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Copper-Trimesate Framework as a Drug Delivery System for Antibiotics: Loading Capacity and Release Behaviour

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Abstract

Copper-trimesate framework has been investigated for its potential to act as a drug delivery system for antibiotics. The material was synthesized under solvothermal conditions and characterized using FTIR spectrophotometer. Drug loading tests were performed in fixed bed columns, on five different weights, 10, 20, 30, 40 and 50 mg of copper-trimesate framework, using ethanol solutions of amoxicillin and doxycycline. Drug release profiling of the antibiotics was conducted in phosphate buffer saline pH 7.4 for a duration of 50 minutes, with solution drawn at interval of 10 minutes for determination of the concentration of the released drug. The weights of amoxicillin per 100 mg of copper-trimesate loaded onto 10, 20, 30, 40, and 50 mg of the material were 88.40, 44.36, 24.19, 18.58, and 15.17 mg. Those of doxycycline were 114.67, 51.62, 35.72, 27.03, and 20.84 mg, implying a decrease in loaded amounts with an increase in the weight of copper-trimesate. Drug release profiling study showed that 59.15 % amoxicillin and 44.95% doxycycline were released in their respective medium during the 50 minutes time investigated. These results reveal the potential of copper-trimesate framework to act as drug delivery system for high drug loading and enhanced bioavailability of the investigated antibiotics.

Keywords: Copper, trimesate, antibiotic, delivery

1. Introduction

Bacterial infections are common and are major causes of global mortality (Ho *et al*., 2019). Dosage forms for treatment of bacterial infections are reportedly effective (Kaal *et al.*, 2024; Chinemerem *et al*., 2022). However, a few problems have been identified as being connected with the use of the antibiotic dosage formulations, including adverse drug effect due to abuse and/or misadministration of the drugs, bacterial resistance of antibiotics due to excessive accumulations in tissues, as well as poor bioavailability of antibiotics in infected sites (Mahmudul Islam *et al*., 2024; Chinemerem *et al*., 2022; Yeh *et al*., 2020; Chifiriuc *et al.*, 2016). A counteraction of these problems requires the application of drug delivery systems which are biocompatible with the body, possess high drug loading capacity, and can enable both controlled and prolonged release of drugs for the complete elimination of the pathogenic bacteria from within the body of the patient (He *et al*., 2021; Chifiriuc *et al*., 2016).

Metal organic frameworks are among the materials being investigated as potential drug delivery systems for targeted and controlled delivery of active pharmaceutical ingredients for a spectrum of illnesses (Mhettar *et al.*, 2024; Maranescu & Visa, 2022; Ma, 2022). They are novel hybrid materials composed of metal-centered building units, known as nodes that are linked by polytopic organic linkers (Yaghi *et al*., 2019). The entire arrangement of metal-building units and organic linkers produces, on the molecular scale, rigid 1D-2D, or 3D-networks of porous cages, known as internal pores (Zhang *et al*., 2020; Dikio & Farah, 2013). The presence of pores in MOFs has been utilized in many applications, such as gas capture and storage (Demir *et al*., 2022), catalysis (Loera-Serna *et al*., 2016), contaminant trapping (Ukachuku *et al*., 2023), and drug molecule encapsulation for drug delivery applications (Maranescu & Visa, 2022; Zhang *et al*., 2020). MOFs also exhibit versatility in identity and structure owing to the infinite number of possible choices of metal/linker combinations (Sharmin & Zafar, 2016). Many kinds of MOFs have been investigated for drug delivery applications (He *et al*., 2021; Lin *et al*., 2017; Lu *et al*., 2015). The attractive properties of MOFs in drug delivery are their flexible bonds that can be manipulated for facile release of active drug components and their reported high pore volume (up to 4 cm^3 per gram) (Lawson *et al.*, 2021), which could serve as spacious stores for considerably large amounts of active pharmaceutical ingredients (Mhettar *et al*., 2024; He *et al*., 2021).

The investigation of copper trimesate (Cu-tri) as a potential delivery system for antibiotics is hinged upon the reported biocompatibility of copper. Copper is an essential micronutrient in humans, necessary for the proper functioning of the body through its role in the promotion of adequate growth, lung elasticity, vascular function, neovascularization, neuroendocrine function, and iron metabolism (Wang *et al*., 2021). It is said to be regulated in the body through intestinal absorption and bile excretion (Wang *et al*., 2021). Trimesic acid, on the other hand, is an exogenous linker with potential for application as a precursor for the preparation of biocompatible MOF drug carriers, given that another linker with structural and functional similarity, benzene-1,4-dicarboxylic acid, has been successfully applied in the production of a metal-organic framework drug delivery system, Fe-MIL-88A, which has been approved as an oral iron supplement (Sun *et al*., 2013).

For the benefit of comparative studies, two classes of antibiotic molecules were chosen for this study, namely, tetracycline and penicillin, represented by doxycycline (DOX) and amoxicillin (AMX) respectively. Tetracyclines are used to treat a wide spectrum of gram-negative and gram-positive bacterial diseases, including infections in the skin, intestine, respiratory tract, urinary tract, genitals, lymphatics, and other body systems. (Levine & O'Connor, 2012; *Tetracycline (Antibiotics) Uses, Dosage, Side Effects*, n.d.; Chopra & Roberts, 2001). Members of the tetracycline family are made up of a linear fused tetracyclic ring and function by inhibiting protein synthesis in the bacteria (Küng *et al*., 2019; Levine & O'Connor, 2012). Penicillins, on the other hand, are antibiotics that belong to a larger family of drugs known as beta-lactam antibiotics (Melo *et al*., 2016; Raynor, 1997). Penicillin functions by binding to molecules on the walls of bacteria, such that after bacterial cell division, the reassembling of the mitotic fragments is prevented, which ultimately leads to the death of the bacteria. All forms of penicillins are derived from a fungus known as *Penicillium chrysogenum, either by direct extraction (natural penicillin) or by laboratory mimicking (semisynthetic penicillin)* (Melo *et al*., 2016; *Penicillin Treatment and Adverse Effects*, n.d.).

2. Materials and Methods

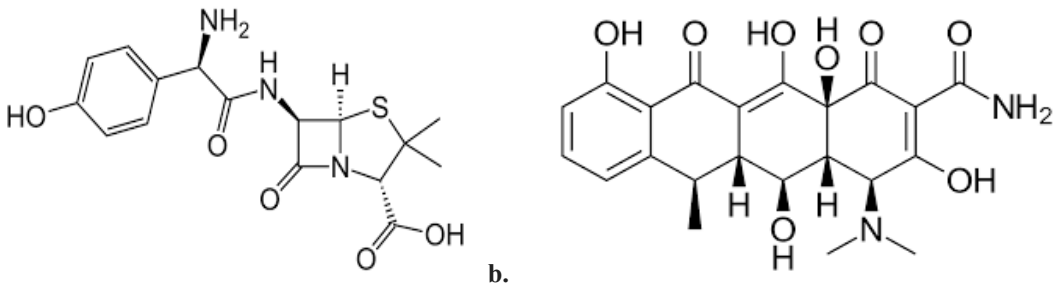
2.1 Reagents, apparatuses and instruments

The reagents for synthesis of copper-trimesate (Cu-tri) were copper nitrate trihydrate ($Cu(NO_3)_2{\cdot}3H_2O$ (from Aladdin Biological Technology Co. Ltd, Shanghai, China), trimesic acid (1,3,5-benzene tricarboxylic acid, from Merck KGaA, Darmstadt, Germany), N,N-dimethylformamide (DMF, from Merck KGaA, Darmstadt, Germany)

Antibiotic formulations were amoxicillin trihydrate ((2S,5R,6R)-6-[[(2R)-2-Amino-2-(4-hydroxyphenyl)acetyl]amino]-3,3-dimethyl-7-oxo-4-thia-1-azabicyclo[3.2.0]heptane-2-carboxylic acid, $C_{16}H_{19}N_3O_5S{\cdot}3H_2O$, M.W=419.45g/mol, from Getham Life sciences, Planegg, Germany), and doxycycline Hyclate (Doxycycline hydrochloride hemiethanolate hemihydrate, $C_{22}H_{24}N_2O_8{\cdot}HCl{\cdot}0.5C_2H_6O{\cdot}0.5H_2O$, M.W=512.94g/mol, from Merck KGaA, Darmstadt, Germany). Both formulations were of analytical grade.

Other analytical grade reagents were methanol, Sodium phosphate dibasic (Na_2HPO_4), Potassium Phosphate monobasic (KH_2PO_4), Sodium Chloride (NaCl) and Potassium Chloride (KCl), all products of Merck KGaA, Darmstadt, Germany.

The instruments employed were, weighing balance, refluxing apparatus, rounded bottom flask, volumetric flasks, mercury thermometer, magnetic stirrer, bar magnet, Orbital shaker (bioevopeak, model SHK-O1750, China),Fourier transform infrared spectrophotometer (Spectrum 400 Model FT-IR/FT-NIR, Perkin-Elmer, USA), an intelligent ultrasonic processor (a product of Shangai Huxi Industry Co. Ltd, China) and a double beam Ultraviolet-Visible spectrophotometer (model SP-IUV7 from Infitek Bioindustry Co. Ltd, Shenzhen, China).



a. **b.**

Fig. 1: Structures of antibiotics (a) amoxicillin (b) doxycycline

2.2.1 Synthesis of copper trimesate framework (Cu-tr)

The synthesis of Cu-tri was performed in accordance with the method described in Dikio and Farah (2013), with modification of solvent type, temperature and duration of refluxing. 16.91 g (0.07mol) of $Cu(NO_3)_2{\cdot}3H_2O$ and 14.71g (0.07mol) of trimesic acid were separately weighed into rounded bottom flask containing 100 mL of N,N Dimethyl formamide. The mixture was refluxed at 140 ^{0}C for 7 hours, under continuous stirring using a magnetic stirrer/bar magnet. Thereafter, contents of reactor were transferred to a beaker, and products collected through decantation and filtration, separating the solvent N,N-dimethyl formamide. The resulting Cu-tri crystals were further rinsed with excess methanol to eliminate trapped solvent molecules, then recovered via centrifugation at 4,000 rpm. Cu-tri crystals were dried at room temperature and stored in a suitable container.

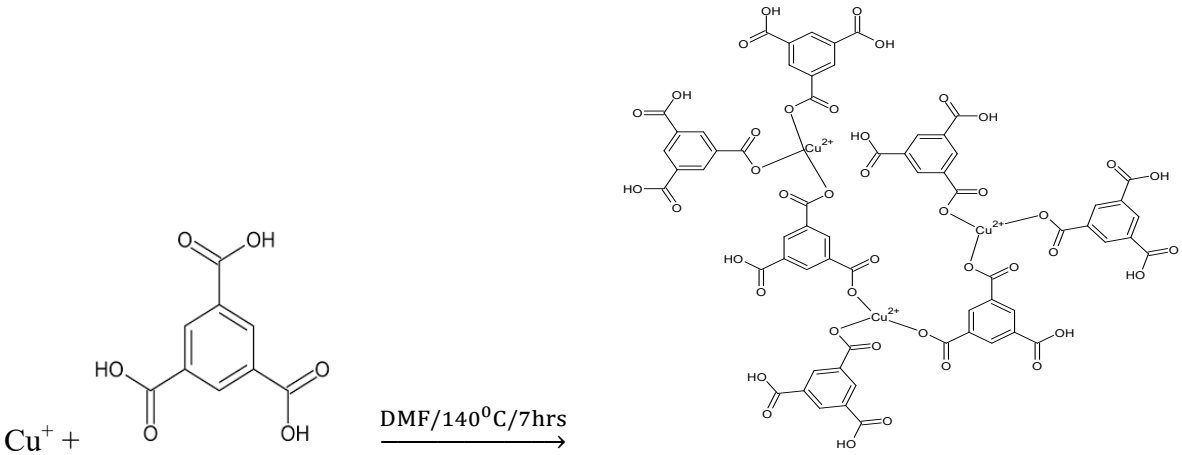


Fig. 2: preparation scheme for copper trimesate (Cu-tri)

2.2.2 Fourier transform infrared characterization of Cu-tri

Dried sample of Cu-tri were placed on a crystal holder and positioned in a near infrared (NIR) cell. The spectral measurement was conducted at a spectral resolution of 4.0 cm^{-1} and a wavenumber range of 4000 to 400 cm^{-1}.

2.2.3 Preparation of solutions of Doxycycline (DOX) and Amoxicillin (AMX)

100 mg each of DOX and AMX was weighed into 50 ml of ethanol. Each solution was mixed thoroughly with the aid of a sonicator to enhance dissolution of drug in ethanol. Thereafter, the concentration of the solution was measured with UV-Spectrophotometer at wavelengths of 240 nm and 229 nm for DOX and AMX respectively

2.2.4 Drug loading studies

To determine the loading capacity of various weights of Cu-tri, 10, 20, 30, 40, and 50 mg of Cu-tri were weighed into five test tubes, each set of five test tubes for each type of antibiotic. 8 ml of the respective antibiotic stock solutions was added to each of the test tubes. Each test tube mixture was agitated with an Orbital shaker at 50 revolutions per minute for 60 minutes to ensure adequate contact and exposure between drug/MOF contents. At the expiration of agitation, the test tubes were left undisturbed for 48 hours to allow for fixed-bed adsorption. At the end of 48 hours, supernatant solution in each tube was analyzed with the UV spectrophotometer at 240 nm and 229 nm wavelengths for DOX and AMX respectively.

2.2.5 Preparation of Phosphate Buffer Saline (PBS) pH 7.4

1 Liter Phosphate buffer saline (PBS) pH 7.4, was prepared in the biotechnology lab of the University of Africa, Toru-Orua, Nigeria, by adding 1.44 g Na_2HPO_4, 0.245 g KH_2PO_4, 0.2 g KCl and 8 g NaCl to 800 ml of distilled water. The pH of the resulting solution adjusted with HCl and NaOH to obtain the desired pH of 7.4, then making up the volume with distilled water to 1 L.

2.2.6 Drug Release Study

100 mg of Cu-tri was weighed into 20 ml plastic tube, into which was added 15 mL drug solution. The mixture was agitated in an Orbital shaker at 50 revolutions per minute for 60 minutes, following which a fixed bed contact was maintained for 48 hours. Upon filtration, the Cu-tri-antibiotic composite was dried at 50 ^{0}C for 24 hours to eliminate any occluded solvent. The solution was analyzed with UV spectrophotometer to estimate the amount of drug unloaded. The amount of loaded drug was estimated through a mathematical difference between the initial concentration of drug, and the amount unloaded onto Cu-tri.

The study of the drug release pattern followed the method described in Uhljar *et. al.* (2021) (Uhljar *et al*., 2021). 50 mg each of the antibiotic loaded Cu-tri (Cu-tri-DOX and Cu-tri-AMX) was weighed into separate beaker. 50 mL of PBS (pH 7.4) preheated to 37 ^{0}C, was added to the beaker, and the beaker and its contents were

stirred with a magnetic stirrer at 30 revolutions per minute. 5 mL of PBS solution was drawn at 10 minutes interval for UV Spectrophotometric analysis, with the drawn volume replaced immediately with fresh media. The release study was conducted for 10, 20, 30, 40, and 50 minutes. The concentration of drugs released into the PBS media was determined using a UV-Visible spectrophotometer, at wavelengths of 240 nm and 229 nm for DOX and AMX respectively.

3. Results and Discussion

3.1 Synthesis of copper trimesate framework (Cu-tri)

Copper trimesate (Cu-tri) was obtained as a blue crystalline material following the solvothermal refluxing of a mixture of copper nitrate and trimesic acid.

3.2 FTIR characterization

The FTIR spectrum is presented in Figure 3. The peaks appear in regions indicative of the formation of copper-trimesate framework. The peak at 3372 cm^{-1} may be assigned to the stretching vibrations of OH bonds of trapped moisture as well as from -COOH of unreacted trimesic acid molecules. The peaks at 2919 cm^{-1} and 2853 cm^{-1} belong to stretching vibrations of aromatic and aliphatic CH bonds of benzene rings and remnant DMF molecules, respectively (Dutta *et al*., 2018; Sutapa *et al*., 2023). Two prominent peaks of medium level intensity are noticed around 1639 cm^{-1} and 1365 cm^{-1}, with a weaker third at 1451 cm^{-1}.. These peaks originate from asymmetric and symmetric stretching vibrations of the dicarboxylate anionic group (OC=O) formed by the deprotonation of the carboxylic acid group (-COOH). The presence of these peaks is a strong indication of the formation of Cu-tri. Additional peaks highlighting the successful formation of Cu-tri are the strong peaks at 1104 cm^{-1} and 980 cm^{-1} representing the stretching vibrations of carboxylate CO bonds attached to Cu. The bands at 725 cm^{-1} to 657 cm^{-1} represent in-plane and out-of-plane bending vibrations of aromatic CH, CC and C=C bonds. While the peaks at 556 cm^{-1} and 486 cm^{-1} are due to stretching vibrations of Cu-O bonds (Kandiah, Usseglio, *et al*., 2010; Dikio & Farah, 2013; Alshorifi *et al*., 2017; Dutta *et al*., 2018; Aamer *et al*., 2021; Alshorifi *et al*., 2022; T. Chen *et al*., 2022; Kalashgrani *et al*., 2023; Chinthamreddy *et al*., 2024; C. Wu & Almuaalemi, 2025)

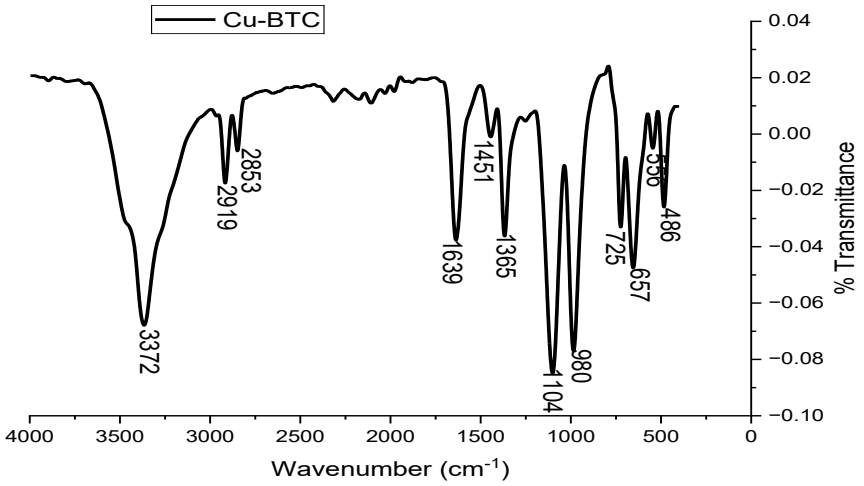


Figure 3: FTIR spectrum of Copper-trimesate framework (Cu-tri)

3.3 Ultraviolet spectrophotometric determination of concentration of stock solution of DOX and AMX

Aliquots of the respective stock solutions of drugs, analyzed with ultraviolet spectrophotometer to determine actual drug solubility in ethanolic stock solution, yielded the results shown in Table 1.

Table 1: Weight concentration of ethanolic stock solutions of drugs

Drug type	Initial expected weight conc. (mg/50ml)	Initial expected weight conc. mg/L	Measured weight conc. (mg/50ml)	Measured weight conc, W, (mg/L)
DOX	100	2000	88.67	1773.45
AMX	100	2000	65.41	1308.13

3.4 Drug loading studies

The results of the drug loading studies to determine the capacity of Cu-tri to contain the drugs DOX and AMX are presented in Table 2 and figure 4. The results were estimated in terms of the weight and percentages of drugs loaded per 100 mg of Cu-tri.

The weight of drug loaded per 100 mg of Cu-tri was determined by the following relation:

$$\text{Weight of drug per 100 mg of Cu-tri} = \left(\frac{(W_i - W_{(\text{Unloaded})}) \times v}{W}\right) \div 10 \qquad (1)$$

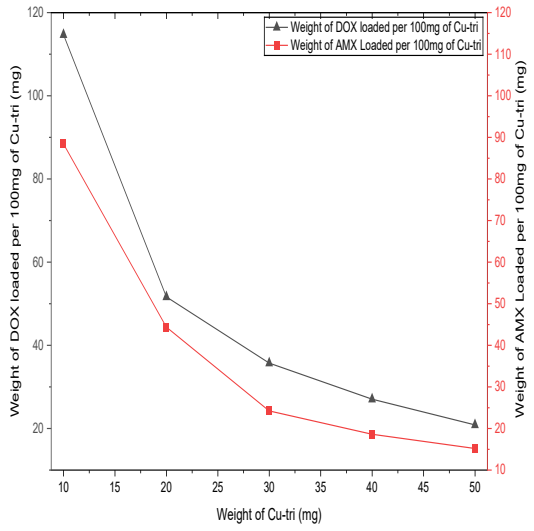
Where v is the volume of drug solution used (8ml = 0.008 L), and w_i is initial weight of drug used, $w_{(\text{Unloaded})}$ is the weight of drug in solution at equilibrium, W (in grams) is the weight of Cu-tri loaded. The initial weight, w, of drugs per liter of drug solutions were 1773.45 mg and 1308.13 mg for DOX and AMX respectively (Table 1). The percentage of drugs loaded per 100 mg Cu-tri was estimated as follows:

$$\%\ \text{drug loaded} = \frac{\text{weight of drug per 100 mg of Cu-tri (in mg)}}{\text{weight of loaded drug (in mg)} + 100\ \text{mg of Cu-tri}} \times 100\% \qquad (2)$$

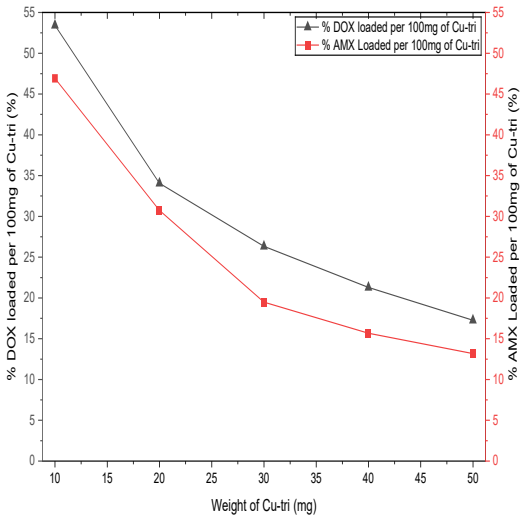
Table 2: Results of the Loading of DOX and AMX onto Cu-tri

Weight of Cu-tri (mg)	Percentage of DOX loaded per 100 mg of Cu-BTC (%)	Weight of DOX per 100 mg of Cu-BTC (mg/100 mg)	Weight of Cu-tri-DOX based on 100 mg Cu-BTC	Percentage of AMX loaded per 100 mg of Cu-BTC (%)	Weight of AMX per 100 mg of Cu-BTC (mg/100 mg)	Weight of Cu-tri-AMX Based on 100 mg Cu-BTC
10.00	53.42	114.67	214.67	46.92	88.40	188.40
20.00	34.05	51.62	151.62	30.73	44.36	144.36
30.00	26.32	35.72	135.72	19.48	24.19	124.19
40.00	21.28	27.03	127.03	15.67	18.58	118.58
50.00	17.25	20.84	120.84	13.17	15.17	115.17

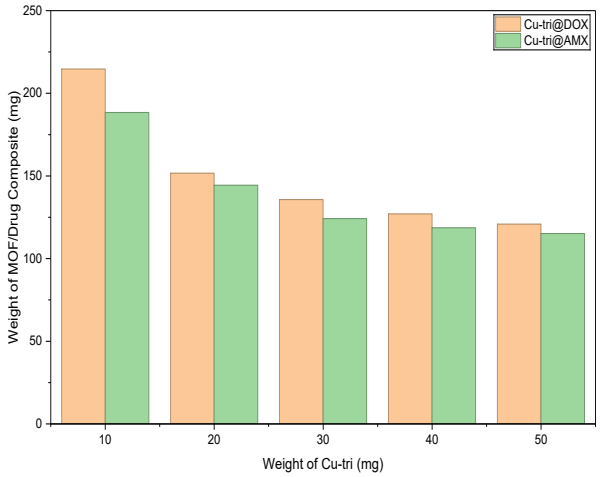
The data presented in Table 2 and Figure 4 are the weights and percentages of DOX and AMX per 100 mg of Cu-tri after 10, 20, 30, 40 and 50 mg of Cu-tri were respectively mixed together with 8 ml each of 1773.45 mg/L and 1308.13 mg/L solutions of DOX and AMX, respectively. The weights of DOX and AMX were 114.67, 51.62, 35.72, 27.03 and 20.84 mg per 100 mg of Cu-tri and 88.40, 44.36, 24.19, 18.58 and 15.17 mg per 100 mg of Cu-tri. The respective weights of MOF/drug composites (Cu-tri-DOX and Cu-tri-AMX) were 214.67, 151.62, 135.72, 127.03 and 120.84 mg for Cu-tri-DOX and 188.40, 144.36, 124.19, 118.58 and 115.17 mg for Cu-tri-AMX. Thus, the percentages of DOX in Cu-tri-DOX and AMX in Cu-tri-AMX were 53.42, 34.05, 26.32, 21.28, and 17.25 % and 46.92, 30.73, 19.48, 15.67, and 13.17 % respectively. These results depict an increased difficulty in loading the drugs onto the carrier, Cu-tri, as its weight increased.



(a)



(b)



(c)

Figure 4: Weight (a) and percentages (b) of DOX (black) and AMX (red) loaded per 100 mg of Cu-tri versus initial weights of Cu-tri, and bar chat representation (c) weight of MOF/Drug composites for the investigated antibiotics

A comparison of the amount of each antibiotic type that were loaded onto Cu-tri, reveals a higher loaded amount for DOX relative to AMX. As shown in figure 4c, the weights of Cu-tri-DOX are higher than those of Cu-tri-AMX in each loading. This could be attributed to two factors, viz: a higher solubility of DOX in the ethanol solution used, relative to AMX (see data in Table 1) and, a stronger affinity of DOX for the investigated drug delivery system, Cu-tri.

3.5 Drug release study

The drug release study was conducted by loading fresh amounts of Cu-tri for the preparation of fresh MOF/Drug composites for the drug release study. Fresh batches of ethanolic stock solution for the drugs were prepared for this purpose (section 2.2.6). The weight concentrations (mg/L) of the ethanolic stock solutions of the drugs are given in Table 3. The weight of drug loaded onto Cu-tri to produce the MOF/Drug composites that was used for the drug release studies is also presented in Table 3.

As described in section 2.2.6, the drug release study was conducted in PBS (pH 7.4) media for 50 minutes, with 5 mL of PBS solution drawn every 10 minutes for UV spectrophotometric analysis and replaced with fresh media every time. This was in order to investigate the rate at which the loaded antibiotic drugs were released from the studied drug delivery system, Cu-tri. The results of the study are presented in Table 4. The release medium, phosphate-buffered saline pH 7.4, was chosen to mimic the pH of the internal body environment, most especially of blood, which is around 7.4. The zero-order plot of cumulative release percentage versus time is given in Figure 5. The results show that 44.95 % of DOX, and 59.15 % of AMX were released after the maximum study time of 50 minutes. The higher cumulative percentage obtained for amoxicillin shows that it exhibits better dissolution in the media and a higher release rate than DOX. It also explains that DOX has a higher affinity to Cu-tri relative to AMX. The relatively rapid release of the drugs demonstrated the potential of Cu-tri as an antibiotic delivery system for enhanced bioavailability.

Table 3: Concentration of ethanolic stock solutions of drugs, and weight of drugs in MOF/Drug composites per 100 mg and per 50 mg of Cu-tri.

Drug type	Measured weight conc. W, per liter (mg/L)	Weigh conc. of Unloaded drug, (mg/L)	Weight conc. of loaded drug (mg/L)	Weight of loaded drugs/100 mg of Cu-tri (mg)	Weight of loaded drugs/50 mg (mg)
DOX	1885.63	275.29	1610.34	24.16	12.08
AMX	1348.33	218.80	1129.53	16.94	8.47

Conc = concentration

Table 4: Results from the study of drug release from Cu-tri-DOX and Cu-tri-AMX composites

Drug release duration (min)	Weight of DOX in 50 mg Cu-tri	Weight of DOX released (mg)	Cumulative weight of DOX released (mg)	Cumulative Release percentage after each given time (%)	Weight of DOX in 50 mg Cu-tri	Weight of DOX released (mg)	Cumulative weight of AMX released (mg)	Cumulative Release percentage after each given time (%)
10	12.08	1.77	1.77	14.65	8.47	1.90	1.90	22.43
20	12.08	1.55	3.32	27.48	8.47	1.43	3.33	39.32
30	12.08	0.95	4.27	35.34	8.47	0.84	4.17	49.22
40	12.08	0.73	5.00	41.39	8.47	0.62	4.79	56.55
50	12.08	0.43	5.43	44.95	8.47	0.22	5.01	59.15

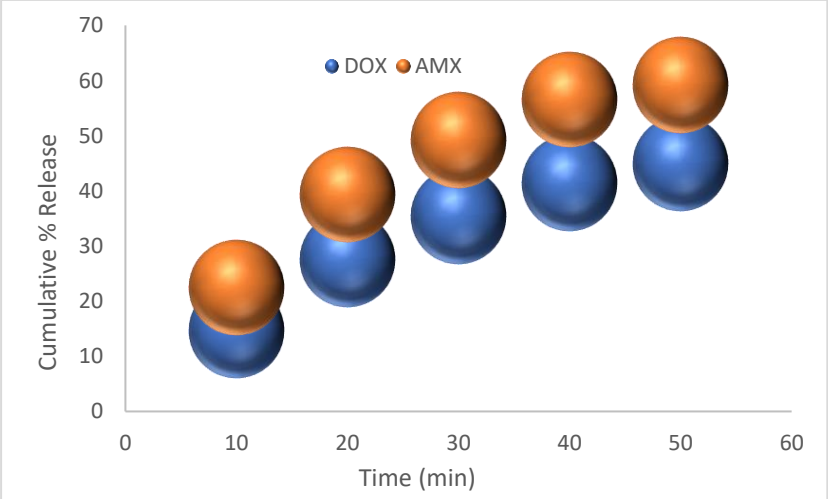


Figure 5: Plots of cumulative percentage of drug released versus time

4. Conclusion

This study was carried out to investigate the potential of a copper-based metal-organic framework, copper-trimesate (Cu-tri), to act as a drug delivery system for antibiotics. Two representative anti-biotics, doxycycline and amoxicillin were utilized for the study. Copper-trimesate framework, Cu-tri, was prepared from copper nitrate and trimesic acid, and characterized with an FTIR spectrometer. The investigation was carried out to determine the quantity of drugs that could be loaded onto various weights of Cu-tri, and the rate at which these loaded drugs will be released from the material. The loading of the drugs onto Cu-tri was carried out via adsorption from ethanolic solution of the drug, while the drug release study was conducted in a pH 7.4 phosphate buffer saline. The results of the drug loading study showed increased difficulty in loading the drugs as the weight of the delivery system, Cu-tri, increased. However, it was relatively less difficult to load doxycycline than to load amoxicillin, as the loading process yielded higher amounts of it in the delivery system, relative to amoxicillin. The results of the drug release study showed that antibiotics were released from Cu-tri at a relatively fast rate, with 49.5% of doxycycline and 50% of amoxicillin released after 50 minutes. Amoxicillin exhibited a faster release rate relative to doxycycline. Given the relatively high quantity of the antibiotics successfully loaded onto Cu-tri, and the relatively high percentages of the drugs that were released in just 50 minutes, the material could be utilized as a drug carrier for antibiotics, for enhanced bioavailability

Supplementary Materials: Supplementary materials are available from the corresponding author upon request.

Author Contributions: *Conceptualization, S.U. and C.I.; Methodology, S.U.; Experiment, S.U and C.I.; Resources, S.U and C.I.; Data Curation, S.U.; Writing—Original Draft, S.U.; Writing—Review & Editing, S.U. and C.I.* All authors read and approved the final version of the manuscript.

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Data Availability Statement: The data presented in this study are available on request from the corresponding author

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Conflicts of Interest: The authors declare no conflicts of interest.

Nomenclature:

Amoxicillin trihydrate ((2S,5R,6R)-6-[[(2R)-2-Amino-2-(4-hydroxyphenyl)acetyl]amino]-3,3-dimethyl-7-oxo-4-thia-1-azabicyclo[3.2.0]heptane-2-carboxylic acid)

Doxycycline (4S,4Ar,5S,5aR,6R,12aS)-4-(dimethylamino)-3,5,10,1,12a-pentahydroxy-6-methyl-1,11-dioxo-1,4,4a,5,5a,6,11,12a-octahydrotetracene-2-carboxamide hydrochloride

Trimesate 1,3,5-benzene tricarboxylic acid

Trimesate anion 1,3,5-benzene tricarboxylate anion

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