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Synthesis of Fe(III) Carboxylate Metal-Organic Framework Functionalized with Cetyltrimethylammonium Bromide and its Application for Loading Anti-hypertensive Drug

A. C. Tella[1]* , M. D. Olawale[2]* , A. O. Oyediran[1] and A. B. Alabi[3]

[1]Department of Chemistry, P.M.B. 1515, University of Ilorin, Ilorin, Nigeria.
[2]Deparment of Physical and Chemical Sciences, Elizade University, Ilara-mokin, Ondo state.
[3]Department of Physics, University of Ilorin, Nigeria
*Corresponding author: ac_tella@yahoo.co.uk, olawalemargaret@gmail.com +2348035019197
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Abstract

Metal-Organic Frameworks (MOFs) have been comprehensively investigated as potential drug carriers. The solvent-based hydrothermal synthesis and *in situ* synthetic modification of Fe(III) carboxylate Metal-Organic Frameworks (MIL-88A) constructed from Iron(III) chloride hexahydrate ($FeCl_3.6H_2O$), fumaric acid and Cetyltrimethylammonium bromide (CTAB) was carried out in water. The MOF was characterized using; X-ray powder diffraction (PXRD), FT-IR spectroscopy, SEM and BET analysis. The modified MOF was applied to load an anti-hypertensive drug of the diuretics family; Amiloride hydrochloride. A high loading capacity (0.162 g/g) of the drug was observed on the CTAB modified MOF. The FT-IR analysis of the loaded MOF showed absorption bands characteristics of the drug, at 3569-3104 cm^{-1} and 1606 cm^{-1} respectively, which were attributed to v(N-H) and v(C=C) present in the drug. BET surface area of 192 m^2g^{-1} was found in the MOF before loading. This however, decreased to 178 m^2g^{-1} after loading of the drug. Also, the Langmuir surface area, pore volumes and diameter decreased due to incorporation of the drug molecules into pores of the MOF. The encapsulation efficiency of this MOF demonstrates that; the use of porous CTAB modified iron carboxylates as potential drug carriers could signify main progress for diuretics therapy.

Keywords: Metal Organic Frameworks, MIL-88A, Amiloride hydrochloride.

Introduction

Drug carriers are materials employed for controlled and targeted release of drugs into biological system. The delivery of therapeutic agents is often limited by low solubility and therefore necessitates the use of transport medium to better improve the activity of drug. These medium usually enhance the control of the drug plasmatic level by increasing drug efficiency and also decreasing its toxicity level thereby, enhancing drug stability by promoting biodegradation and ensuring the delivery of drugs to their site of action. The design of drug carriers represent an ever-evolving task for biomedical materials scientists [1,2]. In drug delivery application, the search for suitable non-toxic carriers with efficiency in delivery of therapeutic agents to the human body is a critical challenge. Until now, several approaches have been considered for biological applications, including organic polymers, liposomes, nanoparticles or micelles [2]. However, low drug-loading capacity and/or uncontrolled release are major set back encountered during their application. To mitigate these challenges, a new compound known as metal-organic frameworks (MOFs) have recently been discovered serving as carriers for biomedical applications [3-5].

MOFs display many desirable characteristics including remarkably high surface areas and huge cavity sizes suitable for drug encapsulation, biodegradability and flexible functionality for postsynthetic modification and incorporation of drugs. In addition, high loading capability of a wide range of lipophilic, hydrophilic or amphiphilic drugs are also recoreded. [6] (Marcelo *et al.,* 2012). Many MOFs with different structural characteristics have been employed for drug delivery applications and as vessels for different

therapeutic agents [7]. The first set of MOFs used is the MIL family (MIL= Materials of Institut Lavoisier) investigated by Ferey and co-workers; MIL-100(Cr) and MIL-101 (Cr) [8](Ferey *et al.*, 2006) while MIL-100(Cr) and MIL-101(Cr) hold huge potentials in drug delivery due to their giant pores sizes of 25-34 Å, extraordinary surface areas of 3100-5900 m^2g^{-1} and big pore volumes up to 2 cm^3 g^{-1}. They are relatively toxic and incompatible for biological applications[9]. Synthesis of MOFs for drug delivery purposes require the use of non-toxicity and biocompatibility of both the metal and organic bridging [10].

However, the non-toxic iron(III) carboxylates MOFs such as MIL-53, MIL-88, MIL-89, and MIL-100) are of particular interest, because of their relative stability under physiological condition [9]. In addition, these MOFs can be constructed in favourable aqueous medium. Horcajada reported the application of MIL-53(Fe) as carrier for ibuprofen (IBU). The drug adsorbed 0.210 g IBU/g MIL-53(Fe) and a gradual release of the loaded drug from the MOF was observed [8]. This novel achievement was ascribed to the pore size of the MOF [9]. Furthermore, Horcajada and coworkers, in 2006 demonstrated exceptionally high Busulfan (an antitumoral drug) loaded in pores of MIL-100 (25 wt %) [7].

Modification of the MOFs surface area is widely employed to improve stabilities, reduces physiological barriers and achieve targeted delivery. Hydrophilic polymers such as poly(ethylene glycol) are commonly employed as a coating materials serving as hydrophilic surface. Amino or carboxyl poly(ethylene glycol) chains was successfully introduced in MIL-88 (Fe) and MIL-100(Fe) as coating materials [11]. Qui and coworkers [12] also reported the use of cationic surfactant cetyltrimethylammonium bromide (CTAB) synthesis in the synthesis of HKUST-1. This work study drug delivery capability of Fe(III) carboxylate MOFs, and also establishes the promising application of this MOFs as potential carriers for anti-hypertensive drugs.

2.Experimental

2.1 Materials and instrumentation

Chemicals and reagents were obtained from Sigma Aldrich and used without further purification. Amiloride hydrochloride drug was obtained from Tuyil Pharmaceutical Ltd. Ilorin, Kwara State. The analyses of carbon, hydrogen and nitrogen were carried out on a Perkin Elmer 204C micro-analyser at Meldac. Powder XRD analysis was performed on a Syntag PADS diffractometer at 294 K using Cu Kα radiation (k=1,54059Å) obtained at Stellenbosch University, South Africa. Zeiss Neon 40 EsB field-emission scanning electron microscopy (SEM) was used to achieve the surface morphology imaging of the MOFs. Fourier-transform infrared (FTIR) spectra of both the bare and loaded MOFs were measured using a Nicolet iS5 (Thermo Scientific) IR spectrometer at the Department of Chemistry, University of Ilorin. Specific surface analysis was done using N_2 adsorption–desorption isotherms Micromeritics Tristar instrument at -196 °C to determine the specific surface area, pore size, and volume of the MOFs.

2.1 Synthesis of $[Fe(FUM)_2(H_2O)(CTAB)]$

The procedure reported by Chalati and coworkers [13] was modified for hydrothermal synthesis of the MOF. Fumaric acid (0.320 g, 2 mmol) and CTAB (1.093 g, 3 mmol) were dissolved in deionized water (30ml). Iron(III)chloride hexahydrate $FeCl_3.6H_2O$ (0.242 g, 1 mmol) dissolved in 20 ml of deionized water was slowly introduced into the solution with stirring. The mixed solution was continuously stirred for an hour with magnetic stirrer at room temperature for homogeneity before it was placed in a 100 mL Teflon-lined autoclave, then heated at 100 °C for 24 hours. The product was recovered by centrifugation, washed with mixture of ethanol and water (1:1) and then dried under vacuum. The equation of reaction is shown in scheme 1.

$$FeCl_3.6H_2O + FUM + CTAB \xrightarrow[100^oC\ (24h)]{\text{Deionized water}} [Fe(FUM)_3(H_2O)(CTAB)]$$

Scheme 1: Hydrothermal synthesis of $[Fe(FUM)_3(H_2O)(CTAB)]$

Yield 60 %; Calcd M.wt.= 436.21 g/mol, Mpt.= 261^{o}C; Anal. Calcd. [$C_{18}H_{22}FeNO_8$]; C, 49.56, H, 5.08, N, 3.21, Fe, 8.64. Found: C, 49.20, H, 5.05 N, 3.10, Fe, 8. 51 IR (KBr, cm^{-1}): 3597, 1606, 1391, 564.

2.2 Drug loading procedure

The procedure described by Tella was adopted for drug loading [6]. The drug loading experiment was arried out by introducing, under stirring for 3 days, 100 mg of the dehydrated MOF (activated overnight at 150 ˚C in an oven) in a 10 mL solution of ethanol containing 300 mg of the drug. After drug immobilization, the remaining ethanol was removed at 100 ˚C. Subsequently, the supernatant was collected after centrifugation (10,000 rpm, 30 min) analyzed by UV-Vis spectrophotometer to determine the change in absorbance of the Amiloride hydrochloride solution after loading. The drug loaded MOF was characterized by FTIR, powder X-ray diffraction (PXRD), SEM and BET analysis. The amount of drug loaded per gram of the MOF (Qe) was calculated using equation (1).

$$Qe = \frac{(Co-Ce)V}{m} \quad (1)$$

Where, Co and Ce are the initial concentration of drug solution and concentration obtained from calibration curve in mg/L respectively, v is the volume of drug solution in L, and m is the mass of MOF used in g.

3.0 Results and discussion

3.1 Infrared spectroscopy

FTIR spectra of pure MOFs and Amiloride HCl@MOFs are shown in Figure 1. The peak at 1,606 in the MOF and 1,676 in Amiloride HCl-loaded samples was assigned to C=O stretching. Significant band shifting and intensity changes due to Amiloride hydrochloride absorption were also observed. The stretching at 3569-3104 cm^{-1} can be attributed to the v(N-H) present in the Amiloride hydrochloride. In addition, the observed broad band at 3597–3119 cm^{-1} region of the MOF signify that the characteristic of the presence of coordinated and lattice water molecules in the MOF[14, 15]. The observed differences in the spectrum indicated the possible incorporation of the functional groups of the drug into the pores of the MOF after loading.

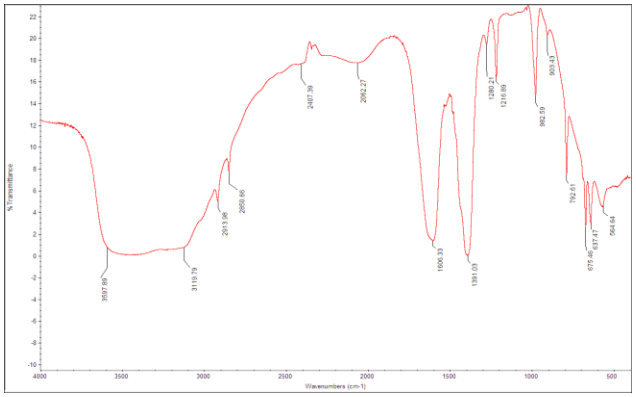

Figure 1A

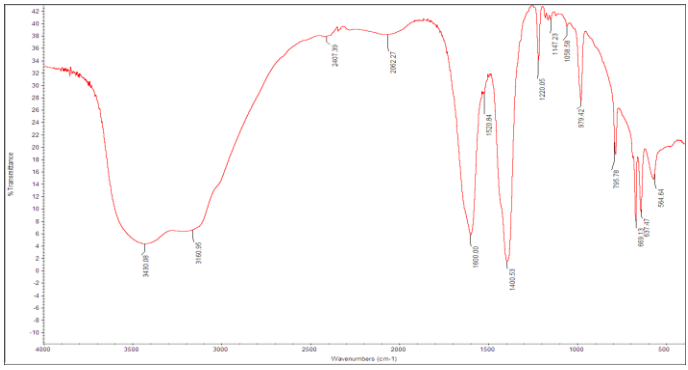

Figure 1B

Figure 1 FTIR spectra of $[Fe(FUM)_3(H_2O)(CTAB)]$ before and after loading of Amiloride hydrochloride

3.2 Powder X-ray diffraction studies

The PXRD data showed that the crystallinity of Amiloride HCl@MOFs was considerably

changed due to the unloaded MOFs (Figure 2). The study also reflected reduction in peaks level and intensity. The PXRD peak positions observed for both Amiloride HCl@MOF and the unloaded MOF matched displaying similarity and indicating stability in the MOF structures after drug loading.[16,17]

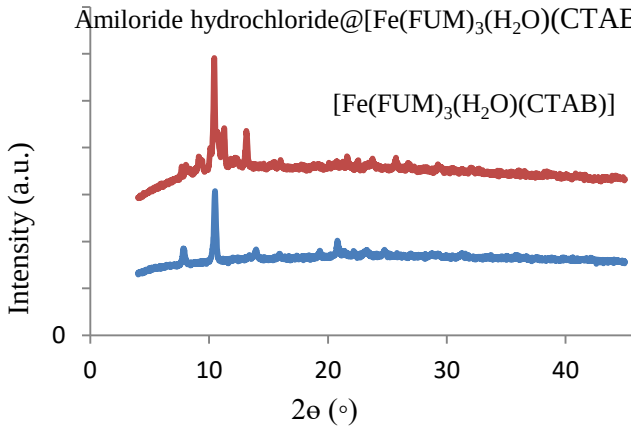

Figure 2 PXRD patterns of the MOF before and after drug loading

3.3 SEM Result

The morphology and particle size of the MOFs were observed by scanning electron microscopy (SEM). Fig. 3 show that the CTAB modified MOF has an hexagonal rod-like morphology [18] and the morphology was retained after drug immobilization on the MOF. An inflated morphology was observed in the SEM image of the Amiloride HCl@MOF when compared with the SEM image of MOF without Amiloride HCl. This attribute suggest that the pore of the MOF is filled with the drug. Result indicates loading of Amiloride hydrochloride within the MOF [17].

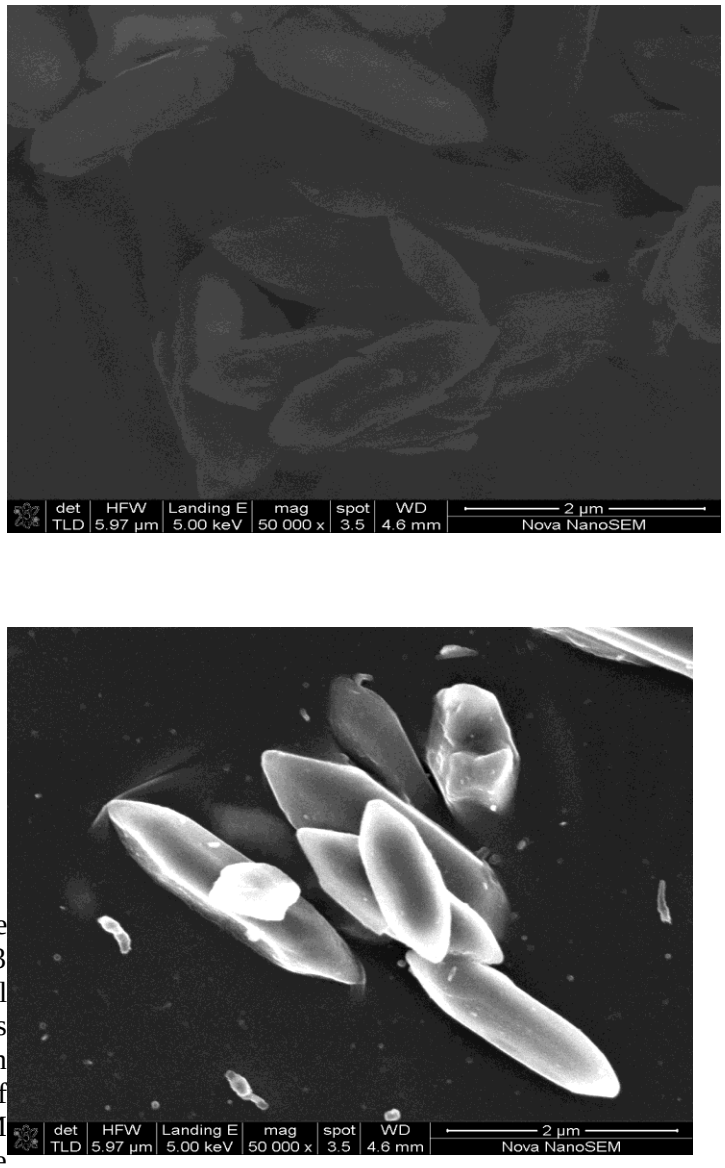

Figure 3 SEM micrographs of $[Fe(FUM)_2(H_2O)(CTAB)]$: before loading (left) and after loading (right)

3.4 BET result

Data obtained from N_2 adsorption-desorption isotherms were analyzed for the determination of the surface area, pore size, and volume. Brunauer–Emmett–Teller (BET) surface area obtained for all MOFs is reported in Table 1. The BET results revealed that the drug loaded MOF

had smaller BET surface area and total pore volume than those of the unloaded MOF [18-20].

Table 1 Textural properties of $[Fe(FUM)_3(H_2O)(CTAB)]$ before and after loading Amiloride hydrochloride

Sample	S_{BET} ($m^2 g^{-1}$)	$S_{Langmuir}$ (m^2g^{-1})	Pore volume ($cm^2 g^{-1}$)	Pore size (nm)
$[Fe(FUM)_3(H_2O)(CTAB)]$	191.87	4362.02	0.049	3.02
Amiloride HCl@$[Fe(FUM)_3(H_2O)(CTAB)]$	178.16	2162.30	0.045	3.00

Conclusion

This study demonstrates the use of biologically compatible porous CTAB modified iron (III) carboxylates metal-organic frameworks as potential carrier for diuretic drugs. Characterization of the MOF was done using IR, Elemental analysis, Powder XRD, SEM, and BET analysis. The successful encapsulation of the drug was confirmed by FT-IR spectroscopy.

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