

Hydrothermally Synthesized Copper Isoleucinate (Bio-MOF-30), Evaluated by Single Crystal XRD Analysis and Drugs Storage Property

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Abstract

TBio-MOF-30 [Cu(C₆H₁₂NO₂)₂(H₂O)] has been hydrothermally synthesized from a biomolecule Isoleucine along with a bio compatible metal cation copper and characterized by single crystal XRD analysis. Bio-MOF-30 crystallized in orthorhombic crystal system with P2₁2₁2₁ space group. *In vitro* drugs adsorption studies of three drugs i.e. terazosine hydrochloride, telmisartan and glimpiride have been successfully carried out in Bio-MOF-30. HPLC studies of drugs loaded Bio-MOF-30 have been carried out to estimate the amount of adsorbed drugs and also to observe slow release of drugs after intervals. Thermograms and powder XRD patterns of Bio-MOF-30 before and after drug adsorption have been recorded to elaborate the phenomenon of drugs adsorption in Bio-MOF-30.

Keywords: Metal Organic Frameworks; Isoleucine; Copper; Single Crystal XRD Analysis; High Performance Liquid Chromatography (HPLC); Terazosine Hydrochloride; Telmisartan; Glimpiride

Introduction

Metal Organic Frameworks (MOFs) are the materials which are important due to their tuneable structural features and multifunctional properties [1]. The signature property of MOFs is their porosity, due to which these materials have well replaced their last century's counterpart (coordination polymers) [2,3]. Thousands of MOFs have been prepared in a short period of time since their discovery. Yet this field is so diverse that there is still a wide space to synthesize new MOFs for better applications [4,5].

As the MOFs are based on the organic linker molecules and the coordinating metal cations so their synthesis and structural diversity mainly depend upon the selection of linker as well as metal cations [6,7]. One key advantage is that the possible linker molecules for synthesis of MOFs are infinite including phosphonates, sulfonates, polycarboxylates, pyridyl, phenolates and amines etc [8-10]. So MOFs of desired properties can be designed for synthesis by functionalization of MOFs with suitable

linkers and metal cations [11-13].

For synthesis of MOFs with better drugs storage properties, nitrogen containing linkers such as amino acids are the best choices which have no toxic effects [14]. Similarly bio compatible metal cations like copper, nickel and manganese are suitable to synthesize MOFs both for *in vitro* and *in vivo* drugs adsorption studies [15].

According to some preliminary research reports, amino group containing linker molecules were used for the construction of frameworks suitable for the drugs adsorption [21-23]. MIL-100, MIL-101(Fe), MIL-101(Cr), MIL-53(Fe), MIL-53 (Cr) have been reported with amount of adsorbed drug 1.37, 0.35, 0.35, 0.22, 0.21 g/g and with time release (days) 6, 3, 3, 21, 21 respectively. Also Bio-MOF-1 and Bio-MOF-100 have been reported in recent years with special topology of amino based linker molecules having drugs storage capacity of 0.2 g/g [24,25].

The present work is based on the hydrothermal synthesis of a new bio metal organic framework (Bio-MOF-30) in which bio linker isoleucine and copper cation (trace element necessary for human health) have been used. This new Bio-MOF-30 has been designed to be used as a drug carrier. *In vitro* studies of drug adsorption have been carried out in the present work, which may lead to the *in vivo* drug adsorption investigations.

Experimental

All chemicals were purchased from Sigma Aldrich and these were of reagent grade and were used as such.

In a cleaned glass beaker Isoleucine (0.17 g, 0.2 mmol) and copper chloride CuCl₂•2H₂O (0.35 g, 0.2 mmol) were dissolved in 10mL distilled water. This solution was well stirred for half an hour. pH of the solution was maintained at 10 by using sodium carbonate (Na₂CO₃). This solution was then transferred to a 23 mL teflon lined autoclave. The autoclave was placed in oven at 150°C for three days. After three days fine quality blue colored elongated crystals were obtained from it. These crystals were

collected, washed with water and acetone and were dried.

Elemental Analysis of Bio-MOF-30, $[C_{12}H_{26}N_2O_5Cu]$,

Theoretical: Cu= 18.59 %, C= 42.15 %, H= 7.68 %, N= 8.19 %,

Experimental: Cu= 18.67 %, C= 42.17 %, H= 7.72 %, N=8.23 %.

(KBr 4000-400 cm^{-1}) : 3641.4(br), 3188.1(br), 3089.8(br), 2636.5(br), 1633.6(br 1548.7(m), 1416.70(m), 1334.6(m), 1274.9(s), 1218.9(s) 1141.8(s), 1029.9(s), 794.6(s), 511.1(s), 459.0 (s), 412.7 (s).

Thermograms of Bio-MOF-30 before and after drug loading were recorded on SDT Q600 under a N_2 atmosphere from 0°C to 600°C at a heating rate of 10°C/min. FT-IR spectra of Bio-MOF-30 (see supplementary material) were obtained from Shimadzu 8400 FT-IR by preparing KBr pellets of Bio-MOF-30. Powder XRD pattern of Bio-MOF-30 before and after drug adsorption were recorded on Bruker D₂ Phaser. HPLC studies of the drugs soaked Bio-MOF-30 were carried out on an HPLC instrument, Waters 2695 Separation Module to estimate the amount of drugs adsorbed and also to observe its slow release after intervals.

For the determination of an XRD crystal structure of Bio-MOF-30, a single crystal was used on a Bruker Smart Apex II CCD area detector diffractometer with graphite monochromated $MoK\alpha$ ($\lambda = 0.71073 \text{ \AA}$) radiation. A crystal of Bio-MOF-30 was mounted in a glass capillary and data were collected at 273 K. For the sake of the data collection and refinements all computer programs used were contained in the Bruker program packages Smart, Saint, and SHELXTL [27].

Direct methods have been used to solve the structure in order to locate the position of copper and most of the hydrogen atoms. Subsequent Fourier Transformation Techniques were used to locate and expand the position of the remaining non hydrogen atoms. Final difference Fourier syntheses described only chemically insignificant electron density. All the hydrogen atoms were placed in surely idealized positions. All non hydrogen atoms were refined by anisotropic method and were further refined with the aid of program SHELXL97 (Sheldrick 1997) by the use of a full- matrix least-square calculation on F^2 .

Preparation of drug soaked sample of Bio-MOF-30

In a typical method 0.1 molar solution of the drug (terazosine hydrochloride) was prepared and Bio-MOF-30 was soaked in it. The drug solution was removed after twenty four hours and fresh solution was added to the material. The process was repeated for twenty days on regular basis. The drug soaked material was removed and saved for characterization. TGA and powder XRD studies were carried out for this drug soaked material. Some amount of drug soaked material was placed in distilled water in a vial and aliquot of water containing released drug was separated from vial after one day. Then same amount of fresh water was added to it and after three days aliquot of water containing released drug were separated from it. The same process was repeated after five, seven, nine and eleven days of placing the soaked material in pure water in vial and all these samples were

saved for HPLC studies. The whole procedure was also repeated for Bio-MOF-30 by using other drugs (telmisartan, glimpiride).

Results and Discussions

Crystallographic studies of Bio-MOF-30

The new synthesized compound crystallized in orthorhombic crystal system with P212121 space group forming one-dimensional crystal lattice based on E-values, successful solution and refinements. SAINT program was used to perform the data reduction. Figure 1 shows the ORTEP drawing of the new material Bio-MOF-30.

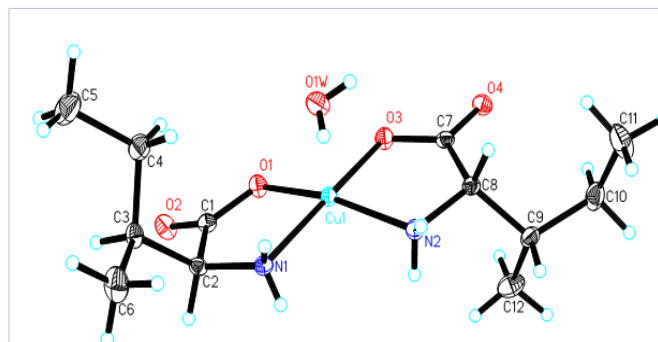


Figure 1: ORTEP drawing of Bio-MOF-30

In an asymmetric unit each copper atom is attached to one water molecule and two bidentate Isoleucinate ligands thus satisfying its five coordination sites. Each of the isoleucinate anion is attached to the copper cation by its nitrogen atom and one of oxygen atoms thus stabilizing its five membered rings. Two isoleucinate ligands coordinate copper in a square plane, satisfying four coordination sites, whereas one water molecule is attached to copper at perpendicular to the isoleucinate-Cu plane. In this way square pyramidal geometry is attained. Different structural views of Bio-MOF-30 along a, b and c axis has been shown below in the Figure 2..

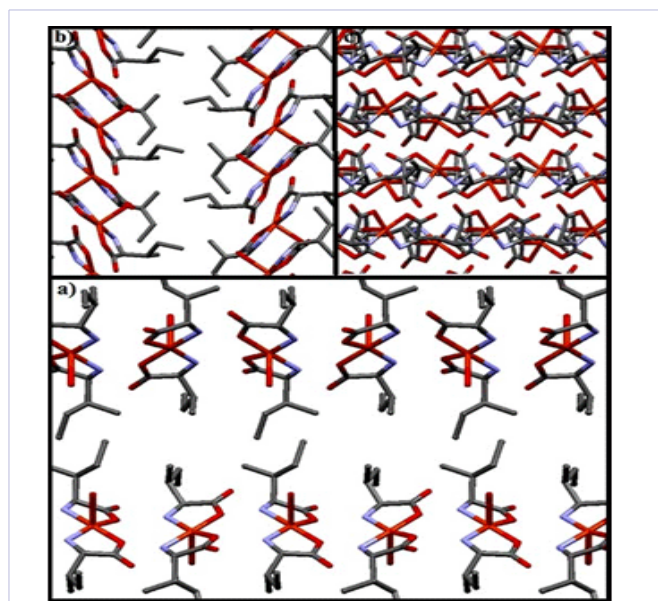


Figure 2: Structural view of Bio-MOF-30 along a, b and c axis

The Cu-O bond lengths are 1.9504(14)Å for Cu(1)-O(1) and 1.9341(14)Å for Cu(1)-O(3). Whereas Cu-N bond lengths are 1.9947(18) Å for Cu(1)-N(1) and 1.9836(18) Å for Cu(1)-N(2). The value of bond angles of O-Cu-O is 91.96(6)° for O(3)-Cu(1)-O(1) and value of N-Cu-N bond angle is 98.82(8)° for N(2)-Cu(1)-N(1).

One dimensional growth of the crystal lattice has been shown in Figure 2. Certain spaces in the crystal lattice are maintained through hydrogen bonding and this packing through one dimensional pillar of lattice results in the development of pores of discrete sizes which can be used for the storage of drug molecules. CCDC-1417408 contains the supplementary crystallographic data for this paper. The data can be obtained free of charge from the Cambridge crystallographic data centre, 12 Union Road Cambridge CB21EZ, UK (fax: (+44)1223-336-033; or E-mail; deposit@ccdc.cam.ac.uk). The crystal data parameters have been summarized in Table 1.

Table 1: Crystal data and Structure refinement for BIO-MOF-30	
Empirical formula	C ₁₂ H ₂₆ N ₂ O ₅ Cu
Formula weight	341.90
Temperature	273(2) K
Wavelength	0.71073 Å
Crystal system, space group	Orthorhombic, P2 ₍₁₎ 2 ₍₁₎ 2 ₍₁₎
Unit cell dimensions	a=5.0212(7)Å b = 10.4206(14) Å c = 13.0071(16) Å
Volume	1564.22(12) Å ³
Z, Calculated density	2, 1.452 Mg/m ³
F(000)	723
Crystal size	0.32 x 0.17 x 0.11 mm
Theta range for data collection	2.50 to 25.49°
Limiting indices	-8<=h<=9, 8<=k<=11, 26<=l<=23
Reflections collected / unique	9255 / 2901 [R(int) = 0.0197]
Completeness to theta = 25.49	99.8 %
Maximum and minimum Transmission	0.8598 and 0.6601
Refinement method	Full-matrix least-squares on F ²
Data / restraints / parameters	2901 / 0 / 205
Goodness-of-fit on F ²	1.062
Final R indices [I>2sigma(I)]	R1 = 0.0226, wR2 = 0.0609
R indices (all data)	R1 = 0.0243, wR2 = 0.0620
Absolute structure parameter	0.014(13)

Drugs adsorption in Bio-MOF-30

Bio-MOF-30 has been explored for its drugs adsorption capacity. Three drugs namely terazosine hydrochloride, telmisartan and glimpiride have been selected for *in vitro* drugs adsorption studies in Bio-MOF-30. Because these three drugs have applications in treatment of hypertension, high blood pressures, cholesterol and sugar levels in human body respectively so the successful incorporation of these drugs for *in vitro* studies will lead towards their usage for *in vivo* studies as well.

Thermogravimetric studies of Bio-MOF-30

TGA plots of both as synthesized material and drug adsorbed material were recorded as given in Figure 3 below and

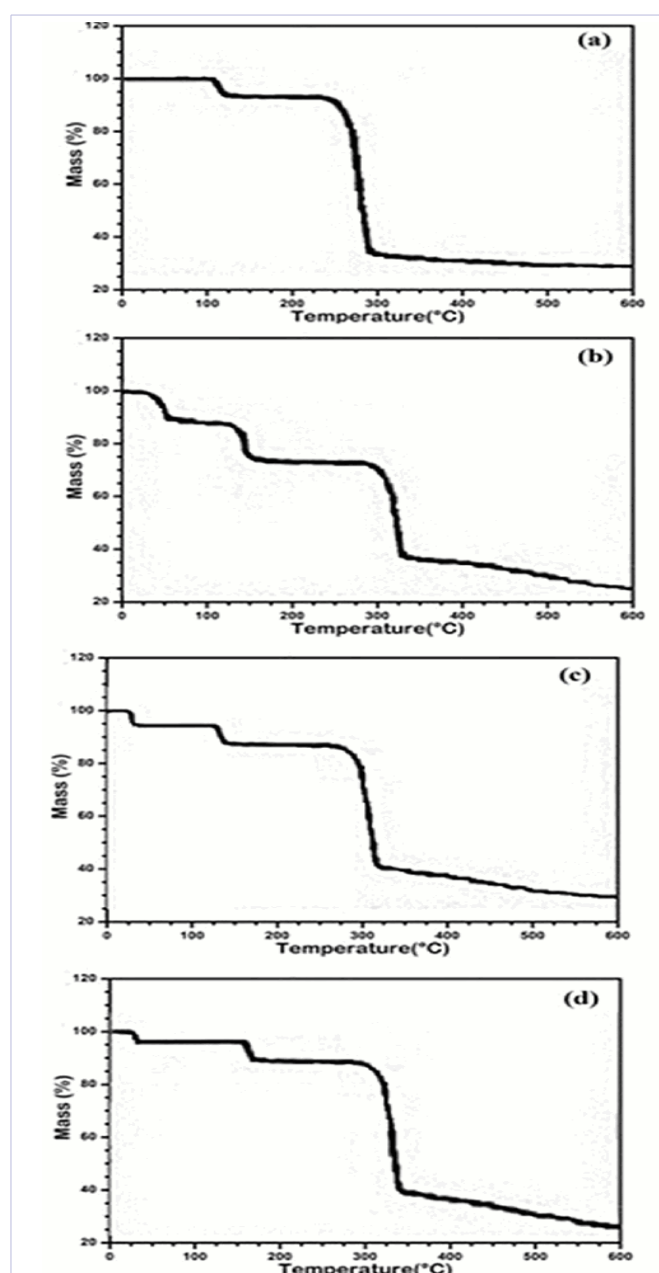


Figure3: Thermogram of Bio-MOF-30 a) Pure b) terazosine loading c) telmisartan loading d) glimpiride loading

compared for the evidences of drug adsorption in Bio-MOF-30. The thermogram of Bio-MOF-30 before the drugs adsorption shows first weight loss of 6 % at 128°C which is due to the loss of coordinated water. Then upto 275°C the framework remains intact, after that the decomposition of framework starts along with ligands which continue till 300°C with major weight loss of 63 %. Decomposition continues gradually uptill 600°C at which weight loss of 68 % shows complete decomposition of framework and formation of metal oxides.

On the other hand the thermogram of the terazosine loaded Bio-MOF-30 indicates the first weight loss of nearly 11 % at 50°C which is due to the loss of adsorbed terazosine molecules. Then up to 145°C the framework shows stability after that weight loss of 24 % can be observed up to 166°C which is due to removal of coordinated water molecule. Gradual decomposition of framework and ligands starts after 300°C. After that maximum weight loss of 60 % at 596°C shows framework decomposition along with the remaining adsorbed terazosine molecules.

Thermogram of telmisartan loaded Bio-MOF-30 indicates the first weight loss of nearly 5 % at 35°C which is due to the loss of adsorbed telmisartan molecules. Then up to 150°C the framework shows stability, after that a weight loss of 13 % is observed up to 155°C which is due to the loss of coordinated water molecule. Then a gradual decomposition of framework and ligands starts which continues till 334°C with maximum weight loss of 68 %. After that at 590°C whole framework decomposes along with the remaining adsorbed telmisartan molecules.

While thermogram of glimpiride loaded Bio-MOF-30 indicates the first weight loss of nearly 4 % at 45°C which is due to the loss of adsorbed glimpiride molecules. The framework shows stability for some time and at 180°C the weight loss of 10 % is observed which is due to the loss of coordinated water molecule. Then up to 345°C the framework remains intact, after that gradual decomposition of framework and ligands starts which continues till 355°C with maximum weight loss of 45 %. At 598°C whole framework decomposes with weight loss of 65 % along with the remaining adsorbed glimpiride molecules.

HPLC studies for the estimation of different drugs in Bio-MOF-30

HPLC studies of drugs soaked Bio-MOF-30 were carried out by using a C-18 Luna 5 μ 100Å (2) Column Phenomenex along with PDA Detector (Waters 2996 photo diode). Size of columns used was 250 \times 4.6mm, while injection volumes of samples used were 20.0 μ L with a flow rate of 1.0mL/min and with a run rate of 8.9 minutes approximately at ambient temperature. Run time and retention time of all samples of drugs were 13.00 minutes and 10.5 minutes approximately. Mobile phase used for procainamide hydrochloride was MeOH: H₂O: TEA (Tri Ethyl Amine); Citrate Buffer: ACN (Aceto Nitrile) for terazosine hydrochloride and MeOH: Citrate Buffer for telmisartan. Whereas Sodium dihydrogen phosphate buffer: ACN (Aceto Nitrile) was used as mobile phase for both glimpiride and rosuvastatin respectively.

582399.66, 23276347, 10678092 were mean peak areas calculated for standards of terazosine hydrochloride, telmisartan and glimpiride respectively. Chromatograms, peak areas of all the samples of water containing released drugs (terazosine hydrochloride, telmisartan, glimpiride) collected after different time intervals for HPLC studies for estimation of drug contents, calculations and estimations of different drugs in Bio-MOF-30,

have been given as supplementary material.

In Bio-MOF-30 three different drugs (terazosine hydrochloride, telmisartan and glimpiride) have been successfully adsorbed. 0.21 g/g material of terazosine hydrochloride has been estimated in Bio-MOF-30. Highest release of terazosine contents from drug adsorbed Bio-MOF-30 was estimated after one day, which gradually decreased with passage of time as has been determined from HPLC calculation of samples collected at different times (see supplementary material) but no terazosine contents were found in aliquot of Bio-MOF-30 taken on the eleventh day.

0.1 g/g material of telmisartan has been estimated in Bio-MOF-30. Highest release of telmisartan contents were estimated in aliquot of water containing released drug after one day which decreased on the third day and no telmisartan contents were found in aliquot of water containing released drug taken on fifth day.

0.6 g/g material of glimpiride has been estimated in Bio-MOF-30. Highest release of glimpiride contents were estimated in aliquot of water containing released drug after one day. Next release was observed after three days. But no glimpiride contents were found after three days.

Powder XRD patterns of Bio-MOF-30

Powder XRD pattern of Bio-MOF-30 in pure form and after drugs adsorption has been recorded as has been given below in Figure 4. Permanent crystalline integrity of Bio-MOF-30 has been revealed from these PXRD pattern after drugs adsorption which indicate that this material has retained its crystallinity even after soaking it in water for several days.

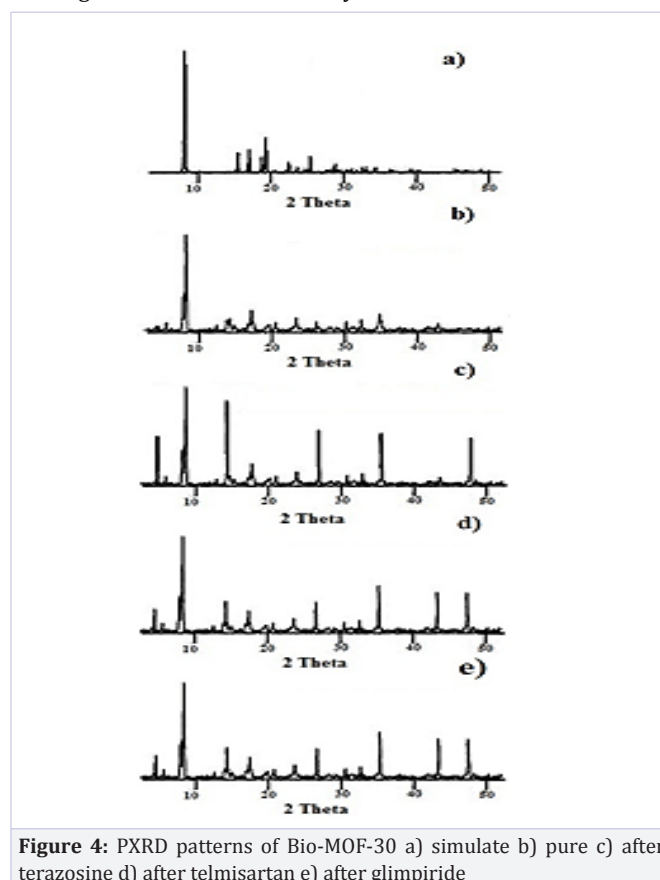


Figure 4: PXRD patterns of Bio-MOF-30 a) simulate b) pure c) after terazosine d) after telmisartan e) after glimpiride

Conclusion

In conclusion the present work describes the hydrothermal synthesis of bio-MOF-30 from a bio linker molecule (Isoleucine) and biocompatible metal cation (copper). This work can lead towards the use of biomolecules for construction of frameworks potentially useful for drugs adsorption. Successful *in vitro* adsorption of three drugs (terazosine hydrochloride, telmisartan and glimpiride) have been explored through Bio-MOF-30 for nine, three and three days respectively with its slow release at times. *In vitro* drugs adsorption studies of Bio-MOF-30 have provided a gateway for *in vivo* drugs adsorption studies as well for the welfare of humans.

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