

Review

Brain-specific targeted delivery of therapeutic agents using metal–organic framework-based nanomedicine

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ABSTRACT

Brain-targeting drug delivery remains a massive challenge due to the complexity and delicacy of the human brain. However, it is of paramount importance because many neurological disorders, such as Alzheimer's disease, Parkinson's disease, and brain tumors, necessitate precise and targeted drug delivery to achieve optimal therapeutic outcomes while minimizing side effects. Metal-organic frameworks (MOFs) represent a remarkable fusion of inorganic and organic materials through diverse connection modes involving inorganic metal ions and organic bridging ligands, forming versatile pore structures. MOF-based nanomedicine has promising potential for targeted delivery of therapeutic agents thanks to their customizable nanostructures and functionalities. The regulated pores within MOFs offer an ideal platform for drug encapsulation. At the same time, the programmable framework environments present potential binding sites for targeted drug delivery to specific cells or lesion sites, particularly in delicate and sensitive organs such as the brain. This targeted approach is crucial to minimize adverse effects on healthy cells. Recent advances have witnessed the utilization of various MOFs combined with functional agents for drug loading, delivery, release, and process monitoring. In this study, we provide an overview of the roles played by MOFs in brain-targeted drug delivery and lay the foundation for the future development of advanced and precise administration strategies.

1. Introduction

Brain diseases encompass a vast spectrum of neurological disorders that affect the brain's structure or function, often impacting an individual's cognition, behavior, and overall well-being. These conditions can be degenerative, such as Alzheimer's disease (AD) and Parkinson's disease (PD), characterized by the progressive loss of brain cells and functions [1,2]. They can also be acute, like strokes or traumatic brain injuries, which can result in sudden and severe impairments [3,4]. Brain diseases are a primary global health concern, as they can significantly diminish a person's quality of life and independence. Advances in neuroscience research are shedding light on the underlying mechanisms of these diseases, offering hope for better diagnostic tools, treatments, and, ultimately, prevention strategies to address this formidable challenge to public health.

As extensive research shows, metal–organic frameworks (MOFs), representing a sophisticated class of hybrid organic–inorganic porous materials [5,6], have demonstrated tremendous potential as brain-targeting nanomedicine [7–9]. Having wide applications in gas adsorption and separation [10–14], energy storage [15–18], luminescence or electrochemistry sensing [19–24], photochemical or electrochemical catalysis [25–30], medical treatment [31–33], industrial product purification [34–37], luminescence materials [38–41], and pollutant extraction [42,43], the efficacy of MOFs has advanced in the past decades through matured understanding of interaction mechanisms among active metal nodes, functional linkers, various guest molecules [44–47], morphology and porosities [48–50]. However, their potential for brain-specific target drug delivery has yet to be well studied.

The advent of precision treatment in tandem with advancements in science and technology has garnered significant attention, owing to its

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potential for significantly reduced side effects compared to traditional therapies, especially in delicate and sensitive organs, such as the brain [51,52]. Precision treatment necessitates highly efficient and selective drug delivery pathways [53–55], which minimize harm to healthy cells and enhance patients' overall quality of life. Abundant porosity is crucial for achieving highly efficient drug delivery, while suitable target sites are indispensable for precise drug release [56,57]. MOF-based nanomedicine, owing to its abundant porosities and customizable framework structures, has emerged as a promising candidate for highly efficient drug delivery and controlled drug release in recent years [58–62].

In this comprehensive review, our primary focus lies in the synergistic combinations of MOF-based nanomedicine with functional agents, common brain disease drugs, the interactions between MOFs and drugs, the drug release of drug@MOFs composites, the monitoring of drug loading, delivery, and release processes, administration methods, and the biocompatibility of the drugs (Fig. 1). In specific scenarios, the integration of functional agents becomes imperative to modulate or enhance specific functionalities of MOFs, thus necessitating the utilization of strategies such as impregnation, template methods, basal growth, and surface coating [63,64]. Next, our attention was directed toward brain-targeted drugs, especially those used in the treatment of AD and PD [65–69]. We extensively cover various approaches to loading drugs into MOFs, ranging from adsorption effects and post-synthesis reactions to in situ templating and self-assembly synthesis [70,71]. To comprehensively address drug release strategies, we compile a summary encompassing chemical and physical stimuli, such as ions, molecules, light, heat, and pressure [72–74]. Additionally, we thoroughly discuss luminescence and electrochemical techniques, along with imaging modalities such as magnetic resonance imaging (MRI) and computed tomography (CT), which play a crucial role in monitoring the drug loading, delivery, and release processes [75–77]. Moreover, we summarize the administration methods and comprehensively evaluate these drugs' biocompatibility, including an analysis of parameters like half-life, toxicity, and the ability to cross the blood–brain barrier [78–80]. Finally, we discuss this field's existing challenges and future development prospects.

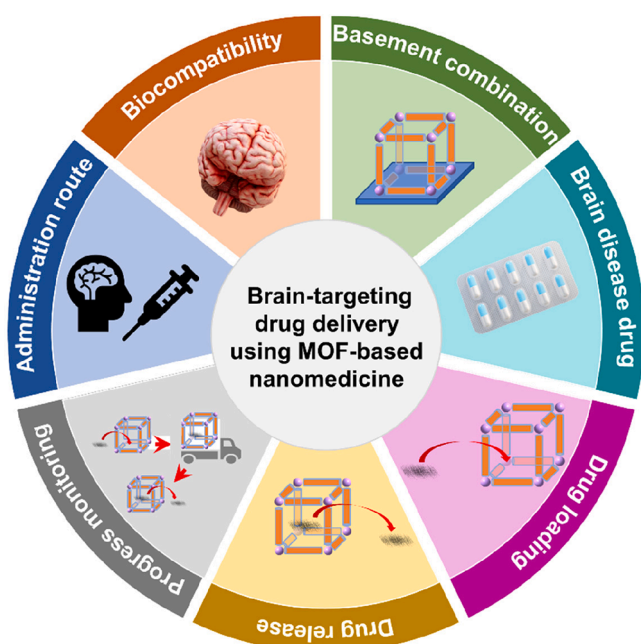


Fig. 1. Scheme of metal–organic frameworks for brain-specific drug delivery.

2. Basement combination

For practical applications, targeted MOF-nanomedicine requires modification with additives to optimize their effectiveness. Introducing nanoparticles (NPs) with inherent enzyme-mimicking properties enhances the drug effects, and many of these NPs also exhibit remarkable photo/electric responses that allow constant monitoring of drug delivery pathways. Additional additives serve as protective barriers, preventing prolonged drug effects, minimizing drug leakages, and reducing the degradation of the underlying MOFs. This section will explore four commonly employed methods for combining MOFs and additives: the impregnation strategy, template method, basal growth, and surface coating (Fig. 2).

2.1. Impregnation strategy

The impregnation strategy is widely employed to amalgamate functional molecules or molecular clusters with MOFs [81,82]. In MOF-based medical applications, NPs are frequently utilized to introduce supplementary functionalities. Gold (Au) NPs, for instance, have been found to exhibit both enzymatic and surface-enhanced Raman scattering properties, thereby offering a promising platform for real-time probing and the development of sensitive bioassays [83,84]. Li et al. employed MIL-101 to adsorb Au NPs, forming Au NPs@MIL-101, which served as sensitive substrates for surface-enhanced Raman scattering and facilitated the detection of environmental and clinical samples [85]. Similarly, Wei et al. employed an impregnation strategy to introduce Au NPs into MIL-101, creating AuNPs@MIL-101 enzymes that functioned as peroxidase mimics for biomedical and catalytic applications [86]. Wang et al. prepared a hybrid nanomedicine, PEG-Au/FeMOF@CPT, for chemo/chemo dynamic therapy, and the introduction of Au NPs via impregnation significantly enhanced the stability of the nanomedicine within the physiological environment (Fig. 3) [87]. Another study by Cai et al. reported a Cu-TCPP(Fe) MOF-based system that efficiently incorporated Au NPs and the ferroptosis inducer RSL3, thereby exhibiting enzyme-like activities for universally suppressing anti-ferroptotic pathways in tumor cells and amplifying ferroptosis damage [88]. Furthermore, Chen et al. constructed Au nanoclusters modified zirconium-based porphyrin MOF, denoted as Au NCs@PCN, which up-regulated proangiogenic and proepithelial cell proliferation factors [89].

Silver (Ag) NPs have shown great promise as an antibacterial system in combating bacterial resistance in the context of drug discovery. Zhang et al. devised a synthetic strategy based on CD-MOFs, integrating the reduction of AgNO₃ and the immobilization of Au NPs in a single step. This approach successfully achieved dual functions: reducing particle size and enhancing stability. Consequently, the resulting system effectively inhibited bacterial growth [90]. In a separate study, Ding et al. introduced Ag NPs to a MOF, further enhanced with caffeic acid, leading to excellent antibacterial effects [91].

To summarize, incorporating metal NPs into or onto MOFs enables the introduction of various functionalities, such as simultaneous enzymatic activity, surface-enhanced Raman scattering, light-heat conversion, and antibacterial properties. These functionalized systems have the potential to enhance the efficacy of drugs and enable real-time monitoring of their effects.

2.2. Template method

The template method extensively incorporates functional particles into MOFs [92,93]. Compared to the impregnation strategy, the template method accommodates more significant components within MOFs, resulting in stronger connections that surpass surface absorption effects. Liang et al. employed self-polymerized dopamine-decorated Au NPs, then coordinated with a Fe-MOF for early clinical diagnosis [94]. Wu et al. combined NH₂-MOFs with porous gold nanoshells (GNS) and drugs to demonstrate an excellent synergistic therapy strategy [95].

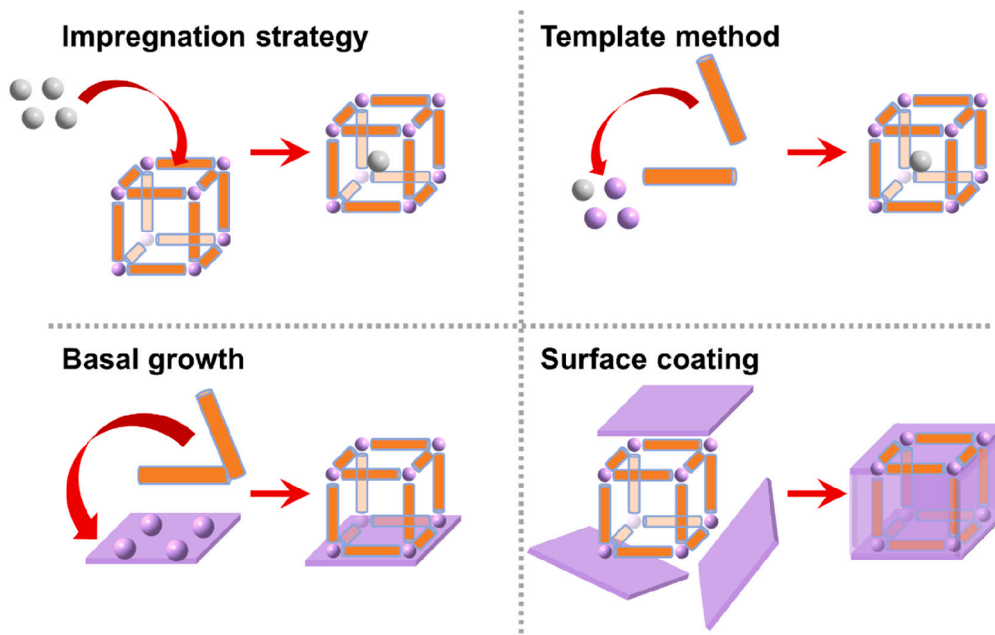


Fig. 2. Combination methods of MOFs and basements.

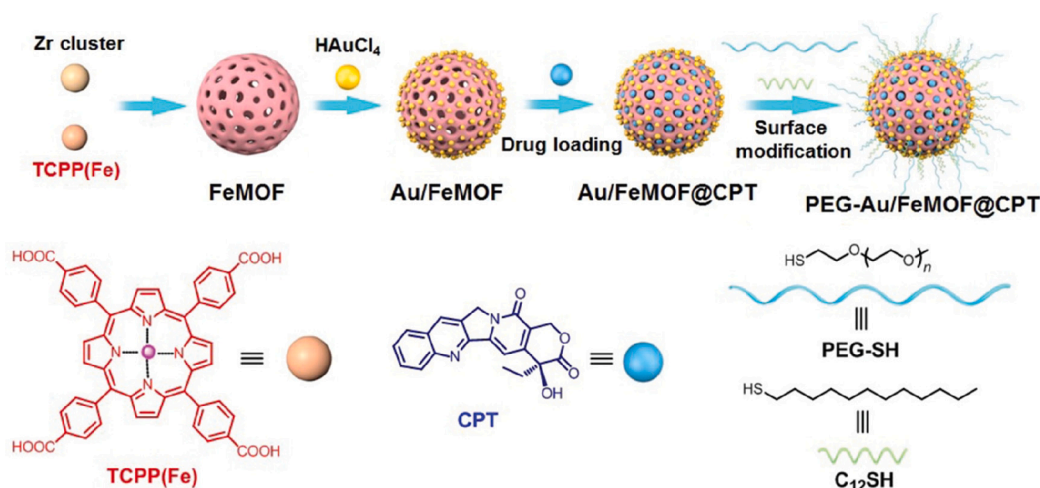


Fig. 3. Preparation of the hybrid nanomedicine PEG-Au/FeMOF@CPT [87]. Copyright 2020, Wiley-VCH.

Furthermore, platinum (Pt) NPs can impart remarkable catalase-like behaviors to the framework. Yang et al. sequentially modified a Zr-MOF with Pt NPs, porous GNS, human serum albumin-gadolinium hybrids (HSA-Gd), and indocyanine green (ICG) to create a hypoxia-resistant and persistent O_2 self-supplement nano platform called ICG-PtMGs@HGd. This platform exhibited improved synergistic phototherapy (Fig. 4) [96]. Additionally, Zheng et al. encapsulated FePt nanoparticles within a Fe-MOF, demonstrating its potential as a multifunctional platform for disease therapeutics and imaging applications [97].

Fe_3O_4 magnetic NPs represent a class of materials with great potential for targeted drug delivery, MRI, and magnetic hyperthermia. These NPs possess desirable properties such as biocompatibility, biodegradability, potential non-cytotoxicity, and superparamagnetic properties [98,99]. In a study by Fu et al., Fe_3O_4 was utilized as a template for synthesizing UiO-66. Subsequently, they incorporated the drug doxorubicin (DOX) to create Fe_3O_4 @MOF-DOX. This system exhibited excellent biocompatibility, a high drug loading capacity, sustained drug release, remarkable MRI capability, and practical

chemotherapeutic efficacy (Fig. 5) [100]. Gumma et al. also employed Fe_3O_4 and ZnO NPs to modify MIL-100(Fe), resulting in Fe_3O_4 @MIL-100 and ZnO@MIL-100, respectively. The drug delivery capacities of these modified MOFs were investigated through doxorubicin hydrochloride. Incorporating Fe_3O_4 NPs resulted in slowed-down drug release kinetics while utilizing ZnO NPs achieved a higher drug loading capacity [101,102].

Like the impregnation strategy, the template method offers the potential to enhance the efficacy of drugs and enables real-time monitoring of their effects when combined with specific substrates. Furthermore, the template method accommodates larger molecules or clusters of molecules. However, it is essential to note that the design and synthesis challenges associated with the template method are heightened due to the unpredictable nature of the introduction route.

2.3. Basal growth

Basal growth offers precise control over crystallization in phase and orientation by leveraging the diverse interactions between metals and

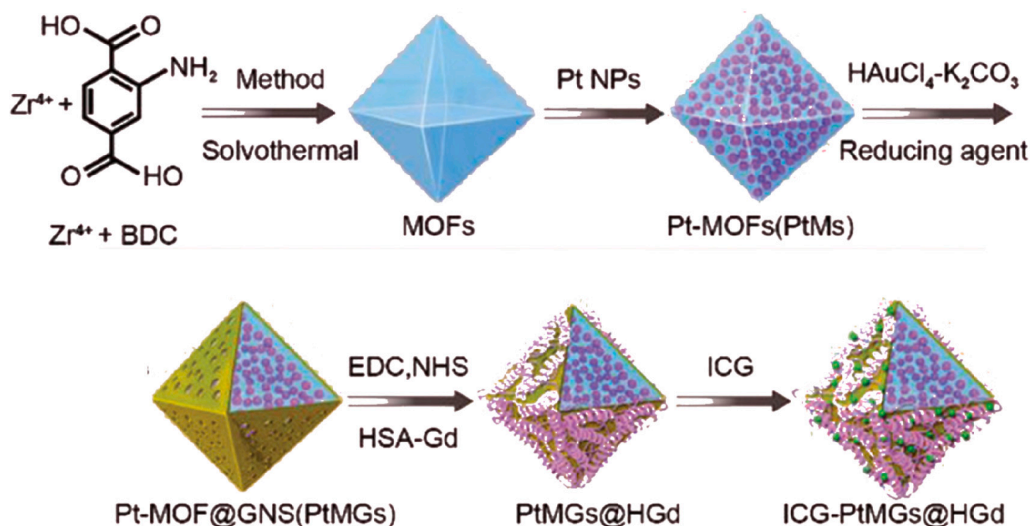


Fig. 4. Schematic illustration of ICG-PtMGs@HGd nanoplateforms [96]. Copyright 2020, Wiley-VCH.

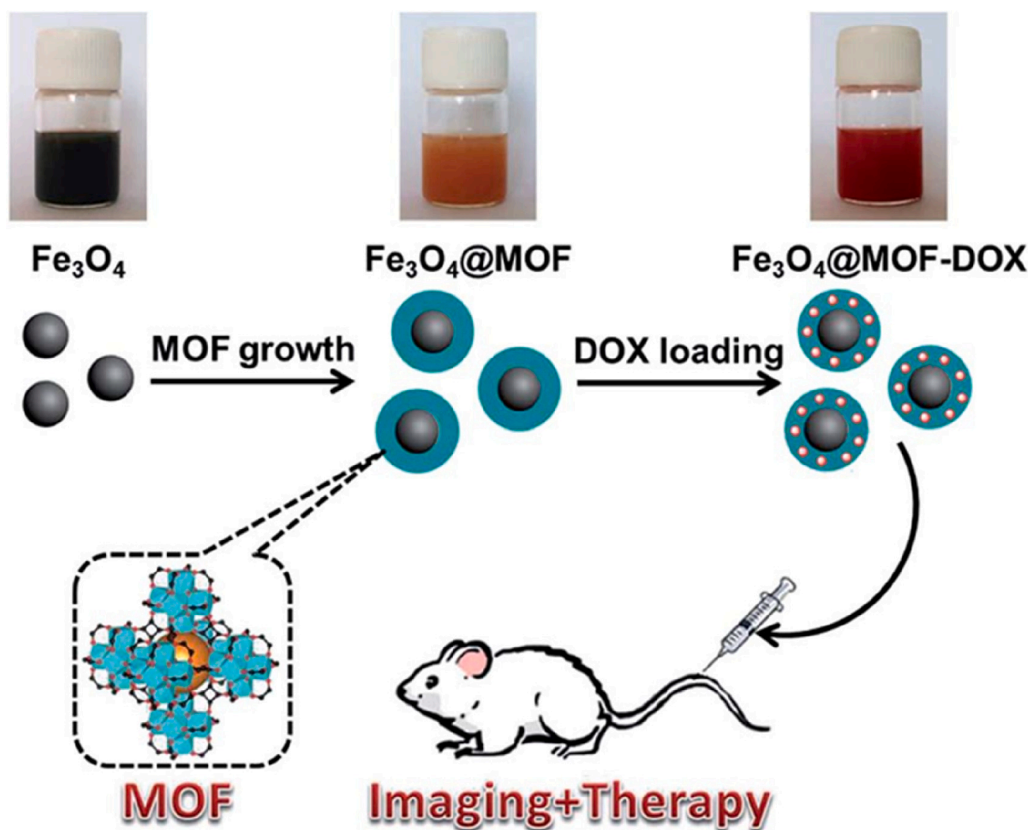


Fig. 5. Schematic illustration of $\text{Fe}_3\text{O}_4\text{@MOF-DOX}$ [100]. Copyright 2016, Royal Society of Chemistry.

ligands. This versatile approach synthesizes various structural motifs with adjustable metrics and properties [103–106]. In the medical field, basal growth is extensively employed to integrate the properties of different components, leading to synergistic heterostructure units that are particularly valuable for disease monitoring and real-time observation.

For instance, Lu and colleagues devised a novel Zn-Zr bimetallic MOF using the MOF-on-MOF method for disease diagnosis and treatment [107]. Similarly, Du et al. utilized the MOF-on-MOF strategy to create a bimetallic FeTb-MOF , which exhibits promising potential for early

diagnosis [108]. Furthermore, Hou et al. synthesized $\text{Au-Pd@UiO-66-on-ZIF-L/CC}$ via the MOF-on-MOF approach for applications in disease pathology [109]. By combining the basement with functional particles, these approaches synergistically enhance the diagnosis and treatment capabilities.

In summary, basal growth presents a powerful means to control crystallization and synthesize diverse structures with tunable properties. The MOF-on-MOF strategy has been widely employed in the medical realm to integrate different components, resulting in emergent properties that find utility in disease monitoring and treatment applications.

2.4. Surface coating

The utilization of sol–gel methodologies for surface coating holds tremendous potential in the development of drug delivery systems. In particular, when applied to silica sol–gel materials, this technique can effectively preserve the activity of bioactive dopants while ensuring exceptional stability for bioactive molecules [110–113]. When combined with MOFs, surface coating via sol–gel methodologies presents a promising approach to minimize direct contact between MOFs and the blood, reducing the potential toxicity of MOFs and improving the mechanical properties of the resulting nanostructured hybrid material.

An example of this approach is demonstrated by Pidko and colleagues, who successfully achieved a combination of anticoagulant and thrombolytic activities within a single hybrid nanomaterial by employing a bioactive nanocoating through the incorporation of Hep_MIL-101(Fe) into a sol–gel derived thrombolytic matrix (Fig. 6) [114]. Wang et al. also employed mesoporous silica materials to coat ZIF-8, creating an efficient drug delivery vehicle for encapsulating doxorubicin hydrochloride in disease therapy [115]. Similarly, Butova and coworkers synthesized silica-coated UiO-66 as a drug delivery carrier for targeted cellular uptake [116]. The surface coating enhanced the composites' colloidal stability in various physiological media and facilitated the grafting of target molecules onto the surface, thereby preventing uncontrolled cargo release.

In summary, applying sol–gel methodologies for surface coating represents a promising strategy for fabricating drug delivery systems. Combining this technique with MOFs offers numerous advantages, including reduced MOF toxicity, improved mechanical properties, enhanced colloidal stability, and controlled cargo release, making it a valuable approach in various biomedical applications.

3. Brain disease drugs

Along with science, technology, and societal development, people pay more attention to their health, which leads to steadily increasing life expectancy. The risks of some illnesses like brain and cardiovascular diseases have increased significantly due to longer lives. Brain diseases are a diverse and complex group of medical conditions that affect the structure and function of the brain. These conditions can range from relatively common ones like migraines and epilepsy to more severe and debilitating disorders such as AD, PD, and multiple sclerosis [117–119]. Neurodegenerative diseases are associated with neuronal dysfunctions and loss in different brain areas of patients (Fig. 7). Brain diseases can manifest in various ways, often leading to cognitive, emotional, and physical impairments. Multiple factors, including genetics, infections, trauma, and environmental influences, can cause them. Understanding and treating brain diseases is a significant challenge for medical professionals and researchers, as the brain remains one of the human body's most intricate and least understood organs. Advances in neuroscience

and medical technology have improved our ability to diagnose and manage these conditions, offering hope for better treatment options and improved quality of life for those affected by brain diseases. However, further research and awareness are crucial to unravel the complexities of these diseases and develop effective therapies. Based on these, researches on targeted delivery for drugs such as metformin, BLZ945, and cannabidiol have attracted more attention to dealing with the complex situations of brain diseases. MOFs possessing advanced porous structures, designable framework environments, and controllable properties and functions have been confirmed as potential drug carriers for a series of drugs to achieve effective transform and controlled release (Fig. 7). Besides, the drug delivery efficiency is highly dependent on the chosen delivery routes, which will be discussed later in details.

3.1. Alzheimer's diseases and Parkinson's disease

AD and PD are two of the most fast-growing neurodegenerative diseases (NDs) worldwide. ADs are characterized by amyloid beta ($A\beta$) deposition, formation of neurofibrillary tangles, and neuronal loss, affecting over five million Americans [117]. Unfortunately, there is still no cure or therapy to stop AD progress so far. PD is characterized by the progressive loss of substantia nigra compacta (SNc) dopaminergic (DA) neurons. PD patients are projected to exceed 12 million worldwide by 2040 [118,119]. A neuroprotective treatment that can reverse or rescue AD and PD symptoms can be a potential solution for both of the clinical challenges. However, no effective neuroprotective drug exists to stop or reverse the loss of DA neurons.

Both AD and PD are progressive and have a significant impact on the daily lives of individuals and their families. While there is currently no cure for either condition, ongoing research aims to understand their underlying mechanisms better and develop more effective treatments to slow their progression and improve the quality of life for those affected.

3.2. Metformin

An emerging approach for developing a neuroprotective treatment for AD and PD is repurposing existing drugs [120–122]. Among the repurposed drugs, metformin, as a commonly used drug for type 2 diabetes, has shown therapeutic effects in AD and PD. Animal studies indicate that metformin can alleviate behavioral impairments in animal models of PD. This is achieved through inhibiting inflammatory responses, preventing neuronal apoptosis, enhancing learning, memory, and cognitive function, and reversing behavioral deficits [120,122]. In a mouse model of PD induced by 1-methyl-4-phenyl-1,2,3,6-tetrahydropyridine (MPTP), it has been demonstrated that metformin can protect SNc DA neurons from degeneration. This protection is achieved through improved clearance of reactive oxygen species (ROS) within mitochondria and autophagy, mediated by AMP-activated protein kinase (AMPK) [123]. Metformin can modulate mitochondrial functions by

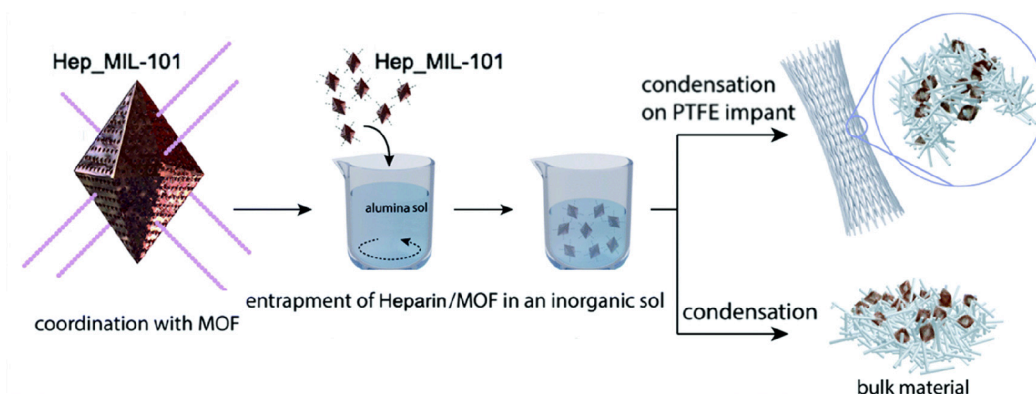


Fig. 6. Schematic illustration of MOF thrombolytic coating [114]. Copyright 2018, Royal Society of Chemistry.

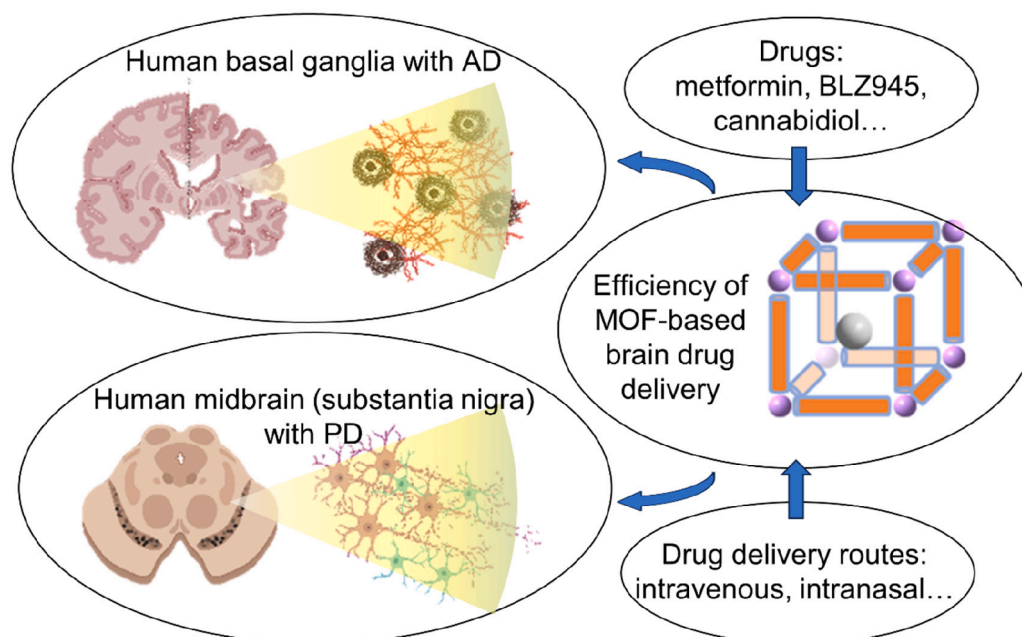


Fig. 7. MOF-based drug delivery for AD and PD and the affected human brain areas.

enhancing mitochondrial fission, promoting respiration, and mitigating oxidative stress [122]. Both in vitro and in vivo studies in mice highlight metformin's role in boosting mitochondrial respiration and fission by activating the AMPK pathway, thereby restoring the life cycle of mitochondria [124]. Moreover, cellular studies suggest that metformin's antioxidant property is achieved by diminishing levels of mitochondrial-derived ROS by activating a transcription factor regulating the expression of antioxidant genes [125].

Furthermore, metformin's prolonged administration (0.1 % w/w) effectively alleviates chronic inflammation, thereby extending both health span and lifespan in mice, though a higher dose (1 % w/w) proves toxic [126]. Additionally, metformin's efficacy extends to rescuing motor deficits and DA neurons in the *C. elegans* PD model induced by mitochondrial hyperactivation [127]. This demonstrates the positive impact of metformin on mitochondrial functions and underscores its therapeutic potential for DA, characterized by evolving mitochondrial defects and heightened oxidative stress throughout the disease's progression.

AD patients have shown a buildup of A β [128]. Pre-clinical studies on AD models have demonstrated the potential of metformin to enhance cognition memory and decrease A β levels [129–131]. Additionally, it has been observed to suppress oxidative stress and neuronal apoptosis [132]. Chiang et al. found that metformin significantly protects human neural stem cells (hNSCs) against mitochondrial dysfunction caused by A β , a process associated with neurodegeneration processes [133]. Ou et al. further reveal that metformin effectively recovers the deficits in spatial memory and attenuates hippocampal neuronal loss in APP/PS1 mice [134]. The function of metformin in diminishing A β plaque and chronic inflammation is achieved through the regulation of AMPK signaling pathways in both the hippocampus and cortex. A cellular study also suggested the neuroprotective effect of metformin on PC-12 neuron-like cells and primary hippocampal neurons, protecting them from hydrogen peroxide-induced neuronal death. This includes restoring abnormal changes in lactate dehydrogenase, oxidative stress, and mitochondrial membrane potential [135].

Although metformin shows neuroprotection in cellular studies and animal models of AD and PD, clinical translation is still hampered by the lack of suitable nanocarriers to improve brain availability and blood half-time and reduce side effects from prolonged therapy [136–140]. The therapeutic efficacy of metformin is highly determined by the local

drug concentrations in the targeted brain area. However, side effects such as vitamin B₁₂ deficiency [141] and gastrointestinal alterations [142] are two main side effects induced by a prolonged and high-dose metformin treatment to ensure enough brain concentration. Moreover, vitamin B₁₂ depletion induced by metformin may further impair motor behaviors [143] and cognitive functions [144], thus worsening PD progression. Existing drug carriers, such as polymeric carriers [145] and bovine serum albumin NPs (Fig. 8a-b) [146], either have low loading efficiency or lack controlled and sustained release. However, MOF-based carriers, such as ZIP-8@alginate [147] and MIL-100@alginate [148] (Fig. 8c-d), possess more significant loading efficiency, with the drug-releasing capability controlled by pH values. In Tahereh's study [148], MIL-100@alginate exhibited a metformin payload of 7.2 wt%. This high loading rate is attributed to the mechanism where metformin molecules traverse the micropores of MIL-100 and enter the larger mesoporous pores within the structure. The drug release results also indicated that the alginate coating on MIL-100 enhanced pH-controlled release. With the alginate coating, less drug was released in gastric pH, while more drug was released in an alkaline environment. This enhancement is due to the carboxyl groups in alginate acid losing their acidic hydrogen under alkaline conditions, transforming into repulsive carboxylate ions with a negative charge. This transformation leads to the expansion of the alginate coating, facilitating the release of entrapped metformin molecules. Another study [147] demonstrated a metformin payload of 6.68 wt% using ZIF-8@alginate. Additionally, they showed that the alginate coating efficiently protected the ZIF-8, which is sensitive to acidic pH.

3.3. BLZ945

Microglia function plays a significant role in the neurodegeneration process. Microglia act as amyloid carriers in AD, transporting A β to unaffected and healthy brain regions [149]. Therefore, targeting the elimination of defective microglia or modulation of microglial function could be a novel therapeutic approach for AD by reducing the propagation of A β and the growth of plaques in brain regions that remain unaffected. The microglial-based studies in AD mainly focus on inhibiting colony-stimulating factor 1 receptor (CSF1R), primarily found on microglia, and shows significantly increased expression in ND [150]. It is reported by Spangenberg et al. that the treatment of CSF1R inhibitors leads to the elimination of microglia by 80 % [151].

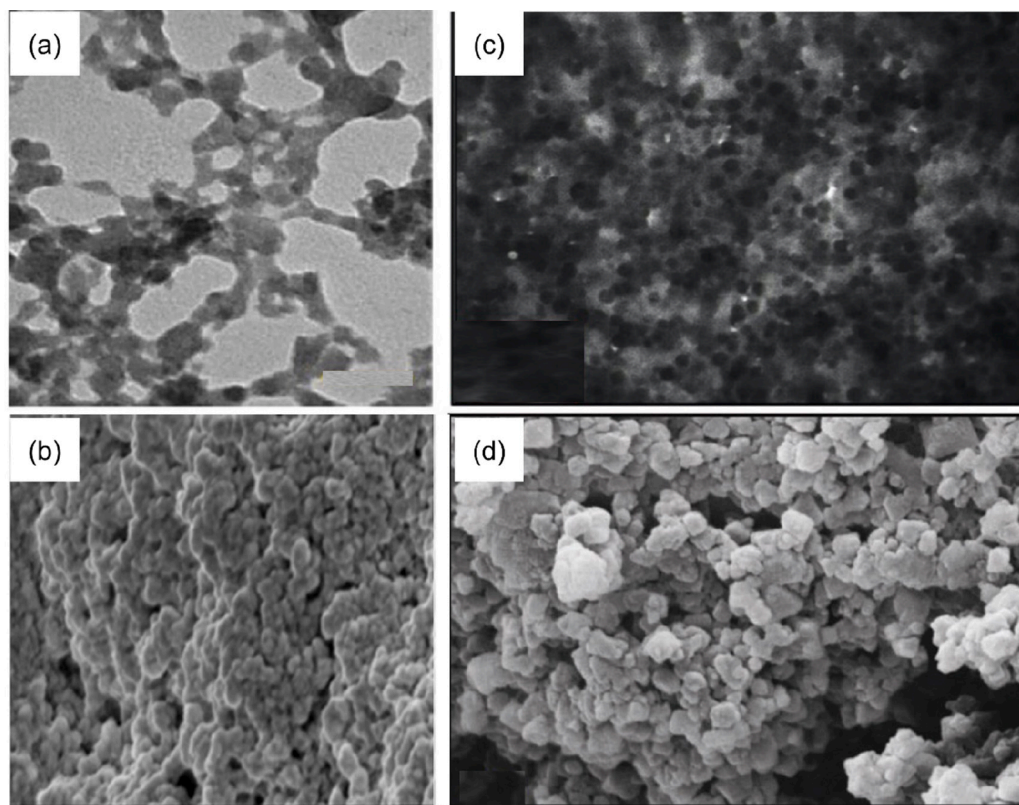


Fig. 8. TEM images of metformin carriers: (a) Polymeric carriers [145]. Copyright 2022, Nature. (b) Bovine serum albumin NPs [146]. Copyright 2014, Springer. (c) ZIP-8@alginate [147]. Copyright 2018, Elsevier. (d) MIL-100@alginate [148]. Copyright 2018, Royal Society of Chemistry.

Interestingly, this microglia elimination does not impact the A β progression. However, it prevents neuronal loss, reduces neuro-inflammation, and improves memory in a transgenic mouse model of AD. BLZ945 is a CSF1R inhibitor with high selectivity and hydrophobic properties [152–154]. Unfortunately, till now, there is limited work on formulating suitable carriers for BLZ945 to realize the controlled and sustained delivery. There is only one reported work formulating BLZ945 with poly(L-glutamic acid)-g-methoxy poly(ethylene glycol)/Combretastatin A4 [155,156]. However, there is no available data on drug release characteristics. Moreover, this type of NP is more cancer-cell-specific and may not be suitable for brain-related diseases.

3.4. Cannabidiol

The previous studies suggest that targeting a single pathway may not delay or stop AD progression [157]. Currently, the cannabinoid system has emerged as a promising therapy for AD because endocannabinoid signaling modulates multiple pathological processes linked to neuro-degenerative processes, including protein misfolding, neuro-inflammation, excitotoxicity, mitochondrial dysfunction, and oxidative stress [158]. The therapeutic effect of cannabidiol (CBD)-based drugs, composed essentially of CBD and delta-9-tetrahydrocannabinol (THC), have been intensively studied to treat neurological disorders, including AD.

Various preclinical studies have also shown that CBD-based drugs can reduce the soluble A β 42 levels [159], protect against A β -mediated neurotoxicity [160], maintain Ca²⁺ homeostasis [161], improve the viability of hippocampal neurons [162], and protect against cognitive impairment with associated behavior disturbances in AD mouse models [163]. Clinical trials (NCT03328676 and NCT02818777) have confirmed that orally administered CBD-based drugs can significantly reduce behavior disturbances associated with dementia and tremor [164,165]. However, their efficacy was limited due to low oral

bioavailability [166].

Facing this challenge, there are fast-growing research activities on developing CBD vehicles, such as lipid [167,168] or microgel [169] carriers, to improve the bioavailability of CBD and enable the controlled release. Nanostructured lipid carriers have been developed to overcome the low aqueous solubility [170]. Efforts have also been made to formulate CBD in a nano-dispersion form to improve its oral bioavailability in humans [171]. Nano-micelle-based nanocarrier for CBD has shown to enhance its water solubility and bioavailability due to the hydrophilic shell of the micelle structure [172]. In addition, the formation of complexes of CBD with β -cyclodextrin can also improve its water solubility [173]. However, none of them can realize the on-demand delivery of CBD to a specific brain area. As a porous nanocarrier with supreme drug loading capacity and tunable surface function, MOF can be a potential candidate to encapsulate CBD to improve the water solubility of CBD molecules and their controlled release [174]. For example, Sharma et al. developed a microporous magnesium-gallate MOF for loading and release of CBD, demonstrating sustained release of CBD due to the MOF's slow degradation in bio-mimicking liquid. The release of CBD was validated by its anti-inflammatory and antioxidant effects in vitro, addressing CBD's low bioavailability and poor aqueous solubility [175]. Recently, a novel γ -cyclodextrin MOF for CBD delivery model was developed, utilizing olivetol as a CBD precursor and analog. This drug delivery system achieved high loading capacities, with γ -cyclodextrin's hydrophobic inner cavity encapsulating non-polar compounds and its hydrophilic outer surface enhancing solubility in aqueous solutions.

Consequently, MOFs hold promise for improving CBD's water solubility and bioavailability [176]. Additionally, MOFs can be combined with magnetic NPs to enable the magnetic-targeting delivery of CBD. One example involves using Fe₃O₄ as a core coated with MIL-100 nanoparticles [177]. In vivo experiments conducted in mice demonstrated that an external magnetic field guided tumor uptake of NPs, and

magnetic treatment enhanced the tumor-curing effect without altering normal tissue functions. Moreover, since the magnetic effect is attributable to the external high-gradient magnetic field, this guiding effect is independent of the surface receptor types, making this application adaptable for various tissue types.

3.5. Proteins and micro ribonucleic acid (miRNA)

Besides the small molecules, proteins and miRNAs are extensively studied as therapeutic agents for AD and PD. Proteins such as pentraxin-3 [178,179] and soluble TREM [180] can modulate microglia activities. Irisin is recognized as one of the proteins induced by physical exercise in the bloodstream, contributing to enhanced brain function by exerting anti-inflammatory effects and enhancing BDNF signaling levels [181]. Clusterin is another protein induced by physical exercise in the bloodstream, and it also improves brain functions by reducing inflammation [182]. There are also some miRNAs with neuroprotection/anti-inflammatory functions [183]. However, in contrast to the above-mentioned small molecules, proteins and miRNAs are not suitable for encapsulation by MOFs due to their relatively large size, which exceeds the pore dimensions of MOFs.

In summary, effective drugs for AD and PD are still rare now (Table 1), as well as minimal drug effects and mechanism studies, which need much further work to study new advanced drugs and drug mechanisms.

4. Drug loading

Drug loading is an essential and intricate process that has garnered significant attention from researchers. The primary objective has been to enhance drug loading capacities and binding strengths with MOFs. Different loading methods are employed depending on the drugs' molecule sizes, functional groups, and potential coordination sites. This section provides a comprehensive overview of four prominent methods: the adsorption effect, post-synthesis reaction, in situ template method, and self-assembly synthesis (Fig. 9).

4.1. Adsorption effect

The adsorption effect stands out as a crucial and highly effective method for drug loading. With their porous structure, MOFs exhibit exceptional cavities capable of accommodating a wide range of diverse species. These species include energy/exhaust gases [184–186], toxic/rare metal cations [187–190], organic solvents/pollutants [36,191–193], and water [194,195], which serve various functions through the adsorption process. In the context of drug loading, the target

Table 1
Small molecule drugs for AD and PD and the currently available drug carriers.

Drug	Neuroprotective function	Hydrophilicity and water solubility	Available drug carrier
Metformin	Increases longevity, eliminates senescent cells, modulates activated microglia, dampens mammalian target of rapamycin signaling and enhanced autophagy	Water soluble	Polymeric drug carrier [145], bovine serum albumin NPs [146], MOFs [147,148]
BLZ945	Elimination of microglia, for AD and traumatic brain injury	Insoluble in water	Copolymers [155]
Cannabidiol	Antioxidant, anti-inflammatory and neuroprotective	Low solubility in water, hydrophobic	Lipid carriers [167,168], microgel [169], nanomicelle [172]

drugs typically establish connections with MOFs through intermolecular forces. Consequently, the loading capacities are primarily determined by the porosities of the MOFs, while the binding strengths predominantly rely on the specific types of intermolecular forces involved.

With the increasing prevalence of an aging population, cardiovascular and cerebrovascular diseases have emerged as the leading cause of death. Alarming, these diseases are now affecting individuals at a younger age [196,197]. Researchers like Rosi and colleagues have investigated procainamide HCl's storage and release mechanisms, an antiarrhythmic drug. They utilized the permanently porous bio-MOF-1, incorporating rigid biomolecule adenine as a building block, achieving a remarkable drug loading capacity of 0.22 g g⁻¹ [81]. In another study, Deng et al. demonstrated the ability to control the release profiles of guest molecules by fine-tuning desirable interactions. They achieved this by modifying MIL-101(Fe) and successfully adsorbing the antibiotic drug doxorubicin and the anti-inflammatory drug ibuprofen. The experimental setup and results are depicted in Fig. 10 [198].

Furthermore, Kong et al. investigated the loading of various drugs into defective UiO-66, including the cardioprotective agent creatine phosphate and eleven other bioactive molecules. Their findings revealed the crucial role defects in MOFs play in facilitating the loading of pharmaceuticals containing phosphate or phosphonate groups [199]. These studies exemplify the ongoing research efforts to explore drug storage and release mechanisms within MOFs for treating cardiovascular and cerebrovascular diseases. By uncovering these fundamental processes, researchers aim to develop more effective therapeutic strategies to combat these life-threatening conditions.

In addition to diseases affecting the brain and other body parts, the following section delves into various diseases, including cancer and inflammation, which have garnered significant attention.

Cancer has emerged as the leading cause of death worldwide, capturing the concern of people over the past century [200,201]. However, traditional antitumor drugs often suffer from severe side effects and limited efficacy due to their poor targeting capabilities [202]. MOFs have garnered substantial interest due to their ease of functionalization, potential biodegradability, and multifunctionality [203]. The design and modification of MOFs offer a convenient means to introduce targeting binding sites. Wang et al. developed a chiral Zn-MOF capable of high drug loading and sustained release of the anticancer drug 5-fluorouracil [204]. Zhou et al. utilized PCN-333(Al) as an enzyme carrier to load the nontoxic prodrug paracetamol, inducing significant cytotoxicity in drug-resistant cancer cells and promoting tumor regression [205]. Zhang et al. established a flexible-on-rigid hybrid-phase MOF system for controlled multi-drug delivery of 5-fluorouracil and alendronate [206]. Fairen-Jimenez et al. successfully loaded the anticancer drug alpha-cyano-4-hydroxycinnamic acid into NU-1000 and NU-901, which exhibited efficacy in killing cells beyond the burst release effect [207]. Tang et al. employed Fe-TCPP to adsorb the anticancer agent dihydroartemisinin (DHA), further coating it with CaCO₃ to enhance anticancer efficiency with minimal toxicity. A visual representation of their approach is presented in Fig. 11 [208]. Chen et al. achieved significantly enhanced tumor delivery specificity and minimal long-term toxicity by loading artesunate into a core-shell MOF derivative, Mn₃Co(CN)₆@MIL-100(Fe) [209]. Nie et al. introduced apatinib into a Zr-MOF and coated it with MnO₂ to facilitate a combination therapy approach, combining photodynamic therapy with antiangiogenics for anticancer treatment [210].

Inflammation serves as the initial response of the body's immune system to injury, infection, and stress. However, chronic inflammation has been closely linked to numerous diseases [211,212]. Recognizing this connection, Férey et al. directed their focus toward loading the anti-inflammatory drug ibuprofen into cubic zero-typical metal carboxylates MIL-100(Cr) and MIL-101(Cr) [213]. Additionally, they explored flexible nanoporous chromium or iron terephthalates MIL-53(Cr) and MIL-53(Fe) as potential carriers, demonstrating excellent drug loading capacities and delivery rates [214].

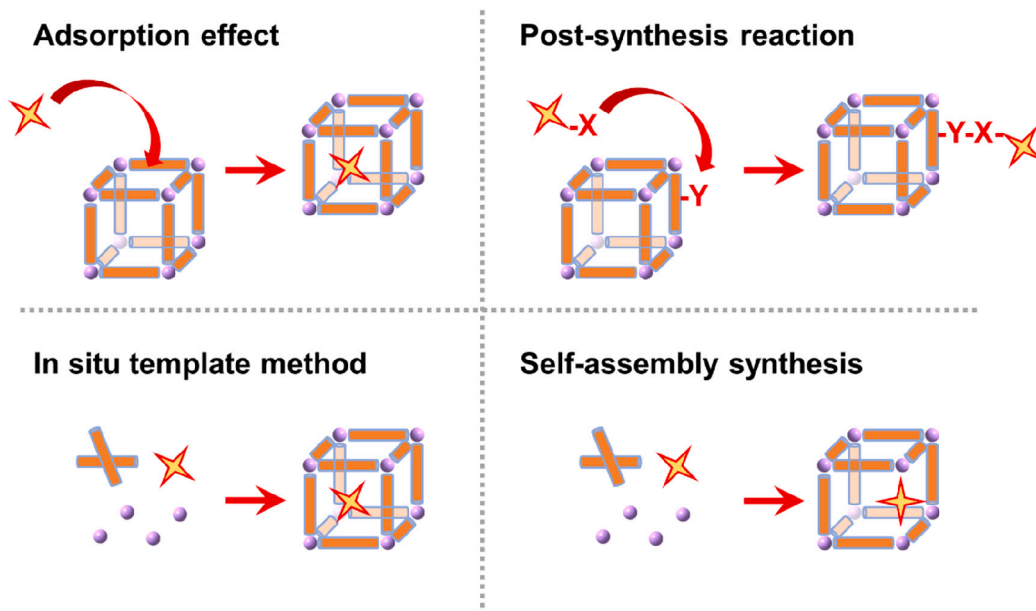


Fig. 9. Drug loading methods through metal-organic frameworks.

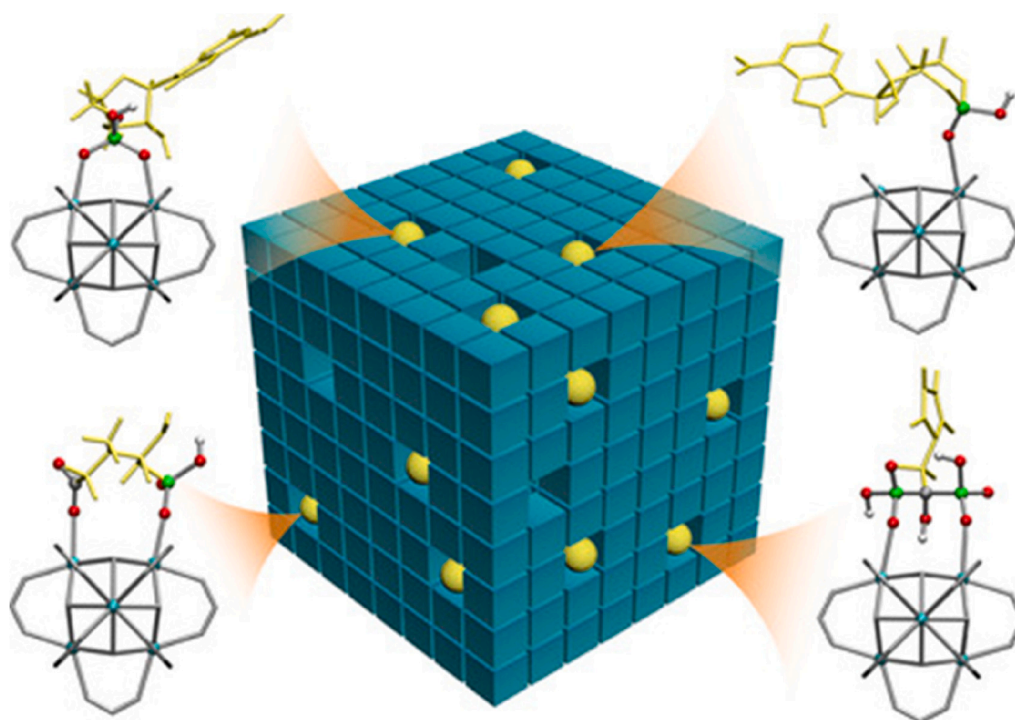


Fig. 10. Schematic structures of drug-loading defective UiO-66 [198]. Copyright 2021, Wiley-VCH.

In summary, the adsorption effect enables the loading of various drugs within the pores of MOFs, facilitating their subsequent delivery and release. This property makes MOFs widely applicable in pharmaceutical applications. However, it is essential to note that small-molecule drugs mainly favor the strategy of drug loading within MOFs due to the limitations imposed by pore sizes and stabilities. The simplicity in design and achievement further contributes to the attractiveness of this approach for small-molecule drugs in combination with MOFs.

4.2. Post-synthesis reaction

The post-synthesis reaction has emerged as a powerful synthetic approach that possesses significantly enhanced properties and functionalities of MOFs, leading to notable advancements in their applications [215–218]. Compared to directly synthesizing functionalized MOFs using functionalized ligands, the post-synthesis reaction allows for the heterogeneous modification of MOFs by forming new bonds. This straightforward design and simple synthesis route enable MOFs to acquire target functions [219,220]. Several active functional groups serve as potential candidates for pre-introduction into MOFs for subsequent modifications. Examples of such groups mainly include the amino group

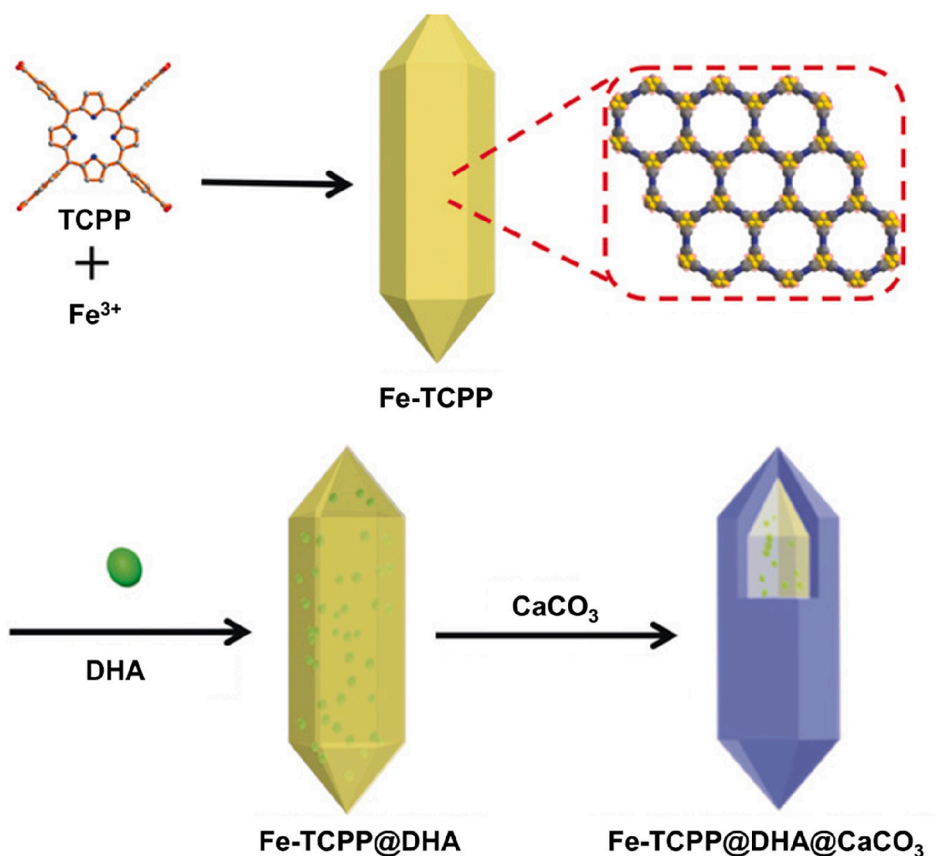


Fig. 11. Schematic illustration of the preparation of Fe-TCPP@HA@CaCO₃ [208]. Copyright 2019, Wiley-VCH.

[221–223], carbon–carbon double/triple bond [224,225], thioether bond [226], and pyridyl group [227]. These functional groups have also found application in the combination of MOFs with drugs.

Among these functional groups, the amino group is frequently employed in MOFs and medicines for drug-loading purposes. Lin et al. successfully loaded the drug ethoxy succinate-cisplatin into NH₂-MIL-101(Fe) in DMF at room temperature, demonstrating controlled release properties (Fig. 12) [228]. Park and Wuttke utilized NH₂-MIL-68(In) and NH₂-MIL-101(Al) to react with functional proteins, showcasing practical covalent attachment of drugs within MOFs with moderate chemical stability [229,230]. Sun et al. leveraged the aldehyde group of ZIF-90 to react with the amino group of the drug doxorubicin via the Schiff base reaction. They further loaded another drug, 5-fluorouracil, through the adsorption effect. This study marked the first report on the disease-targeted co-delivery of two medicines based on nanoscale MOFs [231].

These examples illustrate the versatility of the post-synthesis reaction approach in MOF modification and drug loading. By utilizing various functional groups and reactions, researchers strive to enhance MOFs' functionality and therapeutic potential in drug delivery systems.

Compared to the adsorption effect, the post-synthesis reaction offers the advantage of establishing more robust connections between MOFs and drugs by forming covalent bonds. This enhanced bonding is beneficial for achieving controllable drug release, as the bonds can be selectively broken under specific stimuli such as pH and temperature. On the other hand, drug release is often governed by kinetic factors, making it less controllable in the adsorption effect. Moreover, the post-synthesis reaction allows for the loading of even larger-sized drugs onto the MOF surface. This designable, cost-effective approach relies on modifying simple MOFs to achieve desired functionalities. However, it is essential to note that the main limitation of the post-synthesis reaction method is the requirement for both the drugs and the MOFs to possess compatible functional groups. This limitation restricts the widespread

applicability of this method.

4.3. In situ template method

By incorporating target templates into MOF precursors, it becomes possible to fabricate novel template@MOF materials, which is challenging to achieve using traditional synthesis procedures [232,233]. Various small organic molecules such as solvents, carboxylic acids, and ion liquids [234–237], as well as simple coordination structures like coordination compounds and polyoxometalates [238–240], macromolecules like block co-oligomer, biomacromolecules, and polymers [241–244], are widely employed as templates for the synthesis and combination of template@MOF materials. This approach is also utilized for drug loading onto MOFs.

For instance, Chen and colleagues utilized human immunoglobulin G polyclonal antibody, goat anti-bull serum albumin immunoglobulin G polyclonal antibody, and monoclonal antibody adalimumab as templates to synthesize ZIF-90 and ZIF-8. These materials exhibited high encapsulation efficiencies, enhanced resistance against perturbation environments, and long-term storage capabilities (Fig. 13) [245]. In another study, Wang and coworkers employed a chlorin e6-functionalized DNAzyme as a template for the synthesis of ZIF-8, enabling imaging-guided combined gene/photodynamic therapy [246]. Xie and colleagues adopted an in-situ template to prepare nanoscale ZIF-8 loaded with the natural chemotherapeutic agent curcumin. The resulting material exhibited high drug encapsulation efficiency, good chemical stability, and fast drug release in acidic microenvironments [247].

Furthermore, Forgan and colleagues chose the drug dichloroacetic acid as a template to synthesize UiO-66, which was subsequently coated with poly(ethylene glycol) chains. This modified material demonstrated improved stability, drug release, and cell-uptake properties [248].

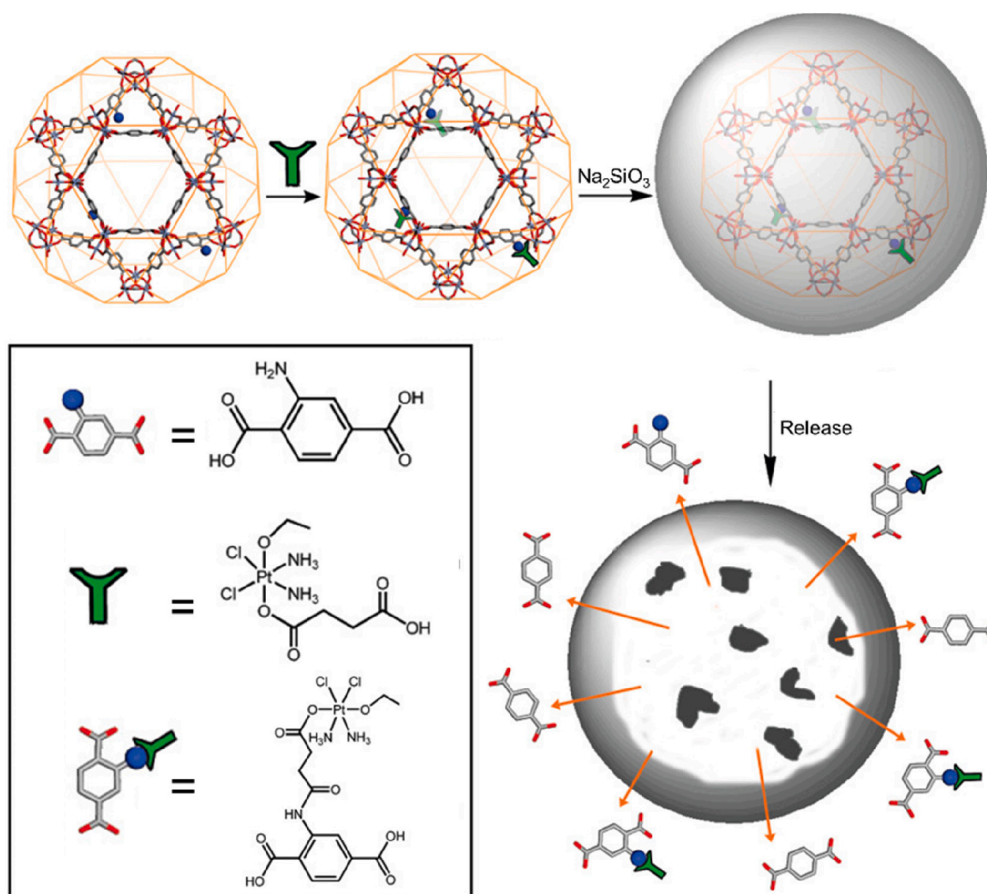


Fig. 12. Schematic drug-loading route of defective $\text{NH}_2\text{-MIL-101(Fe)}$ [228]. Copyright 2009, American Chemical Society.

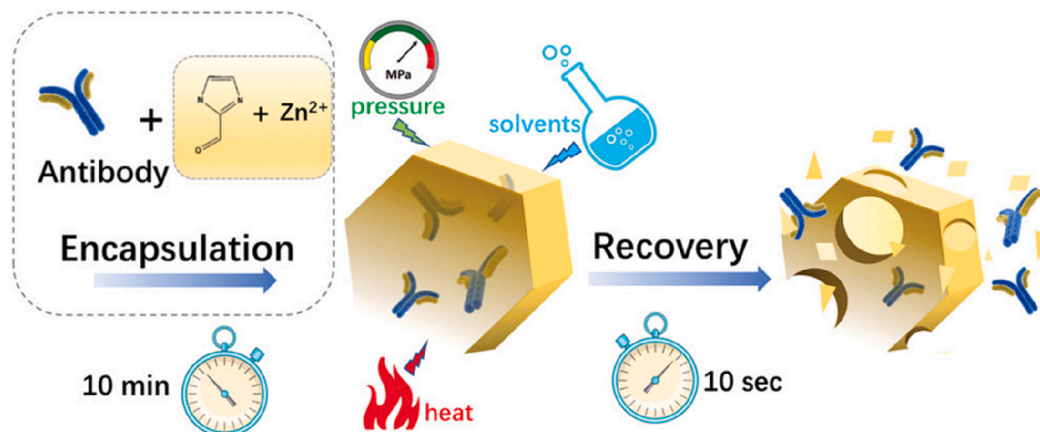


Fig. 13. Schematic illustration of the preparation of antibody@MOFs [245]. Copyright 2019, Wiley-VCH.

In summary, drugs can play a crucial role as templates during synthesis, allowing for their encapsulation within MOFs without restricting particle size, which differs from the adsorption effect. Additionally, the in-situ template method offers a convenient one-pot synthesis approach that saves time compared to the aforementioned methods. However, it should be noted that the outcome achieved through this method can be unpredictable, as it requires considerable effort to design and control various factors, such as the selection of the template, the synthesis conditions, and the final structures. Currently, there is no universal pathway, which constrains the advancement of this method, thereby leaving room for further development and exploration.

4.4. Self-assembly synthesis

Biomolecules with coordination groups can serve as fundamental units for constructing biomedical MOFs, enabling the development of advanced materials for various medical applications [249,250]. Utilizing a self-assembly synthesis method, these biomolecules facilitate the incorporation of drugs with well-defined structures, allowing for controlled release, minimal toxicity, and high drug-loading capacity [251,252]. Several small molecules possessing medicinal properties and biological activities have been employed as ligands for MOF construction.

One notable example is adenine (also known as vitamin B4) and its

derivatives, essential component in the human body and exhibits significant antiviral and cytostatic activities [253,254]. This molecule has been utilized in the construction of bioMOF-1 [81], 446-MOF (Fig. 14a) [188], 1 and 1-NH₂ [255]. Another crucial biomolecule is nicotinic acid (also known as vitamin B3), an essential vitamin in the human body that regulates white blood cells [256]. Nicotinic acid has been employed as a linker in the construction of BioMIL-1 [257], Co/Ni-MOF [258], and bioNICS-1 [259]. Histidine, an essential amino acid for humans, has been identified as a practical component in relieving cardiovascular diseases [260]. It serves as a linking unit in the construction of GH-Cu BioMOF [261], D-his-ZIF-8 (Fig. 14b) [262], and Co-MOF [263].

In addition to bioactive small functional molecules, numerous drugs can serve as ligands for constructing MOFs. Long and colleagues utilized the broad-spectrum anticancer agent olsalazine (H₄olz) as a ligand to synthesize a new series of mesoporous MOF-74 expanded analogs, M₂(olz). These analogs have been assessed as a platform for delivering olsalazine and other encapsulated therapeutics for combination therapy (Fig. 15) [264]. Wang and colleagues also employed olsalazine in the construction of two three-dimensional pillared Co/Cd-MOFs [265]. Devic and colleagues chose gallic acid (H₄gal), known for its anti-allergic, anti-inflammatory, antimicrobial, cardioprotective, neuro-protective, and anticarcinogenic activities, to construct Mg₂(gal)·xH₂O and Mg(H₂gal)·2H₂O. These MOFs exhibit a slow release of gallic acid in the HL-60 cell line [266]. Fairen-Jimenez and colleagues loaded the cancer drug dichloroacetate into UiO-66, which resulted in a reduced required dose compared to the free drug and significantly enhanced drug efficacy [267]. Furthermore, Blanco-Prieto utilized azelaic acid, which possesses antibacterial and anti-inflammatory properties, as a linker to construct BioMIL-5. The antibacterial activity of BioMIL-5 was evaluated against two common Gram-positive bacteria, staphylococcus aureus and streptococcus epidermidis [268].

The utilization of binding drugs in self-assembly synthesis enables comparatively high drug loading efficiency and minimizes toxicity. The targeted drugs can coordinate with the metals and permeate the pores, while other medications can be incorporated into the drug-MOF for combination therapy. Moreover, the controlled release of drugs can be achieved by selectively degrading the MOFs. However, introducing essential coordination units in ligands presents a significant limitation,

restricting the potential applications of numerous medications.

5. Drug release

The control of drug release is a vital and complex process that has received considerable interest from researchers. Notably, there has been a focus on achieving controllable drug release using internal or external stimuli through chemical or physical means. Incorporating internal or external stimuli allows for precise drug release regulation to accomplish the targeted drug delivery effects. Chemical stimuli like ions and molecules and physical stimuli like light, thermal, and pressure can trigger drug desorption, drug exchange, and even framework destruction. In the following section, we present a comprehensive overview of various methods that effectively enable the control over drug release (Fig. 16).

5.1. Chemical stimuli

Chemical stimulation methods can be divided into ion-type and molecular-type stimulations. Ion-type stimulation often relies on H⁺ ions, metal ions, and phosphates. Compared to typical environments, the H⁺ ion concentrations are lower within specific biological contexts, such as the tumor microenvironment, endosomes, and lysosomes [72,269]. Various acid-sensitive MOFs have been utilized in drug delivery systems, which will cause the destruction of the frameworks and release of the drugs. When exposed to high H⁺ ion concentrations, these materials can undergo degradation, facilitating the release of drug payloads. Leveraging these advantageous properties, pH-responsive drug delivery systems based on MOFs have been developed for targeted drug delivery.

MOF-74-Zn serves as an exemplary model within the realm of MOFs due to its possession of accessible metal sites that enable precise drug encapsulation and subsequent controlled release. Arsenic trioxide is a neutral drug securely tethered to the unoccupied metal sites within the MOF structure. In contrast, the drug release behavior exhibits a favorable response to pH variations, with faster release kinetics observed at pH 6.0 compared to pH 7.4 (Fig. 17) [270].

pH-responsive molecule poly(ethylene glycol) methyl ether methacrylate (PEGMA) was modified to fabricate the GQDs@γ-CD-MOF (GQDs for graphene quantum dots) composite through surface-initiated

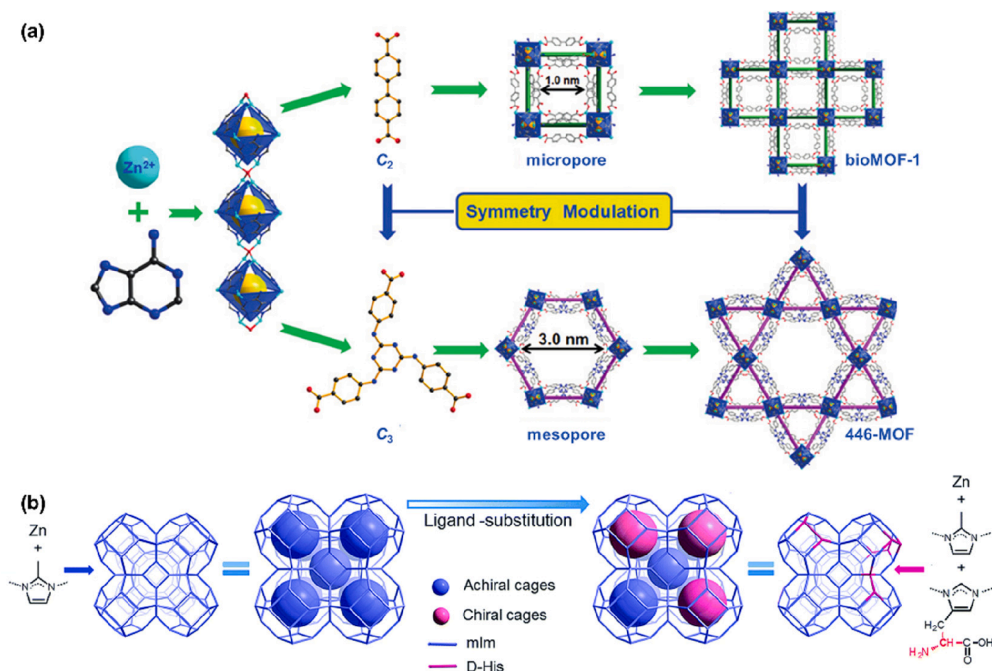


Fig. 14. Structural features for (a) microporous bio-MOF-1 and mesoporous 446-MOF [188]. Copyright 2015, Wiley-VCH. (b) chiral D-his-ZIF-8 [262]. Copyright 2015, Royal Society of Chemistry.

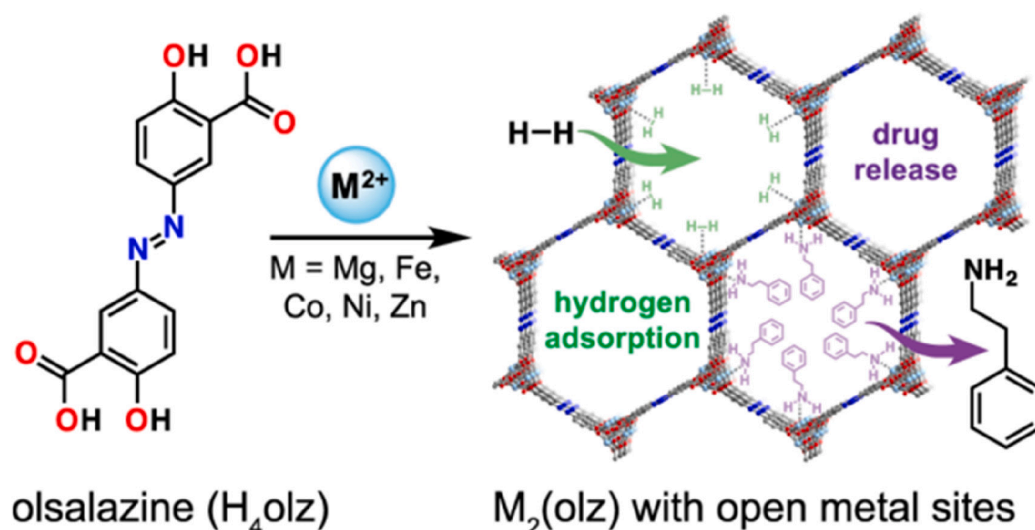


Fig. 15. Construction, structure, and applications of $M_2(olz)$ [264]. Copyright 2016, American Chemical Society.

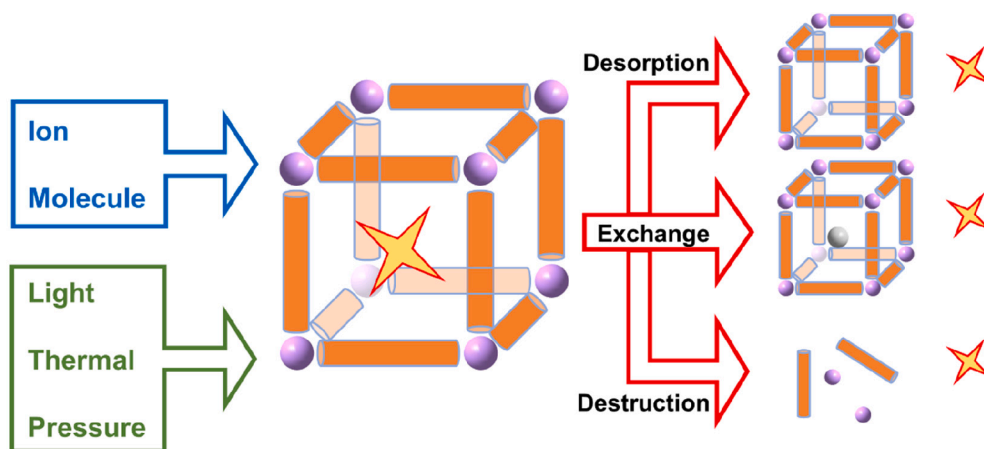


Fig. 16. Drug release methods and processes of drug@MOFs.

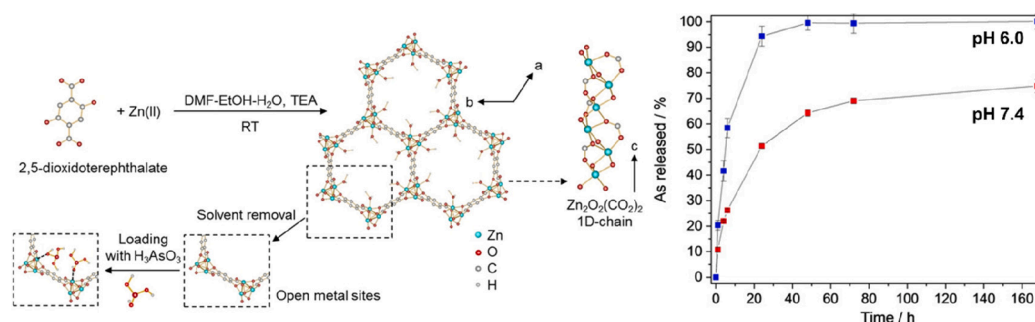


Fig. 17. Schematic representation of the synthesis and crystal structure of MOF-74-Zn, drug-loaded MOF-74-Zn, and drug release from the drug-loaded MOF-74-Zn [270]. Copyright 2020, Wiley-VCH.

atom transfer radical polymerization, which exhibits pH-responsive release function and excellent targeting ability (Fig. 18) [271]. The biocompatible Ti-based MOF MIL-125 was explored as a potential pH-controlled drug delivery carrier that promotes drug release in acidic conditions without tedious post-modification. The mechanism of the pH-responsive drug delivery was attributed to the different stability of MIL-125, confirmed by Cui and Qian [272]. Natarajan and coworkers focused on the fabrication of a europium MOF (Eu-MOF) as a pH-

responsive drug delivery system for seaweed polysaccharide fucoidan by one-pot synthesis method, which exhibited high drug loading efficiency (22.15 %) and pH-responsive controlled release of drug fucoidan (85.3 ± 0.02 % in 48 h at pH 5.0) [273]. Liu and coworkers prepared a Zn-MOF under quickly mild synthetic conditions with ibuprofen incorporated as a ligand, showing remarkable pH-controlled release [274].

Many metal ions have been used as switches for drug release, for example, Mg^{2+} , K^+ , Ca^{2+} , Zn^{2+} , and Pb^{2+} ions. Willner and coworkers

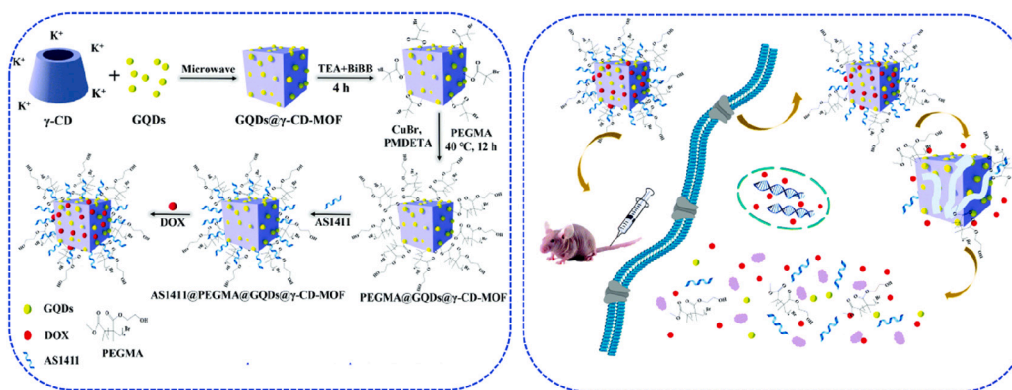


Fig. 18. Schematic illustration of the synthetic procedure for core-shell-structured PEGMA@GQDs@γ-CD-MOF composite and pH-responsive controlled release system [271]. Copyright 2019, Royal Society of Chemistry.

designed smart Mg²⁺-ion-dependent DNAzyme-capped doxorubicin-loaded MOF nanoparticles via integrating the ATP aptamer sequence in the loop domain of the Mg²⁺-dependent DNAzyme. In contrast, the smart carrier provides sense-and-treat functions (Fig. 19) [275]. Yang and coworkers established an intelligent theragnostic nanoplatform based on nano valve operated MOF core-shell hybrids with multi-stimuli responsive drug release in response to pH changes, temperature variations, and competitive agents, like Ca²⁺ and Zn²⁺ ions [276].

As for phosphates, Hsiao and Tsai successfully quantified ibuprofen loading in UiO-66-NH₂, which can be controlled to release in a phosphate buffer solution [277]. Defects were introduced within nano-sized UiO-66 to lock the hybrid phosphonoacetate ligand through Zr-O-P linkages, leaving the carboxyl group free to anchor cisplatin prodrug, which exhibited a controllable release in phosphate-buffered saline solution [278].

In conclusion, chemical stimulation methods have opened up exciting possibilities in drug delivery, offering precise control over drug release in response to various environmental factors. Ion-type stimulations, relying on H⁺ ions, metal ions, and phosphates, have been harnessed to create innovative drug delivery systems.

Molecular-type stimulations contain various biochemicals, especially saccharides, polypeptides, and enzymes, which will destroy the frameworks or the exchange of the guests to release the drugs. Ye and Zhao have pioneered the development of a cutting-edge glucose-responsive MOF-based nano-system for insulin delivery, employing a streamlined one-pot process. This innovative approach capitalizes on the MOF's unique responsiveness to glucose stimulation, enabling it to facilitate the controlled release of insulin. This nano-system has demonstrated remarkable efficacy in achieving glucose-responsive and self-regulated insulin release, marking a significant advancement in insulin delivery technology (Fig. 20) [279]. In another noteworthy

breakthrough, insulin and Au NPs-encapsulated ZIF-8 were meticulously synthesized using a continuous-flow, microfluidic mixing system, all achieved in a single-step process. The catalytic properties of Au NPs were ingeniously harnessed, mimicking glucose oxidase activity to facilitate the oxidation of glucose molecules upon their entry into the porous structure of ZIF-8. This transformation of glucose into gluconic acid and hydrogen peroxide occurred within the confines of the MOF, denoted as Ins-AuNP-ZIF-8, which can trigger the disintegration of ZIF-8, resulting in the controlled release of insulin [280]. In a groundbreaking development, multi-enzyme MOF-based microneedles were ingeniously engineered, incorporating insulin and glucose oxidase within cobalt-doped ZIF-8. These microneedles exhibit stimuli-responsive properties, and their design offers a painless and efficient avenue for glucose-mediated transdermal administration, ushering in a new era of advanced drug delivery technology [281].

Liu, Zhao, and coworkers have designed a hydrogen peroxide/glutathione dual-sensitive nano platform that holds great promise to alleviate the side effects of chemo drugs and improve their therapeutic efficacy. The dual-responsive nano platform prevents the premature leakage of a chemotherapeutic drug and is also sensitive to biologically relevant peroxide and glutathione for the precise delivery of chemotherapeutic drugs [282]. UiO-66 was skillfully modified with amino and phenylboronic acid groups, creating a substrate ideal for loading doxorubicin. Subsequently, a molecularly imprinted polymer was meticulously crafted on the surface of these NPs using the surface molecular imprinting technique, with sialic acid serving as the template molecule, endowing it with the ability to selectively recognize disease cell while offering dual-responsive drug release properties triggered by the acidic pH and glutathione levels [283]. Khiar, Carrillo-Carrión, and coworkers introduced a novel approach for controlled drug release utilizing a nanoscale Zr-based MOF UiO-66 in the presence of the enzyme alkaline

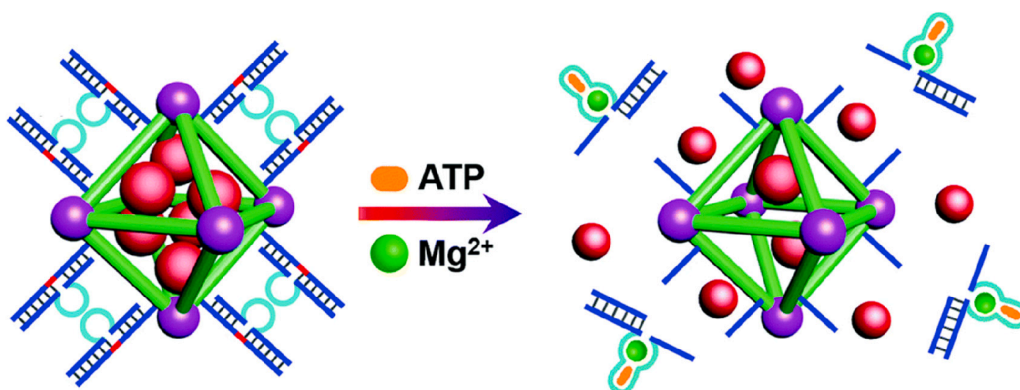


Fig. 19. Loading of MOF nanoparticles with doxorubicin and their capping with DNA scaffolds [275]. Copyright 2017, Royal Society of Chemistry.

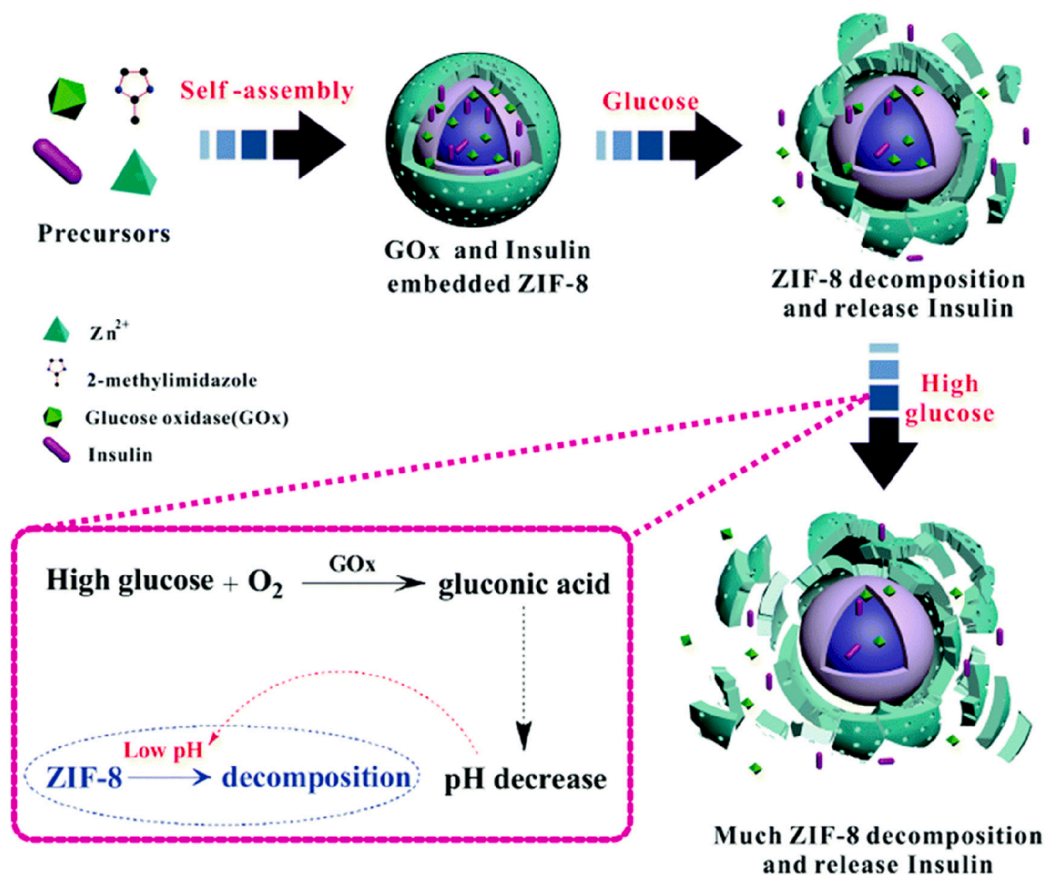


Fig. 20. Schematic illustration of the glucose-triggered insulin release from the MOF-based nanosystem [279]. Copyright 2018, Royal Society of Chemistry.

phosphatase. This remarkable reactivity was made achievable through the pre-treatment of the MOF with $\text{N}_3\text{-PEG-PO}_3$ ligands, marking a pioneering development in drug delivery technology. Cell studies revealed that the functionalization of the MOF with $\text{N}_3\text{-PEG-PO}_3$ ligands improved their intracellular stability and led to a sustained drug release compared to the bare MOF (Fig. 21) [284].

In conclusion, the diverse realm of molecular-type stimulations in drug delivery involving saccharides, polypeptides, and enzymes has witnessed remarkable innovations that promise to revolutionize therapeutic interventions. These groundbreaking developments collectively

represent a significant leap forward in the dynamic field of drug delivery, offering new avenues for tailored and effective therapeutic interventions.

5.2. Physical stimuli

Physical stimulation methods often include light, thermal, and pressure stimulations. Target-sensitive MOFs with loaded drugs can release the drugs under specific external stimuli, which will destroy the functional bonds or accelerate the desorption of the drugs to achieve the

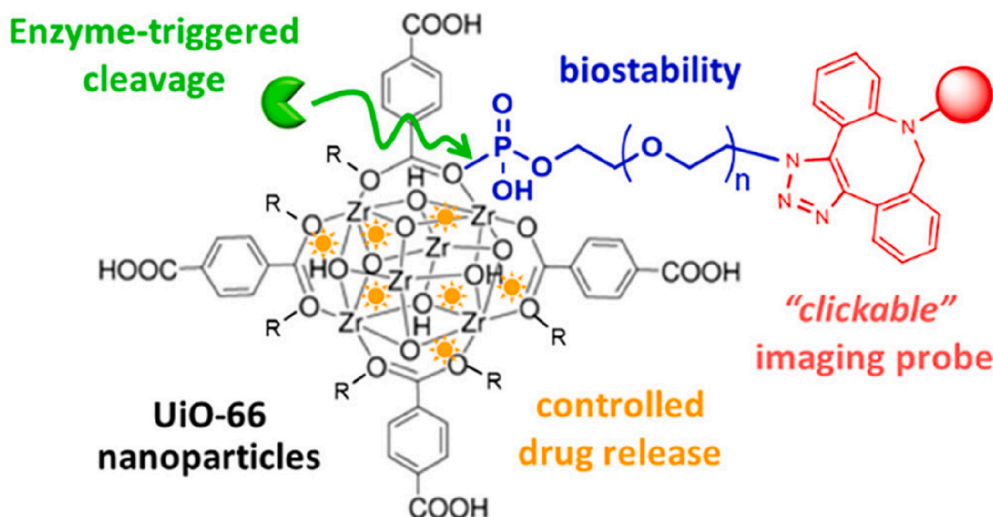


Fig. 21. Scheme of the enzyme-controlled drug release [284]. Copyright 2023, The Authors.

controlled release.

Light-responsive MOFs represent a cutting-edge class of versatile compounds with extraordinary potential across various scientific and technological domains. These MOFs exhibit a remarkable ability to undergo structural changes or trigger specific chemical reactions upon exposure to light, making them exceptionally valuable in applications ranging from environmental remediation to drug delivery and sensing. The underlying mechanism typically involves the photoisomerization of organic ligands or the photodissociation of metal–ligand bonds within the MOF structures, leading to controlled and reversible alterations in their properties [285–290].

Morris and coworkers outlined the synthetic methods for preparing a novel light-responsive MOF UiO-AZB-F. At the same time, upon irradiation with green light, this MOF demonstrates controlled release of chemotherapeutic drug cargo with simultaneous breakdown into low toxicity small molecule components. In comparison, the control sample shows minimal release during the treatment window, demonstrating the stability of particles under non-irradiative conditions [291]. In another study, Wu and coworkers engineered NPs for responsive drug delivery that can be activated by laser or light irradiation. The NPs leverage the unique properties of a redox-responsive selenium-substituted polymer as the outer shell, with a core composed of photosensitive porphyrin zirconium MOF PCN-224. Notably, these NPs loaded with the drug doxorubicin exhibit rapid and controllable drug release when exposed to laser light. The MOF with laser irradiation showed significant tumor growth inhibition than without irradiation [292]. Wu and Liu have successfully synthesized nanocomposites comprising humic acid ZIF-8, which involved the in-situ growth of ZIF-8 on the surface of humic acid modified with polyvinylpyrrolidone. These nanocomposites exhibit impressive photothermal properties, with the temperature rising to 59.4 °C when exposed to near-infrared irradiation for 10 min. The corresponding irradiated group showed enhanced antibacterial efficacy compared to those without irradiation—this synergistic combination of photothermal therapy and zinc ion release results in remarkable antibacterial efficacy [293].

Thermal-responsive MOFs represent a captivating class of materials that exhibit remarkable structural changes and properties in response to changes in temperature. These MOFs are engineered with organic ligands and metal nodes carefully selected to undergo reversible phase transitions or structural alterations within a specific temperature range. When subjected to temperature variations, these MOFs can exhibit tunable adsorption and release capacities, making them ideal candidates for controlled drug release. Thermal-responsive MOFs exemplify the versatility and adaptability of these innovative materials, promising breakthroughs in multiple scientific and industrial fields [294–296].

A series of innovative bimetallic-dual ligand Fe/Tm-MOFs was meticulously designed by Wang and coworkers, which exhibit enhanced electron transfer rates owing to the incorporation of Tm^{3+} ions and the formation of conjugated structures. The photothermal properties of Fe/Tm-MOFs contribute significantly to (OH)-O-center dot generation. Leveraging the drug loading and release capabilities of Fe/Tm-MOFs, a synergistic therapy approach combining photothermal, chemo-, and catalytic therapies has been realized, demonstrating that the release of doxorubicin is responsive to both pH and temperature changes. This development enhances catalytic efficiency and introduces an innovative approach to the design of highly efficient nanotheranostic agents (Fig. 22) [297].

Pressure-responsive MOFs represent a fascinating class of materials designed to undergo structural and functional changes in response to variations in pressure. These MOFs are engineered with carefully selected metal ions and organic ligands that exhibit reversible phase transitions or alterations in their framework geometry when subjected to changes in pressure conditions. The ability to precisely tune these pressure-induced transitions makes pressure-responsive MOFs highly promising for drug delivery [298–301].

Qian, Cui, and coworkers designed a robust zirconium-cluster-based

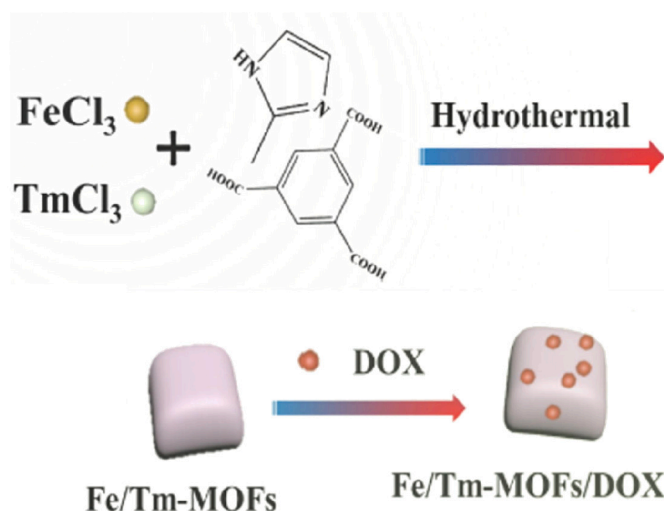


Fig. 22. Fabrication procedure for Fe/Tm-MOFs [297]. Copyright 2022, Elsevier.

MOF ZJU-800 with an excellent 58.80 % drug loading capacity, which shows an adjustable release time of the drug diclofenac sodium from 2 days to 8 days by controlling the degree of compaction between MOF and drug using pressure. The release time was predicted to be continuously prolonged if the pressure was over 30 MPa (Fig. 23) [302].

In summary, physical stimulation drug release refers to the controlled release of pharmaceutical compounds triggered by specific physical stimuli. The fundamental principle behind this drug delivery strategy is to design smart drug carriers that respond to these external cues by releasing the encapsulated drugs in a precise and controlled manner. This approach offers several advantages, including the ability to achieve targeted drug delivery to specific tissues or cells, reduced side effects, and improved therapeutic efficacy. Physical stimulation drug release systems have gained significant attention in recent years due to their potential to enhance the precision and effectiveness of drug therapies while minimizing unwanted systemic effects, making them a promising avenue for advancing healthcare and biomedical applications.

6. Progress monitoring

Progress monitoring in the context of disease and drug management is critical to modern healthcare. It involves the systematic and ongoing assessment of a patient's condition and the effectiveness of the prescribed medications or treatments. This process enables healthcare professionals to track the progression or regression of diseases, ensuring that the chosen interventions are on the right path. It also allows for timely adjustments to treatment plans when necessary, optimizing patient outcomes and minimizing potential side effects or complications. Progress monitoring often utilizes a combination of medical tests, diagnostic tools, and patient-reported data to create a comprehensive picture of a patient's health status. In an era of rapidly advancing medical technology and personalized medicine, progress monitoring is pivotal in tailoring treatments to individual patient needs and improving the overall quality of care. In this part, we will focus on the indirect spectrograph detection pathways of the diseases and drugs through luminescence and electrochemical methods and the direct imaging pathways by MRI and CT.

6.1. Luminescence and electrochemical detection

Luminescence and electrochemical detection are powerful techniques widely employed in various scientific disciplines, particularly in analytical chemistry and biosensing applications [23,303–305].

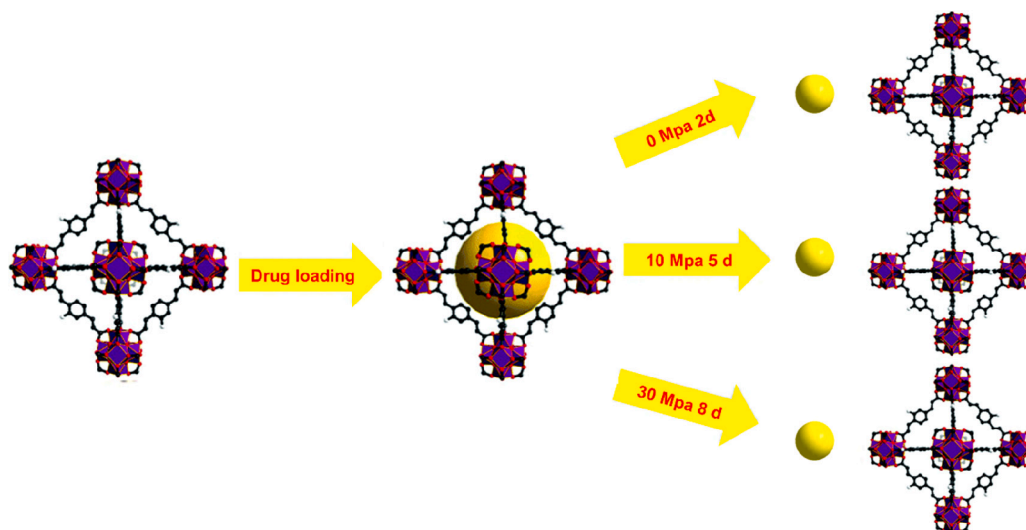


Fig. 23. Pressure-responsive MOF with prolonged release under pressure [302]. Copyright 2016, Royal Society of Chemistry.

Luminescence, which includes phenomena like fluorescence and chemiluminescence, involves the emission of photons from a substance following its interaction with external energy sources or chemical reactions [19,306–308]. Due to its high sensitivity and specificity, it is commonly used to detect and quantify fluorescent molecules, biomarkers, or other analytes in biological assays [21,24,39,82,309–312]. On the other hand, electrochemical detection relies on measuring electrical currents generated during redox reactions at electrode surfaces [313–315]. This technique is particularly valuable in analyzing electroactive compounds, such as neurotransmitters, DNA, and various chemical species [316–320]. Both luminescence and electrochemical detection offer unique advantages, allowing researchers to explore multiple applications, from drug discovery to environmental monitoring, by providing precise, real-time, and often non-invasive detection and quantification.

Luminescence detection is a versatile and widely used analytical technique encompassing several phenomena involving the emission of photons or visible light from a substance when it absorbs energy from an external source [19,306–308]. Luminescence detection provides researchers with a powerful and efficient tool to study and measure various substances and phenomena, contributing significantly to scientific advancements and technological innovations [21,24,39,82,309–312]. Xu, Qu, and coworkers utilized Tb^{3+} as the luminescent center, 1,3,5-benzenetricarboxylate as the building block, and Cu^{2+} as both the signal modulator and recognition unit to construct a pioneering lanthanide-functionalized fluorescent sensor for the detection of $\text{A}\beta$ -peptide monomer—a crucial biomarker for AD. Excitingly, the presence of $\text{A}\beta_{1-40}$ initiates a substantial emission enhancement in the MOF assay, attributable to the strong binding affinity between $\text{A}\beta_{1-40}$ and Cu^{2+} , which mitigates the quenching effect. This sensor demonstrates remarkable sensitivity, boasting a detection limit of 0.3 nM.

Additionally, owing to its capacity to eliminate autofluorescence, this sensor finds utility in the time-gated detection of $\text{A}\beta_{1-40}$ within human plasma, yielding promising results [321]. Ren and coworkers present a homogeneous, highly selective, non-invasive turn-on fluorometric apt sensor for detecting $\text{A}\beta$ oligomers. This innovative approach combines two key elements: (i) the utilization of a luminescent MOF carrying aptamer-modified AuNPs (L-MOF/Apt-Au) as a tracking agent and (ii) the incorporation of enzyme-assisted target recycling signal amplification. Initially, the tracking agent does not fluoresce due to fluorescence resonance energy transfer quenching between the luminescent MOF as the donor and Apt-Au as the acceptor under an excitation wavelength of 466 nm. However, upon introducing $\text{A}\beta$ oligomers

into the tracking agent solution, the Apt-Au on the tracking agent selectively binds with $\text{A}\beta$ oligomers and is subsequently released. This transition switches the luminescent MOF tracer from an “off” to an “on” state. This homogeneous turn-on fluorometric method holds significant potential and practical applications in clinical diagnosis (Fig. 24) [322].

Xu and coworkers employed a streamlined one-step solvothermal approach to craft an MOF incorporating dual ligands, with Eu^{3+} as the metal node. By precisely controlling the size and morphology, ratiometric fluorescence analysis was enabled to achieve the sensitive detection of Zn^{2+} , which is closely associated with Alzheimer’s disease. Significantly, this sensor maintained its structural integrity and retained a fluorescence intensity of at least 95.4 % even after six months of storage in water. Furthermore, its rapid response within 5 s enhances its practical utility. Remarkably, the ratiometric luminescent method-based analysis of Zn^{2+} in AD mouse brains yielded results consistent with those obtained using inductively coupled plasma mass spectrometry (Fig. 25) [323].

Electrochemical detection is also a powerful analytical technique widely used in various fields, including chemistry, biology, and environmental science, which involves the measurement of electrical signals, such as current or voltage, generated during electrochemical reactions at an electrode interface [313–315]. This technique allows for the sensitive and selective detection of a wide range of analytes, including ions, molecules, and biomolecules, by exploiting their inherent electrochemical properties. Electrochemical sensors and biosensors play a crucial role in applications like environmental monitoring, clinical diagnostics, and drug delivery [316–320]. Xu, Zhou, and coworkers developed a highly sensitive electrochemical assay designed to probe beta-site secretase activity, leveraging the unique properties of silver nanoparticles and tyrosine conjugation as tagging and marking methods. The cytosine-rich sequence-templated Ag NPs/Zr-based MOF composite is modified with phenol groups and captured on the microplate’s surface through the conjugation reaction between phenolic groups and tyrosine. This sensitive beta-site secretase detection method exhibits an outstanding linear relationship over the concentration range of 1 to 200 pM, boasting an impressive detection limit of 0.8 pM [324]. In another innovative approach, a nanocomposite is created through the in-situ reduction of chloroauric acid, resulting in the decoration of Au NPs on Fe-MIL-88- NH_2 material via strong Au–N bonds. This nanocomposite significantly enhances the electrochemiluminescence of luminol, establishing a well-functioning basal electrode that ensures a stable background for sensing responses. Integrating aptamers via Au–S bonds on the electrode surface gives the sensor the remarkable capability of specific recognition and binding to the target molecule,

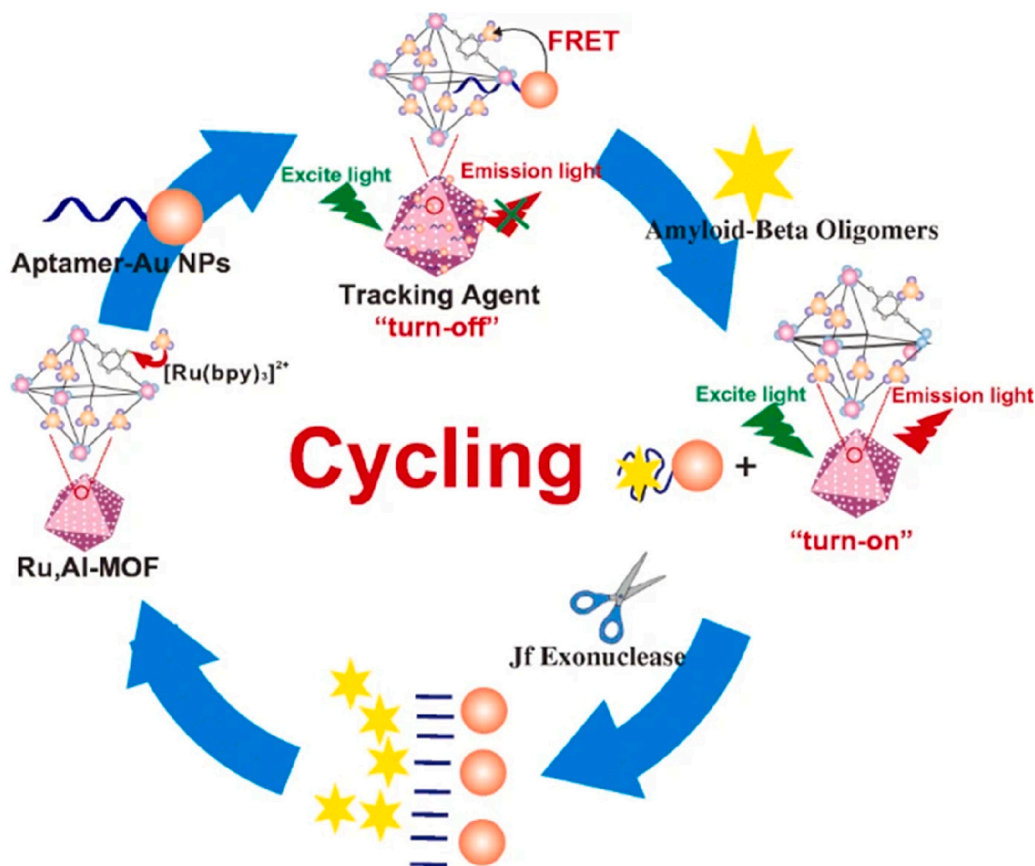


Fig. 24. L-MOF/Apt-Au for detecting A β oligomers [322]. Copyright 2020, Nature.

β -amyloid oligomer. Notably, the degree of inhibition is linearly correlated with the logarithm of β -amyloid oligomer concentration within the range of 0.1 pM to 10 pM, boasting an impressive detection limit of 71 fM. This apt sensor exhibits exceptional selectivity over its analogs, and when tested with human serum samples, it achieves recoveries ranging from 98.9 % to 105.4 % (Fig. 26) [325].

For luminescence detection, the sensing progress is swift and cheap, with non-invasiveness and high sensitivity. However, the low anti-interference capacities and vulnerable intensity towards the environment limit its further development [326–330]. The testing speed and cost are also advantages for electrochemical detection. At the same time, the signal can also be influenced by the objective condition, such as the electrode surface/internal conditions, temperature, bubbles, et al. [331–335]. In summary, both luminescence and electrochemical detections have their strengths and weaknesses, and the choice between them depends on the specific analytical requirements and the nature of the analytes being studied. Researchers often select the technique that best suits the needs of their particular application.

6.2. Magnetic resonance imaging and computed tomography

MRI and CT are powerful medical imaging techniques that have revolutionized diagnostic medicine. These modalities play a pivotal role in non-invasively visualizing the internal structures of the human body, aiding healthcare professionals in the diagnosis, treatment planning, and monitoring of various medical conditions. MRI relies on the principles of nuclear magnetic resonance to create detailed, high-resolution images of soft tissues, offering excellent contrast between different types of anatomical structures. In contrast, CT utilizes X-rays and advanced computational algorithms to produce cross-sectional images of the body, providing remarkable spatial resolution and excellent visualization of bones and dense structures. MRI and CT have significantly enhanced the

ability to investigate the intricacies of the human body, ultimately improving patient care and medical research across a broad spectrum of specialties [75,336–344].

MRI plays a pivotal role in the diagnosis of various diseases, like Alzheimer's disease. However, intrinsic MRI signals alone often provide suboptimal information for disease diagnosis. Consequently, contrast agents (CAs), frequently in paramagnetic compounds or super-paramagnetic nanoparticles, are introduced before or during the MRI scan to enhance imaging quality. Introducing CAs alters the local magnetic environments, resulting in shortened longitudinal relaxation times (T_1) and transverse relaxation times (T_2). While most CAs can concurrently shorten both T_1 and T_2 , various CAs exhibit a preferable effect on one relaxation time or the other. In clinical practice, gadolinium (Gd) complexes are the most commonly employed agents for enhancing T_1 -weighted imaging, whereas iron oxide nanoparticles are preferred for T_2 -weighted imaging [63,345,346]. Lin and coworkers used the reverse microemulsion method to synthesize nanoscale MOFs constructed with Gd^{3+} centers and bridging benzene dicarboxylate and benzene dicarboxylate ligands. These MOFs can serve as highly efficient contrast agents for both T_1 and T_2 -weighted MRI and can be rendered highly luminescent through doping with elements like Eu^{3+} or Tb^{3+} [347]. Boyes and coworkers introduced sodium salicylate, 5-methyl salicylic acid, and salicylic acid into the reverse microemulsion synthesis process, which demonstrated that the inclusion of these hydrotropes offered a straightforward means to modulate the size of a Gd MOF NP, dependent on the concentration of the hydrotrope. Notably, the Gd MOF NPs exhibited the most significant reduction in size distribution, showcasing a notable improvement with percent relative standard deviations nearly 50 % lower than those obtained using the conventional approach from existing literature. Subsequently, they explored the impact of Gd MOF NP size on MRI relaxation properties, which indicated a positive correlation between the surface area of the Gd MOF NPs and their

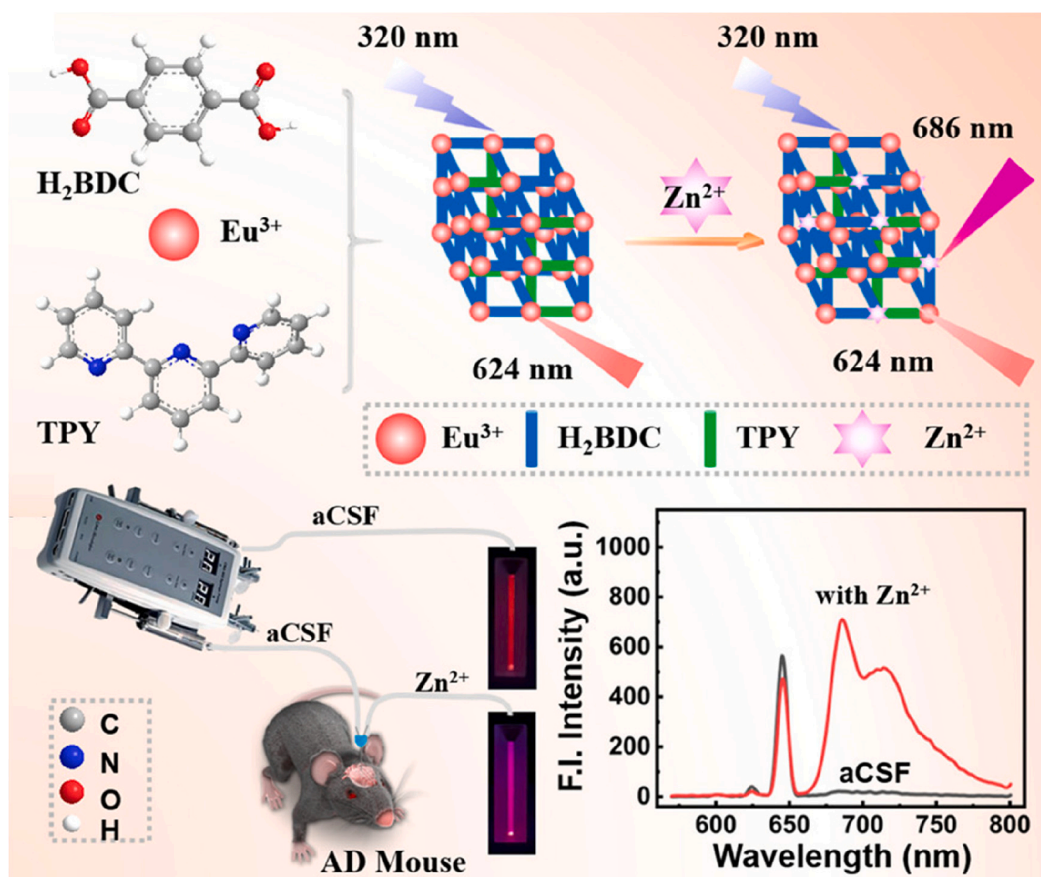


Fig. 25. Illustration of the preparation of the MOF sensor and detection in AD mouse [323]. Copyright 2022, American Chemical Society.

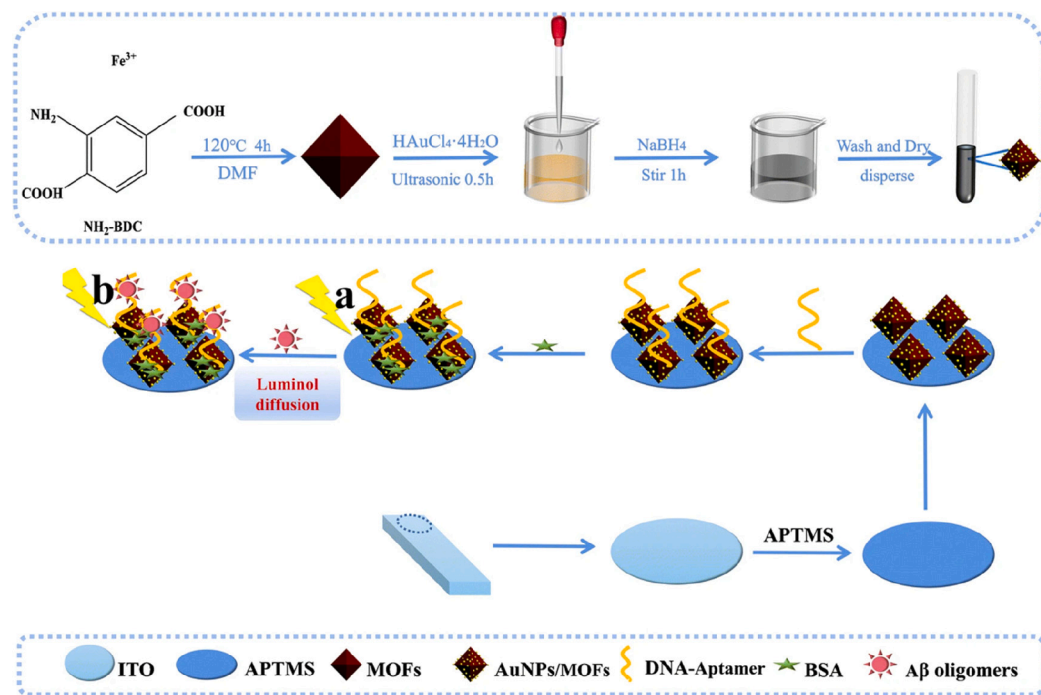


Fig. 26. The fabrication procedure and sensing mechanism of the electrochemiluminescence apt sensor [325]. Copyright 2021, Nature.

longitudinal relativity in MRI [348].

Through precise control of the pH value within the reaction medium, Lin and coworkers synthesized two distinct gadolinium-containing

nanoscale MOFs, all stemming from the same fundamental building blocks (as illustrated). These NMOFs are engineered to accommodate a substantial load of Gd^{3+} centers, rendering them remarkably effective

contrast agents for T₂-weighted MRI. Furthermore, when these MOFs are doped with additional lanthanide ions, such as Eu and Tb, they exhibit pronounced luminescence properties, expanding their versatility and potential applications in various imaging and diagnostic scenarios (Fig. 27) [349].

CT stands as one of the most transformative advancements in medical imaging technology. This non-invasive imaging technique utilizes a sophisticated combination of X-rays and computer processing to produce highly detailed cross-sectional images of the body's internal structures [350–354]. CT has revolutionized the field of diagnostic medicine by offering clinicians and radiologists an unparalleled view of the human body, enabling the detection and diagnosis of various medical conditions, from bone fractures to cancerous tumors. Over the years, CT has evolved into multiple specialized forms, such as contrast-enhanced CT and computed tomography angiography, allowing for even greater precision and accuracy in diagnosis. Its speed, versatility, and ability to capture images from multiple angles make CT an indispensable tool for medical professionals, assisting in treatment planning, surgical guidance, and ongoing patient care [350–354]. Zheng and coworkers ingeniously engineered a biocompatible MOF with an impressive loading capacity to encapsulate FePt nanoparticles, creating a formidable weapon against cancer cells. These multifunctional FePt-MOF NCs have emerged as a promising nanotheranostic agent, seamlessly integrating MRI/CT dual-modal imaging capabilities. The drug delivery system, reliant on MOFs, demonstrates safe and efficient intravenous (i.v.) administration.

Further, the FePt-MOF exhibits remarkable sensitivity to acidic tumor microenvironments, precipitating the release of Fe and Pt ions. This release, in turn, triggers the Fenton reaction, generating a profusion of toxic hydroxyl radicals within the acidic tumor milieu (Fig. 28) [97]. Boyes and coworkers introduced the amalgamation of GdMOF nanoparticles with Au NPs, forging a remarkable MRI/CT bimodal imaging agent, which entails the creation of exceptionally stable hybrid GdMOF/Au NPs composites facilitated by the strategic use of poly(acrylic acid) as

a bridging element between the GdMOF nanoparticles and Au NPs. Subsequent evaluation of these hybrid nanocomposites in MRI and CT imaging unveils their impressive performance characteristics, including high longitudinal relativity in MRI and outstanding CT imaging capabilities. The advent of these GdMOF/Au NPs hybrid nanocomposites ushers in a promising frontier for advancing multimodal imaging probes, promising enhanced diagnostic precision and opening new avenues in medical imaging [355].

In another work, Zhang and coworkers have innovatively harnessed nanoscale MOFs as agents in CT imaging. Specifically, the biocompatibility and CT imaging properties of NMOF nanocrystals, known as UiO-PDT, incorporating iodine-boron-dipyrromethene, have undergone rigorous *in vitro* and *in vivo* assessments. Comprehensive investigations into biodegradability and *in vivo* safety have been meticulously conducted in live animal models. These demonstrate the remarkable absence of severe acute or sub-acute toxicity, even at notably high injected dosages. Notably, *in vivo* CT imaging outcomes reveal the preferential accumulation of UiO-PDT nanocrystals within tumor sites, sparing the surrounding connective tissues and organs in rats bearing hepatomas. The peak imaging performance is achieved approximately 24 h post *i.v.* administration [356]. Another novel bismuth-based MOF, named bismuth-NU-901, was successfully synthesized by Farha and coworkers, whose potential as an X-ray CT contrast agent was systematically investigated. Furthermore, owing to the framework's remarkable density of nontoxic heavy atoms, this MOF's performance as an X-ray CT contrast agent was evaluated. Notably, *in vitro* investigations revealed that this innovative bismuth MOF exhibits approximately sevenfold higher contrast intensity than a zirconium MOF with an analogous topology and roughly 14 times greater contrast than a commercially available CT contrast agent [357].

In summary, both MRI and CT are indispensable tools for diagnosing diseases, planning surgeries, and monitoring treatment responses. The choice between them depends on factors like the specific clinical scenario, the region of the body to be imaged, and the need for soft tissue or

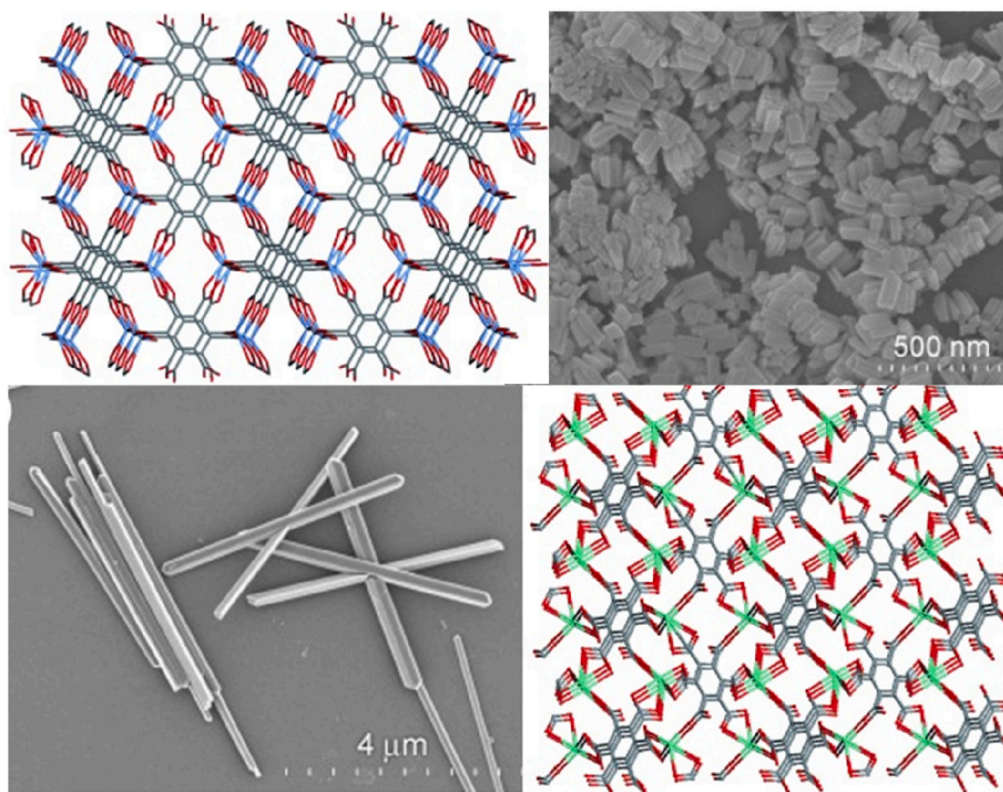


Fig. 27. Nanoscale metal–organic frameworks for T₂-weighted MRI [349]. Copyright 2008, Wiley-VCH.



Fig. 28. Fabrication process and the mechanism of pH-responsive bio nanocomposites for ferroptosis therapy and MRI/CT imaging [97]. Copyright 2020, American Chemical Society.

bone visualization. In general, the two modalities complement each other, with physicians using them interchangeably to comprehensively assess a patient's condition. Unfortunately, the high prices and energy consumption hinder MOFs' actual application process, mainly including the exploration processes for the synthesis and selection of MOFs, large-scale synthesis methods, and treatment of the waste caused using metal salts and organic solvents, which needs further exploration for the scale synthesis methods [358–360].

7. Administration method

In the realm of therapeutic strategies, the precise delivery of drugs into the intricate landscape of the brain has emerged as a paramount challenge. Achieving this precision is pivotal for maximizing therapeutic efficacy while minimizing potential toxicity to the organism. The endeavor to transport nanocarriers to the brain has posed a formidable puzzle for researchers spanning several decades [361,362]. Countless pioneering approaches and inventive concepts have been explored in the quest for a robust delivery technique [363,364], yet attaining success remains an enduring challenge. The most formidable hurdle in this quest lies in navigating the intricacies of the blood–brain barrier (BBB), a natural defense mechanism designed to safeguard the brain from the influx of foreign substances [365]. This barrier's innate architecture affords entry solely to minuscule molecules in the bloodstream [366]. Regrettably, most drugs designed to target the brain in current therapies fall short in traversing this formidable obstacle [367].

The successful translation of MOFs into practical applications for brain-specific delivery of therapeutic agents relies on developing effective administration methods. Several administration methods have been explored to harness the potential of MOFs in drug delivery (Table 2).

Table 2
Comparisons of administration methods in drug delivery.

	Method	Advantage	Disadvantage
Non-invasive	Intranasal	- Bypass the BBB - Rapid absorption - Minimizes systemic exposure - Comfortable for patients	- Limit the dosage - Nasal congestion, nasal enzyme causing degradation - Difference in nasal physiology individually
	Targeted carrier system	- Enabling targeted transport across BBB - Minimizing off-target effects - Extending circulation time - Protecting carriers from degradation	Complex technique, Cost-intensive for large scale production
Minimal-invasive	Intravenous injection (i.v.)	- Rapid absorption - Precise control over the dosage	- Systemic exposure - Hinder by BBB
Invasive	Intracerebral injection	- High precision with high dosage accumulation - Localization - Reduces systemic exposure	- Highly invasive - Risks of tissue damage, infection, or bleeding - Unable to be widespread
	Convection-enhanced delivery	- Achieve wide spreading and uniform distribution - Precise control over the rate and volume of substance - Bypass BBB	- Requires surgical implantation into brain - Risks of infection, bleeding, or tissue damage - Backflow issue

This section discusses various strategies and techniques presented to introduce MOFs into animal bodies for precise and targeted delivery to the brain (Fig. 29).

7.1. Intravenous injection

I.v. injection is one of the most common methods to introduce nanocarriers like MOFs into the bloodstream. This route offers systemic distribution, allowing MOFs to reach the brain via the circulatory system, thus resulting in rapid onset of action and bioavailability in the bloodstream within minutes [368]. This method is suitable for addressing acute conditions and precise control over the dosage by carefully measuring and titrating the number of MOFs administered. However, due to the systemic exposure of MOFs and therapeutic agents, i.v. injection can cause side effects in non-target organs or tissues while transferring the particles to the brain [369,370]. Moreover, achieving brain-specific delivery through i.v. injection poses significant challenges due to the BBB limiting the passage of large molecules and NPs, including many MOFs. Research has shown that therapeutic antibodies delivered i.v. administration is not very effective in penetrating the brain, with only a tiny percentage ($\sim 0.1\%$) of the dose reaching the target area.

To overcome these issues, MOFs can be engineered with surface modifications or functionalization to enhance their ability to cross the BBB selectively and mitigate toxicity. For example, Wang's group designed a MOF-based nanocarrier MILB@LR coated with lipid bilayer and RVG29 peptide to ensure the particles stably circulate in the bloodstream while binding to the protein expressed on the BBB [368].

7.2. Intranasal administration

Intranasal administration has gained attention as a non-invasive method to bypass the BBB by traveling along the olfactory/trigeminal nerve pathways and directly targeting the brain [371,372]. MOFs can be formulated into nasal sprays or powders, facilitating rapid absorption through the nasal mucosa and olfactory pathways. This approach minimizes systemic exposure and offers the advantage of reduced side effects while achieving brain-specific delivery [373]. Also, intranasal administration is generally more well-tolerated and comfortable for subjects and patients since it does not involve invasive procedures like needle insertion. On the other hand, since MOFs must be formulated into nasal sprays, powders, or other appropriate forms for intranasal administration, this may limit the dosage of MOF and therapeutic agents that can be delivered through the nasal route. Other concerns, such as nasal congestion, nasal enzymes causing degradation, and differences in nasal physiology, can also interfere with the effectiveness and variability of drug efficacy and response [374,375]. As this method is newly investigated, scientists and healthcare providers need careful optimization of the particle size, formulation, and dosing to maximize the efficacy of intranasal MOF delivery before translating it into practice.

7.3. Intracerebral injection

For precise and localized brain delivery, intracerebral injection techniques can be employed. This approach involves direct injection of MOFs into specific brain regions using stereotaxic surgery, thus ensuring high precision with high drug concentrations of therapeutic agents. Wang's group used this sophisticated method to inject a manganese-organic framework into the lateral ventricles of MCAo mice to improve ischemic stroke and explore its intrinsic enzyme activity [376].

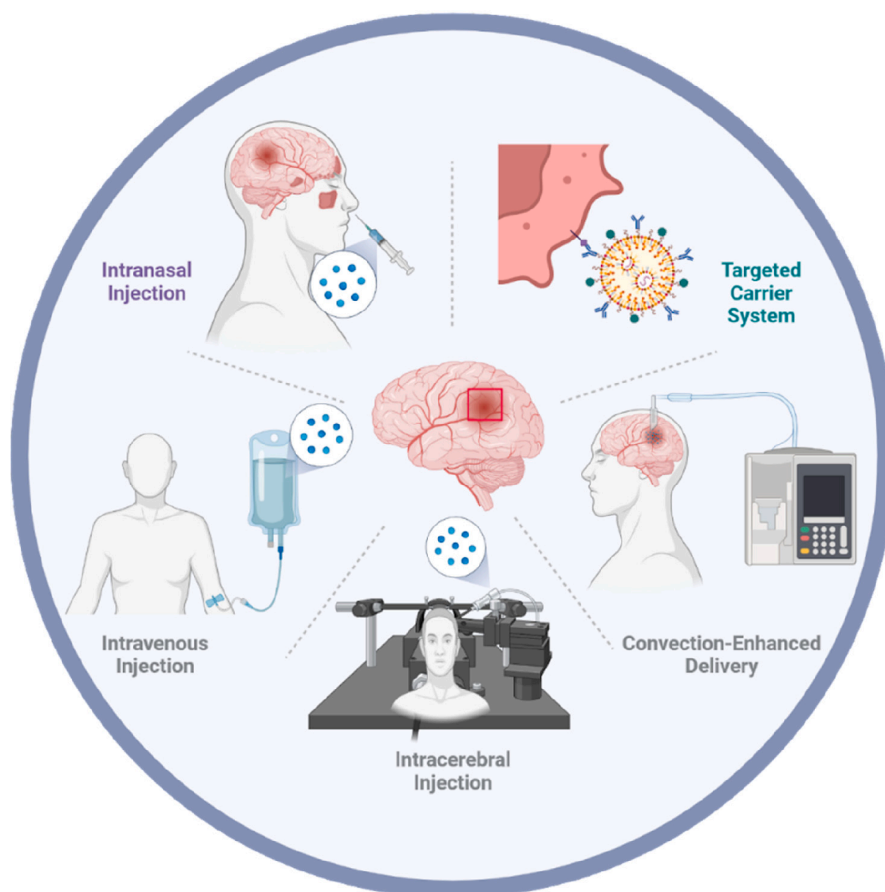


Fig. 29. Schematic illustration of the administration methods for nanocarriers of brain-targeting disease.

While it ensures accurate placement of MOFs within the brain and reduces systemic exposure, this method is a highly invasive intervention that requires careful consideration of inherent risks like tissue damage, infection, or bleeding. In tandem with that, this method is unsuitable for conditions requiring widespread or diffuse treatment in the brain. The challenge arises when trying to reach deep brain regions, especially in humans, as it may require specialized equipment, techniques, and trained personnel. However, intracerebral injection remains valuable for studying specific brain regions and diseases. Researchers and clinicians should weigh the pros and cons and select this method judiciously based on their applications' specific goals and challenges.

7.4. Convection-enhanced delivery

Convection-enhanced delivery (CED) is an emerging technique that relies on pressure-driven flow to distribute MOFs within the brain parenchyma [377]. CED can achieve widespread and uniform distribution of MOFs or therapeutic agents within the brain parenchyma. This is particularly advantageous for treating conditions that require broad coverage, such as brain tumors or neurodegenerative diseases. Researchers and clinicians can exercise precise control over the rate and volume of substance delivery using CED. This control allows for tailoring the distribution profile according to the specific requirements of the treatment. Directly infusing MOFs or therapeutic agents into the brain tissue can overcome some limitations associated with BBB and achieve therapeutic concentrations at sites that are usually inaccessible via systemic administration.

However, CED is still an invasive procedure that requires surgical implantation of catheters or cannulas directly into the brain tissue [378,379]. This carries inherent risks, including the potential for infection, bleeding, or tissue damage. Moreover, the pressure-driven flow in CED can lead to backflow along the catheter track, potentially causing uneven distribution or leakage of the administered substance [380]. Optimizing CED parameters, such as infusion rate and catheter placement, is crucial to avoid overdosing and ensure effective and safe patient delivery.

7.5. Targeted carrier systems

To enhance brain-specific MOF delivery, researchers have explored using carrier systems, such as liposomes or ligand receptors, conjugated with MOFs [381–383]. These carrier systems can be considered “smart vehicles” for MOFs, enabling their transport across the BBB through ligands that specifically bind to receptors or transporters. This strategy offers precise control over the localization of MOFs within the brain. These ligands, often antibodies or small molecules, are carefully chosen based on their ability to recognize and interact with specific receptors or transporters overexpressed on the BBB. By selecting ligands with high affinity for these molecular targets, researchers can facilitate the transport of MOFs across the BBB and tailor the delivery to particular brain regions or cell types. This maximizes therapeutic efficacy and minimizes off-target effects that may arise from systemic exposure to MOFs.

In addition, targeted carrier systems can also improve the pharmacokinetics of MOFs by modifying them with PEG or PLGA to extend their circulation time in the bloodstream while protecting them from degradation, enzymatic cleavage, or premature release. These functionalities enhance the window of opportunity for MOFs to reach the brain, thus offering a versatile solution in combination with other administration methods to improve delivery effectiveness. However, the formulation of targeted carrier systems is complex and may require specialized techniques. This causes the development and manufacturing of targeted carrier systems to be cost-intensive, particularly when considering large-scale production for clinical use (Table 3).

In summary, the successful administration of MOFs for brain-specific delivery of therapeutic agents requires thoughtful consideration of the chosen method's advantages, limitations, and therapeutic goals.

Table 3

Summary of receptor-ligand for surface functionalization of carriers to deliver for brain diseases.

Ligand	Target Receptor / Transporter	Application	Reference
RGD peptides	Integrin receptors (e.g., $\alpha_v\beta_3$)	Targeting glioblastoma and brain tumors	[384,385]
LRP-1 antibodies, angiopep-2, lactoferrin, melanotransferrin, ApoE	Low-density lipoprotein receptor (LDLR, LRP1, LRP2)	Alzheimer's disease therapy and brain tumor treatment	[386–388]
Insulin receptor ligands	Insulin receptor	Addressing neurodegenerative disorders and traumatic brain injury	[389,390]
Antibodies against A β	Amyloid-beta peptide	Alzheimer's disease intervention	[391,392]
Monoclonal antibodies, X26	Transferrin receptor	Targeting brain cancers	[393,394]
Glucose transporter ligands	GLUT1	Treating neurodegenerative diseases	[395,396]

Combining multiple approaches and tailoring MOF properties to enhance brain targeting holds great promise in advancing the field of neuroscience and drug delivery.

8. Biocompatibility

Biocompatibility in the context of drugs is a critical consideration in pharmaceuticals and medicine. It refers to the ability of a drug or medication to interact with the human body without causing harm or adverse reactions. Drug biocompatibility encompasses various factors, including the drug's chemical composition, formulation, route of administration, and its compatibility with the body's physiological processes. Ensuring high biocompatibility is essential in drug development to minimize side effects, allergic reactions, or toxicities. Extensive research and testing are conducted to evaluate how a drug interacts with tissues, cells, and organs to guarantee its safety and efficacy, ultimately leading to the creation of drugs that improve the quality of life and contribute to better healthcare outcomes.

8.1. Blood half-life

The blood half-life of MOF plays a vital role in determining drug delivery efficacy, as it determines whether MOF can extend the duration a drug remains in the body after a single dose. Various studies have examined the half-lives of different MOF structures. For instance, Wang et al. developed a MOF named Glud-MFo-c with a cubic shape and a size of 124 nm (Fig. 30) [397]. In vivo studies revealed a half-life of 4.9 h of this MOF in mouse blood by i.v. administration. MIL-100, a well-studied MOF, exhibited a 2.9 h (200 nm) blood half-life after i.v. injection, acting as a carrier for gemcitabine hydrochloride, as reported by Kush et al. [398]. They also found that the drug encapsulation by MIL-100 increased the bioavailability and extended the half-life of the free drug. Furthermore, Bajaj, et al. demonstrated the enhancement of mebendazole half-life through ZIF-8 in pharmacokinetic studies [399]. After oral administration, the half-life was extended from 1 h (free drug) to 6 h (with ZIF-8). Additionally, using ZIF-8 as a drug carrier increased the drug's solubility by a factor of 11. Ahmadi et al. synthesized ZIP-8 with an average size of 95 nm [400]. This structure has a half-life of 9.47 h in mice following i.v. injection, which is considered a prolonged circulation time.

Suitable surface modifications can further improve MOF's blood half-life. For instance, Hu et al. employed N-acetyl-galactosamine to

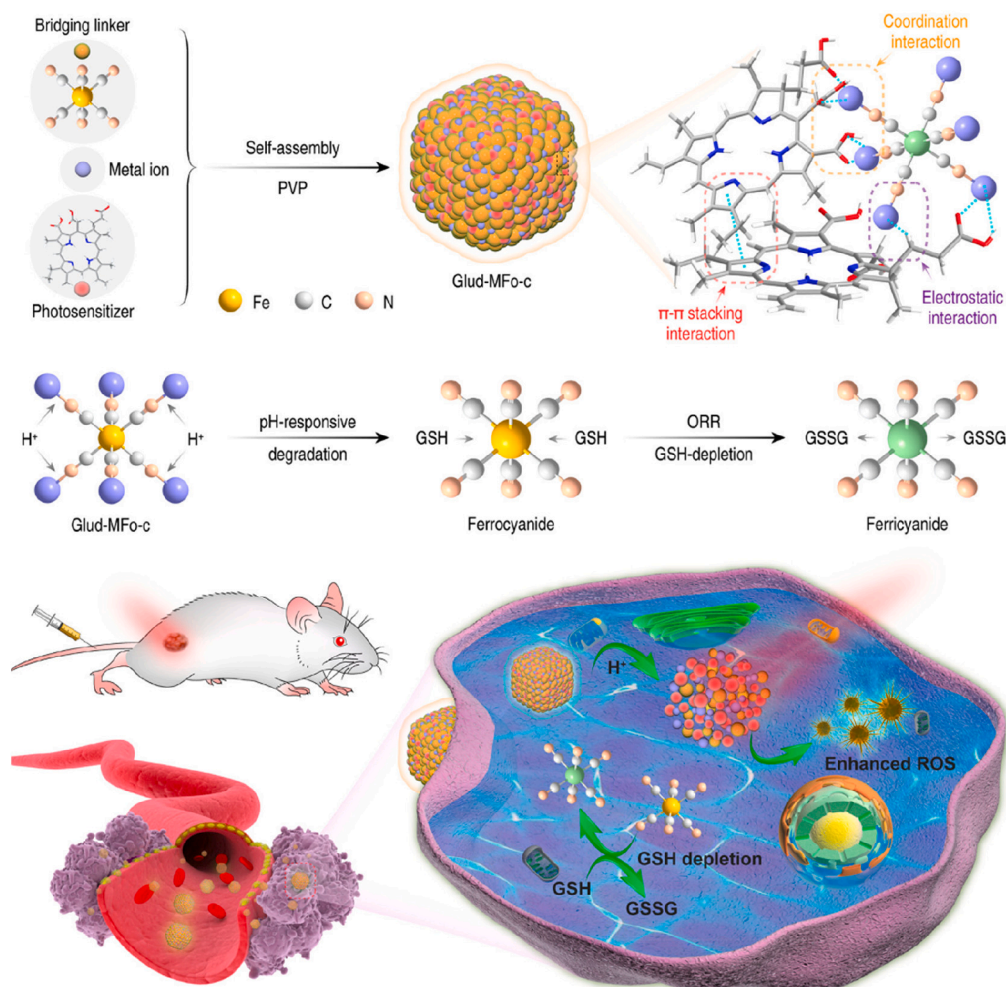


Fig. 30. Schematic diagram of self-assembly Glud-MFO-c nanoagent for enhanced antitumor of PDT by Ce6 via GSH depletion [397]. Copyright 2020, American Chemical Society.

modify ZIF-8, serving as a carrier for sorafenib and glucose oxidase [401]. Compared with other reported work, their modified ZIF-8 displayed a much higher half-life of 18 h following i.v. injection in Sprague-Dawley rats.

8.2. Toxicity

Regarding the toxicity of MOFs, numerous published works have summarized *in vivo* and *in vitro* toxicities associated with various MOF types. For instance, Ruyla et al. conducted a comparison of the toxicity of several MOF NPs, including MOF-74, UiO-66, UiO-67, ZIF-7, ZIF-8, MIL-100, and HKUST-1, in zebrafish embryos *in vivo* [402]. The results displayed distinct toxicity levels: MOF-74(Mg), MOF-74(Co), UiO-66, UiO-67, MIL-100, and MIL-101 exhibited no significant toxicity for at or below the concentration of 200 μM . Conversely, ZIF-7, ZIF-8, and HKUST-1 exhibited a significantly increasing toxicity at the concentration of 200 μM . Notably, the results underscored the crucial role of dissociated soluble metal ions in determining the overall toxicity of MOFs.

When selecting an appropriate MOF for brain-specific drug delivery with lower neurotoxicity, comprehending the biological impact of diverse metal ions and their potential toxicity to neurons is vital. Zn^{2+} ions have been extensively used in various MOF structures. It is reported that a Zn^{2+} ion concentration of 10 ppm in drinking water increases the tangle levels in the hippocampus and spatial memory impairment in a transgenic mouse model of AD [403,404]. Gd^{3+} ion is another

frequently used metal ion in MOFs. A study on primary cortical neurons demonstrated that Gd^{3+} ion at 2–100 μM concentration led to neurotoxicity mediated by induced oxidative stress and inhibition of normal mitochondrial function (Fig. 31) [405]. Both Fe^{2+} and Fe^{3+} ions have been demonstrated to cause neurotoxicity. For instance, direct injection of a Fe^{3+} solution into the rat hippocampus induced neuronal death at a dosage of $1.2 \times 10^{-3} \text{ mg kg}^{-1}$ [406]. Another study compared the toxicity of Fe^{2+} and Fe^{3+} ions in neuroblastoma cells (SHSY5Y) [407]. They found that Fe^{2+} and Fe^{3+} ions induced neurotoxicity at a concentration of 1 μM , with Fe^{2+} showing notably higher neurotoxicity than Fe^{3+} . Conversely, previous works have suggested a possible protective effect of Mg^{2+} ions on DA neurons against degeneration [408]. Adding Mg^{2+} ions at a concentration of 1.2 mM significantly inhibited the neuronal loss induced by 1-methyl-4-phenylpyridinium (MPP+). This work highlighted the potential of Mg^{2+} ions for preventing neuron pathology in the PD model. In summary, Mg^{2+} appears most compatible for brain-related applications among various metal ion types.

9. Conclusion and perspective

MOF-based drug carriers represent a cutting-edge approach to drug delivery systems. These carriers utilize MOFs, highly porous materials with exceptional designable functional structural tunability, as a platform for encapsulating and delivering pharmaceutical compounds. MOFs can be engineered to have specific pore sizes, surface areas, and chemical functionalities, allowing for precise control over drug loading

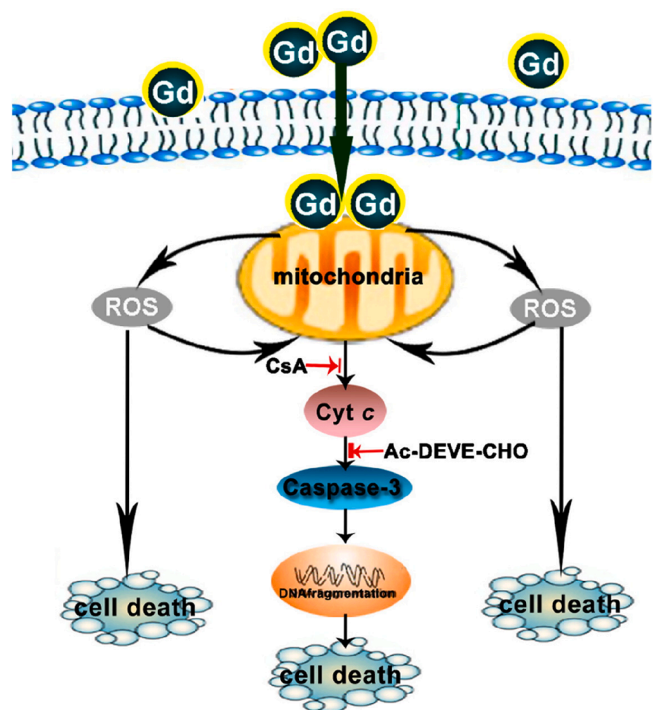


Fig. 31. The proposed pathways for Gd-induced cell death in neurons [405]. Copyright 2010, Elsevier.

and release kinetics. This level of customization enables targeted and sustained drug delivery, improving therapeutic efficacy while reducing side effects. MOF-based drug carriers have shown great promise in various applications, including various diseases. Their versatility, biocompatibility, and ability to respond to external stimuli, including physical and chemical, make them valuable tools in developing advanced drug delivery systems with the potential to revolutionize healthcare and improve patient outcomes.

However, although MOF-based drug carriers offer significant advantages in drug delivery, they also come with several challenges. One primary concern is the potential for MOFs to release toxic metal ions and organic ligands during drug delivery, raising safety and biocompatibility issues. Additionally, MOFs can be susceptible to degradation in physiological conditions, which may limit their long-term stability and effectiveness. While advantageous, precise control over drug release kinetics can also be challenging to achieve consistently. Furthermore, scaling up the production of MOF-based nanomedicine is also challenging for the scale-up mass production of MOFs. Finally, the cost associated with synthesizing and functionalizing MOFs can be prohibitive, hindering their widespread adoption. Addressing these challenges is crucial for realizing the full potential of MOF-based drug carriers and ensuring their safe and effective use in healthcare applications, which needs further studies.

Data availability

Data will be made available on request.

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.

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