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Spectral, Physico-Chemical and Biocidal Studies of Zinc (Ii) Complex with Omeprazole

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Abstract

Metal complex of Zn (II) has been synthesized with 5-methoxy-2[(4methoxy-3, 5dimethyl-2-pyridinyl) methyl sulfinyl]–1H–benzimidazole , a proton pump inhibitor (PPI). Formation of new complex $(C_{17}H_{19}N_3O_3S)_2$ *Zn has been supported by elemental analysis, conductivity measurements and spectral studies including IR,*^{1}*H NMR,UV, magnetic susceptibility, XRD and SEM 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 Zn(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, tetrahedral 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 Aspergillus Niger and A. flavous. It is observed that the complex is a better bactericidal agent than the parent drug.*

Key Words: complex, benzimidazole, ligand, anti-ulcerative.

INTRODUCTION

Before discussing the possibility of the development of new drugs based on the complexes formed from zinc with Omeprazole and its related ligands, physiological features of zinc as a counterpart of the ligand and its complexes should be described briefly here . Zinc plays an essential role as zinc-containing enzymes in many cases or complexes formed with some components in biological systems. In conclusion, the significance of zinc in living systems is recognized in the maintenance of balance and the adjustment of various physiological reactions in delicately controlled homeostatic systems, as in the human body. We can obtain a general view of recent progress on the study of zinc through some reviews [1, 2]. The literature reveals that the complexes of metallic salts are more potent and less toxic in many a cases as compared to the parent drug [3]. These metal complexes are found to be interesting due to their biological applications like antifungal [4], antibacterial [5] and antitumor [6] activity. A large number of drugs have been used to synthesize the complex with many metals with a view to enhance their therapeutic action [7, 8]. Considering the importance of drugs, zinc metal and its complexes; it

has been desired to synthesize and study the metal complexes of Omeprazole (OME) with metals. The present paper describes the synthesis and characterization of Zn (II) with Omeprazole.

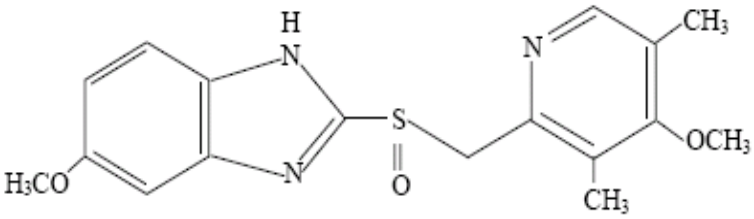

Figure 1: Structure of Omeprazole

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 Zn complex to be diamagnetic.

The IR spectra [9-12] of ligand and complex have been recorded and the probable assignments are given in the Table 2.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 indicate that these groups are involved in the complexation. In the ligand band appearing at 3456 cm^{-1} due to NH stretching remains unaffected in the complex. The band due to ν C= N in the ligand at 1590 cm^{-1} appeared at 1582 cm^{-1} in the Zn complex thereby confirming the coordination through the azomethine nitrogen atom. The IR band at 1038 cm^{-1} in ligand due to aromatic sulfoxide stretching shifted downwards in complex indicating the involvement of oxygen of sulfoxide in complex formation.. The appearance of bands in the far IR region at 429-409 cm^{-1} in the complex may be assigned to M-N frequency. Additional bands 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 appeared at 1380 cm^{-1} in complex might be due to chelate ring formation in the complex.

Table 1: Analytical data of Complex

S. No.	Composition of Complex (m-w.)	Color	Yield %	m. p.	Elemental Analyses (%) : Found (Cal)			
					C	H	N	M
1	$C_{17}H_{19}N_3O_3S$ (345.42)	White	---	156^{0}C	52.71	3.05	11.05	—
2	$(C_{17}H_{19}N_3O_3S)_2$ Zn (756.22)	White	30	210^{0}C	54.00 (54.91)	5.06 (5.30)	11.11 (11.21)	8.64 (8.01)

Table 2: IR Absorption data of the Complex

Ligand and complex	ν(NH)cm^{-1}	ν (C = N) cm^{-1}	ν(S= O)cm^{-1}	ν(M-N)cm^{-1}	ν(M-O)cm^{-1}
$C_{17}H_{19}N_3O_3S$	3456	1590	1038	-	-
$(C_{17}H_{19}N_3O_3S)_2Zn$	3452	1582	1023	425	615

As expected, Zn(II) complex is diamagnetic. The complex is suggested to be tetra-coordinated probably having tetrahedral geometry based on analytical, I.R. and conductance data. On the basis of above studies, following structure may be assigned to the Zn complex of Omeprazole.

NMR Spectra: The ^{1}H NMR spectra [13, 14] of the ligand has the expected characteristic signals. The CH_3 proton shows singlet at δ 2.2 and O-CH_2CH_3 proton at δ 3.5 ppm .The doublet peak observed at δ 4.36 and 4.66 ppm is attributed to CH_2 protons. In addition a multiplet peak at δ 6.9-8.3 may be due to aromatic protons and peak at δ13.2 ppm may be due to NH proton of benzimidazole ring. Signals observed in the complex at region of δ 8.18-8.23 ppm due to azomethine proton either remained unaffected or shifted slightly to higher field with reference to those of the parent ligand and the position of signal due to NH proton remains unaffected in the complexes. The aromatic protons show downfield shifts in the complexes. These observations support the follwing assigned structure to the complex.

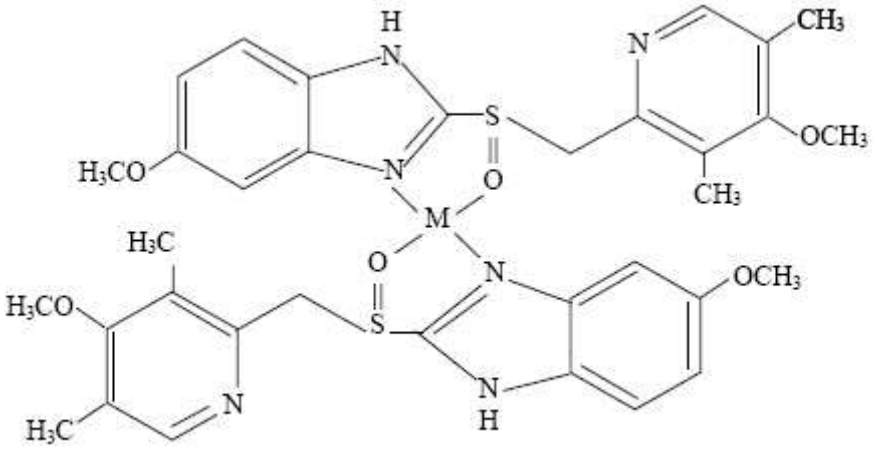

Figure 2: Structure of Omeprazole - Zn Complex

Scanning Electron Micrographs [S.E.M.] : SEM of metal complexes indicate 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) [ZnL_2] are shown in Fig. 3

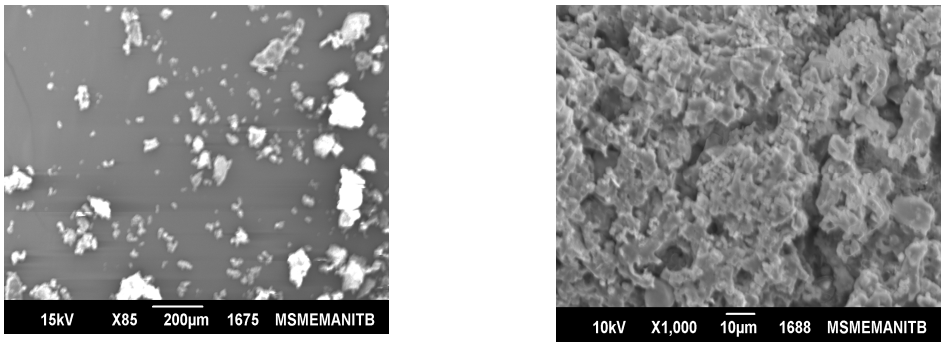

Figure 3 : Scanning electron micrograph of Ligand and its Complexes

X-Ray Diffraction: The crystallinity of the material was analyzed with XRD with k- alpha radiation The X-ray diffraction of Zn (II) complex of Omeprazole is studied . The observed 2θ 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 27. The above index method also yielded miller indices (h, k, l) values, unit cell parameters, volume of unit cell and space group. The observed values fit well with orthorhombic system.

Antimicrobial activity: The antimicrobial activity of the ligand and the complexes were determined by the disc diffusion technique [15]. The compounds were screened in vitro against bacteria *Pseudomonas, Staphylococcus aureus* and two strain of fungi, *Aspergillus 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 ^{0}C for bacteria and 72h of incubation at 25^{0}C for fungi, the diameters of zone of inhibition (mm) thus formed around each disc containing the test compound were measured accurately. The Zn(II) complex showes significant activity against bacteria *Pseudomonas* and *Staphylococcus aureus* and fungi *Aspergillus niger* and *A. flavous* as compared to ligand. These preliminary results show that the activity of the ligand is enhanced when it is presented in the form of metal complex. In view of the foregoing discussions, the high melting points and insolubility in common organic solvents, the following probable structure has been assigned to the Zn (II) complex of Omeprazole.

Table 3 : Antibacterial activity- zone of inhibition {in mm}

S. No.	Compound	*P. Aeroginosa*	*S. Aureus*	*A. niger*	*A. flavous*
1.	Omeprazole	9.2	11.5	11.22	12.11
2.	Zn L_2	11.7	13.3	12.80	19.00

MATERIALS AND METHODS

All chemicals used were of Analytical Grade. Pure sample of Omeprazole (molecular formula $C_{17}H_{19}N_3O_3S$) with molecular weight 345.42 was obtained from Aristro Pharmaceuticals Ltd. Mandideep, Bhopal. Metal salt $ZnCl_2$ 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 on Perkin Elmer FTIR Spectrophotometer in the range of 4000-400 cm^{-1}. Nitrogen was determined by the Dumas method and sulphur was estimated by the Messenger's method. The elemental microanalyses of C, H, and N for ligand were carried out with Thomas and Coleman Analyzer Carlo Erba 7106.

*LIGAND – METAL RATIO***:** To confirm the ligand-metal ratio, conductometric titration using mono-variation method was carried out at 21 ^{0}C. 0.01 M solution of Omeprazole drug was prepared in 70:30 mixture of methanol and water. Similarly, 0.02M solution of ZnCl2 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 [16] of continuous variation modified by Turner and Anderson [17].

SYNTHESIS OF COMPLEXES: The complex was synthesized by mixing the solutions of (70% methanol-water) metal salt solution with that of ligand in 1:2 molar ratio respectively and refluxing the mixture for three and half hours. White ppt. of $(OME)_2Zn$ formed was filtered, washed with mixture of methanol and distilled water (70:30) and dried. Carbon, hydrogen, nitrogen, metal and water were estimated micro- analytically at CDRI, Lucknow.

CONCLUSION

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. Tetrahedral structure for Zn(II) complex have been tentatively proposed. It is observed that the formed complex is a better anti-bacterial agent in comparison to ligand.

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