Matel Organic Frameworks in Drug Delivery: Synthesis and Drug Loading Strategies

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Abstract. Metal-organic frameworks (MOFs), are widely used in the field of biomedicine. This material display the capacity to change the structures. It can achieve the appropriate size of the apertures by changing the preparation conditions. MOFs have numerous benefits due to their inherent qualities. It can serve as a medication carrier and has several advantages. Among them, an important advantage of MOFs as drug delivery systems is their ability to load large amounts of drugs. Moreover, it is biocompatible to use MOFs as drug delivery carriers. Besides, it is also biodegradable so that the use of MOFs is environmental-friendly. Therefore, studying the application of MOFs in drug delivery systems is of great value. The synthesis method has a significant impact on the structure of MOFs. In this work, the synthesis of MOFs for drug delivery applications is the main topic of this article. The synthesis procedures are discussed in detail. In addition, the drug loading strategy of MOFs is also worth studying. This work also summarizes the drug delivery strategies of MOFs. The research of this work will contribute to the further development of MOFs as drug delivery systems.

1 Introduction

Nowadays, getting a drug delivery system (DDS) can be done in a number of ways. For instances, suppositories and intravenous solutions are the commonly used methods among them. Besides, pills, capsules, powders, ointments, and syrups intended for oral use can also achieve drug loading. However, these approaches have shortcomings. For instance, it is challenging to monitor the effects of drugs since the maximum dose must be taken. In addition, repeated doses must be taken and the administration site must be chosen carefully. Besides, the drug content in the blood is unstable. Both the limited bioavailability and an overly fast response have drawbacks. However, as the result of nanotechnology, these issues can be effectively solved by these nanocarriers. It lessens adverse effects by using the nanomaterials as drug carriers. Metal-organic frameworks (MOFs) has attracted much attention from several application domains. In recent years, researchers have conducted a series of studies in this field. It is wekk known that ions and organic ligands make up MOFs. Due to the great adaptability of metal-inorganic centers and organic ligands, the composition and structure of MOFs materials can be designed. Because of these benefits, MOFs stands out as a novel kind of multipurpose material. These materials often consist of many components such as metal ions and organic linkers.

Because of its qualities and structure, MOFs have been investigated as DDS materials in recent years. Till now, the Cambridge Structural Database (CSD) display 99,075 MOF materials [1]. Among them, compounds of the MOF type and synthesized MOFs are included. Additionally, with the growing research interest on MOFs materials, there are more and more types of MOFs materials. Correspondingly, the applicable fields of MOFs are broaderned. This phenomenon has aroused the interest of researchers.

As a result, understanding MOFs and summarizing how they are used in DDS is crucial. The preparation techniques for MOFs are covered in detail in this study. This research aims to elucidate the variations and the properties of the prepared MOFs from multiple perspectives, including pH, ATP, retox, temperature, light, and ions. It displays the properties of MOFs under various conditions. Besides, drug loading strategies of MOFs are also outlined in this work.

2 Synthesis of MOFs

Synthesis technology is of vital importance for exploring MOFs. Many experimental conditions can be changed including temperature, solvent type, reaction duration, and structural characteristics. The existence of ions as well as their crystallization kinetics are factors may affect the synthesis. These factors have an impact on synthesis of MOFs. Usually, the combination of linkers and metal ions constitute MOFs. Choosing a solvent requires careful consideration of all relevant factors. Redox potential, solvent solubility and reactivity should be considered. These factors are going to have an effect on the preparation. The activation energy and thermodynamics are greatly influenced by the presence

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of solvents for reactions. Furthermore, solid-state synthesis is occasionally employed. One commonly used method for creating MOF crystals is to slowly evaporate the solvent. MOFs can be synthesized using a range of methods, such as diffusion synthesis, microwave-assisted synthesis, ionic thermal synthesis, dry gel conversion, electrochemical synthesis, mechanochemical methods, and reversed-phase microemulsions [2].

2.1 Conventional synthesis

Conventional synthesis is the reaction of polar solvents with metal precursors in a confined container. There are evidences that this technique exhibit higher output yields of crystalline MOFs. In a setting with high pressure and temperature, the precursor dissolves more readily. This experimental result confirms the above speculation. The straightforward response pattern justifies the usage of this approach. Moreover, solvents are thermally synthesised, which is a laborious process in an atmosphere with high pressure and temperature. Therefore, time constraints and safety concerns have hindered the solution thermal approach for the synthesis of nano-MOFs (nMOFs). Furthermore, dangerous solvents like DMF are frequently needed for this synthesis [3].

2.2 Microwave

MOFs can also be synthesized quickly via microwave synthesis. Usually, microwave radiation is applied to the reaction mixture to achieve this. The structural strength of the as-prepared MOFs is improved by this technique. Additionally, the structure of MOFs can also be altered. This process display highly efficient, and it has a short cycle with low toxicity. Moreover, good monodispersity can be obtained by using this method.

2.3 Dry gel conversion

Usually, solvent vapor-passed gel precursors are used to create crystalline MOFs. This method has become more and more common recently due to its tiny reaction volume. Additionally, both the yield and efficiency are high. As a solvent media, water is often used in this preparation method. This approach differs from the conventional one. In the conventional approach, two MOFs with different structures are generated if DMF is used which brings difficulties to further usage and analysis. Therefore, the dry gel conversion is more sustainable

2.4 Ionothermal synthesis

Ionic liquids (IL) are used in ionothermal synthesis to replace the organic solvents. This approach involves dissolving a combination of metal salt linkers in IL. ILs are highly well-liked because of its unique characteristics. IL exhibits superior solvent qualities. Different metal salts and linking agents can be dissolved by it. In addition, it is simple to recycle IL, and it is relatively stable within a wide temperature range.

2.5 Diffusion synthesis

Diffusion synthesis can also used to prepare MOFs. Liquids and gases diffuse are parts of the diffusion process. Diffusion gel is also incorporated. The organic binder and the center metal ion are dissolved in an incompatible solvent by the liquid phase. The interaction of metal ions and organic ligands results in MOF crystals. It is also feasible to create two splits of a set of MOFs using this technique. A volatile organic ligand solution is called a solvent. Once there has been enough reaction between the metal ions and the linker, MOFs can be produced. Usually, it is employed in the synthesis of MOFs that are sensitive. The gentler reaction conditions are the reason for this.

2.6 Microfluidic

MOFs can be prepared by using the microfluidic method. Reactants are injected into the microchannels using a syringe pump. The reactant is then injected with the mixture. Reactants are heated to a particular temperature. By this means, MOFs are produced. This strategy aims to achieve a fast and long-lasting way to synthesize MOF

2.7 Reverse phase microemulsion

Reverse phase microemulsion is a new method of preparing materials which is developed in recent years. Reversed phase microemulsion techniques are commonly used by researchers in the laboratory. In order to facilitate a reaction, components are added to water droplets that have been reverse micellarized. By this preparation method, MOFs with controllable size can be obtained. However, the low output is not conducive to commercial promotion .

2.8 Electrochemical synthesis

There are two forms of electrochemical synthesis which are direct synthesis and indirect synthesis. Direct synthesis refers to the preparation of MOFs by directly dissolving metal ions in an organic electrolyte mixture through anodic dissolution. Indirect synthesis utilizes electrochemical reactions to generate intermediates for the preparation of MOFs. The indirect synthesis method for preparing MOFs requires the use of proton solvents to prevent metal decomposition. By optimizing experimental conditions, this preparation method has been reported to have good efficiency.

2.9 Mechanochemical synthesis

Metal precursors and ligating organic ligands are used in this process. When these chemicals are mixed together, complexes of coordination are formed as well as realign intramolecular connections. Before a chemical reaction

occurring in the metal-organic complex, the bonds of molecule are distorted. Nowadays, grinding reactants under mechanical pressure is a widespread practice. By using mechanochemical grinding, the low melting point of the reactants can be resolved. By this way, MOFs with designed structure can be obtained. Furthermore, this approach is a green synthesis approach, because it lessens the requirement for solvents [4-6].

2.10 Sonochemical

With the use of ultrasonic vibration (20-1000 kHz), there are alternating zones of compression and refraction created by the precursor solution. As a result, homogenous nMOFs were created. This method of preparing MOFs is highly efficient and environmentally friendly in contrast to conventional synthesis methods. This process makes use of homogenous nucleation, thus shorter crystallization periods and noticeably smaller particles are achieved [1, 7].

3 Drug loading strategies to MOF

MOFs are characterized by the various structures and huge surface areas. This establishes the frameworks for various loading methods which are used to load the medicine both inside and outside the pores. The most popular techniques are one-step and two-step [8].

3.1 One-step

The active pharmaceutical ingredient and MOFs are mixed directly in one-step drug loading strategy. This method takes advantage of the high drug load. It also makes use of the specificity of the uniform distribution. However, it is challenging to adjust the morphology, physicochemical properties and particle size of MOFs. In order to ensure the stability of the drug in the synthesis process, further precautions are needed [9].

The One pot method is an effective one-step approach for drug loading. For the one-pot method, the drug and MOF precipitate are mixed during the synthesis phase. Drug molecules can be dispersed uniformly throughout the pores of MOFs. The creation of MOFs using this drug transport technique is incredibly economical. It decreases waste and quickens the reaction process [10, 11]. Zheng and colleagues discovered crystals known as zeolite imidazolate frameworks (ZIFs) which have the ability to trap macromolecules such as drugs and dyes. It is possible to disperse the drugs uniformly throughout the crystal.

Co-crystallization is also a one-step method for drug loading in scientific or commercial researches. Pharmacological loading is a common procedure in the simplest scenario of a response. One possible shape for the active component is a three-dimensional supramolecular structure. Upon co-crystallization of the medication and MOF, this structure is formed. The physicochemical properties of drugs are not affected by co-crystallization. It can increase loading efficiency and medication solubility [8]. Additionally, flunomide can be incorporated into γ-CD-MOF by the use of co-crystallization and impregnation methods As it is demonstrated by Terekhova [12].

One-step drug loading can also be achieved through exploying drugs as organic linkers for MOFs. A medication or its prodrug may work together with a particular metal ion to accomplish a certain function. A study on MOF drug delivery systems based on phosphonate was published by Vassaki [13]. Alendronate, pamidronate, etidronate, and neledronate, which are employed as anti-osteoporotic, are successfully loaded by this method.

3.2 Two-step

The medication is kept in a granular form and placed into a prepared nMOF frame using the material loading method. Drugs with molecular sizes which are smaller than the pore sizes of nMOFs, will be confined inside the scaffold by host-guest interactions such as hydrogen bonding. Nevertheless, through electrostatic interactions, bigger drug molecules with opposing charges are probably going to be adsorbed by nMOF [9].

3.2.1 Impregnation

Diffusion/deposition techniques can be used to impregnate MOFs with precursors due to the permeable nature of their structure. It also comes into contact with tiny molecules and metal ions. This procedure usually involves two steps. The MOF solid is first immersed in a precursor-containing solution. Secondly, there is a further reaction (via reduction, breakdown, or other chemical processes) with the adsorbed precursor. This allows the frameworks to accommodate those new functional groupings. The MOFs require several steps to finish by this drug loading method. As a result, MOFs with high stablility are needed [14]. Devautour-Vinot et al. encapsulate caffeine in several MOFs which are members of the UiO-66 (Zr) family by using this impregnation method successfully [15].

3.2.2 Mechanochemical method

Without the use of solvents, this approach mechanically combines medications with MOFs in a solid state. This drug loading strategy is affordable and friendly to the environment [8, 16]. By using a straightforward ball milling method, Noorian et al. successfully loaded the 5-fluorouracil, para-aminobenzoic acid, caffeine, and benzocaine on the MOFs [17].

3.2.3 Covalent binding

Technology of covalent binding utilized both organic linkers and inorganic metal clusters to create a covalent link in the MOF structure. This appealing tactic places a range of products following MOFs, because there is relatively little force of contact between the medication and MOFs. Thus, there are numerous issues to be solved. For instance, the slow exudation of drugs is a problem.

$UiO\text{-}66\text{-}N_3(Zr_6O_4OH_4(C_8H_3O_4N_3)_6)$ nanostructures of MOFs were produced by Morris [18].

4 Stimuli-responsive MOF

MOFs can be workded as specialized drug carriers. It can permeate cells and tissues. It has a high loading capacity. In addition, it also exhibits relatively low cytotoxicity. It is worth noting that MOFs are allowed to be reacted uniquely to disease triggers. Fig.1 shows various response pathways of MOFs to different stimuli [19]. These stimuli can generally be classified into internal and exterior categories. Temperature, pH, redox potential, and hypoxia are examples of internal stimuli. Besides, the difference in enzyme concentration between healthy and diseased cells also belongs to the internal stimuli. External stimuli, however, are dependent upon external variables. Magnetic fields, heat, light, ultrasonic, and electric current are types of stimuli that can elicit responses of MOFs materials. This characteristic of responding to different stimuli enables MOFs as drug carriers to achieve targeted drug release. Modifying MOFs to enable them to recognize diseased cells sensitively is also beneficial for improving drug efficiency and reducing side effects. This research direction is also the trend in the use of MOFs as drug carriers.

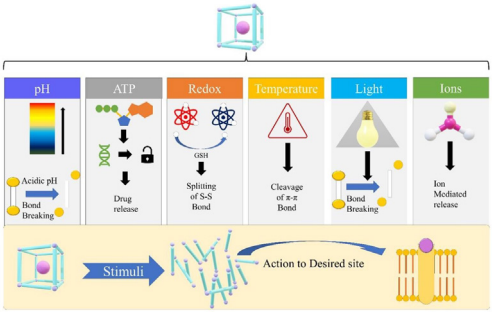

Fig. 1. Response pathways of MOFs to different stimuli [19].

5 Conclusion

MOFs has shown to be a useful drug delivery method in recent years. Its multiple functionalities can be linked to the formation of MOF. Using MOFs as drug carriers display many advantages, such as high drug loading, structural flexibility, high porosity and surface area. Therefore, MOFs is considered as an efficient way for drug delivery. In summary, there is rising support from the scientific community for MOF applications in the biomedical sciences. A large number of technologies related to MOFs for drug delivery have emerged. Reasonably priced and eco-friendly MOF manufacturing techniques are urgently needed. There are also several techniques available to divide the pharmacological load equally. Additionally, site-specific medication delivery is possible, as the result of the stimulus-response capabilities of MOFs. Take its great drug-loading capability into consideration, this technology has great application value and research significance. The active substance could be released in a controlled manner. Therefore, the study of drug delivery strategies is also crucial for the application of MOFs in pharmaceutical delivery systems. This work offers insights on structural composition, preparation methods, and drug loading strategies. Through this research, it is believed that the new preparation method will help expand the technology of MOFs as drug loading carriers. In the future, research on drug strategies will also contribute to the development of this field.

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