OPEN ACCESS

Haya: The Saudi Journal of Life Sciences
Abbreviated Key Title: Haya Saudi J Life Sci
ISSN 2415-623X (Print) | ISSN 2415-6221 (Online)
Scholars Middle East Publishers, Dubai, United Arab Emirates
Journal homepage: https://saudijournals.com

Review Article

Ligating Properties and Antimicrobial Studies of Metal (II) Complexes of Amoxicillin

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DOI: 10.36348/sjls.2022.v07i02.008 | **Received:** 19.01.2022 | **Accepted:** 22.02.2022 | **Published:** 28.02.2022

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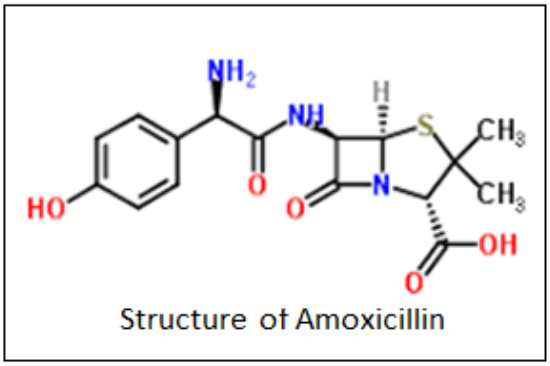
Abstract

Researchers in recent years are working on different approaches to the problem of bacteria resistant to antibiotics through drug modification. The synthesis of metal drug complexes are becoming more popular than their parent drugs because they possess modified pharmacological, toxicological and physiochemical properties. In this study, amoxicillin complexes of copper and zinc (II) ions were synthesized using standard method. The complexes were characterized for aqueous solubility, UV-visible spectral, acid stability, and thermal stability and *in-vitro* antimicrobial activities. The results of the physiochemical properties showed evidence of complex formation between the metals and the ligand. The acid and thermal stability of amoxicillin complexes showed high acid and thermal stability than its parent form. *In-vitro* antimicrobial activity of amoxicillin and its complexes form were studied against *Staphylococcus aureus* and *Pseudomonas aeruginosa.* The results revealed that Amoxicillin complexes of copper (II) ions showed effective antibacterial effect on *Staphylococcus aureus* than its pure form while Amoxicillin Zn^{2+} showed lower antibacterial activity when compared to its parent drug. This study suggests that transition metal complexes of amoxicillin modify the properties of the parent drug.

Keywords: Amoxicillin, antimicrobial, metal complexes, physiochemical properties, transition metals.

1.0 INTRODUCTION

Antibiotic resistance occurs when bacteria undergoes transformation in such a manner that it weakens effectiveness of the antibacterial agent. The problem of bacteria resistance to antibacterial drugs is a global health concern [1-3]. In view of these, researchers are working on different approaches and strategies to find solution to the problem of bacteria resistance to antibiotics through drug modification. Among the various models used to enhance the efficacy of antibiotics, metal drug complexes of transition metals are more popular because they produce compounds with promising antibacterial activities when compared with their parent drugs [1, 4]. Drugs administered in the form of metal complexes possess modified pharmacological, toxicological and physicochemical properties [5]. Many metallic ion-drug complexes have been prepared based on well concerned ideas of improving their efficacy and have been subsequently screened with few, successfully passing clinical trials [6]. Among the properties of the drug altered upon complexation are solubility, absorption energy, stability, partitioning behavior and chemical reactivity [5, 6].



Structure of Amoxicillin

Amoxicillin is a semi-synthetic, broad spectrum antibiotics used for the treatment of a variety

of bacterial infections, skin and urinary tract infections, pneumonia, and strep throat [7]. It binds to one of the penicillin binding proteins which inhibit the final transpeptidation step of the peptidoglycan synthesis in the bacterial cell wall, thus inhibiting biosynthesis and arresting cell wall assembly resulting in bacterial cell death [7]. Literature review shows that there are limited works on the interaction of metal ions with amoxicillin. Accordingly, we have reported the ligating properties and antibacterial Studies of Amoxicillin complexes with Copper and Zinc (II) ions.

2.0 EXPERIMENTAL SECTION

Amoxicillin powder was obtained from Juhel Pharmaceutical Enugu, Analar grade methanol from Honeywell while cobalt chloride and zinc chloride were Analar grade from Sigma-Aldrich and were all used without further purification.

2.1 Synthesis of the Complexes

The complexes were synthesized using modified method described elsewhere [1, 2, 8].

2.1.1 Synthesis of Amoxicillin-Zinc (II) Complex

The complex was synthesized by dissolving 33.1g amoxicillin in 200ml hot methanol and 11.89g $ZnCl_2.2H_2O$ dissolved in 100ml hot methanol was added with constant stirring; and refluxed for 2 hours at 40℃. The mixture was then transferred to a beaker and left in a refrigerator for 4 hours. The yellow precipitate was washed with 200ml deionised water and dried in a dessicator for one week.

2.1.2 Synthesis of Amoxicillin-Copper (II) Complex

The complex was synthesized by dissolving 33.1g amoxicillin in 200ml hot methanol and 11.89g $CuSO_4.6H_2O$ in 100ml hot methanol was added with constant stirring; and refluxed for 2 hours at 40℃. The mixture was then transferred to a beaker and left in a refrigerator for 4 hours. The black precipitate was washed with 200ml deionised water and dried in a dessicator for one week.

2.3 Characterization of the Complexes

The physical properties of the synthesized complexes were determined using the method described in our previous study [1].

2.3.1 Determination of Aqueous Solubility

Saturated solution (10 ml) of each of the complexes and ligand at ambient temperature was evaporated to dryness in an evaporating dish. The mass of the solid left in each case was determined and their solubilities, calculated using the relation:

$$S = \frac{mass}{volume} \times 1000 \quad \ldots\ldots\ldots\ldots\ldots\ldots\ldots\ldots\ldots (1)$$

2.3.2 Determination Acid and Thermal Stability

The relative acid and thermal stabilities of the complexes were determined spectrophotometrically. Solutions of the complexes (0.1 mg/ml) were prepared and their absorption wavelength at maximum absorption band (λ max) in each case was determined. Solutions of each of the complexes and the pure drug were prepared and the temperature regulated to 30℃, 35 ℃ , 40 ℃ , 45 ℃ and 50 ℃ respectively using thermostated water bath (T-160 model). The absorbance of the solutions was measured as they attain the required temperature. Similarly, the same concentration of these solutions was prepared at the pH range of 1-6 and the changes in absorbance measured. These changes in absorbance with pH and temperature are a measure of the stability of the complexes.

2.3.3 UV-visible Spectral Analysis

The UV-visible spectra of amoxicillin and its metal-complexes were recorded using UV-Visible Spectrophotometer model: D-8 Drawell. This scanning spectrum was determined between 200nm and 800nm.

2.4 Antibacterial Activity Test

The in vitro antimicrobial activity of the parent drug and synthesized metal complexes were studied against *Staphylococcus aureus* and *Psedomonas auroginosa* by filter paper disc agar diffusion method. The antibacterial activity was estimated on the basis of the zone of inhibition, minimum inhibitory concentration (MIC) and minimum bactericidal concentration (MBC).

3.0. RESULTS AND DISCUSSION

3.1. Physicochemical properties of the amoxicillin and its metal complexes.

The copper (Cu) (II) and zinc (Zn) (II) complexes of amoxicillin (amx) were synthesized by reaction of metal salts with amoxicillin solution. The percentage yields of the complexes were 72.02% and 78.10% (Table 1). The pH of the complexes was acidic and the aqueous solubility of amx-Zn increased to 108g/l while amx-Cu decreased to 44g/l. The synthesized complexes were coloured exhibiting properties of transition metal complexes.

Table 1: Yield and Physical Properties of Ciprofloxacin, Amoxicillin and their Metal Complexes

Ligands/Complexes	Colour of products	% Yield	pH	Solubility (g/l)	UV (nm)
Amoxicillin	Off white	-	5.33	64	468
Amoxicillin copper	Black	72.02	3.72	44	432
Amoxicillin zinc	Yellow	78.10	5.34	108	360

3.2 Acid and Thermal Stability

The acid and thermal stability data of the ligand and its metal complexes are presented in table 2 and 3 respectively. The acid stability result shows the stability of the metal complexes at the studied pH of 1-6. The result shows a significant difference in the absorbance of amoxicillin and its metal complexes. Amoxicillin copper shows high acid stability than amoxicillin zinc. The result of thermal stability of amoxicillin and amoxicillin complexes shows a significant difference in their absorbance at all studied temperature. The metal complexes show a good thermal stability than the ligands. The high acid and thermal stability of amoxicillin copper over amoxicillin zinc observed in the study may be attributed to the difference in the electronegativity of the metal ions. Copper has ionic electronegativity value of 1.9 Pauling's while zinc was 1.6 Pauling's. High electronegativity of metal atoms increases the covalent character of metal-ligand bond due to electronegativity difference between the metal atom and the donor atom of the ligand [9].

Table 2: Absorbance of the Pure Ligands and Complexes at Different Temperatures.

	Temperature (℃)				
	30	**35**	**40**	**45**	**50**
Amoxicillin	0.019	0.020	0.018	0.011	0.021
Amoxicillin copper	0.185	0.172	0.164	0.151	0.156
Amoxicillin zinc	0.082	0.081	0.082	0.081	0.086

Table 3: Absorbance of the Ligands and their Complexes at Different pH

pH						
Ligands/complexes	**1**	**2**	**3**	**4**	**5**	**6**
Amoxicillin	0.023	0.030	0.034	0.030	0.031	0.027
Amoxicillin copper	0.472	0.193	0.055	0.138	0.189	0.468
Amoxicillin zinc	0.139	0.090	0.109	0.137	0.110	0.186

3.3 Electronic Spectra

The electronic spectral data of the ligand and its metal complexes are presented in Table 1. Amoxicillin showed absorption peak at 468nm while amoxicillin copper and amoxicillin zinc absorbed at 432nm and 360nm respectively. The shift in the absorption of ultraviolet light by the metal complexes shows that copper and zinc (II) ions have an influence on the UV absorption and indicate a reaction between the metal ions and amoxicillin [1].

3.4 Antimicrobial Studies

Antimicrobial activities of amoxicillin-copper and amoxicillin-zinc were tested against gram-negative and gram-positive bacteria using the disk diffusion method. The result of the antimicrobial screening of metal complexes of amoxicillin and pure amoxicillin against *Psedomonas aeroginosa and staphylococcus aureus* are presented in Table 4 and 5. The result showed that amoxicillin had a better zone of inhibition against *Psedomonas aeroginosa* while amoxicillin-zinc had a better zone of inhibition against *staphylococcus aureus* when compared to amoxicillin-copper. The results in table 5 show that amoxicillin had a better MIC against *Psedomonas aeroginosa* followed by amoxicillin-zinc, where against *staphylococcus aureus*; amoxicillin also had a better MIC when compared to the complexes. Although both the complexes can be regarded as a good antibacterial agents that could kill microbes. Amoxicillin and amoxicillin-zinc had a better MBC against *Psedomonas aeroginosa* while amoxicillin had a better MBC against *staphylococcus aureus* when compared to its complexes.

Table 4: Zone Diameter of Inhibition (mm) of the Drugs and their Complexes

	Test Organisms	
Ligands/Complexes	***Psedomonas aeroginosa***	***Staphylococcus aureus***
Amoxicillin	45	27
Amoxicillin copper	21	22
Amoxicillin zinc	30	28

Table 5: Minimum inhibitory concentration (MIC) and Minimum Bactericidal Concentration (MBC) of the Drug and their Complexes

	Test Organisms			
Ligands/Complexes	***Psedomonas aeroginosa***		***Staphylococcus aureus***	
	MIC (mg/ml)	**MBC (mg/ml)**	**MIC (mg/ml)**	**MBC (mg/ml)**
Amoxicillin	12.5	100	50	100
Amoxicillin copper	100	200	50	200
Amoxicillin zinc	50	100	100	200

4.0 CONCLUSION

The synthesis of amoxicillin complexes with Cu^{2+} and Zn^{2+} ions have been realized with their physical, spectroscopic and their antibacterial activities. The acid and thermal stability of the metal complexes were enhanced compared to the pure amoxicillin drug. The antimicrobial screening results clearly demonstrated reduced activity of the complexes against the test strains compared to the parent drug. The study suggests that transition metal complexes of amoxicillin modify the properties of the parent drug.

Conflict of Interest: The authors have not declared any conflict of interest regarding the publication of this paper.

ACKNOWLEDGEMENTS

The financial support from Nigerian Tertiary Education Trust Fund (TETFund) through Institution Based Research (IBR) Project Grant is greatly appreciated. The authors also acknowledge Chemistry Department, Federal Polytechnic Nekede, Owerri, Imo State, Nigeria for the provision of laboratory facilities.

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