

Cu(II), Zn(II), Cd(II) and Hg(II) Complexes of Pantoprazole (PPZH): Synthesis and Characterization

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Abstract

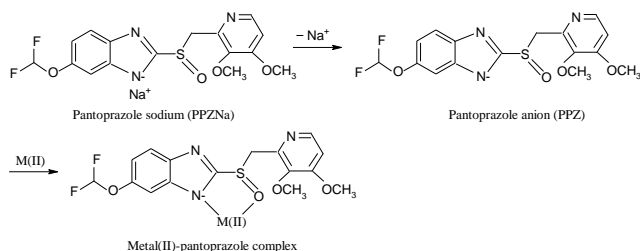
Several metal complexes of pantoprazole, [Cu(PPZ)(H₂O)Cl], [Zn(PPZ)₂], [Cd(PPZ)₂].1.5H₂O and [Hg(PPZ)(H₂O)Cl] have been synthesized and characterized. Elemental analysis, IR, UV-Visible spectral analysis, magnetic measurement, thermogravimetric analysis, differential scanning calorimetric and cyclic voltammetric techniques were used for their characterization. The lipophilic weak base pantoprazole (PPZ) act as a potential bidentate ligand forming coordination complexes with divalent metal ions through anionic imidazolyl N⁻ and O atom of sulfinyl >S=O group. All complexes possess tetrahedral geometry.

Keywords: Pantoprazole, infrared spectrum, thermogravimetry, magnetic susceptibility.

I. Introduction

Proton Pump Inhibitors (PPIs) are a group of drugs that inhibit the activity of pumps transporting hydrogen ions (H⁺) across cell membranes of stomach by blocking hydrogen/potassium adenosine triphosphatase enzyme system (H⁺/K⁺-ATPase). These drugs are used for the treatment in acid induced inflammation conditions and ulcers of the stomach and duodenum, gastro-oesophageal reflux disease, all caused by stomach acid.

The IUPAC name of pantoprazole is 6-(difluoromethoxy)-2-[(3,4-dimethoxy-pyridin-2-yl)methylsulfinyl]-1H-benzimidazole. Pantoprazole is a lipophilic weak base and is poorly soluble in water. It is stable in slightly basic medium¹. However, its sodium salt is freely soluble in water and methanol. In solution, pantoprazole sodium losses its sodium ion attached to imidazole nitrogen in benzimidazole ring and form benzimidazolone anion. The anionic N of the benzimidazolone anion and O atom of sulfinyl group (>S=O) of the anionic drug pantoprazole can coordinate with the metal atom in suitable conditions.



Considering the importance of drugs and their complexes, it is desirable to synthesize and study of the complexes of pantoprazole with metals. It is also known that metal complexes of drug play an important role in biological activities of drug. In many cases metal complexes of drugs are more potent than the parent drug. Elucidation of physico-chemical properties of metal complexes of such drugs might be helpful in determining their biological activities. In this paper we are describing synthesis and characterization of copper(II), zinc(II), cadmium(II) and mercury(II) complexes of pantoprazole.

II. Experimental

Materials

Pantoprazole sodium sesquihydrate (PPZNa.1.5H₂O) was collected from SK+F Pharmaceutical Ltd., Bangladesh. Copper(II) chloride dihydrate, zinc(II) chloride, cadmium(II) chloride monohydrate, mercury(II) chloride, hydrochloric acid, nitric acid, sodium hydroxide and organic solvents etc. used in all synthetic and analytical work were analar grade, either Aldrich (U.S.A.), E. Merck (Germany) or E. Merck (India).

Methods and Equipments

Melting points of the complexes were taken in a melting point apparatus Kruss, Germany, having the capacity of recording the temperature up to 360°C. The solubility of the complexes was determined qualitatively using different solvents in the usual manner. The solvents used were water, methanol, ethanol, acetone and dichloromethane in both cold and hot conditions. The zinc, cadmium and mercury contents of the complexes were determined complexometrically using standard Na₂EDTA solution as the titrating agent. Copper and chloride contents were determined using gravimetric method. The infrared spectra (IR) of the complexes were recorded on a Shimadzu (Japan) Infrared Spectrometer of model IR-470 in the range of 4000-400 cm⁻¹ using KBr pallets. The UV-Visible spectra were recorded using a UV-Visible recording spectrometer, Model UV-1800, Shimadzu (Japan) in the wavelength range 200-1100 nm using methanol as solvent. The thermogravimetric analysis (TGA) of the complexes was carried out with TGA-50 thermogravimetric analyzer, Shimadzu (Japan). The quasi-static thermogravimetric analysis (QSTG) was carried out in a CARBOLITE calibrated muffle furnace of the type CWF 11/5. Differential scanning calorimetric (DSC) analysis was carried out with DSC-60 analyzer, Shimadzu (Japan). Magnetic susceptibility of the complexes was determined by the SHERWOOD SCIENTIFIC Magnetic Susceptibility Balance (M.S.B.), Cambridge, England, Model: Magway MSB Mk1. Cyclic voltammetric measurement was studied

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using CH 602D Electroanalyzer and in a Pyrex glass micro cell with a Teflon cap.

Synthesis

All complexes were synthesized in methanolic medium, except cadmium(II) complex which was synthesized in a mixture of distilled water and methanol (50:50, v/v) at room temperature. Respective metal salts and pantoprazole sodium sesquihydrate were dissolved in minimum volume of methanol or mixture of water and methanol separately. The solutions were mixed together and kept at room temperature for 2-3 hours for crystallization. Dilute NaOH was added slowly into the solution to adjust the desired pH at 10-11, only copper complex was synthesized at relatively lower pH 7-8. The products were isolated from the solution through filtration, washed with methanol for purification and dried in a desiccator over blue silica gel.

All metal pantoprazole complexes are insoluble in water but sparingly soluble in methanol, except cadmium pantoprazole complex which is only soluble in dichloromethane. A summarized synthetic procedure is given in the Table 1.

III. Results and Discussion

Results of the metal content analysis of the complexes are in good agreement with the theoretically calculated values of the proposed formulae. The number of water molecule(s) present in the complexes is validated from the QSTG graph (Fig. 2). The proposed empirical formulae of the complexes are as follows:

- (i) $[\text{Cu}(\text{PPZ})(\text{H}_2\text{O})\text{Cl}]$ (ii) $[\text{Zn}(\text{PPZ})_2]$
 (iii) $[\text{Cd}(\text{PPZ})_2] \cdot 1.5\text{H}_2\text{O}$ (iv) $[\text{Hg}(\text{PPZ})(\text{H}_2\text{O})\text{Cl}]$

Table 1. Nominal composition of reactants used for the synthesis of complexes

Metal salts	PPZNa	Solvent	pH	Complexes
0.0367 g $\text{CuCl}_2 \cdot 2\text{H}_2\text{O}$ in 20 mL	0.2161 g in 20 mL	Methanol	7-8	$[\text{Cu}(\text{C}_{16}\text{H}_{14}\text{F}_2\text{N}_3\text{O}_4\text{S})(\text{H}_2\text{O})\text{Cl}]$
0.1707 g ZnCl_2 in 20 mL	0.8397 g in 20 mL	Methanol	10-11	$[\text{Zn}(\text{C}_{16}\text{H}_{14}\text{F}_2\text{N}_3\text{O}_4\text{S})_2]$
0.2109 g $\text{CdCl}_2 \cdot \text{H}_2\text{O}$ in 20 mL	0.8263 g in 20 mL	Methanol + Water (50:50, v/v)	10-11	$[\text{Cd}(\text{C}_{16}\text{H}_{14}\text{F}_2\text{N}_3\text{O}_4\text{S})_2] \cdot 1.5\text{H}_2\text{O}$
0.2898 g HgCl_2 in 20 mL	0.8267 g in 20 mL	Methanol	10-11	$[\text{Hg}(\text{C}_{16}\text{H}_{14}\text{F}_2\text{N}_3\text{O}_4\text{S})(\text{H}_2\text{O})\text{Cl}]$

PPZNa = Pantoprazole sodium

Table 2. Metal contents and some physical properties of the complexes.

Complexes	Metal, %			Yield*, %	Colour	Melting point, °C	Solubility in water
	Complexometric	Gravimetric	Average				
$[\text{Cu}(\text{PPZ})(\text{H}_2\text{O})\text{Cl}]$	-	12.01	12.01 (12.73)	48.8	Light green	160-168	Insoluble
$[\text{Zn}(\text{PPZ})_2]$	10.97	9.78	10.38 (7.87)	43.2	White	195-203	Insoluble
$[\text{Cd}(\text{PPZ})_2] \cdot 1.5\text{H}_2\text{O}$	14.03	-	14.03 (12.43)	83.1	White	190-204	Insoluble
$[\text{Hg}(\text{PPZ})(\text{H}_2\text{O})\text{Cl}]$	34.99	-	34.99 (31.51)	66.3	White	190-211	Insoluble

The calculated metal contents are in parentheses. *The percent of yield was calculated on the basis of metal content.

The metal content, yield, colour, melting point and solubility in water of the complexes are tabulated in the Table 2.

IR Spectral Analysis: Some important IR peaks for metal pantoprazole complexes are shown in the Table 3. The assignments of the observed frequencies have been made on the basis of literature²⁻⁵. FTIR spectra of PPZNa.1.5H₂O, $[\text{Cu}(\text{PPZ})(\text{H}_2\text{O})\text{Cl}]$, $[\text{Zn}(\text{PPZ})_2]$, $[\text{Cd}(\text{PPZ})_2] \cdot 1.5\text{H}_2\text{O}$ and $[\text{Hg}(\text{PPZ})(\text{H}_2\text{O})\text{Cl}]$ complexes are shown in Fig. 1.

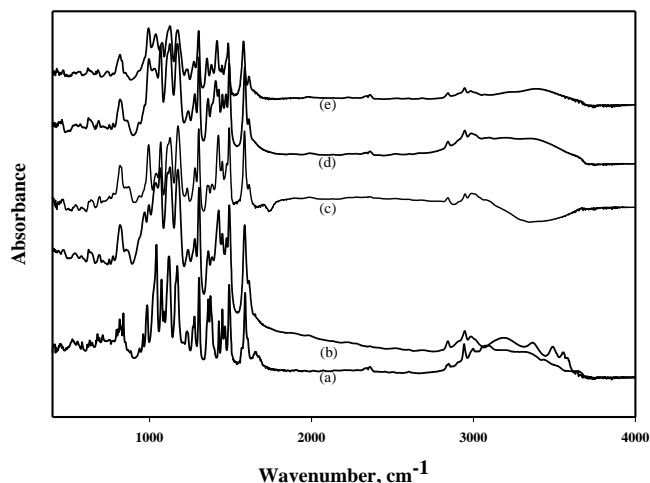


Fig. 1. FTIR spectra of (a) PPZNa.1.5H₂O, (b) $[\text{Cu}(\text{PPZ})(\text{H}_2\text{O})\text{Cl}]$, (c) $[\text{Zn}(\text{PPZ})_2]$, (d) $[\text{Cd}(\text{PPZ})_2] \cdot 1.5\text{H}_2\text{O}$ and (e) $[\text{Hg}(\text{PPZ})(\text{H}_2\text{O})\text{Cl}]$ complexes.

In the spectra, all complexes show weak intensity absorption peaks in the region of 400-560 cm⁻¹ due to the stretching frequency of M-O and M-N bond. The $\nu(\text{S}=\text{O})$ appears at 1046 cm⁻¹ as a sharp strong intensity peak in isolated pantoprazole sodium sesquihydrate, in the complex

Table 3. Comparison of different vibrational frequencies of the complexes.

Complexes	$\nu(\text{M-O})$ cm^{-1}	$\nu(\text{M-N})$ cm^{-1}	$\nu(\text{S=O})$ cm^{-1}	$\nu(\text{C-F})$ cm^{-1}	$\nu(\text{C-N}^-)$ cm^{-1}	$\nu(\text{C=N})$ cm^{-1}	$\nu(\text{C=C})$ cm^{-1}	$\nu(\text{C-H})_{\text{arom}}$ cm^{-1}	$\nu(\text{O-H})$ cm^{-1}
PPZNa.1.5H ₂ O	-	-	1046	1120	1375	1590	1624	3000	3492
[Cu(PPZ)(H ₂ O)Cl]	467	565	990	1116	1363	1585	1613	3000	3350
[Zn(PPZ) ₂]	460	538	1000	1120	-	1588	1620	3000	-
[Cd(PPZ) ₂].1.5H ₂ O	452	538	998	1127	1357	1588	1600	2991	3362
[Hg(PPZ)(H ₂ O)Cl]	418	554	996	1127	1351	1585	1592	2980	3395

ν = Stretching frequency

the corresponding peak appear at 990-1000 cm^{-1} in Cu(II) and Hg(II) complexes as weakly intense and almost disappears in Zn(II) and Cd(II) complexes. This change in absorption intensity supports the participation of $\nu(\text{S=O})$ group in coordination with metal ions through O atom. The C-F bond stretching peak remain unchanged (1116-1127 cm^{-1}) in the complexes as the F atoms do not have any interaction in complex formation. In the free ligand a sharp peak appears at 1375 cm^{-1} is assigned for the stretching vibrations of ($>\text{C-N}^-$) in benzimidazole ring^{6,7}. In Cu(II), Cd(II) and Hg(II) complexes, this $>\text{C-N}^-$ vibration appears as a weak peak at 1351-1363 cm^{-1} and disappears in the case of Zn(II) complex. Lowering of this stretching frequency of vibration after metalation indicates the formation of $>\text{C-N}^- \rightarrow \text{M(II)}$ bond. The stretching frequency of azomethine group, ($-\text{C=N}-$) is at 1590 cm^{-1} in the free ligand⁸⁻¹⁰, and its position remains unchanged in complexes. Characteristic band at 3492 cm^{-1} is assigned for the presence of water in the pantoprazole sodium sesquihydrate, while it appears as a weak broad band at 3350-3395 cm^{-1} due to the presence of coordinated or crystalline water in the complexes. However, the anhydrous zinc complex does not show any absorption frequency in that region.

UV-Visible Spectral Analysis: The electronic spectra of the metal complexes were recorded and the data obtained from the spectral investigations are tabulated in the Table 4.

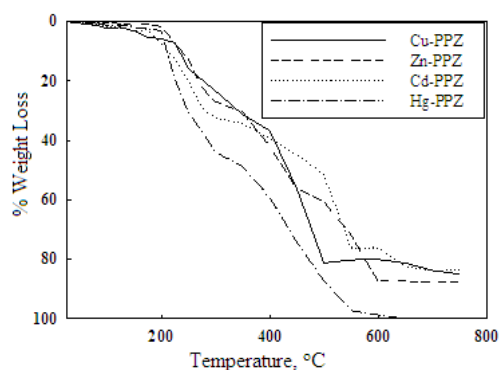
Table 4. Electronic spectral data of the studied complexes.

Complexes	λ , nm
PPZNa.1.5H ₂ O	289, 227
[Cu(PPZ)(H ₂ O)Cl]	893, 340, 288, 204
[Zn(PPZ) ₂]	286
[Cd(PPZ) ₂].1.5H ₂ O	291, 213
[Hg(PPZ)(H ₂ O)Cl]	288

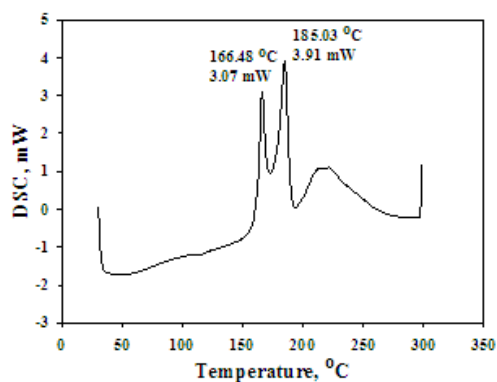
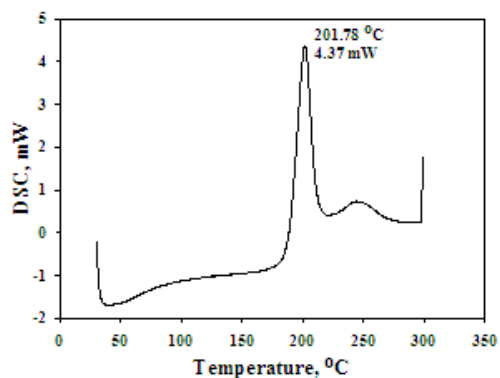
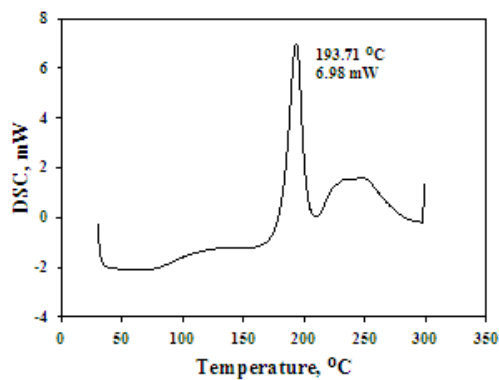
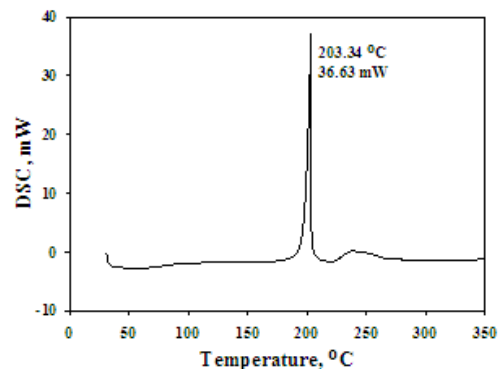
Strong absorption band at 893 nm (11,198 cm^{-1}) in the visible region of the copper complex indicates a ${}^2\text{T}_{2g} \leftarrow {}^2\text{E}_g$ transition. The associated crystal field splitting ($\Delta = 134.068 \text{ kJ mol}^{-1}$) is small suggesting that the copper complex has tetrahedral geometry. Free pantoprazole sodium sesquihydrate has two absorption bands in the UV

region at 289 nm and 227 nm. All complexes show absorption bands of medium intensity at 288-340 nm corresponding to the $n \rightarrow \pi^*$ electronic transition of azomethine ($-\text{C=N}-$) chromophore in pantoprazole molecule⁶. Appearance of this band in UV region confirms the presence of pantoprazole in the complexes. The band observed at shorter wavelength 204-213 nm in the complexes are related with $\pi \rightarrow \pi^*$ transition of C=C group.

Thermal Analysis: The thermograms obtained from the thermogravimetric analysis of the complexes are plotted in the Fig. 2.

**Fig. 2.** QSTG graphs of Cu(II), Zn(II), Cd(II) and Hg(II) complexes of pantoprazole.

The Cu(II), Cd(II) and Hg(II) complexes start losing their weight at relatively low temperature. This accounts for the loss of water of crystallization or coordinated water molecule in the range of 48°C to 200°C. The Zn(II) complex does not show any significant weight loss up to 195°C temperature confirming the absence of lattice water in the complex. The differential scanning calorimetric study of Cu(II), Zn(II), Cd(II) and Hg(II) complexes show a sharp endothermic peak at 166°C (3.07 mW), 201°C (4.37 mW), 193°C (6.98 mW) and 203°C (36.63 mW) respectively, probably due to melting. Continuous oxidative decomposition of the complexes starts below 300°C corroborated by the appearance of endothermic band(s) in the DSC graphs (Fig. 3). The complexes are converted into their corresponding metal oxides within the temperature range of 600-800°C. The end product of mercury(II) complex is volatile and no residue left above 600°C.

Fig. 3 (a). DSC graph of [Cu(PPZ)(H₂O)Cl]Fig. 3(b). DSC graph of [Zn(PPZ)₂]Fig. 3(c). DSC graph of [Cd(PPZ)₂].1.5H₂OFig. 3(d). DSC graph of [Hg(PPZ)(H₂O)Cl]

Magnetic Measurements: The magnetic susceptibilities of the complexes were measured and the results are given in the Table 5.

Table 5. Magnetic measurement data of copper complex.

Complex	C _{Bal}	l/cm	m/g	R	R _o	$\chi_g/\text{cm}^3 \cdot \text{g}^{-1}$	T/K	$\mu_{\text{eff}}/\text{BM}$
[Cu(PPZ)(H ₂ O)Cl]	0.9927	1.8	0.0650	6	-33	1.072×10^{-6}	294	1.12

Cu(II) ion, d⁹ system in a tetrahedral arrangement of ligands has one unpaired electron in t_{2g} level. The observed μ_{eff} for the copper complex is 1.12 BM, significantly lower compare to the value of an ion possessing an unpaired electron (calculated $\mu_{\text{eff}} = 1.73 \text{ BM}$)¹¹. The magnetic susceptibility values of zinc, cadmium and mercury complexes are found either negative or zero, suggesting that they are diamagnetic with a 2+ oxidation state (d¹⁰ system) of the metal ions in the complexes.

The metal contents calculated from the end product of Cu(II) and Zn(II) products are also consistent with the formulae of the complexes.

Cyclic Voltammetric Study: In cyclic voltammetric study, both the peak current and the peak potential for [Cu(PPZ)(H₂O)Cl] complex have shifted compare to those of Cu(II) and associated ligand in their free state. This happens due to strong metal-ligand interaction in the complex. The peak current ratios for Cu(II)/Cu(0) redox system at various scan rates ranges from 2.46-1.83 (Table 6).

Table 6. Data obtained from the cyclic voltammograms of 1.0 mM [Cu(PPZ)(H₂O)Cl] in 1 M KCl solution at different scan rates.

Scan rate, v (mVs ⁻¹)	Cathodic peak current, i _{pc2} (μA)	Anodic peak current, i _{pa2} (μA) (-)	Cathodic peak potential, E _{pc2} (mV) (-)	Anodic peak potential, E _{pa2} (mV) (-)	Peak current ratio, i _{pa2} /i _{pc2}	Peak potential separation, ΔE _p (mV)
25	22.78	55.96	494.0	170.6	2.46	323.4
50	31.63	61.95	513.8	170.6	1.95	343.2
75	33.39	63.71	522.3	170.6	1.91	351.7
100	34.27	62.72	527.9	170.3	1.83	357.6
125	42.18	87.32	542.2	173.6	2.07	368.6

The peak potential separation increases with increasing scan rate reveals that the redox processes are quasi-reversible. Voltammograms of Cu(II), pantoprazole sodium sesquihydrate and [Cu(PPZ)(H₂O)Cl] complex are plotted in Fig. 4 and Fig. 5.

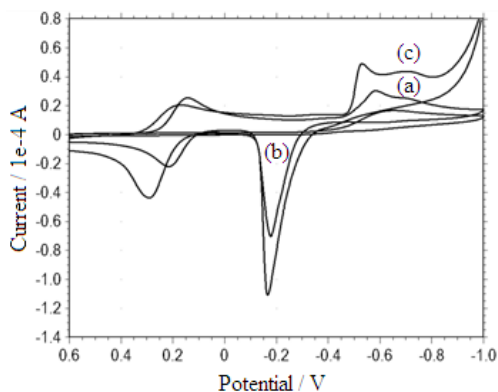


Fig. 4. Cyclic voltammograms of (a) 1 mM Cu(II), (b) 1 mM pantoprazole sodium sesquihydrate solution, and (c) 1 mM [Cu(PPZ)(H₂O)Cl] in 1 M KCl solution at the scan rate 100 mVs⁻¹ in GC electrode.

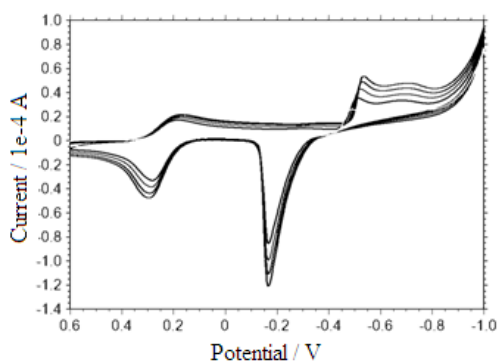
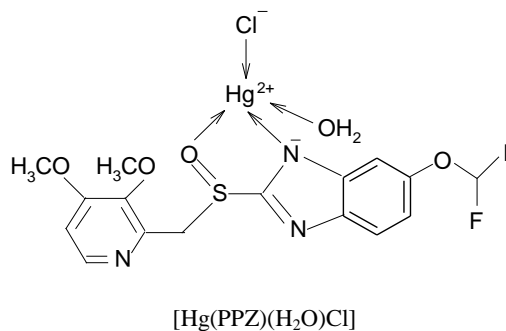
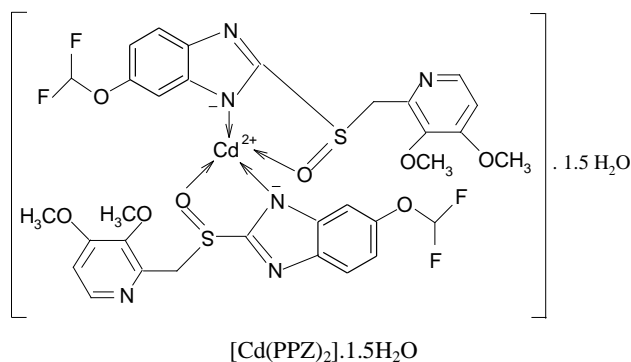
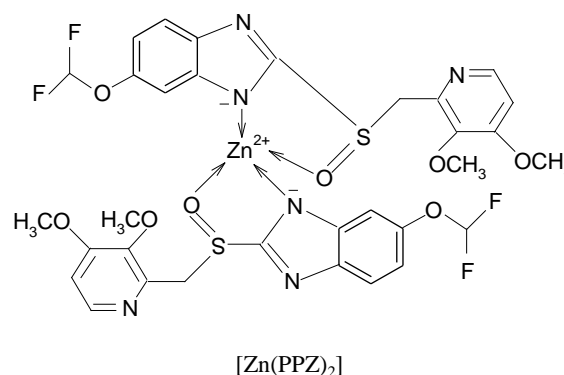
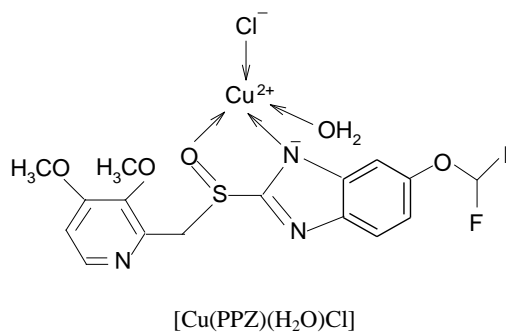


Fig. 5. Cyclic voltammograms of 1 mM [Cu(PPZ)(H₂O)Cl] in 1 M KCl solution with different scan rate of 25, 50, 75, 100 and 125 mVs⁻¹.

IV. Conclusions

From the analytical data, it is concluded that the studied complexes can be formulated as [Cu(PPZ)(H₂O)Cl], [Zn(PPZ)₂], [Cd(PPZ)₂].1.5H₂O and [Hg(PPZ)(H₂O)Cl]. FTIR spectra for the ligand and its complexes show that the pantoprazole anion acts as bidentate ligand which forms complexes with metal ions through C-N⁻ and S=O groups. The appearance of new peaks due to M-N⁻ and M-O bond in the spectra confirms the involvement of N⁻ and O ions/atoms in complexation with metal ions. Thermal analysis shows the different decomposition stage of the metal-PPZ complexes; the first stage of which is associated with the loss of coordinated water/water of hydration in all complexes except zinc complex. From magnetic susceptibility and UV-Visible spectroscopy it is found that Cu-PPZ complex is paramagnetic and has tetrahedral geometry. As expected Zn(II), Cd(II) and Hg(II) complexes are diamagnetic. These complexes are suggested to be tetra-coordinated probably having tetrahedral geometry based on analytical and FTIR data. This is expected because PPIs,

H₂O and Cl⁻ are all weak field ligands. The proposed structural formulae of the complexes are as follows:



Acknowledgement

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