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Metal-organic framework nano structures in drug delivery applications

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Abstract

Formation of coordination bonds between metal ions and organic ligands has led to the development of a new class of material named metal-organic frameworks (MOFs). The highly porous structure with adjustable size, shape, composition and capability of surface modification has made them an interesting object for drug delivery applications. The present paper tried to review the recent advances in the synthesis of nano MOFs as drug carriers, drug loading methods and also described the interactions of MOFs with the biological medium. Finally, perspectives, challenges and future outlooks in the development of MOFs for drug delivery applications have been discussed.

Keywords

Metal-organic frameworks; Drug delivery; Biological medium

1. Introduction

The employment of nanomaterials in therapeutics and diagnostics areas is progressing rapidly. Despite the fact that polymers are one of the most widely used compounds in drug delivery systems, but the metal-organic-frameworks (MOFs) materials have attracted significant interest in the controlled delivery of drug systems. However, since 1989 that Hoskins and Robson (Hoskins & Robson, 1989) reported the synthesis of MOFs for the first time, over 20000 different frameworks of MOFs have been prepared, based on the cambridge database (Furukawa, Cordova, O'Keeffe, & Yaghi, 2013). This increasing interest highlights the high potential of MOFs in drug delivery applications. Porous crystalline framework of MOFs contain rigid organic structures came from the coordination of metal ions (Batten et al., 2013). Metal ions along with the carboxylate linkers create the clusters of rigid frameworks. The multi functional structure of carboxylates enable the association of metal ions into the M-O-C clusters and immobilize them in their place (Hailian Li, Eddaoudi, O'Keeffe, & Yaghi, 1999; Rosi et al., 2005; Yaghi, Li, & Li, 1995). The pore

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size and organic active sites depend on the organic linkers. Figure represents the formation mechanism of MOFs structure.

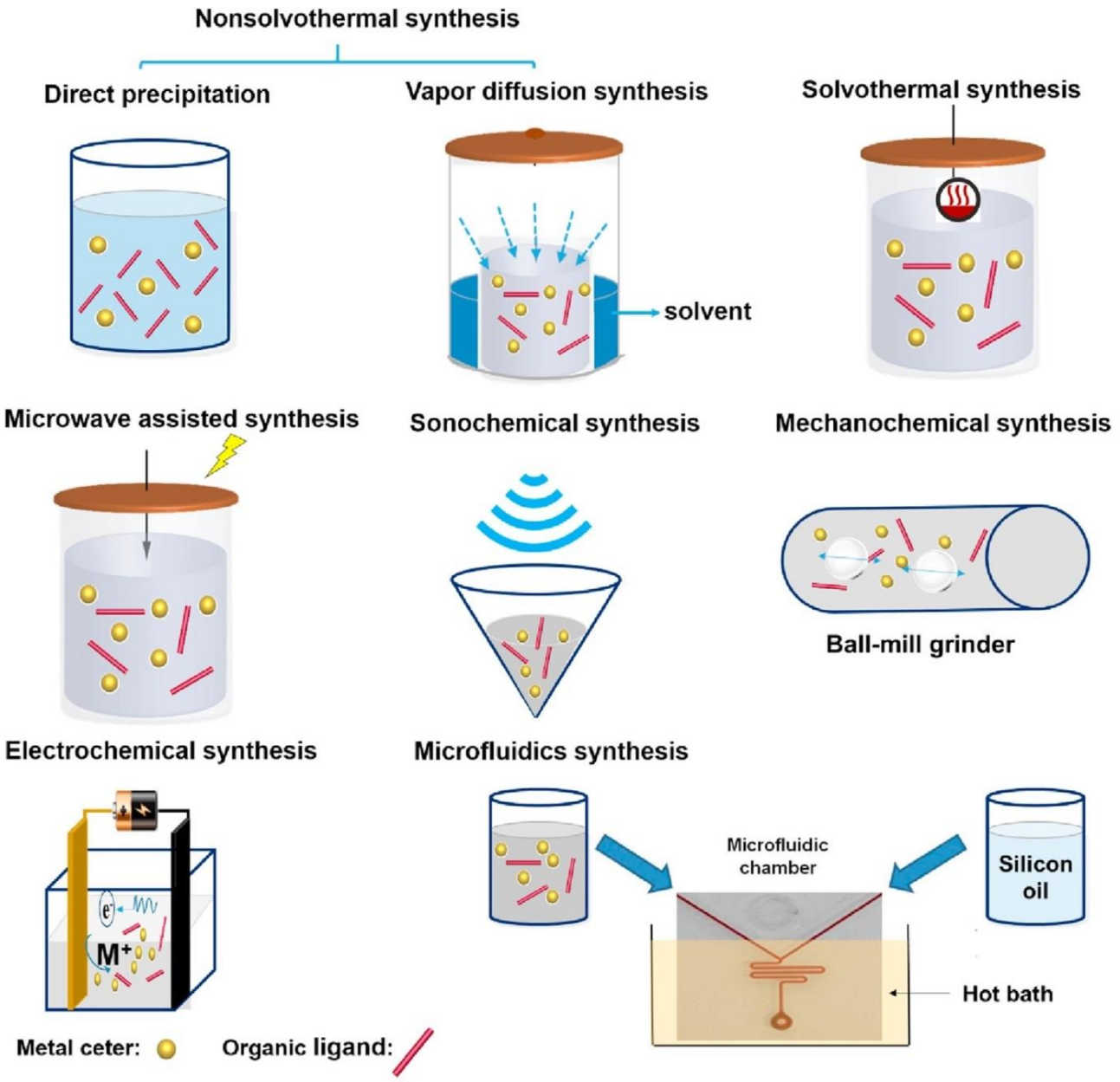

Figure 1. The preparation methods of MOFs

The MOFs are not soluble in water, but incorporating functional groups or surface modification can improve their solubility. Recent developments are reported toward engineering the MOFs structure and developing drug carriers to release water-soluble drugs (Furukawa et al., 2014; Seo et al., 2012). MOFs are flexible molecules with tunable architecture and pores functionalities (Chae et al., 2004). The anionic structure of MOFs can improve the pores hydrophilicity and adsorption or encapsulation of a variety of drugs (Huxford, Della Rocca, & Lin, 2010). The interactions of drug and pores and also the characteristics of porous network can regulate the efficiency of MOFs in drug loading and releasing to the physiological medium (McKinlay et al., 2010). The shape and size of pores in the flexible structure of MOFs can be tailored to host different molecules (Horcajada et al., 2010). Interestingly, surface modification of MOFs does not affect their physicochemical properties. Following the past researches, the present paper tried to depict an overview of the modification of MOFs and drug loading processes. Biological evaluations of

MOFs and future outlook have been also illustrated, which can be helpful for the development of new MOFs-based drug delivery systems.

2. Synthesis of MOFs

Different methods have been used for the preparation of MOFs, which relied on the variation of organic ligands and metal clusters combination. The organic ligand structure can control the shape, size and pores of the MOFs. Some of the commonly used preparation procedures have been summarized here.

1.1. Solvothermal and Nonsolvothermal methods

These conventional preparation methods depend on the temperature used in the synthesis reaction. Nonsolvothermal process happens at room temperature or above. For example, synthesis of MOFs by mixing the precursors at ambient condition, followed by precipitation have been reported. (Cravillon et al., 2009; Tranchemontagne, Hunt, & Yaghi, 2008). Stoddert's group have combined K^+, Na^+, Rb^+ and CD to synthesis CD-MOFs via vapor diffusion method (Smaldone et al., 2010). Using high temperature could yield highly crystalline CD-MOF and reduce the reaction time from days to hours (B. Liu et al., 2016). An aqueous solution of sodium oxalate and CD was mixed with methanol and heated to 160 for 3 days to synthesis β-CD-MOF (Lu et al., 2015). Sha et al. (Sha et al., 2017) also mixed KOH and α-CD, heated at 160 C and obtained α-CD-MOF. Solvothermal and nonsolvothermal procedures are used for the synthesis of MOFs at the small scale. So, developing new synthesis methods at large scale is an important factor. In this way, Ding et al. (Ding et al., 2019) developed a new strategy to increase the productivity, dramatically.

2.2. Microwave assisted synthesis

Preparation of MOFs by using microwave has been widley used because of its benefits as an environmental friendly method and controllability on the size and morphology of MOFs (John et al., 2009; Ni & Masel, 2006). The microwave has been used to synthesis MIL-100 for the fist time within 4 h, which has represented similar physicochemical characteristics to the MIL-100 prepared by usual heating at 220 C for 4 days (Jhung, Lee, & Chang, 2005). Monodispersed nano MOFs (Chalati, Horcajada, Gref, Couvreur, & Serre, 2011) have been achieved via microwave assisted method with higher yields in comparison with other methods. This method has been used to prepare Zr, Ca and Zn based MOFs as drug carriers (Fu et al., 2018; George, Das, & Chowdhury, 2019; Thi Dang et al., 2020). Liu et al. (B. Liu et al., 2017) could optimize the time, temperature and solvent ratios in the microwave method and synthesized both nano and micro scale γ-CD-MOFs within 10 min.

2.3. Sonochemical synthesis

MOFs can be obtained via this easy method rapidly. Upon interaction of high energy ultrasonic waves with liquids and regulating the frequency, the chemical reaction rate is increased as this high level of energy can be adsorbed by the ions in the liquid. Throughout this method, adjusting the frequency can reduce the reaction time, costs and improve the product uniformity. Moreover, it can enhance the yield and safety. By employing ultrasonic waves, the uniform crystals of MIL-88A (Chalati et al., 2011) and MOF-5 (Son, Kim, Kim, & Ahn, 2008) have been obtained.

2.4. Mechanochemical method

This method employs the mechanical force, in stead of solvent for the synthesis, which is regarded as the advantageous of a solvent-free preparation rout. Moreover, mechanochemical process has been considered as a non-hazardeous and cheap method. Friscic et al. (Friscic, Halasz, Štrukil, Eckert-Maksić, & Dinnebier, 2012) has been developed the oxide-based chemistry for the preparation of MOFs and prevented high cost and energy. This simple process has been also used for thermal and pressure-based amorphous ZIFs preparation (Bennett, Keen, et al., 2011; Bennett, Simoncic, et al., 2011).

2.5. Electrochemical method

The electrochemical synthesis is based on the redox reaction through electron transfer between anode and cathode.in order to prepare nano scale MOFs, two electrods are immersed at two sides of the solution of solvent, organic ligand and metal salt, where controlling the voltage, solvent electrolyte and other factors are important. Absence of high pressure and temperature are benefits of this method, which can lead to short reaction time. The nano Cu-MOF (Y. Liu et al., 2021) and DMOF-Zn (Khazalpour, Safarifard, Morsali, & Nematollahi, 2015) have been synthesized by electrochemical method.

3. Drug loading

MOFs have ordered pores and high surface area. Drugs can be attached to the surface or incorporated into the inner structure via one-step and two-step process, as shown in fig 6.

3.1. One-step

One-pot process is the easiest method to integrate drug into MOFs structure, which can be performed during the preparation of MOFs or by utilizing drug as linker in the MOF structure. During the synthesis process, drug can co-crystallize with MOFs to create a big framework contain active compound without changing the physicochemical characteristics of the drug. By using the co-crystallization method, the solubility and loading amount of the drug increase and moreover, IBU (Haiyan Li et al., 2017), leflunmide (Kritskiy, Volkova, Surov, & Terekhova, 2019) and methotrexate (Kritskiy et al., 2020) as poorly soluble molecules can be introduced into the MOF structure. In an economic method, drug can be inserted inside the MOFs matrix. But, the too small size of some MOFs pores such as ZIF-8 (11.6 A^0) cannot let the bulky drug molecules to penetrate into the porosity. However, drug can be mixed with the reactants (linkers and metal ions) during the one-pot synthesis method and incorporated into the MOFs structure. Drugs can be employed as organic linkers during the MOFs formation. A drug delivery system based on the phosphonate MOF has been achieved by using anti-osteoporosis drugs as linkers and Mg or Ca metal ions (Vassaki et al., 2020).

3.2. Two-step

In this strategy, drug is introduced into the MOFs in a drug-solution or the drugs are grinded with MOFs. In one way, the MOFs can be placed in the drug solution and the drug molecules can penetrate into the pores of MOFs, which depend on the pore size, chemical interactions (van der Waals or hydrogen bonding) and MOFs flexibility (Horcajada et al., 2010). For example, IBU molecules could diffuse into the Cu-MOFs channels in a drug solution medium (Javanbakht, Nezhad-Mokhtari, Shaabani, Arsalani, & Ghorbani, 2019). Blending of MOFs with the drug powder is a solvent-free and economic method for drug loading. High amount of caffeine, FU and benzocaine have been loaded by grinding with MOFs (Noorian, Hemmatinejad, & Navarro, 2020). However, different drugs can be incorporated into the MOFs matrix, but the weak chemical bonding usually causes the unsatistafcory release problems. So, formation of strong covalent bonding is a good solution. There are a number of active sites such as hydroxyl and carboxyl groups on the MOFs surface that can form chemical covalent interactions with active groups in the drug molecules structure (Z. Wang & Cohen, 2009). Morris et al. (Morris, Briley, Auyeung, Cabezas, & Mirkin, 2014) could form DNA-MOF conjugate via interaction between functionalized DNA and UiO-66. This obtained compound had higher colloidal stability, cellular interactions and enzyme-loading capacity, compared with un-functionalized UiO-66.

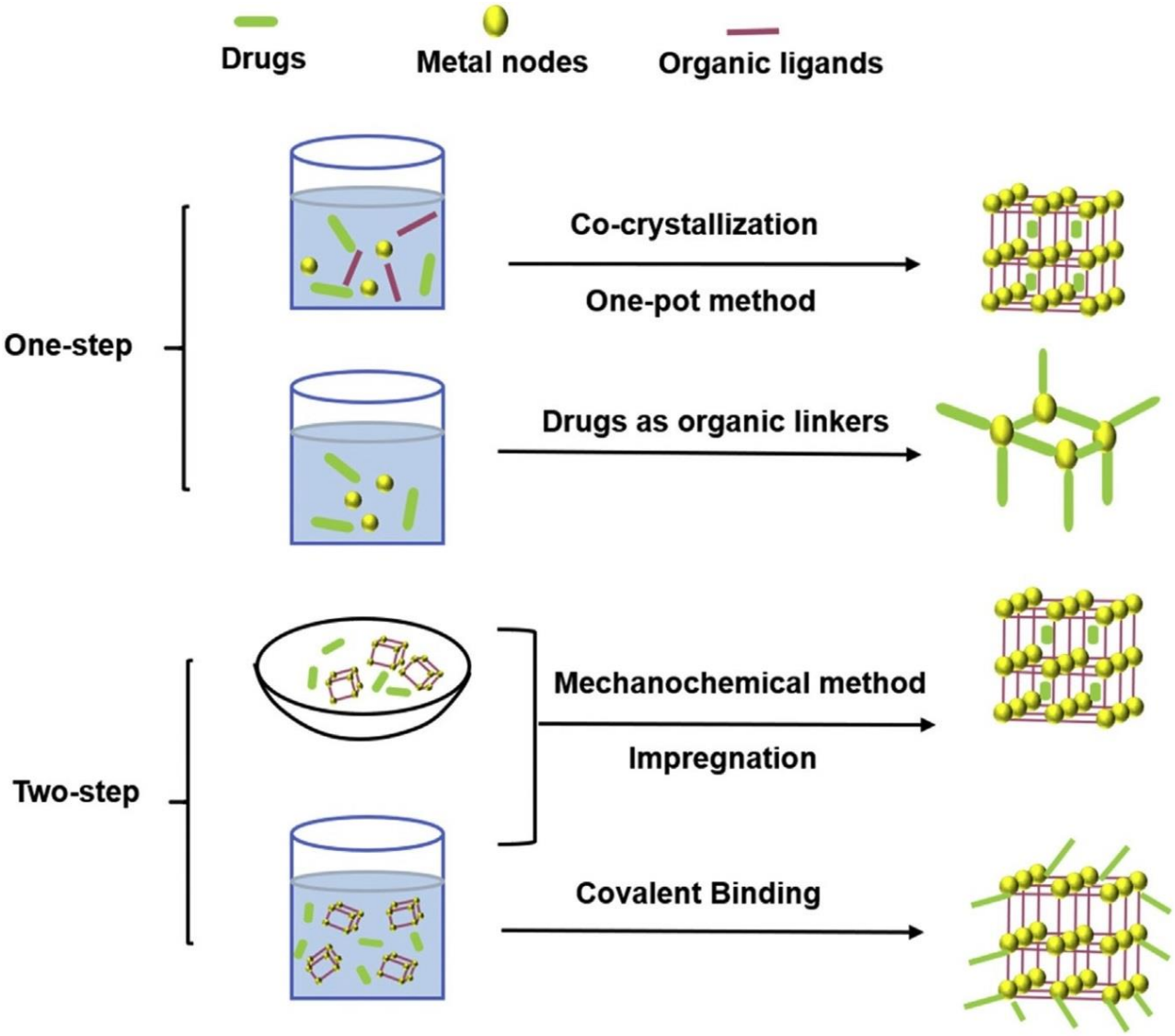

Figure 2. Drug-loading procedures for MOFs.

4. Biological evaluations of MOFs used in cr of drugs

Recently, MOFs have gone through the biological examinations such as cytocompatibility, cellular uptake, tissue interactions and carrying drug into cells. However, most of these studies were *in vitro*, but some reports are available regarding the *in vivo* properties. Biological investigations of Cu-SURMOF 2 exhibited a high degradation rate in cell culture media such as PBS or DMEM, while the dissolution of this compound was not remarkable in water or sea water. In addition, the released Cu ions in the physiological medium had no toxicity and did not influence the attachement and proliferation of rat fibroblasts REF52WT (see Fig. 10). So, the SURMOF 2 could be regarded as a drug carrier with low degradation rate. The cell toxicity of Cu-BTC MOFs have been studied against HL60, NCI-H292, HT29 and MCF-7 cell lines (Lucena et al., 2013; Wu & Yang, 2017). The 5-FU-loaded Cu-BTC MOFs resulted in apoptosis and death of HL60 and MCF-7 cancer cells. But, they could decrease the cytokins and leukocytes, and suppress the inflammation, as studied by peritonitis tests. Horcajada et al. (Horcajada et al., 2010) evaluated the biocompatibility of the iron (III)based nanoporous MIL-100 MOFs hybrids against human multiple myeloma and human leukaemia sells. But, they did not observe any cytotoxicity.

5. Future perspectives

5.1. Perspectives on the Controlled Release of Drugs from MOFs

In order to personalize the patient remedy through the developed molecular medicine, the diagnostics and therapeutics should be connected closely (Horcajada et al., 2010). To do so, nano carriers provide a number of properties such as: absorption of high content of drugs, regulation of the degradation rate and drug release, modifying the surface properties to entrap different drugs and also applications in bio imaging. The modification of the MOFs surface is a critical issue in the biological media, which can not only control the adsorption and release of drugs, but can also enhance the stability and lifetimes, control the interactions with the surrounding media or unwanted cells, and help the MOFs to pass through the physiological barriers and reach the appropriate cells (Fang et al., 2016; D. Wang et al., 2016). McGurie and Forgan (McGuire & Forgan, 2015) have recently reviewed the frequenly used surface modification methods, which can change the bulk features of MOFs. The drug carrying capacity of MOFs is essentially based on their adsorptive potential. However, excessive leaching out the metal ions from their matrix in to the biological media can cause sever toxicity. Incorporating appropriate molecules to the MOFs framework can enhance their stability and inhibit agglomeration; hence decrease the leaking of metal ions. In this regard, MOFs have been functionalized with amino groups, abundantly. Based on the previous reports, attachment of drug along with the cell targeting ligand to the MOFs can endow the infection treatment, bioimaging and cell targeting capabilities at the same time. Figure 14 showed the modification diagram for the Gd-MOFs materials.

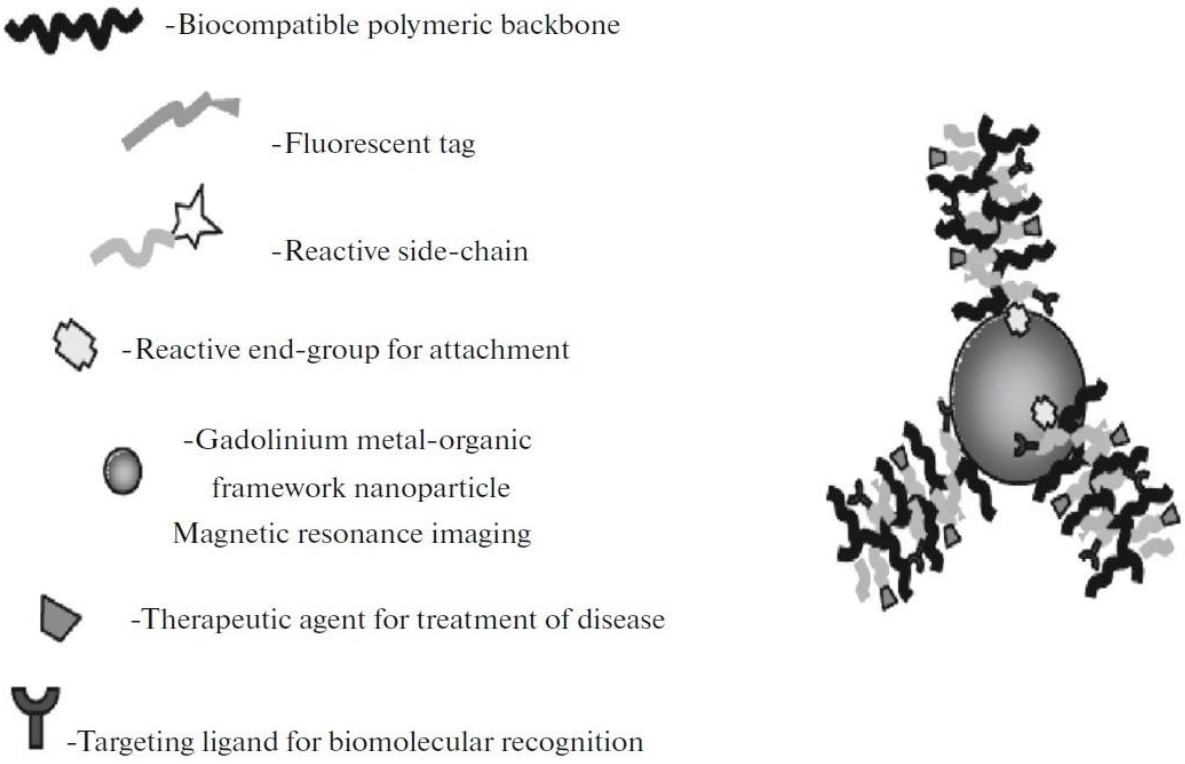

Figure 3. Polymer-modified Gd MOF for drug delivery and imaging (Adapted with permission from (Rowe, Thamm, Kraft, & Boyes, 2009), copyright c 2009 American Chemical Society).

Residual solvents in the MOFs framework after the preparation process is always one of the possible factors that influence the adsorption and release of drugs, since the can alter the coordination of the functional groups and reduce the accessibility. Moreover, diffusion intervention and steric hinderance can complicate the drug loading and delivery procedure. Based on the drugs and MOFs functional groups, characteristics and structure, chemical interactions such as van der Waals, electrostatic, chemisorption

and hydrogen bonding may happen between drug and MOFs, which can improve the drugs stability inside the MOFs and reduce the release rate. The drug loading capacity and release rate, and also the biological responses depend on the morphology and size of MOFs. Most of the studied MOFs have represented the initial burst release in various stages. However, the drug release is expected to follow a zero order rate, but this is not common in MOFs. A number of issues govern the release mechanism, regarding the MOFs degradation procedure, pH-controlled, reduction-controlled, diffusion-controlled, and drug structure decomposition.

5.2. Perspectives on the Biological Evaluations of MOFs Used in CR of Drugs

Employing MOFs in biomedical applications need some investigations surrounding the critical issues such as long-term toxicity and long-term stability in humid conditions (Keskin & Kızılel, 2011). Toxicity of MOFs depends on their size. Systematic circulation is an important factor that can limit the *in vivo* application of these drug carriers. As reported before (Slowing, Vivero-Escoto, Wu, & Lin, 2008), the toxicity of silica nanoparticles is related to the size, where reduction of size to 50-300 nm can facilitate endocytosis with no cytotoxicity. Barbe et al. (Barbé et al., 2004) investigated the circulation of 50 and 250 nm silica within the rats biological system, comprehensively. They have observed that the silica nanoparticles did not incite the immune system even after 1 day of injection, and the particels were excreted out of the body. Similarly, if MOFs are intended to be used in drug delivery systems, surface modification and introducing functionalities, improving biocompatibility and stability are required. For example, Cu- based SURMF 2 was submerged in PBS and a fast degradation was happened, released copper ions. The unmodified Cu-BTC MOFs exhibited high cell toxicity (Lucena et al., 2013), while modification of MOFs by Mn could enhance the cellular uptake in a selective way (Taylor, Rieter, & Lin, 2008). Modification of Gd-based MOFs with RAFT copolymer could lead to cell targeting and cancer treatment (Rowe et al., 2009).

6. Future outlook

In spite of the recently significant increase in the researches on the drug delivery properties of MOFs, this area is still at its infancy. Controlled release of drugs depends critically on the size of MOFs. Reduction of the MOFs sizes to nanometer can help to regulate biocompatibility,blood circulation and increase the pharmacokinetic features of the drugs. Facilitate the endocytosis by the cells without toxic effects, improve bio distribution, minimize the aggregation of residuals and leave them out of the body. The high surface to volume ratio of the nano scale MOFs, provide numerous active site to bond with multiple drugs and deliver high concentration of grug, locally. However, it is still ambiguous whether the size, cytocompatibility and degradation of the MOFs can cross over the features of other nanomaterials being used for the targeting delivery. The MOFs exhibited reliable potential to carry large quantity of biomacromoleculs. Although, the loading and controlled release of drugs is complicated and vary from one MOFs to another. So, it is not easy to find correlation between the release behavior and material structure. Simulation and modeling may help to stimate the relation of structure and property, and supply informative data before the synthesis or modification of novel MOFs and hereby facilitate the selection of the proper MOFs for successful drug delivery. It is necessary to investigate the performance of a newly developed multifunctional MOF, since many factors (cell targeting, bio distribution, drug loading capacity, patient treatment and cellular uptake) can simultaneously influence the results. These factors can define the efficiency and future commercial scale-up procedure and expenses.

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