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Advanced metal-organic frameworks materials for drug delivery

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Abstract. Metal-organic frameworks (MOFs) are porous crystalline polymers composed of coordination reactions between organic ligands and metal ions. They have high loading capacity, high specific surface area, high flexibility and a variety of different material preparation options. In different fields, MOFs also play different roles. It has been employed as a promising material for efficient drug delivery systems due to its unique characteristic and structures. This paper discusses the application of nanoscale MOFs (NMOFs) in the field of drug delivery and introduces its advantages and disadvantages compared with traditional DDSs materials, as well as different methods used as carriers for different therapeutic gases (CO, NO, O_2), thereby achieve targeted delivery of drugs. The different biological toxicity, structural stability, morphology under physiological conditions, and control of pore channels caused by different metal linkers and organic ligands are studied and analyzed, which provides the future development of new drug-carrying systems and MOFs in other drug fields. Insights and guidance.

Keywords: MOFs, NMOFs, Drug Delivery.

1. Introduction

Drug delivery is a process that is highly integrated by dosage form and route of administration, while the latter itself is sometimes considered as the definition of drug delivery. In order to develop suitable drug carriers, efforts have been devoted to studying coordination compounds, including discrete coordination compounds and coordination polymers (CPs). In recent years, the application of polymeric and discrete coordination complexes in drug delivery has been highly valued by researchers, and a large number of results have been achieved.

The drug delivery system (DDS) materials are divided into organic DDS and inorganic DDS [1]. Organic DDS (polymer systems) generally have good biocompatibility. However, they are not able to control the release without well-defined porosity. The inorganic DDS materials (microporous zeolites) have the ability to control the release of drug molecules, but the loading capabilities restrict their application in DDSs. The coordination polymers are the hybrid of the two traditional materials, known as the MOFs.

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Metal-organic frameworks are composed of polydentate organic ligands containing oxygen and nitrogen (mostly aromatic polyacids and polybases) and transition metal ions. The MOFs have a high specific surface area and are easy for functional modification. They have been widely used in gas storage/separation, catalysis, sensing, bioimaging, and drug delivery in recent years. Especially in disease diagnosis and treatment, MOFs have shown great advantages. The first type of MOFs was synthesized as early as the mid-1990s, but their porosity and chemical stability were not high [2]. Therefore, researchers began to study coordination polymers formed by new cationic, anionic, and neutral ligands. Currently, many metal-organic framework materials have been synthesized, mainly based on carboxyl-containing organic anion ligands or used together with nitrogen-containing heterocyclic organic neutral ligands.

Furtherly, nano-drug carriers can improve the metabolic properties of drugs by virtue of their size advantages; they use the active uptake of cells to improve the bioavailability of drugs and improve the solubility and stability of drugs by embedding hydrophobic drugs; they can also effectively penetrate the body barrier and improve the bioavailability of drugs, achieving efficacy and targeted delivery. NMOFs maintain the regularity of traditional framework structures and possess special properties of nanoparticles, such as high permeability and long retention (EPR) effect [3,4]. In light of the advanced research on the above materials, in this paper, the advanced MOF materials and the application of MOF in the fields of assisting the targeted delivery of drugs as auxiliary materials, ideal carriers for therapeutic gases, and optimizing the performance of drug carriers are introduced and analyzed in detail. This paper provides a design strategy for the application and design of MOF and NMOF materials in the field of DDS in the future, which is of great significance to the development of related industries and the solution of problems related to MOF materials and DDS in the future.

2. Materials for drug delivery

2.1. MOFs

Metal ions and organic ligands are joined together by chemical coordination bonds to form porous, crystalline MOFs. Because of its special bonding method and structure, such compounds' porosity, size, shape, and chemical composition are very easy to change. In other words, it is very flexible. Owing to their advanced characteristics, in the past few years, this large family has rapidly emerged in the field of drug delivery, and their applications in biomedicine have attracted much attention. In particular, the nanosized MOFs can be loaded with various disease treatment-related guest substances, such as molecules, proteins, enzymes, genes, photosensitizers, dyes, nanoparticles, etc., and their composites can also give full play to the guest substances for disease treatment.

Moreover, regarding the composition of the composite, the selection of metal ions is very flexible, and different joints and metal constructions will also change its multiple structures and properties. The coordination bond is fragile and precise because the linker and the metal ion are combined through the coordination bond, so the MOF also has high biodegradability. As for the linker of organic matter, there are also many choices, and different choices will also lead to the synthesis of MOFs with different properties and application fields. For example, MOFs with high metabolic scavenging capacity under specific conditions have always been paid attention to and studied because they are usually characterized by low toxicity. In realit, there is an endless variety of ligands and metal ions. Thousands of MOFs have been developed and manufactured using various mixtures. However, when MOFs are used in DDSs, biocompatibility and toxicity are crucial, and in any case, the synthesis of linkers and metals should be done without toxicity [5].

In 2006, Horcajada et al. constructed two cubic zeolites MOFs, MIL-100, and MIL-101, which exhibited a drug loading capacity of up to 60% for ibuprofen was significantly better than the loading capacity of traditional carriers, demonstrating for the first time that the high potential of porous MOFs for drug loading [6]. Since this study was controversial due to the known toxicity of metallic chromium, the team then synthesized two low-toxicity porous iron carboxylate MOFs with loadings of the

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chemotherapeutic drug busulfan up to 25% in rigid mesoporous MIL-100, 5-fold and 60-fold higher than that of the polymer nanoparticle system and liposome, respectively, MIL-101-NH_2-loaded azidothymidine triphosphate and cidofovir reached an unprecedented 42 wt%. Since then, the research on using MOF as a drug carrier has developed rapidly.

2.2. NMOFs

Special characteristics of nanoparticles, such as high permeability and lengthy retention (EPR effect), are present in nanoscale MOFs. When compared to conventional nanoparticle systems, they can efficiently limit drug loss by external biological processes by separating guest molecules in the framework, allowing the diffusion of tiny molecules. The performance of drug carriers can be optimized by surface chemical modification of NMOF. For example, using the amphiphilic self-assembly behavior of PEGylated liposomes to encapsulate NMOF with Mn as the metal center can effectively improve its stability in the physiological environment. It is a visualized nanocarrier integrated with drug delivery. In addition, through the PEG-binding ligand AA (Anisamide) on the surface of the carrier, the efficient binding of δ receptors to most cancer cells can be achieved, and the targeted delivery in the physiological environment can be completed. The results show that compared with NMOF without AA, the particles are easier to enter breast cancer MCF-7 cells by endocytosis [7].

In disease treatment, NMOFs are the most widely used material for drug delivery. Due to the structural diversity and porosity, a variety of drug delivery methods can be designed based on their unique characteristics, for instance: i.) some carboxyl-containing or nitrogen-containing heterocyclic drugs can be directly used as ligands to synthesize NMOFs; ii.) The surface of NMOFs can be further modified for biocompatibility and targeting. After reaching the targeted tissue, the drug can be released by slow degradation of NMOFs or diffusion from the pore structure.

NMOFs can overcome the drug delivery limitations of many drugs, such as poor water solubility, instability, and drug distribution problems. After reaching the targeted tissue, the drug can be released through slow degradation of NMOFs or diffusion from the pore structure.

3. Application of MOFs in drug delivery processes

3.1. Diabetes treatment

The number of people with diabetes worldwide has been increasing in recent years. With current medical technology, type 1 diabetes can only balance the patient's blood sugar by injecting insulin, but patients are more prone to hypoglycemia, which can lead to dangerous occurrences. Therefore, it is particularly important to develop a new insulin delivery system. Glucose responsiveness based on GO_x is the most studied insulin delivery system. Duan et al. self-assembled insulin-GO_x/ZIF-8 from a mixture of Zn(II), insulin and GO_x, thereby creating an advanced glucose-responsive system. Insulin is released when ZIF-8 is broken down because when blood sugar in the body is too high, GO_x catalyzes them into gluconic acid, which changes the local pH in the blood, and the change in pH causes ZIF-8 a series of reactions. When blood glucose concentrations normalized, GO_x no longer catalyzed more glucose, and local pH changes reduced insulin release from ZIF-8, thereby avoiding hypoglycemia [8].

One frequent and deadly consequence of both type 1 and type 2 diabetes is diabetic foot ulcers. Diabetes is linked to ischemia, neuropathy, and deformity, which increase the chance of developing foot ulcers and decrease the probability that the ulcers will heal. Diabetes-related foot ulcers are more likely to necrosis, infection, and involvement of deep tissues like bones because of the diminished blood flow to the lower limbs. Xiao and his co-workers [9] developed FA-modified Cu-MOFs (F-HKUST-1) for treating chronic nonhealing wounds. F-HKUST-1 can promote wound healing. Angiogenesis can be facilitated because FA is added during the synthesis of HKUST-1 to slow the release of Cu(II) ions, thereby increasing the speed of wound healing and reducing toxicity.

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3.2. Cancer treatment

Cancer treatment often needs to face the extremely complex tumor microenvironment. The tissue area of the tumor is more acidic than normal tissue, so the construction of a pH-responsive carrier can achieve targeted drug release at the tumor site, thereby increasing the effective concentration of the drug [10,11]. Recently, pH-sensitive ZIF-8 nanoparticles prepared by Zn^{2+} and 2-methylimidazole have made great progress in the field of responsive drug delivery. When constructing the ZIF-8-loaded anticancer drug doxorubicin (DOX) system, the photothermal responsive polydopamine (PDA) and the phase-change material n-tetradecanol (phase- Change material, PCM) are wrapped on the surface of ZIF-8 to form a composite carrier with a core-shell structure, which not only combines photothermal therapy and chemotherapy but also reduces the cytotoxicity caused by the rapid disintegration of ZIF-8 under acidic conditions [12]. After PDA-PCM@ZIF-8/DOX reaches the acidic tumor site, the ZIF-8 skeleton encapsulated in the polymer slowly disintegrates to complete the drug release. The insoluble PCM in the physiological environment melts and releases the DOX encapsulated in the particles and finally achieved precise drug release under optical control. The results showed that the PCM layer effectively slowed down the release of DOX under a neutral environment and reduced the cytotoxic behavior in a normal physiological environment, while under the dual stimulation of acid and optical stimulation, the drug release amount reached 78%. In vivo model experiments have shown that the dual-responsive particles are more effective in killing tumors than traditional photodynamic therapy or chemotherapy. This achievement opens up a new field of targeted drug release using NMOF as a carrier.

In addition to the use of targeted drug release methods, the treatment of malignant tumors (cancer) is still limited, and many differences also affect the treatment rate of cancer. GO_x-based starving therapy has great potential for tumor therapy. However, the stability of GO_x itself is very poor, and it is difficult to achieve efficient and long-distance delivery in vivo. Since tumor cells have a well-developed internal defense system, This has led to the delay in applying GO_x to real cancer treatment. Fortunately, as novel DDSs, MOFs have good designability, modification, and biocompatibility, which can effectively fix protein structures and prevent their deformation in many harsh environments, thereby greatly expanding proteins such as enzymes. Zhang et al. filled GO_x and prodrug tirapazamine with ZIF-8 as a carrier and wrapped a layer of erythrocyte membrane on the outside. The large cavity of ZIF-8 can significantly improve the loading efficiency of GO_x and can protect GO_x from leakage, deactivation caused by external catalysts, and loss of drug components [13]. The outer erythrocyte membrane can ensure that drugs avoid screening the immune system and prolong blood circulation. When GO_x is delivered to the tumor center, it can also absorb intracellular oxygen and glucose to make the surrounding area of the tumor hypoxic to strengthen the effect of tumor treatment.

3.3. Therapeutic gas delivery

In nature, there are some gases that are considered to have great potential for solving intractable medical diseases due to their various biological effects [14]; they are nitric oxide (NO), carbon monoxide (CO), hydrogen sulfide (H_2S), and Oxygen (O_2). They are also called therapeutic gases. For example, NO and H_2S usually have strong biological cytotoxicity at high concentrations, so in the field of oncology, they are often used for cancer treatment in animal models; delivery of large amounts of O_2 to tumor sites can effectively enhance the effect of drugs to kill cancer cells; Severe anemia [15]and infectious necrosis of soft tissue can be treated with hyperbaric oxygen therapy [16], an FDA-approved treatment option. The reason why these therapeutic gases have attracted the attention of researchers and are considered to be far superior to other classical small molecule drugs in the field of biopharmaceuticals is that: their small size can have extremely high diffusivity and diffusion speed between cell membranes, and they can greatly reduce the toxicity caused by possible bioaccumulation, because their method of excretion is very simple, namely breathing. Nonetheless, therapeutic gases still have major challenges in clinical trials, most notably their short half-lives in humans. It has been reported that the biological half-lives of O2, NO, H_2S and CO range from only 20 milliseconds to 7 hours. So far, among all the carriers suitable for loading therapeutic gases, most nanomaterials have been proved to be toxic to animal cells to varying

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degrees, among which MOFs are considered to be the most efficient and safe because of their large porosity. Therefore, it has a very high drug loading rate. Secondly, because it can flexibly change the materials of metal ions and organic linkers, it can reduce its toxicity to animal and human cells by using metal-organic materials with high biocompatibility. It is found that when MOF is used as a gas carrier, MOF acts as a physical barrier to protect the gas and effectively prolongs its half-life, that it forms a covalent bond with the loaded material by adjusting its hydrophobicity and hydrophilicity, thereby making more precise control of drug release profiles.

3.3.1. Nitric oxide (NO). By using catalytic and non-catalytic methods, precise control of NO donor delivery can be achieved. The non-catalytic system refers to the direct adsorption of NO gas molecules on the surface of MOFs, which facilitates the precise release of NO donors when necessary. In addition, this method can make MOFs have a higher gas affinity. The catalytic system is a catalyst that uses MOFs as NO donors to better decompose NO in the body to achieve therapeutic effects.

Morris et al. experimentally demonstrated that the release profile and stability of NO are highly dependent on the MOFs material [17]. They used copper, nickel, and cobalt as metal linkers combined with organic molecules to form MOFs, and adsorbed NO onto their surfaces, respectively, and found that in the presence of nitrogen (N_2), adsorption in Co-MOF and Ni-MOF, the NO can be completely released within 5 hours, and after a long-term experiment at room temperature, it can be seen that there is no significant change in the amount of NO adsorption between the two. The amount of NO released from the Cu-MOF is negligible.

Reynolds and co-workers synthesized Cu-MOFs (i.e., copper (II) benzene-1,3,5-tricarboxylate (CuBTC) and copper (II) 1,3,5-benzene-tris-triazole (CuBTTri))[18]. They put these Cu-MOFs into polymer substrates such as cotton and polyvinyl alcohol to create the films needed to release NO. They found that CuBTC released 75% of the theoretical NO gas two hours after it was added to the polymer material. In addition, when CuBTC-cotton was reacted with S-nitrosocysteine (CysamNO), a 7-9 times higher yield of NO gas, i.e., 7.1 ± 1.2 mmol, was produced compared to the blank solution within six hours. However, new concerns have emerged about poisoning due to excessive copper accumulation, as CuBTC is unstable in water and in vivo, likely causing copper ions to be released into the surrounding environment, causing copper poisoning to occur. To this end, the Reynolds group replaced CuBTTri as a catalyst for releasing NO. Although the actual release of NO gas dropped to 50% of the theoretical value, its high stability is urgently needed. It has been experimentally found that CuBTTri is very stable in complex strength environments (such as in blood and cell media) due to the use of azole-based ligands.

3.3.2. Carbon monoxide (CO). As a gaseous messenger molecule, carbon monoxide can regulate a series of physiological activities. However, the existing carbon monoxide donors are limited in clinical use due to the lack of targeting and the release rate being too influenced by the outside world. In order to solve these problems, scholars use nanomaterials for drug delivery. Based on this research idea, a preliminary exploration was carried out using nanomaterials as carriers for existing carbon monoxide donors, and many important conclusions and meaningful results were obtained. The performance advantages of nanomaterials can improve the targeting of CO release. The improved release performance is beneficial to promote the application of CO-controlled release nanomaterials in biomedical fields such as inflammation, antibacterial and cancer.

MOFs have the characteristics of large drug load, small toxic and side effects, and low immunogenicity, and are widely used in the field of drug delivery. Boyer et al[19]. synthesized a series of MOFs nanocarriers and combined them with CO donors to obtain a variety of polymer nanoparticles that could release CO. They found that the polymer nanoparticles with slow CO release ability, like CORM-2, could It has a strong inhibitory effect on Pseudomonas aeruginosa. The experimental results show that CO_2 sustained-release nanoparticles have an obvious killing effect on bacteria in suspension or in biofilm, and its effect is better than that of CORM-2 alone. The toxicity of CO slow-release polymer nanoparticles is much less than CORM-2, and its stability and water solubility are also greatly improved.

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Therefore, these excellent, safe and non-toxic CO slow-release polymer nanomaterials have broad application in the field of antibacterial application prospects.

4. Conclusion

MOFs have been widely used in biosensing and drug delivery due to their huge specific surface area, rich porous structure, and modifiability. MOFs also show great potential in disease diagnosis and treatment. However, most of the related research is still in the initial stage, the problems are discussed, and further research is necessary for the below aspects:

1. Biotoxicity of MOFs. There are many components that makeup MOFs, including a large number of metal ions and organic ligands, which will lead to their high biological toxicity. The selection of endogenous biomolecules such as amino acids and nucleotides and metal ions with low biotoxicity, such as Cu and Fe can effectively reduce the biotoxicity of MOFs. At the same time, the biotoxicity of the formed MOFs should also be investigated.

2. The stability of MOFs structure. MOF materials are unstable in aqueous systems, and it will make it difficult for MOF-based functional materials to exert their effects in solution, which may be rapidly degraded in vivo, which cannot achieve the purpose of targeted imaging and sustained drug release. Among them, the extremely poor stability of NMOFs in an aqueous solution can lead to rapid aggregation or rapid disintegration of drugs, which can cause side effects such as apoptosis and tissue abnormalities. The water stability of MOFs can be achieved by selecting ligands in water, carboxylic acid solvents, or high-valence metals.

3. Control of MOFs morphology. The reaction temperature, solvent, time, and concentration all affect the structure and morphology of MOFs. For in vivo imaging and drug delivery, the desired nanometer size needs to be obtained. In addition to investigating different synthesis conditions, it can also be achieved by changing the synthesis technique. For example, by using the microwave-assisted method, smaller MOF particles can be obtained compared to the solvothermal method.

4. The precise regulation of the pore size of MOFs is the focus of the next development in the field of MOFs, which is related to the practical application of MOFs. Adjusting the pore size according to the size of the substance to be separated to achieve high-selectivity sieving is an important development direction of MOFs in the field of separation. MOF materials with excellent screening performance will promote the development of MOFs in gas separation or water treatment fields. The construction of reasonably distributed pore size and active sites in MOFs is also related to the application of MOFs in catalysis and electrochemistry [20].

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