Application and Preparation of Metal-Organic Frameworks for Drug Delivery

Jun Ma

Hong wen school 266000 Qingdao, China

Corresponding author: 100055@yzpc.edu.cn

Abstract. Metal-organic frameworks (MOFs) are attracting the attention of researchers because of their special structural composition and performance, especially for their potential applications in drug loading and controlled release. Compared to conventional drug carriers, metal-organic framework materials have high stability, good efficacy, low toxicity, side effects, and simple synthesis, making them valuable in clinical medicine and drug delivery. In this paper, the preparation: of the steam-assisted method, hydrothermal synthesis method, and green and time-saving method and applications in anti-drug cancers be invested. The three main factors that affect the ability of drug delivery mentioned in this paper are pore size surface area and temperature. MOFs will be the most important material for drug delivery because of their excellent performance and special composition structure also because the selection of appropriate metal-organic frame material carriers is a very critical step to improve the utilization rate of these drugs, which has important practical significance.

Keywords: Metal-organic frameworks; drug delivery; application; preparation.

1. Introduction

Currently, small molecule drugs are often limited by their non-specific distribution throughout the body, resulting in high doses, rapid clearance, poor pharmacokinetics, and high side effects. The term "drug carrier" describes a system that can alter how drugs enter the body and how they are distributed there, control how quickly they are released, and deliver drugs to specific organs. Drug carrier substances are crucial to the study of controlled release preparations. Now there have zeolites, microcapsules and microspheres, nanoparticles, and liposomes. These are more mature materials. In the scientific world, the study of metal-organic frameworks as drug transporters has gained a lot of attention. It has a series of advantages such as stable structure, large specific surface area, variable hole size, and flexible control of structure internal characteristics by changing ligand functional groups, so it is widely used in various fields, such as carbon dioxide capture, catalyst, and so on. In particular, it has shown many outstanding advantages as a drug carrier, such as the selection of appropriate gold in the process of disease treatment It is an organic frame material used as a carrier to load drugs, and the carrier can be delivered to either orally or intravenously into the human body. The process of drug absorption, release, and metabolism in the human body can all be improved thanks to the carrier's protection, but pharmaceuticals themselves can also be improved.

Horcaijada P, [1] first published in the prestigious journal Angew: Chem.In.Ed., two cases of microporous metal-organic frame materials were reported and their effectiveness was studied in controlled drug delivery, using benzene dicarboxylic acid and homobenzic acid and Cr (I), respectively, the metal-organic frame with the high surface area was prepared under solvent thermal condition frame materials MIL-101 (Cr) and MIL-100 (Cr) (Stanemuir)Are 5510m^2/g, 3340m^2 /g), and they were used as drug carriers to study the results, now these two cases of material can effectively load the anti-inflammatory drug ibuprofen, the load is respectively1.376g·g^{-1} and 0.347g·g^{-1}, which are much higher than mesoporous silica. the researchers speculate, maybe the high surface area of the material as well as ibuprofen, the reason for the strong interaction between the hydroxyl group on the Finn molecule and the structure, slow release time. Respectively for about 6 days and 3 days, with a good release effect. The application of MOF materials in drug delivery has been successfully opened, in addition, it can lessen the harmful and adverse effects of medications on the human body while reducing drug consumption during drug delivery. It draws a lot of attention to research its use in drug

loading due to its various benefits. For another purpose, MOF-5 was made using Zn(NO)-6H2O, terephthalic acid, and triethylamine before capsaicin and 5-fluorouracil were added a variety of preparation methods of MOFs for drug transport are described, and their application in currently difficult to treat diseases and their impact on performance are described.

2. Preparations of MOFs

2.1 Steam-Assisted Convention Method

The steam-assisted method avoids the use of toxic gases for example HF and has a higher capacity and efficiency than the conventional hydrothermal method. developed a novel synthesis method that can prepare MIL-100(Cr) via steam-assisted conversion and avoids the usage of HF with a curate reaction time (9 h) and excellent yield (96%), a higher selectivity of N2 from CH4. This method is advantageous and suitable for green large-scale production of MIL-100 (Cr) [2].

2.2 Hydrothermal Synthesis

Hydrothermal synthesis is a method of preparation of materials through dissolution and recrystallization of powders in a sealed pressurized container using water as a solution. The powder produced by hydrothermal methods is superior to other ways of powder production because it has complete grain development, tiny particle size, uniform distribution, light particle agglomeration, inexpensive raw materials, and easy access to adequate stoichiometry and crystal morphologies. Most researchers manufacture MIL-100 (Cr) using the laborious hydrothermal synthesis process, which takes 96 hours and uses HF as a mineralizer. HF is extremely damaging to the environment and human health. In addition, handling the used liquid that contains fluoride ions causes secondary contamination.

2.3 Green and Time-Saving Method

This method does not use HF or other toxic agents in the preparation process and is faster and more environmentally friendly than conventional methods. Because of its large surface area, distinctive porous structure, high stability, and unsaturated metal site, the MIL-100 (Cr) is a crucial element of organic metallurgy. As illustrated in Fig. 1, this material was typically created by adding HF and solvent and allowing it to crystallize for a lengthy period (96 h). In this study, we demonstrate the rapid (15 h) crystallization of MIL-100 (Cr) under HF- and solvent-free conditions. The resulting MIL-100 (Cr) had a large surface area and plenty of porosity [3].

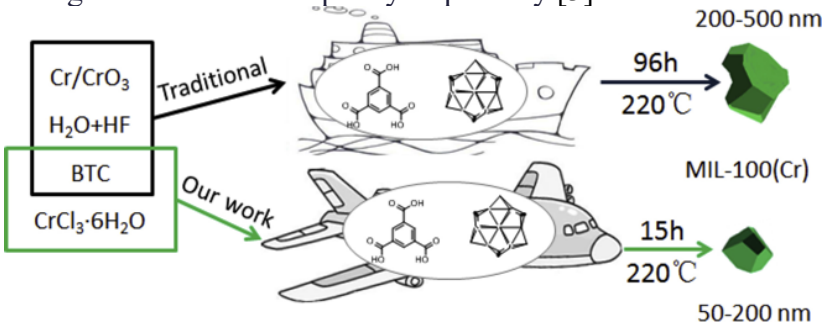


Fig. 1 The comparison of the green step and the traditional step for making MIL-100(Cr) [12].

3. Factors Affecting Drug Delivery using MOFs

3.1 Sizes of the Unblocked Window Openings (Pore Size)

With the increase in pore size, the adsorption capacity increases, and the pore size increase will cause more adsorption. For example, MIL-100 (Cr)has MIL-100 and MIL-101 available in two types of spherical cages. While the latter type of cage has both pentagonal and hexagonal windows, the

former type only has pentagonal windows. The significantly different drug adsorptions in MIL-100 and MIL-101 are explained by the dimensions of the free window apertures [in MIL-100, 4.8×5.8 A (pentagonal), 8.6 A (hexagonal); in MIL-101, 12 A (pentagonal), 14.7×16 A (hexagonal)]. The amount of drug loaded has nothing to do with metal ions, only depends on the pore, Channel size: sustained release experiments in simulated body fluids showed its load Ibuprofen release time was about 21 days, compared with mil-101 (Cr) and MIL-100(Cr). Compared to them, although the load is lower, the release time is longer, mainly because In mil-53 flexible structure, the pore size is small and the hydroxyl groups on ibuprofen are different from the carboxyl group on MIL-53 producing a strong interaction [6].

3.2 Surface Area

A solid object's surface area is a measurement of the overall area that the object's surface occupies. When curved surfaces are present, the mathematical definition of surface area for MOF-74-Fe is much more complicated than the definition of an arc length for a one-dimensional curve or the definition of surface area for multiple surfaces, where the surface area is equal to the sum of the areas of its faces. The researchers speculate that it could be the material's high specific surface area and ibuprofen cause of strong force between hydroxyl group and structure on fenn molecule, slow release time, It was about 6 days and 3 days respectively, and had a good release effect [7,8].

3.3 Temperatures

Adsorption is usually exothermic, so increasing the temperature will reduce the amount of adsorption as soon as adsorption equilibrium is reached. However, at low temperatures, some adsorption processes cannot reach equilibrium in a short period and increasing the temperature will speed up the rate of adsorption and increase the amount of adsorption when Fe_3O_4 at MIL-100(Fe) in a saline environment with a simulated temperature of 37 °C the complete release time is 22 days, and the sustained release effect is good, and the peak concentration of blood drug get effective prevention and treatment, and then improve the therapeutic effect, both have a good target load [9].

4. Applications

4.1 Non-steroidal anti-inflammatory drug carrier

Non-steroidal anti-inflammatory drugs (NSAIDs) refer to a class of anti-inflammatory, antipyretic, and analgesic without glucocorticoid action in the drug field. At present, the treatment of steroidal drugs used in the clinic is a popular pain drug vien has selective cyclooxygenase inhibitors and non-selective cyclooxygenase inhibitors, previously meloxicam, celecoxib, and nimesulide are common, the latter mainly Aspirin, acetaminophen, indomethacin, ibuprofen, etc. Non-seedling class solution [10]. Heat analgesics have been widely used in the world. To improve the efficacy of drugs, it is particularly important to select a suitable drug carrier for prolonging the efficacy time MIL-100-Cr has high thermal stability and multiple selectivities. In 2012, [11] MOF-5 was prepared by direct addition of triethylamine Fluorouracil was used as a model drug, and activated MOF-5 was used as the drug carrier The loading capacity was $0.315 g \cdot g^{-1}$, in vitro the cumulative release was 73.8%, and S-FU, activated MOF-5, activated after the MOF-5 loaded 5-FU drug sample (MOF-5-FU) was used as the target, respectively. In vitro cytotoxicity of activated MOF-5 was studied in PC-12 cells, for 48h. The results showed that 5-FU could be protected by an activated MOF-5 vector Prolong the action time of S-FU drugs with target cells in vivo and reduce the toxic and side effects the results showed that the activated MOF-5 had good biocompatibility and was promising. Further study to become a good carrier of anti-tumor.

4.2 Anticancer Drugs

It is well known that malignancy is a disease with a high mortality rate and that the incidence is

rapidly increasing. However, there has still been no major progress in the effective treatment of the disease**.** Research has been conducted on anti-cancer drugs, such as common anti-tumor drugs such as caustic agents, anti-cancer antibiotics, anti-cancer botanicals, hormones, and anti-metabolites. However, as some of these drugs are poorly targeted, they cannot effectively deliver to the day marker cells in the human body, resulting in poor efficacy. To eliminate these limitations, appropriate drug carriers can be used to effectively achieve therapeutic effects, of which 5-fluorouracil (S-FU)is a clinically used anti-metabolic antitumor drug for a variety of cancers, including gastric, intestinal, and liver cancers. A functional drug carrier based on Mil-101 nano-materials, which has a multifunctional surface structure that prevents the early release of the drug in vivo. Pulmonary pick-up to the MOF body teaches DOX drug satiation. It grows in the lung garden with few side effects It is a biocompatible and biologically healthy MOF material drug in solution in my body and could be a promising platform for future therapeutic agents. In 2016, Tais et al. 's micro anti-threat device made by using the quicksand of the road has been developed**.** Nano-UiO-66-2-NH_2 and nanoparticles were used for the preparation of 5-fluorouracil**.** The results of the material loading and releasing experiments show that the maximum negative self is 27W % at a temperature of 37 degrees Fahrenheit. Nano-UiO-66-2-NH_2 negative I S-FU drug dissolved in PBS**,** can maintain good continuous release, speed constant number up to 0.27h [12].

4.3 Other Drug Carrier

Procainamide hydrochloride is an anti-arrhythmic drug suitable for paroxysmal heart, Tachycardia, frequent premature arrhythmia (with good effect on ventricular premature arrhythmia), atrial frontal movement and atrium Flapping, often used interchangeably with quinidine, but has a short half-life, leading to application. Subject to restrictions. In 2009, An J et al. reported a novel combination of adenine and p-biphenyl biphenyl. Metal-organic frame materials with biological activity were synthesized by using formic acid as a gold mixed ligand (Bio-MOF-1). The material was loaded with procaine hydrochloride glue drug, loaded reached 0.22 GG1, and the in vitro release grade test showed that lucaine hydrochloride was the drug. It was completely released in 0.1molL of PBS buffer solution concentration PH=7.4 for 72h, and the slow release process of procaine hydrochloride gum was tracked by HPLC. The contrast experiment of drug dialysis in water equipped with the instrument has 20% drug release on the whole. During drug release, the characterization showed that the frame of the material remained complete, It is proved that the sustained release effect and stability of the carrier are good for prochloric acid to provide a basis for the application and promotion of amine.

4.4 Traditional Chinese Medicine (TCM)

Many potential herbal monomers have poor solubility, short half-life, and suboptimal metabolism in vivo, limiting their clinical application. Routine administration often leads to increased toxicity and repeated dosing within a relatively short time after administration [12]. As a result, sustained release formulations have attracted widespread interest. MOFs are an ideal carrier material for sustained release drugs because of their high drug load, in vivo degradability and ease of modification. There are often several stages of drug release from the interior of the material. As shown in Fig.2, first, a portion of the drug on the surface of the material is dissolved and released, then the drug inside the material gradually diffuses outwards with a concentration gradient, and as the skeleton collapses, the drug enclosed in the cavity of the material is released. In addition, a portion of the drug may have some affinity to the material (hydrogen bonding, π-π conjugation, electrostatic adsorption) and this portion of the drug is eventually released. With the continuation of several stages, a continuous slow release of the drug is eventually achieved. Latifi et al synthesized MIL-53-coated thymol, showing high loading capacity and controlled release. The nano platform allowed the continuous release of thymidine over 24 hours. The study also showed different delivery properties of three MOFs to the thymus and found that the delivery effect was significantly correlated with the pore size of the MOFs. In addition, the tunable and easily modifiable structure of MOFs allows for programmable and personalized drug release patterns. Structural modification of MOFs to alter the affinity between drug

and carrier can effectively control the drug release rate; modification of the pore size of MOFs is another strategy to modify the drug release rate. orellana-Tavra et al [12] functionalist Zr-MOFs by introducing -Br, -NO_2 and -NH_2 into the MOFs and could observe that each MOF has a completely different release behavior, with the -NH_2-modified MOFs being able to release cinnamic acid slowly and continuously over 15 days, whereas the other 2 molecularly modified MOFs were unable to release all cinnamic acid completely. Molecular modification is one of the strategies to effectively adjust the rate of drug release. Researchers need to consider the affinity between the molecule and the drug to obtain the desired release behavior if the irreversible binding between the molecule and the drug can lead to dead adsorption, making the encapsulated drug not fully released and resulting in waste. Therefore, the modifying groups should be chosen appropriately according to the characteristics of the drug and the needs of the disease. On the other hand, MOFs consist of metal ions and organic ligands, and there is often a coordination bond or force between the herbal components and the metal ions or ligands in the MOFs. This force shifts the drug to its stable isomer or complex, thus enhancing its stability.

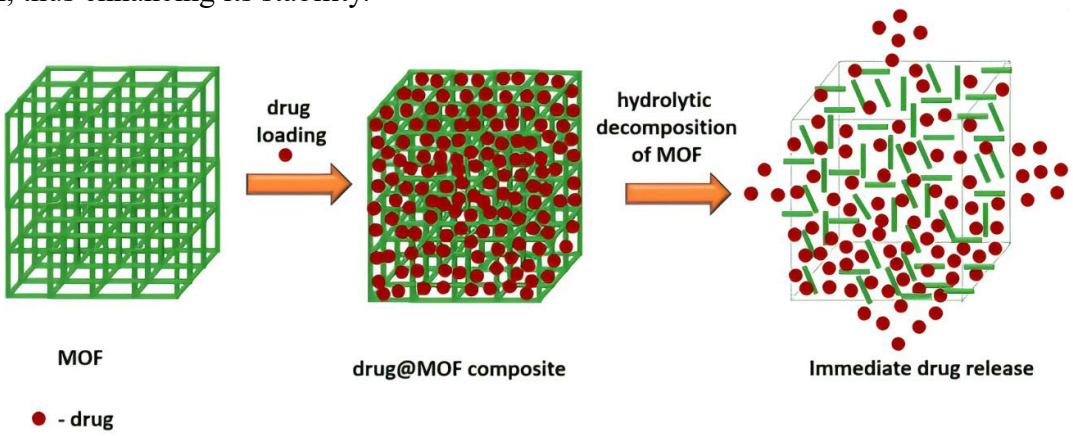


Fig. 2 A fix for insoluble drugs [13].

5. Summary

In summary, metal-organic framework materials used as drug carrier loading show the advantages of high biological safety, high drug load, strong targeted transport, easy control of release and low price. for some drugs that are unstable, poorly targeted and highly toxic in human body, the selection of appropriate metal-organic frame material carrier is a very critical step to improve the utilization rate of these drugs, which has important practical significance. The preparation of the steam assisted method, hydrothermal synthesis method and green and time saving method and applications in anti-drug cancers be invested. The hydrothermal synthesis method is a traditional method for preparation of MIL-100(Cr), but now because of the HF used in method and take 96 h so researchers developed green and time saving method it only take 15h can finished, when it used for anti-cancer it shows excellent performance in drug carrying and goes to the place more faster than traditional drug carrier (zeolite).Compared with other drug carrier, a metal organic framework materials research is still in the stage step, all aspects of clinical trials are still not mature, therefore, researchers need to continue to study in this field, its safety used in the treatment of diseases, prevention of skilled play an important role, is a kind of is expected to achieve critical applications in the field of drug delivery and medical drug carrier.

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