

Coated Metal-Organic Framework Composites for Anti-Cancer Drug Delivery: Preparation and Applications

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Abstract. Metal-organic frameworks (MOFs) are made from metal ions and various organic ligands, which have been demonstrated to be an essential material used as drug delivery vehicles because of their large surface area, simple functionalization, high porosity and excellent biocompatibility. Recently, coated MOFs are promising approaches to overcome the limitations of pure MOFs in drug delivery systems with improved targeting, better biodistribution and lower cytotoxicity. In this review, the preparation and applications of polymer-coated MOFs, magnetic core-shell MOFs and membrane-coated MOFs are mainly introduced. The polymer-coated MOFs with high structural and functional flexibility achieve greater drug loadings via covalent grafting and polymerization. Magnetic core-shell MOFs can effectively detect the location of tumors by applying a magnetic field. Their enhanced biodegradability is realized due to the presence of these magnetic agents. Membrane-coated MOFs, especially for cancer cell membranes and red blood cell membranes, are capable of making drug substances more durable in the immune system and preventing them from being digested with improvement in tumor-targeting and biointerfacing effects. These coated MOFs and corresponding MOFs with detailed modifications result in better therapeutic efficacy in anticancer activities, providing new insights into the development of chemical synthesis and biomedical applications.

Keywords: Metal-organic frameworks, polymer-coated MOFs, magnetic core-shell MOFs, membrane-coated MOFs, drug delivery system, anticancer.

1. Introduction

Cancer is a major threat to the human health systems and results in severe damage to the immune system with uncontrollable cell division, leading to numerous fatalities annually. Although chemotherapy was developed and several therapeutic drugs were administered to the patients, the intrinsic limitations reduced their efficacy and ability to control drug release. These drawbacks include poor biodistribution, poor pharmacokinetics and several potential side effects. A drug delivery system (DDS) is designed to enable a therapeutic molecule selectively to reach its sites of action [1]. Currently, liposomal, nanoparticulate albumin-based DDS and inorganic mesoporous silica-based DDS are prevalent. However, Inorganic porous materials are less ideal due to their toxicity and comparably weaker stability and degradability [2]. Likewise, liposomes as DDS suffer from low loading capacity, short half-life, low solubility, and occasional leakage or fusion of encapsulated drug molecules [3]. In recent years, scientists have made efforts on developing drug nanocarriers to enhance biocompatibility, reduce cytotoxicity and improve the overall performance of drugs in cancerous theranostics. This nano-platform provides a more sophisticated and extensive pathway to medicate cancer.

Metal-organic frameworks (MOFs) are porous crystalline substances synthesized from metal ions or clusters interlinked by organic ligands [4]. MOFs are equipped with a large surface area, high porosity, simple functionalization and improved biocompatibility which are beneficial to the drug delivery system. Meanwhile, MOFs have demonstrated their utility of being used as a delivery vehicle and ability to control their size, structure and porosity, high drug loadings, enhanced stability, synergistic drug loading or release [5, 6]. These unique properties enable them to adsorb therapeutic

molecules on their surface or open channels, as well as keep these molecules processed inside the MOFs. Zeolite imidazolate frameworks-8 (ZIF-8) prepared from zinc molecules and 2-methylimidazole ligands coordinated in framework structure with high stability, easy synthesis, inherent porous property and high loading capacity [7]. Although pioneering research work has demonstrated that ZIF-8 is a suitable agent in DDS, the potential risks such as limited biocompatibility and ambiguous level of toxicity are presented which can pose a threat to the cancer therapeutics [8]. Therefore, to date, the literature has expanded the structural complexity and features through the construction of coated MOFs such as polymer-coated MOFs, magnetic core-shell MOFs and membrane-coated MOFs to minimize the risks of pure MOFs delivering alone and achieve a more desirable effect in the DDS [4, 9, 10]. Among the various MOF-based composites, coated MOFs are further developed in which scientists aimed to enhance MOF porosity and functionalization in biomedical applications [4].

One of the further modifications is to synthesize polymer-coated MOFs, leading to greater biocompatibility, improved stability, enhanced targeting and controlled drug release of the adsorbed molecules. Compared to pure polymers that are flexible and malleable solids, MOFs are multifunctional and utilized in the biomedical field and DDS. Through covalent grafting and polymerization, the large surface areas and high porosity are advantages for polymer-coated MOFs to encapsulate high drug loading capacities. They are flexible enough to adapt to the structure and other chemical or physical properties of the drug substances [4]. Magnetic core-shell MOF nanocomposites are another primary coated MOFs that can attract the substances to the specific sites by applying a magnetic field to improve their biocompatibility and targeting. In terms of diagnosis, magnetic core-shell MOFs can detect the existence of tumors and locate them as precisely as possible. In the co-delivery of drugs, magnetic core-shell MOFs increase the cell-killing percentage by improving their biodegradability and enhancing multi-functionalization [9]. Membrane-coated MOFs have attracted attention in the DDS which makes substances be presented in the immune system for longer and accumulated in the circulatory system, rather than being digested or metabolized. Cancer cell membrane and red blood cell membrane are two main types of membrane-coated MOFs that have achieved better targeting and composite [10].

Overall, MOF coated with different types of substances can be synthesized through chemical means to improve their therapeutic efficacy in anticancer activities, including drug release, loading capacity, level of cytotoxicity and stability. In this article, the preparations and applications of polymer-coated MOFs through the methods of covalent grafting and polymerization, magnetic core-shell MOFs and membrane-coated MOFs in cancer theranostics will be analyzed.

2. Polymer-coated MOFs

MOF-polymers have become the research interest as it is found that the composite possesses enhanced functionalities, namely colloidal stability, stealth, targeting and slow degradation. An increase in porosity is also attained, making polymer-coated composites more effective in biomedical applications.

2.1. Preparation of polymer-coated MOF composites.

Typically, the polymer coating is introduced post-synthetically through covalent grafting or polymerization, which leverage the formation of covalent bonds with the MOF core or through forming hydrogen bonds or electrostatic attractions respectively [11].

2.1.1. Covalent grafting.

Covalent grafting describes covalent bonding between the polymer chain and surface of MOFs which are prepared by attaching ligands such as $-NH_2$, $-Cl$, and $-OH$ [4]. Then, the standard organic synthetic techniques establish the grafting between polymers and MOF structures through click chemistry and coordination modulation. In the first step, usually, suitably functionalized monodentate and bidentate ligands are incorporated into the MOF system through synthesis. Then with the help

of the modulator, a polymer coating would be formed on the MOF. The polymer is formed either directly or indirectly with the modulator. Lazaro et al. synthesized UiO-66 nanoparticles with polyethylene glycol (PEG) and poly(L-lactide) (PLLA) copolymer coating [12]. First, they prepared UiO-66, adding one modulator with N_3 . Then, through a copper (I)-catalyzed dipolar cycloaddition between the azide moiety on the modulator and the propargylic moiety on the functionalized PEG and PLLA, the polymer coating was formed and attached via covalent bonds with the modulator. The polymer coating was confirmed with measurements from mass spectrometry (MS), infrared spectroscopy (IR), and thermogravimetric analyzer (TGA).

2.1.2. Polymerization.

In the realm of polymers, MOFs have enhanced performance on drug loading and DDS, specifically cancer theranostics. Accordingly, Yang et al. suggested two polymerization methods in which every monomer inside MOF pores reacts with MOF structures catalyzed by light, heat and chemical initiators or the entire polymers bond with the MOF surface through intermolecular forces. These two polymerization methods can be widely performed over MOFs with chemical and thermal instability [4]. They also utilized sacrificial MOF templates which contribute to the establishment of three-dimensional pore design. These procedures may be difficult to control since it is uncertain that the monomers have diffused homogeneously through the entire MOF structure. Furthermore, the compatibility of one particular MOF and its initiator should be taken into consideration to avoid MOF decomposition. To exemplify, N-isopropylacrylamide (NIPAM) monomers have been introduced to UiO-66 through surface-initiated RAFT polymerization in Rabiee et al. [13]. The formation of p(NIPAM)-GMA-UiO-66 demonstrated a smaller hydrodynamic particle size between 75 nm and 120 nm which can readily reach the targeting site and improve the effectiveness of delivery. In terms of cellular uptake of drugs, it is observed that cells and nanocarriers can interact appropriately, resulting in a more homogeneity of the nanocarriers and greater stability. Alternatively, Hu et al. conducted extensive research by attaching the entire polymer to the MOF surface in which the delivery of both doxorubicin hydrochloride (DOX) and cisplatin (CDDP) was achieved by using UiO@Poly, a more promising approach to maximize the synergistic antitumor effect [14]. After surface polymerization, the particle size of polymer-coated MOFs remained relatively stable and the presence of polymeric coating improved biocompatibility as only negligible hemolysis of less than 2% was shown. There was also a negligible amount of cytotoxicity, suggesting excellent biocompatibility and improved performance in therapeutic effect.

2.2. Polymer-coated MOF composites for anti-cancer drug delivery.

2.2.1. Biocompatibility.

In drug delivery, excellent biocompatibility indicates a benign interaction between the body tissues and the materials, without eliciting any unusual or unwanted response such as vigorous inflammation like neutrophils and macrophages [15]. Good biocompatibility is essential for the DDS to fulfill its physical function of transporting the enclosed active ingredients to the tissue or cell under interest. Biocompatibility depends on numerous factors from the composition of the materials, and the size of the DDS, to the anatomical characteristics of body tissues. Owing to this, metal-organic frameworks' easily tailorable composition through substituting coordination metal or the organic linkers, controllable size and shape through modifying preparation conditions or methods, and functionalizing their surface through post-synthetic modifications are particularly suitable for the tune and optimizing the biocompatibility of MOF DDS [6]. Polymer poly (ethylene glycol) (PEG) has been post-synthetically introduced onto the surface of MOFs to achieve desirable nanoparticle biointerfacing [16]. A hydration layer would typically be formed after the PEGylation process. Meanwhile, steric stabilization is also observed, which further reduces interactions between the material and its environment and enhances the blood circulation process, indicating better biocompatibility. Rakhshani and co-workers synthesized UiO-66-NH₂/DOX with poly (N-vinyl caprolactam) (PNVCL) to investigate anti-cancer activity against A546 lung cancer cells in vitro [17]. It also involves the

dispersion of MOF nanoparticles in PNVCL solutions of varying concentrations (1% and 2%) to produce nanoparticles with different thicknesses of polymer coating under a 24-hour stirring and the rinse of the final product. The release of DOX from the composite with thinner PNVCL coating was faster compared to its counterpart. Their biocompatibility is higher than pure UiO-66-NH₂ NMOFs as well. It also led to an improvement in cytotoxicity after 72 hours, resulting in enhanced efficiency of chemotherapy and targeted delivery of DOX to A546 lung cancer cells.

2.2.2. Release kinetics.

The release kinetics or release patterns of the embedded active ingredients from the formulation play a significant role as it directly affects the localized concentration of the drug in the body tissues under interest, thereby influencing the effectiveness of the formulation in achieving wanted clinical performance. Typically, a DDS is expected to release the drug over an intended period. Sustained-release, controlled release, and delayed-release are highly desirable for quality treatments as well [18]. As the methods of adding polymer coating allow for easy control over the thickness of the polymer shell and the polymer shell could retard the degradation of the MOF composites, various studies have strived to explore the possibility of tailoring release kinetics through coatings. Silica-coated MOF nanocomposites exhibit better biocompatibility, colloidal stability, dispersibility in water and tuneable functionality with numerous silyl-derived species. Lin et al. first constructed a MOF nanoparticle, NCP-1 core from c,c,t-(diamminedichloroplatinum) Platinum(IV) (DSCP) and terbium (III) cations, then coated a layer of amorphous silica onto the aforementioned core to synthesize NCP-1' [19]. The positive correlation between the thickness of the silica shell and the duration of reaction or the number of moles of tetraethyl orthosilicate used provided the possibility for adjusting the dimension of the outer silica shell. The group produced NCP-1'-a with a 2 nm thick silica coating and NCP-1'-b with a 7 nm thick silica coating and then investigated the relationship between the thickness of silica-coating and controlled release behavior. As evident in Fig. 1, when analyzed in a 4-(2-hydroxyethyl)-1-piperazineethanesulfonic acid (HEPES) buffer of pH 7.4 at 37 °C, the dissolution half-lives of NCP-1', NCP-1'-a and NCP-1'-b were around 1 h, 5.5 h and 9 h accordingly, signaling successful control over the rates of release of platinum-containing species. The rates of release from NCP-1'-a and NCP-1'-b are sufficient for the nanoparticles to circulate in the body and become accumulated in the tumorous regions.

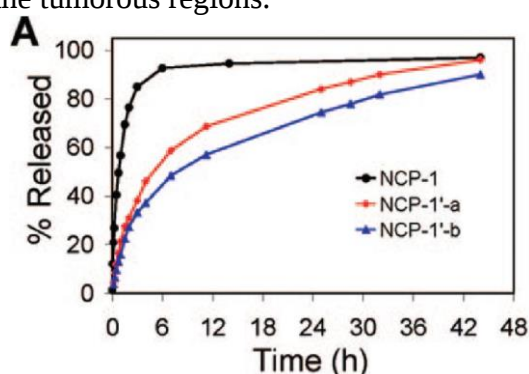


Figure 1. Release profiles for as-synthesized NCP-1, NCP-1'-a, and NCP-1'-b obtained by plotting the %Pt released against time [19].

2.2.3. Targeting.

Targeting is achieved via specifying the moieties on the drug molecules or the DDS directly into its targeted region in the body, namely specific organs, tissues, cells or even subcellular levels. Successful targeting can help overcome certain toxic effects caused by conventional drug delivery and reduce the number of active ingredients required for efficacious therapy [20].

Another advantage of polymer coating on MOFs is that it allows further surface functionalizations without interfering with the MOF core structure or the entrapped active ingredients. In 2018, Zhang et al. reported a detailed theragnostic investigation of MIL-100(Fe)@HA-PDA composite, a curcumin-loaded MIL-100 (Fe) which was afterward coated with polydopamine-modified hyaluronic

acid (HA) [21]. The group used non-tumorous MRC-5 cells and CHO cells as controls for the cancerous HeLa cells and A549 cells. They then treated the cells with both PDA/MIL-100 (Fe) and curcumin. It was evident that the intracellular uptake of the active ingredient, curcumin, in HeLa cells and A549 cells were higher than the controls when treated with modified MOF nanocomposite. This was attributed to an increased number of CD44 on tumorous cells and the favorable interactions between HA and CD44 receptors. An in vitro study on the nanocomposite's cellular uptake and targeting capabilities indicated better targeting towards tumor cells.

2.2.4. Synergism.

Drug synergism is when two or more drugs have interacted in a DDS that causes the overall impact of those substances to be greater than the individual impacts of each drug [22]. It is usually achieved by using a physical combination approach such as chemotherapies integrated with other measures and co-delivery of anticancer drugs. Rabiee et al., in comparison with the free-polymer structures, p(NIPAM)-GMA-UiO-66 is more suitable for the codelivery of DOX and pCRISPR owing to its higher drug payload efficiency of 55.9%, minimal cellular toxicity, better cellular internalization and faster transfection efficiency [13]. Similarly, through in vitro stability and hemolysis assay, Hu et al. concluded that the outer polymeric layer plays a key role in stabilizing the inner UiO and improving biocompatibility [14]. UiO@Poly in DOX and CDDP delivery shows a desirable drug loading and release in which the accumulative release for DOX is 82% and for CDDP is 58%. Hence, polymerization reactions between polymers and MOF surfaces lead to enhanced performance in anti-cancer treatment and DOX delivery.

3. Magnetic core-shell MOFs

Magnetic nanoparticles (NPs) are appropriate agents in many biomedical fields because of their magnetic and electrochemical characteristics. Iron oxide has long been employed as the magnetic core due to its excellent magnetic properties, which are suitable for magnetic resonance imaging (MRI), magnetic separation, and magnetic hyperthermia. Magnetic core-shell MOFs, with the magnetic nanoparticle as the core and highly porous MOF material as the outer layer, acquire both functionalities associated with the magnetic property and the high drug loading capacity, surface functionality, and synergistic capability from the MOF, making them more versatile in anti-cancer diagnosis and therapeutics [9].

3.1. Preparation of magnetic core-shell MOFs

3.1.1. Solvothermal Method.

To date, there are numerous pioneering studies on the synthetic methods of magnetic core-shell metal-organic framework composites. The first one is the solvothermal method, in which poly(styrenesulfonate, sodium salt) or polyvinylpyrrolidone (PVP) are often used as promoters. Li et al. utilized this idea to prepare Fe₃O₄@/IRMOF-3 [23]. First, they dissolved Zn(NO₃)₂ and NH₂H₂BDC, the precursors of IRMOF-3, into 2 mL dimethylformamide (DMF). Then they added 0.2 g of polyvinylpyrrolidone to the mixed solvent consisting of 4 mL ethanol and 6 mL DMF, which was later mixed with the precursor solution. Lastly, Fe₃O₄ nanoparticles were added and an ultrasonic treatment was performed for 20 minutes. The mixture was then heated with vigorous stirring at 373 Kelvin for 4 hours to finally obtain the Fe₃O₄@/IRMOF-3. PVP was performed as the stabilizer for Fe₃O₄ to be well dispersed in the solvent and as the promoter for IRMOF-3 precursors to attach to Fe₃O₄ nanoparticles' surface.

3.1.2. Step-by-step Assembly Strategy.

Another frequently used synthetic method is the step-by-step assembly method. According to Fig. 2, spherical mercaptoacetic acid (MAA)-functionalized Fe₃O₄ nanoparticles were dispersed alternatively in metal ions and organic ligands solvated in ethanol, and multiple synthetic cycles were

performed to finally arrive at the core-shell structure. Qiu and co-workers were the first to report such a method in their attempt to synthesize $\text{Fe}_3\text{O}_4@[\text{Cu}_3(\text{btc})_2]$ as they dispersed MAA-modified Fe_3O_4 nanospheres alternatively in ethanolic H_3btc and $\text{Cu}(\text{OAc})_2$ [24]. It was worthwhile to note that the functionalization with MAA was crucial as the copper cations must first bind to the carboxylate moiety on the surface of Fe_3O_4 . Then btc-units could bind to the copper ions. The thickness of the outer MOF layer could be regulated by adjusting the above-mentioned procedure.

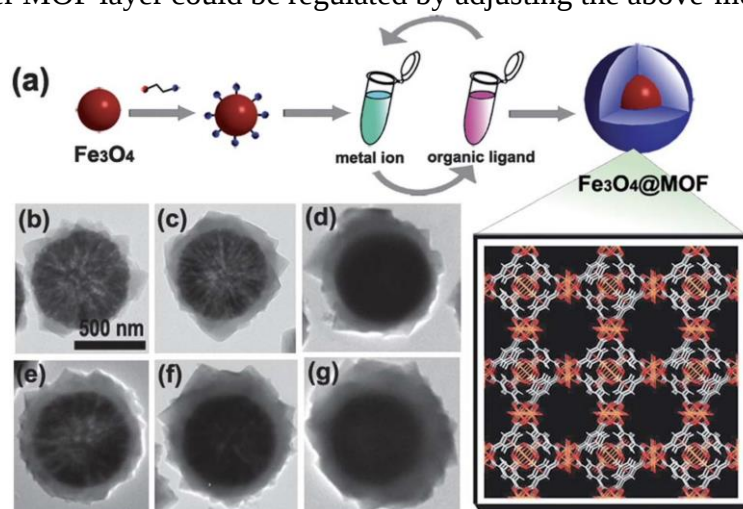


Figure 2. (a) Schematic representation of the step-by-step synthesis of $\text{Fe}_3\text{O}_4@MOF$ (b)-(g) TEM images of magnetic core-shell MOF nanoparticle, $\text{Fe}_3\text{O}_4@[\text{Cu}_3(\text{btc})_2]$ [24].

3.2. Magnetic core-shell MOFs for anti-cancer drug delivery

As magnetic core-shell MOF composites encompass the magnetic core, they can be administered to specific anatomical sites or tissues when guided by an external, deep penetrating magnetic field. MRI and controlled hyperthermia could also be simultaneously employed when the magnetic core-shell MOFs are exposed to an oscillating magnetic field [25].

Wang et al. synthesized a multi-functional magnetic core-shell structure according to the synthetic scheme shown in Fig. 3, $\text{Fe}_3\text{O}_4@\text{poly}(\text{acrylic acid})/\text{Au}$ nanoclusters/zeolitic imidazolate framework-8 (ZIF-8) nanoparticles ($\text{Fe}_3\text{O}_4@PAA/\text{AuNCs}/\text{ZIF-8}$), which can concurrently fulfill diagnostic and visual-guided synergistic functions [26]. It possessed both a tri-model cancer imaging, which consisted of MRI, computed X-ray tomography and fluorescence imaging, and chemotherapy into one MOF composite. An investigation of the magnetic properties was set up in which an external magnet was placed beside the suspension of $\text{Fe}_3\text{O}_4@PAA/\text{AuNCs}/\text{ZIF-8}$ nanoparticles, and the brown-colored MOF composite gathered rapidly, leaving a transparent solution behind. This proved that $\text{Fe}_3\text{O}_4@PAA/\text{AuNCs}/\text{ZIF-8}$ could be delivered to specific sites when guided by an external magnetic source, MRI, and magnetic separation, on top of its advantages of high drug loading capacity granted by the highly porous ZIF-8.

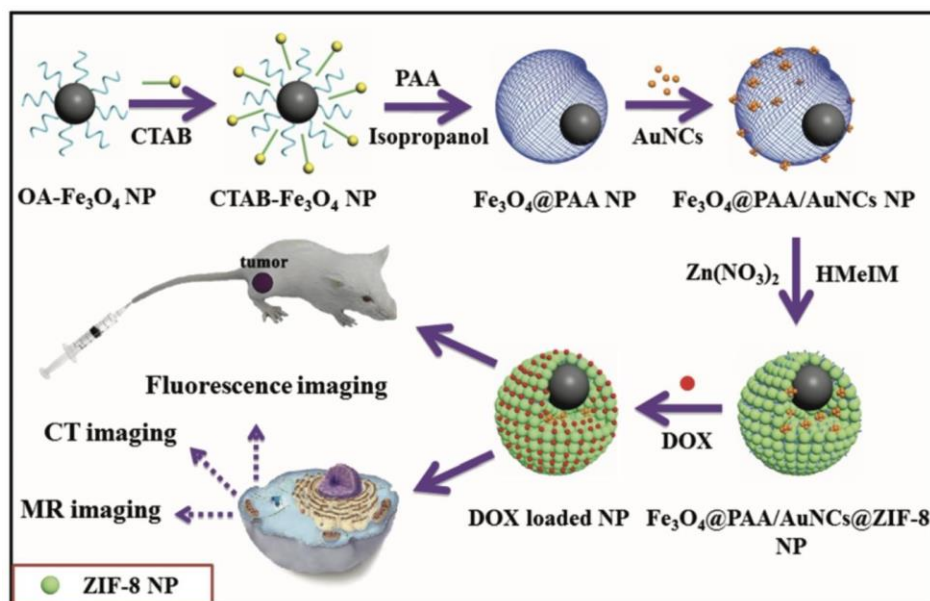


Figure 3. Schematic illustration of the preparation of Fe₃O₄@PAA/AuNCs/ZIF-8 composite nanoparticles for simultaneous tri-modal cancer imaging and chemotherapy [26].

4. Membrane coating

Under most situations, immune responses stimulated by drugs are undesirable as they would cause faster clearance rates of drugs and inflammation. Membranes obtained from natural sources offer a viable possibility for biomimicry as they are often less immunostimulatory and possess remarkable specificity and sensitivity towards the environment. As the cell membrane-coated MOF composites have inherent properties belonging to the source cells, various functionalities could be attained, namely specific targeting, biocompatibility, and lengthened internal circulation [28].

4.1. Preparation of membrane-coated MOF composites

4.1.1. Physical extrusion.

Physical extrusion is utilized extensively in earlier works. In physical extrusion, nanoparticles and the purified cell membrane are co-extruded through a porous material. A mechanical force from the extrusion facilitates the nanoparticle core to go across the layer of the cell membrane, resulting in vesicle-particle fusion. Hu et al. used this particular method to coat the erythrocytemembrane over poly (lactic-co-glycolic acid) (PLGA) [29]. They reported that the mechanical force caused the PLGA nanoparticles to cross the lipid bilayer of the erythrocyte membrane. When the process was repeated, problems including incomplete or inconsistent coating and varying particle sizes were solved.

4.1.2. Sonication-based Approach.

A sonification-based method was found later, and it resembled the previous physical extrusion method except for the source of energy. In this technique, the disruptive forces are sourced from the ultrasonic energy, and they similarly result in the spontaneous formation of the desired coating. It is worthwhile to note that material loss is reduced as compared to the physical extrusion method. Zhang et al. first collected erythrocyte membrane obtained vesicles, then blended them with TPZ-GOx-ZIF-8 nanoparticles and sonicated the mixture for 60 seconds to obtain TPZ-GOx-ZIF-8@eM nanoparticles [30].

4.2. Membrane-coated MOFs for Anti-cancer Drug Delivery.

Most related to the anti-cancer theme, the cancer cell membrane is a top candidate for avoiding immune response and specific binding to cancerous cells via homotypic adhesion. This makes it suitable for enhancing biocompatibility through biomimicking and for targeting tumors [28].

4.2.1. Tumor-targeting Effect.

To exploit the tumor-targeting effect of cancer cell membrane coating, Li et al. held a study [23]. They first prepared a porphyrinic-metal organic framework, PCN-224, from platinum (II) meso-tetra(4-carboxyphenyl) porphyrin and zirconium. Subsequently, they coated the PCN-224 framework with 4T1 cancer cell membrane. The MOF composite could achieve both photodynamic effect and oxygen sensing, aiming for more effective anticancer photodynamic therapy and monitoring the oxygen levels in the tumorous regions. In vivo study reported that 4T1 cancer cell membrane-coated PCN-224 could successfully accumulate in the 4T1 tumors. It was found that the coating significantly enhanced the cytotoxicity of the MOF composite towards 4T1 cancer cells because of this selective and preferential homotypic uptake. This study proved the great potential of cancer cell membrane coating as a functionalization possibility for precise targeting.

4.2.2. Biomimetic Modifications.

Membrane-coated MOFs derive the properties of cell membranes such as the strong ability of immune evasion, endowing the MOFs with longer circulation time in blood, better ability to accumulate in tumors, and fewer risks to elicit an undesirable immune response.

Erythrocyte membrane has long been studied for nanomedicine applications primarily due to its relatively long life span of 120 days. The presence of self-marker CD47 and regulatory proteins also results in the excellent immune evasion capabilities of red blood cells. Fang et al. coated erythrocyte membrane on MOF ZIF-8 to form TGZ@eM for delivery of prodrug tirapazamine (TPZ) and glucose oxidase (GOx) [31]. According to the reported in vivo experiment results, the half-life was approximately doubled from TGZ's 2.4h to TGZ@eM's 4.7 hours, allowing for better accumulation of the composite to the tumor. TGZ@eM, with a longer blood circulation time, achieved better treatment against tumors. Similarly, Gao et al. coated erythrocyte membrane over oxygen and ICG-loaded MOF UiO-66 and observed its pharmacokinetics [32]. As compared to uncoated O₂@UiO-66@ICG, O₂@UiO-66@ICG@RBC showed longer circulation in the blood and better evasion from the immune system, arriving at overall better photodynamic therapy effects.

5. Conclusion.

In summary, MOFs have exceptional promise as drug delivery platforms for anticancer therapeutics. Recent significant progress made in designing novel MOF composites for enhanced performance in terms of the most valuable properties of drug delivery devices, in particular for anticancer diagnostic and theranostic functions, were reviewed. Promising MOF-based systems, including preparations and applications of polymer-coated MOFs, membrane-coated MOFs, and magnetic core-shell MOF composites have been introduced. Polymer-coated MOFs enjoy better biocompatibility, controllable release kinetics, possibilities for targeting functionalization and synergistic considerations. The magnetic core-shell MOF nanostructures are favorable for combined functionalities of MRI, hyperthermia, and drug delivery and externally guided targeted delivery to extremely specific sites in the body. The membrane-coated MOFs exhibit elevated biocompatibility, viable targeting, and are less immunostimulatory. However, there are still challenges to be overcome for such systems to be extensively reviewed and proceed to the next stage of clinical development. Firstly, more effort is needed to produce versatile, biocompatible MOF composites with suitable in vivo toxicity and pharmacokinetics, instead of exploring the enhancement of single properties of MOFs. More systemic evaluation of the toxicity of MOFs and their in vivo biodegradation must be installed to optimize MOF composites' performance. Moreover, other coating materials such as co-polymer, lipid, co-membrane, further surface functionalization of magnetic core-shell MOF nanostructures and modifications can be considered to provide joint benefits and multifunction beyond simply theranostic platforms.

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