Applications of MOFs in Drug Delivery

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Abstract. The main research focus of this article is the application of Metal-Organic Frameworks (MOFs) in drug delivery applications. The review primarily concentrates on the methods used for loading drugs into MOFs, their response to stimuli, potential applications, and limitations. The article begins with discussing the limitations of traditional drug delivery systems and introduces MOFs as a potential solution to these limitations. The drug loading strategy section describes the three main methods for loading drugs into MOFs, including their respective benefits and drawbacks. The stimulus response release program section explores various stimuli that can trigger drug release from MOFs, including physical, chemical, and biological factors, and provides examples of how MOFs can respond to these stimuli. The section on application and challenges provides an overview of current studies exploring the potential of MOFs in biomedical applications, including cancer therapy, antibacterial therapy, and anti-inflammatory therapy, while also highlighting the key challenges facing MOFs research, such as biocompatibility and toxicity. Finally, the article concludes by offering prospects for future developments in MOFs research. This review article provides a significant resource for drug delivery researchers and practitioners who wish to investigating the possibility of utilizing MOFs as novel drug delivery vehicles.

Keywords: Metal-Organic Frameworks, Drug Delivery, Stimulus-responsive release, Biomedical applications.

1. Introduction

Drug delivery constitutes a significant aspect of contemporary medicine, encompassing the techniques employed to introduce or disseminate pharmaceutical agents throughout the human body. These methods can enhance the safety and therapeutic efficacy of medications by modulating their pharmacokinetics, pharmacodynamics, toxicity, immunogenicity, and spatial distribution [1]. Drug delivery systems may also safeguard pharmaceutical compounds from degradation, thereby facilitating more efficient targeting of the intended site [2]. Generally, drug delivery can be categorized into administration routes and packaging modalities. Considering that the routes of administration are mainly limited to oral, injectable, inhalational, and transdermal approaches, the focus of research has shifted towards exploring various packaging modalities for pharmaceutical compounds.

In addition to enhancing therapeutic efficacy, another important role of drug carriers is to protect functional molecules from external environmental influences. This can potentially reduce the storage requirements of some drugs and extend their shelf life, which not only reduces drug costs but also enables drugs to potentially reach impoverished areas where proper storage conditions are not available.

Traditional drug packaging systems such as liposomes, micelles, and polymers are often limited by their physical and chemical properties, resulting in various restrictions such as low solubility, instability, small loading capacity, and poor targeting [3]. In some cases, these systems may also have serious negative impacts such as biotoxicity. As a result, new packaging materials that are efficient, economical and less toxic are increasingly in demand. One popular area of research in this field is drug delivery systems based on nanoparticles.

The combination of metal ion clusters and organic linking agents results in a mixed porous material known as Metal-Organic Frameworks (MOFs). Since Yaghi's group reported the selective binding of guests in MOFs in 1995, their potential in separation, catalysis, and storage has been widely researched. MOFs possess unique properties, such as high surface area, customizable pore size and

shape, adjustable chemical functionality, and diverse structural composition, making them an ideal choice for various applications [4]. The use of MIL-100 and MIL-101 to deliver ibuprofen indicates that these properties make also MOFs potential candidates for drug delivery applications, where they are able to encapsulate various drug formulations in their pores or on their surfaces and facilitate controlled release in response to various stimuli [5].

MOFs can be synthesised in a variety of ways, such as solvothermal synthesis and mechanochemical synthesis. The chosen synthetic technique can affect the characteristics of MOFs, including their morphology, size distribution, crystallinity, and stability [6]. MOFs possess the capability to undergo functionalization with diverse set of groups comprising but not limited to peptides, polymers, amino acids, and biomolecules. Such functionalization can augment their biocompatibility, targeting efficacy, and ability to respond to stimuli [7].

Due to the various types of interactions that MOFs can offer, such as physical adsorption, chemical conjugation, covalent linkage, coordination bonding, etc., miscellaneous drugs ranging from traditional small molecule drugs to emerging large molecule ones can all be packaged and delivered using MOFs. Furthermore, by using different organic components or modifying them, various factors including pH value, temperature, magnetic field, light, and enzymes can trigger MOFs to release the carried functional molecules [8]. Based on this, it is feasible to achieve time and space-controlled release of drugs loaded into MOFs through appropriate stimuli. These characteristics of MOFs attributes that render them more favorable to a broad spectrum of uses such as anti-cancer, anti-viral, bacterial infection and inflammation treatments , in contrast with traditional drug transport mediums.

This paper will discuss the advancement of MOFs as potential vehicles for biomedical use in various applications. First, different strategies for loading drugs into MOFs will be described, along with their pros and cons. Then, various stimulus-responsive release programs applied to MOFs will be introduced. Examples of the application directions currently being studied for MOFs will also be provided. Finally, the current challenges facing research on MOFs are summarised and relevant prospects for future developments are provided.

2. Drug Loading Strategy

2.1. Surface Adsorption

Surface adsorption is a simple and direct loading strategy. Due to their high porosity and vast surface area, MOFs are considered to be an ideal candidate for efficient adsorption. Typically, the desired compounds can be adsorbed onto the surface of already synthesized MOFs through weak interactions, such as van der Waals forces, dipole interactions, and hydrogen bonding, by simply stirring them in a solution containing the desired compounds [6].

Surface adsorption does not require many demands regarding the pore size and dimensions of MOFs, but weak interactions lead to leaching issues that cannot be avoided. Based on this consideration, stronger interactions, such as covalent bonding, have been proposed. Due to the composition of MOFs, their surface usually contains various functional groups, which are feasible sites for covalent bonding.

This strategy allows for the separation of synthesis and loading of MOFs into two independent stages, thereby offering flexibility in choosing appropriate methods to prepare MOFs. However, since this strategy primarily focuses on the surface properties of MOFs, the choice of organic linkers or modifications to the surface of MOFs is crucial.

2.2. Encapsulation Strategy

Surface binding methods usually cannot fully utilize the large cavities of MOFs, which are highly beneficial for loading. This leads to the encapsulation strategy, which involves loading drugs into the pores of MOFs through molecular sieving and/or interactions. Encapsulation provides protection for drugs from external factors and is particularly useful for sensitive molecules (such as DNA, RNA, and proteins) while solving the leaching problem [9]. Encapsulation is typically achieved through

one-pot synthesis. This means that drug synthesis conditions are constrained by the drug. Dry synthesis is also available for some solution-sensitive drugs. In some specific cases, it is also feasible to enclose drugs in MOFs through the pores. Further modifications may be employed to encapsulated MOFs to enhance their stability and targeting efficacy. Although the encapsulation strategy has a relatively more complex configuration method, it provides better protection for packaged drugs, and can load a wider range of molecular types [6].

2.3. Direct Assembly

As a drug delivery system, MOFs are typically expected to disintegrate at the appropriate timing and location in the body, which facilitates the release of drugs and the metabolism of MOFs. Instead of using separate functional molecules, they can be incorporated as a component of MOFs during synthesis to enable their release upon MOFs disintegration in vivo. The synthesis of MOFs can be achieved through a simple method of mixing metal clusters and functional molecules in a reaction mixture, which does not necessitate strict synthesis conditions that could harm the functional molecules. This encapsulation mechanism can also protect functional molecules from adverse factors such as harsh chemical environments, temperature, and degradation enzymes to a certain extent [10]. However, the problem lies in that biologically active molecules are often flexible and have low symmetry, which limits the range of active molecules that can form stable MOFs with good structure [6]. Biomimetic mineralization is a method for encapsulating biomacromolecules by inducing the formation of protective MOFs around functional biomacromolecules such as proteins, enzymes, DNA, etc., to enhance their stability [11]. Similar to the encapsulation strategy, MOFs built by direct assembly can also be further modified. However, due to the organic linkers being limited to the desired functional molecules, such modifications are typically mild and do not affect their release and function.

3. Stimulus Response Release Program

By performing specific modifications to MOFs, they can be made to respond to particular stimuli, prompt the discharge of the drugs they contain. This enables controlled or automated drug release and enhances targeting specificity. There are various strategies for achieving this. One common method is to use a coating that responds to specific stimuli to lock MOFs, allowing them to release their payload only when the coating is unlocked through stimulation. Another method involves utilizing stimuli to degrade MOFs to release the payload. The types of stimuli that can be used are diverse, including physical factors such as light and heat, chemical substances such as ions and oxidation/reduction agents, and biologically active molecules such as enzymes and ATP. Different types of stimulus response have different applications [12].

3.1. Glucose Responsive Insulin Release System: Ins-GOx/ZIF-8

Diabetes is a persistent health condition marked by increased levels of glucose in the bloodstream caused by either insulin deficiency or resistance. As the intake of highly processed foods and added sugars increases while physical activity decreases, diabetes is becoming an increasingly challenging health issue for humans. Exogenous insulin is crucial for diabetes patients.

Recently, glycemic-responsive insulin (GRI) has become a hot topic in research. Ins-GOx/ZIF-8 constitutes an insulin release mechanism using Zeolitic Imidazolate Framework (ZIF-8) and Glucose Oxidase (GOx), reported by Duan and his team [13]. The synthesis of this system is achieved through a straightforward one-pot method at moderate conditions. The solution containing zinc nitrate, 2-methyl imidazole (Hmim), insulin, GOx, and polyvinylpyrrolidone (PVP) is stirred for 30 minutes, resulting in the formation of Ins-GOx/ZIF-8 as a white precipitate with a high insulin encapsulation efficiency of 80.6%.

Under hyperglycaemic conditions, the conversion of glucose to gluconic acid takes place upon the entry of glucose into the composite by GOx. This, in turn, results in the acidification of the

surrounding environment, causing the quick disintegration of ZIF-8 and subsequent discharge of insulin. Meanwhile, stable ZIF-8 at low glucose levels acts as a barrier for insulin release, achieving automated control of insulin release and avoiding the risk of hypoglycemia [13].

3.2. Glutathione-Responsive Nanoparticles: CCM@MOF-Zr (DTBA)

Cancer stands out as a significant contributor to global mortality rates with many forms posing as formidable adversaries to treatment, resulting in a heightened sense of danger to human health. Chemotherapy remains the primary treatment for most cancers. However, it has several disadvantages, including poor specificity, toxicity to normal cells, high stability, and drug resistance, which can result in low treatment efficacy and significant suffering. Nevertheless, the dissimilarities in microenvironments of tumor and non-cancerous tissues may be exploited to achieve site-specific release of chemotherapy drugs, thereby improving treatment outcomes and reducing toxicity. For example, nanoparticles such as CCM@MOF-M(DTBA), in which M represents Fe, Al or Zr, have been reported by Lei et al. The MOF-M(DTBA) with 4,4'-dithiodibenzoic acid (4,4'-DTBA) as a linkage, which can be cleaved by GSH. Even when administered in large quantities, CCM, which is a natural polyphenol, is deemed to be well-tolerated and safe, and has demonstrated anti-cancer characteristics. However, CCM rapidly degrades in physiological environments and has low water solubility, resulting in poor bioavailability. However, by encapsulating CCM within MOF-Zr(DTBA), its degradation is prevented. CCM@MOF-M(DTBA) nanoparticles can enter cells via the EPR effect and endocytosis. The excessive production of GSH within malignant cells causes the disintegration of MOF-M (DTBA), which results in the liberation of CCM for the purpose of destroying the cancerous cells. In vitro tests have shown that CCM@MOF-Zr(DTBA) releases 85% of CCM in approximately 5 hours under tumor-like conditions (pH=5.5, presence of GSH), whereas only about 50% of CCM is released in approximately 22 hours under normal tissue cell conditions (absence of GSH, pH=7.4). This demonstrates a good response to the tumor microenvironment, with rapid CCM release in tumors and the advantages of packaging CCM in a normal physiological environment [14].

3.3. pH-Responsive Cu2+-Disulfide Release Carrier: DSF@HKUST

Another example of an anti-cancer agent is DSF@HKUST reported by Chen et.al. Disulfiram (DSF) is a widely used drug for treating alcohol addiction and alcoholism. It was recently discovered to exhibit broad-spectrum anti-cancer activity when administered concurrently with copper ions to form Cu-diethyldithiocarbamate ($Cu(DDTC)_2$) moieties. In a controlled nucleation method, nano-sized HKUST nMOFs were synthesized through coordination of Cu^{2+} with 1,3,5-benzenetricarboxylic acid molecules, and then loaded with DSF using free diffusion. Due to its high hydrophobicity, DSF@HKUST can have its stability significantly enhanced by the addition of a zwitterionic polymer (1,2-distearoyl-sn-glycero-3-phosphoethanolamine-N-[amino (polyethylene glycol)-2000], DSPE-PEG2000-NH_2), which can be immobilized on its surface through hydrophobic interactions. The acidic conditions at the tumor site triggers HKUST-1 to degrade, which results in the discharge of copper ions and DSF. Formation of $Cu(DDTC)_2$ takes place by the reaction between copper ions and DSF. This toxic complex has a tendency to affect biomolecules and restrict the growth of tumors. Furthermore, in the presence of copper ions, the Fenton-like reaction occurs and generates reactive oxygen species using hydrogen peroxide. It consequently leads to the creation of oxidative stress and damage in malignant cells. As a result, DSF@HKUST can deliver chemotherapy, chemodynamic therapy, and nanocatalytic therapy simultaneously to eradicate cancer cells. In addition, DSF@HKUST has the capability to serve as a photothermal and photoacoustic imaging agent by transforming near-infrared light into sound and heat signals through absorption. This feature enables DSF@HKUST to provide real-time imaging guidance and enhanced thermal ablation for tumor therapy [15].

3.4. Mn(II)-Based Photosensitizing Therapeutic Material

The production of reactive oxygen species (ROS) within cancer cells upon exposure to specific light waves is induced by photosensitizers (PSs) in photodynamic therapy (PDT), resulting in cellular damage and apoptosis. This treatment method is highly selective, with minimal invasiveness, low systemic toxicity and enhanced spatiotemporal resolution in comparison to conventional chemotherapy [16,17]. However, PDT faces various obstacles such as low stability, poor water solubility, and limited PSs and light penetration depth. MOFs can improve photodynamic therapy by boosting solubility, stability and PS targeting, and by offering multifunctional platforms for combination therapies. For instance, MOFs can integrate PSs on surface or within their pores, significantly improving water solubility and safeguarding PSs against degradation. In addition, MOFs can be functionalized with targeting ligands or stimuli-responsive groups for controlled PSs release and active/passive targeting of tumor tissues [17]. One application of MOFs in photodynamic therapy involves the use of nanoscale MOF materials with Mn(II) as an active center to treat hypoxic solid tumors. Hypoxia is a common issue in tumors due to their abnormally high metabolic rates, which reduces the effectiveness of PDT. Lu and his colleagues proposed the use of a novel nano-sized MOF material, Mn-MOF, to address the issue of oxygen deficiency [16]. Mn-MOF provides oxygen required for PDT by catalyzing the decomposition of hydrogen peroxide through the Mn(II) active site, and generates ROS through porphyrins. This method has been shown to effectively address the hypoxia issue. In experiments on mice with breast cancer tumors, it was found that Mn-MOF significantly increased oxygen concentration and enhanced PDT. Further experiments were conducted using the probe 2',7'-dichlorofluorescein diacetate to examine the effect of Mn-MOF on ROS levels in both normoxic and hypoxic cells. The results indicated that among the Metal-MOF materials tested, Mn-MOF exhibited the most superior performance. In summary, Mn-MOF may be a promising candidate for enhancing the therapeutic effect of PDT by alleviating hypoxia [16].

4. Current Challenges Encountered and Possible Research Directions

As an emerging material, MOFs have shown enormous potential. However, their research has also encountered some difficulties and challenges. As a result of these challenges, there are now clearer directions for future feasible research.

4.1. Safety Assessment System

When it comes to drugs, safety is often the top priority. As a newly emerging drug carrier, MOFs currently lack a complete safety evaluation system. To establish such a system, the following issues must be considered. First, it is important to evaluate the stability and biocompatibility of MOFs under physiological conditions to ensure their safety and effectiveness in drug delivery. In addition, testing the stability and biocompatibility of MOFs in different biological systems (such as cells, tissues, organs, or animals) is also important to assess potential toxicity or side effects. Some studies suggest that in vitro tests, such as cell viability assays, biodistribution analysis, or hemolysis tests, can provide useful information about the stability and biocompatibility of MOFs, while in vivo tests, such as pharmacokinetic studies, toxicity studies, or imaging studies, can provide more comprehensive data to help assess their safety. Furthermore, due to the variety of MOF components, it is also essential to conduct quantitative and qualitative studies on the toxicity of its components (degradation products) and metabolites [7]. These are very helpful for comparing different types of MOFs to determine which MOFs are most suitable for drug delivery applications.

4.2. Efficiency

Efficiency here refers to the ability of MOFs to accurately deliver drugs to their targets and release the carried drug molecules. There are two main ways to improve their efficiency.

Firstly, MOF characteristics and functions can be adjusted to optimize their drug loading and release kinetics for ideal drug delivery. Factors such as pore size, surface area, functionality, stability,

and degradation rate can all affect MOF drug loading and release dynamics. A strong binding between MOFs and drug molecules could cause poor drug release, while overly loose binding can lead to low loading capacity and poor protection of drug molecules by MOFs. Research on stimuli-responsive types of MOFs may offer some insight in this area.

Targeting is another important characteristic as high drug concentration is expected to be maintained at the target site while low concentration maintained elsewhere. Improving MOFs' targeting and absorption ability in specific cells or tissues is crucial for enhancing drug bioavailability and efficacy. To achieve this, MOFs' surface properties such as charge, hydrophobicity, or functional groups can be modified to enhance their affinity and specificity towards certain cells or tissues. Additionally, the incorporation of targeting ligands or preparations such as antibodies, peptides, or inducers into conjugated MOFs can enhance their targeting efficacy and decrease their nonspecific binding. Moreover, the required characteristics vary depending on the route of administration (injection, oral intake, etc.), such as acid resistance, intestinal absorption rate, and logP.

4.3. Costs

Currently, there are numerous high-quality MOFs with promising applications. However, due to their high manufacturing costs, large-scale application is not yet feasible. This may be attributed to expensive synthetic materials, complex synthesis and modification processes, or strict translation environments. Therefore, in order to reduce costs, increase yield, and develop new synthetic and functionalization methods, it is crucial to explore new manufacturing approaches. Along this exploration, having new high-quality MOFs with desired performance and functionality may be discovered unexpectedly. Furthermore, the environmental friendliness of manufacturing methods should be carefully considered as an important factor..

5. Conclusion

MOFs have shown significant potential as emerging hybrid porous materials in drug delivery applications. This review discusses various strategies for loading drugs into MOFs, such as surface adsorption, encapsulation, and direct assembly, as well as their advantages and disadvantages. The review also introduces different types of stimuli that can trigger drug release from MOFs. Furthermore, the review provides examples of current applications of MOFs in drug delivery, such as anticancer therapy, treatment of diabetes using exogenous insulin, and photodynamic therapy. However, the review also acknowledges the challenges and limitations that the development of MOFs for drug delivery faces, such as biocompatibility, stability, toxicity, scalability, and regulations. Therefore, further research and investigation into these issues and exploring new approaches to examine novel methods for enhancing the effectiveness and composition of MOFs for drug administration. Further in vivo investigations and clinical examinations are vital to validate the safety and effectiveness of MOFs in delivering drugs. Moreover, it is imperative to encourage cross-disciplinary collaboration to catalyze the progress of drug delivery using MOFs and facilitate its incorporation into clinical settings.

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