Development of Zinc and Copper- carboxylate metal-organic frameworks (MOFs) as potential drug Carriers

Adedibu C. Tella[1*], Felicia E. Williams[2], Olalere G. Adeyemi[3], Lukman O. Alimi[4] and Sunday J. Olatunji[1].

[1]Department of Chemistry, University of Ilorin, P.M.B 1515, Ilorin Nigeria

[2]Department of Clinical Pharmacy and Pharmacy Practice, University of Ilorin, P.M.B 1515, Ilorin Nigeria

[3]Department of Chemical Sciences, Redeemer's University, Ede, Nigeria

[4]Department of Chemistry and Polymer Science, Stellenbosch University, 7602, Stellenbosch, Western Cape, South Africa

**Correspondence Author: ac_tella@yahoo.co.uk; +2348035019197*

ABSTRACT

Introduction: Metal-organic frameworks (MOFs) are promising drug nano-vehicles due to their biocompatibility and high porosity. This study explored the feasibility of synthesizing Copper-isonicotinate and Zinc-fumarate mechanochemically and utilizing the compounds for the loading of Ibuprofen and Urea respectively.

Methods: Zinc-fumarate [$Zn(fum)(H_2O)_2$] and Copper-isonicotinate [$Cu(INA)_2].H_2O$] metal-organic frameworks (MOFs) were synthesized by solvent-free mechanochemical technique. These compounds were characterized using elemental analysis; UV-Vis and Fourier transform infrared (FT-IR) Spectroscopies and X-ray powder diffraction (XRPD). The MOFs were investigated for the loading of Ibuprofen and Urea respectively based on their porosities for better drug interaction and high loading using UV-VIS spectroscopy.

Results: The synthesized Zinc-fumarate [$Zn(fum)(H_2O)_2$] exhibited a very high drug loading capacities of 98 ± 1.45 wt% of Ibuprofen while the synthesized Copper-isonicotinate [$Cu(INA)_2].H_2O$] exhibited a slightly high drug loading capacities of 44 ± 0.95 wt% of Urea.

Conclusion: Zinc-fumarate and Copper-isonicotinate MOFs are potential candidates for drug loading.

Keywords: Metal-organic frameworks, Loading, Solvent-free, Drugs, X-ray powder diffraction

INTRODUCTION

Development of an effective absorptive material for efficient loading and delivery of drugs is of great importance in both life and pharmaceutical sciences. The improvements of drug delivery have been carried out using different methods such as complexation and the use of drug carrier[1]. MOFs have become

promising drug nano-vehicles due to their biocompatibility with high porosity (high surface areas and large pore sizes) which allows post-synthetic grafting of drug molecules[2,3]. Metal-organic frameworks are porous crystalline inorganic materials prepared by combining metal ions and organic linkers[4–6], their high structure porosity,[5] makes them applicable in many fields such as gas storage[6,7], molecule adsorption[8], nano particle in-pore assembly[9-11], catalysis[12,13] , drug delivery[14–18], ion exchange[19,20], and several optoelectronic[21] applications. The syntheses of MOFs are carried out in solution at reaction temperature between 25 ^{o}C and 220 ^{o}C depending on the solvent and method used. However, there is always issue of solvent remaining in the frameworks when solvent-based method is used for the synthesis of MOFs in which the subsequent solvent removal can cause the collapse of the network[22]. To eliminate solvent remaining in the frameworks, much effort has been made to create a more effective and easier method which will not involve the use of solvent. Mechano-chemical synthesis is a solvent-free route for the synthesis of metal organic frameworks. This solvent-free synthesis leads directly to powder formation which requires no further treatments. Mechano-chemical syntheses have many advantages over solvent-based synthesis: simplicity of the process, eco-friendly, ease of handling and the cost of production is cheap[23]. In the synthesis of MOFs, carboxylic acid is commonly used as organic linker[24-26] due to their ability to coordinate in more than one point and high structural stability. Many dicarboxylates such as itaconate, succinate, trimesate, terephthlate, fumarate, isophthlate, glutarate, adipate, malonate, oxalate, and isonicotinate[27-31] are very useful ligands in this purpose.

The objective of this study was to synthesize Zinc-fumarate [$Zn(fum)(H_2O)_2$] and Copper-isonicotinate [$Cu(INA)_2$].H_2O] mechano-chemically and utilize these

MOFs for the loading of Active pharmaceutical ingredients (APIs), Ibuprofen and Urea respectively.

MATERIALS AND METHODS

Materials

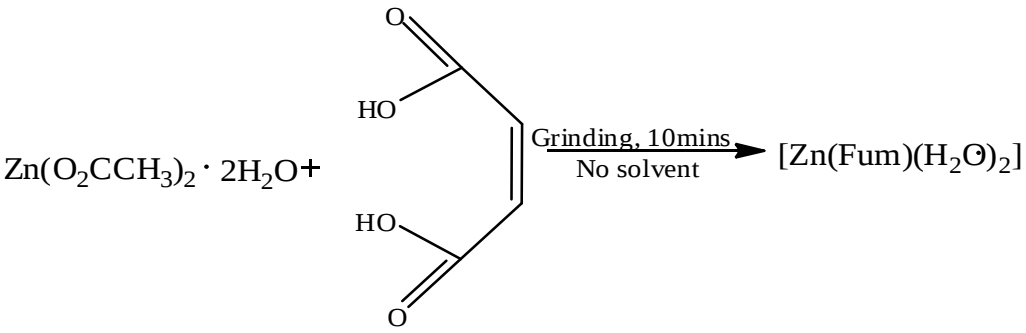
All the reactants are commercially available and were used without further purification. Copper acetate dihydrate ($Cu(OOCCH_3)_2 \cdot 2H_2O$, 99%), isonicotinic acid (INA, 99%), zinc acetate dihydrate ($Zn(CH_3COO)_2.2H_2O$, 99%) and fumaric acid ($C_4H_4O_4$, 99%) were purchased from BDH and Aldrich Chemicals. Ibuprofen (92%) and Urea (99%) were gotten from Tuyil Pharmaceutical Industries Limited, Ilorin.

Synthesis of the MOFs

Synthesis of $[Zn(fum)(H_2O)_2]$

$[Zn(fum)(H_2O)_2]$ was synthesized mechano-chemically similar to a reported method[32].

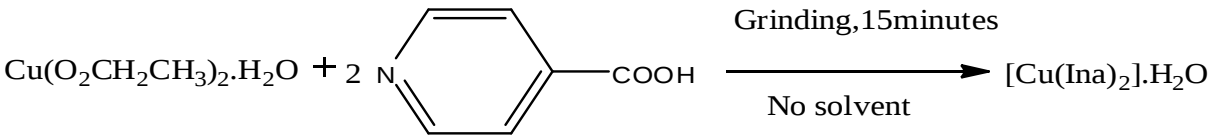
This MOF was synthesized by pulverizing fumaric acid (0.116 g, 1 mmol) and Zinc acetate $[Zn(CH_3COO)_2.2H_2O]$ (0.219 g, 1 mmol) together continuously for fifteen minutes to a fine powder at 27 ± 2 ^{o}C using Retsch MM200 stainless steel ball-mill vessel equipped with steel balls (20g). The white powder obtained was washed with 5 mls of methanol to remove unreacted starting materials and dried at 27 ± 2 ^{o}C. This was done in batches to produce the quantity needed for the loading of drugs. The equation of the reaction is shown below:



Yield: 90%, Anal. Calcd M. wt.= 215.4 g/mol, M. pt.>300^{o}C, Anal. Found (Calcd) % for ($C_4H_6O_6Zn$): C, 22.43 (22.28); H, 3.80 (3.72); N, 0.02 (0.00), IR (KBr, cm^{-1}): 3566, 3090, 2874, 1888, 1685, 1541, 1448, 1419, 1273, 609, 447.

Synthesis of [Cu(INA)$_2$].H$_2$O

[Cu(INA)$_2$].H$_2$O was synthesized mechano-chemically from Copper acetate dihydrate (Cu(OOCCH$_3$)$_2$·2H$_2$O) and Isonicotinic acid (INA) similar to a reported method[33]. Isonicotinic acid (0.246 g, 2 mmol) and Copper acetate [Cu(CH$_3$COO)$_2$.H$_2$O] (0.199 g, 1 mmol) were accurately weighed into different agate mortar which had been washed and dried. The reactants were ground together for 15 minutes till homogenous at 27 ± 2 ^{o} C. The blue powder obtained was washed with 5 mls of methanol to remove unreacted starting materials and dried at 27 ± 2 ^{o} C. This was done in batches to produce the quantity needed for the loading of drugs. The equation of the reaction is shown below:



Yield: 90%, Anal. Calcd M. wt.= 310 g/mol, M. pt.>300^{o}C, Anal. Found (Calcd) % for ($C_{12}H_{10}N_2O_5Cu$): C, 44.10 (46.45); H, 3.04 (3.23); N, 8.30(9.03), IR (KBr, cm^{-1}): 3460, 3064, 1722, 1550, 1552, 1232, 848, 777, 578, 457.

Drugs loading experiment.

The procedure described by Rodrigues *et al.* [34] was used for loading of drugs into MOFs.

IBUPROFEN

Ibuprofen (2.06 g) was dissolved in ethanol (0.1 L) to prepare a stock solution of 0.1M. Serial dilution of the stock solution with ethanol was used to prepared lower concentration of Ibuprofen solutions (0.01 M – 0.04 M). The Ibuprofen solution was scan at ultraviolent region with SHIMADZU UV-1650pc UV-VIS spectrophotometer and the highest absorption was observed at 262 nm (λmax). The absorbance for each concentration prepared was taken and used to plot the calibration curve. Before loading, the $[Zn(fum)(H_2O)_2]$ was activated at a temperature of 150 ^oC in an oven. The Ibuprofen loading was carried out by stirring the activated $[Zn(fum)(H_2O)_2]$ (100 mg) in Ethanol solution (0.145M, 10ml) of the ibuprofen at room temperature for 7 days[34]. After drug immobilization, the suspension was filtered, and the residual was characterized using Fourier transform infrared (FT-IR) spectroscopy and power X-ray diffraction (XRPD). After filtration, the drugs concentration was calculated from the absorbance that was obtained from the UV-visible spectrophotometer.

UREA

Urea (0.6 g) was dissolved in distilled water (0.1 L) to prepare a stock solution of 0.1M. Serial dilution of the stock solution with distilled water was used to prepared lower concentration of Urea solutions (0.04 M – 0.06 M). The Urea solution was scan at ultraviolent region with SHIMADZU UV-1650pc UV-VIS spectrophotometer and the highest absorption was observed at 268 nm (λmax). The absorbance for each concentration prepared was taken and used to plot the calibration curve. Before loading, the $[Cu(INA)_2]$ was activated at a temperature of 150 ^oC in an oven. The Urea loading was carried out by stirring the activated

[$Cu(INA)_2$] (100 mg) in aqueous solution (0.503 M, 10mL) of the Urea at room temperature for 3 days[34]. After drug immobilization, the suspension was filtered, and the residual was characterized using FT-IR and XRPD. After filtration, the drugs concentration was calculated from the absorbance that was obtained from the UV-visible spectrophotometer.

RESULTS

Characterization and properties of Drug Carrier

The synthesized MOFs were confirmed to be [$Zn(fum)(H_2O)_2$] and [$Cu(INA)_2$].H_2O as determined by elemental analysis, infrared spectra and also the XRPD patterns[33, 35, 36].

Experimental characterization of the drug–[$Zn(fum)(H_2O)_2$] MOFs.

The loading of ibuprofen on the [$Zn(fum)(H_2O)_2$] was ascertained by UV–Vis spectroscopy

(Figure1). This technique was used to quantify the mass of ibuprofen adsorbed on the [$Zn(fum)(H_2O)_2$] after 7 days. The calibration curve showed that 98 ± 1.45 wt % of ibuprofen was adsorbed on the [$Zn(fum)(H_2O)_2$].

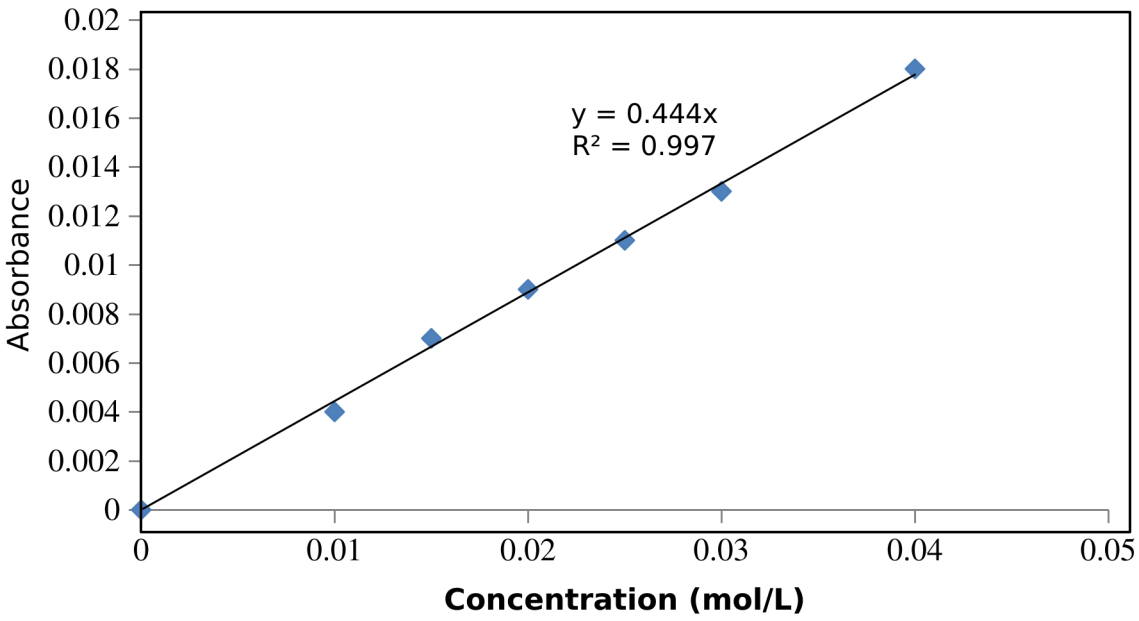


Figure 1: Calibration Curve obtained from the absorption spectrum in the ultraviolent-visible spectral region for the Ibuprofen solution.

The absorbance, concentration, percentage and mass of ibuprofen before and after loading on [Zn(fum)(H_2 O)$_2$] at 30 ± 2^{o}c are as shown in Table 1.

Table 1: Absorbance, concentration, percentage and mass of ibuprofen before and after loading on [Zn(fum)(H_2O)$_2$] at 30 ± 2^{o}c.

Variables	Before loading	After loading
Abs. of Ibuprofen	0.064	0.001
Conc of Ibuprofen	0.145M	2.27×10^{-3} M
% of Ibuprofen	100%	1.56%
Mass of Ibuprofen	300mg	5mg

To establish these findings, these MOFs were characterized by Fourier transform infrared spectroscopy (FTIR) before and after loading which were used for comparison. The FTIR spectra of

the MOF and drug absorbed in pores of the MOF are presented in Figure 2.

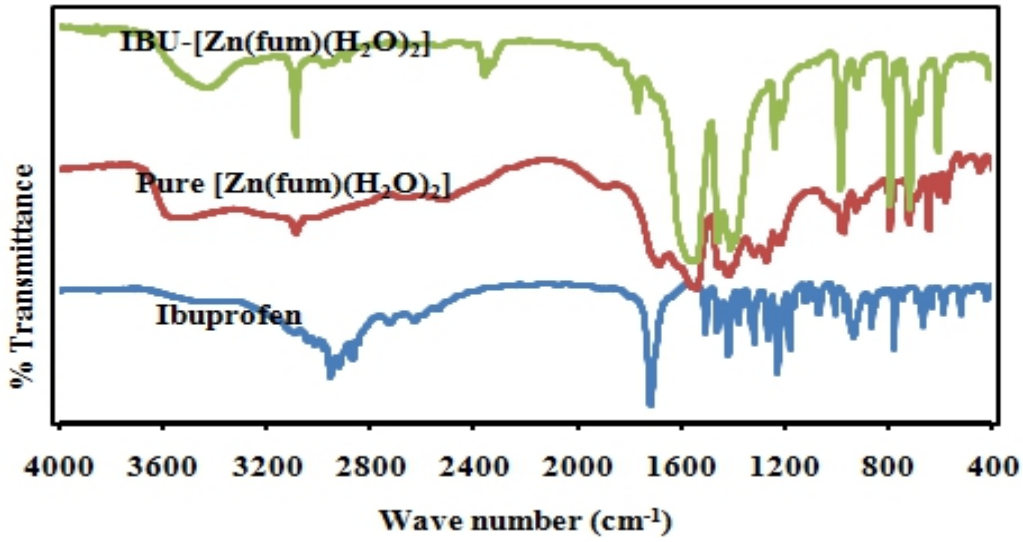


Figure 2: Infrared spectra of [Zn(fum)(H_2O)$_2$] before and after loading of Ibuprofen

The MOFs were further characterized using XRPD. Significant changes of peak positions and relative intensities were further observed for the MOF Ibuprofen–[Zn(fum)(H_2O)$_2$] compared with their dissociated forms (Figure. 3), indicating the interaction of Ibuprofen into MOF pores.

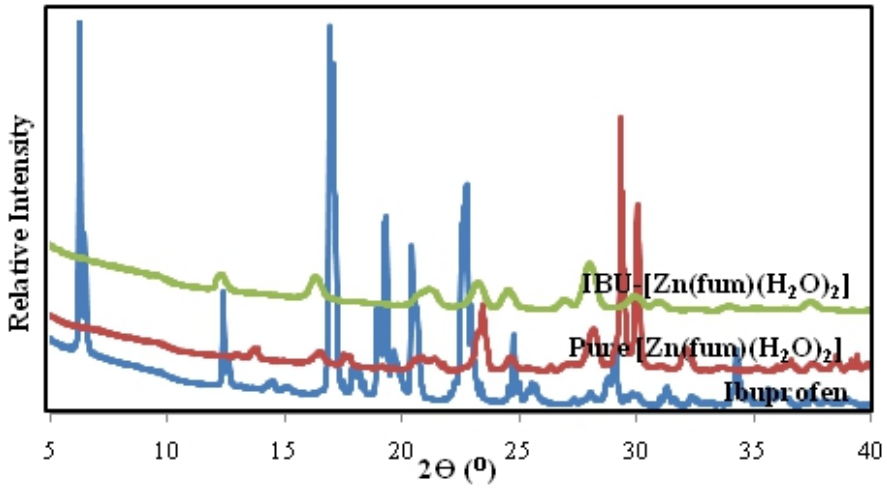


Figure 3: XRPD of [Zn(fum)(H_2O)$_2$] before and after loading of Ibuprofen

Experimental characterization of the drug–[Cu(INA)$_2$] MOFs.

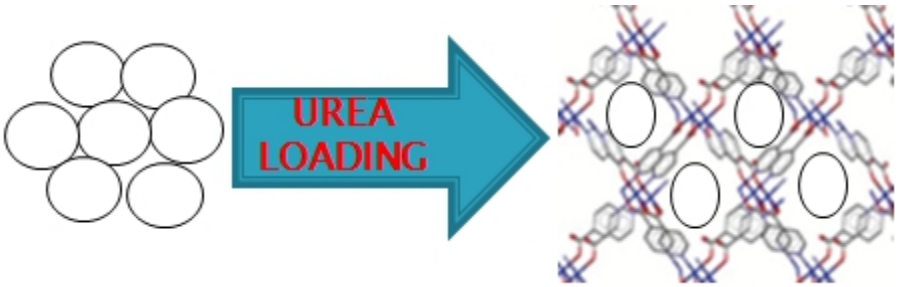


Figure 4: Scheme for loading Urea into [Cu(INA)$_2$][37]

The loading of Urea into [Cu(INA)$_2$] was ascertained by UV–visible spectroscopy (Figure. 5). This technique was used to quantify the mass of Urea adsorbed on the [Cu(INA)$_2$] after 3 days. The calibration curve showed that 44 ± 0.95 wt % of Urea was adsorbed on the [Cu(INA)$_2$].

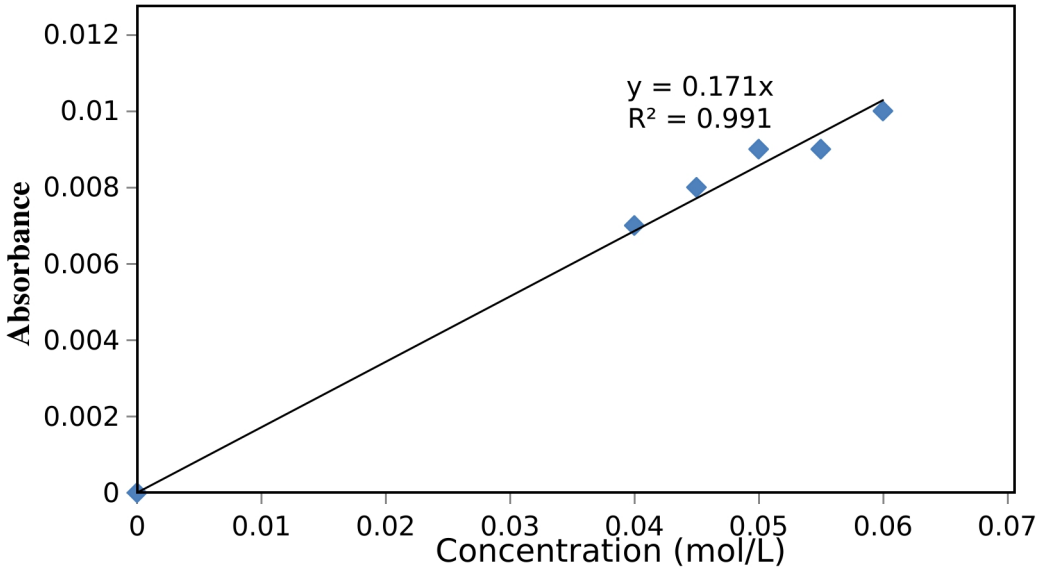


Figure 5: Calibration Curve obtained from the absorption spectrum in the ultraviolent-visible spectral region for the Urea solution.

Urea was absorbed into the [$Cu(INA)_2$] MOFs (Table 2). The [$Cu(INA)_2$] encapsulate 44 mg of Urea per gram of dehydrated MOF. Urea-[$Cu(INA)_2$] did not exhibit any alternation of colour compared to the pure framework.

Table 2: Absorbance, concentration, percentage and mass of urea before and after loading on [$Cu(INA)_2$].H_2O at 30 ± 2°c.

Variables	Before loading	After loading
Absorbance	0.086	0.048
Conc of Urea	0.503M	0.281M
% of Urea	100%	56.14%
Mass of Urea	300mg	168.4mg

The FTIR spectra of the MOFs [($Cu(INA)_2$] before and after loading with urea is shown in Figure 6.

The changes observed in the spectra of MOFs after loading indicated the possible involvement of additional functional groups into the pores of the MOFs.

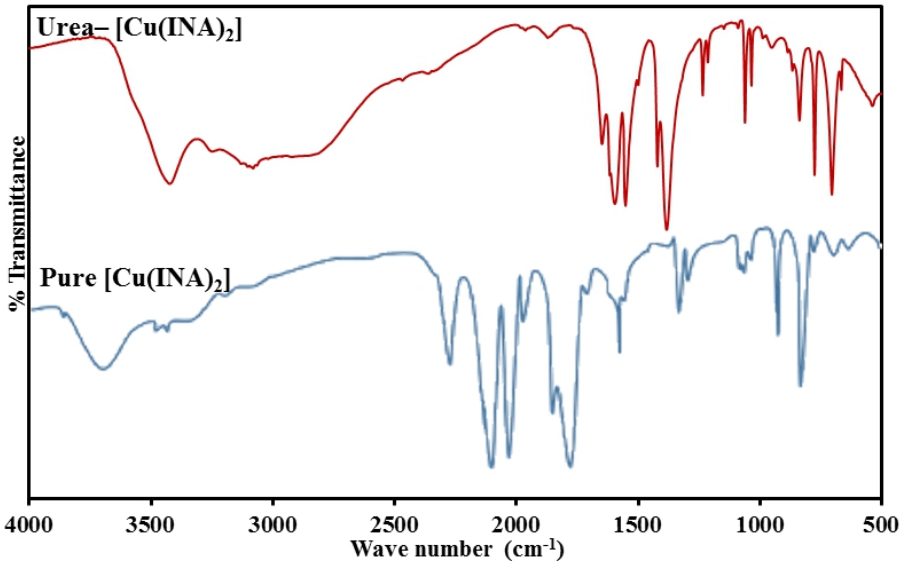


Figure 6: Infrared spectra of $[Cu(INA)_2]$ before and after loading of Urea

In addition to the IR, the loading of the urea in the MOFs was confirmed using XRPD. Significant changes of peak positions and relative intensities were further observed for the MOF $[Cu(INA)_2]$ compared with their dissociated forms (Figure. 7), indicating the interaction of urea into MOF pores.

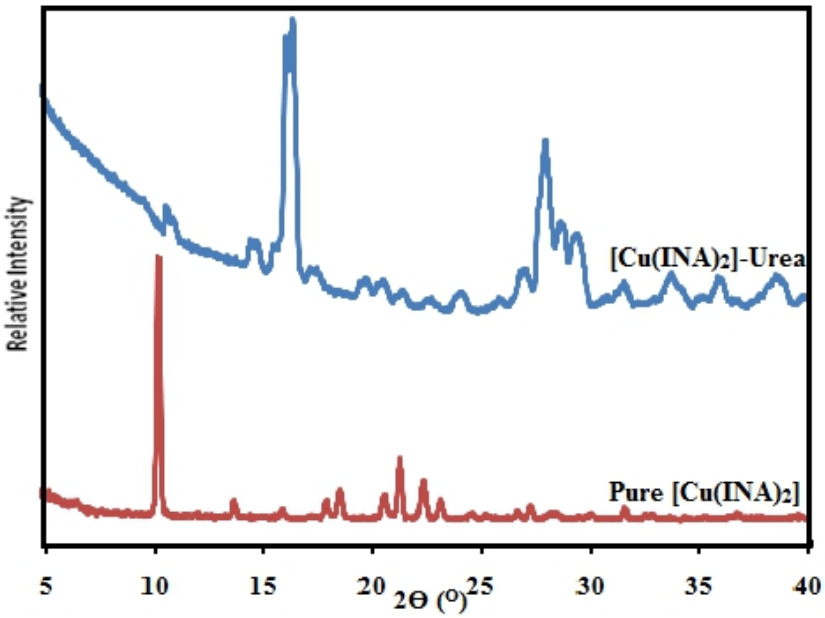


Figure 7: XRPD of $[Cu(INA)_2].H_2O$ before and after loading of Urea

DISCUSSION

$[Zn(fum)(H_2O)_2]$ has shown an unprecedented loading of Ibuprofen. This was attributed to high porosity of $[Zn(fum)(H_2O)_2]$ and hydrophobic character of Ibuprofen[37]. From this, $[Zn(fum)(H_2O)_2]$ can uptake 98 mg of ibuprofen per gram of dehydrated MOF. The white colour characteristic of the $[Zn(fum)(H_2O)_2]$ framework remained unaltered during the 7 days, when it was kept immersed in the ibuprofen solution.

Characterization of the MOFs by Fourier transform infrared spectroscopy (FTIR) before and after loading reveal that the changes observed in the spectrum

indicate the possible involvement of those functional groups in the pores of the MOF after loading. It is reflecting the nature of MOF and shows significant band shifting and intensity changes due to ibuprofen absorption. Characteristic stretching vibrations of ν(O-H) and ν(C=C) (aromatic) were further observed for the ibuprofen– [Zn(fum)(H_2O)$_2$] MOF at 3446 cm^{-1} and 1560 cm^{-1} respectively compared with their dissociated forms (Figure. 2). This indicates the absorption of ibuprofen into [Zn(fum)(H_2O)$_2$] MOF. In addition, the ν(C=O) showed as an acid carbonyl (1770 cm^{-1}) due to the presence of ibuprofen in the pores of the MOFs.

The in X-ray powder diffraction (XRPD) pattern for [Zn(fum)(H_2O)$_2$] is an effective method to investigate structural properties of a synthesized material. High intensity Bragg diffraction peaks are observed at 2θ = 29.33, 29.47 and 30.02 with low intensity peaks at 2θ = 9.99, 13.89, 16.63, 17.83, 21.06, 21.44, 23.79, 24.77, 28.27, 32.34, 35.41, 36.62, 37.70, 38.66 and 39.42 for pure [Zn(fum)(H_2O)$_2$]. The observed XRPD pattern of Ibuprofen-[Zn(fum)(H_2O)$_2$] are not identical with that of the pure [Zn(fum)(H_2O)$_2$]. The three (3) high intensity Bragg diffraction peaks observed on the pure [Zn(fum)(H_2O)$_2$] were totally absent on the Ibuprofen-[Zn(fum)(H_2O)$_2$] due to the incorporation of Ibuprofen into [Zn(fum)(H_2O)$_2$] pores. Also some new low intensity Bragg diffraction peaks were observed on the Ibuprofen-[Zn(fum)(H_2O)$_2$] which are not present on the pure [Zn(fum)(H_2O)$_2$], these are at 2θ = 12.42, 16.64, 21.42, 23.38, 24.71, 28.08, 30.18, 31.21, 32.68, 34.29, 35.66 and 37.70. The appearance of new peaks on the Ibuprofen-[Zn(fum)(H_2O)$_2$] spectrum indicated the possible absorption of Ibuprofen into the pores of the frameworks.

The effect of pH on the binding of the guest molecules has been considered through the representation of their protonation states. Ibuprofen can be unprotonated with a formal charge of -1 or protonated with a formal charge of

0[34]. Simpler molecules have a low number of degrees of freedom and interact through a well-defined pattern of molecular interactions. That is the case of compounds such as Ibuprofen. Ibuprofen binds along one of the sides of [Zn(fum)(H_2O)$_2$] surface via electrostatic and π - π interactions. Electrostatic interactions occur between the ibuprofen carboxylic group (COO^-) and Zn^{2+} cation in the MOF surface, whereas π - π stacking takes place between the unsaturated carbon (C=C) of host and guest. Protonated and unprotonated states of the Ibuprofen molecule led to the same binding conformation[34].

Regarding the Urea-[Cu(INA)$_2$] MOFs, it exhibits very high drug storage capacities. This was attributed to high porosity and interesting flexible structures, for drug delivery.

Comparison of the infrared spectrum of the MOF before and after the loading of Urea, showed that the IR spectrum after loading showed some new characteristic frequencies due to the encapsulation of Urea in the MOF. Characteristic band of N-H and C-N were observed for the MOF Urea– [Cu(INA)2] compared with their dissociated forms, indicating that the absorption of Urea into [Cu(INA)$_2$]. Characteristic of ν(N-H), ν(C-N) (amide) and ν(C=O) were further observed for the MOF Urea–[Cu(INA)$_2$] at 3423 cm^{-1}, 1384 cm^{-1} and 1642 cm^{-1} respectively compared with their dissociated forms, indicating the absorption of urea into [Cu(INA)$_2$].

The X-ray powder diffraction (XRPD) is an effective method to investigate structural properties of a synthesized material. High intensity Bragg diffraction peaks (Figure 7) is observed at 2θ = 10.20 with low intensity peaks at 13.40, 17.48, 17.66, 21.74, 22.44, 25.92, 26.28 and 32.34 for pure [Cu(INA)$_2$]. The observed XRPD pattern of Urea-[Cu(INA)$_2$] does not match the pattern of the pure [Cu(INA)$_2$]. New peaks were observed on the Urea-[Cu(INA)$_2$] which are not

present on the pure [$Cu(INA)_2$]. These are 2θ = 10.60, 10.90, 14.56, 15.50, 15.83, 16.11, 16.89, 17.37, 19.39, 19.38, 20.12, 20.98, 22.26, 23.57, 25.32, 26.43, 27.25, 28.00, 28.67, 30.76, 32.96, 35.10, 37.57 and 38.82. The appearance of new peaks on the Urea - [Cu $(INA)_2$] indicated the possible absorption of urea into the pores of the frameworks.

CONCLUSION

This study demonstrated the use of MOFs for loading of ibuprofen and urea drugs. Zinc-fumarate [$Zn(fum)(H_2O)_2$] exhibits a very high drug loading capacities of 98wt% of Ibuprofen while copper-isonicotinate [$Cu(INA)_2$] exhibits a moderate drug loading capacities of 44wt% of Urea. The MOFs preparation procedure is simple, green and cheap, and can be used as potential materials for drug delivery.

ACKNOWLEGMENTS

Tuyil Pharmaceutical Industries Ltd Ilorin is highly appreciated for donation of some of the materials used for this study.

REFERENCES

1. Nagy ZK, Balogh A, Vajna B, Farkas A, Patyi G, Kramarics A, et al. (2012). Comparison of electrospun and extruded Soluplus®-based solid dosage forms of improved dissolution. J. Pharm. Sci. 101 (1): 322 - 332.

2. Huxford RC, Rocca JD, Lin W. (2010). Metal-Organic Frameworks as Potential Drug Carriers. Curr. Opin. Chem. Biol. 14 (2): 262 - 268.

3. Cohen SM. (2007). New approaches for medicinal applications of bioinorganic chemistry. Curr. Opin. Chem. Biol. 11 (2): 115 - 120.

4. Janiak C. (2003). Engineering coordination polymers towards applications. Dalton Transactions. 2781–2804.

5. Yaghi OM, O'Keeffe M, Ockwig NW, Chae HK, Eddaoudi M, Kim J. (2003). Reticular Synthesis and the Design of New Materials. Nature. 423: 705-714.

6. Murray LJ, Dinca M, Long JR. (2009). Hydrogen Storage in Metal Organic Frameworks. Chem. Soc. Rev. 38: 1294 – 1314.

7. Morris RE, Wheatley PS. (2008). Gas storage in nanoporous materials. Angew. Chem. Int. Ed. 47(27): 4966 – 4981.

8. Li JR, Kuppler RJ, Zhou HC. (2009). Selective gas adsorption and separation in metal organic frameworks. Chem. Soc. Rev. 38: 1477 - 1504.

9. Meilikhov M, Yusenko K, Esken D, Turner S, Van Tendeloo G, Fischer RA. (2010). Metals@MOFs - loading MOFs with Metal Nanoparticles for Hybrid Functions. Eur. J. Inorg. Chem. 2010 (24): 3701 – 3714.

10. Müller M, Hermes S, Kähler K, Van den Berg MWE, Muhler M, Fischer RA. (2008). Loading of MOF-5 with Cu and ZnO Nanoparticles by Gas-Phase Infiltration with Organometallic Precursors: Properties of Cu/Zno@MOF – 5 as catalyst for methanol synthesis. Chem. Mater. 20 (14): 4576 -4587.

11. Müller M, Zhang X, Wang Y, Fischer RA. (2009). Nanometer-sized titania hosted MOF-5. Chem. Commun. 1: 119 - 121.

12. Lee J, Farha OK, Roberts J, Scheidt KA, Nguyen ST, Hupp JT. (2009). Metal Organic Framework Materials as Catalysts. Chem. Soc. Rev. 38:1450 - 1459.

13. Ma L, Abney C, Lin W. (2009). Enantioselective catalysis with homochiral metal organic frameworks. Chem. Soc. Rev. 38: 1248.

14. Horcajada P, Chalati T, Serre C, Gillet B, Sebrie C, Baati T, et al. (2010). Porous Metal-Organic-Framework Nanoscale Carriers as a Potential Platform for Drug Delivery and Imaging. Nat Mater. 9: 172 - 178.

15. McKinlay AC, Morris RE, Horcajada P, G. Férey G, R. Gref R, P. Couvreur P, et al (2010). Metal-organic frameworks for biological and medical applications. Angew. Chem. Int. Ed., 49 (36): 6260 - 6266.

16. Horcajada P, Serre C, Vallet-Regi M, Sebban M, Taulelle F, Ferey G. (2006). Metal-Organic Frameworks as Efficient Materials for Drug Delivery. Angew. Chem. Int. Ed., 45 (36): 5974 -5978.

17. Horcajada P, Serre C, Maurin G, Ramsahye NA, Balas F, Vallet-Regi M, et al. (2008). Flexible porous metal-organic frameworks for a controlled drug delivery. J. Am. Chem. Soc., 130 (21): 6774 - 6780.

18. Huxford RC, Della JR, Lin W. (2010). Metal-Organic Frameworks as Potential Drug Carriers. Curr. Opin. Chem. Biol., 14 (2): 262 - 268.

19. Vyasmudri SY, Maji TK. (2009). Sixfold interpenetrated diamondoid network of Cu(I): Synthesis, structure, selective anion exchange and luminescence properties. Chem. Phys. Lett. 473 (4-6): 312 – 316.

20. Maji TK, Matsuda R, Kitagawa SA. (2007). Flexible interpenetrating coordination framework with a bimodal porous functionality. Nat. Mater. 6: 142 - 148

21. Guo Z, Cao R, Wang X, Li H, Yuan W, Wang G, et al. (2009). A Multifunctional 3D Ferroelectric and NLO-Active Porous Metal−Organic Framework. J. Am. Chem. Soc. 131 (20): 6894.

22. Klimakow M, Klobes P, Rademann K, Emmerling F. (2012). Characterization of mechanochemically synthesized MOFs. Microporous Mesoporous mater. 154: 113-118.

23. Pichon A, James SL. (2008). An array-based study of reactivity under solvent-free mechanochemical conditions—insights and trends. CrystEngComm. 10: 1839 – 1847.

24. Biradha K, Ramanan A, Vittal JJ. (2009). Coordination Polymers versus Metal Organic Frameworks. Cryst. Growth Des. 9 (7): 2969 – 2970.

25. Yaghi OM, Li G, Li H. (1995). Selective binding and removal of guests in a microporous metal–organic framework. Nature 378:703-706.

26. Kitagawa S, Kitaura R, Noro S. (2004). Functional Porous Coordination Polymers. Angew. Chem. Int. Ed. 43 (18): 2334 – 2375.

27. Pachfule P, Balan BK, Kurungot S, Banerjee R. (2012) One-dimensional confinement of a nanosized metal organic framework in carbon nanofibers for improved gas adsorption. Chem. Commun. 48: 2009 - 2011.

28. Dalai S, Mukherjee PS, Zangrando E, Lloret F, Chaudhuri NR. (2002). A novel class of interpenetrated 3-D network of a dimeric cupric-tetracarboxylate unit. J. Chem. Soc. Dalton Trans. 6: 822 – 823.

29. Pochodylo AL, LaDuca RL, (2010). Substituent Dependent Dimensionality in Luminescent Zinc Isophthalate Coordination Polymers Containing Bis(3-pyridylmethyl)piperazine. Z. Anorg. Allg. Chem. 636 (15): 2568 – 2573.

30. Martin DP, Montney MR, Supkowski RM, LaDuca RL, (2008). Cadmium Glutarate Coordination Polymers Containing Hydrogen-Bonding Capable Tethering Organodiimines: From Double Interpenetration to Supramolecular Cavities Containing an Unprecedented Water Tape Morphology. Cryst. Growth Des. 8 (8) 3091- 3097.

31. Mukherjee PS, Konar S, Zangrando E, Mallah T, Ribas J, Chaudhuri NR. (2003) Structural Analyses and Magnetic Properties of 3D Coordination Polymeric Networks of Nickel(II) Maleate and Manganese(II) Adipate with

the Flexible 1,2-Bis(4-pyridyl)ethane Ligand. Inorg. Chem. 42 (8): 2695 - 2703

32. Tella AC, Owalude SO, Nzikahyel S, Arise RO,(2015) Solid-state synthesis of isostructural tetrachlorometallate salts of amodiaquine : Crystal structure of $[CdCl_4][C_{20}H_{24}ClN_3O]$.Med.Chem. Res. 24:3949 - 3957

33. Tella AC, Owalude SO, Ojekanmi AC, Oluwafemi OS. (2014). Synthesis of copper–isonicotinate metal–organic frameworks simply by mixing solid reactants and investigation of their adsorptive properties for the removal of the fluorescein dye. New J. Chem. 38: 4494 - 4500

34. Rodrigues MO, de Paula MV, Wanderley KA, Vasconcelos LB, Alves Jr , Soares TA. (2012). Metal Organic Frameworks for Drug Delivery and Environmental Remediation: A Molecular Docking Approach. Int. J. Quant. Chem. 112 (20): 3346-3355.

35. Pichon A, Lauzuen-Garey A, James SL, (2006). Solvent free synthesis of a microporous metal organic frameworks. CrystEngComm. 8: 211 - 214.

36. Lim S, Suh K, Kim KY, Yoon M, Park H, Dybtsev DN, Kim K. (2012). Porous carbon materials with a controllable surface area synthesized from metal–organic frameworks. Chem. Commun. 48 (60): 7447-7449.

37. Keskin S, Seda K (2011). Biomedical Application of Metal Organic Frameworks. Ind. Eng. Chem. Res 50 (4): 1799-1812.