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Metal-organic frameworks in oral drug delivery

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ABSTRACT

Metal-organic frameworks (MOFs) offer innovative solutions to the limitations of traditional oral drug delivery systems through their unique combination of metal ions and organic ligands. This review systematically examines the structural properties and principles of MOFs, setting the stage for their application in drug delivery. It discusses various classes of MOFs, including those based on zirconium, iron, zinc, copper, titanium, aluminum, potassium, and magnesium, assessing their drug-loading capacities, biocompatibility, and controlled release mechanisms. The effectiveness of MOFs is illustrated through case studies that highlight their capabilities in enhancing drug solubility, providing protection against the harsh gastrointestinal environment, and enabling precise drug release. The review addresses potential challenges, particularly the toxicity concerns associated with MOFs, and calls for further research into their biocompatibility and interactions with biological systems. It concludes by emphasizing the potential of MOFs in revolutionizing oral drug delivery, highlighting the critical need for comprehensive research to harness their full potential in clinical applications.

1. Introduction

Advancements in medical sciences rely not only on discovering new drugs but also on the innovation of effective delivery systems for these therapeutic agents [1,2]. Drug delivery systems (DDS) are essential in ensuring that medications are delivered to the correct part of the body, at the right time, and at the proper dosage [3,4]. Metal-organic frameworks (MOFs) are at the forefront of this innovation. MOFs are constructed by integrating metal nodes with organic linkers to form highly porous structures suitable for drug delivery (Fig. 1) [5]. Examples include Zr-MOF (UiO-66) and Fe-MOF (PCN-600), which demonstrate significant stability and functionality (Fig. 1). These frameworks, including others like Zn-MOF (ZIF-8) and Mg-MOF (MOF-74), are tailored for specific applications due to their adjustable properties such as pore size and chemical functionality (Fig. 1) [5,6]. However, why metals and organics? The fusion of metal nodes with organic linkers is pivotal. Metals provide rigidity, ensuring that the framework is stable. Meanwhile, the organic components bring functionality and flexibility [5,6]. Hence, the way these

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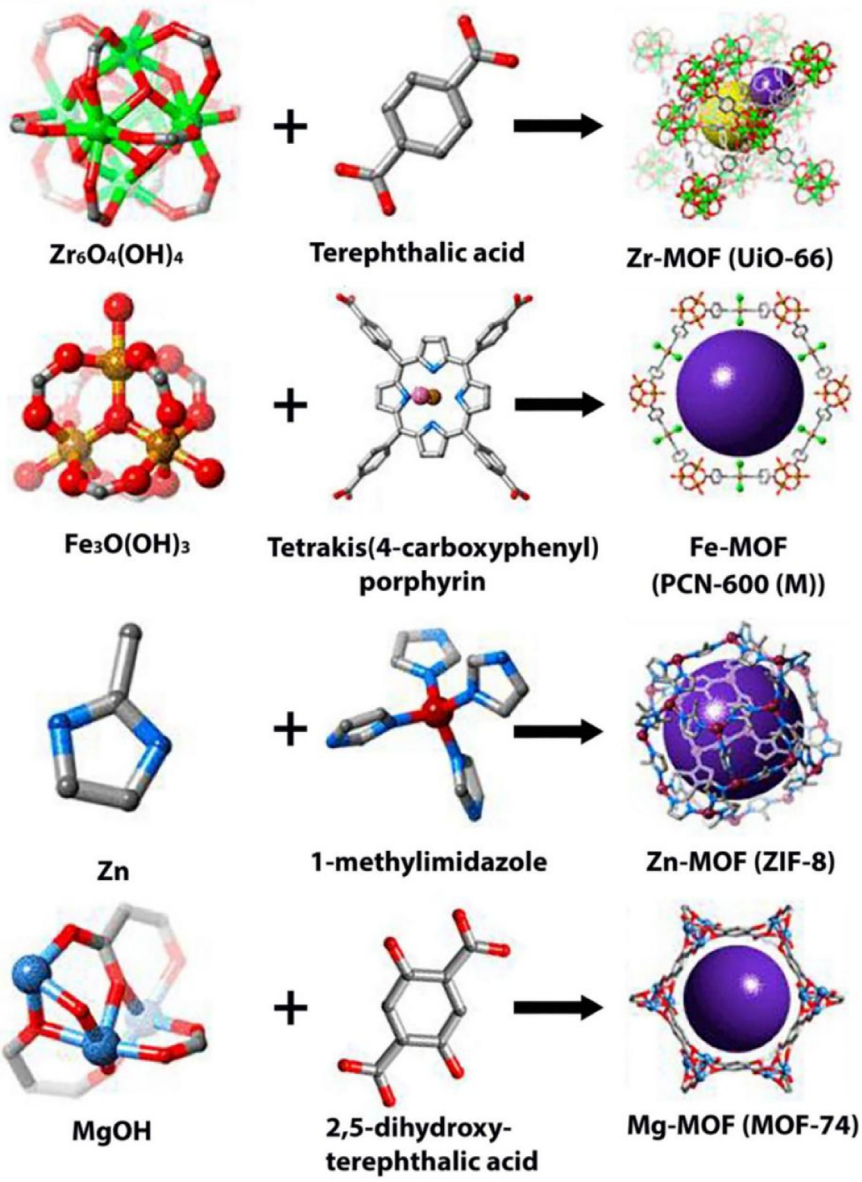

Fig. 1 – Schematic representation of the synthesis of various MOFs, where metal clusters such as $Zr_6O_4(OH)_4$ and $Fe_3O(OH)_3$ are intricately combined with organic linkers such as H_2BDC and TCPP. The resulting structures include cubic Zr-MOF (UiO-66), known for its robustness, and porphyrin-incorporated Fe-MOF (PCN-600 (M)), illustrating the versatility and functional adaptability of MOFs. Additionally, ZIF-8 and MOF-74 exemplify the synthesis of frameworks with exceptional thermal stability and gas adsorption properties using 1-methylimidazole and 2,5-dihydroxy-terephthalic acid as linkers, respectively. Reproduced with permission from [6]; Copyright 2017 ACS.

metals and organic groups connect gives MOFs their unique, robust and porous structure, making them valuable in many applications [6,7].

Since their introduction in 1989 by Hoskins and Robson [8], MOFs, also recognized as coordination polymers, have garnered significant attention. Fast forward to 2006, Horcajada and his colleagues pioneered the concept of employing MOF nanoparticles (MOF-NPs) for drug delivery [9]. In their groundbreaking study, they utilized two chromium (Cr)-based MOFs, MIL-100 and MIL-101. Impressively, these MOFs encapsulated up to 1.4 g ibuprofen (IBU) per gram and showcased a controlled release over 3 to 6 d for MIL-100 and MIL-101, respectively [9]. This innovation opened the door to a myriad of medical applications for MOFs, ranging from gas delivery for wound healing [10-12] to advanced sensing techniques [12,13].

Oral administration is preferred for its simplicity and convenience for patients [1,14], yet it faces challenges like drug stability under acidic stomach conditions and poor drug bioavailability due to water solubility issues [15,16]. Unlike traditional delivery systems such as micelles, liposomes, silica, and polymeric nanoparticles, MOFs distinguish

themselves with their high surface area and customizable properties. These features position MOFs as promising agents to revolutionize oral drug delivery [15,17-23]. Additionally, the physical and chemical attributes of MOFs can be readily customized through modifications to pore size and shape, as well as alterations to the chemical properties, achieved by manipulating inorganic clusters and organic ligands [24-26]. Given their porous nature, MOFs can encapsulate drug molecules to enhance solubility, protect against the harsh digestive environment, and ensure sustained release, effectively addressing many challenges associated with oral drug administration [2,27-30].

However, the excitement surrounding MOFs is not only tempered by their own inherent set of challenges but also by the challenges presented by the highly acidic environment of the body [31,32]. Their very high porosity, which is usually beneficial, can also make them somewhat brittle and not always stable, especially when they come into contact with water or in the acidic pH of the stomach [32-35]. In such acidic environments, the protonation of organic linkers and metal leaching can lead to MOF degradation, compromising their structural integrity and functionality. This means that while MOFs have considerable potential for different uses, they need to be carefully checked to ensure that they are suitable for specific purposes.

Therefore, as with any emerging scientific innovations, MOFs introduce a series of questions and considerations. Are they safe for human consumption? How do they fare in terms of toxicity? Can the lab successes with MOFs be scaled up to meet the pharmaceutical industry's demands? And, importantly, where do they fit within the complex regulatory landscapes? The transition of MOFs from lab to clinical use presents challenges but holds transformative potential for patient care. MOFs enhance drug delivery, allowing oral administration of drugs otherwise unsuitable due to digestive instability, thus improving patient adherence and health outcomes [36]. While exploring their potential, it is crucial to address the challenges traditional oral DDSs face, such as poor drug solubility, instability in the digestive tract, and low bioavailability.

In conclusion, this review on MOFs in advanced oral DDSs positions us at the threshold of a potentially transformative era in pharmaceutical sciences. Through this exploration, we aim to shed light on the opportunities MOFs present and the challenges that must be overcome to make a significant impact in the field of oral drug delivery.

2. Advantages of MOFs in oral drug delivery

Addressing these challenges, MOFs offer cutting-edge advantages for oral drug delivery. With high drug-loading capacities, controlled release mechanisms, and protection from harsh gastrointestinal (GI) conditions, MOFs enhance the efficacy and precision of oral therapeutics. Their tunable structures promise not only enhanced bioavailability but also tailored drug delivery strategies, marking them as significant advancements in medical technology [36]. Hence, the advantageous properties of MOFs for oral drug delivery are diverse and impactful, some of which are discussed below.

2.1. *High loading capacity*

High drug loading capacities (LC) stand out as a pivotal advantage of MOFs in the context of oral drug delivery (Table 1). This attribute stems from their highly porous structure, which provides an extensive surface area and volume to accommodate pharmaceutical compounds. Unlike conventional drug carriers, MOFs can encapsulate a larger amount of drug molecules within their pores and onto their surfaces. Studies have demonstrated that MOFs show a Brunauer–Emmett–Teller (BET) surface area ranging from 1,000 to 7,000 m^2/g, which is markedly higher than the 700 to 1,200 m^2/g range seen in mesoporous silica [37]. Complementing the surface area, the pore volume of MOFs ranges from 1.04 to 4.40 cm^3/g, dwarfing the 0.6 to 2 cm^3/g offered by mesoporous silica [37]. In regard to the practical aspect of drug loading, MOFs demonstrate a superior insulin (INS) LC of 350 to 397 mg/g, a considerable improvement over the 261 mg/g LC of mesoporous silica [2,38,39]. In summary, MOFs exhibit superior performance across all three metrics when compared to mesoporous silica, with a minimum of approximately 1.34 times to a maximum of approximately 6 times better in terms of surface area, pore volume, and drug LC. Moreover, the charge of the metal ions can facilitate electrostatic interactions with drug molecules, especially if the drug is ionized. Positively charged metals can interact with negatively charged drug molecules and *vice versa*, which can affect the loading and release behaviors of the drug [40]. The zinc-based MOF (Zn- MOF), ZJU-64-NSN, anointed with an anionic network rich in thiadiazole groups, demonstrates a potent affinity for the cationic drug procainamide (PA), facilitating ultrafast PA loading of 21.2 wt% in merely 1 min [30]. This rapid loading is indicative of the strong ionic interactions between the drug and the MOF. Therefore, these advantages maximize the efficiency of each dosage by delivering more therapeutic agent per unit volume, potentially reducing the frequency of dosing and improving patient compliance. Furthermore, the ability to load significant quantities of drugs into MOFs means that smaller and fewer pills or capsules may be needed, which can enhance patient comfort and adherence to treatment regimens. Hence, this immense internal surface area, combined with the material's customizable nature, makes MOFs a playground for chemists. By selecting different metals and organic ligands or by post-synthesis modification, scientists can tailor-make MOFs for specific applications [27,41].

2.2. *Controlled and sustained drug release*

MOFs can be engineered to degrade or change structure at specific pH levels, releasing their payloads only in certain environments (such as the less acidic pH of the intestines, as opposed to the stomach). This can be used to protect drugs that are sensitive to stomach acid and to ensure release at the intended site of absorption (Table 1). In a study, the efficacy of a zirconium (Zr)-based MOF (NU-1000) as a carrier for oral INS delivery was evaluated [2]. The encapsulated INS@NU-1000 was exposed to both gastric acid (pH 1.29) and neutral

Table 1 – Key properties of MOFs enhancing oral drug delivery.

Property	Feature	Details	Ref.
High Loading Capacity	Various MOFs	ZJU-64-NSN: 21.2 wt% in 1 min	[30]
		GEN@MIL-100: 27.1 wt%	[46]
		IBUNa@UiO-66-PDC: 27.60 wt%	[19]
Controlled and Sustained Release	Controlled Release	NU-1000: 10% release at pH 1.29; 91% at pH 7.0	[2]
		UiO-66-PDC: Minimal release at pH 2.0; near-complete at pH 7.4	[19]
	pH-Responsive Release	ZJU-64-NSN- 20% release at pH 2.0; 70% at pH 7.4 in 10 h	[30]
Protection from GI Environment	Al-MOF for OVA	Al-MOF: Retains 90% activity, withstands GI fluids	[45]
	Ti-nanoMOF for aspirin	Ti-nanoMOF: Maintains structural integrity under GI conditions	[44]
Protection from GI Environment	Al-MOF	Retains 90% activity, withstands GI fluids	[45]
	Ti-nanoMOF	Maintains structural integrity under GI conditions	[44]

(pH 7.0) solutions, representing the stomach environment and physiological conditions, respectively [2]. The results, ascertained through UV–visible spectroscopy, indicated that only 10% of INS was released in the acidic condition after 1 h, suggesting robust protection by NU-1000 [2]. In contrast, under neutral conditions, a substantial release of 91% was observed, signaling the degradation of NU-1000 and subsequent INS release. These outcomes underscore the potential of NU-1000 as an oral INS delivery system, offering protection in the stomach and targeted release in the bloodstream [2].

The pH-responsive drug delivery capability of ibuprofen sodium (IBUNa) into a Zr-MOF (UiO-66-PDC) was explored by monitoring its drug release in PBS at pH 2.0 and 7.4, approximating stomach and intestinal conditions, respectively, at 37 °C [19]. At an acidic pH of 2.0, mimicking stomach conditions, the drug release was minimal, with only approximately 10% of the drug being released. This can be attributed to the protonation of the pyridine heterocyclic rings in the framework, leading to electrostatic interactions that tightly hold the anionic drug IBUNa [19]. At a neutral pH of 7.4, representative of the intestinal environment, the drug release was significantly accelerated, with most of the drug being released within the first few hours and nearing completion after 72 h. The shift to a neutral pH results in deprotonation, which diminishes the electrostatic attractions and allows for the efficient release of the drug [19]. This differential release pattern exhibits a pronounced pH-responsive drug delivery capability of UiO-66-PDC within the digestive system, highlighting its promising potential as an oral drug delivery vehicle.

Metal ion charges can influence drug interactions and release behaviors. For example, the ZJU-64-NSN, with its anionic thiadiazole-rich network, shows a strong affinity for the cationic drug PA [30]. Notably, in an acidic environment with a pH 2.0, the release of PA was substantially inhibited, with only ~20% of the drug released after 50 h, demonstrating the interaction's resilience in gastric-like conditions [30]. In contrast, a neutral pH 7.4 resulted in a marked increase in the release rate, with over 70% PA release in the initial 10 h, underscoring a pH-responsive release ideal for drug delivery in the intestinal region [30]. These findings highlight the potential of MOFs in delivering drugs effectively at specific sites within the body, harnessing pH differences for targeted therapy.

2.3. *Protection from the harsh GI environment*

The GI tract presents several challenges, including acidic pH in the stomach and the presence of enzymes that can degrade drugs before they reach their absorption sites in the intestine. To enhance MOF stability in the GI tract, some studies (Table 1) have synthesized stable MOFs with hard bases (*e.g.*, carboxylate-based ligands) and high-valent metal ions (*e.g.*, Zr^{4+}, Ti^{4+}, Fe^{3+}, and Al^{3+}) [42-45]. In this way, MOFs provide a protective environment for drugs as they pass through the harsh GI tract, which is essential for oral drug delivery. MOFs can encapsulate drugs within their pores, shielding them from acidic conditions and enzymatic degradation. The stability of MOFs under different pH conditions allows drugs to remain intact in the stomach. In a study, an aluminum-based MOF (Al-MOF) was utilized to encapsulate ovalbumin (OVA), a model antigen, for oral vaccination. This Al-MOF system was designed to protect OVA from degradation in the stomach's acidic environment and from denaturation by digestive enzymes, facilitating its intact delivery to the intestine for effective immunization [45]. The study revealed that these Al-MOFs exhibited exceptional stability, retaining approximately 90% of β-galactosidase activity over nine weeks across variable temperatures, thus eliminating the necessity for refrigeration [45]. Furthermore, the OVA@Al-MOFs withstand the harsh conditions of simulated GI fluids, maintaining their structural and functional integrity, which underscores their efficacy in protecting antigens during GI passage [45]. In another study, a titanium-based MOF (Ti-nanoMOF), specifically tetragonal titanium (IV) aminoterephthalate MIL-125-NH_2, was evaluated for its potential as an efficient oral therapeutic agent for the detoxification of salicylate (aspirin) intoxication [44]. The Ti-nanoMOF was then characterized for stability under simulated GI tract conditions. MIL-125-NH_2 retains its crystalline structure and microporosity when subjected to conditions that mimic the human GI tract [44]. When tested in gastric media (HCl, pH 1.2 at 37 °C for 2 h), followed by intestinal conditions (simulated intestinal media, SIF; pH 6.8 at 37 °C for 24 h), MIL-125-NH_2 maintained its structural integrity [44]. The results were confirmed through powder X-ray diffraction (PXRD) of the recovered GI contents, which showed that MIL-125-NH_2 possesses a remarkably high stability, retaining its crystalline structure throughout the GI tract after 24 h [44].

Furthermore, the protective capabilities of MOFs can be tailored through the choice of metal ions and organic linkers that construct the framework. Some MOFs can also take advantage of pH-responsive linkers that respond to pH changes as the MOF moves from the stomach to the intestine, triggering the release of the drug at the desired location. In the present study, the synthesis of a zirconium-based MOF (Zr-MOF), designated UiO-66-PDC, was accomplished utilizing the ligand H_2PDC (2,5-pyridinedicarboxylic acid) [19]. Remarkably, the structural composition of UiO-66-PDC remained robust, exhibiting no significant degradation after prolonged exposure to aqueous conditions for 5 d. The encapsulation of the anti-inflammatory agent IBUNa into the MOF matrix was achieved with a drug LC quantified at 27.60 wt%, referred to as IBUNa@UiO-66-PDC [19]. A pH-responsive release profile was observed, with preferential release in an intestinal simulated environment (pH 7.4) over a gastric simulated environment (pH 2.0). This differential release characteristic highlights the potential of UiO-66-PDC for targeted drug delivery in oral administration applications [19].

In summary, MOFs serve as a versatile platform for oral drug delivery by offering protection from the acidic and enzymatic environment of the GI tract, ensuring that drugs are released in a controlled manner at the site where their absorption is maximized and minimizing potential gastric side effects.

2.4. *Enhanced drug solubility and bioavailability*

MOFs, with their unique porous structure and high surface area, offer significant advantages in enhancing the solubility and bioavailability of orally administered drugs, particularly for those with poor water solubility (Table 1). Encapsulating these drugs in MOFs increases their dissolution rate in GI fluids, thereby improving oral bioavailability. A study by Botet-Carreras et al. [46] focused on encapsulating genistein (GEN), a bioflavonoid with anticancer properties, within MIL-100 (Fe) nanoparticles. This approach achieved a drug loading of 27.1 wt% and resulted in a 62-fold increase in bioavailability compared to free GEN. Additionally, the GEN@MIL-100 formulation boosted the drug's plasma levels by 12-fold, increased the mean residence time (MRT) by 4-fold, and extended the drug half-life by 5.5-fold compared to free GEN [46]. Similarly, the use of UiO-66(Zr) was explored for magnolol, a bioactive compound with low solubility [47]. The encapsulation within UiO-66 (Zr) more than doubled the relative bioavailability of magnolol, with significant improvements in the area under the curve (AUC) and a marked increase in systemic drug presence over time [47]. These MOFs also allow for controlled drug release, which is beneficial for hydrophobic drugs. The gradual release of drugs in the stomach and intestines enhances absorption. Moreover, MOFs can be engineered for optimal drug-MOF interactions through hydrogen bonds, π-π stacking, and electrostatic forces. Specifically, UiO-66 (Zr) demonstrated a high drug LC for magnolol of 72.16% $\pm$ 2.15% after 36 h [47].

In summary, MOFs can revolutionize oral drug delivery by increasing the solubility of poorly soluble drugs, protecting them from the gastric environment, and controlling their release rate, all of which contribute to enhanced bioavailability and therapeutic efficacy.

3. Exploring MOFs in oral drug delivery

The advancement of materials science has been significantly enriched by MOFs, crystalline materials known for their unique composition of organic ligands and metal ions. These structures, notable for their diversity and functionality, are increasingly relevant in oral drug delivery. MOFs offer a versatile platform for drug encapsulation and controlled release, with a focus on enhancing bioavailability and targeted delivery. This exploration delves into various MOFs designed for oral use from 2018 to 2023, examining their structural features and the innovative methods used to improve drug therapies, thereby highlighting their potential to revolutionize oral medication efficacy and precision.

3.1. *Zr-MOFs*

In 2008, a pioneering study by Lillerud et al. introduced a novel class of Zr-MOFs [48]. Among these, the UiO series, which takes its name from the University of Oslo, has been particularly noteworthy. These structures are composed of $[Zr_6O_4(OH)_4(RCO_2)_{12}]$ clusters that form octahedral shapes, which are linked by linear dicarboxylate ligands to create expansive, porous networks [49,50]. Typically, represented by the formula $[Zr_6O_4(OH)_4(L)_6]$n, where 'L' represents the organic linkers, these frameworks are distinguished by their Zr_6 clusters. These clusters, along with their variations, have become a staple as inorganic secondary building units (SBUs) in the design and development of a broad spectrum of Zr-MOFs that have been reported in the literature since their discovery [49,50]. In the study of Zr-MOFs, researchers have successfully synthesized frameworks that incorporate three or four carboxylate groups in their linkers. For instance, the use of a flat linker known as tetrakis(4-carboxyphenyl)porphyrin (TCPP) with Zr_6 building units leads to the creation of structures such as PCN-223 and PCN-224, depending on the connectivity of the Zr_6 units [51,52]. Similarly, a compound called 1,3,6,8-tetrakis(p-benzoate)pyrene, when connected with Zr_6 units, forms structures known as NU-901 and NU-1000 [53]. The robust Zr-O bonds and the durability of their SBUs endow Zr-MOFs with remarkable chemical, thermal, and aqueous stability [50]. This stability, coupled with their structural versatility, has resulted in the discovery of different types of Zr-MOFs, each with potential utility in various applications [49,50]. The biocompatibility of zirconium, which naturally occurs in the human body at an average of 300 mg and with a recommended daily intake of 4.15 mg [29,54], has stimulated increased academic research into the use of Zr-MOFs for biomedical purposes. However, the scope of this review is specifically tailored to examine Zr-MOFs (Table 2) that have been utilized in the context of oral drug delivery.

The two studies present advancements in the field of Zr-MOFs for oral INS delivery, each utilizing the unique properties of Zr-MOFs to overcome the challenges associated with the oral administration of INS. In a study conducted

Table 2 – MOFs in oral drug delivery: types and case studies (2018–2023).

Materials	Year	Drug	Drug loading method	DrugLE/ LC	Release kinetics	Stability	Biocompatibility and safety	Key findings	Conclusion/ implications	Refs
NU-1000 (Zr-based)	2018	INS	Simple immersion	40 wt%	Slow degradation in bloodstream simulation, 10% release in stomach acid	Stable in simulated stomach and bloodstream conditions	Not mentioned	High INS loading, protects in stomach acid, retains activity	Potential for oral INS delivery	[2]
UiO-66 (Zr-based)	2020	Magnolol	Simple impregnation	72.16% ± 2.15% at 36 h	Not mentioned	Not mentioned	No toxicity at 2,000 mg/kg in rats	Higher bioavailability with Uio-66(Zr) carrier	Potential carrier for poorly soluble drugs	[47]
UiO-66, UiO-66-NH_2, UiO-66-COOH, UiO-67, Zr-NDC and CS	2020	FU	Simple immersion	66.28% in Zr-NDC	Limited release in acidic environment, significant in intestinal fluid	Improved stability with CS coating	Not mentioned	Controlled release, enhanced oral bioavailability of 5-FU	Effective for oral administration of FU	[55]
UiO-66-PDC (Zr-based)	2021	IBUNa	Simple immersion	27.60 wt%	pH-responsive, 10% release at pH 2.0, complete in 72 h at pH 7.4	Excellent stability in water for 5 d	Increased toxicity	pH-responsive release in the digestive system	Promising for oral drug delivery in varying pH	[19]
UiO-68-NH_2 (Zr-based)	2022	INS	Simple immersion	LC: 33 wt%	<20% release in 24 h in GI conditions, complete release in 10–12 h in PBS	Strong acid-proof stability	No noticeable side effects or toxicity in diabetic rats	Protective environment, transferrin coating enhances intestinal transport	Effective for oral INS delivery with high bioavailability	[42]
UiO-66 (Zr-based)	2023	Captopril/IBU	Simple immersion	LE, Captopril: 99.78%, IBU: 96.65%	Slower release rates in an acidic medium than phosphate buffer	Stable across pH 1 to 11	Not mentioned	Enhanced loading capacity, modulated release rate by pH	Effective for drug delivery, especially water-soluble drugs	[29]
MIL-127 (Fe-based)	2018	Aspirin (ASA)	Contact with different ASA concentrations	LC: ~0.14 g/g	No release of salicylates after medium change	Exceptional GI stability	Good biocompatibility, safe in ASA overdose	Significant reduction in GI absorption of salicylates	Efficient for oral detoxification	[60]
MIL-100 (Fe-based)	2020	INS	Simple immersion	LC: 4.6% LE: 77.1%.	Protected from rapid degradation in acidic conditions, released in simulated intestinal fluid	Resistant to gastric acid environment	Over 80% viability of Caco-2 cells after 48 h	Increased intestinal absorption in mice, enhanced plasma INS levels in rats	New strategy for effective oral protein delivery	[39]

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Table 2 (*continued*)

Materials	Year	Drug	Drug loading method	DrugLE/ LC	Release kinetics	Stability	Biocompatibility and safety	Key findings	Conclusion/ implications	Refs
NH_2_MIL101 (Fe-based)	2021	Exendin-4	Simple immersion	LC: 40.2%; LE: 87% ± 1.7%	Mainly diffusion and disintegration of nanoparticles	Not explicitly mentioned	Tested against Caco-2 and E12 cells, showing biocompatibility	Higher movement ability in mucin, zwitterionic nature aids mucus transportation	Promising for oral delivery of exendin-4, potential in diabetes treatment	[59]
MIL-100 (Fe-based)	2021	GEN	Simple impregnation	LC: 27.1 wt%	Burst release in first 30 min, then over 3 d	Assessed under simulated physiological conditions	Not mentioned	Improved oral bioavailability, prolonged drug release	Enhances oral bioavailability of GEN, potential in antitumor treatments	[46]
MIL-88B (Fe-based)	2022	NO from DNIC-2	Post-synthetic modification	Not mentioned	Burst release in first 30 min, followed by progressive delivery	pH-dependent decomposition, protected under acidic conditions	Over 80% viability of human intestinal cells	Improved oral bioavailability, effective blood pressure reduction	Promising for enhanced oral delivery of NO, improved bioavailability	[43]
MOF-5 (Zn-based)	2020	5-FU	Simple immersion	LE: 84.1%	Sustained release in GIT conditions	Not explicitly mentioned	Toxicity against HeLa cells	CMC-coated 5-FU@MOF-5 showed sustained release and notable toxicity against HeLa cells	Potential for colonic administration of 5-FU	[67]
ZJU-64-NSN (Zn-based)	2022	PA	Simple immersion	LC: 21.2 wt%	Enhanced stability with PEG coating, targeted intestinal release	Improved chemical stability with PEG coating	Not explicitly mentioned	Fast loading and controlled release of PA in the targeted intestinal surroundings	Effective for oral drug delivery, particularly for PA	[30]
Zn-MOF with Sodium Alginate	2022	siRNA targeting TNFα	Encapsulation in MOF and sodium alginate hydrogel	Not mentioned	Designed to prevent premature release in GI environment	Survives low pH environment in stomach and small intestine	Uptake by macrophages, cell viability assessed	Significant reduction in progression of colitis in mice	Improves protection and enhances delivery of MOF-siRNA to the colon for UC treatment	[68]
CMC/Cu-MOF@IBU	2018	IBU	Simple immersion	LE: 93.0%, LC: 279.2%	Controlled release in GIT conditions	High stability for drug dosing over an extended period	Low cytotoxicity to Caco-2 cells	Controlled drug release and high stability in intestinal tract conditions	Effective controlled DDS for oral administration of IBU	[77]

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Table 2 (*continued*)

Materials	Year	Drug	Drug loading method	DrugLE/ LC	Release kinetics	Stability	Biocompatibility and safety	Key findings	Conclusion/ implications	Refs
Cu-MOF	2019	IBU	Simple immersion	LC: 48.19 wt%	Sustained release in GIT conditions	Better protection against stomach pH	Low toxicity against Caco-2 cells	Efficient controlled drug delivery in GIT conditions	Potential oral DDS for IBU	[20]
IITI-3 (Cu-MOF)	2023	INS	Loaded into IITI-3 and modified with gelatin	LC: 20 wt%	Studied under different pH conditions	Stable in biological fluid pH ranges from 3 to 10	Good biocompatibility and hemocompatibility	Stability across a wide pH range, suitable for GI conditions	Promising for controlled INS delivery, potential in oral delivery systems	[78]
Ti-based MOFs with TEOS	2018	IBU	Resolving IBU into n-hexane solution and adding MOFs	LC: ~10 wt%	95% release in 24 h in PBS	Observed stability after 48 h in PBS at 37 °C	Good biocompatibility with L929 cell lines	Effective size reduction and controlled drug release	Potential as drug carriers with good biocompatibility and controlled release	[84]
MIL-125-NH_2 (Ti-nanoMOF)	2019	ASA	Adsorption in MIL-125-NH_2	High ASA adsorption capacity of 2.59 mol/mol	Controlled release in GI tract	High stability in GI tract conditions	Safe, protective effect against ASA overdose	Outperformed Norit@activated carbon in ASA detoxification	Promising oral therapeutic agent for ASA detoxification	[44]
Al-MOF	2019	OVA	Encapsulation *in situ* in Al-MOF crystals	LC: 14.7% ± 1.3%, LE: 94.1% ± 4.8%	Sustained release over approximately 7 d	Extraordinary stability in normal saline and harsh GI conditions	Utilized yeast capsules for transport across the intestinal epithelium	Al-MOFs provided significant protection and facilitated transport of OVA	Promising strategy for oral administration of vaccines, offering protection and effective transport	[45]
K-based CD-MOFs	2021	IMC	Dissolution in anhydrous ethanol and loading into CD-MOF	40.2% in CD-MOF, increased to 94.0% when encapsulated with Eudragit® RS	Higher dissolution rate for IMC/CD-MOF; reduced initial burst release after encapsulation	Eudragit® RS encapsulation regulates release rate and potentially offers protection	CD-MOF nanocrystals showed higher dissolution rate than raw IMC; encapsulation reduced burst release	Promising for sustained drug release, especially for poorly soluble drugs	γ-CD-MOF	[107]
Mg-MOF-74	2023	IBU, 5-FU, Curcumin	Wet-impregnation	LC: 30, 50, and 80 wt%, respectively.	Direct function of drug solubility and molecular size	High stability in GI tract conditions	Not mentioned	High solubility and small molecular size lead to faster release rates	Importance of physical and chemical properties of drugs in MOF-based DDSs	[114]

in 2018, researchers investigated the use of an acid-resistant Zr-MOF, NU-1000, for oral INS delivery [2]. The goal was to protect INS from the acidic environment of the stomach and enable its release in the intestines, where it can be absorbed into the bloodstream. The MOF was shown to encapsulate INS effectively, with a LC of 40 wt%, and protected it from degradation in simulated stomach acid, releasing only a minimal amount in these conditions [2]. The MOF demonstrated stability and protected the INS effectively, releasing only 10% of the hormone in simulated stomach acid after 60 min [2]. The second study in 2022 explored an oral INS delivery system using transferrin-coated acid-resistant Zr-MOF (UiO-68-NH_2) nanoparticles (Fig. 2A and 2B) [42]. These nanoparticles showcase a high INS LC of 33 wt% and are designed to protect INS in the stomach's acidic environment while promoting absorption in the intestines [42].

The release kinetics demonstrate a controlled release, with less than 20% of INS released in simulated GI conditions over 24 h and almost complete release in neutral conditions within 10–12 h [42]. The T@I@U formulation, comprising transferrin-coated, acid-resistant MOF nanoparticles, exhibited superior performance in INS delivery in mice. This was highlighted by a robust fluorescence signal, indicating efficient INS absorption and sustained release, peaking at 8 h and persisting for 12 h (Fig. 2C and D) [42]. In terms of organ distribution, strong fluorescence in the liver mirrored the natural INS secretion pathway, in contrast to the negligible signal from free INS, which degraded quickly in the GI tract, and the minimal signal from the I@U group (Fig. 2E) [42]. Notably, confocal imaging confirmed that T@I@U uniquely crossed the intestinal epithelial barrier, effectively reaching the intestinal villi, a feat not achieved by the other formulations (Fig. 2F). Moreover, this system significantly enhances oral bioavailability, achieving 29.6%, and shows a pronounced hypoglycemic effect in diabetic rats without noticeable side effects [42]. This study, in conjunction with the first, emphasizes the potential of MOFs in safeguarding and controlling the release of INS, enhancing its oral bioavailability, and offering a promising alternative to traditional INS delivery methods.

Building on the exploration of MOFs for INS delivery, another study delves into enhancing the oral bioavailability of magnolol, a compound with a wide spectrum of biological activities, including anti-inflammatory, antimicrobial, and potential anticancer effects [47]. The study utilized the Zr-based MOF UiO-66 (Zr) for the impregnation of magnolol, aiming to overcome its traditionally low bioavailability, which is typically approximately 4%–5% [47]. The MOF demonstrated a high drug loading efficiency (LE) of 72.16% ± 2.15% for magnolol, and the *in vitro* release study indicated a significant increase in the bioavailability of magnolol when delivered through the MOF, with the relative bioavailability nearly doubling [47]. This approach mirrors the strategies seen in INS delivery studies, where MOFs are employed to protect and effectively deliver bioactive molecules orally.

In the realm of oral drug delivery for cancer treatment, a study synthesized a series of Zr-MOFs, including UiO-66, UiO-66-NH_2, UiO-66-COOH, UiO-67 and Zr-NDC, with the latter incorporating 2,6-naphthalene dicarboxylic acid [55]. Among these, Zr-NDC was notable for its superior drug LC, particularly for the anticancer drug 5-fluorouracil (5-FU). To improve the oral bioavailability of 5-FU, Zr-NDC was modified with chitosan (CS), which increased drug loading to 66.28% and controlled the drug release of 20% in acidic stomach conditions and 70% in intestinal fluid [55]. This approach promises to enhance the effectiveness of oral chemotherapy treatments.

Continuing the trend of utilizing Zr-MOFs for oral drug delivery, UiO-66-PDC, where PDC stands for H_2PDC, was developed (2021) to carry IBUNa, enhancing its stability against stomach acidity [19]. The MOF demonstrated a drug LC of 27.60 wt% and exhibited pH-sensitive release characteristics, releasing only approximately 10% of the drug at a stomach-like pH of 2, while releasing the majority within the first 5 h at an intestinal pH of 7.4 [19]. Biocompatibility assessments using MTT assays with 4T1 cells indicated that UiO-66-PDC was biocompatible, further supporting its potential as an oral DDS [19].

In a study conducted in 2023, Zr-MOFs were investigated to enhance the LC and control the release of captopril and IBU in different pH environments, which is crucial for oral DDSs [29]. These MOFs, Zr-MOF1 and Zr-MOF3, synthesized through chemical methods, and Zr-MOF2, created using a solvothermal method, show increased surface areas and pore volumes, which are beneficial for drug loading. These MOFs showed high drug loading efficiencies, nearly 99.8% for captopril and 96.65% for IBU [29]. Drug release was pH-responsive and crucial for targeted delivery within the GI tract, and the MOFs were stable across a wide pH range. Specifically, the release kinetics showed that in a phosphate-buffered solution at pH 7.4, which simulates intestinal conditions, the release of drugs was more significant compared to the release in a buffered solution at pH 1.2, mimicking stomach acidity [29].

Collectively, these studies illustrate a progressive enhancement in the design and functionality of MOFs for oral drug delivery. From INS to cancer treatments and anti-inflammatory drugs, MOFs have shown remarkable potential in improving the bioavailability and stability of orally administered drugs. The evolution from simple encapsulation to targeted delivery and pH-responsive release mechanisms reflects the dynamic nature of this research area and its promise for future pharmaceutical applications.

3.2. *Iron-based MOFs (Fe-MOFs)*

Fe-MOFs have emerged as promising vehicles for drug delivery owing to their high drug-loading capacities, favorable biocompatibility, and versatile functionalities. In a pioneering study conducted in 2006, Horcajada and coworkers introduced an innovative category of MOFs characterized by their expansive pore sizes, notably MIL-100(Cr) and MIL-101(Cr) [9]. The acronym "MIL" refers to the Materials of the Institute Lavoisier. These frameworks were distinguished by their Cr core and the integration of organic linkers, specifically 1,3,5-benzenetricarboxylate or 1,4-benzenedicarboxylate (H_2BDC). The resulting MOFs demonstrated a remarkable capacity for encapsulating significant amounts of IBU, indicating their potential utility in drug delivery applications [9]. However, the potential *in vivo* oxidation of trivalent Cr to its hexavalent state, which is highly toxic, poses a significant concern. In

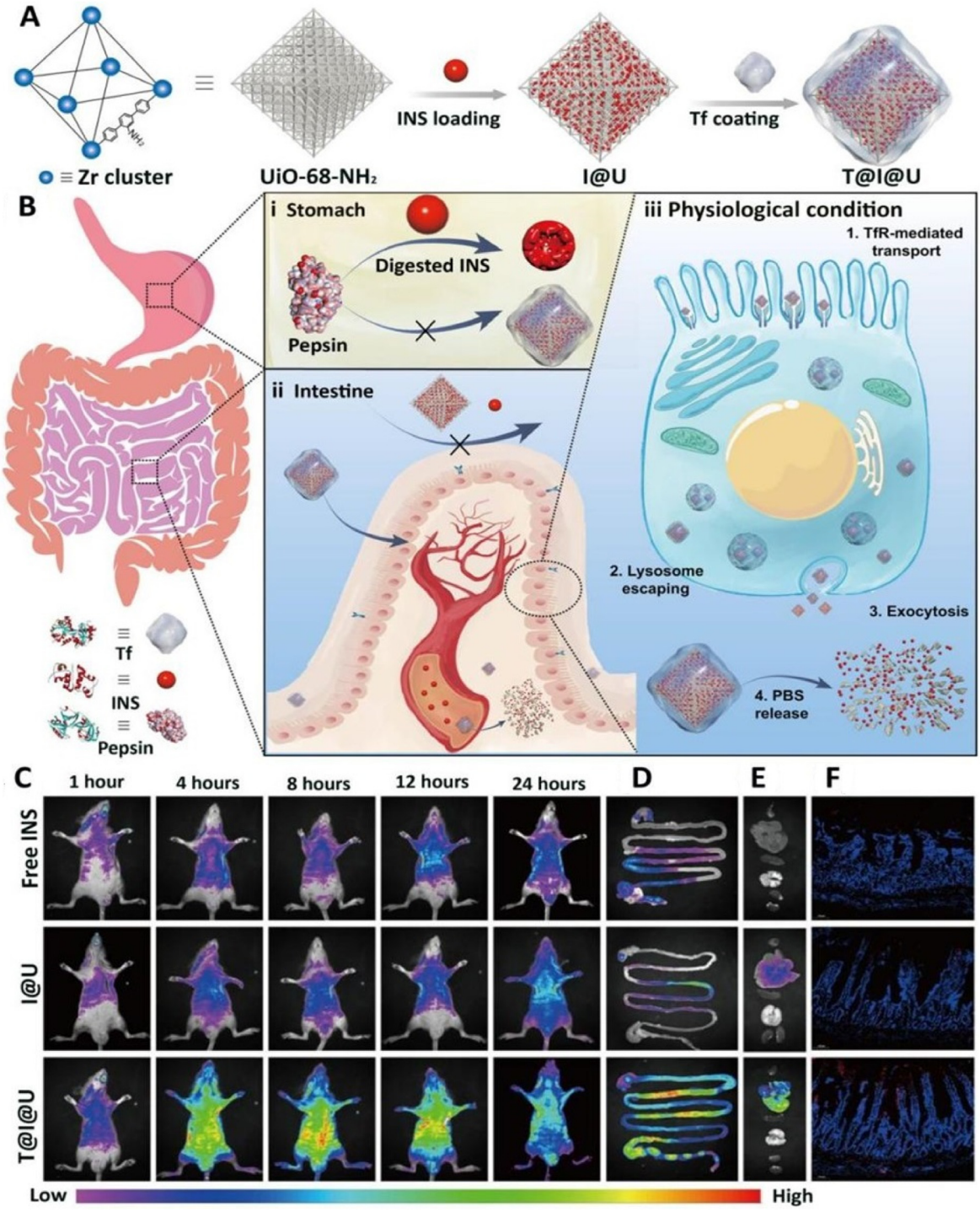

Fig. 2 – Illustrative depiction of the transferrin-coated, acid-resistant nano MOF (nMOF) system designed for the oral administration of INS. (A) Outline of the creation process of amino-functionalized UiO-68-based nanostructures (UiO-68-NH2). (B) Demonstrates the *in vivo* pathway of the transferrin-adorned UiO-68-NH2 nanosystem for oral intake, tackling both the challenging acidic environment of the stomach (i) and the barriers posed by epithelial cell layers (ii). (iii) The transferrin-layered UiO-68-NH2 nanosystem facilitates significantly enhanced absorption by intestinal cells under normal physiological conditions. (C) Displays the *in vivo* fluorescence pattern and intensity of RITC-labeled INS following oral administration of various INS formulations at distinct time intervals. (D) *Ex vivo* fluorescence imaging of the intestines and (E) images of major organs, such as the heart, liver, spleen, lung and kidney (arranged top to bottom), in mice observed 4 h after oral INS administration. (F) Confocal laser scanning microscopy (CLSM) visuals of cross-sectioned intestinal tissues in rats captured 2 h postoral administration of differing INS formulations. Reproduced from [42]; copyright 2022 AAAS.

response to this issue, these researchers turned to trivalent iron (Fe), a less toxic alternative, to create MIL-53(Fe). This Fe-MOF demonstrated a notable IBU LC of approximately 20 wt%, and the drug was fully released after three weeks in simulated body fluid at 37 °C *in vitro* [56]. Subsequently, in pursuit of safer alternatives, researchers developed MIL-101(Fe) and MIL-100(Fe), which were reported in 2009 and 2010, respectively [57,58]. Horcajada's team advanced drug delivery technology by synthesizing a suite of Fe-MOFs, namely, MIL-53 (Fe), MIL-88 (Fe), MIL-100 (Fe), and MIL-101 (Fe). These MOFs were crafted using different combinations of materials and organic linkers: MIL-53 (Fe) with $FeCl_3{\cdot}6H_2O$ and terephthalic acid (H_2BDC), MIL-88 (Fe) with $FeCl_3{\cdot}6H_2O$ and fumaric acid, MIL-100 (Fe) with iron powder and trimesic acid, and MIL-101 (Fe) with $FeCl_3{\cdot}6H_2O$ and amino H_2BDC. Each MOF's unique composition contributes to its ability to effectively encapsulate and deliver drugs [58]. These frameworks are distinguished by their nontoxicity and porous nature, which enables them to serve as efficient carriers for the targeted delivery of a variety of drugs aimed at combating cancer and HIV. The drugs encapsulated within these MOFs, such as busulfan, azidothymidine triphosphate, doxorubicin, and cidofovir, benefit from enhanced delivery mechanisms. Furthermore, these MOFs have the potential to merge treatment with diagnostic functions, paving the way for more personalized and precise medical treatments [58]. These Fe-MOFs were designed to carry drugs, leveraging the lower toxicity profile of iron compared to Cr. The introduction of these MOFs represented a significant advancement in the field of drug delivery, offering a more biocompatible option for the encapsulation and controlled release of therapeutic agents. In the context of this review, we delve into various case studies that highlight the use of Fe-MOFs in oral drug delivery (Table 2). These studies collectively underscore the potential of Fe-MOFs as innovative carriers for therapeutic agents, offering insights into their drug-loading capacities, release mechanisms, and biocompatibility, which are critical for effective oral DDSs.

In a 2020 study, researchers approached the persistent challenges of oral INS delivery, specifically its degradation in the stomach and insufficient intestinal absorption [39]. They engineered a cutting-edge nanocomposite microsphere system incorporating Fe-MOF nanoparticles, known as MIL-100, which demonstrated a notable INS LC of 35% [39]. These nanoparticles were further modified with sodium dodecyl sulfate (SDS), enhancing INS permeation through *in vitro* Caco-2 monolayer models (Fig. 3A). To augment the system's resistance to the harsh gastric environment, the Ins@MIL100/SDS nanoparticles were encased within biodegradable microspheres composed of mPEG-b-PLLA [39]. This biocompatible polymer not only provides additional protection against stomach acidity but also facilitates the gradual release of INS in the intestinal fluid (Fig. 3B). In Fig. 3C, cellular uptake of INS-loaded nanoparticles, visualized using CLSM with RhoB-Ins as a model, showed clear red fluorescence in cells treated with Ins@MIL100 and Ins@MIL100/SDS, unlike cells with free INS. The Ins@MIL100/SDS treatment led to more intense fluorescence than Ins@MIL100, indicating enhanced internalization of INS by Caco-2 cells due to MIL-100 nanoparticles and further improvement with SDS modification [39]. Fig. 3D shows that INS encapsulation in Ins@MIL100 or Ins@MIL100/SDS notably increased its permeation through Caco-2 cell monolayers, with over 60% penetration in 8 h. These results, consistent with the cellular uptake data, indicate that MIL-100-based nanoparticles significantly enhance INS transcellular transport. Upon oral administration in BALB/c nude mice and diabetic rats (1 h postadministration), strong rhodamine B fluorescence in the intestines of mice treated with Ins@MIL100/SDS@MS (Fig. 3E) indicated successful protein delivery by the MOF-NP microspheres, with this fluorescence persisting for 8 h [39]. Therefore, the Ins@MIL100/SDS@MS nanocomposite system significantly improved the intestinal absorption of INS compared to the administration of free INS or the unencapsulated Ins@MIL100/SDS [39]. This led to substantially elevated plasma INS levels for an extended period of over 6 h in diabetic rats, which effectively reduced blood glucose levels [39].

Building on advancements in oral INS delivery, another study in 2021 focused on enhancing the oral bioavailability of the peptide exendin-4, which has significant therapeutic importance but has challenging delivery dynamics due to the harsh GI environment [59]. In their innovative research, Zhou et al. developed a delivery system using zwitterionic hydrogel-coated Fe-MOF (NH_2–MIL-101) nanoparticles to encapsulate exendin-4, a drug used in type 2 diabetes treatment [59]. The nanoparticles were engineered to enhance the oral bioavailability of the peptide. The study reported a notable drug LE of 92.3%, with the nanoparticles achieving a drug loading content of 0.417 g/g [59]. The release kinetics were carefully evaluated, revealing a slow and controlled release of exendin-4 in a neutral Tris–HCl buffer (pH 7.4), while a phosphate buffer induced a rapid release, demonstrating the system's pH sensitivity [59]. This pH-responsive behavior is crucial for protecting the peptide in the acidic stomach environment and releasing it when it reaches the more neutral intestines. When tested *in vivo*, the MOF nanoparticle-based system significantly enhanced the plasma concentration of exendin-4 in a diabetes rat model, maintaining elevated levels for over 8 h post administration [59]. The relative pharmacological availability was quantified at 17.3%, indicating a substantial improvement over traditional delivery methods [59]. This study highlights the potential of MOF nanoparticles in transforming the oral delivery landscape for peptides such as exendin-4. Building on advancements in oral delivery systems, researchers approached the low oral bioavailability of GEN, a flavonoid with antitumor potential, by encapsulating it within MIL-100 [46]. This encapsulation strategy aimed to mitigate the poor water solubility and rapid metabolism of GEN. The study achieved a notable GEN loading of 27.1 wt% in the MIL-100 (Fe) nanoparticles. Upon testing, approximately 40% of GEN was released within the first 30 min, followed by a sustained release over the subsequent 3 d [46]. This encapsulation not only protected GEN from premature metabolic breakdown but also facilitated prolonged release, enhancing its bioavailability for potential oral antitumor applications [46].

In a pivotal study, researchers explored the efficacy of MIL-127, a biocompatible MOF, as an oral detoxifying agent for decontaminating drugs commonly involved in

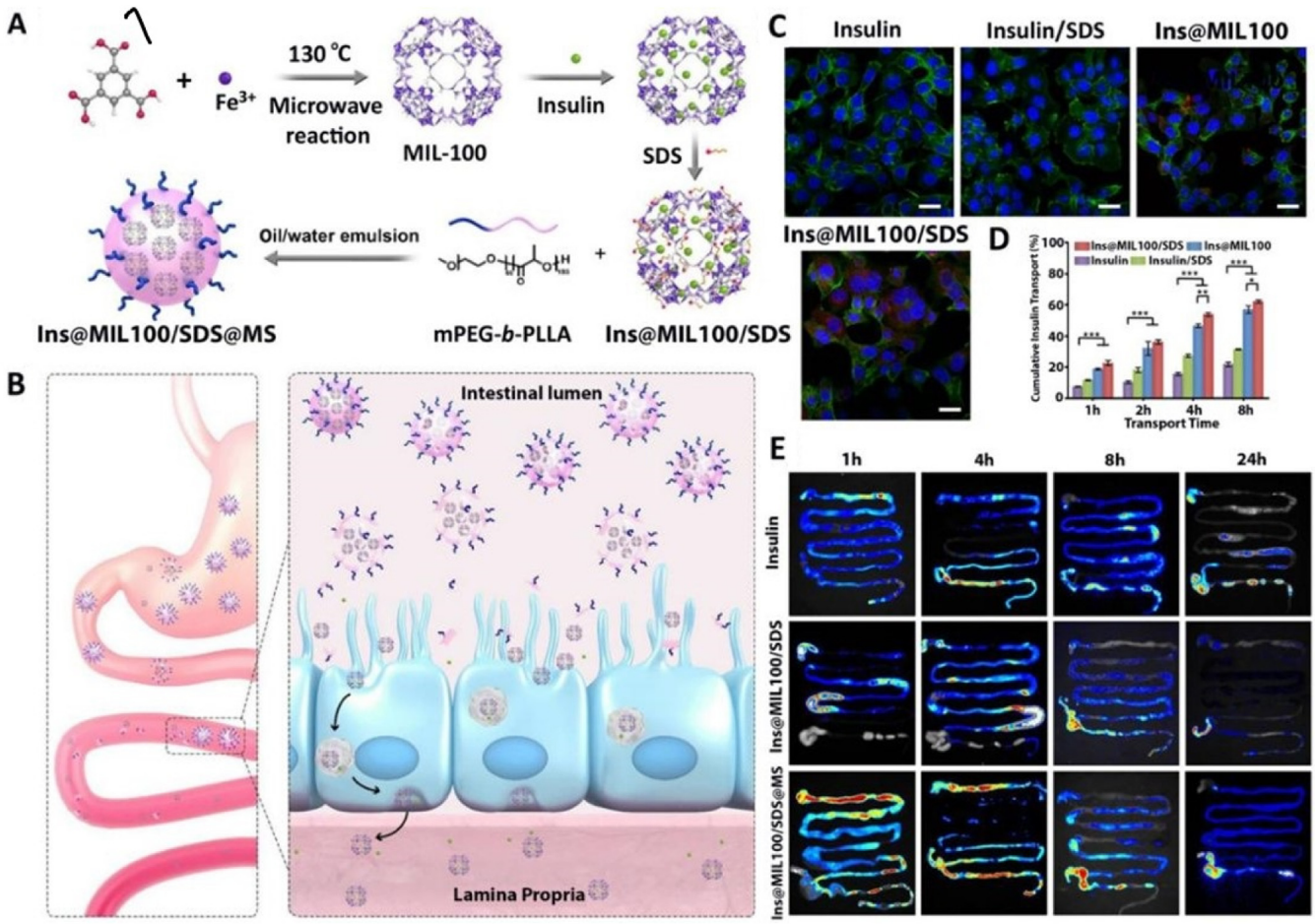

Fig. 3 – (A) A diagrammatic representation detailing the creation of the Ins@MIL100/SDS@MS nanocomposite. (B) A schematic depiction of the journey of Ins@MIL100/SDS@MS through the stomach, followed by the disintegration of the microspheres in the intestine, leading to the exposure and subsequent infiltration of the Ins@MIL100/SDS composite through the intestinal epithelium. (C) Depiction of uptake by Caco-2 cells observed after exposure to various treatments: free INS, free INS combined with SDS, Ins@MIL100, and Ins@MIL100/SDS. Rhodamine B-labeled INS (RhoB-Ins) served as the model INS for this experiment. A 20 μm scale bar was used for reference. (D) The diagram tracks the passage of INS across Caco-2 cell monolayers over various time frames ($n = 3$), utilizing fluorescein isothiocyanate-labeled INS (FITC-Ins) as the model INS for this analysis. (E) Postoral administration, ex vivo fluorescence imaging of the intestines showcases the distribution of RhoB-labeled INS (Rho-Ins) in the Ins@MIL100/SDS and Ins@MIL100/SDS@MS treatments at different intervals. Reproduced with permission from [39]; Copyright 2020 ACS.

overdoses [60]. MIL-127, composed of iron(III) trimers and azobenzenetetracarboxylate anions, demonstrated a high affinity for aspirin (ASA), a commonly overdosed medication, with an impressive LC of approximately 0.14 g/g under simulated GI conditions [60].

The comparison with activated charcoal and UiO-66 revealed that while these substances released 11% and 24% of adsorbed ASA upon transitioning from gastric to intestinal conditions, MIL-127 showed no such release, indicating superior affinity and stability [60]. Notably, MIL-127 maintained exceptional GI stability, with less than 9% degradation, and was found to be excreted in feces without severe toxicity, ensuring its integrity along the GI tract. This minor GI degradation resulted in slight iron absorption in the duodenum and jejunum but did not lead to any significant toxicity [60]. These findings suggest that MIL-127 can significantly reduce the GI absorption of salicylates by more than 40-fold, offering a protective effect against ASA overdose and preventing histological damage in the stomach and jejunum [60]. The study concludes that MIL-127 and potentially other MOFs could serve as efficient and safe oral detoxifying agents, marking a promising advancement in the treatment of drug overdoses.

In another study, researchers engineered a novel oral delivery system for nitric oxide (NO), a key regulator in cardiovascular health, by immobilizing a dinitrosyl iron complex (DNIC-2) onto MIL-88B MOF to create a DNIC@MOF microrod [43]. This system aimed to improve the oral bioavailability of NO for chronic cardiovascular disease treatment. The MIL-88B MOF, composed of biocompatible Fe^{3+} and 1,4-benzenedicarboxylate (H_2BDC), was designed to release DNIC-2 under specific conditions. DNIC-2, serving as

an NO prodrug, was encapsulated within the MOF through a postsynthetic modification process. The release kinetics of NO from DNIC-2 indicated a burst release in the first 30 min, with continued release over 3 d [43].

Incorporating the transformer-like behavior, the DNIC@MOF microrod responds to the acidic gastric environment by transforming to protect the encapsulated DNIC-2, ensuring its stability against degradation. As the microrod transitions to the neutral pH of the intestines, it undergoes controlled decomposition, releasing DNIC-2 in a targeted manner, which then liberates NO. Therefore, DNIC@MOF demonstrated stability in acidic environments, transforming to protect DNIC-2, and decomposing in neutral pH to release NO [43]. Biocompatibility tests showed over 80% viability of human intestinal epithelial cells, suggesting safety for oral use [43].

A significant finding was the increase in oral bioavailability of NO from 29.7% with DNIC-2 alone to 65.7% when conjugated with MIL-88B, indicating a 2.2-fold improvement [43]. The study concludes that the DNIC-2@MOF microrod is a promising strategy for enhancing the oral delivery of NO, with potential benefits for long-term cardiovascular disease management.

These case studies collectively highlight the innovative and transformative potential of Fe-MOFs in oral drug delivery. They offer a glimpse into the future of personalized medicine, where such frameworks could provide tailored therapeutic regimens with enhanced efficacy and safety profiles. As we continue to explore the capabilities of Fe-MOFs, their role in revolutionizing drug delivery and patient care becomes increasingly evident, marking a new era in the treatment of various diseases.

3.3. *Zn-MOFs*

The exploration of Zn-MOFs for drug delivery has been a dynamic field of study, with MOF-5, synthesized from zinc nitrate and H_2BDC, serving as a foundational structure since its inception by Yaghi and his team in 1999 [61]. MOF-5 undergoes structural changes in varying water concentrations, a process driven by hydrolysis that involves water molecules interacting with the MOF's metal sites. This instability is partly necessary to allow the body to process and eliminate the MOF after it has delivered its therapeutic payload [62]. To balance this, MOF-5 must maintain sufficient stability to function effectively before it degrades in the body. Hybrid frameworks, such as MOF-5/Mag-H, which incorporate inorganic building blocks, are engineered to enhance both stability and flexibility, making them suitable for drug delivery applications [62].

Researchers synthesized nanoscale Zn-MOFs (ZnBDP_X MOFs) using zinc ions and functionalized organic spacers (H_2BDP_X; X = H, NO_2, NH_2, OH) [63]. The stability of these ZnBDP_X nanoparticles was rigorously assessed under simulated physiological conditions relevant to both intravenous and oral drug delivery, demonstrating excellent stability, particularly for ZnBDP_OH, which formed a protein corona to prevent aggregation [63]. The study further explored drug loading and release, revealing that the MOF surface area and ligand functionalization significantly influenced the delivery of two antitumor drugs, mitoxantrone and RAPTA-C [63]. ZnBDP_OH and $ZnBDP\_NH_2$ MOFs enabled controlled drug release, while $ZnBDP\_NO_2$ and ZnBDP_H facilitated faster release, underscoring the potential of MOFs in drug delivery applications [63].

Zeolitic imidazolate frameworks (ZIFs), which are a subset of Zn-MOFs, are constructed from Zn(II) ions linked with imidazolate or its derivatives. These structures are extensively utilized in oral DDSs (Table 2) due to their favorable properties [64-66]. In a study, a novel pH-responsive dual DDS utilizing ZIF-8 was developed [65]. This system features a core-shell nanofiber membrane made from poly(lactic acid)/chitosan (PLA/CS), with the hydrophilic drug Astragalus polysacharin (APS) in the core and the hydrophobic drug camptothecin (CPT) in the shell. ZIF-8 NPs create a protective layer on PLA/CS, forming multifunctional PLA/CS@ZIF-8 nanofiber membranes [65]. These membranes exhibit enhanced hydrophilicity, surface roughness, and controlled drug release in both acidic and neutral environments. The release mechanism for both APS and CPT involves diffusion and framework corrosion, with *in vitro* tests confirming the system's cytocompatibility. The PLA/CS@ZIF-8 nanofiber membranes hold promise as a versatile, pH-responsive dual drug release system [65]. In exploring the frontier of oral DDSs, Zn-MOFs have garnered significant attention due to their unique chemical versatility and biocompatibility. In this study, MOF-5 was utilized to encapsulate the anticancer drug 5-FU, aiming to enhance oral delivery efficiency [67]. The encapsulation efficiency of 5-FU within MOF-5 reached 84.1%, facilitated by hydrophobic interactions and π-π stacking between the drug and the framework's organic ligands [67]. A key innovation was the application of carboxymethylcellulose (CMC) to coat the drug-loaded MOF-5, which provided protection through the digestive system and enabled sustained release under GI tract conditions [67]. The controlled release was demonstrated in drug release tests, and the system's cytotoxicity against HeLa cells was confirmed via the MTT assay, indicating its potential to reduce side effects compared to intravenous drug delivery [67]. This suggests that the CMC/5-FU@MOF-5 composite could be a viable candidate for targeted colon drug delivery, offering a strategic approach to cancer treatment. In the realm of oral drug delivery, the study of anionic MOFs such as ZJU-64-NSN represents a significant advancement [30]. This Zn-MOF, with its one-dimensional channels adorned with thiadiazole groups, was engineered to enhance the oral bioavailability of PA, a cationic drug often compromised by gastric degradation. The synthesis of ZJU-64-NSN was meticulously controlled to produce nanoscale crystals, facilitating an ultrafast drug LC of 21.2 wt% within just 1 min [30]. To bolster the MOF's stability and prevent premature drug release, a polyethylene glycol (PEG) biopolymer coating was applied, ensuring that PA was released predominantly in the intestinal tract where absorption into the bloodstream is optimal [30]. This innovative approach to oral drug delivery showcases the potential of MOFs such as ZJU-64-NSN to overcome the limitations of traditional administration methods, providing a controlled release mechanism that could significantly improve therapeutic outcomes [30]. In addressing the challenges of oral drug delivery for ulcerative

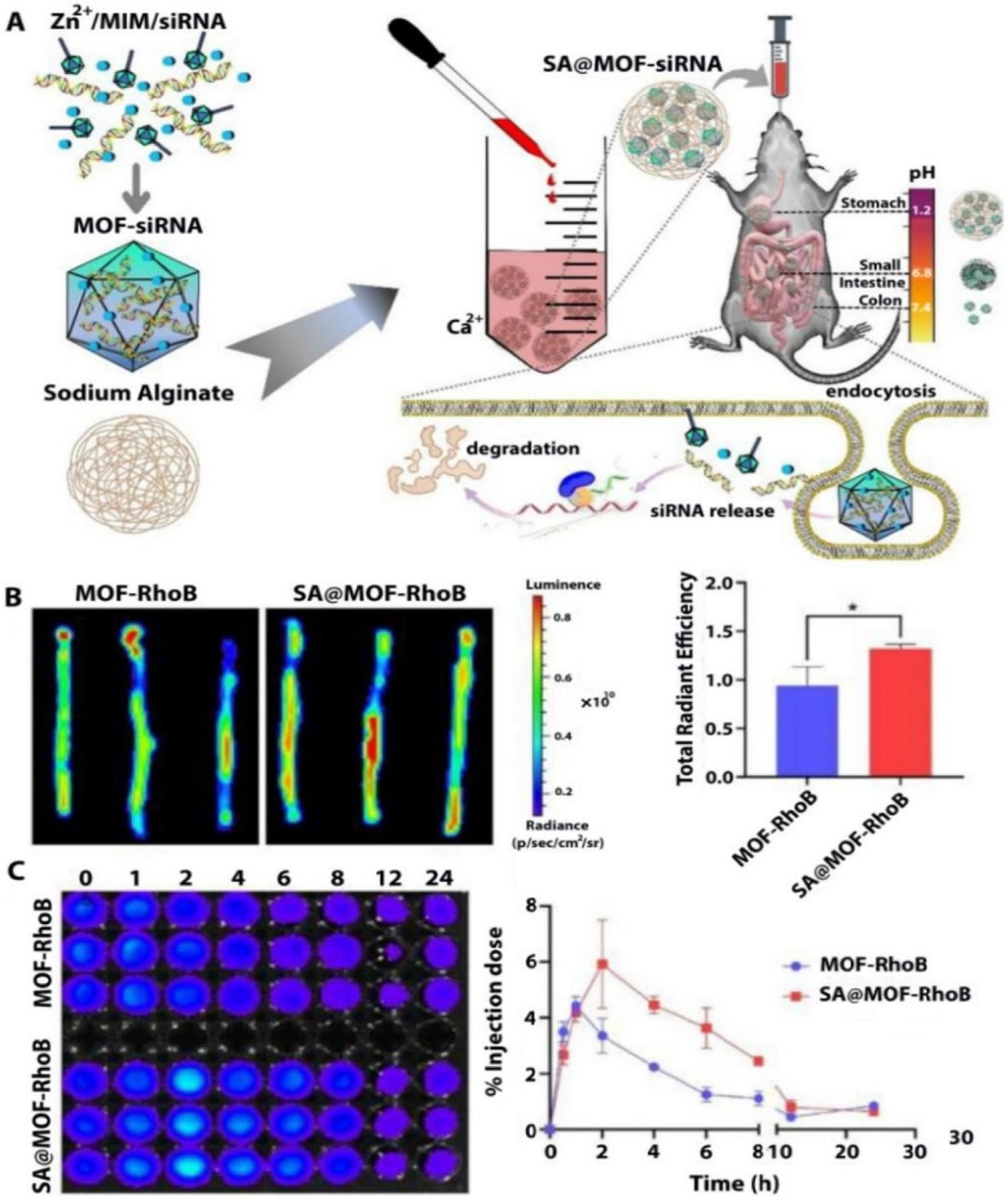

Fig. 4 – (A) Diagrammatic representation of the envisioned hydrogel–metal-organic framework composite system (SA@MOF-siRNA) designed for ulcerative colitis therapy. (B, C) Depiction of colon targeting and the circulation of MOF-RhoB and SA@MOF-RhoB in the bloodstream. (B) The spatial distribution of these particles within the colon as captured by a multimodal optical *in vivo* imaging system, with a corresponding graph showing the statistical analysis of fluorescence intensity. (C) Measurement of RhoB concentration in blood serum, accompanied by a side graph illustrating the temporal changes in serum fluorescence intensity. An asterisk indicates a significance level of $P < 0.05$. Reproduced with permission from [68]; copyright 2022 BMC.

colitis treatment, a study developed a Zn-MOF hybridized with sodium alginate to form a protective hydrogel (Fig. 4A) [68]. This innovative system encapsulated small interfering RNA (siRNA) targeting TNFα, a critical inflammatory agent in ulcerative colitis [68]. Zn-MOF, synthesized from zinc nitrate hexahydrate and 2-methyl imidazole, was designed to shield the siRNA as it traversed the GI tract, ensuring stability and targeted release in the colon.

The system shows its ability to withstand the low pH of the stomach and to release siRNA in the more neutral pH of the intestines [68]. Biocompatibility assessments indicated that MOF-siRNA was nontoxic and well tolerated by macrophages.

Moreover, mice with DSS-induced ulcerative colitis were orally administered RhoB-labeled MOF-RhoB and SA@MOF-RhoB. After 12 h of administration, stronger fluorescence intensity was observed in SA@MOF-RhoB than in MOF-RhoB in the colon, as confirmed by multimodal *in vivo* imaging and statistical fluorescence analysis (Fig. 4B) [68]. Blood samples showed higher concentrations of SA@MOF-RhoB, indicating enhanced absorption and prolonged circulation in the blood (Fig. 4C), highlighting its potential for inflammation control. Furthermore, these findings demonstrated that the hydrogel-MOF hybrid system significantly reduced the progression of colitis in animal models, avoiding common side effects such as weight loss and bloody stools [68].

In conclusion, these studies collectively underscore the transformative potential of Zn-MOFs in enhancing the efficacy and safety of oral DDSs. By offering controlled release, targeted delivery, and improved stability, Zn-MOFs stand at the forefront of innovative therapeutic solutions, paving the way for more effective and patient-friendly treatments for a variety of ailments.

3.4. *Copper-based MOFs (Cu-MOFs)*

Cu-MOFs are emerging as a significant class of materials in the biomedical field due to their exceptional physicochemical properties. Copper ions (Cu^{+2}/Cu^{+}) in MOFs can modify crucial antioxidants in cancer cells, such as glutathione, and produce damaging radicals through Fenton-like reactions, offering a targeted approach to cancer cell destruction [69]. Copper homeostasis is crucial for organismal health, as both excessive and deficient copper levels are associated with various diseases. Abnormal copper concentrations and metabolism at disease sites, particularly in cancer, present a promising therapeutic target [70,71]. Additionally, Cu-MOFs are gaining interest due to copper's essential role in various biological processes, such as respiration, metabolism, and cell signaling [72,73].

HKUST-1, also known as MOF-199, is a well-known three-dimensional (3D) Cu-MOF that was first reported by Chui et al. in 1999. It features a structure composed of dimeric cupric tetracarboxylate units, where each copper ion is coordinated with four oxygen atoms from two molecules of 1,3,5-benzenetricarboxylic acid [74]. In addition, Cu-TCPP MOFs with TCPP, stand out as a notable category within two-dimensional Cu-MOFs [75]. A study explored a Cu-MOF, HKUST-1, for drug delivery, encapsulating the drug baclofen. This compound was integrated into a CMC hydrogel, enhancing drug release control in the GI tract. *In vitro* tests indicated improved release uniformity and significant cytotoxicity against human colon cells, suggesting potential for targeted drug delivery [76].

Emerging case studies further highlight the promising role of Cu-MOFs in revolutionizing oral drug delivery (Table 2). In exploring innovative solutions for oral drug delivery, two studies have made significant strides using Cu-MOFs to improve the bioavailability and controlled release of IBU [20,77]. The first study encapsulated IBU within Cu-MOFs and further embedded these into pH-sensitive gelatin microspheres (Cu-MOF/IBU@GM). This design aimed to utilize the protective properties of the microspheres to achieve stable and controlled release of the drug within the GI tract. The Cu-MOFs, synthesized from copper nitrate and H_2BDC, demonstrated a drug LE of 48.19 wt%, with release kinetics evaluated under simulated GI conditions [20]. *In vitro* drug release tests simulating GI conditions revealed that the gelatin-encapsulated Cu-MOF/IBU microspheres provided enhanced protection against stomach acidity and prolonged drug stability. Biocompatibility tests indicated low toxicity against Caco-2 cells, suggesting suitability for oral delivery [20].

Furthering this research, the second study encapsulated Cu-MOF@IBU within a CMC hydrogel bead to form a pH-sensitive nanocomposite [77]. This CMC encapsulation significantly altered the release behavior, while Cu-MOF@IBU alone released approximately 95% of the drug within 2 h in an acidic environment, the CMC/Cu-MOF@IBU nanocomposite extended the release to only 70% over 8 h [77]. CMC serves as a diffusion barrier, and its pH-sensitive properties enable controlled release that protects the drug from stomach acidity and facilitates more sustained release in the intestines [77].

These investigations underscore the potential of Cu-MOFs in creating more effective DDSs for oral administration. Both the gelatin microspheres and the CMC hydrogel beads have been shown to be promising carriers, enhancing the stability and controlled release of IBU, which could be applied to other therapeutic agents as they pass through the digestive system.

Building on the advancements in Cu-MOFs for oral drug delivery, a study explored the potential of a gelatin-coated Cu-MOF, named IITI-3, for controlled oral INS delivery [78]. IITI-3, synthesized with a novel linker, aimed to address oral delivery challenges by ensuring stability in the GI tract and maintaining INS bioavailability [78]. The MOF demonstrated a 20 wt% INS LE and stability across a pH range of 3 to 10, suitable for the varying conditions of the GI tract. [78] Additionally, IITI-3 was confirmed to be biocompatible and hemocompatible, indicating its safety for medical use [78]. The study's findings suggest that IITI-3 is a promising material for the controlled oral delivery of INS, potentially offering a new approach to diabetes treatment.

In conclusion, the development of Cu-MOFs for drug delivery represents a burgeoning field that holds great promise for improving therapeutic outcomes. These frameworks offer a versatile platform for the targeted and controlled release of drugs, addressing the challenges of oral drug delivery and paving the way for new treatment modalities.

3.5. *Titanium-based MOFs (Ti-MOFs)*

The Ti-MOFs feature a distinctive networked structure. This intricate configuration emerges from the self-organizing reaction where titanium ions or clusters bond with targeted functional groups, notably those with carboxyl or nitrogenous heterocyclic molecules. Meenakshi and collaborators, in 2009, achieved a milestone by synthesizing the first Ti-MOF connected through carboxylic acid. This was accomplished by combining titanium isopropoxide (Ti(i-OPr)4) with H_2BDC, resulting in the formation of MIL-125 [79]. Ti-MOFs are distinguished by their advantageous properties, which include notable biocompatibility, exceptional catalytic

oxidation, and effective photocatalytic attributes [80-85]. In comparison to alternative MOFs, Ti-MOFs are of interest due to their significant biocompatibility, reduced toxicity, and enhanced chemical durability [80,85,86]. Currently, two fundamental types of Ti-MOFs, pristine MIL-125 and its amino-functionalized derivative MIL-125-NH_2, along with their composite forms, such as AgNP@MIL-125-NH_2, PCN-224 (Zr/Ti), PAN/CA/MIL-125/TiO_2, and MIL-125-Hb, have been utilized as transporters for diverse pharmaceutical agents, as well as in applications targeting antibacterial and anticancer therapies [85,87-91]. Studies have shown that MIL-125 and its amino-functionalized form, MIL-125-NH_2, are utilized as carriers for a range of drugs, such as chloroquine (CQ) [92] and diclofenac sodium (DS) [93]. The biocompatible Ti-MOF MIL-125 has been explored for pH-responsive drug delivery, releasing drugs preferentially in the acidic environment of inflamed or tumor tissues (pH 5.4–6.0) [93]. The compatibility of MIL-125 with DS was assessed, revealing a substantial LC of 13.6 wt% [93]. Release studies in PBS at varying pH levels (8.0 to 5.4) at 37 °C, analyzed via HPLC, showed that DS@MIL-125 significantly prolonged the release half-life of DS at pH 5.4 to 16 h, eightfold longer than DS alone. Cumulative release at pH 5.4 reached 80% of the loaded DS, while at pH 6.5, 7.4 and 8.0, the release was 62%, 55% and 35%, respectively, indicating a targeted release at more acidic, disease-affected sites [93]. These findings suggest MIL-125′s potential as an effective carrier for anti-inflammatory and antitumor therapies. MIL-125 and MIL-125-NH_2 have been identified as potential carriers for CQ, with both materials demonstrating a high capacity for drug loading due to their high surface areas [92]. Sustainable release of CQ from these carriers was observed, with approximately 70% of the drug being released over a period of 13 d in a phosphate buffer solution [92]. The findings from these experiments suggest that Ti-MOFs could serve as effective carriers for CQ, facilitating its slow release. A recent study (Table 2) has advanced drug delivery technology by creating smaller, biocompatible Ti-MOFs using tetraethyl orthosilicate (TEOS) [84]. This innovation aimed to harness the drug delivery potential of MOFs, particularly for controlled-release applications. The synthesized Ti-MOFs, when tested with IBU as the model drug, demonstrated a drug LE of approximately 10%. Remarkably, these MOFs released approximately 95% of the IBU within 24 h, indicating a highly efficient release mechanism [84]. Stability tests showed that even after 48 h in phosphate-buffered saline at 37 °C, the MOFs remained stable, with biocompatibility confirmed by positive L929 cell line assays [84]. The introduction of TEOS resulted in a 42.78% size reduction of the MOFs, underscoring their potential as effective drug carriers in targeted therapy applications [84].

Ti-MOFs, particularly those modified with amino groups, have shown increased chemical stability in water [94], making them promising candidates for oral drug administration despite previous concerns regarding MOF porosity and water instability [95,96]. In a comparative study (Table 2), the Ti-nanoMOF, MIL-125-NH_2, was evaluated for its efficacy in oral aspirin detoxification against other MOFs, including MIL-53(Fe), MIL-53(Fe)−2OH, MIL-100(Fe), UiO-66(Zr), UiO-66(Zr)−NH_2, ZIF-8(Zn), and the traditional detoxifying agent Norit@activated carbon [44]. MIL-125-NH_2 exhibited an exceptional aspirin adsorption capacity of 2.59 mol/mol, which was significantly higher than the capacities of Norit@activated carbon, recorded at 0.017 and 0.023 mol/mol [44]. Under simulated GI conditions, MIL-125-NH_2 proved to be exceptionally stable, with less than 35% degradation, and it remained effective in aspirin adsorption [44]. *In vivo* studies confirmed its safety and indicated a significant reduction in serum salicylate levels, demonstrating its potential as an effective oral therapeutic agent for aspirin detoxification [44].

In summary, Ti-MOFs have made remarkable strides from their inception to their use in oral drug delivery. Their stability and controlled release capabilities in the GI tract make them promising for future oral therapies. These developments underscore Ti-MOF's potential to transform oral drug administration, ensuring safe, efficient, and targeted treatment options.

3.6. *Al-MOFs*

The pioneering synthesis of an Al-MOF, MIL-53(Al), by Loiseau et al. in 2004 marked a significant advancement in the field of MOFs [97]. This MOF, typically produced via a hydrothermal method involving aluminum nitrate and 1,4-benzenedicarboxylic acid, is lauded for its exceptional stability in acidic conditions, distinguishing it from its counterparts [97]. Subsequent research has demonstrated that Al-MOFs are versatile materials with applications ranging from waste removal and antibacterial treatments to DDSs [45,98,99]. Furthermore, a study delved into the efficacy of modified aluminum-benzene dicarboxylate-based MOFs for the removal of methotrexate (MTX) from wastewater. NH_2_MIL-101 was identified as the most effective, with a high MTX adsorption capacity of 457.69 mg/g due to its large surface area and functional groups [99]. The adsorption followed a controlled process, aligning with Langmuir isotherm and pseudo-second-order kinetics, and was spontaneous and exothermic [99]. NH_2_MIL-101 also proved to be recyclable with minimal capacity loss after multiple cycles, highlighting its potential for sustainable wastewater treatment and drug delivery applications [99]. In a related innovative study (Table 2), researchers engineered Al-MOF to address the challenges of oral vaccination, such as antigen degradation by gastric acid and proteases and the physical barriers of the intestinal epithelium [45]. The Al-MOFs encapsulated the model antigen OVA with high efficiency, achieving a loading content of 14.7% and a LE of 94.1%. Characterization of these Al-MOFs revealed their exceptional stability, capable of withstanding ambient temperature fluctuations, acidic gastric conditions, and proteolytic digestion [45]. The encapsulated OVA was released in a sustained manner over approximately 7 d, showcasing the potential of Al-MOFs for prolonged antigen delivery. A pivotal aspect of this study was the strategic use of yeast capsules derived from Saccharomyces cerevisiae, which served as a "Trojan horse" to ferry the Al-MOF-armored OVA across the intestinal barrier [45]. This strategy effectively targeted the membrane phagocytic pattern-recognition receptor Dectin-1 on M cells, enhancing vaccine uptake and the subsequent immune response. The study's findings suggest that the combination of Al-MOFs with

yeast capsules could significantly improve the oral delivery of vaccines, offering a protective and efficient delivery system that could pave the way for new vaccination strategies [45].

In conclusion, these studies collectively underscore the versatility and potential of Al-MOFs in environmental and healthcare applications, from purifying wastewater to innovating oral vaccine delivery, reflecting the expansive possibilities that these materials hold for future technological and medical advancements.

3.7. *Potassium-based cyclodextrin MOFs*

In a pioneering contribution to the field of biocompatible materials, Smaldone et al. unveiled the synthesis of a novel cyclodextrin MOF (CD-MOF) [100]. This MOF, distinguished by its high symmetry, porosity, and ultrahigh surface area, is crafted exclusively from edible components: potassium ions, ethanol, and CD [100]. The distinctive blend of water solubility and nontoxicity in CD-MOFs has broadened the horizons in the biomedical domain, especially in the realm of DDSs [101,102]. In a study (Table 2), lansoprazole (LPZ) was effectively integrated into CD-MOFs utilizing a sophisticated cocrystallization technique, which involved the interaction of LPZ with γ-CD in the presence of potassium ions (K^+) [103]. The resulting K-based CD-MOFs demonstrated a significant drug LC, achieving a payload of 23.2% ± 2.1% by weight, indicative of a 1:1 molar ratio between LPZ and γ-CD [103]. Remarkably, the drug retained its spectroscopic integrity within the CD-MOFs even after two years of storage. Raman spectroscopy confirmed the homogeneity of the drug incorporation, revealing that each particle of the CD-MOFs maintained a consistent chemical composition [103]. This homogeneity in drug loading and the stability of the drug within the CD-MOFs underscore their potential as a reliable medium for drug delivery applications. Furthermore, potassium cation-based β-CD MOFs (K-βCD-MOFs) were synthesized and optimized for rapid crystallization [104]. The research revealed that the drug LC of these MOFs is influenced by the size and lipophilicity of the drug molecules, with IBU achieving a loading of 7.4 wt% [104]. The solubility of IBU was significantly enhanced when incorporated into K-βCD-MOF, demonstrating the framework's potential to improve the water solubility of pharmaceuticals [104].

The development of sustained-release DDSs using CD-MOFs is gaining momentum. Overcoming the challenge of low drug loading in CD-MOF microspheres, which hinders their efficacy for oral formulations, is a current research focus [105]. Encapsulating CD-MOFs with organic polymers has emerged as a promising strategy to bolster their stability in aqueous conditions and enhance drug loading without compromising their structural properties, paving the way for advanced oral drug delivery applications [106]. In a study, the goal was to augment the oral bioavailability and modulate the release kinetics of indomethacin (IMC), a drug challenged by poor water solubility (Table 2). To address this, researchers encapsulated γ-CD-MOF nanocrystals synthesized from γ-CD and K^+ within Eudragit® RS microspheres using spray drying technology [107]. Drug loading into CD-MOF nanocrystals achieved an efficiency of 40.2%, which significantly improved to 94.0% upon encapsulation with Eudragit® RS [107]. This encapsulation not only enhanced the dissolution rate of the IMC compared to its raw form but also successfully moderated the initial burst release of the drug, indicating a controlled release profile. The microspheres exhibited a smooth surface and maintained the cubic shape of the CD-MOF nanocrystals, with sizes between 200 and 700 nm [107]. Stability was conferred by the Eudragit® RS polymer, which protected the CD-MOF structure and regulated the drug release rate. Pharmacokinetic studies in rats showed that IMC-loaded CD-MOF nanocrystals and further encapsulated microspheres significantly improved the oral bioavailability of IMCs [107]. These findings demonstrate the potential of this spray-drying encapsulation technique in creating oral DDSs that enhance solubility and provide sustained drug release.

In conclusion, the body of research on CD-MOFs for oral drug delivery underscores a clear trajectory toward enhancing the bioavailability and controlled release of drugs. The encapsulation of CD-MOF nanocrystals with polymers such as Eudragit® RS represents a significant leap in this direction, offering a promising platform for the future of oral DDSs. These advancements not only highlight the potential of CD-MOFs in improving drug solubility and stability but also pave the way for new, more effective oral therapeutic interventions.

3.8. Magnesium-based MOFs (Mg-MOFs)

Magnesium (Mg), an essential mineral for human health, plays a pivotal role in bone matrix synthesis, osteoblast activity, and bone mineralization processes [108-110]. Additionally, it possesses anti-inflammatory properties through the regulation of inflammatory cytokines, contributing to its therapeutic profile [111]. Mg-MOFs, notably Mg-MOF-74, represent a sophisticated fusion of essential minerals with organic molecules for medical use [112]. This framework, which combines Mg ions with 2,5-dihydroxyterephthalic acid, stands out for its potential as a carrier for therapeutic agents, utilizing the natural advantages of Mg to promote health benefits [112].

In the realm of osteoporosis treatment, bone pain stands as a primary concern, often managed clinically with ketoprofen. However, the chronic oral administration of ketoprofen is associated with adverse effects. To address this challenge, researchers have developed Ket@Mg-MOF-74, an innovative oral DDS that leverages Mg-MOF-74 technology [113]. This multifunctional approach comprehensively tackles bone pain, bone mass loss, and inflammation associated with osteoporosis. Mg-MOF-74 demonstrated remarkable stability, while Ket@Mg-MOF-74 exhibited controlled release capabilities for both ketoprofen and Mg ions in solution [113]. *In vitro* experiments underscored its potential to mitigate pain-related gene expression, enhance osteogenic cytokine production, and reduce pro-inflammatory factor secretion. Ket@Mg-MOF-74 represents a promising oral delivery system for osteoporotic pain management, offering a comprehensive approach that combines pain relief, anti-inflammatory action, and bone formation promotion [113]. In another study (Table 2), Mg-MOF-74 was investigated for its potential to fine-tune the release of orally delivered drugs, examining IBU, 5-FU, and curcumin [114]. These drugs were selected

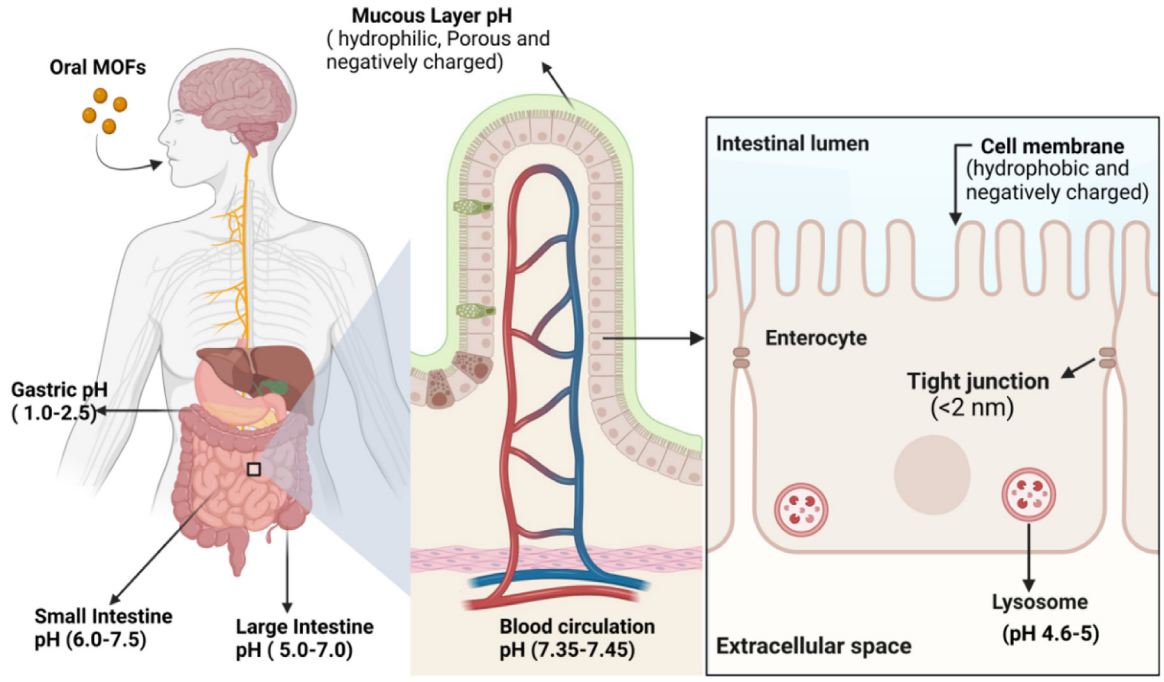

Fig. 5 – Addressing the Complexities of Oral MOF Delivery: Navigating Toxicity, Stability, and Physiological Barriers in the Gastrointestinal Tract and Beyond. This image illustrates the transit of oral MOFs through the GI tract. It highlights the challenges posed by the varying pH levels, from the highly acidic stomach to the neutral blood circulation, and the biological barriers, such as the mucosal layer and enterocyte cell membranes. The MOFs must remain stable while traversing these barriers to reach systemic circulation and deliver their therapeutic payload effectively. Created with BioRender.

for their diverse solubility and molecular sizes and were incorporated into the MOF at 30, 50 and 80 wt% loadings [114]. The study's findings have significant implications for oral drug delivery. The solubility and size of the drug influenced its release from Mg-MOF-74, with 5-FU released most rapidly, suggesting a benefit for drugs requiring fast absorption in the GI tract [114]. Conversely, curcumin's slower release profile points to the potential for creating sustained-release oral formulations [114]. This research underscores the versatility of MOFs in creating customized release profiles for oral drugs, which is crucial for improving bioavailability and therapeutic effectiveness. Mg-based biomaterials, especially Mg-MOF-74, have shown great potential in enhancing oral drug delivery by leveraging their bone health and anti-inflammatory benefits. The ability of Mg-MOF-74 to modulate drug release offers the promise of more effective, body-compatible oral therapies with fewer side effects. This technology could be transformative, allowing for tailored drug release profiles that enhance the bioavailability and effectiveness of oral medications.

4. Challenges and limitations of using MOFs in oral drug delivery

The quest to revolutionize drug delivery mechanisms has led to the advent of MOFs. As promising as they appear, it is essential to recognize that they are not without potential challenges and limitations, especially when considering their deployment in oral drug delivery (Fig. 5). Delving deeper into these concerns ensures a holistic perspective and paves the way for strategic advancements in this field.

4.1. *Potential toxicity concerns*

In the realm of oral drug delivery, MOFs present a unique set of challenges and considerations, particularly concerning their toxicity. These challenges are primarily influenced by factors such as dose, physicochemical properties, biotransformation, and chemical composition [115], all of which are critical in determining the safety and efficacy of MOFs when used for oral administration.

One of the key concerns with MOFs in oral delivery could be the certain dose of MOFs and their ability to bypass physiological barriers and accumulate in specific tissues or organs [36,115,116]. This characteristic can potentially lead to severe side effects [116]. The physicochemical properties of MOFs, including size and shape, are also crucial. The smaller MOF nanoparticles, due to their increased penetration ability, can disrupt cellular processes, potentially leading to inflammatory responses or even cellular apoptosis in severe cases [117]. However, this reduced size can lead to faster degradation due to a larger surface area exposed to the biological environment, necessitating a careful assessment of their colloidal stability or agglomeration behavior, especially for particles smaller than 200 nm [118-120].

The surface chemistry of MOF NPs is crucial, serving as the main interaction point with biological systems and greatly influencing their toxicity. This interaction often involves the generation of reactive oxygen species (ROS) on the

surface of MOFs, leading to oxidative stress, which is a precursor to cellular damage and various forms of chronic diseases if exposure is prolonged [121]. Chemical stability under biologically relevant conditions is another critical factor affecting the toxicity of MOFs [115,122]. The unique composition of MOFs, comprising both inorganic and organic components linked by coordination bonds, means that their degradation behavior in different cellular compartments can lead to a higher local concentration of potentially toxic metals or organic linkers. For instance, the degradation of certain MOFs in the acidic environment of lysosomes could release zinc ions at concentrations high enough to induce cytotoxic effects such as mitochondrial dysfunction or DNA damage [35,115]. The varying pH values in different parts of the human body, especially within the GI tract, can significantly impact the degradation rate of MOFs, influencing their stability and subsequent toxicity [123,124].

The chemical composition of MOFs, encompassing both inorganic metal clusters and organic building blocks, is a determinant of their overall toxicity [125]. Different metals used in MOFs exhibit varying levels of cytotoxicity, and this is often correlated with their rate of degradation in biological media [115]. The nature of the organic linker is equally important, as different linkers can have varying effects on the biofriendliness and toxicity of the MOFs [115,125]. The hydrophobic or hydrophilic nature of these linkers can influence the rate at which MOFs are excreted from the body, with hydrophobic linkers typically associating with lipid droplets and leading to slower removal [115,126].

In summary, the application of MOFs in oral drug delivery requires a thorough understanding of their toxicological profile. This includes careful consideration of their size, shape, surface chemistry, stability under physiological conditions, and chemical composition. Such an understanding is vital to harness the potential of MOFs in delivering therapeutic agents effectively and safely through the oral route.

4.2. *Challenges of MOFs in GI tract*

4.2.1. *Stability issues in the GI environment*

The acidic environment of the stomach, characterized by a low pH typically ranging from 1 to 2 due to the presence of hydrochloric acid (Fig. 5), plays a crucial role in digestion and pathogen defense [127]. However, this highly acidic milieu can present significant challenges for the stability and functionality of materials such as metal MOFs introduced into the body for biomedical applications, such as DDSs [40,128].

Here are some detailed points on the implications of the acidic environment of the stomach on MOFs: (1) Acidic degradation of MOFs. Many MOFs are constructed with metal nodes that are connected by organic linkers. These linkers are often susceptible to protonation or hydrolysis under acidic conditions, leading to the breakdown of the MOF structure [34,129]. The degree of susceptibility to acid varies widely depending on the chemical nature of the MOF. For instance, in acidic environments, metal ions and protons compete to bond with the organic linkers in MOFs, leading to the breakdown of MOFs with softer metal components such as ZIF-8(Zn) [123]. In contrast, in basic or alkaline environments, hydroxide ions replace organic linkers, accelerating the degradation of MOFs with harder metals such as MIL-100(Fe) or UiO-66(Zr) [124,130]. (2) Protonation of organic linkers. The organic linkers in MOFs can sometimes contain functional groups such as amines, carboxylates, or others that can be protonated in an acidic environment [115]. This protonation can disrupt the coordination bonds between the linkers and the metal nodes, potentially leading to framework collapse [115,117]. 3) Metal leaching. When MOFs decompose in an acidic environment, the metal ions can leach out. Not only does this destroy the framework, but it can also pose toxicity issues if the metals are not biocompatible or if they exceed safe concentration levels in the body [131,132]. (3) Kinetics of degradation. The rate of degradation of MOFs in an acidic environment is also a critical factor. Fast degradation can lead to a burst release of any encapsulated drugs [133], while slow degradation might fail to release the drug payload effectively [132].

4.2.2. *Mucosal epithelial barrier*

The epithelial mucous layer (Fig. 5), a sophisticated biological hydrogel, is a crucial first line of defense in oral DDSs. It consists of an epithelial mucous layer interspersed with aqueous pores approximately 200–300 nm in diameter, functioning as a selective diffusion barrier [40]. This layer discriminates between molecular passages, facilitating the transport of certain small molecules while obstructing those of substantial size [134-136]. For MOFs that exceed 300 nm, there is a predisposition for rapid mucus clearance due to their size. The intrinsic hydrophilic and negatively charged nature of the mucous layer, attributed to the presence of lipids, proteins, and glycosylated mucins, endows it with selective permeability characteristics [134,135,137,138]. Particles that are hydrophilic and bear a neutral charge traverse this mucus layer without impediment, in stark contrast to charged entities that may engage in repulsive or adhesive interactions with mucins [139]. As MOFs navigate successfully through this mucosal layer, they next encounter the epithelial cell membranes, presenting another critical barrier for oral drug delivery [36,40]. The transition from mucus layer interaction to cellular membrane penetration highlights the multifaceted role of the mucosal epithelial barrier in regulating drug delivery.

The mechanisms of transmembrane absorption include transcellular route and paracellular route. MOFs that possess hydrophobic and positively charged surfaces are preferentially internalized via the transcellular pathway. This route involves the direct passage of MOFs through cell membranes, typically via endocytosis, where they are enveloped by the cell membrane and internalized within endocytic vesicles [140]. Conversely, the paracellular route, involving passage between epithelial cells, is less feasible for MOFs due to tight junctions that restrict openings to less than 2 nm [141,142]. Therefore, the design of MOFs primarily focuses on enhancing their capability to undergo transcellular absorption [45]. However, the epithelial absorption of such hydrophilic and neutrally charged entities is naturally inhibited by the hydrophobic and negatively charged properties of the cell membrane. Particles with properties aligned for transcellular uptake are therefore essential for effective drug delivery. Once internalized, MOFs encounter the lysosomal environment, which is highly acidic

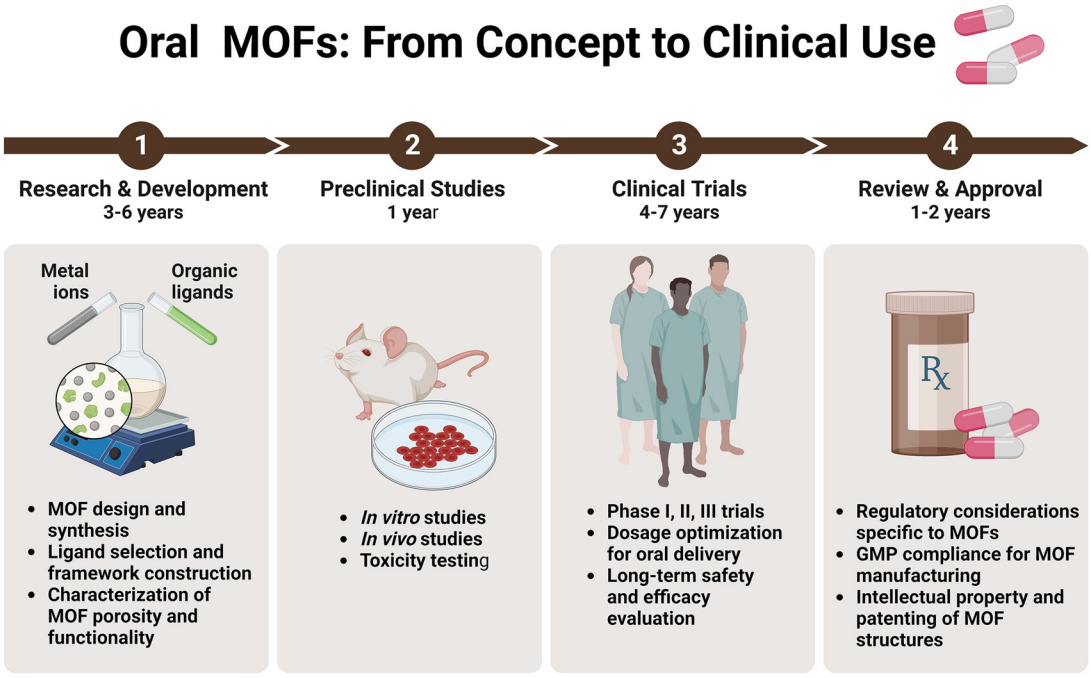

Fig. 6 – Infographic illustrating the sequential stages in the development of oral MOFs for drug delivery, highlighting the research and development phase, preclinical and clinical testing, and the final review and approval process for clinical use. Created with BioRender.

and may lead to the destabilization of the MOFs, potentially inducing the premature release of the encapsulated drugs and causing toxic effects [40]. This underscores the need for careful consideration in the design of MOF-based systems to ensure stability, controlled release, and biocompatibility [40,143]. Navigating both the mucous and cellular barriers presents significant challenges in the engineering of MOF-based delivery systems that must synergistically fulfill the requirements of both barriers [40]. This section not only highlights the critical role of the mucosal epithelial barrier in oral drug delivery but also illustrates how understanding transmembrane absorption mechanisms is essential for designing effective MOF-based systems.

4.3. *Challenges of MOFs in blood*

Within the physiological context of human blood, maintaining a pH value between 7.35 and 7.45 and enriched with phosphate ions (PO_3^{-4}), a distinct interactive dynamic with MOFs emerges (Fig. 6). The robust coordination capacity of PO_3^{-4} with metal ions, driven by the availability of lone-pair electrons from the oxygen atoms in the phosphate structure, has the potential to undermine the porous integrity of MOFs, such as ZIF-8 [119,144]. This interaction not only risks the structural collapse of the MOFs but also raises concerns about MOF-induced red blood cell (RBC) aggregation and hemolysis [119]. Moreover, this phosphate-triggered MOF disintegration can make it difficult to deliver drugs to the exact place where they are needed. Additionally, the release of organic ligands and metals during this process can be inadvertently toxic to the human body.

5. Possible ways to overcome the challenges for oral delivery of MOFs

Addressing the challenges of oral delivery for MOFs involves various innovative approaches, each targeting specific aspects of MOF performance and safety. These strategies are crucial in optimizing MOFs for effective and secure drug delivery.

5.1. *Tackling toxicity concerns*

To mitigate or eliminate the potential toxicity of MOFs, a variety of approaches can be adopted. A proactive step is to undertake comprehensive toxicity assessments using doses that exceed the typical concentrations employed in clinical settings [145]. Particularly vital is the evaluation of orally administered MOFs, examining their pharmacokinetic profiles, including absorption, distribution, metabolism, and excretion (ADME), in *in vivo* models, alongside *in vitro* dose-response studies [146-148]. Furthermore, the application of surface modifications, such as polymer coatings, can substantially enhance the colloidal and chemical stability of MOFs. These alterations not only deter the unsolicited adsorption of biomolecules, fats, or proteins but also mitigate the formation of a biocorona, which is advantageous for navigating specific physiological routes [121]. A case in point is MIL-100 (Fe), a MOF that has garnered attention in toxicity research due to its potential in biomedical contexts. This MOF illustrates the efficacy of surface modifications: native MIL-100 (Fe) particles tend to clump together in physiological environments, yet this is significantly counteracted when molecules such as CD or cross-linked PEG are attached

to their surface, thus enhancing their overall stability [130,149,150]. The development of materials with built-in safety features, an approach termed "safe-by-design," is becoming increasingly prevalent [151,152]. MOFs, with their customizable metal clusters and organic linkers, stand out as a particularly versatile and forward-looking material class within this paradigm. This "safe-by-design" principle is applicable throughout the life cycle of MOFs, from their initial synthesis and drug incorporation phases to subsequent surface modifications.

The fabrication of MOF nanoparticles adhering to safe and sustainable design standards is readily attainable. Utilizing only biocompatible materials and chemicals, such as solvents, acids, bases, mineralizing agents, and modulators, significantly reduces the risk of toxicity if the MOFs are to break down [153,154]. The shift toward more conscientious research practices is evidenced by recent studies. These include methods for creating MIL-100 (Fe) without the use of toxic substances and techniques for incorporating drugs into MOFs and applying surface coatings in water-based, nontoxic environments, indicating a move toward more responsible and sustainable material synthesis in the industry [149,155].

5.2. *Strategies to overcome GI tract challenges with MOFs*

To navigate the rigorous conditions of the GI tract and harness the potential of MOFs in drug delivery, several tailored strategies can be employed. The development of MOFs that are inherently resistant to acids involves using metal ions and organic linkers that remain stable in the stomach's low pH conditions. By selecting materials that are less likely to break down in acid, these MOFs can maintain their structure and function [2,42]. In the realm of developing acid-resistant MOFs, a study conducted by Chen et al. serves as a pertinent example [2]. They investigated a Zr-MOF known as NU-1000, designed for the oral delivery of INS. INS is particularly vulnerable to degradation in the stomach's acidic environment, and the objective was to use NU-1000 to encapsulate and safeguard it against such conditions [2].

Enhancing MOFs after they are initially synthesized is another strategy. This post-synthesis enhancement can include adding groups to the MOF that are not affected by acid or replacing parts of the MOF that are sensitive to acid with parts that are more resistant. A concrete example would be the use of silane coupling agents [84,112,156-158]. These agents can introduce silanol groups to the MOF structure, which, upon further condensation, form a silica-like protective layer on the surface of the MOF particles [112,159]. This silica layer is known for its chemical resistance and can protect the MOF from the acidic environment of the stomach [112,159]. In the work presented by Huang et al., Fe-MOF featuring Fe(II) ions and 1,1′-(1,4-butanediyl)bis(imidazole) was developed and utilized for encapsulating doxorubicin [160]. The Fe(II)-imidazolate bonds within the MOF structure demonstrated an increased rate of degradation in acidic environments, leading to a more rapid release of the drug at a pH of 5.5 as opposed to a neutral pH of 7.4. To mitigate this swift degradation and regulate drug release, researchers applied a silica coating to the surface of the MOF, which effectively slowed the decomposition of the nanocarrier under acidic conditions [160].

Another approach to improve stability is encapsulating MOFs within microspheres. This encapsulation provides an additional protective layer, ensuring that the MOFs remain intact and functional as they navigate through the GI system. A novel biodegradable nanocomposite microsphere incorporating INS-loaded Fe-MOF nanoparticles (MIL-100) has been developed [39]. These microspheres are designed to safeguard the MOF nanoparticles from rapid degradation in the acidic milieu of the stomach, ensuring their integrity until they reach the intestine [39]. Upon reaching the simulated intestinal fluid, the microspheres facilitate the release of the encapsulated INS, effectively mimicking the desired *in vivo* release profile [39].

Post-modifications, especially surface coatings with protective shells such as polymers such as CS [55], alginate [68], gelatin [20], and PEG, have been used to increase MOF stability. In an innovative study, researchers synthesized Zr-NDC, a Zr-MOF, and modified it with CS to enhance the oral delivery of 5-FU [55]. The CS modification significantly increased the stability of the MOF in the GI tract, addressing a major challenge in the oral administration of 5-FU [55]. This stability-focused design of the CS-coated Zr-NDC MOF presents a promising strategy for improving the stability and oral bioavailability of Zr-MOF and 5-FU, respectively. A study investigated the oral delivery of IBU using a Cu-MOF encapsulated within pH-sensitive gelatin microspheres [20]. Due to the rapid decomposition of Cu-MOF in acidic conditions, a swift release of the drug was noted at pH 1.2, with 95 % of IBU released within 2 h [20]. In contrast, the application of a GM polymer coating resulted in a more controlled release, with approximately 72 % of the drug released over 8 h in a pH sequence of 1.2, 6.8 and 7.4, reflecting the pH-sensitive nature of the gelatin polymer and the diffusion barrier provided by the GM [20]. The PEGylated DDS PEG/PA@ZJU-64-NSN was developed to enhance the oral bioavailability of PA by protecting it against degradation in the gastric environment [30]. The incorporation of PEG into the Zn-MOF significantly improved the chemical stability of the PA@ZJU-64-NSN complex [30]. Hence, implementing these methods can significantly enhance the durability and effectiveness of MOFs as drug carriers, enabling them to transport therapeutic agents safely through the acidic sections of the GI tract.

5.3. *Overcoming the challenges of MOF in blood*

Addressing the challenges presented by the bloodstream for MOF-based delivery systems requires meticulous design to achieve both therapeutic efficacy and compatibility with blood components [161]. Hemocompatibility is of particular concern, as MOFs must not induce adverse reactions such as hemolysis or interfere with the normal function of blood cells [161-163].

To ensure safe interaction with blood, MOFs can be designed with biocompatible metals and linkers that resist degradation and prevent the release of potentially toxic ions, showing their hemocompatibility [161]. For example, using biocompatible materials such as zirconium or copper in the MOF structure can improve blood compatibility due to

their stability and low toxicity [161,164]. Zirconium-based MOFs, in particular, have been studied for their resistance to degradation in biological environments, resulting in hemocompatibility [164].

Additionally, coatings can be applied to MOFs to reduce their reactivity with blood components and to avoid triggering the body's immune response [165,166]. Coatings, such as hydrophilic polymers (*i.e.*, PEG and gelatin), can be employed to create a stealth-like effect, allowing MOFs to circulate undetected by the immune system and thereby reducing the possibility of clearance by phagocytic cells. Additionally, by attaching PEG to the surface of MOFs, researchers aim to control the interactions between these nanoparticles and biological media, such as blood plasma [58,78,165,167]. A study by Mobin et al. highlights the hemocompatibility of IITI-3, a gelatin-coated Cu-MOF designed for oral INS delivery [78]. This MOF's stability and blood compatibility make it a promising candidate for safe oral drug administration, ensuring that it can pass through the digestive system and into the bloodstream without causing adverse reactions.

6. Regulatory considerations for clinical translation and opportunities

The clinical transition of MOFs faces a rigorous regulatory pathway (Fig. 6), chiefly managed by the U.S. Food and Drug Administration (FDA) and the European Medicines Agency (EMA), which necessitates specific demonstrations of their safety and efficacy tailored to their unique properties as oral DDSs [168]. Key to navigating this regulatory landscape is demonstrating the unique safety challenges and efficacy potentials of oral MOFs, including their biocompatibility and stability under physiological conditions. Critical to the approval of oral MOFs is a thorough assessment of their safety and biocompatibility [14,169]. Specific evaluations focus on the impacts of MOFs and their biodegradation products, which are crucial for ensuring patient safety and meeting stringent regulatory standards [115,122]. Another significant hurdle is the scale-up from laboratory synthesis to industrial production, maintaining MOFs' consistency, purity, and stability, each of which is essential for ensuring reliable drug delivery and regulatory compliance [170]. Such consistency is crucial for ensuring reliable drug delivery and patient safety.

Furthermore, the clinical translation of oral MOFs necessitates a series of preclinical and clinical tests. Initially, their safety and efficacy must be established in animal models [171,172]. Following successful preclinical results, MOFs enter a phased approach in clinical trials, each phase designed to systematically evaluate their safety, dosage, efficacy, and side effects in humans [115]. To date, more than 90,000 MOFs have been documented, and it is predicted that over half a million MOF structures exist, offering an extensive array of MOF configurations for exploration and practical use [173,174]. Despite this, the first clinical trial utilizing MOFs was launched in 2018 with the objective of improving the efficacy of X-ray radiotherapy (RT) in cancer therapy [NCT03444714]. To date, only one MOF has progressed to a phase I clinical trial [173]. This indicates that there is still a significant amount of research and development needed before MOFs can become a commonplace option in clinical settings. The biosafety of materials like MOFs is paramount in clinical settings. Despite promising applications, no MOF-based therapeutic agents have yet received FDA approval, emphasizing the critical need for focused development on their safety profiles. It has been three decades since MOFs were first discovered, and materials based on MOFs are only now beginning to demonstrate their potential, particularly in delivery systems such as oral administration. Key challenges that must be addressed include enhancing the stability and biocompatibility of MOFs in the GI and circulatory systems. A specific area of focus should be on postmodifications of MOFs, aiming to endow these materials with smart, responsive behaviors within the GI environment, including lumen, mucous layer and epithelial interactions.

Moreover, a thorough understanding of the behavior of MOFs inside the body, including their administration, circulation, degradation, and elimination, is crucial. Factors such as biodegradability, particle size, and controlled substance release during breakdown require careful planning and detailed attention for effective oral delivery systems. The ongoing evolution of oral MOF-based delivery systems is an exciting prospect. It spans from fundamental design and structure formation to *in vitro* and *in vivo* transport dynamics, responsive actions, and ultimately, their application in clinical settings (Fig. 6). This journey demands a multidisciplinary approach, combining innovative research with rigorous regulatory compliance to ensure the safe and effective use of MOFs in medicine.

7. Concluding remarks and future perspective

This review has illuminated the dynamic and promising field of MOFs in advanced oral DDSs. With their unique blend of metal ions and organic linkers, MOFs offer groundbreaking approaches to overcoming challenges in oral drug delivery. Their capabilities in enhancing drug solubility, bioavailability, and controlled, targeted release have showcased transformative potential in pharmaceutical sciences. MOFs have high drug-loading capacities, tunable structures, and the ability to protect drugs from harsh GI environments, marking a significant leap in medical therapeutics. The versatility of different MOFs, such as Zr, Fe, Zn, Cu, Ti, Al, K and Mg-based frameworks, further enhances their applicability across a wide spectrum of drugs and therapeutic needs.

However, the journey of MOFs from laboratory research to clinical application is not without challenges. A comprehensive understanding of the complex *in vivo* fate of MOFs and their loaded passengers, including their biodistribution and stability, is crucial. This understanding can be enhanced by surface modification and functionalization. There is a scarcity of *in vivo* data on MOFs, and mimicking the degradation mechanism of MOF particles *in vivo* remains challenging due to the complex nature of body fluids. Furthermore, most studies have primarily focused on the bioavailability and biodistribution of drugs after oral administration, with a notable lack of comprehensive

pharmacokinetic mechanisms covering the entire ADME process. Future research should pay closer attention to aspects such as enzymatic degradation (*e.g.*, CYP450) and efflux transporters (*e.g.*, P-gp), which play a significant role in the absorption and permeation of therapeutics. Continued research is needed to fully understand and mitigate potential toxicity concerns, focusing on developing MOFs with optimal size, shape, surface chemistry, and stability under physiological conditions. Optimizing the route and dosage of administration is necessary, along with identifying appropriate animal models for *in vivo* testing and employing advanced 3D *in vitro* preclinical evaluations.

Advancements in the synthesis of MOFs, particularly in tailoring their pore sizes, surface functionalities, and degradation rates, are essential. Future research should also consider the scalability of MOF production and the regulatory landscape, ensuring that lab successes can be translated into commercially viable products. Establishing standardized safety and efficacy guidelines for MOF-based DDSs will require a collaborative approach among scientists, industry stakeholders, and regulatory bodies.

In conclusion, while the potential of MOFs in revolutionizing oral drug delivery is undeniable, significant research and development, coupled with regulatory compliance, are essential for their successful clinical translation. With continued research and innovation, MOFs could significantly enhance the efficiency of drug delivery, reduce side effects, and improve patient compliance, leading to better health outcomes.

Declaration of Competing Interest

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.

CRediT authorship contribution statement

Aun Raza: Conceptualization, Data curation, Formal analysis, Methodology, Software, Visualization, Writing – original draft, Writing – review & editing. **Wei Wu:** Conceptualization, Supervision, Writing – review & editing.

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