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REVIEW ARTICLE

OVERVIEW OF METAL-ORGANIC FRAMEWORK BASED DRUG DELIVERY SYSTEMS

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ABSTRACT

While the last few decades have brought about significant advances in the area of novel drug delivery systems, there is still scope for further research. One of the areas that is gaining prominence is Metal Organic Frameworks (MOFs), a class of compounds that is exhibiting potential in drug delivery. MOFs are coordination polymers, new class of highly tunable hybrid materials self- assembled from organic bridging ligands and metal ion cluster connecting points that display permanent porosity, thus showing great promise for myriad of applications in biomedicine, gas storage, catalysis, separation and sensing. Scaling down these materials to nano sizes has conferred potential advantages such as structural and chemical diversity, high loading capacity and intrinsic biodegradability. In this review article, we will be mainly focusing on design and development of MOFs. Also we will be focusing on recent developments with respect to drug delivery, encapsulation and surface modification for MOF/nanoMOF and their future prospects.

INTRODUCTION

Metal Organic Framework are compounds consisting of metal ions or clusters coordinated to organic molecules to form one, two or three-dimensional structures that can be porous (Li, 1999; Evans, 2002; Evans, 1999 and Kitagawa, 2004). MOFs have unique properties such as high drug loading capacity, high surface area, wide range of pore sizes, desirable drug release kinetics, small size, improved pharmacokinetics, biodegradability and biocompatibility which provide entirely new ways to manipulate, store and react to wide variety of substances (Alexis, 2008; Ferrari et al., 2005; Li et al., 2008; Li, 2012 ; Sanha, 2008 and Xu, 2010). This has lead to development of applications in areas such as pharmaceuticals, medical imaging and sensing (Murphy, 2008; DiPasqua, 2008; Cobley, 2011 and Paxton, 2005). Most of the new molecule entities that have been abandoned due to high lipophilicity or poor bioavailability can be reworked upon by incorporation into MOFs. This is because MOFs can be designed to allow for encapsulation and controlled drug delivery of such molecules (Della, 2011; Taylor, 2008; Vallet, 2007 and Rieter, 2006). Scientists have applied this approach to several anti-tumor and anti-retroviral drugs to overcome the challenges posed in successful delivery of these drugs to target sites (Della, 2011; Taylor, 2008; Vallet, 2007 and Rieter, 2006).

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MOFs have attracted the interest of researchers as well as industrialists in past decade and the number of publications related with MOFs has increased remarkably. There has been a surge of research activities carried out on MOFs in recent times. A large number of publications available give us an insight into the structure and applications of MOFs. This review article is an attempt to compile all available literature into a concise form and serve as starting point for carrying out further research for benefit of mankind. An attempt has been made to compile literature pertaining to structure of MOFs, methods of manufacture of MOFs and their applications in pharmaceutical dosage forms.

MOFS: Structure and Types

Several types of MOFs have been mentioned in scientific publications. They vary in their structure and methods of synthesis. Different organic groups such as Br, NH_2, $-OC_3H_7$, $-OC_5H_{11}$, $-C_2H_4$, $-C_4H_4$ and metal ions such as Fe (III), V(III), Cr(III), Al(III) and Fe(III) have been included in the framework (Eddaoui et al., 2002; Serre, 2004; Whitfield, 2005; Horcajada, 2007 and Surbl, 2006). Some important MOFs used for drug delivery are discussed below in brief:

Isoreticularmof (IRMOF-1)

Isoreticular MOFs (IRMOFs) are those in which pore size and functionality could be varied systematically. MOF-5(IRMOF-

1) constructed from octahedral Zn-O-C clusters and benzene links, can be functionalized with organic groups -Br, NH_2, -OC_3H_7, -OC_5H_{11}, -C_2H_4, and –C_4H_4. Their pore size can be widely varied from 3.8 to 28.8Å by using long molecular struts such as biphenyl, tetrahydropyrene, pyrene and terphenyl. The biggest limitation in these Zn_4O based IRMOFs could be their water sensitivity and chemical instability, although their thermal stability is quite high (usually higher than 300°C). These MOFs have been reported to be used for storage and separation Gas storage and separation (Eddaoui, 2012).

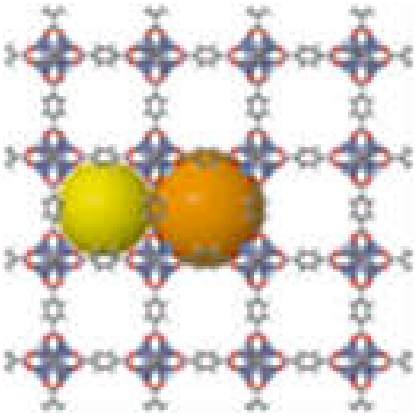

Figure 1. 1IRMOF-1 or MOF-5

Material institute lavoisier (MIL) family

These include series of porous metal carboxylates, which are based on trivalent cations, such as V (III), Cr (III), Al (III) and Fe (III). Important MIL series of MOFs are MIL-47, MIL-53, MIL-88, MIL-89, MIL-100, MIL-101, and MIL-74-Fe (II) and so on, where the numbers 47, 53, 88 etc denote topology. The biggest advantage of MIL series of MOFs lies in their framework stability in water, which is unusual for highly porous MOFs. MIL-53(Sc) is a metal organic framework (MOF) made up of Scandium and Oxygen (ScO_6) nodes with 1, 4-benzodicarboxylic acid struts between the nodes. The MIL series of MOFs can be used in catalysis, gas storage and as Drug Delivery systems for human use (Serre, 2004; Whitfield, 2005; Horcajada, 2007 and Surbl, 2006).

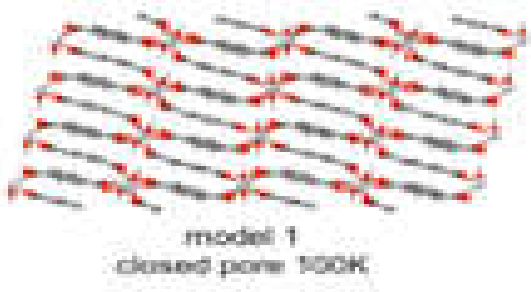

Figure 2. MIL-53

Hong kong university of science and technology (HKUST-1)

These MOFs are made up of copper nodes with 1, 3, 5 – benzenetricarboxylic acid struts between them. The spheres represent the pore sizes within the framework which can be used for gas storage. HKUST-1 MOFs find application in catalysis and separation of Carbon dioxide, Nitrogen, Oxygen, Hydrogen gas and n-butane (Chui, 1999).

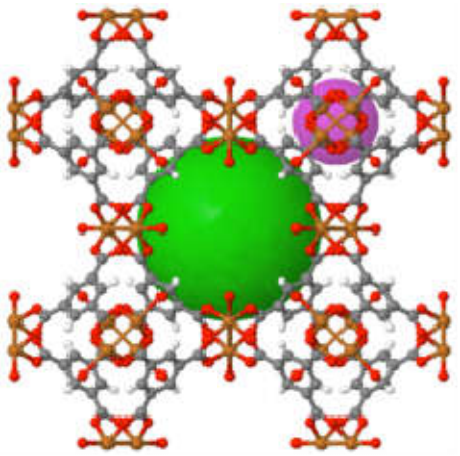

Figure 3. HKUST-1

Zeoliticimidazolate frameworks (ZIFS)

These are special types of porous crystalline materials with tetrahedral network similar to those of Zeolites, in which transition metals (Zn, Co) replace tetrahedral coordinated Si atoms while imidazolate linkers replace Oxygen bridges. ZIF-8 MOF made by zinc ions coordinated by four imidazolate such as HKUST-1, UMCM-1 and so on rings in the same way as Si and Al atoms are covalently joined by bridging oxygens in zeolites. The sphere represents the pore size within the framework which can be used for gas storage. ZIFs have been used in Catalysis, Controlled Encapsulation, and scrubber for removing Carbon dioxide from gas (Park, 2006).

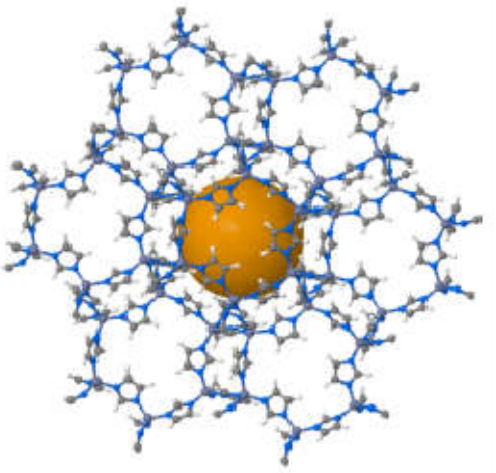

Figure 4. ZIF-8

Universitetetioslo (UIO-66)

This is a MOF made up of [Zr_6O_4 (OH) $_4$] clusters with 1, 4-benzodicarboxylic acid struts. The orange sphere shows the primary pore size and the green sphere shows the secondary pore size, both of which can be used for gas storage (Sabine Devautour, 2012). Applied as adsorbent for removal of aquatic arsenic contamination (Wang, 2015).

Nottingham mof (NOTT-112)

It is a complex MOF made up of Cu_2O_{10} nodes with 1, 3, 5-tris (3', 5'-dicarboxy [1, 1'-biphenyl]-4-yl) benzene linkers. The

spheres show the pore size which can be used for gas storage (Yan, 2009).

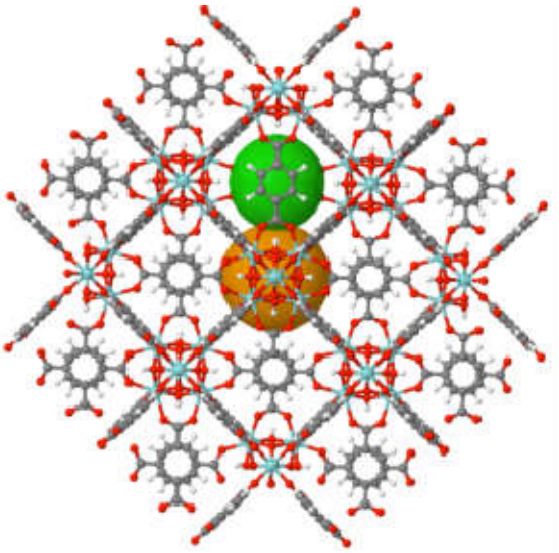

Figure 5. UiO-66

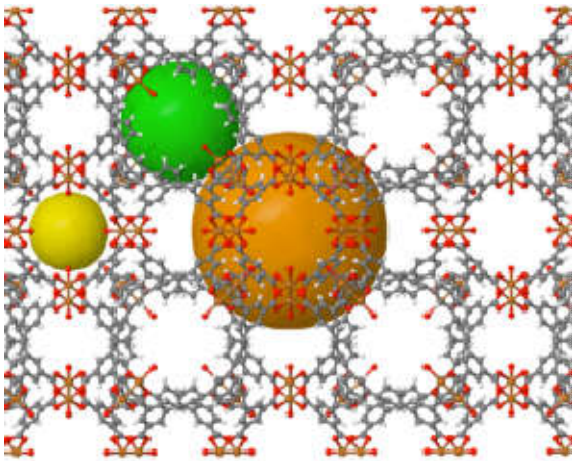

Figure 6. NOTT-112

While there are numerous types of MOFs, each has their own advantages, drawbacks and applications in different fields. However, while selecting MOFs for pharmaceutical applications, especially for drug delivery to target sites, careful consideration of their properties should be done. The MOFs should be biocompatible and non-toxic. Their particle size should be in nanometer range and controlled carefully to have narrow size distribution. They should have high loading capacity and allow large doses of drugs to be entrapped in their pores. The microenvironment in their pores should be amphiphilic so that both hydrophilic as well as lipophilic drugs can be accommodated. Presence of Lewis acid sites is a must for catalysis. Finally the selected MOF should be capable of controlling the release of drug and thus prolonging the duration of action of the drug (Gref, 1994). The ultimate challenge for any carrier for drugs is its behavior under physiological conditions. Studies carried out on MOFs in-vivo revealed the intrinsic instability of uncoated nanoscale MOFs (Guerrero-Martinez, 2010). This was overcome by surface treatment of MOFs by covalent coating (Guerrero-Martinez, 2010). They also underwent aggregation in presence of water. As against this, surface modified nanoMOFs showed improved drug release profile, improved water dispersibility, reduced plasma protein binding, bypassing of reticuloendothelial system (RES) and targeting of drug molecules. Materials used for surface treatment of MOFs should have desirable characteristics such as-

- They should not penetrate inside porous structure.
- They should be stable under physiological conditions.
- They should not interfere with entrapped drugs.
- They should confer nanoMOF colloidal stability.
- They should be obtained in aqueous media in single step without using any toxic additive.

Two general strategies used to modify nanoMOF surfaces include coating with organic polymers and surface modification using silica. Agastoni *et al.* studied the effect of surface modification of porous MOFs with silica shell (Agostonil, 2015). The drawbacks of using Tb (III) were that their degradation led to release of Gd or Tb species with potential toxic side effects. Hence to overcome this noncovalent coating method using cyclodextrin for surface modification was tried. Outer surface of MOFs can be functionalized and stabilized by coating with cyclodextrins which are safe and bio-compatible (Agostonil, 2015). Cyclodextrin molecules bearing strong iron complexing groups (phosphates) were firmly anchored to nanoMOFs surface, within few minutes, simply by incubation with aqueous nanoMOF suspensions. In addition, phosphate cyclodextrins (CD-P) were also studied for their surface modification properties. More than 75% coating was achieved in less than 15 minutes. CD-Ps were found to be bulkier than the nanoMOF windows. Also they formed strong coordination bonds with iron Lewis Acid sites on the MOFs.

The CD-P coating was stable in aqueous solution as well as in phosphate buffer. As against this, dextran coated MOFs exposed to phosphate buffer showed significant coating detachment (Agostonil, 2007). These finding led to conclusion that the coating species with larger rigid sections larger than the windows of the nanoMOFs should be used to avoid pore filling. Drug release after coating and without coating also evaluated to prove that the coating with CD-P does not interact with drug release. In this study, triphosphorylated form of Azidothymidine triphosphate (AZT-TP) was used as model []. Drug loading of 8% was achieved after coating loss of (±1.3) % due to surface modification. CD coating does not act as diffusion barrier for AZT-TP. Coatings stable in body fluids can be further functionalized with targeting ligands; these results pave way for versatile surface modification of nanoMOFs for targeted multifunctional drug delivery. ZIF-8 nanospheres are uniform 70 nm particle with single-crystalline structure. Several small molecules like fluorescein and anti cancer drug camptothecin were encapsulated in ZIF-8 molecule. These 70 nm particles facilitated cellular uptake, and pH –responsive dissociation of ZIF-8 framework resulting in endosomal release of the small-molecule cargo, rendering the ZIF-8 scaffold as ideal drug delivery vehicle.

Stability of ZIF-8 nanospheres were evaluated at low pH and under physiological conditions. It was immersed in phosphate buffer solution at pH 7.4 and pH 6 and release of fluorescein cargo from ZIF-8 was monitored by fluorescence of the supernatants. At the end of 24 hours less than 10% release of

fluorescein was seen at neutral pH whereas 50% of encapsulated fluorescein was released within one hour in acidic pH. This pH driven disintegration can be exploited for selective cargo release in acidic environments. Encapsulation of camptothecin into these nanospheres was successful (in situ encapsulation) with drug loading amount 2% and loading efficiency of 30%. It showed significant decrease in EC_{50} value from fluorecein-ZIF-8 particles (22 to 45μg/ml), suggesting successful delivery and release of cytotoxic CPT in cells. CPT-ZIF-8 treated cells showed increased cell death relative to free CPT treatment (Jia, 2014). Recently Lu et al attempted to improve functional characteristics of ZIF-8 by adsorbing polyvinyl pyrrolidone (PVP) onto nanoparticle surfaces (Guang, 2012). The study led to conclusion that weak coordination interaction between pyrrolidone rings (C=O) and Zinc atoms in ZIF nodes led to stabilization of nanoparticles in solution. In addition interaction between apolar groups of PVP and organic linkers may be responsible for the stabilization.

Encapsulation of bimolecules in MOFs has attracted attention because of ability to control the function, properties and stability of trapped molecules. Recently, MOFs which are self assembled from 3D DNA (guest) and presynthesized MOFs (host) by electrostatic and hydrophilic interactions have shown promise in field of DNA nanotechnology. The biophysical characterization of these MOFs is achieved by fluorescence spectroscopy, quartz crystal microbalance (QCM) and transmission electron microscopy. 3D DNA encapsulation into MOFs will allow us to explore the function of synthetic hosts for conformational and functional control of encapsulated 3D DNA. This new composite keeps 3D DNA nanostructure more stable than only 3D DNA nanostructure in DI water at room temperature and stores amount of genetic information. Making DNA as a guest for MOFs and MOFs become as a new platform for development of DNA nanotechnology (Yongmei, 2014).

Methods for synthesis of nano mof

Spray drying method

In this method a metal ion and an organic ligand which is at least bidentate are introduced into a spray dryer in presence of solvent. The two react giving MOF which is simultaneously dried in the spray drier. The dried MOFs are collected and processed further. Advantage of this technique is that it directly produces dry crystalline MOFs out of the initial liquid reagents and also reduces the reaction time required for synthesis of MOFs. This method is applicable at industrial level. Usually metal ion is provided in salt form. It is versatile method to assemble the nanoMOFs yielding spherical hollow superstructures with diameter smaller than 5μm. It mimics the emulsions used by chemist but does not require secondary immiscible solvents or surfactants. These hallow superstructures can be processed into stable colloids whose disassembly by sonication affords discrete homogenous nanoMOFs. It can encapsulate active species from NaCl to Fe_3O_4 nanoparticles (ComamalaDaniel, 2013). Lanthanide-organic framework nanothermometers can be prepared using spray drying method operative over wide range of temperature –in particular cryogenic range. Maspoch et.al. contributed in the synthesized MOF nanoparticles of Tb (III) and Eu (III), the first lanthanide framework (Zhuopeng, 2015).

Emulsion based interfacial approach

This method can be conveniently used for production of large scale hollow nanospheres and has great potential to open up new avenues to MOF nanocomposites incorporating various nanomaterials in non agglomerated fashion with predesigned functionalities.This facile emulsion based interfacial reaction method can be used for large scale synthesis of hollow zeoliticimidazolate framework 8(ZIF-8) nanospheres with controllable thickness. The inherently porous structure of ZIF-8 shells enables encapsulated catalysts to show size selective hydrogenation reactions (Robert, 2011).

Microwave assisted solvothermal synthesis

Microwave-assisted MOF synthesis yields high quality MOF crystals in a reaction time ranging from about 5 seconds to about 2.5 minutes, compared to hours and days required in conventional solvothermal and hydrothermal method. Adapted to make non-linear MOFs, it involves heating MOF precursors, such as a metal or metal oxide and an organic ligand, in a microwave oven for a period sufficient to achieve crystallization. Synthesis is carried out in a conventional microwave oven, using closed vessel as solvothermal reactor. Prepared solutions were heated by microwave irradiation. Then the synthesized particles were separated by centrifuging, washed with deionized water and dried at room temperature (Guang, 2012). Zinc oxide nanostructures were prepared by reaction of Zn $(CH_3COO)_2.2H_2O$ with water, in 2-propanol as solvent, via a facile microwave assisted solvothermal method. Deionized water was added in same solution, and solution heated by microwave irradiation for 1, 2 and 3 min. The synthesized ZnO nanoparticles were separated centrifugation washed with deionized water and dried at room temperature (Zheng, 2006).

Synthesis of nanosized crystal of isoreticular MOF using surfactant

The mechanism of nanocrystal growth with the assistance of hexadecyltrimethylammonium bromide (CTAB) as surfactant was studied by systematically changing the parameters of the preparation. This is a general method for the controlled synthesis of nanosizedisoreticular metal organic framework (IRMOF-n) crystals, which has good monodispersity and crystallinity. Nano-IRMOF-1 and -3 crystals are produced as examples (Mingyan, 2011).

Template free assembly of mesoporus MOFs

Carbon dioxide dissolves in organic solvents to form CO_2-expanded liquid (CXL). The volume of CXL differs depending on the pressure in the reaction chamber (Li. Peng, 2014). This property of CO_2 can be used to synthesize mesocellular MOFs with large megapores (13-23nm). CO_2 also has a viscosity lowering effect and thus accelerates the reaction between the metal salt and the organic linker. CO_2 also helps in extraction of solvent and recovery of product. CO_2 can be easily removed by reducing pressure in the reaction chamber. This reaction is carried out at room temperature Peng et.al. reacted H_3BTC with Cu $(OAc)_2.H_2O$ in stainless steel autoclave in the presence of CO_2 under pressure (Li. Peng, 2014). The resultant mesoporous MOFs had average pore diameter ranging from 10

nm to 30 nm depending upon CO_2 pressure inside the chamber. It was confirmed that higher CO_2 pressure led to formation of porous MOFs with large mesopores and thinner pore walls.

Solvent evaporation method

Yang *et.al*. have reported a template free solvent evaporation method for construction of large scale meso and macroporeMOFs (Seung Yang, 2014). In this study, crystals of IRMOF-1 were treated with dimethyl formamide (DMF) or anhydrous chloroform. Subsequent evaporation of solvent led to formation of interconnected 3D wormhole-like macroporous structure while maintaining parent microporosity (Seung Yang, 2014). The micropores, along with the mesopores and macropores, provide ion storage sites and ion transport channels that are potential drug holding sites.

Solvent free mechanochemical conditions

This procedure involves grinding of two or more solids with a mechanical ball mill in absence of solvent. The fluorescence probe, MN-ZIF-90 was synthesized by simply stirring ZIF-90 with malonitrile in toluene at room temperature. The reaction mixture was washed extensively with toluene to remove excess of malonitrile then soaked in CH_2Cl_2 for three days.[44] Several papers cite methods of synthesis of MOFs with large pore sizes or flexible, breathing frameworks but are not covered in this review (Suresh, 2013; Haoquan Zheng, 2016; Yanfeng Yue, 2015; Yanfeng Yue, 2015 and Souvik, 2015).

Current research on mof based drug delivery systems

Many trials have been carried out using MOF as drug delivery systems and continuous effort has been made to eliminate their shortcomings. Few of the case studies done are discussed herein.

MOF as controlled drug delivery system

First group of MOFs to be investigated as a potential drug delivery system is the MIL family, pioneered by Ferey and co-workers (Rachel, 2010). This MIL family had a great promise in drug delivery for their attractive characteristics which include large pores (25-34 Å), with large surface area (3100-5900 m^2/g) and ability to incorporate functional groups into the framework. The potential for prolonged release makes MIL-53 an ideal candidate for sustained release drug delivery. Such MOF with hydrophobic pores are ideal for encapsulation of drug molecules with poor aqueous solubility. MOFs can be modified to include hydrophilic pores that can carry positive and negative charges. MOF is anionic so its utility in storage and release of cationic drugs via exchange with cations in biological fluid was investigated. The MOF was loaded with 0.22g of hydrochloride salt of Procainamide, an antiarrythmic drug, per gram. Procainamide therapy is limited by its rapid clearance from body, requiring dosing every 3-4 hrs. The drug release behavior from MOF was observed using HPLC; complete release observed at 72 h in phosphate buffered saline (PBS). In contrast the drug loaded MOF was dialyzed against pure water and showed only 20% of drug release suggesting that majority of procainamide is released by cations present in PBS. The framework was found to be remained intact in these conditions.

Encapsulation in ZIF-7 and ZIF-8

Anticancer drug doxorubicin was encapsulated in ZIF-7 and ZIF-8 and controlled release of drug from these two ZIFs was achieved by external stimuli like change in pH and upon contact with biomimetic system (Chandan, 2015). The study revealed that ZIF-7 remained intact upon change in pH from physiological condition to acidic condition and ZIF-8 successfully released drug under acidic condition, while both acted as excellent excipients for drug release when in contact with micelles or liposomes. Drug release rate from ZIF can be easily modulated using different liposome and ZIFs, which implies for lot of possibilities for ZIFs as a good drug delivery system. It was observed that 40% and 52% drug was incorporated inside ZIF-7 and ZIF-8 respectively. The more stable ZIF-7 took more time to release drug whereas ZIF-8 released the drug rapidly (Chandan, 2015).

MOF-74-Fe (III)

It is prepared through a post oxidation using neutral crystal MOF-74-Fe (II) since it cannot be directly synthesized using ferric salts. It is positively charged and shows very low cytotoxicity upon P12 cells (cell line derived from pheocytochromocytoma of rat adrenal medulla) performed as indicated by MTT assay. It was used for entrapment of Ibuprofen containing carboxyl group which was deprotonated by addition of sodium hydroxide solution formed ibuprofen anion Ibu^-.The drug load was 15.9wt % through anion exchange and salt penetration. Two release processes with different rate were observed due to coordinated and free anions of ibuprofen. Encapsulation of ibuprofen does not change the morphology and no significant layers were observed on surface of microcrystals, indicating drug particles were well dispersed in the channels of the porous materials. Thus, precise control over the content of coordinated anions of drug may tame the release kinetics, consequently making the drug work as designed (Hu. Quan, 2014).

Modified organic linker of IRMOF

Inanother study to improve delivery of anti-cancer drug tamoxifen, organic linkers of the IRMOFs-14 and IRMOFs-16 were modified by inserting an acid and aromatic hydroxyl group to introduce active binding site for drug through acid-base and hydrogen-bond interaction. Replacement of hydrogen atom with hydroxyl moiety in organic linker of MOF was critical for gaining the acid-base and hydrogen bond interaction. Maximum interaction energies with tamoxifen were found around 16.16 kcal/mol for modified IRMOF-14 and 18.32 kcal/mol for IRMOF-16. This combined noncovalent interaction had appreciable multipoint binding without over binding making it a desirable drug delivery system. Absorption and delivery are without its strength prohibition giving timely release of drug within body. This can be used potentially for many other important drugs (De-Yun, 2015). On similar lines other experiments carried out based on modification of organic linkers of MOFs by introducing hydrophobic functional groups into pores of structures, were made to strengthen the M-O bonds. It was found to improve

the water resistance of MOFs in efficient manner. Incorporation of hydrophobic functional groups (e.g. methyl and nitryl) on ligands leads to hydro stable MOF. Encapsulated busulfan having high payload efficiency up to 21.5%. (17.2 wt %) was synthesized and it progressively released drug without any "burst effect". Based on its solublizing properties and low boiling point, Dichloromethane was selected as medium for encapsulation of Busulfan. The obtained complex was characterized by infrared spectra, PXRD, and N_2 sorption (Emmanuel, 2014). Chemical analysis indicated that desolvated MOF showed a remarkable busulfan absorption capacity with encapsulation efficiency higher than the busulfan loading done earlier in MIL-88A, MIL-53, and MIL-89. This hydro stable MOF was nontoxic. This framework also showed very high CO_2 selective capture compared to all other gases.

Highly porous metal organic framework for delivery of multiple therapeutic agents

Such MOFs has been used to entrap an antibiotic drug molecule, an active metal ion and biologically active gas. All three were released simultaneously but at different rates. The method is effective even when one component of the material is less active against particular strains of bacteria offering way to avoid issues with resistance. M-CPO-27(MOF-74) series of material and copper based HKUST-1 (CuBTC) structure having high porosity along with potential for creating under coordinated metal sites (open metal sites) were used for multiple therapeutic delivery (Alistair, 2008). Ni as active metal, meteronidazole (100mg) as antibiotic drug and NO as active antibacterial active gas were loaded into the MOF using methanol as medium. Both HKUST-1 and Ni-CPO-27 have been reported as ideal candidates for binding large quantities of NO and releasing it on exposure to moisture trigger in biologically active quantities (Mckinlay, 2008 and Xiao, 2007). Drug release from MOF loaded with all three was confirmed using Magic angle spinning, NMR (nuclear magnetic resonance) and through evaluation of extent of delivery of different agents. Relative rate of release was observed both in water and PBS.

NO release was measured using chemilumniscence methods, Metronidazole using UV method and metal ion using atomic absorption spectroscopy. Relative rate was found to similar in water and PBS. For Ni-CPO-27, release of NO (□2 mmol g ^{1}) was completed in 30 min, Metronidazole (0.2 mmol g ^{1}) completes release after 6 hr and metal ions (□0.09 mmol g) much more slowly (4% after 6 hrs). When HKUST-1 was used as ligand, Metronidazole release was completed in 120 hr while delivery of metal ion was same as that in Ni-CPO-27. This showed there is not only scope to deliver multiple agents at different rates but to tailor the delivery rates of drugs using different MOFs. This drug combination was effective against both gram positive and gram negative bacteria. Many bacterial strains were tested and no metabolic activity observed indicating NO/metronidazole loaded MOF showed a significant increase in antibacterial activity. Reduction in bacterial burden was observed up to 10 days, due to both fast and long lived bactericidal action (Xiao, 2007). This strategy is not limited to antibacterial agents but could easily include any drug molecule in combination with metal ion or biologically active gases. However further studies need to be carried out inorder to confirm its usefulness in medical applications.

Denovo approach

While MOFs are synthesized in organic solvent medium, enzymes are degraded in the same. To overcome this drawback, Shieh *et al.* carried out aqueous phase synthesis of ZIF-90 (Shieh, 2013). Here, aqueous Zinc nitrate solution was mixed with an aqueous solution containing appropriate amounts of imidazolate-2-carboxaldehyde (ICA), catalase and capping agent. Upon stirring the mixture for 10 min at room temperature, the biocatalyst catalase was embedded in the ZIF-90 network. It was observed that ZIF-90 prevented leaching of catalase thus preventing its degradation by Proteinase K. This augments the role of ZIF-90 in sheltering of the biocatalyst. This technique can be extended to other biomolecules such as proteins, DNA and RNA (Fa-Kuen, 2015).

MOF for imaging and drug delivery

Iron carboxylate of NMOF of MIL-101 structure was synthesized and post synthetic modifications of highly porous NMOF were done for delivering high payload of imaging contrast agent and the anticancer drugs such as Cisplatin (DellaRocca, 2011). Novel porous polymeric fluorescence probes such as MN-ZIF-90, ZIF-90 with their distinct chemical stability and porous framework nature, provide potential for nontoxic molecular recognition in living cells with higher selectivity. This offers unlimited potential for sensing and detection applications. ZIF-90 exhibits an intense blue luminescence when excited under visible light. It is luminescent sensor for metal ions, anions and organic small molecules. Malonitrile moiety linked to walls of ZIF-90 via free aldehyde group allows for covalent fictionalization with malonitrile (Knoevenagl condensation reaction), the malonitrile units undergo a specific reaction with thiol compounds with an enhancement of photoluminescence. This novel porous probe MN-ZIF-90 can be used for detection of H_2S and biothiols (Haiwei, 2014). H_2S produced in CVS has been found to lead to dilation of blood vessels and lowering blood pressure (Haiwei, 2014).

Cysteine on other hand can be converted to powerful antioxidant, thus preventing free radical damage to deoxyribonucleic acid membranes of cells and reduce risk caused by acetaminophen overdose (Haiwei, 2014). Hence recognizing thiol containing species especially signaling them in living cells is crucial for understanding of biological processes. MN-ZIF90 is prepared by mechanochemical method by simply stirring ZIF90 along with malonitrile in toluene at room temperature. The excess of malonitrile in pores is washed with toluene, further soaked in dichloromethane for 3 days. This leads to hypsochromic shift in H_2S solution, double bond is conjugation broken. This probe detected cysteine at concentration as low as 25μmol/L with a noticeable change in fluorescence intensity (Haiwei, 2014). *Invitro* viability assays were performed on HeLa cells (human epithelial cells of stain maintained in tissue culture) to evaluate the potential use of MN-ZIF-90 as contrast agent for optical imaging and probe fluorescence.Using 3-(4, 5-dimethylthiazol-2-yl)-5-(3-carboxymethoxyphenyl)-2-(4-sulfophenyl)-2H-tetrazolium(MTS) assay method, no cell death was reported

after 48h of incubation with MN ZIF-90. Hence this novel open framework fluorescent probe can be used for nontoxic targeting biomolecules and long term labeling of cells (Haiwei, 2014).

Multifunctional nanocarriers for targeted bioimaging and drug delivery

Novel aptamer-guided nanocarrier based on mesoporous metal organic framework (MOF) shell and up-conversion luminescent $NaYF_4:Yb^{3+}/Er^{3+}$ nanoparticles (UCNPs) were used for first time to achieve these goals. These UCNPs, chosen as optical labels in biological assays and medical imaging, can emit strong green emission under 980 nm laser. [62] Lanthanide-doped upconversion nanoparticles (UCNPs) with outstanding optical imaging properties are capable of converting near infrared radiation to visible lights. This new generation of bioprobes namely UCNPS@MOF nanocomposites with ß- $NaYF_4:Yb^{3+}/Er^{3+}$ core and MIL-100(Fe) shell are prepared via interaction method at room temperature. Covalently conjugating AS1411 (a 26-mer guanine-rich oligonucleotide) aptamer on surface of UCNPs@MOF NCs helps in targeting cancer cell since it can bind to nucleolin. (a receptor for AS1411 and overexpressed on plasma membrane of tumor cells). Studies on anticancer drug DOX-loaded UCNPs@MOF NCs revealed that the MOFs could specifically recognize cancer cells and go across the cell membrane by possible receptor mediated enocytosis pathway (Kerong, 2015). It shows a promising strategy for increasing chemotherapeutic efficiency and monitoring cancer progression simultaneously.

Conclusion

Future aspects are quite bright for MOF and NMOF as drug delivery systems and for wide number of other applications. Although numerous studies being carried out in this field showing many of the positive aspects of MOFs, there is a need to extensively study various aspects of MOFs and improve their capability of holding and stabilizing the drug as well as targeting drug delivery to desired sites of action. They should be capable of being synthesized by conventional techniques thereby eliminating need for specialized equipment. This requires coordinated efforts of the pharmacist, the chemist and involves application of principles of physics, chemistry and biotechnology and shows great potential in treatment of diseases hitherto considered difficult to treat.

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