The applications and synthesis of metal-organic frameworks in nano-drug delivery

Xianhan Xu*

School of UIA, Kunshan, Jiangsu, China

*Corresponding author: milo. zhang@uiachina.com

Abstract. Nowadays, the incidence of cancer has been increasing a lot at a very high percentage, and it has become one of the illnesses that damage the human body. Chemotherapy is currently the conventional cancer treatment. Most chemotherapeutic drugs are not selective. During drug delivery, only part of them can reach the tumor lesions, and part of them will be absorbed by normal tissue cells, causing serious side effects. Nowadays, metal-organic frameworks with high selectivity, high adsorption capacity, high diffusion speed and low energy consumption had shown great research value in the field of biomedicine and are considered to be the most promising new generation of porous functional material. In this article, the synthesis of MOFs, including hydrothermal, liquid phase diffusion, microwave, mechanochemical and ultrasound method was introduced. Additionally, the MOFs based on pH value sensitivity, the sensitivity of the light, temperature stimuli-responsive and the sensitivity of magnetic field drug delivery system were highlighted. The development of novel porous MOF materials not only reduces the harm suffered by patients during the treatment process but also can precisely transport drugs to the cancerous site to reduce the loss of drugs during transportation, making the cost of cancer treatment more acceptable to civilians. It is of great significance to the overall average life expectancy of human beings.

Keywords: nano-drug carriers, MOFs, applications, synthesis

1. Introduction

In recent years, the incidence of cancer has been increasing, and it had become one kind of the majority of diseases that threaten human health. Chemotherapy is currently the conventional treatment for tumors, and it has therapeutic effects on primary tumors, metastases and subclinical metastases. However, most chemotherapeutic drugs are not selective. During the drug delivery process, only part of them can reach the tumor lesions, and part of them will be absorbed by normal tissue cells, causing serious adverse reactions and seriously blowing the patient's physical and mental health. Nano-drug carrier is a nano-scale sub-particle drug delivery system, which attaches drug molecules to the surface of nano-materials, or wraps them inside nano-materials, which can change the way drugs enter the organism and their distribution in the body. The size of nano-drug carriers is usually between 10-200 nm, which is larger than drug molecules and smaller than organelles, which makes nanomaterial suitable for drug loading and can transport drugs to tumor tissues [1]. Compared with traditional chemotherapeutic drugs, nano-drugs have good and stable drug release kinetics, prolong the circulatory half-life of drug delivery systems, and have fewer side effects, which have attracted extensive attention from researchers. At present, there are kinds of nano-drug delivery systems, including Liposome drug carriers, polymer-drug carriers and inorganic nanocarriers and MOF that have been studied and applied in nano-drug delivery systems.

Liposome drug carriers are usually vesicle structures composed of natural phospholipids or synthetic lipids as raw materials, which have good biocompatibility and can carry hydrophilic or hydrophobic drugs [2]. Liposomes are nontoxic and biodegradable but have poor stability and low drug loading. Compared with other types of drug carrier materials, the application of liposomes in sustained drug release has been studied earlier, and a variety of liposome-based nanomedicines have been successfully developed. Polymer nanocarriers include polymer nanoparticles, dendrimers, and polymer micelles. Polymer nanoparticles have a high drug-loading capacity and can be selectively targeted for drug delivery, and play an important role in medication delivery systems. They can also be decorated with different functional substances, such as polyethylene glycol, to improve drug

delivery at tumor sites [3]. Polymer nanoparticles have good biodegradability and biocompatibility, so they have higher bioavailability. Many polymers have different physicochemical properties and can be combined with molecules with antitumor activity such as chitosan for combined chemotherapy and administration [4].

Inorganic nanoparticles were widely used in medical fields such as drug delivery [5] and bioimaging due to their relatively simple synthesis and surface modification methods. Inorganic nanoparticles can not only effectively load antitumor drugs, but also deliver specific receptor-targeting agents to tumor tissues, which can be used for multifunctional tumor therapy [6]. Recent studies have shown that drug delivery systems found by metal-organic frameworks (MOFs) reveal the great potential in the area of biomedicine. MOFs are kinds of organic-inorganic hybrid material formed by a kind of discrete coordination bond that was first synthesized by the cooperation between the Yaghi research team and the Kitagawa research team in 1995 [7]. Although the history of MOFs was only about 20 years it still attracted a lot of scientists because of their high selectivity, adsorption, diffusion rate and low energy consumption. Nowadays, scientists had designed and produced about 2000 kinds which include many famous series such as ZIF, MIL and MAF and many others. MOFs had shown their large potential in gas storage, gas separations, chemical sensing and the drug delivery industry in the two decades. MOFs have many advantages over traditional nanocarriers. MOFs have high diversity than others by changing the kind of metal ions and ligands to design the suitable material for specific drugs. MOFs are easily modified and functionalized, for example, scientists can get targeting or stimuli-responsive carrier materials obtained by post-synthesis modification. MOF materials generally have a large specific surface area and porosity, thus providing high drug loading, MOF material is assembled through coordination bonds, so it is a biodegradable material that can be metabolized by the human body. MOFs can be stored stably for a long time.

2 The Synthesis of MOFs

2.1 Hydrothermal Method

The hydrothermal way is a making way in which metal ion sources and organic ligands are placed in a sealed pressure vessel together with water or other solvents to synthesize MOF nanoparticles under a high temperature and high-pressure environment. The MOFs produced by the hydrothermal method has the merits of complete grain development, small particle sizes, uniform distribution and high synthesis efficiency. The Kim research team synthesized rapidly and continuously many kinds of famous MOFs with homogeneous and heterogeneous compositions by a hydrothermal method using integrated microfluidic control[8]. However, researchers cannot detect the growth mechanism of crystals under that conditions.

2.2 Liquid Phase Diffusion Method

The liquid-phase diffusion method is to mix the metal ion source, organic ligand and diffusion solvent uniformly in a certain proportion, place it in the reactor, and stir for some time [9]. First, two layers of matter of different densities are formed, one is the precipitation solvent and the other is the product encapsulated in the solvent, which is separated by a layer of solvent. At the interface, crystal growth occurs after the precipitant gradually diffuses into the separation layer. Commonly used diffusion solvents include methanol, N,N-dimethylformamide, and the like. The biggest feature of this method is that it can be operated at room temperature which is defined as about 30 Celsius degrees, and the operation is simple. Yang et al. [10] synthesized hydrated copper sulfate and 4-amino-1,2,4-triazole by solution-phase diffusion method, by changing the ratio of metal to a ligand and adding a structure directing agent, to synthesize different materials spatial structured Cu-MOFs.

2.3 Microwave Method

The microwave method is to fully dissolve the metal ion sources and organic ligands, place them in a microwave-assisted synthesizer, and naturally cool them in the air to obtain crystals. In the

process of microwave heating, the molecular vibration increases which is caused by the high energy from the microwave, and the temperature of the inner and outer surfaces of the material rises at the same time, so the heating rate is faster. The microwave method can be considered a very important and fast way to achieve a quick synthesis of MOFs. This method can also control the size and morphology of MOF molecules well. The long research team prepared ZIF-7 and ZIF-60 nanoparticles by microwave super-assisted synthesis with several advantages including the reaction time is short, the synthesis method is simple, the size of the obtained nanoparticles is small, and the structure can be adjusted as they wish [11].

2.4 Mechanochemical Synthesis Method

The mechanochemical synthesis method does not require adding any solvent or only a litter amount of solvent which reduces the amount of the waste chemical material that can be eco-friendly. The metal ion sources and organic ligands are used as raw materials, and the ball milling reaction is carried out through a ball mill and the chemical conversion is carried out to obtain MOF nanoparticles and small molecular products. The mechanochemical synthesis method is relatively simple to operate, reduces the use of organic solvents, the synthesis method is environmentally friendly that do not produce waste or dangerous impurity, and can obtain quantitative yields in a short time (usually 10-20 min). Tao's research team synthesized Ni-MOF nanorods in only 1 min by adding organic solvents such as water and a small amount of ethanol to mechanical ball milling. After 180 min, the yield and crystallinity of Ni-MOF did not change significantly [12].

2.5. Ultrasound Synthesis Method

Sonochemistry is an interdisciplinary subject combining physical and chemical methods, and it has only attracted researchers' attention in recent years. The ultrasonic method is to use the micro-jet and shock wave emitted by the sound to induce or consolidate the force and dispersion force of the product. In this way, the morphology and structure of synthetic materials can be controlled, such as MOF nanosphere materials, MOF nanorod materials, MOF nanoring materials, etc. Its advantages are short reaction time and tunable crystal morphology.

3 The Application of MOFs in Drug Delivery

MOF has tunable pores, large specific surface area, controllable structure, and easy surface functionalization which provides conditions for the loading and controllable release of drug molecules. By controlling the structural assembly units, MOFs can have different structure-directed functions The weak interaction formed by the discrete coordination bonds, between metal ions or the clusters and organic ligands makes MOFs more easily biodegradable. These excellent properties make MOFs an intelligent and controllable nano-drug carrier with high research value and large potential.

In 2006, Férey et al. first claimed the application of MOF in drug delivery [13]. They synthesized MIL-100(Cr) and MIL-101(Cr) by hydrothermal method using chromium metal and chromium nitrate as ion sources and 1,3,5-trismellitic acid and terephthalic acid as ligands, respectively. (As shown in Figure 1), two Cr-based MOFs have a certain loading capacity for the antitumor drug ibuprofen (IBU). In SBF simulated body fluids, the loadings of MIL-100 and MIL-101 to IBU can reach 0.35 g g-1 and 1.4 g g-1 separately. However, the recognized toxicity of chromium-based materials to living organisms limits the further application of MIL-100(Cr) and MIL-101(Cr) as nano-drug carriers.

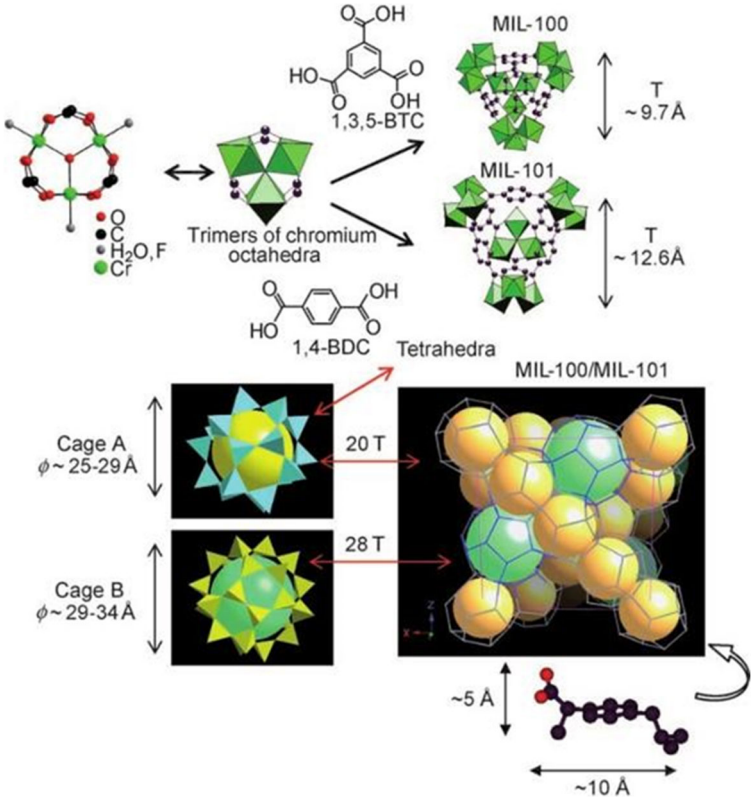

Fig. 1 Top: 3D schematic of MIL-100 and MIL-101, Bottom: 3D schematic for the framework of MIL100 and MIL-101 [13].

Flexible porous MOFs were used in drug delivery systems by Férey et al. in 2008 [14]. Using ferric chloride as the ion source and terephthalic acid as the ligand, they synthesized low-toxicity MIL-53(Fe) by a hydrothermal method. The flexibility of the MIL-53(Fe) framework makes its pore size match the magnitude of the drug molecule. In adaptation, the interactions between the drug molecule and the carrier are optimized, so that the drug can be released slowly with zero-order kinetics, and the bioavailability of the drug is improved.

3.1. PH value sensitivity MOFs-Based drug delivery systems

Telomeres at the ends of chromosomes can determine cell aging and death. During cell division, damaged telomeres are repaired by telomerase, allowing cells to proliferate indefinitely. In the process of division, cells need a lot of nutrients, which makes the growth environment of cancer cells in a state of hypoxia for a long time. The anaerobic respiration of cells will produce weakly acidic substances such as CO_2, resulting in a certain weak acidity in the surrounding tissue environment of cancer cells, so its pH value is lower than that of normal tissue cells. According to this property, pH-responsive nano-drug carriers can be designed. pH response is currently the most widely studied type of drug delivery system response

Fang et al. [15] employed a one-pot method to encapsulate the autophagy inhibitor chloroquine diphosphate (CQ) in ZIF-8 nanoparticles and modified it with polyethylene glycol-folate (FA-PEG) to enhance the carrier biocompatibility properties and targeting of drug effects (Figure 2). The binding of folic acid to the highly expressed folate receptor on the surface means the face of HeLa cells can accelerate the release of FA-PEG/CQ@ZIF-8 by cells, thereby promoting drug accumulation in HeLa cells which is a special kind of cell in the human body. In an acidic environment, ZIF-8 breaks down, prompting the rapid release of CO. By quantitatively measuring autophagy-related proteins and detecting autophagic flux in cervical cancer HeLa cells, it was found that the formation of autophagosomes and autophagic flux were significantly reduced after cells were cured with FA-PEG/CQ@ZIF-8.

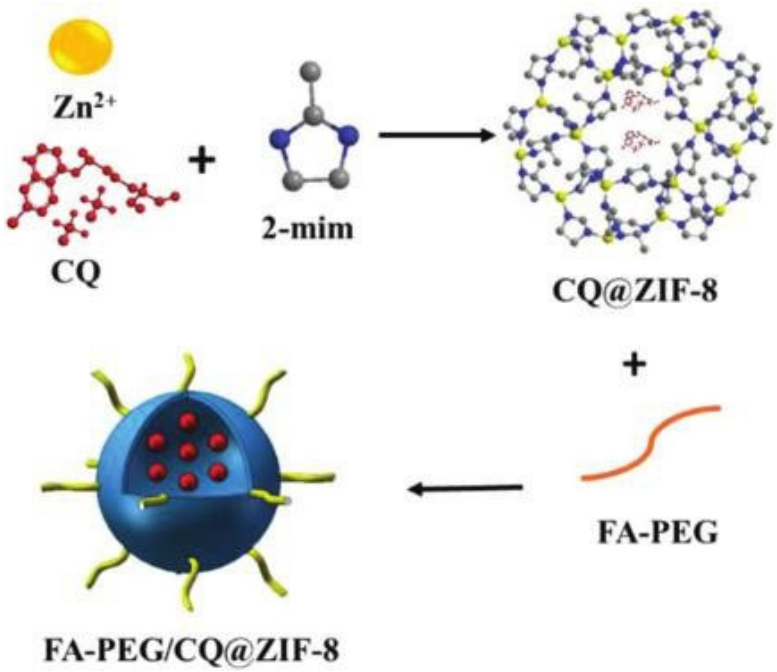

Fig. 2 The planned process for the making of FA-PEG/CQ@ZIF-8 nanoparticles [15].

3.2 The sensitivity of light MOFs-Based drug delivery system

Under the irradiation of specific wavelengths of light, controlled release of drugs can be achieved through molecular configuration changes, chemical bond cleavages (which connect the metal ions and the organic part), or photothermal conversion [16]. The light response can be controlled spatially and temporally with high precision and can penetrate deep into diseased tissue without causing damage to other tissues. The method of responding to exogenous light is usually to select photosensitive organic compounds as the ligands of MOFs. Liu et al. [17] designed a light-responsive nano-drug carrier made by hafnium ions and bis-(alkylthio) alkene (BATA), which is synthesized on a polyethylene glycol (PEG) surface which means that the face of the material. After modification and common loading with the photosensitizer chlorin e6 (Ce6) which can be an important material for the method and the drug doxorubicin (DOX) also is a very important reactant, it can be used for photoresponsive drug delivery under red light irradiation at 660 nm (Figure 3). NCP-Ce6-DOX-PEG generates singlet oxygen under the 660 nm red light.

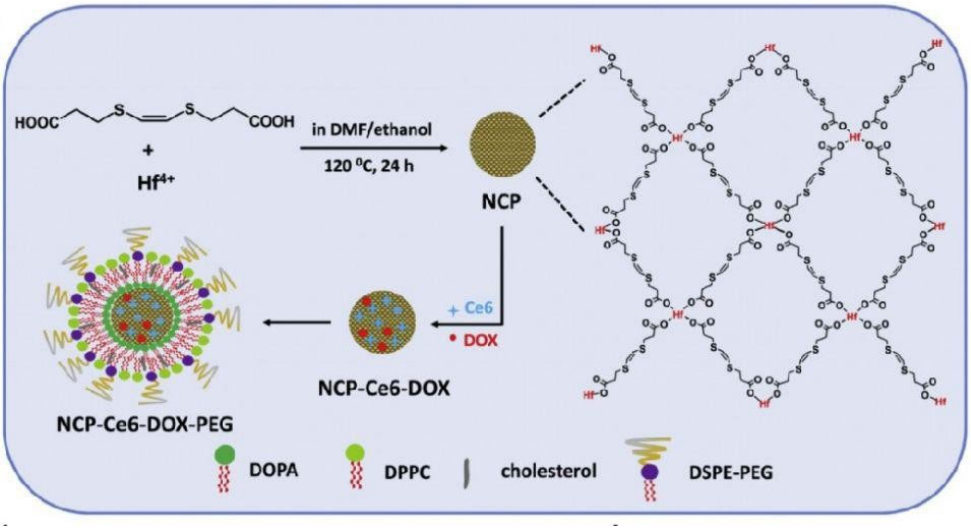

Fig. 3 The schematic graph for the making of NCP-Ce6-DOX-PEG nanoparticles [17].

3.3 Temperature stimuli-responsive MOFs-Based drug delivery system

Changes in ambient temperature can cause changes in the properties of thermally responsive materials, and some polymers can respond well near physiological temperatures Temperature stimuli-responsive drug delivery systems can be designed by modifying thermo-sensitive polymers onto the surface of MOFs. In addition, there are also some ions with temperature-sensitive properties. Nagata et al. [18] modified a temperature-responsive polymer (PNIPAM) onto the surface of UiO-66. When the temperature is lower than the cloud point of PNIPAM (about 31 °C), it is easily dissolved in water; when the temperature is increased, PNIPAM will form an aggregate (as shown in Figure 4). When the temperature changes, the conformation of PNIPAM grafted to the surface of MOF will change, so that the "on" (low temperature) and "off" (high temperature) states of the modified UiO-66 can be switched to realize the controlled release of the drug.

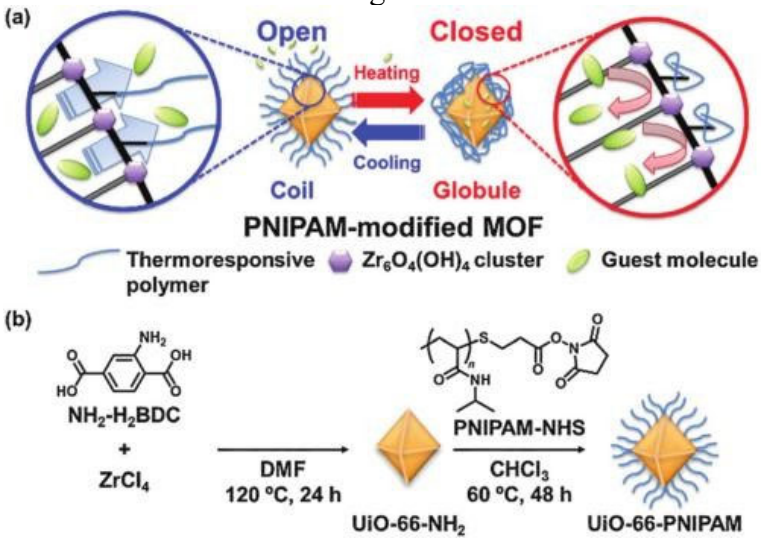

Fig. 4 (a) The planned graph of controlling release using MOF-PNIPAM at various temperatures, (b) making for MOF-PNIPAM (UiO-66-PNIPAM) [18].

3.4 The sensitivity of magnetic field MOFs-Based drug delivery system

Through the combination of MOF and magnetic materials or magnetic MOF, nano-drug carriers with magnetic responsive properties can be constructed. Under the interaction of an outward magnetic field, the drug can be targeted and delivered to the tumor lesions, resulting in drug release. In addition, magnetically responsive MOF nanocomposites can also be used for magnetic resonance imaging (MRI). Ke et al. [19] obtained Fe3O4@MIL-100(Fe) magnetic nanotubes by a step-by-step assembly method and obtained a magnetic stimulation-responsive drug delivery system by loading the drug ibuprofen (IBU). The Fe3O4 magnetic core imparts high magnetic properties to the drug carrier-controlled drug release. The high porosity of the MOF shell ensures a good load capacity (0.31 gg-1) for IBU. In PBS 7.4 buffer solution at 37°C, the sustained release of IBU can be achieved for 70 h.

4 Summary

At now, the application of MOF materials in biomedicine has received more and more attention. When its particle size is regulated to the nanoscale, nano-MOFs can be used as effective nanocarriers for imaging, chemotherapy, photothermal therapy or photodynamics. The treatment provides medicines. MOFs are considered promising nano-drug carriers due to their structural diversity, tunable pore size, ultra-high specific surface area, and ease of functional modification. In this article, the synthesis and application of MOFs in drug delivery systems were introduced. The device and development of stimuli-responsive nano-drug carriers is an important topic in the area of cancer treatment at present. Due to the ease of functionalization of MOFs, responsive drug carriers based on MOFs have received extensive attention. Stimuli-responsive anticancer drug carriers are a series of

materials that can change their physicochemical properties or conformation under specific stimuli. They are usually designed based on the unique microenvironment of the tumor. In addition, tumor cells often need to secrete the necessary life activities. Some specific enzymes lead to overexpression of certain enzymes. n addition, tumor cells often need to secrete some specific enzymes to complete the necessary life activities, which leads to the overexpression of some enzymes. According to these special microenvironmental forms at the tumor site, by rationally designing drug carrier materials with stimuli-responsive functions, the controlled release of drugs at the tumor site can be achieved, the circulation time in the body can be prolonged, and the anticancer effects of the drug can be improved a lot. Based on the above studies and discussions, this paper suggests based on the sensitivity of magnetic fields to produce drug delivery systems that have great potential despite less research today. Compared with other kinds of stimuli-responsive drug delivery systems, based on the sensitivity of magnetic fields to produce drug delivery systems are easier to implement accurately because they are more straightforward. The pH stimuli-responsive drug delivery system may not be targeted because the human body can not produce such high pH changes. Also, the human body can not experient temperature change which temperature a stimuli-responsive drug delivery system. And the paper believes it is hard to make a bulb in the body, so the light stimuli-responsive drug delivery systems may also not be suitable for use in drug delivery. Therefore, it is believed that a new Fe-based MOF can be designed and modified to have stronger ferromagnetism to achieve magnetic stimulation-responsive drug delivery.

References

[1] Delorme V, Lichon L, Mahindad H, et al. Reverse poly(epsilon-caprolactone)-g-dextran graft copolymers. Nano-carriers for intracellular uptake of anticancer drugs [J]. Carbohydrate Polymers. 2020, 232: 115764.

[2] Karewicz A, Bielska D, Gzyl-Malcher B, et al. Interaction of Curcumin with Lipid Monolayers and Liposomal Bilayers[J]. Colloids & Surfaces B Biointerfaces, 2011, 88(1): 231-239.

[3] Du C, Liang Y, Ma Q, et al. Intracellular tracking of drug release from pH-sensitive polymeric nanoparticles via FRET for synergistic chemo-photodynamic therapy [J]. Journal Of Nanobiotechnology. 2019, 17(1): 113.

[4] Zhang E, Xing R, Liu S, et al. Advances in chitosan-based nanoparticles for oncotherapy [J]. Carbohydrate Polymers. 2019, 222: 115004.

[5] Senapati S, Sarkar T, Das P, et al. Layered Double Hydroxide Nanoparticles for Efficient Gene Delivery for Cancer Treatment [J]. Bioconjugate Chemistry. 2019, 30(10): 2544-2554.

[6] Huang H-C, Barua S, Sharma G, et al. Inorganic nanoparticles for cancer imaging and therapy [J]. Journal Of Controlled Release. 2011, 155(3): 344-357.

[7] Yaghi O M, Li G M, Li H L. Selective binding and removal of guests in a microporous metal-organic framework [J]. Nature. 1995, 378(6558): 703-706.

[8] Kim J, Cho H-Y, Ahn W-S. Synthesis and Adsorption/Catalytic Properties of the Metal Organic Framework CuBTC [J]. Catalysis Surveys From Asia. 2012, 16(2): 106-119.

[9] Chen X Y, Zhao B, Shi W, et al. Microporous metal-organic frameworks built on a Ln3 cluster as a six-connecting node [J]. Chemistry Of Materials. 2005, 17(11): 2866-2874.

[10] Yang E, Wang X, Zhang C, et al. Three new MOFs with unusual CuII6 cluster, linear CuII chain and triangular CuII3 core motifs tuned by sulfonate group: Synthesis, structures and magnetic properties [J]. Science China-Chemistry. 2013, 56(4): 465-474.

[11] Ni Z, Masel R I. Rapid production of metal-organic frameworks via microwave-assisted solvothermal synthesis [J]. Journal Of the American Chemical Society. 2006, 128(38): 12394-12395.

[12] Beldon P J, Fabian L, Stein R S, et al. Rapid Room-Temperature Synthesis of Zeolitic Imidazolate Frameworks by Using Mechanochemistry [J]. Angewandte Chemie-International Edition. 2010, 49(50): 9640-9643

[13] Cai W, Chu C-C, Liu G, et al. Metal-Organic Framework-Based Nanomedicine Platforms for Drug Delivery and Molecular Imaging [J]. Small. 2015, 11(37): 4806-4822.

[14] Horcajada P, Serre C, Maurin G, et al. Flexible porous metal-organic frameworks for a controlled drug delivery

[J]. Journal Of the American Chemical Society. 2008, 130(21): 6774-6780.

[15] Adhikari C, Das A, Chakraborty A. Zeolitic Imidazole Framework (ZIF) Nanospheres for Easy Encapsulation and Controlled Release of an Anticancer Drug Doxorubicin under Different External Stimuli: A Way toward Smart Drug Delivery System [J]. Molecular Pharmaceutics, 2015，12(9): 3158-3166.

[16] Li H, Chen C, An Q, et al. Photo-responsive nanoparticles for beta-lapachone delivery in vitro [J]. Chinese Chemical Letters. 2018, 29(9): 1347-1349.

[17] Liu J, Yang G, Zhu W, et al. Light-controlled drug release from singlet-oxygen sensitive nanoscale coordination polymers enabling cancer combination therapy [J]. Biomaterials. 2017, 146: 40-48

[18] Nagata S, Kokado K, Sada K. Metal-organic framework tethering PNIPAM for ON-OFF controlled release in solution [J]. Chemical Communications. 2015, 51(41): 8614-8617.

[19] Ke X, Song X, Qin N, et al. Rational synthesis of magnetic Fe3O4@MOF nanoparticles for sustained drug delivery [J]. Journal Of Porous Materials. 2019, 26(3): 813-818.