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Synthesis, Physico-Chemical, Spectral And Biocidal Studies on New Complex of Copper (II) Containing Benzaimidazole Moiety

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ABSTRACT

Metal complex of Cu(II) has been synthesized with Rabeprazole drug that is 2-([4-(3-methoxypropoxy)-3-methylpyridin-2-yl]methylsulfinyl)-1H- benzimidazole, a proton pump inhibitor (PPI). Formation of new complex has been supported by elemental analysis, conductivity measurements and spectral studies including IR,^{1}H NMR,UV, magnetic susceptibility, ESR,TGA,XRD,SEM and mass spectral studies . The molar conductance measurements of the complex in DMSO indicate that the complex is non-electrolytic in nature. Analytical data and stochiometry suggest ligand metal ratio of 2:1 for Cu(II) complex. The spectroscopic results show the involvement of C=N and S=O groups in coordination to the central metal ion. Based on spectral studies, tetragonally distorted octahedral geometry has been proposed for the complex. The ligand and its complex were tested for their antibacterial and antifungal activities against bacteria Pseudomonas, Staphylococcus aureus and fungi A. niger and A. flavous. It is observed that the complex is a better bactericidal agent than the parent drug.

Keywords: Complex, Benzimidazole, Ligand, PPI, XRD, SEM.

INTRODUCTION

Before discussing the possibility of the development of new drugs based on the complexes formed from Copper with Rabeprazole and its related ligands, physiological features of copper as a counterpart of the ligand and its complexes should be described briefly here. Copper belongs to the essential metal group [1]. It is required for normal metabolism in man [2-4]. It performs a vital role in hemopoieses , maintenance of vascular and skeletal integrity and structure of nervous system. Since coordination forms of copper are always more stable as compared to ionized forms, it exists in biological systems in a variety of complexes [5-8].

The literature reveals that the complexes of metallic salts are more potent and less toxic in many cases as compared to the parent drug [9]. Persual of the bacteriostatic studies has shown that copper complexes of sulphonamides are more useful than their parent drugs [10]. Copper complex with tetracaine hydrochloride and also with procaine were prepared and used as local anesthetics [11]. Metal complexes are found to be interesting due to their biological applications like antifungal [12], antibacterial [13] and anti-tumor [14]

activity. A large number of drugs have been used to synthesize the complex with many metals with a view to enhance their therapeutic action [15-16]. Considering the importance of drugs, copper metal and its complexes it has been desired to synthesize and study the metal complexes of Rabeprazole with metals. The present paper describes the synthesis and characterization of Cu(II) with Rabeprazole.

MATERIALS AND METHODS

All chemicals used were of Analytical Grade. Pure sample of Rabeprazole molecular formula $C_{18}H_{21}N_3O_3S$ with molecular weight 359.450 was obtained from Aristo Pharmaceuticals Ltd. Mandideep. Metal salt $CuCl_2.2H_2O$ was of Merck Chemicals. The solvents used were distilled water and methanol. Metal-ligand ratio was calculated using Systronics digital conductivity meter; IR spectra were obtained from CDRI Lucknow (Instrument used Perkin Elmer FTIR Spectrophotometer) in the range of 4000-400 cm^{-1} as KBr pellets and nujol mull in CsI optics. The Electronic spectra were recorded on Perkin Elmer Lambda 25 UV spectrometer. The FAB mass spectrum was recorded at room temperature on Jeol SX-102 FAB mass spectrometer at CDRI Lucknow. Magnetic susceptibility measurements were received from CAT Indore (Instrument used-Vibrating Sample Magnetometer).X-band ESR spectra was recorded in IIT Mumbai on E-112 ESR spectrometer with specification of X-band microwave frequency (9.5 GHZ).Nitrogen was determined by the Dumas method and sulphur was estimated by the Messenger's method. The analysis of carbon, hydrogen and nitrogen was performed on a Carlo Erba 7106 analyzer. Thermograms (TGA and DTA curves) of complexes were recorded at I.I.T.Rudkee on instrument Exstar TG/DTA 6300.

Ligand - metal ratio: To confirm the ligand-metal ratio, Conductometric titrations using mono-variation method were carried out at 21°C. 0.01M solution of Rabeprazole drug was prepared in 80:20 mixture of methanol and water. Similarly, 0.02M solution of $CuCl_2.2H_2O$ was prepared in the same solvent. The ligand was titrated against metal salt solution using mono-variation method. Conductance was recorded after each addition. From the equivalence point in the graph it has been concluded that the complex formation has taken place in the ratio of 2:1 (L:M). Stability constants and free energy changes were also calculated by using Job's method[17] of continuous variation modified by Turner and Anderson[18].

Synthesis of complexes: The complex was synthesized by mixing the solutions of (80% methanol) metal salt solution with that of ligand in 1:2 molar ratio respectively and refluxing the mixture at low temperature for two hours. The mixture was refluxed and the solution was kept for a few days. A green colored crystalline complex of $[(RAB)_2(H_2O)_2Cu]$ formed was filtered, washed with 80% methanol and dried.

RESULTS AND DISCUSSION

The synthesized complex is a stable solid. It is soluble in DMF and DMSO and insoluble in all other organic solvents. Analytical data and conductometric studies suggest 2:1 [L: M] ratio. Measured conductance values of this complex are too low to account for its electrolytic behavior. The magnetic studies indicate the Cu complex to be paramagnetic Carbon, hydrogen, nitrogen, metal and water were estimated micro-analytically at CDRI, Lucknow and given in table 1.

Table 1 : Analytical data of the Complex

S. No.	Composition of Complex (m.wt.)	Color	Yield %	m. p.	Elemental Analyses (%) : Found (Cal)			
					C	H	N	Metal
1	**$C_{18}H_{21}N_3O_3S$** (359.45)	white	-	99 ^{0}C	60.15 (60.12)	5.89 (5.81)	11.69 (11.67)	—
2	$C_{36}H_{46}N_6O_8S_2Cu$ (818.416)	green	30	132 ^{0}C	52.83 (52.00)	5.17 (5.91)	10.26 (10.67)	7.75 (7.91)

Infra-Red Spectra: The IR spectra of ligand and complex have been recorded and the probable assignments are given in the table 2[19-22]. The IR spectra of the complex indicate that the ligand behaves as bidentate and co-ordinates to the metal via C=N and sulphonic acid group. The shift of the **ν** C = N and **ν** S=O by 10-15cm^{-1} in the complex indicates that these groups are involved in the complexation. In the ligand, band appearing at 3438 cm^{-1} due to NH stretching remains unaffected in the complex. The band due to ν C= N in the ligand at 1585 cm^{-1} appeared at 1570 cm^{-1} in the Cu complex thereby confirming the coordination through the azomethine nitrogen atom. The IR band at 1032 cm^{-1} in ligand due to aromatic sulphoxide stretching shifted downwards in complex indicating the involvement of oxygen of sulfoxide in complex formation. Band appearing at 3580 cm^{-1} might be due to coordinated water molecule The appearance of bands in the far IR region at 429-409 cm^{-1} in the complex may be assignable to M-N frequency. Additional band in the complex in the region 615-608 cm^{-1} compared with IR spectra of free ligand has tentatively been assigned to M-O frequency and new band appearing at 1380 cm^{-1} in complex might be due to chelate ring formation in the complex.

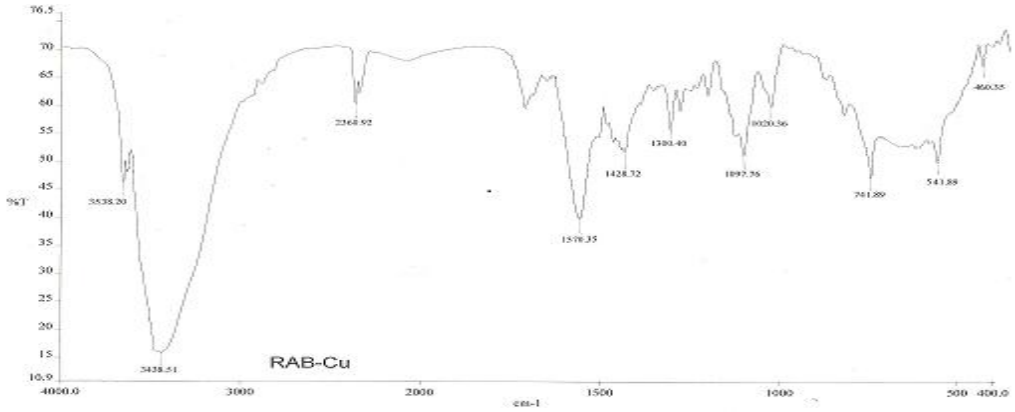


Figure 1: IR spectra of $[Cu(RAB)_2(H_2O)_2]$ Complex

Table 2: IR bands (cm^{-1}) and their assignments for rabeprazole and its Copper(II) complex

Vibration modes	ν(NH)	ν(C=N)	ν(S=O)	ν(M-N)	ν(M-O)	ν(M-O)
$C_{18}H_{21}N_3O_3S$	3438	1585	1032	--	--	--
$(C_{18}H_{21}N_3O_3S)_2Cu(H_2O)_2$	3435	1570	1027	425	610	3580

Electronic Spectra: The electronic spectra[23] of $(C_{18}H_{21}N_3O_3S)_2Cu(H_2O)_2$ exhibits a single broad, asymmetric band in region 12820 cm^{-1} assignable to $^2B_{2g} \leftarrow {}^2B_{1g}$ transition in analogy with expected tetragonally distorted octahedral geometry. The broadness of the band may be due to dynamic and Jahn-Tellor distortion. It is further supported by the high μ_{eff} value in the range 1.89-1.92 B.M.

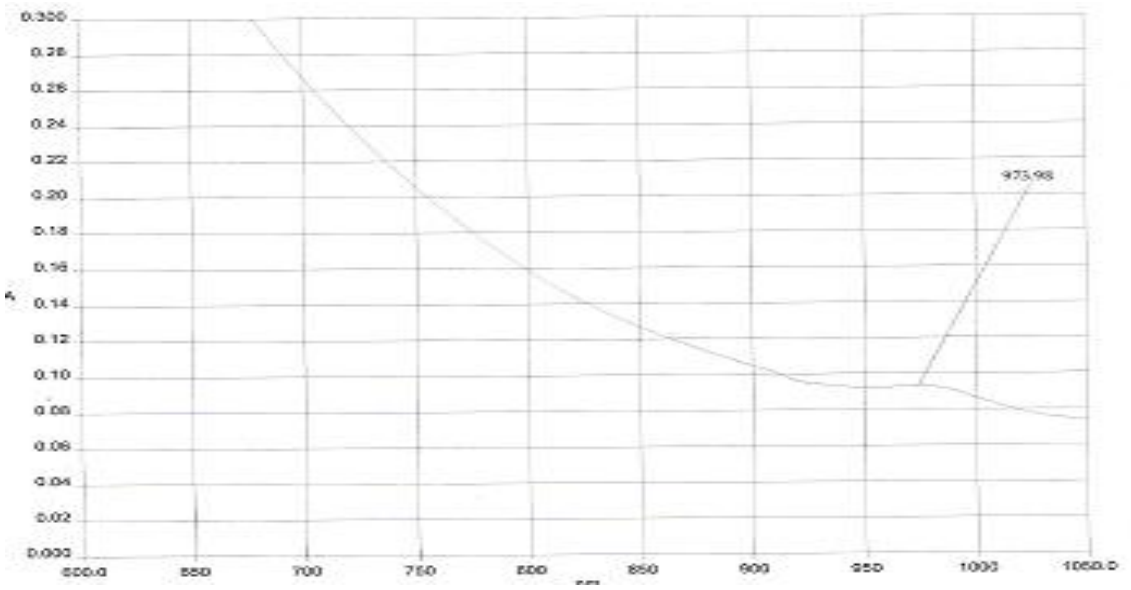


Figure 2: Electronic spectra of $[Cu(RAB)_2(H_2O)_2]$ Complex

ESR Spectra: ESR spectra of powdered samples of $[Cu(RAB)_2(H_2O)_2]$ complex was recorded at room temperature. When the monomeric species change into dimeric species having axial symmetry and identical sites, the 'g' values also change due to the change in symmetry[24]. The spectra have asymmetric bands with two 'g' values $g_{\parallel}$ and $g_{\perp}$ .The trend $g_{\parallel}>g_{\perp}>g$ (2.002), indicates that unpaired electron lies predominantly in the d_{x2-y2} orbital of copper (II) ion, this spectral features are characteristic of axial symmetry[25-27]. The values of the σ bonding parameter, α2, show appreciable covalence character in the metal-ligand bond. Similar spectral observations have been observed by many workers for copper (II) mononuclear complexes [28-30].Based on these observations copper(II) complex may have octahedral geometry. The $g_{\parallel}$ or 'g_{av}' values of the complex is found to be less than 2.3, which indicate considerable covalent character to the Cu-L bond[31] this value is in consistent with Cu-O and Cu-N bonded copper complexes in substituted imidazole and benzimidazole containing complexes.

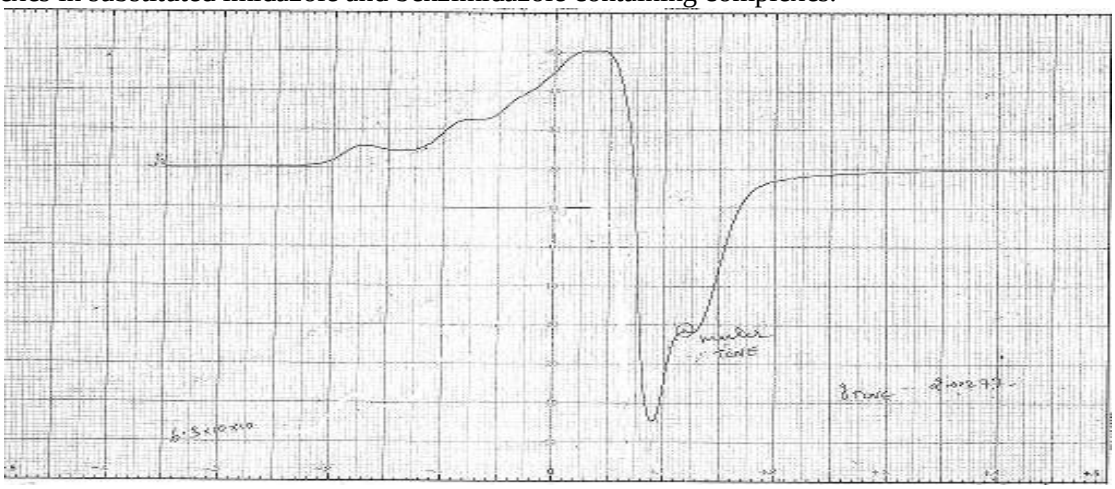


Fig 3: ESR spectra of Rabeprazole-Cu Complex

Mass spectra : The FAB Mass spectrum[32] of $Cu(RAB)_2(H_2O)_2$ showed an important molecular ion peak at m/z =818,which corresponds to molecular weight of complex supported for the dimeric structure. Beside

this peak the complex showed the fragment ion peak at m/z =358, indicating fragmentation of dimer molecule to momomer. The intensity of peaks gives an idea about the abundance and stability of fragments.Other important peaks were observed at m/z54, 117,196,227,242,270,316,358,422,487,715,818 as a result of fragmentation of ligand from the complex by the formation of radical cations such as the peak observed at m/z 117 corresponds to $[C_7H_5N_3]^{\cdot+}$ indicating the benzaimidazole ring. The peak at m/z at 54 is due to $C_4H_6^{\cdot+}$. The peak at m/z 242 is due to remaining part of the ligand other than benzaimidazole ring corresponds to $[C_{11}H_{16}O_3S]^{\cdot+}$. Intense peak was observed at m/z 227 and 196 attributed to loss of CH_3 and OCH_3 from $[C_{11}H_{16}O_3S]^{\cdot+}$.

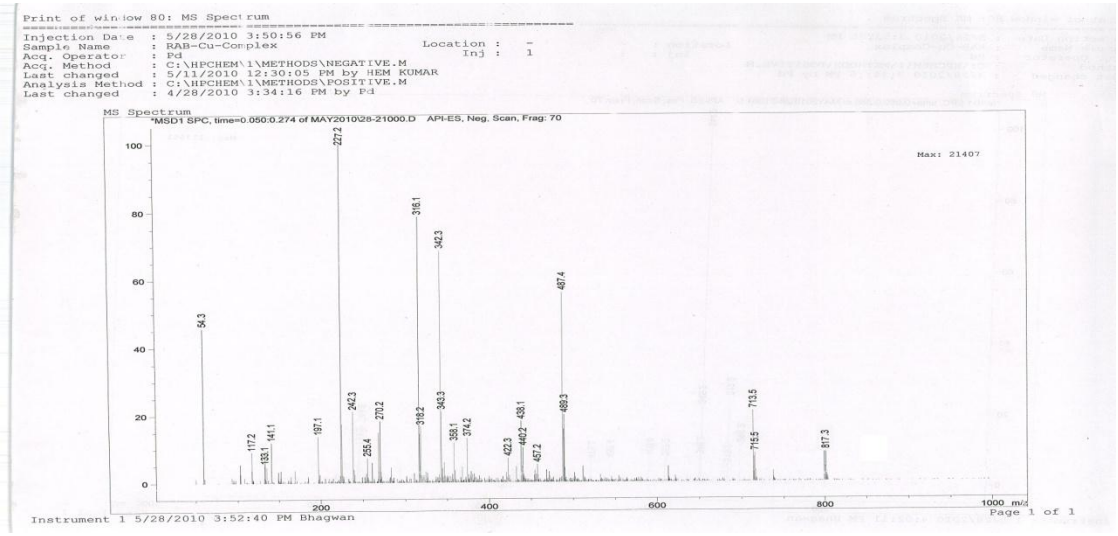


Fig 4: Mass spectra of Rabeprazole-Cu Complex

Thermal analysis: The thermal decompositions of the Cu(II)complex was studied using the TG and DSC technique[33]. The thermo- gravimetric studies of the complex was carried out in the temperature range 30-700 ^{0}C with a sample heating rate 10 ^{0}C/min in air atmosphere. The weight-loss step between 175-200 ^{0}C may correspond to the elimination of coordinated water molecules. The weight-loss step between 250-450 ^{0}C may be attributed to the loss of organic moiety of the complex molecule. The final decomposition continues up to 700 ^{0}C and on further increasing the temperature no weight loss is observed which may be attributed to formation of stable metal oxide.

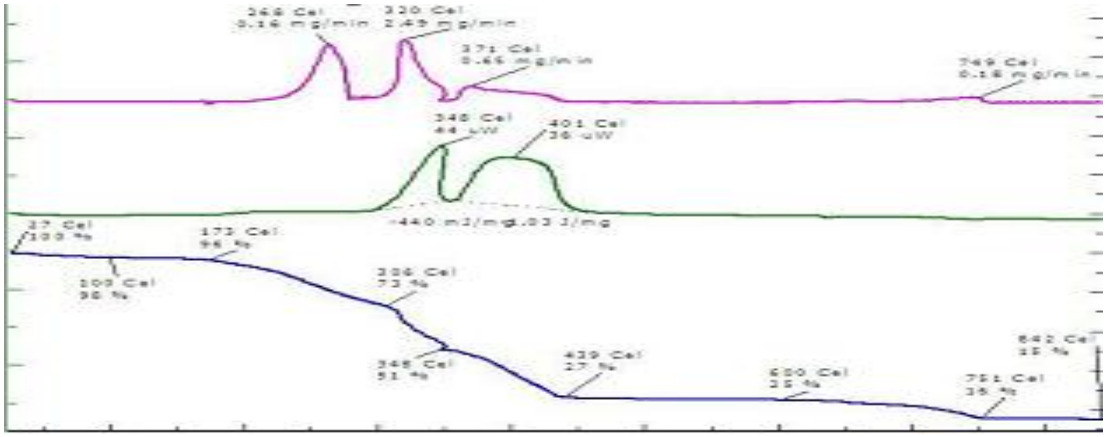


Figure 5: DSC/DTG and TG Curve of [Cu $(RAB)_2(H_2O)_2$] Complex

X-Ray Diffraction: The crystallinity of the material was analyzed by XRD with k alpha radiation The X-ray diffraction of Cu(II) complex of Rabeprazole is studied. The observed 2θ values with relative intensity more than 10% are indexed and have been used for evaluation. The X-ray diffraction pattern of the complex with respect to their prominent peaks has been indexed by using computer software[34]. The observed values fit well with orthorhombic system to give a unit cell dimensions a = 14.42857, b = 10.25224, c = 5.430303 with α=90, β=90 and γ = 90 .Its Lattice type is P.

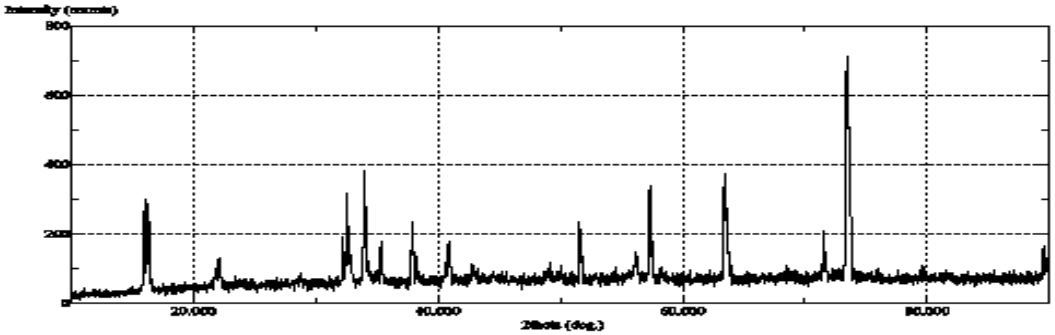
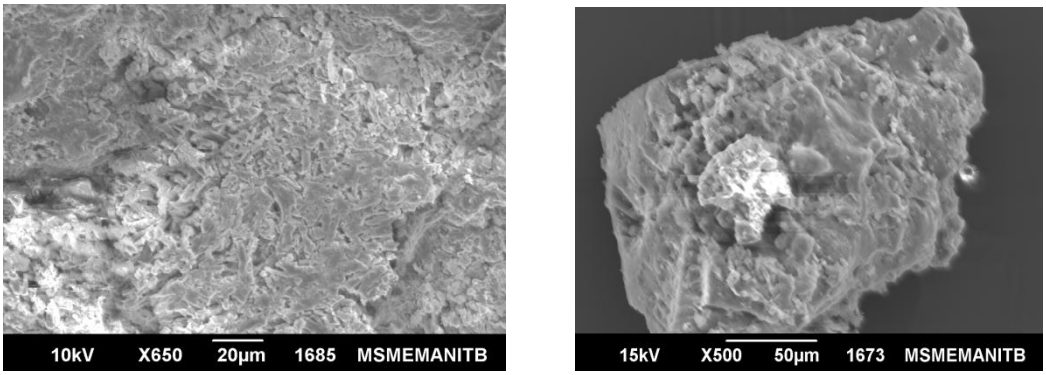


Fig 6: XRD Graph for $Cu(RAB)_2(H_2O)_2$] Complex

Scanning electron micrograph [S.E.M.]**:** SEM of metal complex indicates the presence of well defined crystals free from any shadow of the metal ion on their external surface. The representative micrographs of a) Ligand b) [Cu $L_2(H_2O)_2$] are shown in Fig. 7. These results reveal that after complexation the size of the complex gets reduced to much extent than their parent drug. To find out the maximum efficiency of the drugs and their metal complexes, studies on the particle size analysis are being considered very helpful[35]. The bioavailability of low solubility drug is often intrinsically related to the drug particle size. By reducing particle size, the increased surface area may improve the dissolution rate of the drug to allow a wider range of formulation approaches and delivery technologies[36]. Particle size and rate of dissolution not only affect the peak time and level but it may also affect the apparent pattern of drug pharmaco-kinetics[37].



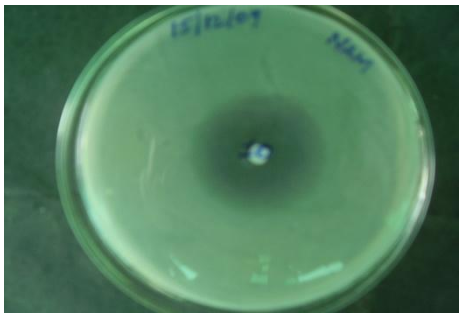
(a) **(b)**

Figure7: Scanning electron micrograph of Ligand and its Complexes

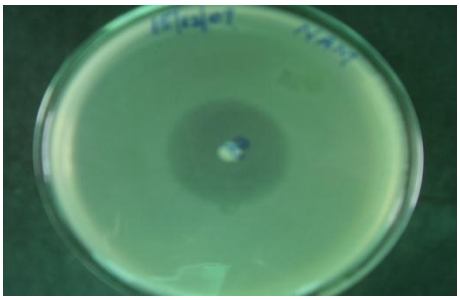
APPLICATIONS

Antimicrobial activity : It is found that the use of complexes metal ions with antibiotics or other therapeutic agents represent an effective therapeutic method for the eradication of gastrointestinal microbes for example, for infections caused by H.*pylori*, the dietary metal complexes can be used in

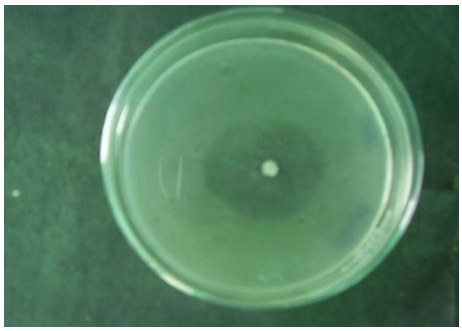
conjunction with antibiotics or agents such as proton pump inhibitors e.g. Rabeprazole[38]. If metal complexes of PPIs exhibit antimicrobial activity than there is no need of additional antibiotics with PPIs. With this view the antimicrobial activity of the ligand and the complex were determined by the disc diffusion technique [39]. The compounds were screened in vitro against *Pseudomonas, Staphylococcus aureus* and two strains of fungi, *A. niger* and *A.flavous*. A 1mg/ml solution in DMF was used. The standard used was gentamycin sulphate. The bacterium was maintained on nutrient agar and the agar media were incubated for different microorganism culture tests. After 24h of incubation at 37°C for bacteria and 72h of incubation at 25°C for fungi, the diameter of zone of inhibition (mm) thus formed around each disc containing the test compound were measured accurately. The Cu(II) complex shows significant activity against bacteria *Pseudomonas, Staphylococcus aureus* and fungi *A. niger* , *A.flavous* as compared to the ligand. These preliminary results show that the activity of the ligand is enhanced when it is presented in the form of metal complex. Better activities of some metal complexes as compared to the ligand can be explained by chelation theory. The theory explains that decrease in polarizability of the metal could enhance the liphophilicity of the complexes which leads to the break- down of permeability of the cells resulting in interference with normal cell processes.



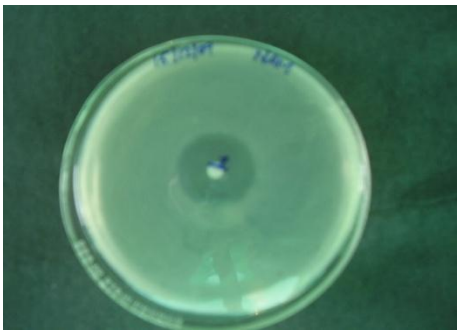
Effect of RAB-Cu(II) on *P. aeroginosa*



Effect of RAB-Cu(II) on *A. flavous*



Effect of RAB-Cu(II) on *A. niger*



Effect of RAB-Cu(II) on *A. flavous*

Figure 8: Effect of metal complexes on Bacterial cultures and Fungi cultures

CONCLUSIONS

The ligand molecule acts as a bidentate ligand. The spectroscopic results show the involvement of C=N and S=O groups in coordination to the central metal ion. Spectral studies suggest that Cu-complex possess octahedral geometry. It is observed that the formed complex is better anti-bacterial agents in comparison to ligand. In view of the foregoing discussions, the high melting points and insolubility in common organic solvents, we have assigned following probable structure of the complex of Rabeprazole.

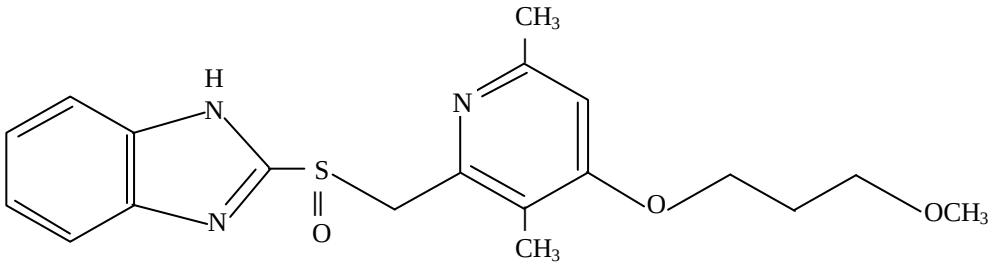


Figure 9: Structure of Rabeprazole

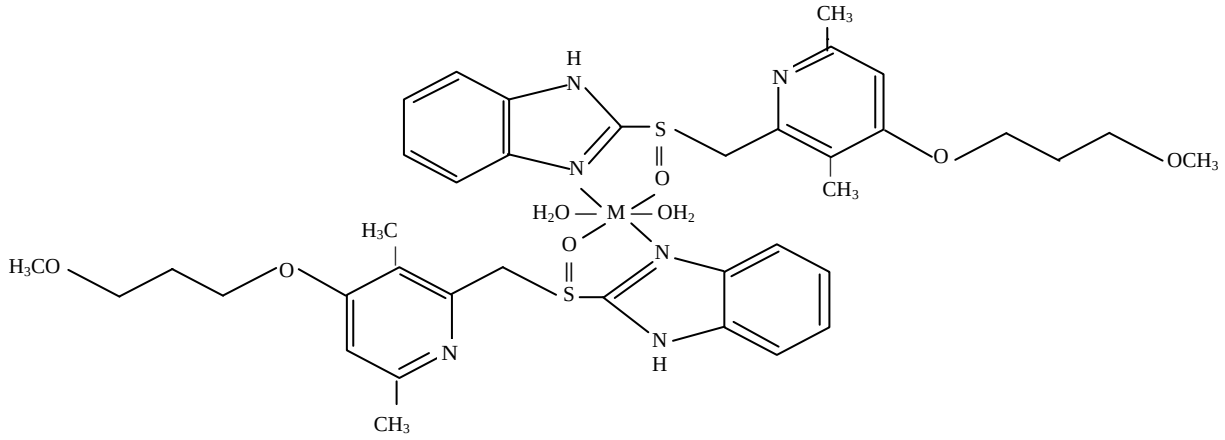


Figure 10: Structure of Rabeprazole - Cu Complex

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