Advanced coordination polymer materials for drug delivery systems

Jiaxiong Huo 1,∗

1Beijing No.80 High School, China

∗2WWRRYet@ak1788.cn

Abstract. Coordination polymers demonstrated outstanding performance and ability in drug delivery resulting from their porosity and combinatory structure of non-metal and metal. Previous research has made considerable efforts on different aspects of coordination polymers, including syntheses, modifications and pre-clinical studies. Furthermore, among those coordination polymers, metal organic frameworks turn out to be the one that performs best. Therefore, recent researches are more and more inclined to using MOFs as drug delivery systems. This literature review will talk about the current synthesis methodologies of coordination polymers (especially MOFs) and the drug delivery using coordination polymers bulk system, nano-scale coordination polymers system and nano-scale coordination colloids system. Specifically, the mechanisms and the properties of the synthesizing methods and drug delivery systems. This review will conclude the current development of coordination polymers used as drug delivery systems and the newest synthesized approaches. At the same time, the review will also make an outlook towards the future development of the coordination polymers’ drug delivery systems.

Keywords: Metal Organic Frameworks, Drug Delivery, Coordination Polymers.

1. Introduction
Nowadays, as the categories and functions of drugs increased and developed, drug delivery has become one of the most important issues in pharmacology. Currently, the ideal drug carriers are expected to possess a considerable drug loading and be able to release the drug molecules in a well-manipulated way without causing any toxic substances to be generated while carriers degrading in tissues and organs. Liposomes, nanoparticles and micelles are the most common categories for organic carriers. Those materials are biocompatible and are able to deliver drugs in a well-targeted and precise way. However, those materials most can only be loaded with drug molecule only for less than 5% of its mass [1]. In contrast, inorganic carriers such as silica or metals demonstrated considerable drug loading, but with a relatively weak compatibility and toxicity control. Under such a backdrop, Metal-Organic Framework (MOF) emerged. MOFs were first proposed in 1995 [2]. It’s a hybrid material that combines metals as nodes and organic molecules as linkers [3]. They performed both large drug loading and flexibility. The central metals of MOFs are all transition metals in the periodic table, and the most common are iron (Fe) and chromium (Cr).

After those nanoscale coordination polymers are applied in drug delivery, they've demonstrated well performance in adsorption and stability. Therefore, researchers started researching further development.
that could be made on the synthesis approaches and the range of materials that could be carried by the coordination polymers, nitric oxide, for instance.

This review will conclude the current situation of the synthesize approaches of coordination polymers and the existing drug delivery systems of coordination polymers. Furthermore, the review will give an outlook on the future development and application of coordination polymers.

2. Synthesis of MOFs in drug delivery

So far, scientists have attempted plenty of approaches to synthesize MOFs in drug delivery, including a wide variety, demonstrating different properties, advantages and disadvantages. This section is going to enumerate different synthesis categories and analyze their advantages and disadvantages.

2.1. Conventional synthesis

Convention synthesis is a category of synthesis achieved by heating under the condition of different temperatures. According to the temperature of the synthesis required, MOFs can be generally classified into two types: non-solvothermal synthesis and solvothermal synthesis [4].

2.1.1. Nonsolvothermal synthesis. Non-solvothermal synthesize are reactions that mainly occur below the boiling point used. Some MOFs can be directly formed by mixing the reactants together under room temperature, including HKUST-1, ZIF-8, MOF-5 or MOF-74. Some of them, such as ZIF-8, demonstrated good thermal and chemical stabilities [5, 6].

Another nonsolvothermal synthesis method is vapor diffusion approach. It’s one of the earliest approach for synthesizing CD-MOFs. Through researches, a wide variety of γ-CD-MOFs could by synthesized by combining γ-CD with metal cations such as K+ [7]. A relatively high temperature is vital in some of the synthesis in order to have a high yield and better crystalline structure. Moreover, through rising the temperature to 50°C, time took for the reaction to take place could be decreased significantly.

2.1.2. Solvothermal synthesis. Solvothermal synthesizes are the reactions that could occur at the temperature over the boiling point. Putting water and alcohol together with β-CD and Na2C2O4 at the temperature of 160°C for 3 days long. Sha’s group [8] got a new MOF product, alkaline and α-CD when heat under 433K for four days long. The synthesis of MOF-5 could be carried out under the temperature of 105°C in order to achieve a higher yield than room temperature. [9]

Solvothermal synthesizes and nonsolvothermal once are restricted to synthesize MOFs in laboratories. Therefore, it’s significant to discover new routes for the manufacture of MOFs for industry usages. While for CD types of MOFs, Ding’s group [10] had used a different synthesizing approach which is using industrial crystallization, this could lead to the increment of the productivity for dozen times compared with the conventional synthesis approaches.

2.2. Microwave-assisted solvothermal synthesis

The synthesis of MOFs under microwave and hydrothermal conditions has been widely applied because of its advantages in rate of reaction and productivity. MIL-100 was the first category of MOF synthesized through this approach. MIL-100 of chromium can be synthesized at 220 °C for 4h under such conditions. The CP synthesized through this route demonstrated well performance as the MOF made in the previous research using tradition approach [11].

Compared with other approaches to producing MOFs, microwave-assisted synthesis demonstrated a far higher productivity in the main products with extraordinarily small pores compared with the previous once. Which indicates that the efficacy of adsorption and drug diffusion can be improved significantly. Moreover, this synthesizing approach can produce a MIL-100 (Fe) without fluorine in a couple of minutes, which means it gradually approaches the aim of environmental friendly science. This approach opened the way for synthesizing large-scale NMOFs for bio-medical applications.

Liu’s group [12] also synthesized a category of CD-MOFs within only ten minutes with such approach. They optimized different conditions such as temperature, time, and solvent ratios. Moreover,
it was discovered to be an approach of choice for crystallizing many different MOFs such as MIL-53 of iron.

2.3. Sonochemical synthesis
Sonochemical synthesis is a method that is relatively easy in process and rapid in reaction rate. When a sound wave with high power enters liquids, massive of bubbles are produced and they will cause collisions and will lead to the boost for temperature up to 5000 Kelvin and the pressure in the reaction vessel will reach to a thousand bar. This will result in an extremely high rate of heating and cooling down for more than 1010 K per second, which is quite favorable for the fine crystals to grow. HKUST-1, another type of MOF was synthesized by adding alcohol, H2O and DMF under a specific conditions. The nano-crystalline pores in the size of 10*10^10 nm, are generated for merely five minutes. Increase the time will lead to bigger crystalline pores for 50*10^200 nm and further sonication will make the crystalline structure unstable. This approach will be applied to synthesize the crystals of MOF-5 with pore size of 5*10^-5 mm and MOF-74 of manganese with pore size of 0.6 mm. Ultrasound is also capable to produce tiny nano-scale monodisperse MIL-88A nanoMOFs. However, the yield of such reaction is quite low.

2.4. Mechanochemical synthesis
Mechanochemistry is a field that use mechanical force make inductions and triggers the transformation of chemical substances. Such method demonstrates benefits of producing a synthetic path without or only contains an extremely small amount of solvents compared with conventional synthesis methods that are carried out in microwave or solution. Moreover, the mechanochemical approach had been proven to be an environmental friendly method that possess high productivity of the final MOF product. Another experiments done about such synthesizing approach had made significant improvements the efficiency of energy utilizations. For MOFs’ mechanochemical synthesis, metal oxide-based studies are carried out under room temperature through routes with lower energy cost and solvent requirement developed by Friscic et al. [13]. It could reduce the materials expense and the energy consumption significantly. Such a facile method was also mentioned in several categories of ZIFs synthesizes.

2.5. Summary and outlook of synthesis method
The methodologies and strategies in synthesizing MOFs have experienced significant development whether in the improvement of conventional approaches or the invention of new strategies. In addition, the range of MOFs that could be manufactured had been enlarged dramatically, especially in the discovery of MOFs of new metals such as chromium and zinc. Such a wide range of synthesis could be developed because of the alteration of factors of the surrounding environment, such as temperature, pressure, solvent and reaction time, all causes a huge change in the properties and performances of the resulting product. [14] Subsequently, to improve the adsorption and other characteristics of MOFs, pore sizes and the internal environment of the pores are expected to be altered [15]. This could be a possible orientation to keep carrying on a study on the synthesis of MOFs.

Furthermore, another field worth further developing is the removal of toxicity of MOFs. As mentioned, MOFs consist of central metal elements and organic linkers surrounding them. Therefore, the central metal element could result in the toxicity of MOFs, chromium, for instance. Consequentially, therapies requiring using MOFs encapsulated drugs will lead to additional patient issues.

In brief, the main orientation of further study should concentrate on improving the efficacy and controlling the toxicity of the therapies. [16]

3. Drug delivery systems
Nowadays, more and more coordination polymers emerged. Those materials are combination of organic and inorganic materials. The structure of coordination polymers consist of a central metal atom which must a transition element and the organic linkers surrounding it. Despite the highly-simplified structure, those coordination polymers demonstrated both the positive properties of organic and inorganic
conventional materials. They possess the electromagnetic properties and outstanding thermal stabilities metal or ionic inorganic materials, and also the molecules-related properties such as polymer properties or biocompatibility from organic materials. This explains the reason why coordination polymers often demonstrate unique and extraordinary functions contrasted with simple inorganic or organic materials.

3.1. Coordination polymers as drug delivery systems

There are mainly two ways to apply bulk coordination polymers: deliver drug molecules and deliver nitric oxide.

3.1.1. Coordination polymers used in drug delivery. So far, the first recorded use of the CPs (coordination polymers) in drug delivery industry was in 2006 by Ferey’ group [17]. MIL-100 and MIL-101, two types of chromium-based MOFs, were used as drug carriers, and the drug carried was Ibuprofen (IBU). Both two categories of carriers demonstrated a considerable amount of drug loading: 35% of MIL-100 and 140% of MIL-101. Such an outstanding drug loading successfully decreased weight loss of the drug molecules. The drug release process was performed in a simulate body at 37°C. Both of the two types of polymers had demonstrated a “two-step” release procedure. For the zero-order release of MIL-100, it could bind the drug molecules in first 2hs, and then it sudden experienced a slow but steady release process for 3 days. While for MIL-101, a release type named “Higuchi”, a diffusion process, occurred throughout the first 8hs. It is then followed by a slow rate drug releasing process sustained for 6 days. During the adsorption stage, coordinate bonds are formed between the drug loading absorbed by the carries and central metal atom. The energy stored in this bond was assessed for around 73.17KJ/mol by Jiang. He also claimed that as the drugs are absorbed, and the chromium is gradually saturated, the interactions of Ibuprofen will decrease. This explains why the release rate of Ibuprofen is remarkably fast in the first stage. Another study carried out by Ferey [18] reported a flexible coordination polymer as DDS. The two types of CPs: MIL-53(Cr) and MIL-53(Fe) was selected. Same with the previous experiment, two step release was observed. Herein, the first stage of release took for around three weeks to complete. The procedure was generally the same, despite the presence of a sudden rapid diffusion was observed for the iron CP. Such phenomenon may implied the fact that central metals' properties could influence the release stage of drug delivery. The structure of either two types of CPs remained constant throughout the entire process. Such phenomenon was attributed to the exchanging process of matters between the media which is SBF and the drug molecules. In addition, a strong hydrogen bond that stores a considerable amount energy was generated between the -COOH group of the drug molecules and the -OH group in CP.

3.1.2. Coordination polymers delivering nitric oxide. NO is a vital component many tissues or systems in humans’ body such as immune systems. Therefore, solid carriers of NO have a bright future in biomedical applications due to their irreplaceable status in daily life. Because of the weak Van Der Waal’s forces between NO molecules, NO is under gaseous state under r.t.p. Because of large difference between NO other common seen nano-scale drugs, the drug adsorption and diffusion process could be completely different. A wide variety of conventional materials had already been used as deliverers of NO, but they turned out to be unideal. Morris and his co-workers reported the first use of CPs in delivering NO [19]. They used HKUST-1 as the carrier of NO, which is a porous coordination polymer of tricarboxylate copper benzene. NO was first adsorbed into the dehydrated HKUST-1. Under 298K and one bar pressure, adsorbing capacity of HKUST-1 is over 3*10⁻³ mole per gram. Such capacity is much taller than the conventional carriers. However, the total amount of NO released was only for around 2*10⁻⁶ mole per gram. Such magnitude is far smaller than 3*10⁻³ mole per gram. Through testing, using HKUST-1 as NO carriers demonstrated promising antithrombotic ability as original NO does. One problem of HKUST-1 is the unstable property in biological solutions. This may lead to decomposition or even the production of toxic matters.
3.2. Nanoscale coordination polymers as drug delivery system

Compared with bulk coordination polymers’ delivery systems, the biggest difference is that the period of drug release can be shortened from days to hours, benefiting from its small size. Many advantages of using nano-scale coordination polymers (NCPs) had been discovered, including an enhanced drug solubility, high efficiency when crossing the membranes of organs, a better tolerance from the human tissues and an improved cellular uptake and transport. Thus, NCPs have become a trendy choice for drug delivery systems.

Lin’s team first used NCPs as a drug delivery system [20]. The NCP they used was disuccinatocisplatin (DSCP). It was produced through the reaction between antisolvent and precursor solution. Herein, the drug loading was 73.7%. Silica was used as a stabilizer in the experiment. Two types NCPs were generated: one with a shell of 2 nanometres thick while the other one with a shell of 7 nanometres thick. Research showed that a factor that could affect the release rate is the thickness level of the stabilizer, which is silica. Herein, the NCP without any encapsulation demonstrated an one hour half-life, whereas the two NCPs with a different thickness level of silica each demonstrated half-life for about five and a half hours and nine hours.

They also discovered a new strategy for drug delivery: post-synthetic modification [21]. Such a modification procedure was done after the carrier was synthesized. To ensure the occurrence of post-synthetic modifications, researchers incorporated the two reactants: NH2-BDC and terephthalic acid. NMOF (Nano Metal-Organic Framework), an iron based MOF with MIL-101 structure, can varies with the amount of the reactants presented. NMOF will then react with Br-BODIPY to generate NMOF-2 particles. NMOF was react with [ESCP], c, c, t-[PtCl2(NH3)2(OE)2(O2CCCH2CH2CO2H)] as well, and generate NMOF-3 particles. The release process from NMOF-3 demonstrated a halflife of around 14 hours. The entire drug release process was finished within 80 hours. Post-synthesized NMOF-1c also presented a promising anti-cancer efficacy as the molecules before it was modified.

3.3. Coordination polymer colloids as drug delivery systems

Maspoch’s team first started to use CP colloids to stabilize the drugs. In their study, the colloids are produced by a single reaction: aqueous Zn(NO3)2 with ethanoic 1,4-Bis benzene. The flexibility of the conformation of bix resulted in amorphous colloids. The spheres of colloids could be controlled within the range of 100 to 1500 nano-metres. They reported that the CP colloids could be used in the encapsulation of magnetic particles, organic dyes or quantum dots [22].

Moreover, Maspoch had also done another research about how coordination polymer colloids can be used for drug delivery system. Four anti-cancer drugs SN-38, Doxorubicin (DOX), daunomycin (DAU), and camptothecin (CPT) was used as prototype. In the experiment, the efficiency of the encapsulation of drug can be upped to 21% of the initial concentration. The research was carried out at 37°C with PBS in a dialysis bag. Another colloidal sphere of zinc demonstrated a rapid release rate of almost 80% of the drug in only 8 hours. The remainder maintained a relatively slow release for around two days. The rapid stage should be attributed to the desorption and diffusion process, while the factor that restricted the rate of second stage was the rate of erosion of the colloids inside the buffer, which is used to work as an intermediate barrier [23].

4. Conclusion

Through analysis and the display of recent studies on CPs as drug delivery systems, the current drug development condition had already received considerable advancements. For drug carriers themselves, the categories of MOFs had been diversified significantly: more types of MOFs emerged, more types of central transition metal atoms and structures were used. Furthermore, more institutions had participated the invention of new MOFs such as the Materials of Institut Lavoisier. Moreover, researchers are consistently attempting to improve the compatibility between drug molecules and carriers. In brief, remarkable improvements had been made in the recent decades.

Now, MOFs had been increasingly widely applied to drug delivery industry, whether through nano-scale coordination polymers, coordination colloids or bulk coordination polymers as drug delivery
systems. Based on the improvements made in synthesis approaches or carriers itself, more researches had done in the post-synthetic modifications. Those modifications altered the structure after the process of MOFs’ synthesis to improve the stability or the rate of drug adsorption or drug release.

However, after significant advancements made on coordination polymers in the last decade, the main issue had been transformed how to ensure the occurrence of a robust translation materials into clinical usages. So far, one of the biggest issue is that the processes that were largely carried out in vitro studies won’t goes through the route for clinic or human body environment. Therefore, it’s obvious that the priority of the research on coordination polymers as drug delivery systems ought to be inclined to preclinical studies and experiments on animals as sample.

References