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Innovative carrier in cancer therapy: utilization of ZIF-8 as a nanocarrier for combination cancer pharmacotherapy: a review

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Keywords: metal organic frameworks, combination therapy, functionalization surface, drug loading

Abstract

Metal–Organic Frameworks (MOFs) have rapidly emerged as versatile nanoparticles system for their use in biomedical field, especially in drug delivery. Of the materials in this class, zeolitic imidazolate framework ZIF-8 has recently captured significant interest due to its tunable structure and significant potential for surface modification. It is these same features which allow ZIF-8 to act as a suitable carrier in both single agent and combination therapy. In particular, surface chemistry will be reiterated throughout the present article as significant in improving the physicochemical stability, biocompatibility and targeted drug delivery of the materials. In addition, through well-designed modification strategies ZIF-8 herein we propose to show controlled release profiles, improved colloidal stability, and improved therapeutic efficacy. This review will discuss recent advances made in the surface engineering of ZIF-8 and present salient design principles and functionalisation techniques and their usefulness in the area of drug-delivery applications.

1. Introduction

Cancer is still one of the leading causes of death worldwide and continues to exert heavy pressure on global health systems [1, 2], although there have been significant advances in diagnostic and therapeutic methodology in malignant lesions such as breast and lung cancer which continue to have a high rate of incidence and mortality [3, 4]. Though the standard treatment of surgery, chemotherapy, and radiotherapy of malignant lesions has resulted in a significant improvement in the therapy of patients, this modality of treatment is often limited by serious side effects and poor specificity of action, resulting in damage to normal tissues, and a change in the quality of life of the patient [5, 6]. To meet the challenges of treatment of malignant lesions, significant attention has been directed to the drug-delivery system with the object of improving the efficacy of the therapy while minimizing systemic toxicity [7]. Nanoparticle-mediated combination therapy, in particular, enables the co-delivery of multiple therapeutic agents with distinct physicochemical and pharmacological characteristics within a single platform [8].

MOFs, especially ZIFs, have emerged as promising anticancer carrier due to their attractive characteristics among various nanoparticles. These metal organic frameworks have recently paid attention because they integrate features of both inorganic and organic chemistry [9, 10]. Furthermore, surface of MOFs has ability to functionalize easily, enabling the attachment of specific molecules, and they have a high drug loading capacity while allowing for controlled drug release. Consequently, MOFs represent a compelling platform for drug delivery applications in the biological area [11].

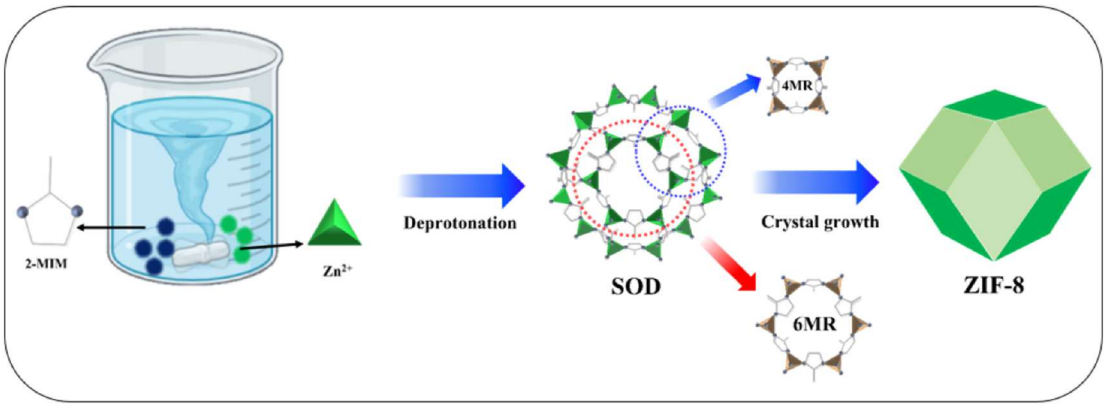

Figure 1. Schematic illustration of the formation of sodalite structured ZIF8. Reproduced from [20]. CC BY 4.0.

ZIFs among MOFs have attracted significant attention owing to their exceptional attributes such as well define structure, various functionalities of their surface [12, 13], with a prominent features its pH- responsive drug release [14]. From a biological perspective, ZIFs demonstrate an exceptional stability under physiological conditions and effectively prevent premature drug leakage. Moreover, their capability for efficient cellular uptake renders them strong candidates for use as drug delivery systems [15, 16]. It is well established that ZIF-8 is a MOF structurally analogous to zeolites. Both ZIF-8 and ZIF-67 possess a microstructure based on a sodalite cage topology, in which 2-methylimidazole (MeIM)- links neighboring zinc and cobalt ions, respectively [17–19], as shown in figure 1.

ZIF-8 has preparation in different techniques, including solvothermal synthesis, ultrasound- assisted synthesis, mechanochemical approaches, and accelerated aging methods. it can be readily synthesized in substantial quantities by combining zinc salts and 2-methylimidazole linker in water or polar organic solvents at ambient condition [21, 22].

The forementioned studies by researchers Cravillon *et al* [23] and Pan *et al* [24] demonstrated the successful synthesis of ZIF-8 using diluted zinc salt and 2-MeIM in solution at room temperature. This technique offers a several advantages over both solvothermal and microwave-assisted solvothermal methods, primarily due to its reduced energy consumption. Moreover, the room temperature approach results in a higher product yield and, smaller crystal size, and requires lower energy, and shorter reaction times. These attributes are particularly advantageous for the application of ZIF-8 nanocrystals in biomedicine.

Uniquely, this review presents an in-depth and integrative discussion of using nanoparticles ZIF-8 as a combination anticancer carrier a comprehensive understanding of how ZIF-8, thereby providing valuable insights into the optimization of drug delivery strategies facilitated by this versatile nanomaterial, particularly through surface functionalization to enhance cargo loading. This level of detail and synthesis distinguishes the review as a valuable resource for guiding future research and practical innovations in the drug delivery field.

2. Properties and loading approches of ZIF-8 nanoparticles

ZIFs, is a part of MOF frameworks family, that have non-toxic properties and remarkably large accessible cavities [25, 26]. ZIFs have a crystalline structure similar to natural zeolites. The characteristics of ZIF-8 provides thermal stability across a wide temperature range, and chemical stability in comparison to other MOFs [27]. Specifically, ZIF-8 is composed of zinc metal salt has tetrahedrally coordinated connected by 2-methylimidazole organic linkers, forming bond angles of approximately 145°, resembling the Si–O–Si angle found in zeolites structure [28, 29]. The ZIF-8 structure stabilized by a combination of π–π stacking interactions and hydrogen bonds. This configuration forms a coordination framework with a central octahedral pattern surrounded by tetragonal and hexagonal faces, resulting in large pore diameters of approximately 11.6 Å and a surface area of 0.4 nm^3 [30].

Research indicates that ZIF-8 exhibits minimal sudden or unexpected drug release at a neutral pH of 7.4. while collapsing at a pH of 5.4–6, consistent with the acidity typically found within the tumor microenvironment, understanding its potential utility as a pH-responsive drug carrier [31, 32]. Furthermore, ZIF-8 possesses low toxicity, and excellent stability; at elevated temperatures, zinc ions transition to a volatile state, leading to the development of a distinct pore structure [33].

The high surface area and adjustable pore size of ZIF-8 allows the encapsulation process of a wide range of therapeutic drugs, as its remarkably large and accessible pores can accommodate considerable quantities of

agents. This encapsulation not only protects therapeutic agents from degradation but also allow their targeted delivery to tumor sites [34]. The amount of drug loaded into the ZIF-8 carrier is directly influenced by the physical characteristics of the carrier such as volume, surface area, pore dimensions, and framework flexibility demonstrating a clear relationship between drug loading capacity and structural features [35].

Morphology of ZIF-8 framework have been reported by numerous studies, described that ZIF-8 has a polyhedral structure, particularly dodecahedron and hexagonal forms, which consider to be the most common ZIF-8 morphologies, whereas cubic structures are rarely observed. There appears to be no consistent relationship between ZIF-8 morphology and the synthesis method [36]. Instead, key reaction parameters, such as molar ratio of zinc metal to organic linker and the reaction temperature, play a critical role in controlling morphology [37]. Collectively, these physical characteristics allow ZIF-8 exhibit efficient loading and release of agent molecules, while maintaining chemical stability under biological conditions [38].

Compared with other nanoparticles carriers, such as nanomicelles and liposomes, ZIF-8 shows a superior encapsulation efficiency and improvement in the stability of drugs. Its biocompatibility, biodegradability, and non-toxicity make it all the more attractive for application in biomedical field [39].

ZIF-8 has been identified as a highly effective drug delivery system characterized by low toxicity, particularly at lower concentrations not exceeding 30 μg, at which its toxicity is considered negligible [40]. A notable attribute of ZIF-8 is its capacity to function as a protective barrier for therapeutic agents, thereby enhancing treatment efficacy while diminishing potential side effects, as well as safeguarding drugs integrity against degradation at tumor sites [41].

In drug delivery system, two main approaches have been extensively utilized for ZIF-8. The first method, known as the impregnation technique, involves the physical adsorption of drugs or agents onto the exterior of metal–organic frameworks after their synthesis. This process permits drug molecules to penetrate MOFs through their porous structure, which is usually done by capillary forces, electrostatic interactions, or coordination reactions. It is specially applicable to the therapeutic agents of the dimensions of which are smaller than pores sizes of the MOFs [42]. The pore window size, chemical composition, and flexibility of MOFs are critical factors for the successful incorporation of drugs [43].

The second technique is *in situ* synthesis (one pot method), in which drugs are incorporated into ZIF-8 during its synthesis, enabling the loading of therapeutics of various sizes by introducing imperfections into the framework. The objective of this approach is to prevent drug leakage prior to carrier degradation. However, achieving effective drug loading and controlled release requires strong interactions between the drugs and MOFs, as well as a uniform distribution of the drugs within the pores of the modified ZIF-8 structure [44]. One disadvantages of this method is its relatively low loading capacity [45].

2.1. Combination drug delivery mechanism by ZIF-8

(A) **pH-triggered disassembly and coordination chemistry**

ZIF-8 offers numerous advantages for use in drug delivery systems [46]. The imidazole ligands in ZIF-8 can undergo deprotonation to form an anionic, multi-terminal ligand with strong basicity. Upon coordination with the metal ions, these imidazole ligands form highly stable interactions [47]. For biomedical applications, both the metal ions and organic ligands must exhibit good biocompatibility, making it essential to avoid highly toxic metal ions such as Cr and Ni. In contrast, metal ions such as Fe, Zn, and Mn are more suitable, as they are essential elements involved in human physiological processes [12].

ZIF-8 has been shown to remain stable under neutral conditions but degrades readily in acidic environment [48, 49]. Previous literatures have established that ZIF-8, particularly the Zn-N coordination bonds, retains structural stability at physiological pH (7.4), thereby maintaining its crystalline structure and securely entrapping the therapeutics loading [50]. However intrinsic instability of ZIF-8 has been observed in tumor tissues, which typically exhibit a pH range of 5.5–6.0 [51]. The pH- responsive behavior of ZIF-8 during drug release can be explained by the protonation of the imidazolate group at pH values between 5.0–6.0. This protonation weakens and ultimately disrupts the zinc -imidazolate coordination bonds, resulting to disassembly of the nanostructures and subsequent release of the encapsulated drug [52, 53].

(B) **Drug loading and functionalization mechanisms**

The excellent drug loading capacity of ZIF-8 arises from its pours architecture and chemically versatile coordination environment [36]. The framework contains coordinatively unsaturated Zn^{2+} sites that allow the simultaneous encapsulation of drugs with diverse physicochemical properties [54]. Hydrophobic drugs are typically confined within the hydrophobic pores through van der Waals force or π–π interactions, whereas hydrophilic or charged drugs can be adsorbed onto the external surface or coordinated to Zn^{2+} nodes via electrostatic or coordination interactions. This explanation is supported by

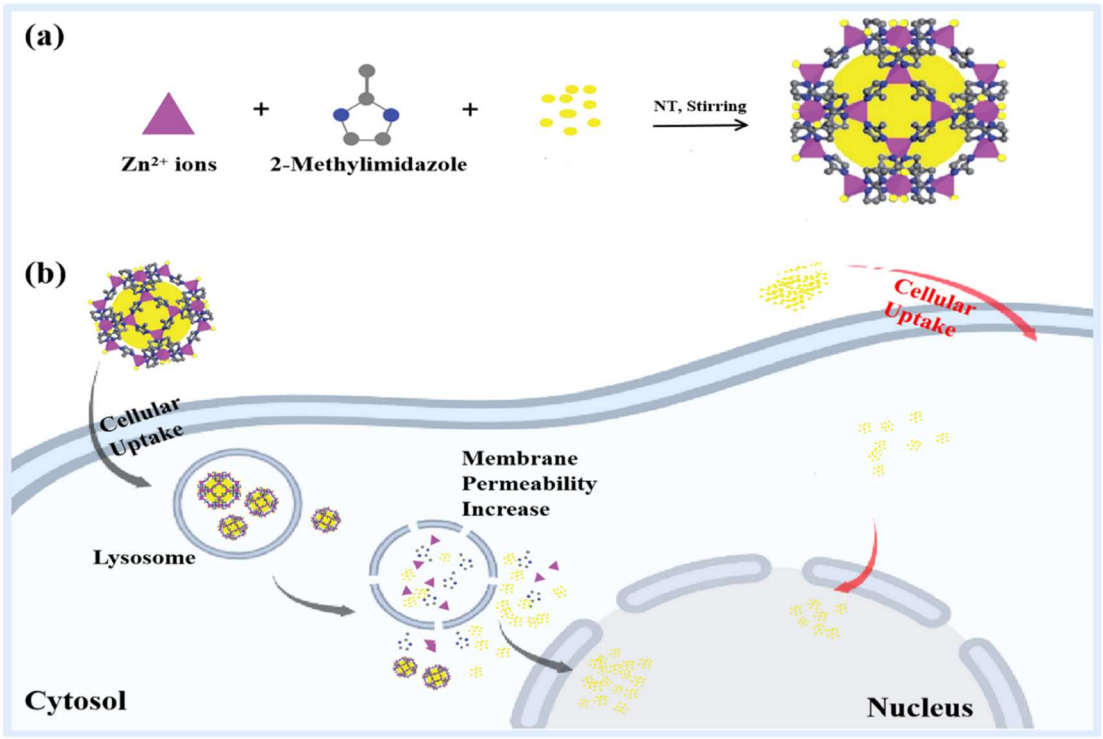

Figure 2. Preparation, transfer and bioeffects of drug@ZIF-8. (a) Encapsulating drug with ZIF-8 using one pot method (b) Transport, release and drug @ZIF-8 in cancer environment. Reproduced from [11]. CC BY 4.0.

a pervious study by Haghi *et al* who established the co-loading of the hydrophilic drug doxorubicin (DOX) and the hydrophobic compound epigallocatechin-3-gallate (EGCG) into ZIF-8 framework. Molecular-dynamics simulations revealed that DOX interacted primarily through electrostatic forces, while EGCG associated mainly through van der Waals interactions, supporting the concept that hydrophilic or charged drugs interact via electrostatic or coordination mechanisms [55]. ZIF-8 has also been shown to improve the stability of BIBR 1532 in aqueous conditions and enhance its cellular uptake, as illustrated in figure 2 [11].

Modified MOFs enable the efficient delivery of drugs with diverse sizes, molecular weights, and chemical properties. Drug molecules that are comparable in size to the MOFs pores can diffuse into the framework structure and be effectively stored through host and guest interactions [56]. Molecules containing specific functional groups may also be encapsulated by forming chemical bonds with the active sites of the ligands. Furthermore, peptides and proteins macromolecular, can be incorporated into tunable metal frameworks [57].

ZIF-8 can be effectively employed for one-step synthesis and drug delivery only when the administered drug contains an acidic functional group. However, many potent therapeutics agents lack such groups, which significantly restricts the applicability of ZIF-8 as a universal drug carrier. Thus, approaches to overcome this limitation are urgently needed. In one study, Zhang *et al* attempted to load cytarabine (Ara) into ZIF-8; however, due to the absence of an appropriate functional group, achieving a high drug loading capacity was not achievable.

To address this challenge, they proposed conjugating cytarabine (Ara) with a novel indocyanine green derivative (IR820) to form a prodrug, which was subsequently encapsulated within ZIF-8.This innovative approach substantially enhanced drug-loading capacity, demonstrating that structural modifications or related strategies can strengthen drug-carrier interactions and ultimately improve the loading efficiency of metal–organic frameworks (MOFs) [58].

2.2. ZIF-8 nanoparticles as monotherapy and combination therapy carrier

The use of ZIF–8 for the targeted delivery of chemotherapeutic agents to tumour tissues is widely regarded as one of the most effective strategies in cancer research [59]. ZIF-8 stands out among other zeolite imidazolate frameworks (ZIFs) due to its numerous advantageous features, particularly its exceptional drug - loading capabilities and pH-responsive behaviour [60]. Its unique cage-like three-dimensional zeolite -like network structure makes ZIF-8 an excellent candidate for a wide range of drug delivery applications [61].

Shaoxuan *et al* employed hyaluronic acid- coated ZIF-8 as a carrier for curcumin, achieving enhanced therapeutic efficacy in breast cancer treatment [62]. In another study, Mingxiang Xu *et al* developed a nanosystem composed of rapamycin-encapsulated ZIF-8 with the aim of overcoming chemotherapy resistance [63].

The use of ZIF pores provides a homogeneous and controllable environment with a large surface area, enabling efficient loading of both hydrophilic or hydrophobic drugs [64]. Nanoparticles serve as effective drug carriers by offering controlled delivery of multiple therapeutics, improving physicochemical properties, and enhancing drug solubility, stability, clearance, targeting, theragnostic capabilities, and combination therapy outcomes [65]. The nanoparticles-based co-delivery of therapeutic agents offers several advantages over the administration of a single drug, one of the most significant being the synergistic effect: two drugs can act through distinct pathways simultaneously, resulting in enhanced tumors cell killing and reduced development of multiple resistance (MDR) [66].

The concept of co-delivering more than one drug using MOFs has been introduced to address the decline in anticancer efficacy associated with MDR. Zhang *et al* reported the first multi-drug MOF-based carrier- PEG-FA/(DOX+VER) @ZIF-8 system prepared by co-loading doxorubicin (DOX) and verapamil hydrochloride (VER) via a one-pot synthesis, followed by surface, the carrier was modified modification with polyethylene glycol-folic acid (PEG-FA). The loading capacities for DOX and VER were approximately 8.9% and 32%, respectively. Furthermore, the half maximal inhibitory concentration (IC_{50}) of PEG-FA/(DOX+VER) @ZIF-8 was significantly lower than that of free DOX or DOX@ZIF-8 in both MCF7/A and B16F10 cells lines. Conjugation with PEG-FA additionally enhanced tumor accumulation and improved therapeutics outcomes [67].

Combination therapy extends beyond the mere physical mixing of individual drugs; it provides several advantages over monotherapy, particularly when a synergistic effect is achieved [68]. Table 1, presents various therapeutics combination delivered using ZIF-8. When strong synergism is present, lower drug concentrations can be used, reducing treatment related toxicities [69]. Combination therapy also helps protect normal cells from cytotoxic effects. Particularly, long-term monotherapy can drive cancer cells to active alternative survival pathways, reducing treatment efficacy [70].

By contrast, multidrug treatments increases the likelihood of eliminating all cancer cells, including cancer stem cell populations responsible for recurrence and resistance. This approach also facilitates targeted treatment of tumour heterogeneity. Multidrug resistance, often driven by the overexpression of efflux transporters such as P-glycoprotein, is a major cause of chemotherapy failure. Using a zeolitic framework as a co-delivery platform offers significant potential for 1) overcoming multidrug resistance and 2) enhancing drug- targeting capabilities [71].

In a study by Sun (2020), heparin-coated metal–organic frameworks were employed as a dual-delivery system for doxorubicin and quercetin in the treatment of lung carcinoma. Combination chemotherapy has emerged as a superior strategy in cancer therapy because it enhances cytotoxicity while reducing adverse effects. In this study, a hybrid nanoparticle was developed as a targeted carrier for the co- delivery of doxorubicin (DOX) and quercetin (QUE) for lung cancer treatment. The nanoparticles exhibited no observable toxicity and significantly increased apoptosis in cancer cells [72].

In another study titled 'Co-delivery of pirfenidone and siRNA in ZIF-based nanoparticles for dual inhibition of hepatic stellate cell activation in liver fibrotic therapy', Kaili Wang and colleagues (2023) examined the association between liver fibrosis and various liver diseases, including viral infections, alcoholism, and autoimmune disorders. Their outcomes showed that vitamin A-modified nanoparticles efficiently accumulated in fibrotic liver tissue and specifically targeting hepatic stellate cell HSCs, thereby enhancing nanoparticle internalization. These results show strong evidence supporting the potential anti-fibrotic efficacy of the system [73].

Yu *et al* carefully examined a nanoplatform composed of HA/ZIF–8@ICG@IMQ for the treatment of cold tumours. This structure of nanoparticle integrates the photothermal agent indocyanine green (ICG) with the immune adjuvant imiquimod (IMQ), yielding a marked enhancement in antitumor immune responses and promoting prolonged immune memory formation [74]. Likewise, Zhang *et al* preparation ZIF-8 framework nanoparticles HA/IR820@ZIF–8 and mannan (MAN) / (R837+1MT) @ ZIF–8, as shown in figure 3-A [59].

The intrinsic porosity of ZIF-8 makes it highly effective for simultaneous encapsulation of multiple pharmaceutical agents. Zhou *et al* employed a pore space partitioning (PSP) strategy to co-load 5-fluorouracil (5-Fu) and ursolic acid (UA), optimizing the pore architecture of ZIF-8 to achieve a synergistic therapeutic effect. The 5-Fu &UA@ZIF-8 formulation demonstrated significant greater cytotoxic than either single drug formulations (5-Fu@ZIF-8 or UA@ZIF-8), attributable to the synergistic interactions between the two compounds. As a results, the co-delivery system exhibited strong anticancer effect against 4T1 cells [75].

Zhou *et al* employed a methodology known as pore space partitioning (PSP) to achieve effective encapsulation and pH-controlled co-delivery of two guest molecules, 5-fluorouracil (5-FU) and ursolic acid (UA). This approach optimized the utilization of the pore space within ZIF-8, thereby enhancing the overall therapeutic effect. Notably, this co-system showed superior cytotoxic efficacy compared with the 5individual system, attributable to the synergistic effects of the combined compounds [75].

Table 1. Demonstrated various formulations of drug-loaded ZIF-8.

Authors	Drug 1	Drug 2	Anatomy of the cancer	Final results	References
Yan x et al. (2025)	NO donor L-arginine (L-Arg)	H_2O_2 precursor Vitamin K3 (VK3)	Breast cancer	Both loaded drugs achieved synergistic effect which increase oxidative stress and reacts with L-Arg to produce NO.	[91]
Li D et al. (2025)	Saikosaponin A (SSA)	doxorubicin (DOX)	Breast cancer	The co-drugs SSA and DOX facilitates synergistic effect which mitigating the cardiotoxic effects linked to DOX administration. The utilization of ZIF-8 as a co-delivery carrier enhancing the bioavailability of the therapeutic agents for the treatment of triple-negative breast cancer (TNBC)	[92]
Sheik A et al.(2024)	cellulase (CL) enzyme	resveratrol (Resv)	Breast cancer	The results shown that ZIF-8 @ CL & Resv improves targeted delivery to breast cancer cells, with a controlled release profile. This, along with reactive oxygen species (ROS) generation and mitochondrial depolarization, triggers apoptosis.	[93]
Ke Q et al. (2024)	bioenzyme glucose oxidase (GOx)	5-fluorouracil (5-FU)	Breast cancer	The degradation of ZIF-8, induced by acidity, results in the gradual release of Zn^{2+} and agent 5-FU within the acidic microenvironment tumors. As the protective coating of ZIF-8 diminishes, released GO_x leads to the depletion of intratumoral glucose (Glu), thereby employing a starvation therapy approach.	[94]
Radhakrishnan.K.et al. (2023)	curcumin (CUR)	5-fluorouracil (5-FU)	Breast cancer	The synthesized CUR-loaded CS-coated 5-FU@NZIF-8 exhibited dimensions conducive to the nanoscale range. This formulation demonstrated a significantly enhanced cytotoxic effect on MCF-7 cells, achieving a cell death rate of 83.2%. In comparison, free CUR resulted in a cytotoxicity of 58.5%, 5-FU alone produced a 60.6% cytotoxicity, and the combination of CUR and 5-FU without a drug carrier yielded a cytotoxicity of 67.7%.	[95]
Zhan L et al. (2023)	glucose oxidase (GOx)	doxorubicin (DOX)	Breast cancer	Integrated with Go_x- mediated starvation therapy, chemo-photothermal therapy by using our designed nanoplatform obtains a synergistic therapeutic efficiency for restraining tumor growth.	[96]
Zhou Z et al. (2023)	ursolic acid (UA)	5-fluorouracil (5-FU)	Breast cell	the finding presents that codelivery of 5-FU and UA allow 5-FU&UA@ZIF-8 to have good performance against of anticancer 4T1 cells.	[75]
Liu B. et al. (2022)	doxorubicin, DOX)	indocyanine green, ICG	breast cancer	The results show the synthesis of DOX/ZICG-FA composite improve the targeting specificity to cancer cells and, also have great value for chemical and photothermal combined therapy.	[97]
Meng X. et al. (2022)	Glucose Oxide (GO_x)	Metformin (Met)	Breast cancer	The results show both drugs loaded had good biocompatibility and negligible systemic toxicity. This novel system Met/Go_x @His/ZIF-8∼RGD approach exhibits promising potential as an effective strategy in clinic to treat cancer.	[98]

Table 1. (Continued.)

Authors	Drug 1	Drug 2	Anatomy of the cancer	Final results	References
Su Y et al. (2022)	curcumin (Cur)	indocyanine green (ICG)	Cancer cell	The system of ICG&Cur@ZIF-8 presented exceptional proficiency in encapsulating of ICG owing to its superior photothermal capacity. The co-delivery of dual therapeutic agents may bring multiple opportunities for biomedical application.	[99]
Abd Al-jabbar S. et al. (2022)	Gemcitabine Hydrochloride (Gem)	Amygdalin (Amy)	MCF-7 cells.	The results show the encapsulated of both drugs Gem and Amy were released from pH-sensitive drug delivery systems. Also, BSA-Gem@ZIF-8/Dopa/GA was more effective in MCF-7 cells than BSA-Gem-Amy@ZIF-8/Dopa/GA..	[100]
Chen et al. (2022)	BSA proteins	T7 RNA polymerase	Cancer cell lines (HeLa and MCF-7).	The results show that the delivery of ZIF-8 mediated of metal ion-dependent DNA zyme/light-up RNA transcription amplification probes for sensitive live cell telomerase imaging	[101]
Zhang X. et al. (2021)	doxorubicin (DOX)	phototherapy agent of indocyanine green (ICG)	Breast cancer	The results indicated that the drug had a high payload ratio, a sustained release, low side effects and a good tumor suppression effect. Upon laser irradiation, ICG in DIMP produced ROS and rise the temperature in tumor site, which improve of efficacy than free ICG.	[102]
Singh R. et al. (2021)	doxorubicin (DOX)	cyclophosphamide (CP)	MCF-7 and MDA-MB-231 breast cancer cell	The finding presents that the DOX@ZIF-8/GO–FA/CP have a synergistic cytotoxic effect compared to the combination of both the drugs without ZIF-8/GO–FA when treating breast cancer cell lines	[103]
Meng X et al. (2021)	disulfiram (DSF)	doxorubicin (DOX)	Breast tumor	The finding showed that the constructed system enhances the combination therapy and, also, provide a new strategy for using existing drugs combining with traditional chemotherapeutic agents to battle cancer.	[104]
Fu X. et al. (2021)	Doxorubicin (DOX)	peptide (i.e., H4R4)	HeLa and 4T1 cells	The results show that Dox and H4R4@ZIF-8 have confirmed a considerable enhance of drug delivery by facilitating escape from endosomes and lysosomes. Dox & H4R4 @ ZIF-8 could pointedly inhibit the tumor growth while showing a slight system cytotoxicity.	[105]
Sun X. et al. (2021)	doxorubicin (DOX)	indocyanine green (ICG)	4T1 cells, U87MG cells, and A549 cells	The development of the high-performance H-PMOF nanoplatform provides new insights into the design of MOF-based multifunctional nanomedicines for the combination of cancer therapy and precise therapeutics.	[106]

Table 1. (Continued.)

Authors	Drug 1	Drug 2	Anatomy of the cancer	Final results	References
Chen X. et al. (2020)	Green tea polyphenols, namely, (–)-epigallocatechin-3-gallate (EGCG)	doxorubicin (DOX)	Mouse HeLa tumor model,	Photothermal-chemotherapy could ablate the tumor with a significant synergistic effect and potentiate the anticancer efficacy. Thus, the results indicate that EZPPD renders the pathway of a clinically promising candidate that utilization in antitumor treatment.	[107]
Fang C. et al. (2020)	indocyanine green (ICG)	Tirapazamine (TPZ)	7702 normal cells and Huh7 cancer cells	The results provide a significant effect against cancer cell, in both vitro and in vivo, is achieved due to the combined effects of intracellular ROS, H_2S and activated TPZ enabled by ZSZIT nanoparticles. This result has shown a highly potential platform that enables gas-amplified cancer therapy with high efficacy	[108]

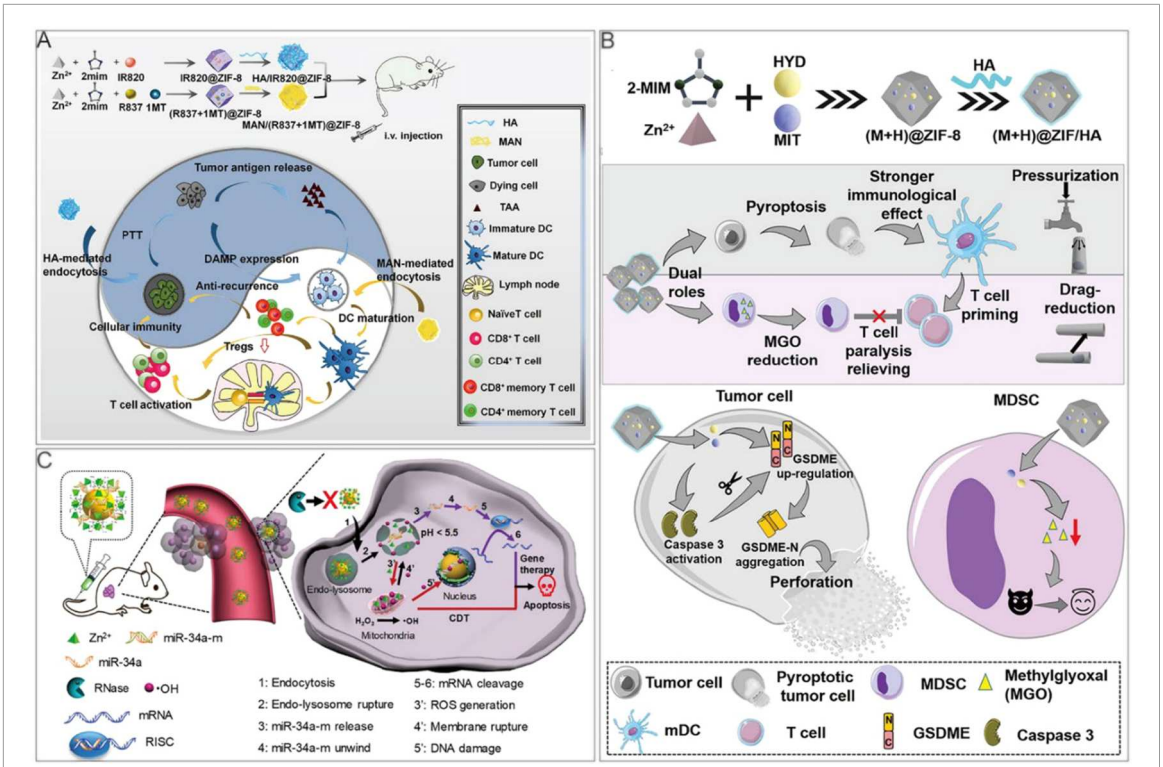

Figure 3. Illustration of the some ZIF-8 nanoparticles applications in dual drug delivery. Reproduced from [59]. CC BY 4.0.

Combination therapy also offers the advantage of protecting normal cells from harmful effects while exerting enhanced cytotoxicity toward cancer cells [76]. In principle, an effective drug combination demonstrating strong synergy can be developed from individual agents that display minimal or no efficacy when administered alone. However, retrospective analyses indicate that single agents with strong intrinsic activity frequently exhibit significant therapeutic benefit when used in combination. Notably, when both drugs are highly potent, the resulting combination may be less synergistic yet still provide a significant therapeutic advantage [77].

An essentials procedure are demand when designing an effective combination system to understanding the mechanisms underlying resistance to anticancer drugs and improving clinical outcomes [78]. Common alterations in signalling pathways in response to cytotoxic and targeted therapies include dysregulation of apoptosis, cyclin-dependent kinases, tumor suppressor genes, and growth factors [79]. By targeting these multiple pathways, combination therapies aim to maximize selective cancer cell death while diminishing adverse effects [80].

2.3. Uptake mechanisms of ZIF-8

Various strategies have been explored to modify the surface of ZIF-8 carrier for targeted drug delivery in cancer therapy. The conjugation of ZIF-8 surface with targeting ligands are widely employed techniques. These ligands selectively recognize and bind to receptors overexpressed on cancer cells, thereby enhancing uptake of nanoparticle [81, 82]. This targeted delivery approach ensures that therapeutic agent is directed to the tumor site and taken up by cancer cells, similar to a navigation system guiding the treatment. For instance, ZIF-8 nanoparticles can be modified with ligands that enhance their recognition and uptake by specific cancer cells, increasing the effectiveness of chemotherapeutic drugs while reducing side effects. These modified nanocarriers enter tumor cells primarily through receptor-mediated endocytosis, as see in figure 3(B). Therefore, attaching targeting ligands to ZIF-8 surface greatly enhances the accuracy and efficiency of drug delivery in cancer treatment [34].

3. Limitations influencing drug loading efficiency

The limitations of MOFs have been addressed using numerous investigations. One of these studies focused on utilization of intelligent techniques to modify the surface and morphologies of these MOFs. Researchers have employed two primary methods for the post-synthetic modification MOFs and manipulated their surface chemistry [83].

Table 2. Shows different drugs can be loading by ZIF-8 in different techniques.

	Type of drugs loading by ZIF-8	Nature of drugs	Loading capacity	Synthesis techniques
1	doxorubicin (DOX) [112]	hydrophobic drug	20 %	one-pot synthesis method
2	natural physcion (PHY) [113]	hydrophobic drug	11.49%	nano-precipitation technique
4	Curcumin (CCM) [114]	hydrophobic drug	40.2%	one-pot synthesis method
5	Fluorouracil (5FU) [115]	hydrophilic drug	16.45%	one-pot synthesis method
6	Indocyanine green(ICG) [116]	hydrophilic drug	16.8 ± 3.1	one-pot synthesis method
	Cyanine-5.5- (Cy5.5)	hydrophobic drug	4.1 ± 0.8	
7	Caffeine [117]	Amphiphilic drug	$28.1 \pm 2.6\%$	one-pot synthesis method
			25%	impregnation method
8	6-mercaptopurine(6-MP) [118]	Amphiphilic drug	—	one-pot synthesis method

The first technique involves, coordinating functional groups with the metal-binding sites of the MOFs. This method is particularly suitable for large macromolecules such as polysaccharides and polymers that possess functional groups such as -COOH, NH_2, and C=O. These Functional groups have a perfect ability to electrostatically interact with MOFs and facilitate targeted modification.

The second approach involves modifying the linkers of MOFs to incorporate functional groups [84]. However, it is important to note, that this approach may influence the morphology of the resultant product or reduce its yield. These two methods lack selectivity, and simultaneously increase the size of the MOFs when coordinating with macromolecules, which limits their practical application. Therefore, there is a critical need for selective functionalization methods to effectively introduce different functional groups onto MOFs [85].

However, the use of metal organic framework as drug carriers presents an interesting opportunity to overcome these limitations. These frameworks have the ability to stabilize drugs through encapsulation process or attachment to their surface, thereby facilitating their enter into cell and enabling, precise delivery to a specific population of cells, resulting in targeted therapy. Moreover, these nanomaterials offer the advantage of controlled release at the intended target site, ensuring optimal drug efficacy and minimizing undesirable side effect [86].

Another interested features related to MOFs are capable to control particle size during synthesis. By increasing the ligand-to-metal ratio, excess ligands can effectively coat the crystal seeds, thereby preventing their interaction with metal ions. Consequently, the hindered crystal growth due to an abundance of ligand results in the formation of smaller size of MOF particles. An alternative strategy for modulating the particle size of synthesized the MOFs involves the incorporation of modulating agent within the synthesis system. This agent served as a buffer for the ligands, enhancing the interaction between the metal and ligand [87].

Different techniques can be used for drug loading within framework such as physical entrapment, covalent bonding, and host–guest interactions as mentioned previously. Physical encapsulation, utilizing adsorption and capillary force, leverages MOF porosity to enhance drug loading, while optimizing the dimension of pore size boosts the loading capacity [88]. Covalent bonding anchors drug's functional group to the end group over MOFs surface for better retention and controlled release [89]. Final techniques is host–guest interactions, meanwhile, are influenced by external stimuli factors such as pH and temperature. The drug loading mechanism depends on the physicochemical properties of both the drug and the framework, including pore size and desired release kinetics, making MOFs effective candidates for (DDS) [90].

4. Types of drugs for cancer treatment

Chemotherapy remains the most commonly used treatment for cancer, and doxorubicin (DOX), 5-fluorouracil (5-FU), cis-platinum, camptothecin (Cam), paclitaxel (PTX), dichloroacetate (DCA), and curcumin (CCM) are frequently administrated drugs. Notwithstanding their usage, these drugs suffer from limitations such as inadequate solubility. Utilizing MOFs or their composites has proven efficacious in delivering these drugs [109]. Based on their solubility, chemical drugs can be classified into three groups, hydrophobic, hydrophilic, and amphiphilic [110]. Previous study has demonstrated that ZIF-8 can encapsulate hydrophilic and hydrophobic drugs. Furthermore, drug ligands or linkers can be attached to the external surface of the metal–organic frameworks (MOFs) to enable combination therapy or multimodal treatment of cancer [111]. As shown in table 2.

5. MOFs (ZIF-8) surface functionalization techniques

Comprehending the general interactions between MOFs and functional molecules is fundamental for effective surface modification. Covalent functionalization establishes stable chemical bonds, whereas non-covalent approaches exploit weaker offering reversibility and flexibility. Overall, surface modification enhances MOFs colloidal stability, targeting efficiency, loading capacity, and controlled release behavior [119]. However, some disadvantages, including cytotoxicity and diminished biocompatibility, should be taken into consideration. A comprehensive understanding of both the benefits and limitations of external surface adjustment is imperative for the rational design for MOFs in biomedical field [120].

Two techniques can be conducted on MOFs crystals to function on the surface 1) coordination modulation, which includes functionalization the MOFs via synthesis, and 2) post-synthetic modification (PSM), where functionalization occurs after the crystalline material has been produced [121].

These delivery systems must consist of carriers without any toxicity and exhibit specific attributes, including controlled release (as opposed to sudden release), high drug load capacity and efficiency, manageable degradation, potential for surface modification, and detectability using a range of imaging techniques. Recently, the implementation of MOFs in drug delivery systems has attracted considerable interest among researchers due to their inherent properties and easy functionalization [122].

MOF surface properties, such as the charge of the MOFs surface, hydrophilicity or hydrophobicity and ligands connect to the surface, have an important impact on their interaction with living media. To enhance the biological compatibility of MOFs, scientists have suggested modifying the surface functionalization to improve the intracellular fate and cytotoxicity of MOFs [123].

Functionalization techniques involves the augmentation of materials by incorporating new functions, features, capabilities, or properties by modifying in their surface chemistry [124]. In addition to possessing a substantial cargo loading capacity, materials must satisfy other criteria to achieve precise functionality within a living organism. These requirements include high biocompatibility, prolonged circulation time, and the ability to evade the immune system. Metal–organic frameworks (MOFs) possess these advantageous characteristics, thereby facilitating their entry into the bloodstream and enabling passive delivery to lesion sites via the enhanced permeability and retention (EPR) effect. However, relying solely on the EPR effect for drug accumulation at the lesion sites presents certain limitations. Consequently, alternative strategies are required to enhance drug accumulation [125].

An alternative approach for functionalizing MOFs while reducing toxicity included the design of functional molecules as essential building blocks. Several reactive chemical groups in biomolecules are capable of coordinating with inorganic metals [126]. The pore size of the zeolite pores must be adjusted based on specific drug requirements. Furthermore, the difference in hydrophilicity between zeolites and drugs may affect the loading capacity although this hurdle can be overcome by modifying the zeolite surface. Thus, the zeolite surface can be tailored according to the specific cargo required for delivery [127].

MOFs can be functionalized using two techniques, *in situ* and post -synthesis functionalization.

5.1. *In situ* functionalization

The incorporation of guest species within the pores or matrices of MOFs materials, such as MOFs, significantly enhances of their physicochemical properties [128]. It is essential to consider factors such as size and shape matching between the mesoporous channels and guest molecules for successful host- guest interactions [129].

Effective encapsulation may still be achievable even when the pore dimensions of the host material are inferior to the dimensions of the guest molecules. Additionally, the strength of host–guest interactions influences the ease with which guests can enter the host framework and their orientation within the pores [130].

Two main methods are commonly used to modulate the coordination in mesoporous synthesis: functionalization during synthesis and post-synthetic modification (PSM) after crystallization. Coordination modulation techniques include introduction a modulator, a monodentate ligand, into the reaction mixture to compete with the bridging ligands for metal coordination of during crystallization. This modulation can either facilitate or impede crystal growth by affecting the coordination equilibrium of the MOFs material [121], as shown in figure 4.

The modulation coordination strategy involves the alteration of the external surface characteristics of metal organic frameworks (MOFs) through the combination of a monodentate ligand, referred to as a modulator, into the reaction medium. This modulator exhibits a chemical structure analogous to that of polydentate ligands and competes for coordination with metal ions during the MOFs crystallization process. The introduction of the modulator perturbs the coordination equilibrium by competing the metal ions with the bridging ligands present in the metal ions. As a result, the modulator can either promote or inhibit crystallization.

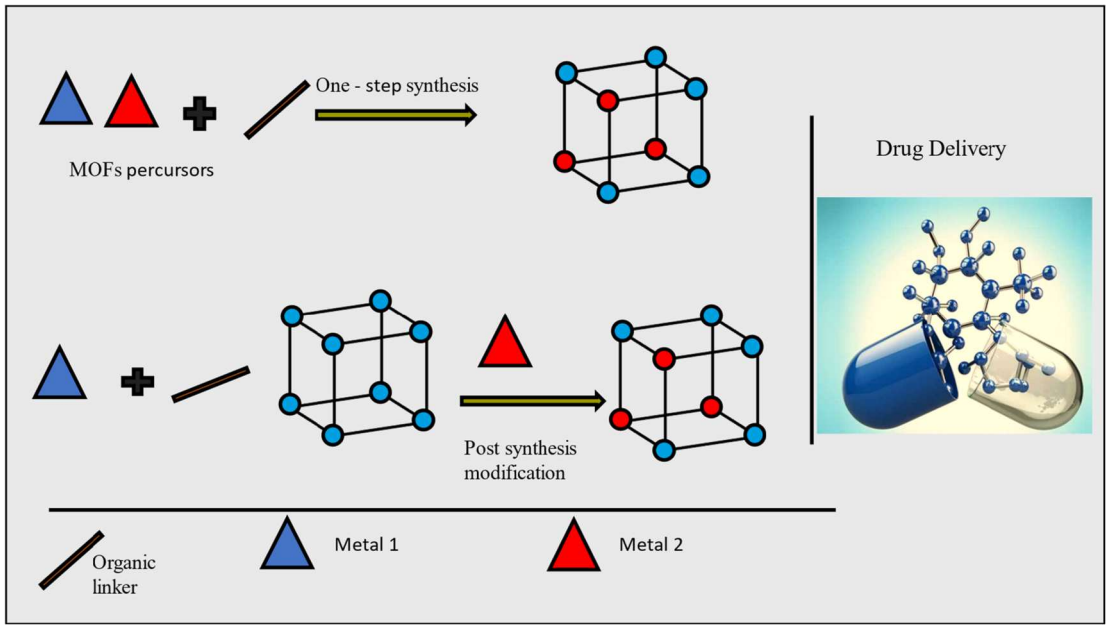

Figure 4. Techniques for the Synthesis of Metal–Organic Frameworks (MOFs): (A) Technique of the one-step synthesis method and (B) Technique of the post-synthesis modification method.

In situations where crystal growth is facilitated, the modulator assumes a regulatory role in the crystallization process [131].

Ross Frgan (2020) represents a category of coordination polymers including metal ions or clusters that are interconnected by organic struts. These compounds have garnered significant attention in the field of chemistry and material science, resulting in the publication of thousands of structures. The modulated self-assembly approach, which involves the incorporation of modulator molecules via synthetic combinations, has emerged as a fundamental technique for synthesis of the MOFs. This method was developed to enhance crystallinity, regulate particle size, induce defects, and selectively form specific phases [132].

5.2. Post Synthesis Functionalization

Post-synthetic modification is a process that aims to alter the surface of MOFs or create new materials through the incorporation of organic functional moieties and crosslinking agents onto MOFs particles. The objective of this methodology is to reduce the quantity of functionalized materials utilized, while preserving the essential characteristics of MOFs, including elevated crystallinity, substantial surface area, and a structural composition characterized by uniform metal–ligand bonds [133, 134].

Because MOFs are synthesized through the coordination of organic linkers with metal ions, a modification strategy entails directing alterations towards the organic linker within the MOF molecules. For example, Xie *et al* studied the covalent attachment of NH_2–poly (ethylene glycol) modified folic acid (PEGFA) with an amino group within ZIF–90 via aldimine condensation. The resultant modified nanoparticles displayed enhanced biocompatibility and effective targeting of cancer cells [135].

The procedures of post- synthetic modification (PSM) were initially proposed in 1999 by Lobkosky *et al* and Kim *et al* as strategies for functionalizing the internal porosity of MOFs. However, it was not until 2007, following the introduction of the term 'post-synthetic modification,' by Cohen and Wang, that the field commenced its substantial expansion. Furthermore, these PSM techniques can also be employed to modify the external surfaces of crystals [136].

Alves *et al* (2021) applied the 'click' PSM techniques to functionalize the surface of MOF with folic acid ligand, facilitating the precise delivery of curcumin, an anticancer drug agent, to tumour cell [137].

Wang *et al* (2018) demonstrated a distinctive method for the adaptable and reversible functionalization of the MOFs by the applying the phenol-inspired lipid molecule DPGG. This technique effectively maintains the structural integrity and porosity of metal organic frameworks, thereby opening up new opportunities for designing functional materials inspired by MOF for a range of applications [138].

In post synthesis method, drug molecules are positioned on the MOFs surface. These molecules act as connectors for pre-synthesized MOFs. The interaction implied by this approach encompasses chemical coordination and covalent bonds between metal nodes and organic linkers and the employed cargo. Moreover, these post synthesis techniques retain their unaltered MOFs structures [139].

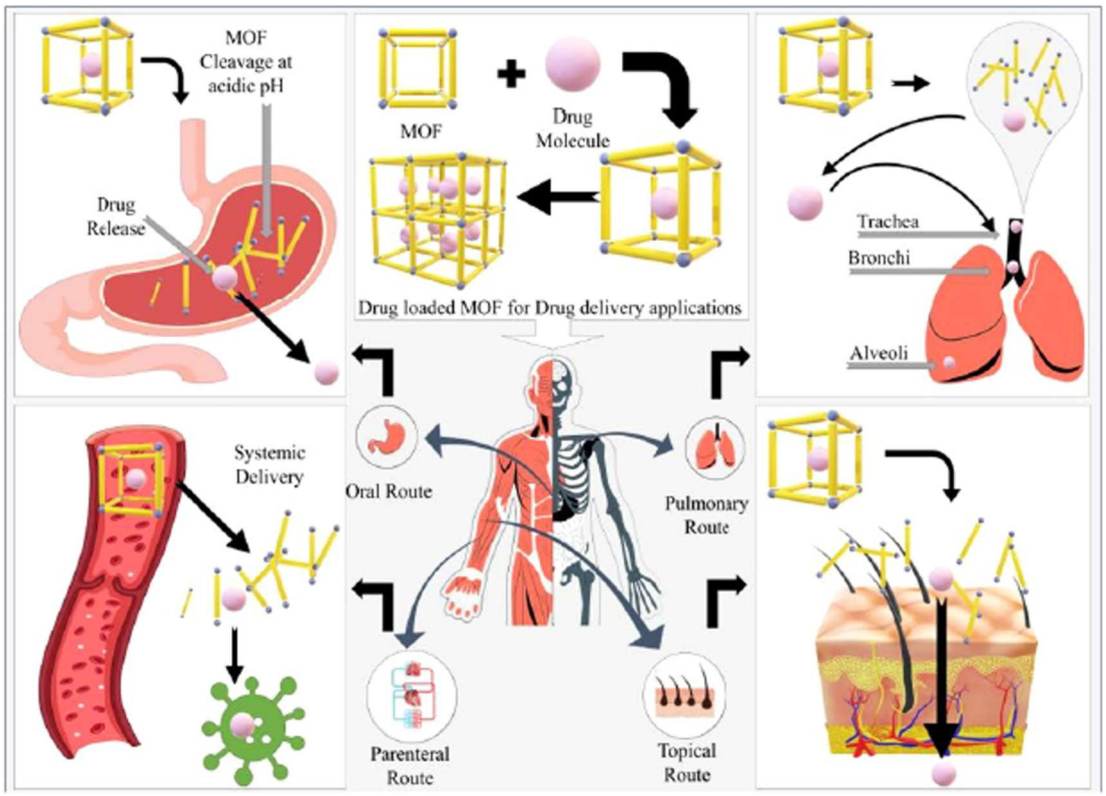

Figure 5. Schematic illustration routes of Metal organic framework administration. Reproduced from [147]. CC BY 4.0.

5.3. Toxicity, Long -term stability and biodegradability of surface-functionalized MOFs in drug delivery systems

The nanoparticle surface serves as an essential interface for interactions with biological systems. In the case of the MOFs the physicochemical properties strongly shape their behaviour *in vivo*, including biodistribution, organ accumulation, and routes of clearance [140], as illustrated in figure 5.

For example, the prolonged retention of HKUST-1 and its degradation products in different tissues raises important safety concerns. The excessive deposition of copper deposition is in all probability leading to interference with physiological homeostasis, leading to chronic oxidative stress, inflammation, and eventual tissue damage. Organs such as the liver and kidneys are particularly vulnerable, as constant exposure to elevated Cu^{2+} levels can impair normal function and contribute to toxicity-related disorders [141].

The important properties of MOFs that are indicting to being responsible for biocompatibility, including the particle size, morphology, and hydrophobicity. A comparative study by Wagner *et al* examined the toxicity of two structurally distinct MOFs, MIL-160 and ZIF-8. MIL-160 displays a cubic morphology with sharp edges, whereas ZIF-8 adopts a smoother, flower-like structure. Although both materials exhibit relatively uniform particle sizes (8–10 μM for MIL-160 and 1–2 μM for ZIF-8), the smaller particles demonstrated a higher surface area and correspondingly increased cytotoxicity. Moreover, MIL-160 sharp-edged morphology may further contribute to cellular damage. Hydrophobicity also plays an important role, as it can modulate how these nanoparticles interact with biological environments and influence their overall safety profile [142].

To alleviate the cytotoxic activity of MOFs a more biocompatible material can be derived from those existing MOFs by post-synthetic modification techniques and also by rendering it biocompatible through the functionalization of those MOFs with specific ligands. One method of biocompatibilizing the MOFs may include the modification of their structures with those of polyethylene glycol (PEG) which may be used to enhance the biocompatibility of MOFs while minimizing the toxic effects of said MOFs thus rendering the most suitable for applications in drug delivery. The introduction of amino acids, peptides and proteins may significantly improve the biocompatibility and decrease the cytotoxicity. The size of the pores of the MOFs may be implicated in this factor since diminutive pore diameters will also limit the ability of metabolism and the diffusion of oxygen to the cells and increase cellular stress and toxicity [143].

Zhang *et al* studied the pulmonary toxicity of UiO-66, ZIF-8, and HKUST-1, and evaluated the oxidative stress mechanisms and inflammation induced by these MOFs. The results of the study showed that HKUST-1 induced significant cytotoxicity, oxidative stress, and apoptosis in lung cells, whereas UiO-66 and ZIF-8

exhibited minimal toxicity. The study also found that copper ions released from HKUST-1 can cause damage to cellular structures and processes, leading to various toxic effects [144].

MOFs often exhibit weak stability, especially in aqueous environments, under acid/base conditions, with changing thermal conditions, and mechanical. The stability of MOFs is important as they intended for practical use. To address this challenge, considerable effort has been directed toward enhancing the stability of MOFs, resulting in noteworthy advancements in recent years. The degradation of MOFs in water vapor or liquid water typically involves a sequence of substitution reactions, wherein metal-coordinated linkers are displaced by water molecules or hydroxide ions. Therefore, strengthening the coordination bonds between the secondary building units and organic linkers has emerged as a pivotal strategy for enhancing the stability of MOFs [145, 146].

5.4. Pharmacokinetics and *in vivo* performance of surface-functionalized MOFs in drug delivery systems

Surface functionalization plays a pivotal role in modulating the pharmacokinetics and *in vivo* performance of nanocarriers [148]. One of the most noteworthy of MOFs is their ability to release cargo at environment-responsive. By maintaining drug concentration within the therapeutic window, MOFs address challenges in conventional pharmacokinetics that require frequent dosing to offset rapid clearance by the kidneys and liver. Their tunable porosity and responsiveness to stimuli such as pH, light, or ultrasound enable controlled, sustained drug release, thereby enhancing therapeutics efficacy while minimizing dosing frequency and adverse effects [9].

MOFs nanoparticles have been extensively modified to improve their behaviour *in vivo* [149]. Such modification enhances aqueous dispersibility, minimize plasma protein binding, evades macrophage clearance, and enables targeted cellular interactions. Moreover, coating MOFs surface can be engineered to absorb specific wavelengths for photothermal conversion, catalyse the generation of reactive oxygen species (ROS) reactions to produce reactive oxygen species (ROS), and enhance detectability through imaging techniques such as photoacoustic imaging, MRI, and CT [120].

By coating surface of ZIF-8 with hydrophilic polymers such as polyethylene glycol (PEG) or polyvinylpyrrolidone (PVP) colloidal stability of framework is increased and aggregation is prevented under physiological conditions. The toxicity of the framework is also reduced [150]. PEGylation also imparts 'stealth' characteristics that minimize recognition and clearance by the mononuclear phagocyte system, resulting in prolonged blood retention and enhanced tumor accumulation via the enhanced permeability and retention (EPR) effect [151].

Similarly, ligand functionalization with targeting moieties such as folic acid, RGD peptides, or antibodies facilitates receptor-mediated uptake, increasing localization within tumor tissues while reducing off-target deposition in healthy organs [82]. In addition, biomimetic coatings using cell membranes or proteins can modulate biodistribution and immune evasion, further improving *in vivo* therapeutic efficacy such as targeting and cell interactions [152]. Collectively, these functionalization strategies optimize important parameters such as pharmacokinetic profile, biological stability, and targeted delivery of ZIF-8-based systems in cancer therapy [81].

6. Challenges and current Limitations of MOFs applications

Nanocarriers are required to be stable, resistance to aggregation, and able to retain drugs until a target site is reached. The stability of nanocarriers is important to prevent any compromise *in vivo* efficacy. The stability of nanocarriers must be determined as part of the characterization [153]. Zeolites exhibit properties of considerable interest in the biomedical field, such as prolonged biological stability and the ability to modulate functions of immune system. These properties have attracted considerable attention in this area. Moreover, zeolites hold promise for DNA delivery to cells, it may be achieved through endocytosis by cellular internalization. However, the problem of cytotoxicity associated with zeolites in concentrations above 30 μg is a considerable restriction against their use established by the preceding studies. For example, erionite is implicated in the promotion of carcinogenesis. Nonetheless, this adverse characteristic may be exploited therapeutically in cancer treatment by leveraging the antiproliferative and proapoptotic properties of zeolites [127]. In conclusion, ZIFs show promise for the development of functional nonarchitectures with diverse applications. Although they possess unparalleled advantages, there is a need for increased emphasis on the execution of *in vivo* investigations, particularly for assessing their biocompatibility and toxicity. Because MOFs are degradable materials, there is a need to gather additional data on their mechanism and metabolic properties within the body to gain a comprehensive understanding [58].

The stability of MOFs during synthesis is considered as an important parameter, particularly when used in drug delivery. Numerous strategies can be conducted to improve the stability of MOFs, including

functionalization and selection appropriate compositions and structures. Therefore, when using MOFs, it is also important to examine their surface modification and their ability to control particle size distribution. As a result of these surface alterations, MOFs become more stable, and drug delivery can be enabled through different physiological barriers as well [154].

In the biological field, MOFs have several significant advantages in the early stages of its use. To facilitate the widespread adoption of these technologies in the field nanomedicine, a number of challenges must be systematically overcome [155].

One of these challenges is the formation of nontoxic MOFs characterized by outstanding chemical stability, high biocompatibility, and optimal pore dimension. These characteristics must be carefully considered when incorporating MOFs into drug delivery systems to ensure the production of safe framework nanoparticles. To address this issue, metals with low toxicity such as iron, zinc, calcium, and magnesium, which are commonly used in the construction of biocompatible MOFs, are essential for bodily functions [156].

Nevertheless, the primary obstacle in realizing this potential resides in progressing methodologies to enhance MOF characterisation , demanding the fulfilment of the following prerequisites: (i) Biocompatibility (ii) Achieving high loading and protection of drug molecules (iii) Prevention of premature release before reaching the target (iv) facilitating effective cellular uptake (v) promoting efficient endosomal escape (vi) attaining controllable release rate to achieve optimal local concentration (vii) targeting the cell. Outer surface functionalization is essential to meeting these requirements. Depending on the specific case, this may involve better anchoring the drug, enhancing of the biocompatibility of the MOF particle, or facilitating tracking of its movement within the body [121].

Furthermore, it is crucial to have precise control over the size of MOF particles. MOFs particles dimension has a deep influence on their interaction with living cells, including processes such as cellular endocytosis and systemic circulation dynamic. In the context of drug delivery, it is imperative to explore the degradation mechanism of MOFs. Additionally, efforts should focus on the development of multifunctional MOFs structures specifically designed for targeted therapies that capable of facilitating sustained drug release. This approach will enhance the customization of MOFs for diverse treatment requirements, thereby improving the treatment outcomes. Moreover, although preliminary *in vitro* and *in vivo* studies have suggested the relative safety of MOF, investigations pertaining to their long-term chronic toxicity, metabolic pathways, and elimination behaviours remain significantly under-explored [157].

The biostability of MOF is a critical consideration, as they must maintain stability within the biological environment to prevent premature degradation prior to drug release. Regarding toxicity, MOFs must be nontoxic to cells and tissues to ensure their safety. Addressing these challenges namely, ensuring biostability, biocompatibility, and economic viability is imperative for the successful translation of MOFs into clinical applications [147].

7. Future perspective and conclusion

This research emphasizes on MOFs advantages in general and ZIF-8 in particular, in advancing combination anticancer therapy and improving current treatment limitations. combined drug within MOFs offers clear advantages, such as achieving of synergistic drug interactions and improvement of therapeutic effectiveness, further studies are needed to determine whether MOF-based combination therapy truly outperforms other nanocarriers *in vivo* application. Challenges still available, especially in prolong impregnation of ZIF-8 under physiological conditions, whereas the limited understanding of the biodistribution and pathways of degradation, or of potential toxicity associated with metal ion release. Addressing these issues is essential for translating ZIF-8–based systems from laboratory research to clinical use. Despite these obstacles, ZIF-8 remains to stand out due to its environmentally friendly and low cost-effective synthesis routes, good porosity, high surface area, tunable chemistry, biocompatibility, and pH-responsive drug-release behavior. Also, surface of ZIF-8 can be easily functionalized with various ligands, metals, or polymers, further enhancing loading efficiency and enabling the design of multifunctional therapeutic platforms. These features make ZIF-8 a fascinating candidate for applications not only in drug delivery, but also in imaging, sensing, and tissue engineering. Looking ahead, integrating dual or even multidrug within ZIF-8 nanoparticles offers a promising approach for designing more powerful and accurate anticancer therapy. By leveraging its capacity to modulate release kinetics and reduce off-target toxicity, ZIF-8 carriers may substantially improve therapeutic outcomes. Continued research into optimizing structural stability, diminishing toxicity, and deepening *in vivo* understanding will be key to unlocking the full biomedical potential of this versatile material

Declarations

The authors declare that there is no confilct of interest. All authors have read and approved the final manuscript.

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