Applications of Metal Organic Frameworks in Drug Delivery and Therapy

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Abstract: Metal organic frameworks (MOFs) are organic-inorganic mixtures formed from metal ions and organic ligands under relatively mild conditions. MOFs are widely used as drug carriers due to their low toxicity, high drug load, good biocompatibility, and functional diversity. Stimulus-responsive MOFs materials have attracted extensive attention in the field of drug delivery materials and biological applications. This article highlights the different types of stimulus-responsive MOFs materials, including pH-Responsive MOFs, magnetically-responsive MOFs, ion-responsive MOFs, temperature-responsive MOFs, and pressure-responsive MOFs. MOFs materials are very effective as intermediates for drug transport. In this thesis, we mainly studied the advantages of MOFs as intermediates. It is stable and can be safely degraded, and it makes the antibody easier to attach, and have strong plasticity.

1 INTRODUCTION

MOFs are organic-inorganic mixtures formed from metal ions and organic ligands under relatively mild conditions (Batten, Champness, Chen, 2013). The stability of MOF is influenced by many factors, including the operational environment, metal ions, organic ligands, coordinate geometry of metal ligands, hydrophobicity of interstitial surfaces. The study of MOF stability helps rationalize the influence of several factors and design stable framework structures wisely. The relatively volatile coordination relationships of the skeletal support structure are seen as the cause of the limited stability of the MOF. Therefore, the stable structure of the MOF would need to be highly coordinated. They have been extensively studied in the basic fields of catalytic intermediates capture and energy transfer and the potential practical applications such as gas storage and separation, heterogeneous catalysis, chemical sensing, biomedical applications, and proton conduction (Chughtai, Ahmad, Younus, 2015). Many early MOFs made from divalent metals, such as Zn2+ or Cu2+, showed extremely high porosity and showed promise for widespread use, but ultimately proved unsuitable for harsh conditions due to stability issues (Eddaoudi, Kim, Rosi, 2002); (Deng, Doonan, Furukawa, 2010).

Drug delivery systems (DDS) are typical of the research achievements about new preparations and dosage forms in modern pharmacy, the crystallization of modern scientific and technological progress. The system has made great progress in the theoretical system, design of new preparation and preparation process, and application in clinical treatment, mainly including oral slow and controlled release system, transdermal drug delivery system, and targeted drug delivery system. Recent research about this topic has made a big process because people have already found an almost perfect carrier for drug delivery, which is MOFs. MOFs are regarded as the perfect material because they have many advantages that other carriers do not have (Neuberger, Schöpf, Hofmann, 2005).

Compared with other organic porous materials and inorganic materials, MOFs have the following characteristics. Firstly, MOF materials are highly adjustable. MOFs are a hybrid porous material whose pore surface properties can be adjusted to suit drug

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delivery needs. Secondly, partial MOFs can be adjusted according to needs so that their toxicity to the human body is controlled in an acceptable range to achieve a relatively stable carrier. Because active functional groups can be inserted into the surface of MOFs, it is easier to modify the surface to meet the use requirements. Thirdly, the drug can be loaded by introducing functional ingredients or changing the body's flexibility, and then the speed and size of its release can be controlled. Finally, MOFs can achieve the purpose of making targeted drugs by introducing stable special materials. By changing the NMOFs after the contact surface, MOFs can be transformed into a method that can make it have the advantages of nanosensors. For example, the targeting and bioavailability of drugs can be improved, the stability of drugs can be increased, the efficacy can be improved, and the toxic and side reactions can be reduced. It can also make the drug into the human body at all levels of the tiny blood vessels, and pathological tissue cells play a therapeutic role. MOFs have essentially large surface areas, highly ordered porosity, and clear structures that give these materials the ability to load and release different cargoes, especially therapeutic agents (Ma, Moulton, 2011).

This review will focus on the development of MOFs in the field of controlled drug release and effective cancer treatment, including drug nanocarriers and cancer treatment systems composed of single MOFs, stimulus-responsive MOFs, and multifunctional MOFs. This document also covers basic methods for the application of MOF to biology. Finally, the development prospects and challenges of MOF are under discussion.

2 STIMULI-RESPONSIVE MOFs FOR DRUG DELIVERY

Stimulus-responsive MOFs materials have attracted extensive attention in the field of drug delivery materials, especially in the field of biological applications. As a result, Stimulus-responsive MOFs have become popular candidate materials for controlling drug release. Generally, stimulus-response MOFs can be divided into single stimulus-response types and multiple stimulus-response types. Next, we will discuss the main response methods for these two MOFs (Feng, Wang, Zhang, 2019).

2.1 Single-Stimuli-Responsive MOFs for Drug Delivery

2.1.1 pH-Responsive MOFs

All porous MOF nanosensors are stimulated by external stimulation. However, the pH-responsive MOF is the most widely studied, especially in cancer treatment, because acidic bonds are particularly sensitive to the tumor microenvironment and coordination external doctor many studies have investigated the pH response of MOF to drug delivery and cancer therapy (Freeman, Arrott, Watson, 1960).

Recently, Qian's group described an interesting cationic nanocarrier, ZJU-101 (Zhejiang University, ZJU) MOF, for delivering the anionic drug diclofenac sodium. The cation material of the body is in zirconium and 2,2′-bipyridine-5,5′-dicarboxylate (BPYDC) ligand. And the high carrying capacity of diclofenac sodium was 0.546 g/g. The release rate of diclofenac sodium in inflammatory tissues (pH = 5.4) was higher than that in normal tissues (pH = 7.4) because the ion exchange between the anions in PBS and the drug is more frequent under acidic conditions. As a result, the coulomb interaction between the cation ZJU-101 and the anionic drug is weakened. As a result, diclofenac sodium-sensitive to pH is expected to be a promising carrier of anti-inflammatory drugs (Angelos, Khashab, Yang, 2009).

2.1.2 Magnetically-Responsive MOFs

Due to the potential benefits of magnetic response systems with respect to magnetic separation, magnetic targeting, magnetic resonance imaging (MRI) and magnetic hyperthermia, drug delivery is quite diverse. Therefore, the administration of magnetic drugs is a unique strategy for improving the therapeutic effect of concentrating the drug delivery probe at the tumor site. Since the method was first proposed by Watson et al. in the 1960s, many MOFs materials have been found to have good magnetic properties and can be used for drug separation and drug delivery (Cavka, Jakobsen, Olsbye, 2008); (Hergt, Dutz, Müller, 2006); (Jurgons, Seliger, Hilpert, 2006); (Kumar, Mohammad, 2011). In 2014, Guan and colleagues reported on a one-step in situ pyrolysis method for producing γ-Fe_2O_3@MOF. In their work, γ-Fe_2O_3@MIL-53 (LA) demonstrated its potential for controlled magnetic separation and drug liberation. As anticipated, magnetic nanocomposites showed a controlled release behavior in 37 salines. That is, the capsule IBU is fully released after 7 days

in 3 stages. About 30% of the drug is released rapidly within the first 3 hours in the first stage. Then 50% of the drug was released within 2 days. Finally, the remaining 20 percent of the drug was released within five days. This confirms that magnetic γ-Fe_2O_3@MIL-53 (AL) is a feasible drug delivery material (Lee, Hyeon, 2012).

2.1.3 Ion-responsive MOFs

Ion-responsive MOFs open up new drug delivery pathways. The strong electrostatic interaction between the drug and the frame enables it to control the diffusion and release of the drug in the drug carrier. Therefore, the strong electrostatic interaction between ionic drugs and ion frames is particularly interesting because the release of ionic drugs is a chemically stimulated reaction process that occurs only in ion exchange. For example, Tamames-Tabar et al. investigated the cytotoxicity of MOFs containing Fe, Zn, or Zr central metals on human cervical cancer cell lines (HeLa) and mouse macrophages (J774). The cytotoxicity of Fe-MOFs was less than that of Zn-MOFs and Zr-MOFs. Although Zn and Fe are trace elements found in the human body, Zn ions can compete with Fe and Ca ions to bind ion channels, alter metabolism, and damage cells. Gao et al. demonstrated Fe-MOFs' relative biocompatibility by finding that more than 80% of human aortic smooth muscle cells survived exposure to 200 μg/mL Fe-Mil-53-NH2-FA-5-FAM/5-FU. Similarly, nh2-MIL-88 (Fe) or NH2-MIL 88(Fe)/Br was incubated at 2000 μg/mL. More than 90% of human primary corneal epithelial cells remain active, and Fe-MOF exhibits relatively low cytotoxicity as an imaging agent. The IC50 of MIL-88A(Fe) on J774 cells was 57±11 μg/mL. Mil-100 (Fe) showed no cytotoxicity to human leukemia cell line CCRF-CEM and human multiple myeloma cell line RMI-8226 at 10 mm. By intravenous administration of 220 mg/kg of Fe-MOFs MIL, the concentrations of MIL-100 and MIL-88A, MIL-100 and MIL-88B-4CH3 were reduced, supporting the explanation of MOFs. These things have successfully become practical iron (Wu, Zhou, Li, 2014).

2.1.4 Temperature-responsive MOFs

In general, temperature-sensitive nanotransporters are materials that are sensitive to small temperature variations at a physiological temperature of 37. Sada et al. demonstrated a switchable UIO-66 PNIPAM nanocarrier by immersing UIO-66-PNIPam in a guest solution and loading L2L m-catechol, caffeine, and procaine into the nanocarrier (Fig. 1a), and then evaluated the release behavior at 25 oC or 40 oC (Fig. 1b). As expected, the release increases to 25 and stops at almost 40 (Fig. 1c), indicating that the controlled release results in temperature changes. In recent years, two zinc MOFs were synthesized. The anti-cancer drug MTX was loaded into both MOFs by single immersion, and the loading amounts of ZJU-64 and ZJU-64-CHS were 13.45% and 10.63%, respectively. ZJU-64 and ZJU-64-CH loaded with MTX were released at 37 oC for 72 h with the same amount of release, but at 60 oC for 1.5 h and 6 h, respectively, indicating that ZJU-64 and ZJU-64-CH have potential application value as temperature-sensitive drug carriers (Wu, Yang, 2017); (Nagata, Kokado, Sada, 2015).

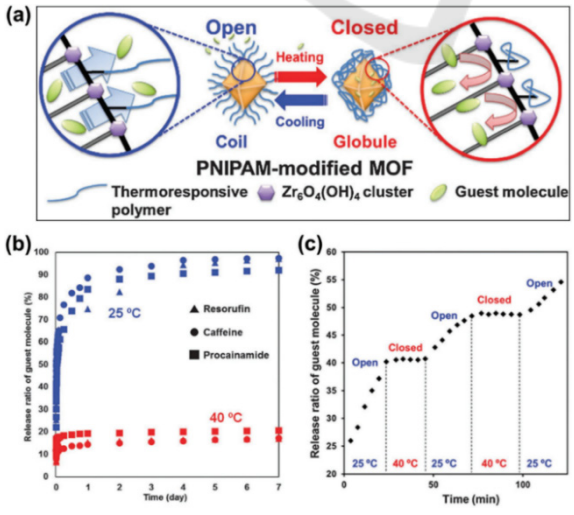

Figure 1: a) The controlled release profiles of UiO-66-PNIPAM. b) Release behavior of drug-loaded UiO-66-PNIPAM in the water at 25 °C and 40 °C for seven days. c) Temperature-responsive release behavior of UiO-66-PNIPAM resorufin in water at 572 nm (Lin, Hu, Yu, 2016).

2.1.5 Pressure-responsive MOFs

To avoid premature drug release before reaching pathological tissues, several effective, responsive MOFs have been developed to prolong drug release time and significantly improve treatment outcomes. In addition to the stimulus-response MOFs mentioned above, pressure is also used to control drug release. For example, Qian and colleagues documented a Zr-based MOF constructed from (2E,2E)-3,3-(2-fluoro-1,4-benzene) diacrylic acid (F-H2PDA) and zirconium clusters with a loading capacity of 58.80 wt% of high-model drug diclofenac sodium (DS). Different pressures can adjust the release kinetics of MOF-loaded DS, and the release time can be extended to 2-8 days. This demonstrates the effectiveness of stress control drug release (Nagata, Kokado, Sada, 2015).

2.2 Multiple-Stimuli-responsive MOFs for Drug Administration

Because of the intricacy of the human environment, the capacity to precisely convey drugs in people utilizing single incitement responsive MOF materials is restricted. Notwithstanding, multi-boost reaction MOFs can be utilized as a superior choice to further develop drug load limit and chemotherapy proficiency (Jiang, Zhang, Hu, 2016); (Ogoshi, Kanai, Fujinami, 2008); (Strutt, Zhang, Schneebeli, 2014); (Zhang, Zhao, 2013).

By incorporating pH esteem and additionally serious restricting response techniques into a solitary medication nanocervator (Fig. 2), the medication nanocervator with CPS as the terminal has high embodiment proficiency, unimportant early delivery, immaterial cytotoxicity, and optimal biodegradability and biocompatibility. In the R bunch, MOF multistimulus delicate nanocervors with CP5 ring as the guard were additionally examined. For instance, another CP5-covered UIO-66-NH5-FU nanocarrier was reported. In this work, UIO-66-NHH is adjusted by the emphatically charged quaternary ammonium salt Astals (Q) through the contrarily charged CP5 ring arrangement pseudotaxane goes about as an energizer with responsive supramolecular gating to direct medication discharge. Because of the great partiality among zinc and fluorouracil, zinc * can be utilized as a cutthroat glue to trigger delivery by specialists. Furthermore, the expanded temperature will likewise debilitate the non-covalent bond cooperation among CP5 and the stem, in this manner animating medication discharge. Thusly, cp5-gated MOF-based double boost responsive medication nanocarriers give new freedoms to treating focal sensory system sicknesses. (Si, Xin, Li, 2015)

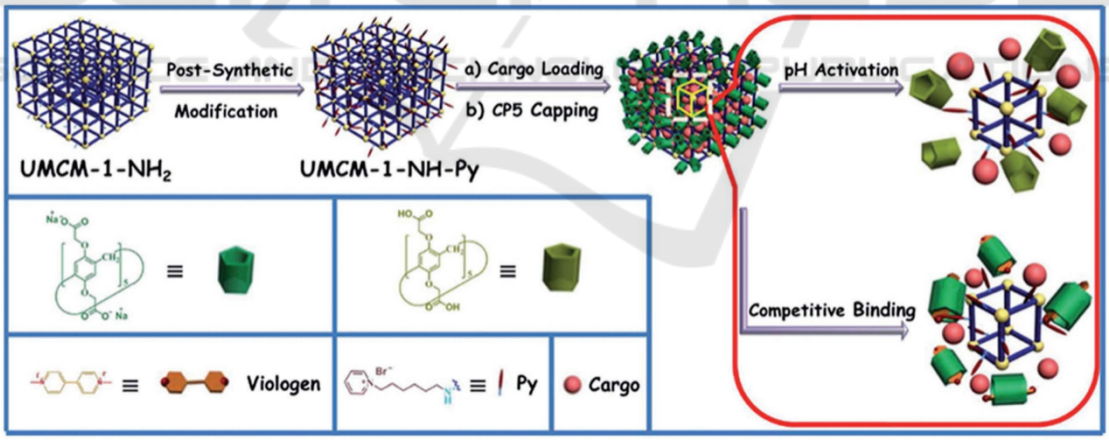

Figure 2: Schematic delineation of double improvements responsive DDS dependent on UMCM-1-NH2 NMOF gated by pillararenes. Recreated under the details of the CC-BY-NC-3-0 unported license (Doane, Burda, 2012).

3 MOFs FOR ANTIBODY TRANSPORT

As a biological drug, the antibody is an important part of immunotherapy and plays an important role in scientific research, medical diagnosis and disease treatment. However, many biological drugs, including antibodies, have disadvantages such as poor internal stability, easy aggregation and easy degradation, which greatly reduce the efficacy. Polymer is one of the most commonly used carriers to maintain antibody stability, but polymer has certain immunogenicity and lacks biosafety. Therefore, it is imperative to develop a simple and efficient biologic

drug stabilization material. So we found that MOFs are intermediates for drug transport. The advantages of MOFs as intermediates are as follows.

3.1 Stability and Security Degradation

Yao Chen of Nankai University, and Shengqian Ma, of the University of South Florida used MOFs as a protective layer to prevent antibodies from accumulating or inactivating in complex environments in the body. The protected antibody has good thermal, chemical and mechanical stability and can stay at 4↔50 °C, 25 °C min-1 when temperature changes rapidly. More importantly, with the right stimulus, antibodies can be fully released within 10 seconds. At the same time, MOFs are almost all degraded, avoiding the immunogenicity and biosafety problems of residual materials (Tan, Song, Zhang, 2016).

3.2 Antibody Adhesion

MOFs are widely welcomed as drug carriers in the biomedical field. MOFs is an ideal drug carrier. On the one hand, there are many ways to bind drug molecules to MOFs nanoparticles differently. On the other hand, the combination of drugs and MOFs nanoparticles can be adjusted to improve the drug adsorption rate of MOFs nanoparticles. Abhik et al. synthesized and used Fe_3O_4@MIL-100 to load the anticancer drug doxorubicin. The study structure showed that Fe_3O_4@MIL-100 could improve the drug loading rate of adriamycin and achieve the purpose of drug release. Zhou et al. Ni@MOFs-74 (Ni) were synthesized by the one-pot method, and it was found that Ni@MOFs-74 (Ni) has high porosity and strong magnetic properties, which can greatly improve drug loading rate. The results showed that Ni@MOFS-74 (Ni) loaded ibuprofen up to 4.1 mg/g. Lazaro et al. used Zr-MOFs combined with dichloroacetic acid and 5-fluorouracil to enhance in vitro cytotoxicity (Tan, Song, Zhang, 2016).

3.3 Highly Modifiability

MOFs has good material modification property. The remaining uncoordinated carboxyl groups in MOFs are derived. Under the activation of EDC and SULfo-NHS, antibody molecules were covalently modified by peptide bonds, and a kind of antibody functionalized MOFs material was developed. Then MOFs materials were grown in situ on ZnO substrates to construct a cell recognition and capture platform. The captured cells were observed and counted by ESEM and confocal fluorescence microscopy. Several factors affecting the capture of tumor cells by antibody-functionalized MOFs materials were studied, including co-incubation time, cell concentration, material morphology and different cell lines. EpCAM antibody modified MOFs have a strong specific capture ability for EPCAM-positive cell lines, and the capture efficiency is greatly affected by cell concentration and material morphology. McF-7 cells are preferentially attached to the needle-like structure of the material. Europium complex is superior to antibody-functionalized ZnMOFs in biocompatibility. In addition, the cytotoxicity of ZnMOFs depends on the amount of material used. In contrast, the cytotoxicity of the Eu complex did not change significantly over the range of concentrations used in the experiment (Tan, Song, Zhang, 2016).

4 CONCLUSION

In summary, stimulus-responsive MOF materials can be divided into single stimulus response and multi-stimulus response. The single stimulus response includes pH-Responsive MOFs, magnetically-responsive MOFs, ion-responsive MOFs, temperature-responsive MOFs and pressure-responsive MOFs. Magnetic response system has great advantages in magnetic separation, magnetic targeting and magnetic resonance imaging. Specific advantages are reflected in the accurate release of drugs, accurate imaging and other aspects. The strong electrostatic interaction between drug and frame makes MOF material have many advantages in drug delivery and release. In addition to stimulus-responsive MOF materials, pressure can also be used to control drugs. They stand out in the field of drug delivery because of their strong drug loading capability, high microbial capacity and easy functional properties.

More efficient synthesis for MOF materials is a very promising research direction. The traditional synthesis method has a long reaction time, high reaction temperature, large organic solvent, and complex reaction equipment, which has become the bottleneck.

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