Metal-Organic Frameworks for Drug Delivery

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Abstract. Nowadays, metal-organic framework (MOF) materials are used in the application of sustained release of drugs. Because of high efficiency, good stability and varied properties, MOFs have shown great potential and a promising future in terms of delivery. In this article, many factors which can have a significant impact on the release during the slow release of a drug were introduced, such as temperature, pH, permeability and toxicity. This article also analyses the performance of different types of MOF in the study of different drugs, including coordination complexes, coordination polymers, and microscale coordination polymers. With an in-depth understanding of the different conditions, the process of designing and producing sophisticated MOF materials can be promised.

Keywords: Drug delivery system, metal-organic frameworks, factor.

1. Introduction

A drug delivery system (DDS) has been studied as a drug delivery carrier, which includes organic and inorganic traditional aspects. Organic DDS performs good biocompatibility, however, it has no controlled release quite often without good porosity. In comparison, the manner of the released drug molecules can be easily controlled by inorganic DDS, but the limited loading capacity is one key factor that limits its potential. With the successfully hybrid and inorganic DDS, coordination polymers were hence introduced, which are metal-organic frameworks (MOF) in other words. The superior properties of MOFs, such as high porosity, flexible compositions and structures, interchangeable sizes, varied functionalities, high loading capacity, and good biocompatibility, have made them suitable hosts for drug administration. [1].

In drug delivery, MOF is mainly used as a drug carrier, which can be divided into discrete coordination complexes, bulk coordination polymers and nanoscale and microscale coordination polymers. To be specific, discrete coordination complexes can perform sufficient lipophilicity and solubility, salsalate and aspirin are two representative examples which use this kind of MOFs as drug carriers. In terms of bulk coordination polymers, drug loading capacities and drug release kinetics are the advantages that make them suitable for drug delivery, nitric oxide (NO) for example. As in nanoscale and microscale coordination polymers, they are more flexible than most drug carriers due to their sizes and property advantages like solubility and secular uptake, therefore they are the specific MOF that has been suggested as the potential materials for treating life-threatening diseases like cancer. Based on the requirements of the specific drug, MOF also shows the flexibility of its capability. This article mainly introduces the role that MOF is playing in the area of drug delivery, including factors influencing MOF, types of MOF and applications of MOF.

2. Factors affecting drug transport of MOFs

MOF materials play a role in the protection and precise positioning of drugs in the system of drug delivery. This is because targeted therapy is particularly important in cancer treatment. Generally, the delivery efficiency of MOF materials is affected by many factors, such as temperature, permeability and toxicity.

2.1. Temperature.

Temperature is a vital factor that influences the efficiency of a drug's slow-release, and the body itself exerts a certain temperature influence on the drug. Especially with temperature-sensitive slow-release systems, the properties of the drug used are also altered, thus the release of the drug is regulated. For example, the Zr-based MOF ZJU-801 system uses (2E,2′E)-3,3′-(naphthalene-1,4-diyl) diacrylic acid as an organic binding agent for exceptional medicated delivery. Under the condition of PBS (pH 7.4) at 25, 37, 45, and 60 °C loaded ZJU-801's release of DS over 24 h were examined [1]. According to the results, the DS-release rate increased as the temperature increased. The graph indicates trifling releases at 25 and 37 °C, however, an increase is shown at 45 °C and especially at 60 °C, which the rate was almost 3.4 times faster compared to the rate at 37 °C and 10.3 times at 25 °C. As a result, ZJU-801 is a promising candidate for temperature-triggered drug release [1].

2.2. pH Values.

As the human body contains acidic substances such as stomach acid, pH values can create a significant impact in terms of medication release. According to an experiment that used Zr-MOF-loaded Pyropheophorbide-a (PPa) for improving photodynamic therapeutic efficacy, Zr-MOF-PPa@PAH is chemically stable. The lesion with the blood can be reached in the neutral physiological environment of the body and can be readily released in the tumour microenvironment, avoiding damage to normal cells. The human physiological environment is approximately 7.4 and the pH of tumour tissue is 6.0 to 6.8, while the pH can be as low as 5.2 in some organelles and nuclear endosomes. The experiment discovered that the pH value is higher when the drug release is lower. When different pH values (5.6, 6.5, 7.4) were carried out by the release experiments, the samples released PPa, and the amount of PPa between 0 and 12 h was recorded. The highest release of PPa was achieved at pH 5.6, 45.8% at 6 h, 76% at 12 h and the lowest at pH = 7.4. (Fig. 1) Therefore, the Zr-MOF-PPa@PAH nanoparticles were released in the normal physiological normal environment, enabling better aggregation at the tumour site and improving the photodynamic efficacy [2].

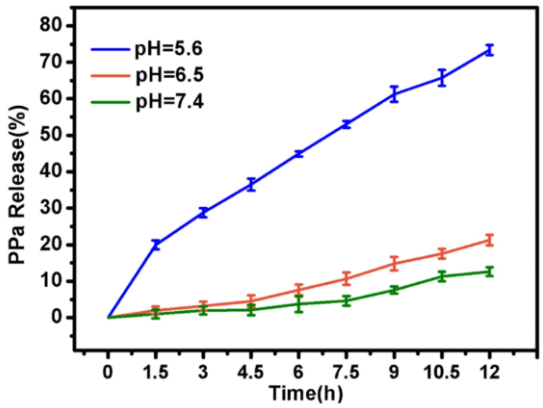


Figure 1. Zr-MOF-PPa@PAH is released in response to pH stimulation [2].

2.3. Permeability

The ability of nanodrugs to enter cells is particularly important in cancer therapy. Pyropheophorbidea (PPa) is commonly presented at fluorescence imaging and capable of performing high monomorphic oxygen quantum yield, good biocompatibility and strong tissue penetration, but its small molecular size, poor water solubility and tendency to aggregate in a physiological environment limit its widespread use in tumour therapy. HepG-2 cells were treated with Zr-MOF-PPa@PAH. After a CO_2 incubator is carried out the incubation, the observation of cells' internalization behaviour can be observed by fluorescence inverted microscopy. At 15 min after drug treatment, a faint red fluorescence appeared in the cells. This indicates that Zr-MOF-PPa@PAH

entered the cells. Also, the red fluorescence became stronger and stronger as time extended, indicating that Zr-MOF-PPa@PAH entered the cells completely [2].

2.4. Toxicity

The use of nanomaterials as DDS requires them to have low or no toxicity to the organism during transport. For example, in the experiments with Zr-MOF-loaded PPa, the survival rate of PPa and Zr-MOF-PPa@PAH nanoparticle-treated HePG-2 cells was nearly 100% under no light irradiation, indicating that both were safe and non-darkly toxic [2].

3. MOFs used as drug delivery

Due to MOF's unique structures and properties, it brings out several advantages that address its suitability in the field of drug delivery. The large pore surfaces and volumes of MOFs offer a high drug adsorption capacity. The internal pores and external surfaces of MOFs are all functional. additionally, a healthy contrast agent can be potentially used by MOF as well as bioactive constituents on their frameworks as well as a well-performed biodegradability. Specifically, three major types of MOF have been widely studied for drug delivery: discrete coordination complexes, bulk coordination polymers, and nanoscale and microscale coordination polymers [5].

3.1. Discrete coordination complexes

In this century, scientists have developed a new method for lipophilicity modification, in which transition metal-containing drugs can't solubility can also be modified. With the utilization of weak supramolecular interactions like the coordination bonds to connect with the ancillary ligands (AL), the combination can be suitable for specific scenarios and cases [5]. To be specific, the discrete coordination complexes can perform unique properties which their building blocks could't exhibit. One main aim of the development of Discrete coordination complexes is hence to construct smart materials based on their dynamic and reversible natures [6]. They have shown great potential in recent studies, not only as drug carriers but also in sensing, catalysis and so on. Compounds containing non-steroidal anti-inflammatories (NSAIDs) as a ligand in Cu^{2+} complexes, Cu-NSAIDs, are a well representative discrete coordination complex in terms of drug delivery [7]. Compares to organic materials, the coordination complex is a more complicated system with the attendance of transition metals. Take lipophilicity as an example, it can be altered by coordination chromophore, hydrogen bonds or size effect. The lipophilicity of Cu as AL for Aspirin (ASP) has been studied recently, CuII-ASP-AL to exact. After the synthesis of several mixed-ligand CuII complexes homologous series, partition coefficient (log P) is utilized as determining the levels quantitatively.

Recent studies have shown that ASP-5 ($Cu(ASP)_2(Pyridine)_2$), 6 ($Cu(ASP)_2(Isonicotinamide)_2(AcCN)_2$) and 8($Cu(ASP)_2(Nicotinamide)_2$) have log P values of -0.7001, -0.4674 and -0.5257, which indicate relatively low lipophilicity. It also has been proven that the complexes with dicopper chromosphore are more lipophilic compared to monocopper complexes. One major factor that causes this phenomenon is the fact that monocopper complexes contain hydrated species, which offer an increase in aqueous solubility and thus a decreased lipophilicity. In the field of drug delivery, lipophilicity is a very significant property that creates a direct impact on drug uptake and metabolism. In addition, high lipophilicity means a high possibility for the drug carrier to bind with molecules other than the target. With that, it is obvious that MOFs like ASP-5, 6 and 8 can perform better stability in the drug delivery process.

Moreover, salsalate (SAS) substituted Aspirin with the use of the same drug carrier. It stated a strong evaluation of the factor of size effect on lipophilicity. SAS-4 ($Cu_2(SAS)_4(4\text{-Benzyl-Pyridine})_2$) and 5 ($Cu_2(SAS)_4(4\text{-Phenyl-Pyridine})_2(THF)_2$) have shown a dramatic increase in log P (0.06467 and 0.7481) due to the attendance of aromatic AL. To be specific, they have enhanced their lipophilicities because of their large molecular sizes. Even though the lipophilicity level is higher than carrying

aspirin, it is still considered to be acceptable. A material that has such capabilities can potentially make a huge contribution to the field.

3.2. Bulk coordination polymers

Bulk coordination polymers are also essential MOF in drug delivery. After years of development, it has been divided into two specific branches, delivery of drug molecules and delivery of nitric oxide (NO) molecules. Since transition metal ions and multidentate organic ligands are the two most significant compositions in this kind of MOF, they can perform the properties of both inorganic and organic DDS, thermal properties and biocompatibility for example. However, their potential can be explained by the following factors: large surface area, high porosity, low toxicities to certain metals, good physical and chemical stabilities, and well-defined chemical compositions [7]. Besides, their drug loading capacities are considered to be high, and their drug release kinetics are relatively well-controlled, meaning that they are suitable for drug delivery.

Specifically, in drug delivery, zinc-Adeninate coordination polymers have been reported recently, which can release cation-triggered drugs. The coordination polymer $[Zn_8(ad)_4(BPDC)_6O{\cdot}2Me_2NH_2$, 8DMF, $11H_2O]n$(ad, adeninate; BPDC, biphenyldicarboxylate), or bio-MOF-1, has been chosen to be the suitable carrier. According to the results, the bio-MOF-1 can release 70% of the carried drugs in 10 hours, and complete the following 3 days. However, the future of this drug isn't quite promising considering its loading capacity and procainamide released are relatively unfulfilling in other bulk coordination polymer capabilities, MIL class materials for example.

NO is commonly used as sedation and pain relief in the medical field, which is in a gaseous state at normal temperature and pressure [7]. In terms of NO delivery, the NO carrier is needed to be selected separately due to NOs different dimensions and molecular weight. In recent years, HKUST-1 is a representative example of a NO carrier among the various NO carriers that have been discovered in the past decades [7]. NO can be adsorbed onto dehydrated HKUST-1, which HKUST-1 has a higher adsorption capacity than most organic materials and zeolites (1 bar is over 3 mmol/g). When it comes to NO-releasing, water plays the role of a nucleophile to trigger the release process. However, the HUKST-1 is unable to release all the NO it carries. Specifically, only 0.002 mmol/g of the NO can be released, which is not even at the same magnitude compared to the amount adsorbed. Also, HUKST-1 has a risk of causing toxic issues considering it is relatively unstable under biological solutions.

3.3. Nanoscale and microscale coordination polymers

Nanoscale and microscale coordination polymers. As their name suggested, these kinds of polymers offer positive aspects due to their size: improved drug solubility, effective biomembrane cross-fertilization, improved tissue tolerance, and improved cell absorption and transport. [7]. Because of their developed formulation techniques, Nanoscale and microscale DDSs are commercially accessible.

Recently, $[Tb_2(DSCP)3(H_2O)_{12}]n$ (DSCP, disuccinatocisplatin) NCP, or NCP-1, had been reported back in 2008, which is the first nanoscale coordination polymer for drug delivery utilization. According to recent studies, the scientists have successfully coated a layer of silica around NCP-1 while caring drug (DSCP) content, which NCP-1-a (2nm shill thickness) and NCP-1-b (7nm shell thickness) can be obtained (Fig. 2). According to the results, NCP-1-a and NCP-1-b have a half-life of 5.5 hours and 9 hours, which are significantly higher than the NCP-1 particles without silica shell (1 hour). This property is beneficial in terms of controlling drug release in the human body.

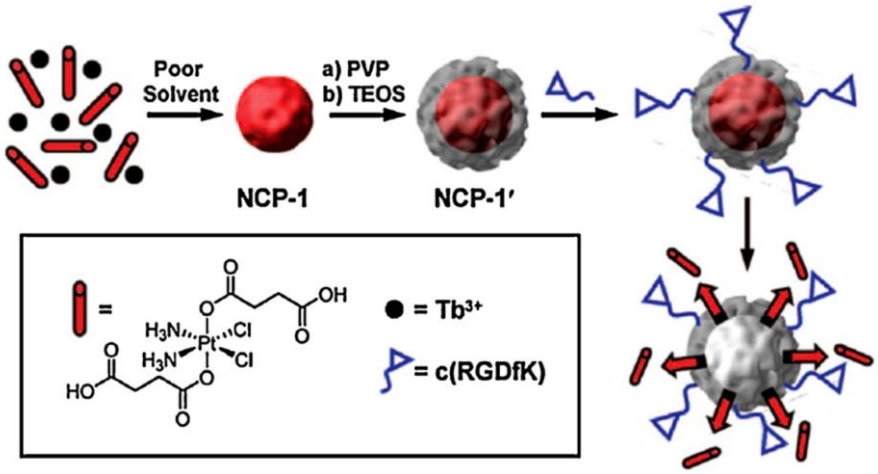


Figure 2. Illustration of NCP-1 in drug delivery [7].

Scientists also discovered non-toxic MIL(Fe) Coordination polymers as nanoparticles [7]. After 10 days of the administration, MIL shows no sign of toxicity and high drug loading capacities even compares to normal nanoscale particles. For instance, as MIL is carrying a drug called busulfan (Bu), which is a common anticancer drug and releases AZT-TP, it shows 5 times higher loading capacity and 60 times higher lipophilicity than organic drug carrier. Also, MIL has shown reasonable stability: it only degraded 10% three days after the AZT-TP has been full releases. As a potential platform for drug distribution, the scientists suggested its great potential for treating potentially deadly diseases.

4. Application of MOFs in drug delivery

MOFs are with a great number of advantages that make them a uniquely suitable material for drug delivery. They can adsorb the functional group molecules of the drug on the surface or keep them inside their framework. This is due to their large surface and high-level structures. Moreover, MOFs can combine with the functional group molecules through a covalent bond, by multiple sorts of synthesis. Therefore, MOFs become a promising drug deliverer. Compared to traditional drug deliverers for chemotherapy, the problem of side effects of superfluous use of drugs. Some recent research showed that MOF nanocarriers used in targeted drug delivery, can both raise the uptake of the drug and regulate the release of it.

As mentioned, MOFs have many advantages over other materials, they have been studied for years as an objective drug carriers. Drugs, generally, are stored in MOF nanocarriers through encapsulating in situ, which is a comparatively simpler method, or through post-synthesis. To prevent the untimely release of the drug, drugs that are thermostable are loaded with the former method. Post-synthesis, on the other hand, would not destruct the drugs since it gives a milder environment.

4.1. Universal DDS

One category of MOFs is called zeolite imidazolate framework, also known as ZIF. ZIFs have become an essential material in chemical and medical domains, for instance, separation and drug carriers. ZIF that contains 2-methylidazolate and zinc ions is categorized as ZIF-8. It is an ideal drug deliverer as it is considered stable not only thermally but also hydrothermally [9-12]. Moreover, the physiological stability and instability if acidic enable it to be ideal in pH-responsive DDS. In an experiment, ZIF-8 was involved in the reaction of 5-fluorouracil delivery, which is a delivery of pH-responsive medicines. They obtained one extraordinary capacity with post-synthesis of approximately 660mg of 5-FU and 660g of ZIF-8. As suggested by the results, in a mildly acidic buffer solution at pH=5.0, the release of the drug is quicker than in the solution with pH=7.4. [13]. Encapsulation of the drug in situ can prevent the hindering of the access to MOF for the molecules of larger scale due to the microporous structure, and thus prevent premature release of drugs, in contrast to post-synthesis [14].

4.2. Anti-cancer DDS

A significant factor in the defeat of cancer chemotherapy was multidrug resistance (MDR), which is mainly caused by overexpression of efflux carriers [15,16]. An experiment by the Luan group chose verapamil hydrochloride, known as VER, as the inhibitor for an efflux transporter called P-glycoprotein to overcome MDR, and meanwhile selected DOX as an anticancer drug [17]. One essential link was encapsulating DOX and VER into ZIF-8 through a one-pot process since this can produce identical nanoparticles that are very thermodynamically stable. In addition, they stabilized ZIF-8 with methoxypoly (ethylene glycol)-folate (PEG-FA) to achieve extended circulation and directed administration of active medications (Fig. 3).Their lab report suggested that the reversal of the DOX MDR improved DOX internalization and strengthened its anticancer effect by boosting its cytotoxicity [18].

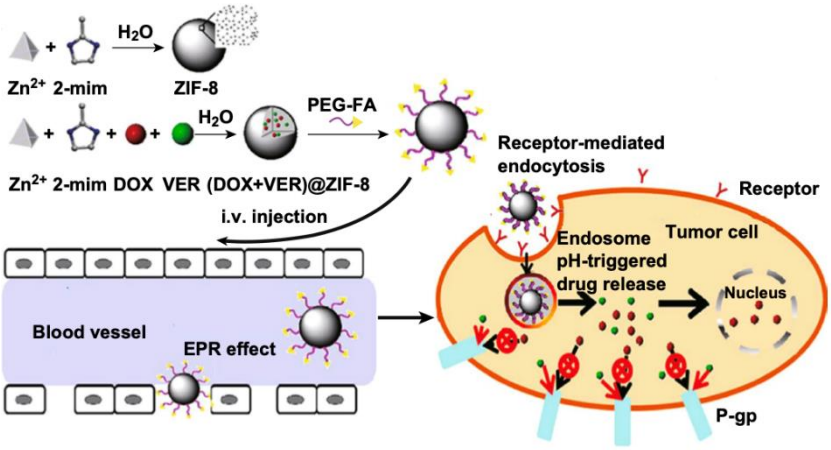


Figure 3. ZIF-8 was stabilized with methoxypoly (ethylene glycol)-folate (PEG-FA) to achieve extended circulation and directed administration of active medications [18].

4.3. Nucleic acid-MOF DDS

The category of biomolecules containing RNA (ribonucleic acid) and DNA (deoxyribonucleic acid) is Nucleic acid. Nucleic acids are differentiated by sugar moiety types. They are essential in genetic information storage and expression. MOF nanocarriers can prevent degradation and increase the rate of cellular uptake. Mirkin group, in 2014, announced the first conjugates of nucleic acid-MOF nanoparticles [12]. They first used solvothermal synthesis to obtain azide-functionalized nanoparticles UiO-66-N_3. Then DBCO-functionalized DNA was used to modify the surface of this nano-MOF. The results showed that synthesized conjugates gave greater colloidal stability and improved efficiency of cellular uptake when transfection agents are absent.

5. Conclusions

In drug delivery systems, metal-organic frameworks (MOFs) are regarded as very promising nanocarriers due to their superior advantages including pore opening, made-to-measure composition and structure, and adjustable size., compared to other materials used in drug delivery. In this article, the factors influencing the drug transport by MOFs, and the types and applications of MOFs are discussed. In the section exploring factors, temperature, pH value, permeability and toxicity were mentioned. Different MOFs and drugs are affected by different factors to a different extent. MOFs are applied in the delivery of universal drugs, anticancer drugs, and nucleic acid-MOF drug delivery systems. MOFs can prevent the early release of drugs, strengthen the anticancer effect by boosting its cytotoxicity and decrease the possibility of degradation of the genetic information.

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