Research Progress of Drug Delivery System of Metal-Organic Framework Materials in Drug Release Mechanisms

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Abstract: Metal-organic framework materials (MOFs) are promising drug carriers due to their high specific surface area, tunable pore structure, efficient loading and controlled release of drugs and excellent biocompatibility. In recent years, their application in targeted therapy and controlled release has attracted much attention. In this paper, we systematically review the preparation of MOFs as drug delivery systems for drug loading and their drug release mechanisms, focusing on three release strategies: diffusion control, chemical bond breaking and framework structure change. It was shown that MOFs could realise precise drug release through pH response, redox triggering and environmental stimuli. MOFs could synergistically deliver antigens and adjuvants in vaccine carriers to significantly enhance immune response. Despite the significant advantages of MOFs in targeting and stability, their biodegradability and large-scale production still need to be further optimised. The study provides insights for designing intelligent drug delivery platforms and promotes MOF applications in biomedicine.

1 INTRODUCTION

With the increasing demand for precision medicine and targeted therapies, the design and optimisation of Drug Delivery Systems (DDS) have become a hot research topic in biomedical engineering. As an important research direction in modern medicine, it aims to enhance the therapeutic effect and reduce the side effects of drugs by improving drug stability, targeting, and release efficiency. Traditional delivery vehicles (e.g., liposomes, polymer microspheres) find it challenging to meet the demand for precise delivery in complex pathological environments due to defects such as low drug loading capacity, poor release controllability, and insufficient biocompatibility (Allen&Cullis 2013). In recent years, Metal-Organic Frameworks (MOFs), highly ordered porous crystalline materials formed by self-assembling metal ions or clusters with organic ligands, have a highly reticular structure (Della et al. 2011). With their ultra-high specific surface area (up to 7000 m^2/g) and tunable pore size (0.5-10 nm), they are effective in loading and protecting drug molecules in the field of drug delivery and enabling controlled drug release by modulating their pore size and surface properties (Furukawa et al. 2013). Over the past decade, metal-organic frameworks (MOFs) have received extensive attention and intensive research as drug delivery carriers. Numerous hydrophilic, hydrophobic, and amphiphilic drug molecules have been successfully encapsulated, loaded, or attached to the framework architecture of MOFs. They can be precisely released at the lesion site for practical therapeutic effects. The homogeneous pore structure of MOFs can efficiently incorporate drugs into their cavities, and the large internal surface area of MOFs significantly enhances the drug loading capacity. In addition, many MOFs' weak ligand bonding properties make them degradable, which provides a strong guarantee for the smooth release of drugs. As a novel drug delivery carrier, MOFs can effectively overcome a series of limitations faced by traditional drug delivery systems, such as poor drug stability, low water solubility, and insufficient distribution at the tumour site (Zhao 2018). In drug delivery systems, MOFs can transport drugs to cells under endogenous (e.g., pH, ions, etc.) or exogenous stimuli (e.g., light, temperature, ultrasound, pressure, etc.) to achieve precise and controlled release of drugs (Li et al. 2022). By applying this method, changes in the physiological environment or the application of external stimuli are regulated to precisely control the release of the drug at a specific site and time, thus enhancing the drug's efficacy.

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The non-toxic effects, targeted and stimulus-based delivery systems, multiple drug loading properties, and continuous release have enriched the applications of MOFs in drug delivery, biocompatibility, and biodegradability over the last decade. One of their most important properties, which scientists continue to explore, is the ability of MOFs to interact with biological systems (Maranescu&Visa 2022). In addition, MOFs can achieve targeted delivery through surface modification, further improving the therapeutic effect of drugs and demonstrating great potential for application. Despite the many advantages of MOFs in drug delivery, their research in drug release mechanisms is still in the exploratory stage. An in-depth study of the drug release mechanism of MOFs is of great significance for optimising their structural design, improving drug delivery efficiency, and realising clinical applications.

In this study, the latest research progress of MOFs in drug release mechanism is reviewed, and three ways of synthesis of synthetic MOFs drug-carrying system synthesis and the strategies of their structure design and performance optimisation under different release mechanisms are discussed. The article first introduces MOFs' basic structure and properties, then elaborates on their diffusion-controlled release, stimulus-responsive release, and cutting-edge research results. This article aims to provide a reference for researchers in related fields and to promote further research and application of MOFs in drug delivery—framework structure change release.

2 MOFs DRUG DELIVERY SYSTEM PREPARATION

MOFs are mainly composed of two parts: metal nodes and organic ligands. Metal ions or metal clusters are the backbone of MOFs, and they act as nodes, which are connected to organic ligands through ligand bonds. Common metal ions include transition metal ions (e.g., Zn^{2+}, Cu^{2+}, Fe^{2+}, etc.). Organic ligands usually contain multiple electron donors, which can flexibly select the therapeutic needs (targeting, release mechanism). Their high efficiency and controllability can assist in forming stable (e.g., a carboxyl group, amino group, etc.) and coordinate metal ions between the moiety. Preparation of MOFs according to the nature of the drugs (hydrophilic and hydrophobicity) lays the technological foundation. Conventional synthesis methods for the drug delivery system include solvothermal and non-solvothermal methods. The solvothermal method is carried out at high temperature and pressure and is suitable for synthesising MOFs with good crystallinity; the non-solvent thermal process is carried out at ambient temperature and pressure, which is simple to operate, but the crystallinity of the product is relatively low. For example, MIL-53(Al), MOF-5, etc., can be synthesised by mixing solutions at room temperature. At the same time, the solvothermal method is suitable for preparing MOFs with higher crystallinity (Moharramnejad et al. 2023).

Currently, there are three main ways for MOFs to load drugs. The first is the two-step encapsulation method, the second is the one-step encapsulation method (one-pot method), and the third is the molecular coordination method in which the drug molecule is made into a pre-drug coordinated with metal ions.

2.1 Two-Step Encapsulation Method

The first step is to synthesise the backbone structure of the MOFs carrier; the second step is to load the drug by mixing the drug solution with the MOFs and stirring them at room temperature or heating so that the drug is loaded into the porous structure of the MOFs or adsorbed on the surface of the MOFs through the intermolecular force between the host and guest molecules or the ion exchange two-step encapsulation method (Yu et al. 2023). The advantage of this approach is that MOF synthesis and drug loading can be optimised independently, and the crystallinity, pore size, and morphology of MOFs can be precisely controlled by adjusting the synthesis conditions (e.g., temperature, pH) to avoid drug molecules interfering with the nucleation process. Drug loading conditions (concentration, time, solvent) can also be optimised independently to increase the drug loading capacity.

2.2 One-Step Encapsulation (One-Pot Method)

In the reaction system of the one-step encapsulation method for synthesising MOFs, metal precursors, organic ligands, and drug molecules are added simultaneously to form drug-loaded MOFs through a self-assembly process or co-crystallization in a single step. The drug molecules are encapsulated in situ into the pores of the MOFs (Yu et al. 2023). The advantage of this method is that no post-processing loading step is required, and the step of synthesising the MOF backbone is eliminated, reducing the time and cost; also, mild synthesis conditions (e.g., room

temperature, aqueous phase) can avoid drug degradation.

2.3 Coordination of Drugs as Organic Ligands

The drug-as-organic-ligand coordination method involves the coordination of a drug molecule with a suitable metal ion node so that the drug molecule is directly involved as a ligand in synthesising a drug-carrying system. A suitable drug molecule is first selected to ensure it has a ligand group such as carboxylic acid, amino, hydroxyl, etc. The drug molecule must form stable coordination bonds with metal ions (e.g., Zn^{2+}, Fe^{3+}, Zr^{4+}) while maintaining pharmacological activity. The advantages of this approach are that the drug acts as a backbone component, the drug loading is significantly higher than that of physical adsorption, and the release kinetics are regulated by the strength of the ligand bonds to achieve precise drug release.

3 DRUG RELEASE MECHANISMS IN MOFS DRUG DELIVERY SYSTEM

Drug release from MOFs drug delivery system is achieved by breaking the chemical or linkage bonds of MOFs, causing their structure to disintegrate and thus releasing the drug. Using the delivery system of the prepared MOFs drug, it is transported to the organism to reach a specific location and further stimulated using the characteristics of its microenvironment to cause its cleavage to achieve the targeted treatment and effect of the drug. The following are three drug-release mechanisms from MOFs.

3.1 Diffusion-Controlled Releases

Drug molecules slowly diffuse to the external environment through the pores or surface of MOFs, and the pore size, pore hydrophilicity, and the interaction of drug molecules with the pore wall determine the release rate. The pore size and porosity of MOFs are the key factors influencing the diffusion of drugs. Larger pore sizes and higher porosity can reduce the diffusion resistance of drug molecules in the pore channels, thus accelerating the drug release rate. For example, MOFs with larger pore sizes can allow drug molecules to move more freely in and out of the pore, similar to a spacious channel, enabling rapid diffusion of drug molecules into the external environment. In addition, the interaction between drug molecules and the pore walls of MOFs can also affect diffusion.

3.2 Release by Chemical Bond Breakage

The type of chemical bond formed between MOFs and drug molecules determines the ease of breaking, which in turn affects the trigger conditions and rate of drug release. The primary release mechanism for chemical bond breaking is ph-responsive release. The microenvironment of many diseases (e.g. tumours) has a unique pH, which is usually lower than that of normal tissues (tumour microenvironments have a pH of about 6.0-6.5, whereas normal tissues have a pH of about 7.4). Drug release can be triggered in specific pH environments by designing pH-sensitive MOFs. Ligands containing protonatable groups (e.g., amino, carboxyl, etc.) are selected. In an acidic environment, protonation of these groups alters the pore structure of the MOFs, resulting in drug release. pH-responsive release mainly consists of three mechanisms:

(1) Protonation-driven chemical bond dissociation. This mechanism contains two modes of action: one, for MOF materials containing ionisable functional groups (e.g. imidazole, amino, carboxylic acid, or pyridine groups), the ligand is deprotonated under physiologically neutral conditions, and when the microenvironment is acidified the protonation effect leads to destabilisation of the metal-ligand coordination, triggering the decomposition of the framework structure and the release of the drug; and the other, based on the acid-sensitive chemical bonding (e.g. ether, hydrazone or amide bonding) Secondly, based on acid-sensitive chemical bonds (e.g., ether, hydrazone or amide bonds), a drug-MOFs composite system is constructed, and the covalent bonds are hydrolysed under acidic conditions to achieve controlled drug release. (2) Charge reversal-mediated electrostatic release. Due to the change of pH value in the focal area, the surface charge of the drug molecule changes, resulting in the original electrostatic attraction between it and the carrier of the MOFs changing to repulsion, which triggers the drug molecule to detach from the carrier. (3) pH response regulation of intelligent gating system. By modifying pH-sensitive functional materials as the protective layer on the surface of MOFs, the protective layer undergoes conformational transformation or degradation in the acidic microenvironment, thus opening the pore to achieve drug delivery (Wang et al. 2023).

The unique pH-responsive release of MOFs, applied in vaccine carriers, can enable antigens and adjuvants to be simultaneously and efficiently delivered to the target cells, thus minimising off-target release and improving vaccine efficacy. Compared with soluble antigens, antigens in MOFs are preferentially taken up, processed, and delivered by antigen-presenting cells (APCs). Encapsulation of ovalbumin (OVA) and non-methylated cytosine-guanine dinucleotide deoxyribonucleic acid (CpG ODN) in ZIF-8 resulted in pH-responsive release of OVA-CpG@ZIF-8 nanoparticles, which were able to deliver OVA and CpG ODN to APCs efficiently. It induced a stronger immune response than the OVA, CpG and ZIF-8 mixture alone. Induce a stronger immune response (Zhang et al. 2021). pH-responsive release of the MOFs vaccine vector OVA-CpG@ZIF-8 NPs achieves controlled release of the antigen OVA through its structural degradation in acidic environments. This property enables them to efficiently release antigens in specific organelles in organisms, enhancing the immunological effect of vaccines and providing a new strategy for vaccine delivery and immunotherapy.

3.3 Release of Frame Structure Changes

The types and ratios of metal ions/clusters and organic ligands of MOFs, as well as the connection modes, determine the stability of their framework structures. By designing these structural parameters rationally, responsiveness to external stimuli (e.g., light, heat, ionic competition, etc.) can induce the framework's collapse, dissolution, or pore expansion, thereby modulating the drug release behaviour. For example, to overcome the problem of premature release of conventional MOFs in front of the focal tissue, researchers developed the responsive metal-organic frameworks (MOFs) described above, which significantly prolonged the release time of the drug and improved the therapeutic efficacy. In addition to the typical stimulus-response, pressure has also been used to control drug release. Recently, a zirconium-based MOF constructed from (2E,2E')-3,3'-(2-fluoro-1,4-phenylene) is acrylic acid (F-H2PDA) and zirconium clusters and featuring a high drug loading of the model drug diclofenac sodium (DS) with a drug loading of 58.80 wt% was developed, which was attributed to its enhanced polarity and prolonged organic spacing. The system innovatively uses pressure to modulate the drug release kinetics, prolonging the release for 2-8 days to achieve sustained release. This provides new ideas for responsive MOF-based drug delivery (Wang&Yang 2017).

There are intracellular differences in the redox microenvironment, with higher concentrations of glutathione (GSH) in tumour cells (up to 10 mM) and lower concentrations of GSH in normal cells (about two mM). In addition, reactive oxygen species (ROS) levels are higher in tumour cells. These substances can trigger a redox reaction, prompting the dissociation of ligand bonds or a change in the valence state of the metal centre, leading to the structural disintegration of the metal-organic framework carriers, thus enabling the controlled release of encapsulated drugs. The drug can be released by designing redox-sensitive materials (e.g., MOFs, polymers, etc.) to undergo structural changes in highly reducing or oxidising environments.

Significant advances have been made in intelligent delivery systems based on tumour metabolic profiling in recent years. Glucose oxidase (GOD) loading is often used to control insulin release in response to glucose. GOD can convert glucose into gluconic acid and hydrogen peroxide, thus acidifying the microenvironment. A decrease in pH can activate acid-sensitive chemical bond breaking, further triggering the pH response mechanism for drug release. The researchers constructed a composite nano-delivery system based on a metal-organic framework (ZIF-HA) to achieve tumour microenvironment-responsive drug release by co-loading silver nanocubes (AgNCs) and GOD. During abnormal glycolysis in tumour cells, GOD catalysed glucose oxidation to generate hydrogen peroxide, triggering the gradual dissociation of AgNCs into Ag^+ ions and nanoscale silver particles (AgNPs), which exerted anti-tumour effects through ion release and nanoparticle synergy. In vivo experiments showed that the system significantly inhibited tumour growth in a hormonal mouse model without causing significant systemic toxicity, demonstrating excellent biosafety (Li et al. 2021).

4 CONCLUSION

In this study, we systematically elucidated the core advantages of MOFs in drug delivery and their mechanism of action. Through the synergistic effect of diffusion control, chemical bond breaking, and dynamic framework remodelling (triple release mechanism), MOFs can respond to the characteristics of the tumour microenvironment (e.g., low pH, high GSH concentration) and significantly enhance drug targeting and efficacy. These mechanisms provide a

theoretical basis for applying MOFs in drug delivery and confirm their advantages in improving therapeutic efficacy and safety. As a new generation of intelligent drug carriers, MOFs promote the cross-fertilisation of nanomedicine disciplines and provide an innovative solution to the problems of low drug utilisation and off-target toxicity in clinical translation.

Although some research results have been achieved in MOF drug delivery systems, some limitations remain. Regarding biocompatibility and degradation, the degradation products and long-term biological effects of some MOFs materials in vivo are still unclear, and further research is needed to develop more biocompatible MOFs materials. Regarding the precise regulation of drug release, the current release mechanism research focuses on the single stimulus-response, and there are fewer studies on the synergistic reaction of multiple stimuli and the precise spatial and temporal regulation of drug release. In the future, we can deeply explore the multi-modal stimulus-response of the MOFs drug delivery system to realise the exact release of drugs in a specific time and space. Regarding clinical translation, the MOFs drug delivery system and the actual clinical application are in the laboratory research stage. It is necessary to strengthen the cooperation between industry, academia, and research to promote the clinical translation process to benefit the patients as soon as possible. Through interdisciplinary collaboration and technological innovation, MOFs are expected to achieve breakthrough applications in cancer therapy, vaccine development, and regenerative medicine and provide an efficient and safe delivery platform for precision medicine, thus enhancing therapeutic efficacy and improving patient prognosis.

REFERENCES

Allen, T.M. & Cullis, P.R. 2013. Liposomal drug delivery systems: From concept to clinical applications. *Advanced Drug Delivery Reviews* 65(1): 36-48.

Della, R.J., Liu, D. & Lin, W. 2011. Nanoscale metal-organic frameworks for biomedical imaging and drug delivery. *Accounts of Chemical Research* 44(10): 957-968.

Furukawa, H., Cordova, K.E., O'Keeffe, M., et al. 2013. The chemistry and applications of metal-organic frameworks. *Science* 341(6149): 1230444.

Li, B.T., Kou, B.G., Jiang, Y.J., et al. 2022. Anti-tumor drug delivery and tumor therapy based on metal-organic frameworks. *Cancer Res Prev Treat* 49(8): 832-837.

Li, Y., Gao, Z., Zhang, Y., et al. 2021. MOF-shielded and glucose-responsive ultrasmall silver nano-factory for highly-efficient anticancer and antibacterial therapy. *Chemical Engineering Journal* 416: 127610.

Maranescu, B. & Visa, A. 2022. Applications of metal-organic frameworks as drug delivery systems. *International Journal of Molecular Sciences* 23(8): 4458.

Moharramnejad, M., Ehsani, A., Shahi, M., et al. 2023. MOF as nanoscale drug delivery devices: Synthesis and recent progress in biomedical applications. *Journal of Drug Delivery Science and Technology* 81: 104285.

Wang, C.L., Situ, T.X., Yan, X., et al. 2023. Research progress in drug target delivery and release mechanisms based on metal-organic frameworks. *Chinese Journal of Veterinary Medicine* 59(5): 100-105.

Wang, M.X. & Yang, Y.W. 2017. Metal-organic framework (MOF)-based drug/cargo delivery and cancer therapy. *Advanced Materials* 29(23): 1703614.

Yu, J.Y., Lin, Z.Z. & Cao, W. 2023. Research progress of bio-metal organic frameworks in drug delivery system. Journal of China Pharmaceutical University 54(1): 23-33.

Zhang, G., Fu, X., Sun, H., et al. 2021. Poly(ethylene glycol)-mediated assembly of vaccine particles to improve stability and immunogenicity. *ACS Applied Materials & Interfaces* 13(12): 13978-13989.

Zhao, G.Z. 2018. Synthesis of Nano-Metal-Organic Frameworks and its application in cancer diagnosis and therapy. *Hefei: University of Science and Technology of China.* 16-21