WORLD JOURNAL OF PHARMACEUTICAL RESEARCH
SJIF Impact Factor 8.084
Volume 9, Issue 9, 36-43. Research Article ISSN 2277– 7105

SYNTHESIS, CHARACTERIZATION AND ANTIMICROBIAL STUDIES OF CIPROFLOXACIN COMPLEXES WITH COBALT, COPPER AND IRON (II) IONS

Nleonu E. C.*[1], Nnaoma I. E.[2] and Ojiuko I. A.[3]

[1]Department of Chemistry/Biochemistry, Federal Polytechnic Nekede, Owerri- Imo State, Nigeria.

[2]Department of Pharmaceutical Technology, Federal Polytechnic Nekede, Owerri- Imo State, Nigeria.

[3]Department of Biology/Microbiology, Federal Polytechnic Nekede, Owerri- Imo State, Nigeria.

Article Received on
01 July 2020,
Revised on 21 July 2020,
Accepted on 11 August 2020,
DOI: 10.20959/wjpr20209-18418

***Corresponding Author**
Nleonu E. C.
Department of Chemistry/Biochemistry, Federal Polytechnic Nekede, Owerri- Imo State, Nigeria.

ABSTRACT

Ciprofloxacin complexes of cobalt, copper, iron and zinc (II) ions were synthesized and its physicochemical, spectroscopic and antibacterial properties were evaluated. The physicochemical and spectroscopic results indicate evidence of complexes formation between the metals and ligands. Antibacterial studies showed that the complexes of ciprofloxacin complexes shows improve inhibitory effects on *staphylococcus aureus* than its parent form.

KEYWORDS: Ciprofloxacin, Metal complexes, Characterization, Antibacterial.

1.0 INTRODUCTION

Metal – drug complexes are more popular nowadays due to their greater antimicrobial activities than their pure form.[1,2] Research has shown significant interest in utilization of transition metal complexes as drugs to several human diseases. Development of transition metal complexes as drugs is not an easy task as considerable effort is required to get a compound of interest.[3] Transition metal complexes are the most widely used chemotherapeutic agents and make a large contribution to medicinal therapeutics in a way that is unimaginable years back.[3,4]

Antimicrobial resistance is fast becoming a global concern with rapid increase in multidrug resistant bacteria. To overcome the alarming problem of microbial resistance to antibiotics, the discovery of novel active compounds against new targets is a matter of urgency.[5] Currently, most research focuses on the structure of quinolone-metal complexes; however, the research on the nature of complexes is neither comprehensive nor deep.[6] The synthesis of metal-drugs complexes have been known to broaden the spectrum of their activity including antibiotics. Ciprofloxacin (quinolone) has been suggested to be novel agents that can be complexed to metallic ions to enhance their efficacy. So far little material is available on transition metal complexes of ciprofloxacin.[7]

Ciprofloxacin is recognized as one of the most effective antibiotics of the quinolone drug class[8] and has been used for the treatment of urinary tract infections, sexually transmitted diseases; and infections of the respiratory and digestive tract.[9] It has a zwitterinic structure which accounts for its good solubility in acidic and basic solvents, while experiencing poor solubility in water, ethanol, methanol and chlorofoam.[10] Herein, we reported the synthesis and characterization of metal complexes of ciprofloxacin with cobalt, copper and iron (II) ions. The in-vitro antibacterial activities of ciprofloxacin and newly synthesized drug-metal complexes were investigated against gram positive and negative organisms.

2.0 Experimental

Ciprofloxacin hydrochloride was obtained from Juhel Pharmaceutical Enugu, methanol was Analar grade from Honeywell while cobalt chloride, copper sulphate, and iron chloride were Analar grade from Sigma-Aldrich and were all used without further purification.

Synthesis of the Complexes

Synthesis of Ciprofloxacin-Cobalt (II) Complex

The complex was synthesized using the modified method adopted elsewhere[11] by dissolving 33.1g ciprofloxacin in 200ml hot methanol and 11.89g $CoCl_2.6H_2O$ 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 blue precipitate was washed with 200ml deionised water and dried in a dessicator for one week.

Synthesis of Ciprofloxacin-Copper (II) Complex

The complex was synthesized using the method adopted elsewhere[11] by dissolving 33.1g ciprofloxacin in 200ml hot methanol and 11.89g $CuSO_4.6H_2O$ 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 green precipitate was washed with 200ml deionised water and dried in a dessicator for one week.

Synthesis of Ciprofloxacin-Iron (II) Complex

The complex was synthesized using the method adopted elsewhere[11] by dissolving 33.1g ciprofloxacin in 200ml hot methanol and 8.53g $FeCl_2.6H_2O$ 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 red 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 elsewhere.[12]

Determination of Aqueous Solubility

Saturated solution (10 ml) of each of the complexes and ligands 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 were calculated using the relation:

$$S = \frac{mass}{volume} \times 1000$$

Thermal and Acid Stabilities

The relative thermal and acid stabilities of the complexes will be determined spectrophotometrically. Dilute solutions of the complexes (0.1 mg/ml) were prepared, their absorption spectra generated and the wavelength at maximum absorption band (λ max) in each case noted. Six 0.1 mg/ml solutions of each of the complexes were prepared and the temperature regulated to 30℃, 35℃, 40℃, 45℃ and 50℃ respectively. The absorbance of the solutions was measured as they vary in 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.

UV-visible Spectral Analysis

The UV-visible spectra of the metal-complexes of ciprofloxacin were recorded using Drawell Model: D-8 UV-Visible Spectrophotometer. This scanning spectrum was determined between 200nm and 800nm, which can be seen in the result and discussion.

Infra-Red Spectral Analysis

The samples (raw materials and synthesized complexes) were recorded on an IR spectrometer Happ-Genzel in the range of 400-4000cm^{-1} by preparing sample with potassium bromide.

Antibacterial Activity Test

Antimicrobial activity of the parent drug and metal complexes were tested against two different species of bacteria (gram-positive and negative) namely: *Staphylococcus aureus* and *Psedomonas auroginosa* by filter paper disc agar diffusion method.

3.0 RESULTS AND DISCUSSION

3.1 Yield and Physical Properties

The percentage yield and some physical properties of ciprofloxacin and their complexes are presented in Table 1. The results of aqueous solubilities determined at 28±2^{0}C shows that the metal complexation of the drugs improves its aqueous solubility except in ciprofloxacin cobalt complex and these improvements in solubility can be applied in parenteral administration of these drugs.[12]

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

Ligands/Complexes	Colour of products	% Yield	pH	Solubility (g/l)	UV (nm)
Ciprofloxacin	Off white	-	5.00	109	275
Ciprofloxacin cobalt	Blue	85.70	3.98	126	352
Ciprofloxacin copper	Green	83.74	3.19	85	351
Ciprofloxacin iron	Red	80.64	2.77	74	370

3.2 Thermal Stability

The changes in absorbance with temperature for the pure ciprofloxacin and their complexes are shown in Table 2. Ciprofloxacin and their metal complexes shows no significant differences in the absorbance at all studied temperatures (30℃ – 50℃). This shows that the concentration of both the drugs and their complexes were still high even upto 50℃, thus both the drugs and their complexes are thermally stable at this temperature although the complexes showed improved absorbance when compared to their corresponding ligands. The result shows that loss of drugs to deterioration during storage may be minimized when stored in

their complex form.

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

	Temperature (℃)				
Ligands/complexes	**30**	**35**	**40**	**45**	**50**
Ciprofloxacin cobalt	2.394	2.376	2.375	2.346	2.371
Ciprofloxacin copper	2.366	2.376	2.378	2.354	2.384
Ciprofloxacin iron	2.435	2.405	2.418	2.363	2.443

3.3 Acid Stability

The absorbance of solutions of such of the ligands and their metal complexes of different pH are given in Table 3. The changes in absorbance with change in pH are a measure of the acid stability of the metal complexes. Complexation offers a useful means of manipulating the redox potentials of drug molecules, which determines reactivity and stability of the metal complexes.[12,13] There is no significant difference in absorbance of the ligands and complexes of ciprofloxacin in the studied pH. Ciprofloxacin-iron complex shows an appreciable acid stability than pure ciprofloxacin and other ciprofloxacin complexes.

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

	pH					
Ligands/complexes	**1**	**2**	**3**	**4**	**5**	**6**
Ciprofloxacin cobalt	2.294	2.343	2.347	2.360	2.338	2.348
Ciprofloxacin copper	2.366	2.352	2.347	2.342	2.360	0.324
Ciprofloxacin iron	2.435	2.410	2.389	2.402	2.369	2.324

3.4 IR Spectrum

The infra-red spectrum of ciprofloxacin and their complexes were studied in order to get further information about the coordination behavior of the ligands and their complexes. The comparison of the infra-red spectra of the free ligands and their complexes shows formation of metal complexes.

3.5 UV Analysis

Results of UV spectra of ciprofloxacin and their metal complexes are presented in Table 1. The UV values of the complexes compared with that of the pure ciprofloxacin. The shift in the absorption of UV of metal complexes with the pure ligands shows that metal ions have an influence on the UV absorption and indicate complex formation between the metal ions and ligands.

3.6 ANTIBACTERIAL STUDIES

The inhibition zone diameter, minimum bactericidal concentration and minimum inhibitory concentration of the ligands and their complexes are presented in Table 4 and 5 respectively.

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

	Test Organisms	
Ligands/Complexes	***Psedomonas aeroginosa***	***Staphylococcus aureus***
Ciprofloxacin	55	22
Ciprofloxacin cobalt	38	32
Ciprofloxacin copper	44	26
Ciprofloxacin iron	43	26

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)**
Ciprofloxacin	12.5	50	100	200
Ciprofloxacin cobalt	25	100	50	100
Ciprofloxacin copper	25	100	100	250
Ciprofloxacin iron	25	100	100	200

Ciprofloxacin complexes shows improved antibacterial activity against *staphylococcus aureus* when compared to the pure drugs. Ciprofloxacin complexes showed lower antibacterial activities when compared to their corresponding pure drugs. Metal complexes of ciprofloxacin complexes exhibited exceptional antimicrobial properties.[7,8,14] Thus, the ciprofloxacin complexes obtained in this study showed a wide range of antibacterial activities on both gram negative and gram positive bacterial studied.

4.0 CONCLUSION

The synthesis of ciprofloxacin and complexes with Co^{2+}, Cu^{2+} and Fe^{2+} ions have been realized with their physical, spectroscopic and their antibacterial activities. The physical properties show that the complexes of ciprofloxacin have advantage over the pure drugs. Ciprofloxacin complexes complex shows effective antibacterial effect on *staphylococcus aureus* indicating that their metal complexes enhances the activity of the parent ligand.

Conflict of Interest

The authors have not declared any conflict of interest regarding this work.

Funding

This research work was funded by Nigerian Tertiary Education Trust Fund (TETFund) through Institution Based Research (IBR) Project Grant 2019 (TETFUND/DRSS/POLY/NEKEDE/2014/RP/Vol.1).

ACKNOWLEDGEMENTS

The authors would like to acknowledge TETFund for their financial support, Management of Federal Polytechnic Nekede, Owerri for providing research facilities and Mr. Ezeibe A.U for his technical support.

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