acc. Chem. Res. 47 (2014) 459–469. https://doi.org/10.1021/ar400151n.

Metal Organic Frameworks in Biomedicine: Innovations in Drug Delivery

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Declaration of interests

☒ The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

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Graphical Abstract