

FIRST-ROW TRANSITION METAL COMPLEXES OF OMEPRAZOLE AS ANTI-ULCERATIVE DRUGS

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ABSTRACT

Omeprazole (OME) is a proton pump inhibitor (PPI). PPIs have enabled to improve the treatment of various acid-peptic disorders. OME is a weak base and it can form several complexes with transition and non-transition metal ions. In the present paper, we are describing series of transition metal complexes of omeprazole i.e., 5-methoxy-2[(4methoxy-3, 5dimethyl-2-pyridinyl) methylsulfinyl]-1H-benzimidazole with Cu^{II}, Mn^{II}, Co^{II}, Ni^{II}, Fe^{II}, Zn^{II} and Hg^{II}. These complexes were characterized by elemental analysis, molar conductivity, IR, NMR, magnetic susceptibility, UV-visible spectral studies, ESR, SEM and X-ray diffraction. Based on the above studies, the ligand behaves as bidentate O, N donor and forms coordinate bonds through C=N and S=O groups. The complexes were found to non-electrolytic in nature on the basis of low values of molar conductivity. Analytical data and stoichiometry analysis suggest ligand to metal ratio of 2:1 for all the complexes. Electronic spectra and magnetic susceptibility measurements reveal octahedral geometry for Mn(II), Co(II), Ni(II), Fe(II) and Cu(II) complexes and tetrahedral for Hg(II) and Zn(II) complexes. Ligands and their metal complexes have been screened for their antibacterial and antifungal activities against bacteria *Pseudomonas*, *Staphylococcus aureus* and fungi *Aspergillus niger* and *A. flavus*.

Keywords: Complex, Omeprazole, Antibacterial, Ligand, Stoichiometry

INTRODUCTION

A peptic ulcer, also known as PUD or peptic ulcer disease is an ulcer of an area of the gastrointestinal tract that is usually acidic and thus extremely painful. Ulcer results from a complex interplay of acid and chronic inflammation induced by *Helicobacter pylori* infection [1-2]. Most of the times, ulcers are associated with *Helicobacter pylori*, a spiral-shaped bacterium that lives in the acidic environment of the stomach. Reflux of acid and stomach contents can cause irritation or damage of the lining of lower esophagus. If this damage is continuous, it can cause gastro-esophageal disease (GERD) [3-5]. Ulcers can also be caused or worsened by drugs such as aspirin and anti-inflammatory drugs. A class of drugs, called, proton pump inhibitors (PPIs) [6-8], blocks the production of acid by the stomach. PPIs are substituted benzimidazoles and are lipophilic weak bases that cross the parietal cell membrane and enter the acidic parietal cell canaliculus. In this acidic environment, the PPIs become protonated producing the activated sulphonamide from the drug that binds covalently with the H⁺, K⁺ ATPase enzyme resulting in irreversible inhibition of acid secretion by the proton pump. The drugs in the same class include omeprazole, lansaprazole, rabeprazole, and pantoprazole [9] and are used for the treatment in acid induced inflammation

conditions and ulcers of the stomach and duodenum, gasteo-oesophageal reflux disease, all caused by stomach acid. The therapeutic activity of coordination compounds has been evaluated extensively [10-11]. Some important examples of inorganic based drugs are metallocene anti-tumor complexes [12], gold anti-arthritis compounds [13] and lithium antidepressants [14]. In all these cases, work is largely focused on elucidating the action mechanism of these complexes. Biological science literature reveals that the complexes of metallic salts are more potent and less toxic in many cases as compared to the parent drug [15]. Considering the importance of drugs and their complexes, it has been desired to synthesize and study the metal complexes of Omeprazole with metals. The present paper reports the synthesis, characterization and antimicrobial activity of a very common PPI, omeprazole, with first row transition metals like Cu^{II}, Mn^{II}, Co^{II}, Ni^{II}, Fe^{II}, Zn^{II} and Hg^{II}.

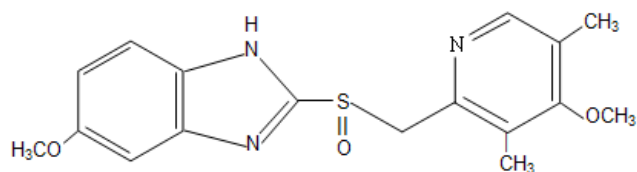


Fig 1. Structure of Omeprazole

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EXPERIMENTAL SECTION

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 Pharmaceutical Ltd. Mandideep, Bhopal. All Metal salts $CuCl_2 \cdot 2H_2O$, $NiCl_2 \cdot 4H_2O$, $CoCl_2 \cdot 6H_2O$, $FeSO_4 \cdot 7H_2O$, $MnCl_2 \cdot 7H_2O$, $ZnCl_2$ and $HgCl_2$ were 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 $4000-400\text{ cm}^{-1}$). Magnetic susceptibility measurements were received from CAT Indore (Instrument used-Vibrating Sample Magnetometer). 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 titrations using mono-variation method were carried out at $21\text{ }^\circ\text{C}$. Solution of 0.01 M omeprazole drug was prepared in [70:30] mixture of methanol and water. Similarly, 0.02M solutions of metal salts were prepared in the same solvent. The ligand was titrated against metal salt solutions 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 complexes were synthesized by mixing the solutions (70% methanol) of metal salt with that of ligand in 1:2 molar ratios respectively. The thick precipitates of different colors for different metal salts were observed. By adjusting the pH with the addition of dilute NaOH solution and refluxing the mixtures for three and a half hours colored crystalline complexes were obtained. The complexes were filtered, washed with (70:30) mixture of methanol water and dried. Carbon, hydrogen, nitrogen, metal and water were estimated microanalytically at CDRI, Lucknow.

RESULT AND DISCUSSION

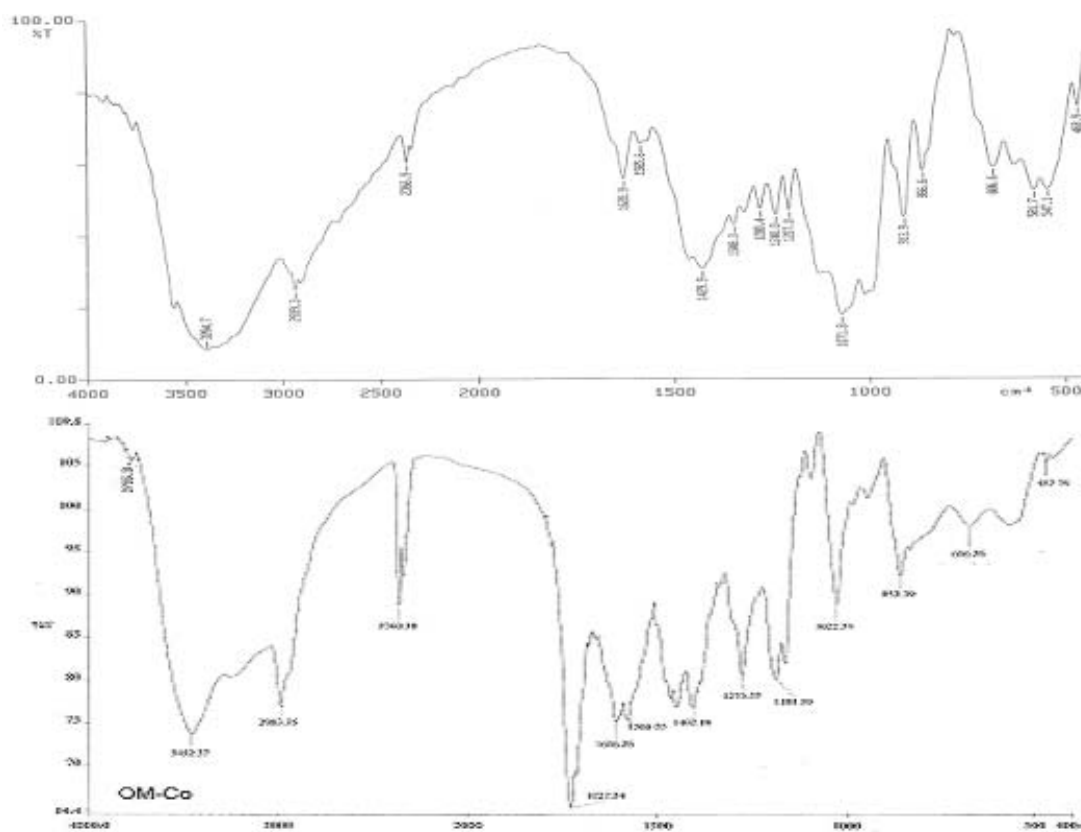
The synthesized complexes are stable solids. They are soluble in DMF and DMSO and insoluble in all other organic solvents. Analytical data and conductometric studies suggest 2:1 [L:M] ratio. Measured conductance values of these complexes are too low to account for their electrolytic behavior. The magnetic studies indicate the Mn(II), Co(II), Ni(II), Fe(II) and Cu(II) complexes to be paramagnetic while Zn(II) and Hg(II) complexes to be diamagnetic.

Table 1. Analytical data of complexes

| S. No. | Composition of Complex (m-wt.) | Color | Yield % | m.p. $^\circ\text{C}$ | Elemental Analyses (%) : Found (Cal) | | | |
|--------|--|------------------|---------|-----------------------|--------------------------------------|----------------|------------------|------------------|
| | | | | | C | H | N | M |
| 1 | $(C_{17}H_{19}N_3O_3S)$ (345.42) | White | | 156 | 52.71 | 3.05 | 11.05 | — |
| 2 | $(C_{17}H_{19}N_3O_3S)_2Mn \cdot (H_2O)_2$ (781.801) | PINKISH WHITE | 48 | 205 | 52.23 (53.20) | 4.89 (4.51) | 10.74 (10.47) | 7.02 (7.12) |
| 3 | $(C_{17}H_{19}N_3O_3S)_2Fe \cdot (H_2O)_2$ (782.710) | Maroon | 86 | 220 | 52.17 (52.00) | 4.89 (4.91) | 10.73 (10.67) | 7.13 (7.91) |
| 4 | $(C_{17}H_{19}N_3O_3S)_2Co \cdot (H_2O)_2$ (785.796) | PINK | 66 | 212 | 51.96 (36.90) | 4.87 (4.91) | 10.69 (10.67) | 7.49 (7.69) |
| 5 | $(C_{17}H_{19}N_3O_3S)_2Ni \cdot (H_2O)_2$ (785.553) | Pista Green | 71 | 175 | 51.98 (36.92) | 4.87 (4.95) | 10.69 (10.67) | 7.47 (7.66) |
| 6 | $(C_{17}H_{19}N_3O_3S)_2Cu \cdot (H_2O)_2$ (790.363) | GREEN | 62 | 199 | 51.66 (51.70) | 4.84 (4.91) | 10.63 (10.77) | 8.03 (8.91) |
| 7 | $(C_{17}H_{19}N_3O_3S)_2Hg$ (891.732) | White | 75 | 210 | 45.79 (45.91) | 4.29 (4.30) | 9.42 (9.22) | 22.49 (23.01) |
| 8 | $(C_{17}H_{19}N_3O_3S)_2Zn$ (756.22) | WHITE | 77 | 215 | 54.00 (54.91) | 5.06 (5.30) | 11.11 (11.21) | 8.64 (8.01) |

Table 2. Stability constant, Free energy change, Molar conductance and Magnetic- moment data of complexes

| S. No. | Composition of Complex (m-wt.) | Stability constant logK(L/mole) | Free Energy change $-\Delta F$ (Kcal/mole) | Molar conductance ($\text{ohm}^{-1}\text{m}^2\text{mol}^{-1}$) | Magnetic Moment (B.M.) |
|--------|--|---------------------------------|--|--|------------------------|
| 1. | (C ₁₇ H ₁₉ N ₃ O ₃ S) ₂ Zn | 10.7471 | 15.9751 | 14.6 | — |
| 2. | (C ₁₇ H ₁₉ N ₃ O ₃ S) ₂ hG | 10.5231 | 14.9751 | 10.34 | — |
| 3. | (C ₁₇ H ₁₉ N ₃ O ₃ S) ₂ Fe. (H ₂ O) ₂ | 11.1692 | 15.9466 | 10.6 | 5.20 |
| 4. | (C ₁₇ H ₁₉ N ₃ O ₃ S) ₂ Mn.(H ₂ O) ₂ | 12.088 | 17.03 | 12.01 | 5.62 |
| 5. | (C ₁₇ H ₁₉ N ₃ O ₃ S) ₂ Cu.(H ₂ O) ₂ | 11.1704 | 15.5905 | 13.0 | 1.75 |
| 6. | (C ₁₇ H ₁₉ N ₃ O ₃ S) ₂ Ni. (H ₂ O) ₂ | 11.4204 | 16.1746 | 12.13 | 3.06 |
| 7. | (C ₁₇ H ₁₉ N ₃ O ₃ S) ₂ Co.(H ₂ O) ₂ | 11.4208 | 16.039 | 14.08 | 4.65 |

**Fig 2.** IR spectra of Omeprazole and its [Co(OME)₂.(H₂O)₂] Complex

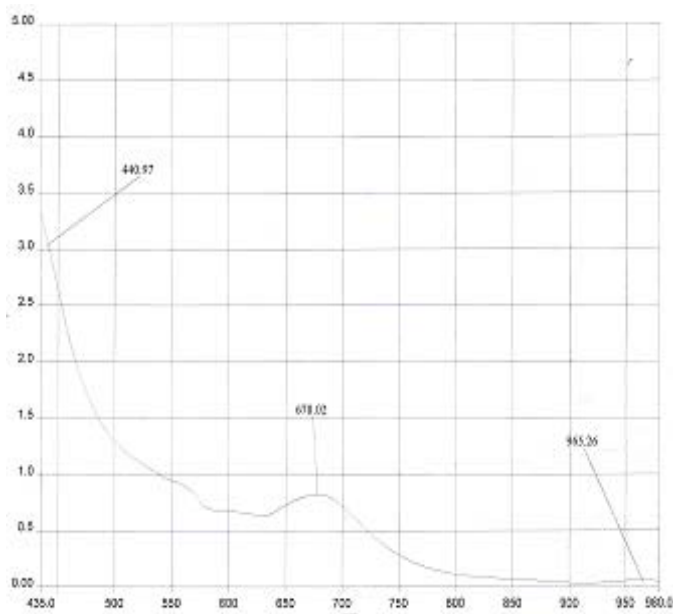
I.R. Spectra

The vibrational spectra [18-21] for the free ligand omeprazole when compared to those of its complexes provided meaningful information regarding the bonding sites of the ligand (Table 3). The IR spectra of the complexes indicate that the ligand behaves as bidentate and co-ordinate the metal via C=N and sulphonic acid group. The shift of the $\nu_{\text{C=N}}$ and $\nu_{\text{S=O}}$ by 10-25 cm^{-1} in the complexes indicates that these groups are involved in the complexation. In the IR spectra of omeprazole, strong band at 3456 cm^{-1} is assigned to the secondary NH stretching vibrations. This band remains unaltered or shifted to the higher wave number in the complexes suggesting non-involvement of secondary

NH group in coordination with metal ions. The medium to strong bands appearing at 1585 cm^{-1} in the free ligand are assigned to C=N stretching vibration of the azomethine group based on the available reports. The IR band at 1070 cm^{-1} in ligand may be due to aromatic sulfoxide stretching in complexes shifted to lower frequencies. The weak intensity non-ligand bands observed in the complexes in the regions $625\text{-}608 \text{ cm}^{-1}$ and $429\text{-}409$ are assigned to $\nu_{\text{M-N}}$ and $\nu_{\text{C-N}}$ stretching vibrations, respectively. Band appearing at region $3654\text{-}3619 \text{ cm}^{-1}$ due to coordinated water molecules and new band at $1380\text{-}1390 \text{ cm}^{-1}$ in complexes might be due to chelate ring formation in them.

Table 3. IR Absorption data of the complexes

| Ligand and complex | $\nu_{\text{N-H}}$ cm^{-1} | $\nu_{\text{C=N}}$ cm^{-1} | $\nu_{\text{S=O}}$ cm^{-1} | $\nu_{\text{M-N}}$ cm^{-1} | $\nu_{\text{M-O}}$ cm^{-1} | $\nu_{\text{(H}_2\text{O)}}$ cm^{-1} |
|---|--|--|--|--|--|--|
| $\text{C}_{17}\text{H}_{19}\text{N}_3\text{O}_3\text{S}$ | 3456 | 1585 | 1070 | - | - | - |
| $(\text{C}_{17}\text{H}_{19}\text{N}_3\text{O}_3\text{S})_2\text{Fe}(\text{H}_2\text{O})_2$ | 3459 | 1576 | 1020 | 415 | 610 | 3565 |
| $(\text{C}_{17}\text{H}_{19}\text{N}_3\text{O}_3\text{S})_2\text{Mn}(\text{H}_2\text{O})_2$ | 3469 | 1572 | 1018 | 412 | 609 | 3535 |
| $(\text{C}_{17}\text{H}_{19}\text{N}_3\text{O}_3\text{S})_2\text{Ni}(\text{H}_2\text{O})_2$ | 3465 | 1568 | 1019 | 410 | 617 | 3544 |
| $(\text{C}_{17}\text{H}_{19}\text{N}_3\text{O}_3\text{S})_2\text{Co}(\text{H}_2\text{O})_2$ | 3462 | 1560 | 1022 | 422 | 624 | 3545 |
| $(\text{C}_{17}\text{H}_{19}\text{N}_3\text{O}_3\text{S})_2\text{Cu}(\text{H}_2\text{O})_2$ | 3466 | 1565 | 1017 | 417 | 621 | 3557 |
| $(\text{C}_{17}\text{H}_{19}\text{N}_3\text{O}_3\text{S})_2\text{Zn}$ | 3468 | 1570 | 1018 | 426 | 615 | - |
| $(\text{C}_{17}\text{H}_{19}\text{N}_3\text{O}_3\text{S})_2\text{Hg}$ | 3456 | 1575 | 1021 | 428 | 609 | - |

**Fig 3.** Electronic spectra of $[\text{Ni}(\text{OME})_2(\text{H}_2\text{O})_2]$ Complex

Electronic spectra and magnetic susceptibility data

The electronic spectra of the Ni(II), Co(II), Mn(II), Fe(II) and Cu(II) complexes were taken in DMSO (10^{-3}M) solution. The Co(II) complex exhibit three bands at 981 nm, 539 nm and 385 nm respectively, assignable to ${}^4\text{T}_{2g}(\text{F}) \leftarrow {}^4\text{T}_{1g}(\text{F})$ (ν_1), ${}^4\text{A}_{2g}(\text{F}) \leftarrow {}^4\text{T}_{1g}(\text{F})$ (ν_2) and ${}^4\text{T}_{1g}(\text{P}) \leftarrow {}^4\text{T}_{1g}(\text{F})$ (ν_3) transitions which indicate octahedral [22] geometry of the complex. The proposed geometry is further confirmed by high μ_{eff} value in the range 4.89-5.24 B.M [23-24]. The Ni(II) complex exhibits three bands at 955nm, 540nm and 440nm which are assigned to ${}^3\text{T}_{2g}(\text{F}) \leftarrow {}^3\text{A}_{2g}(\text{F})$ (ν_1), ${}^3\text{T}_{1g}(\text{F}) \leftarrow {}^3\text{A}_{2g}(\text{P})$ (ν_2) and ${}^3\text{T}_{1g}(\text{P}) \leftarrow {}^3\text{A}_{2g}(\text{F})$ (ν_3) transitions indicating octahedral [22] geometry of the complex. The geometry of Ni (II) complex is further confirmed [23-24] by the high μ_{eff} value in the range 3.09-3.20 B.M. The electronic spectra of the paramagnetic Mn(II) complex displays three absorption bands at 408 nm, 441 nm and at 600 nm which can be assigned to ${}^4\text{E}_g(\text{G}) \leftarrow {}^6\text{A}_{1g}$, ${}^4\text{T}_{2g}(\text{G}) \leftarrow {}^6\text{A}_{1g}$ and ${}^4\text{T}_{1g}(\text{G}) \leftarrow {}^6\text{A}_{1g}$ transitions respectively

indicating octahedral [22] geometry of the complex. The geometry of Mn(II) complex is further confirmed [23-24] by the high μ_{eff} value in the range of 5.85-5.98 B.M. The Cu(II) complex exhibits a single broad, asymmetric band in region 780 nm may be assigned to ${}^2\text{B}_{2g} \leftarrow {}^2\text{B}_{1g}$, ${}^2\text{E}_{2g} \leftarrow {}^2\text{B}_{1g}$ transitions are in analogy with expected tetragonally distorted octahedral geometry. The broadness of the band may be due to dynamic and Jahn-Teller distortion. It is further supported by the high μ_{eff} value in the range of 1.89-1.92 B.M. The Fe(II) complex exhibits two bands at 397 nm and 695 nm. The first band is assigned to charge transfer while the second band may be due to the transitions ${}^5\text{E}_g \leftarrow {}^5\text{T}_{2g}$ indicating octahedral [22] geometry of the complex. The proposed geometry is further confirmed by high μ_{eff} value in the range [23-24] 5.92-5.24 B.M. As expected, Zn(II) and Hg(II) complexes are diamagnetic. The complexes are suggested to be tetra-coordinated probably having tetrahedral geometry based on analytical, electronic spectra and conductance data.

NMR Spectra

The ${}^1\text{H}$ NMR [25-26] spectra of the ligand has the expected characteristic signals. The CH_3 proton shows singlet at δ 2.2 and $\text{O-CH}_2\text{CH}_3$ 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 ppm may be due to aromatic protons and peak at δ 13.2 may be due to NH proton of benzimidazole ring. Signals observed in the complexes at region of δ 8.18-8.23 ppm due to the azomethine proton either remained unaffected or shifted slightly downfield 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 assigned structure to the complex.

Scanning Electron Micrographs [S.E.M.]

SEM of metal complexes 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; $[C_{17}H_{19}N_3O_3S]$ b) $[FeL_2(H_2O)_2]$, c) $[CuL_2(H_2O)_2]$, d) $[CoL_2(H_2O)_2]$, e) $[NiL_2(H_2O)_2]$, f) $[ZnL_2(H_2O)_2]$ are shown in Fig. 5.

ESR Spectra

ESR spectra of powdered samples of $[Cu(OME)_2(H_2O)_2]$ 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 [27]. 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 $d_{x^2-y^2}$ orbital of copper (II) ion. The values of the σ bonding parameter, α_2 , show appreciable covalence character in the metal-ligand bond. Based on these observations copper (II) complex may have octahedral geometry.

X-ray diffraction

The crystallinity of the material was analyzed with XRD with K-alpha radiation. The X-ray diffraction of Cu(II) complex of L₁ is studied as a representative system. 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 [28]. 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 to give a unit cell dimensions $a = 6.3314 \text{ \AA}$, $b = 8.5059 \text{ \AA}$ and $c = 15.405 \text{ \AA}$.

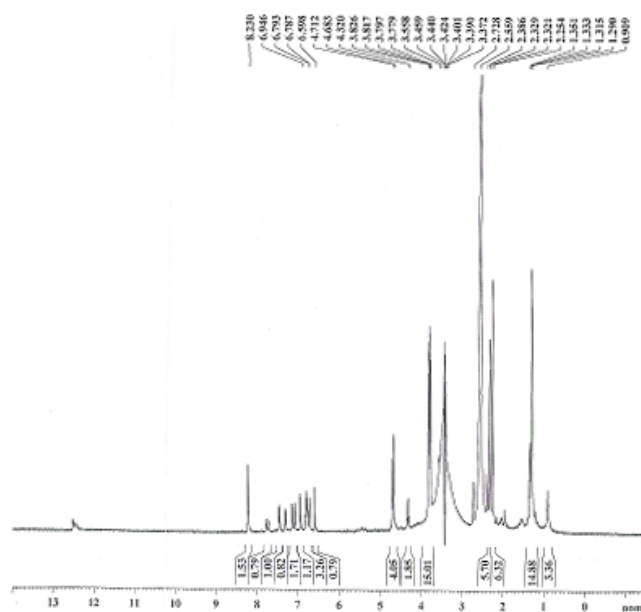


Fig 4. NMR spectra of Omeprazole and its $[Zn(OME)_2]$ Complex

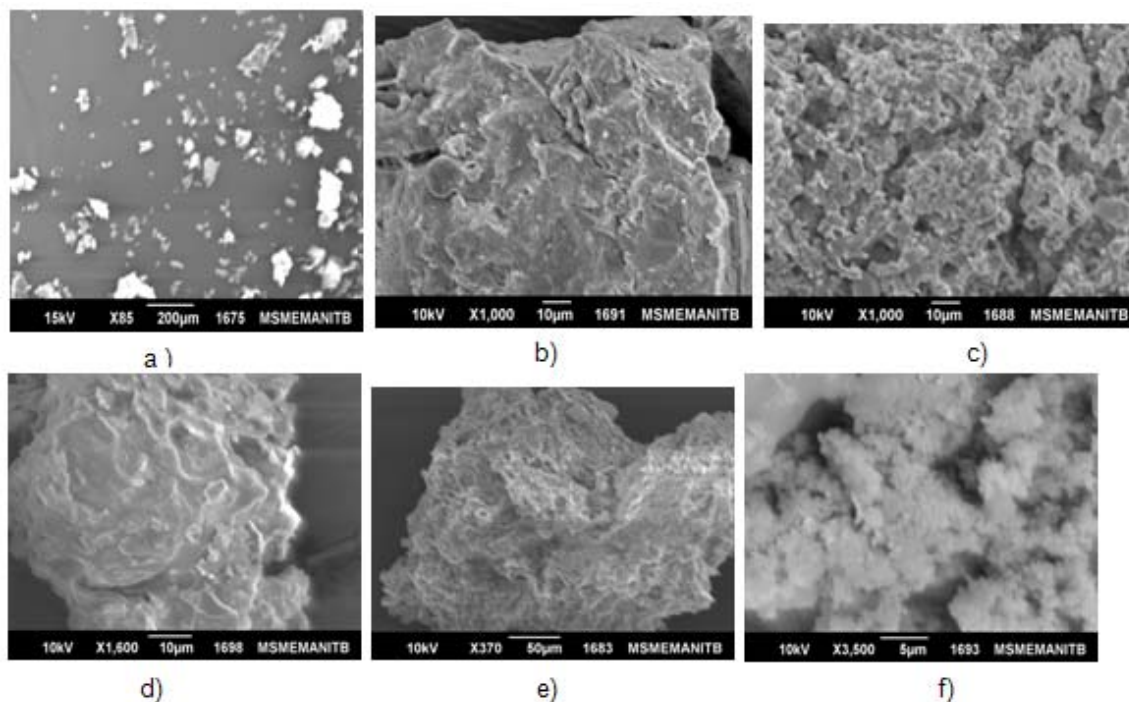


Fig 5. Scanning electron micrograph of Ligand and its Complexes

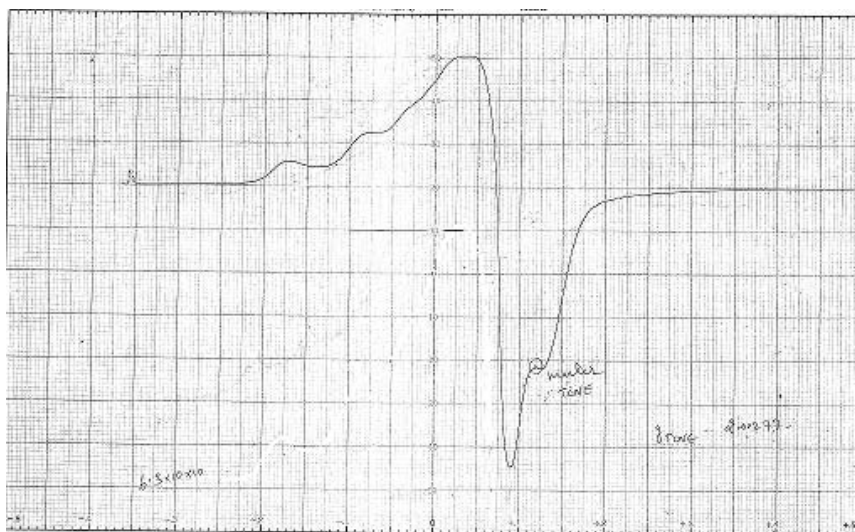


Fig 6. ESR spectra of Omeprazole-Cu Complex

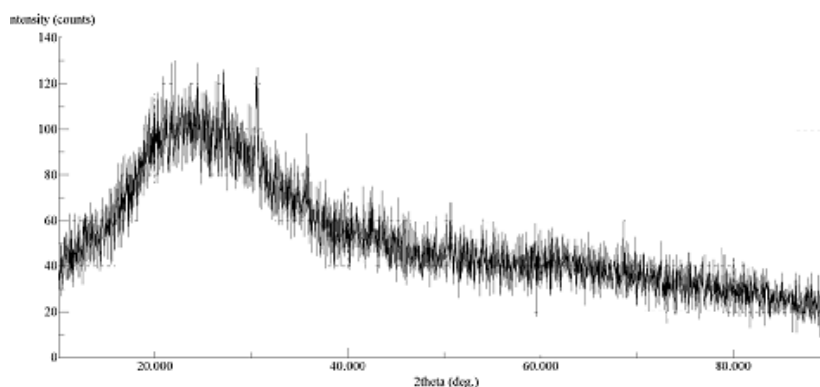


Fig 7. XRD Graph for $[\text{Cu}(\text{OME})_2 \cdot (\text{H}_2\text{O})_2]$ Complex

Thermal analysis

The thermal decompositions of the Ni(II) complex was studied using the TG and DSC technique. The thermo gravimetric studies of the complex was carried out in the temperature range 30-800 °C with a sample heating rate 10 °C/min in air atmosphere. The weight-loss step between 175-200 °C may correspond the elimination of coordinated water molecules. The weight-loss step between 250-450 °C may be attributed to the loss of organic moiety of the complex molecule. The final decomposition continuous up to 800 °C and on further increasing the temperature no weight loss is observed which may be attributed to formation of stable metal oxide.

Antimicrobial activity

The antimicrobial activity of the ligand and the complexes was determined by the disc diffusion

technique [29]. The compounds were screened in vitro against *Pseudomonas*, *Staphylococcus aureus* and two strain of fungi, *Aspergillus niger* and *A. flavous*. A solution of 1 mg/mL in DMF was used. The standard used was gentamicin sulphate 1 mg/mL and solvent control was used to know the activity of the solvent. The bacterium was maintained on nutrient agar and the agar media were incubated for different microorganism culture tests. After 24 h of incubation at 37 °C for bacteria and 72 h of incubation at 25 °C for fungi, the diameter of zone of inhibition (mm) thus formed around each disc containing the test compound was measured accurately. All complexes show significant activity against bacteria *Pseudomonas* and *Staphylococcus aureus* as compared to ligand. The Co(II) complex is shown to be less active than the ligand in fungi *Aspergillus niger* and Mn(II) complex in fungi *A. flavous*. 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

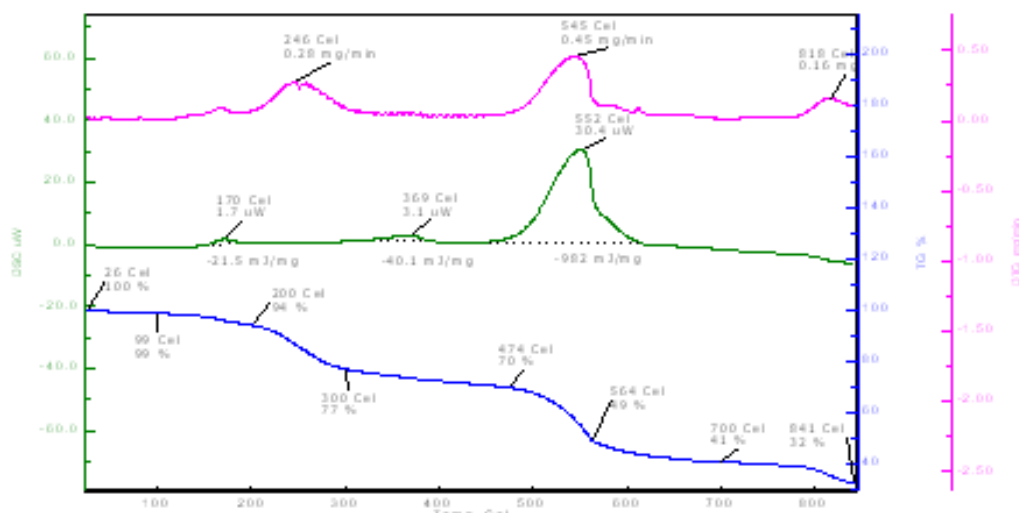


Fig 8. TGA/DTA and DSC Curve of $[\text{Ni}(\text{OME})_2 \cdot (\text{H}_2\text{O})_2]$ complex

as compared to the ligand can be explained by chelation theory. The theory explains that decrease in polarizability of the metal could enhance the lipophilicity of the complexes which leads to the breakdown of permeability of the cells resulting in interference with normal cell process.

CONCLUSION

In view of the foregoing discussions, the high melting points and insolubility in common organic solvents, we have assigned following probable structure of the complexes of omeprazole.

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