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SYNTHESIS, CHARACTERIZATION AND ANTIMICROBIAL STUDIES OF SOME METAL COMPLEXES OF DRUG METFORMIN WITH COPPER (II) METAL

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ABSTRACT

Synthesis of Cu(II) complexes with m Metformin were characterized by analytical data, elemental analysis, molar conductance, thermogravimetric analysis. The structural investigation performed by UV spectral technic. Molar conductance values indicate neutral nature of metal complexes. Antimicrobial activity studied at different concentration (MIC method) by disc diffusion technique. The drug metal complexes found to be significant antibacterial and antifungal agents.

KEYWORDS

Metal Complexes, Antimicrobial activity and Metformin.

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INTRODUCTON

Metal complexes are anonymous part of the biological activities taking place in the human and animal bodies¹. Some metal complexes organo-metallic compounds have been used in medicine for long time. Supplement containing metal ions was needed for a person with type 2 diabetes mellitus, according to its important role in glucose metabolism². Metformin hydrochloride decreases fasting plasma glucose, postprandial blood glucose and glycosylated hemoglobin [HbA1c] levels, which are reflective of the last 8-10 weeks of glucose control. Metformin hydrochloride may also have a positive effect on lipid levels^{3,4}. Copper plays important role in the biological system, like in the active center of many enzymes participating in redox reactions and it is strongly connected with proteins such as ceruloplasmin and albumins^{5,6}.

MATERIAL AND METHODS

Materials

Metformin API was used as received and the chemical copper sulphate and solvent used were AR grade.

Physical measurement

Molar conductance of the complexes was measured in DMF at $1 \times 10^{-3} \text{M}$ using ElicoCM-180 conductometer. Elemental analysis (CHN) was carried out using Thermo finnigan, Italy CHN analyzer, carried out on a Perkin Elmer USAA. InfraRed spectra ($4000\text{-}400\text{cm}^{-1}$) in KBr disc were recorded on Bruker, Germany spectrophotometer. The NMR spectra were taken with TMS reference. The solvent used was DMSO. The magnetic moment data obtained by Gouy-lussac magnetic balance at room temperature with calibration of Hg $[\text{Co}(\text{NCS})_4]$.

Antimicrobial Studies

The antibacterial and antifungal activity of Drug as Ligand and Cu(II) complexes towards the microorganism like *Staphylococcus aureus* and fungi *Aspergillus niger* was carried out by using disc diffusion method. The assay was performed in flat bottom 96 well plate. 1st column was used as negative control while second column onward the test drug was added. resazurin (6.75mg ml^{-1}) was added to all wells and incubated at 37°C for another 24 hours. Change of colour was observed and recorded. The lowest concentration prior to colour change was considered as Minimum Inhibitory Concentration. DMSO and tetracycline was used as negative and positive control respectively. Plates were incubated at 37°C for 24 hours. The zone of clearance for antibacterial activity and was measured in mm.

Synthesis of the Complexes

A hot ethanolic solution of Metformin (10mmol,) was added to ethanolic solution Cu(II) (5mmol). The resulting reaction mixture was refluxed for 4-5 hours. After cooling, the precipitate obtained was collected, filtered, washed with ether, recrystallized from ethanol and dried in vacuum.

RESULTS AND DISCUSSION

The analytical, physical, molar conductance data and magnetic moment values are shown in Table No.1. Ligand is chloroform soluble and solubility of metal complexes is in DMSO. The elemental analysis elucidate that metal to ligand ratio is 1:2 in this complex. Neutral nature of metal complexes was proved by the lower value of molar conductivity data.

IR Spectral data

IR spectral data are mentioned in Table No.2. IR spectra revealed, $\nu(\text{C}=\text{N})$ of band at 1598cm^{-1} is most characteristic band of azomethine, which shifted to $15\text{-}20\text{cm}^{-1}$ to lower wave number side in this complex. The Schiff base shown a band at 1650cm^{-1} , is assignable to the $\nu(\text{C}=\text{O})$ group of chromone system. The broad band observed at $3500\text{-}3400\text{cm}^{-1}$ and other band at $810\text{-}870\text{cm}^{-1}$ that suggest the presence of water molecules in the metal complexes^{7,8}. The spectral band observed in the spectral range of $600\text{-}400\text{cm}^{-1}$ corresponds to $\nu(\text{M}-\text{O})$ and $\nu(\text{M}-\text{N})$ vibrations respectively⁹. Thus the interpretation of IR data suggest that Schiff base ligand (Fig. 1) in reported complexes is bidentate and the coordination of metal ion Cu (II) with Metformin through azomethine nitrogen. The position in the coordination sphere would be completed by water molecule.

¹HNMR Spectra

The ¹HNMR spectrum of ligand recorded in chloroform and its Ni(II) and Fe(III) metal complexes recorded in DMSO. The ¹HNMR data have summarized in Table No.3. The spectrum of ligand shows following signals: 8.07ppm (H, S, -HC=N- azomethine proton); 2.35ppm (3H, S, -CH₃ protons); 6.9- 7.9ppm, however for Drug Metal complexes the NMR signal of azomethine proton shifted to downfield as compared to NMR signal. Thus, there is confirming the metal complex formation.

Antimicrobial Activity

In comparison to tetracycline reference the complex formed shows little anti-fungal and anti-bacterial activity, as the drug metformin is used rather in case of the diabetic treatments.

Table No.1: Molar conductivity data and magnetic moment of Metformin and Copper ion complexes

S.No	Compound	Colour	M.P. (°C)	% Found				Molar Cond. (ohm ⁻¹ cm ² mol ⁻¹)	μ _{eff} (BM)
				C	H	N	M		
1	L	white	225	%	4.06 (4.45)	58%	—	0.63	—
2	[Cu ²⁺ metformin) 2(H ₂ O) ₂]	blue	303	20%	3.37 (4.42)	62%	2%	2.11	2.15

Table No.2: IR spectral data of Metformin and its complex with copper ion

S.No	Compound	ν(C=N)	ν(N-H)	ν(M—N)
1	L	1580cm ⁻¹	3368cm ⁻¹	-
2	(Cu L ₂) (H ₂ O) ₂	1573cm ⁻¹	3290cm ⁻¹	550cm ⁻¹

Table No.3: ¹HNMR spectral data of Metformin and its complex with copper ion

S.No	Compounds	Chemical shift (ppm)	Assignment
1	Metformin	8.07	(H, S, -HC=N- azomethine proton)
		2.35	(3H, S, -CH ₃ protons)
2	[Cu(L) ₂ (H ₂ O) ₂]	8.24	(H, S, -HC=N- azomethine proton)
		2.33	(3H, S, -CH ₃ protons)

Table No.4: MIC (ppm) microbial activity

S.No	Microorganism	L diameter of zone of inhibition (mm)				[Cu(metformin) ₂ (H ₂ O) ₂] diameter of zone of inhibition (mm)				Standard
		250 ppm	500 ppm	1000 ppm	2000 ppm	250 ppm	500 ppm	1000 ppm	2000 ppm	
	<i>S. aureus</i>	4	5	10	12	5	6	12	10	16
	<i>A. niger</i>	4	16	9	15	8	9	10	13	12

Table No.5: TGA of Metformin Copper complex

S.No	Complex	Temperature (°C)	Weight loss found (calcd%)	Assignment
1	[Cu(L) ₂ (H ₂ O) ₂]	25-270	4.73(4.97)	2H ₂ O
		271-630	41.50(42.87)	C ₈ N ₁₀ H ₂₂
		>631	53.77(52.16)	C ₈ O ₁ N ₁₀ H ₄₄

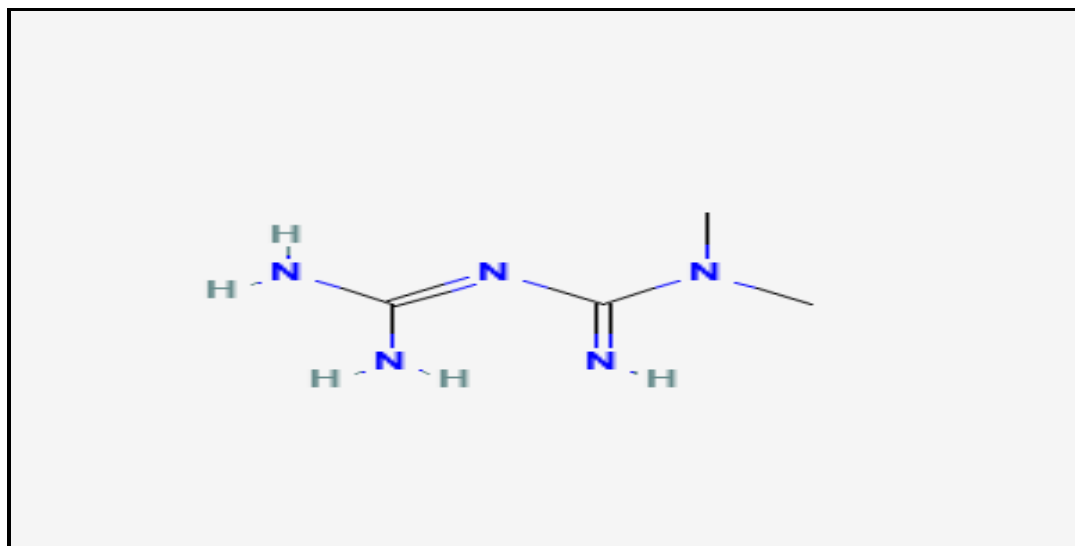


Figure No.1: Structure of Ligand (L)

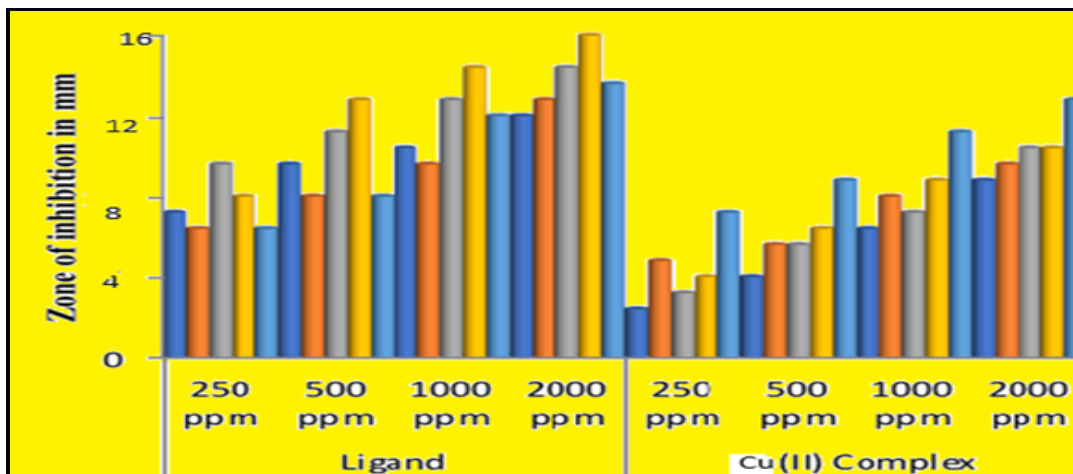


Figure No.2: Antimicrobial activity of the Metformin and its Cu(II)

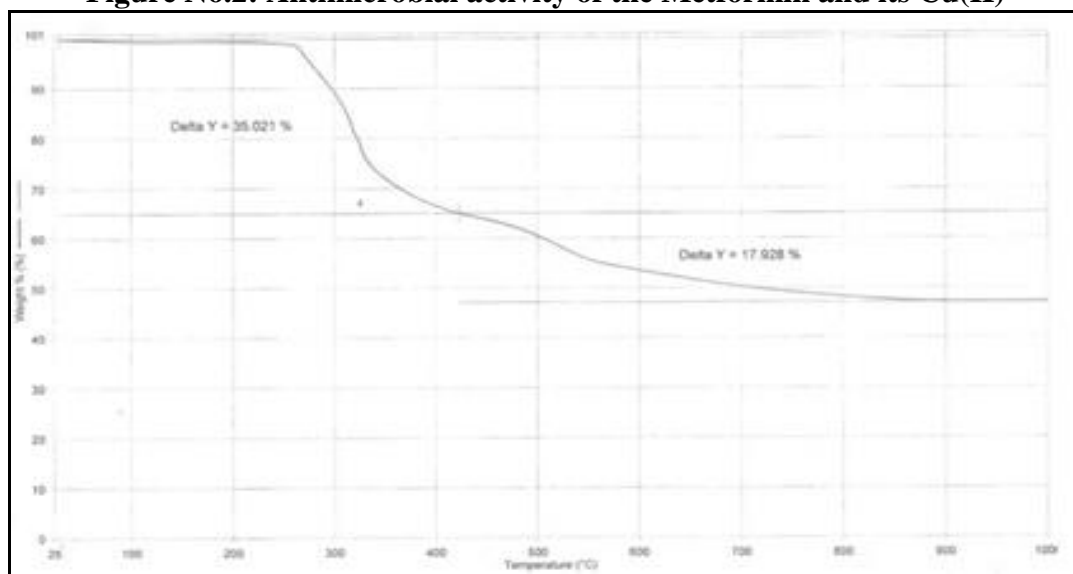


Figure No.3: TG graph of Cu^{2+} Metformin Complex

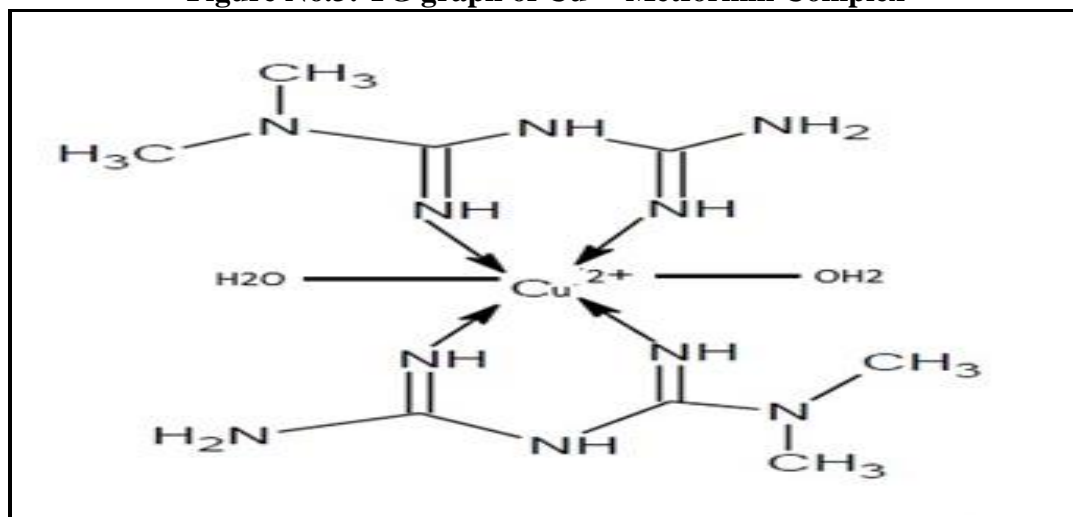


Figure No.4: Proposed structure of Cu^{2+} Metformin Complex

CONCLUSION

Cu(II) complex was synthesized with diabetic drug metformin characterized by using UV-Vis, IR and ¹HNMR spectral studies interprets that the ligand forms bidentate complex with metals coordinated through azomethine nitrogen. TGA data suggest stability of the complex. Octahedral geometry of complexes has been predicted by electronic and magnetic moment data. Coordinated water molecules. Antimicrobial activity was studied by MIC and disc diffusion method. The prepared compounds were show only moderate antimicrobial activity against bacteria and fungi.

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CONFLICT OF INTEREST

We declare that we have no conflict of interest.

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