Physico-Chemical Characterization and Synthesis of Transition Metal Complex of Omeprazole

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ABSTRACT: The many activities of metal ions in biology have stimulated the development of metal based therapeutics. A wide range of metal complexes are already in clinical use, and encourage further studies for new metallodrugs, The biological activity of many drugs has been shown to be enhanced on complexing with metal ions, hence promoting their use in Pharmacology Additionally, increasing knowledge of the biological activities of simple metal complexes guided many researchers to the development of promising chemotherapeutic compounds which target specific physiological or pathological processes. The present work deals with the synthesis of metal complex derived from anti-ulcerative drugs and its physico-chemical analysis to find out ligand- metal ratio of this complex in solution. The complex of Co (II) salt is prepared. For the structure elucidation of this complex "Monovariation method" has been used to ascertain the ligand-metal ratio in the complex. The stability constant of the formed complex was calculated by molar conductance measurement using Modified Job's method. The analysis has been carried out using conductometry and pHmetry.

Keywords: anti-ulcerative drugs, transition metals, complexes, ligand, conductometry.

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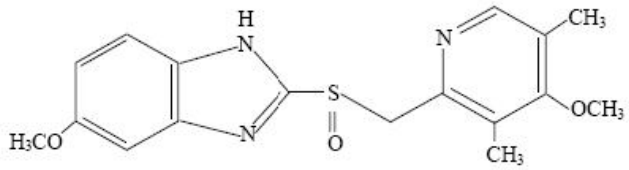
INTRODUCTION

Omeprazole (OMZ), 5-methoxy-2-[[(4-methoxy-3,5-dimethyl-2-pyridinyl)methyl]sulphinyl]-1H-benzimidazole is the first member of the "proton pump inhibitors" that are widely used for the prophylaxis and treatment of both gastro-duodenal ulcers and symptomatic gastro-oesophageal reflux [1]. Also, it is highly effective in the treatment of Zollinger–Ellison syndrome [2].



Omeprazole

The therapeutic importance of OMZ was behind the development of many analytical methods for its determination in the pharmaceutical formulations and/or biological samples. These methods include spectrophotometry [3-13], electrochemical methods [14], HPLC [15-17], and electrophoresis [18]. The molecular interactions between the electron donating pharmaceutical compounds [19–23] and the electron

acceptor metals are generally associated with the formation of complexes [24]. Complexes of metallic salts are more potent and less toxic in many cases as compared to the parent drug [25]. A large number of drugs have been used to synthesize the complex with many metals with a view to enhance their therapeutic action [26-27], it was important to determine the association constant for OMZ-metal complexes beside the method development. The present account details deals with the synthesis of metal complexes derived from anti-ulcerative drugs and their physico-chemical analysis to find out ligand-metal ratio of these complexes in solution.

EXPERIMENTAL

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 . Metal salt $CoCl_2.6H_2O$ was of Merck Chemicals. The solvents used were distilled water and methanol. Metal-ligand ratio was calculated using Systronics digital conductivity meter, 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 : Nayer and pandey [28] proposed monovariation method, which is an extension of mole ratio method of Yoes and Jones. To confirm the ligand-metal ratio, conductometric titrations using monovariation method were carried out at 21^0 C. 0.01 M solution of Omeprazole drug was prepared in 80:20 mixture of methanol and water. Similarly, solutions of metal salt $CoCl_2.6H_2O$ was prepared in same solvent of 0.02 M concentration. 20 ml of ligand was diluted to 200 ml with same solvent. The ligand was titrated against metal salt solution using monovariation method. Conductance was recorded after each addition. Graph is plotted between corrected conductance and volume of metal salt added. 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 [29] of continuous variation modified by Turner and Anderson [30].

Table 1: Conductometric Titration between Omeprazole and $CoCl_2.6H_2O$

S. No.	Vol. of Metal Salt	Observed Conductance(ms)	Corrected Conductance(ms)
1	0	0.07	0.07
2	1.0	0.12	0.12
3	2.0	0.16	0.16
4	3.0	0.24	0.24
5	4.0	0.30	0.31
6	4.5	0.36	0.37
7	5.0	0.39	0.40
8	5.5	0.42	0.43
9	6.0	0.45	0.46
10	7.0	0.47	0.49
11	8.0	0.50	0.53
12	9.0	0.52	0.55
13	10.0	0.55	0.58
14	11.0	0.56	0.60
15	12.0	0.57	0.61

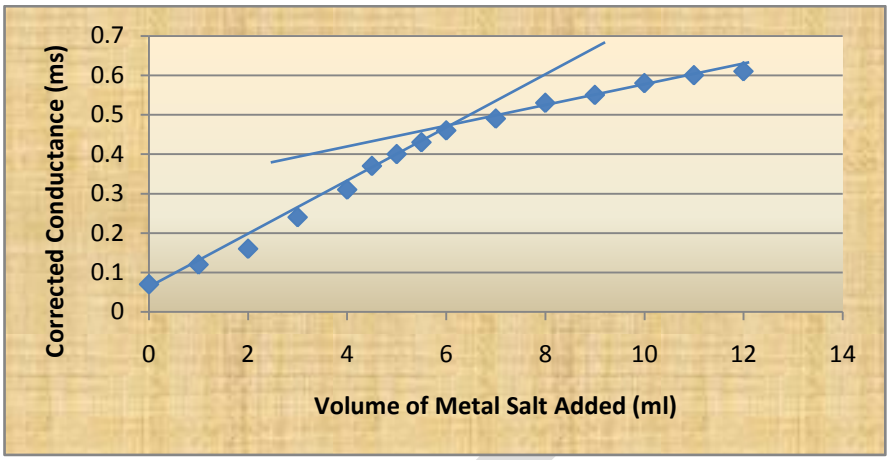


fig – 1 Conductometric titration between Omeprazole--Cobalt Chloride

Modified Job's Method of continuous variation[3] for determining composition and stability constant of complex : Modified Job's Method of continuous variation[3]for determining composition and stability constant of complex: Equimolar solutions of ligand and metal solutions were prepared and three series C1, C2, C3 of solutions were made. In set C1 metal salt solution was filled with volume 0.0 ml to 12.0 ml and total volume was made to 12.0ml in each. Similarly, in C2 ligand solution was filled and set C3 was prepared by mixing metal salt solution from 0.0ml to 12.0ml and ligand solution from 12.0ml to 0.0ml. Conductance was recorded for each solution.Δ Conductance was calculated using formula $C_1+C_2-C_3$. The process was repeated by changing the concentration of solutions of ligand and metal. Graphs were plotted between corrected conductance versus mole metal-ligand ratio. The compositions as well as stability constant were determined from the equivalence point in the graph. The study was carried out using Omeprazole drug as ligand and Co(II) as metal salt. The results are recorded in table 2(A) and 2(B).

TABLE 2(A): Modified Job's Method
Concentration of Metal- 0.005 M Concentration of Ligand - 0.005 M

Ratio	Conductance (mS)				
	M:S(C_1)	S:L(C_2)	M: L(C_3)	ΔCONDUCTANCE ($C_1+C_2-C_3$)	Corrected Δ Conductance
0:12	0.01	0.0195	0.01	0.0195	0.0
1:11	0.07	0.0157	0.05	0.0357	0.017
2:10	0.13	0.0165	0.1	0.0465	0.029
3:09	0.19	0.0123	0.14	0.0623	0.044
4:08	0.25	0.0151	0.19	0.0751	0.059
5:07	0.31	0.0181	0.26	0.0681	0.050
6:06	0.36	0.0105	0.31	0.0605	0.044
7:05	0.4	0.0122	0.36	0.0522	0.037
8:04	0.47	0.0122	0.44	0.0422	0.029
9:03	0.52	0.0151	0.5	0.0351	0.023
10:02	0.56	0.0156	0.55	0.0256	0.016
11:01	0.63	0.0105	0.62	0.0205	0.009
12:0	0.67	0.0101	0.67	0.0101	0.0

TABLE 2(B) Modified Job's Method

Concentration of Metal- 0.003 M Concentration of Ligand - 0.003 M

Ratio	Conductance (mS)				
	M:S(C_1)	S:L(C_2)	M:L(C_3)	ΔCONDUCTANCE (C_1+C_2 - C_3)	Corrected Δ Conductance
0:12	0.01	0.0158	0.01	0.0158	0.0
1:11	0.04	0.0154	0.03	0.0254	0.010
2:10	0.09	0.0142	0.07	0.0342	0.020
3:09	0.12	0.0135	0.09	0.0435	0.030
4:08	0.17	0.0121	0.13	0.0521	0.040
5:07	0.22	0.015	0.19	0.045	0.037
6:06	0.25	0.0105	0.22	0.0405	0.032
7:05	0.28	0.0142	0.26	0.0342	0.027
8:04	0.32	0.0181	0.31	0.0281	0.022
9:03	0.35	0.01	0.34	0.02	0.016
10:02	0.38	0.0086	0.37	0.0186	0.010
11:01	0.42	0.0084	0.42	0.0084	0.005
12:0	0.47	0.0032	0.47	0.0032	0.0

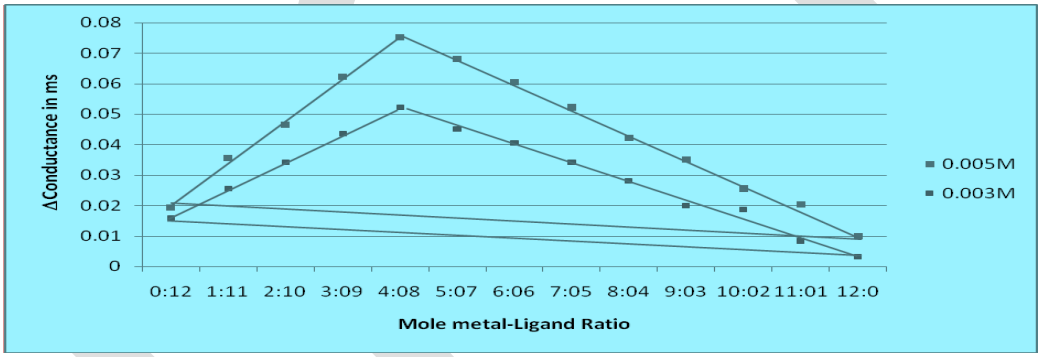


Fig – 2(a): Modified Job's Method

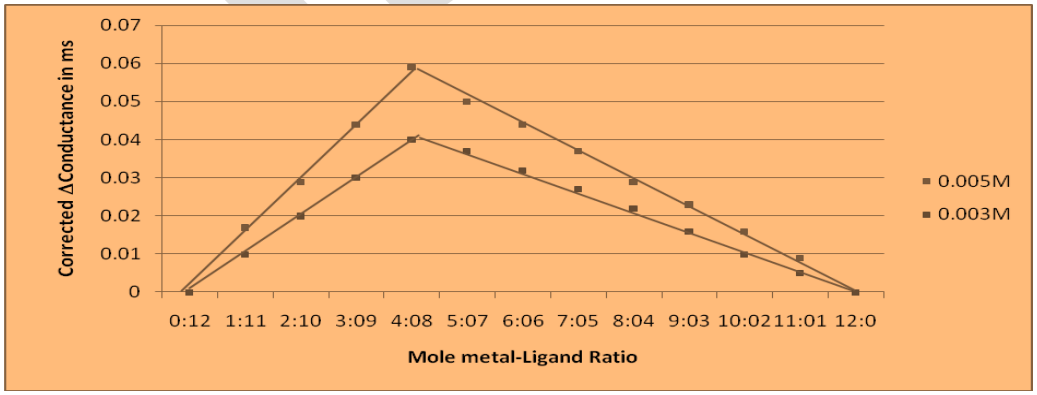


Fig – 2(b): Modified Job's Method

SYNTHESIS OF COMPLEXES: 0.01M solution of Omeprazole and 0.005M solution of cobalt chloride were prepared separately in 80:20 methanol-water mixtures. Ligand solution was added gradually with constant stirring to metal salt solution and pH was adjusted to 7.5 by adding ammonia solution. The color of mixture was pink with violet colored precipitate. The resultant solution was refluxed for 3 and half hours. Violet colored crystalline product was obtained. Product was filtered, washed, dried and then finally weighed. Yield was found to be 80%. Carbon, hydrogen, nitrogen, metal and water were estimated micro analytically at CDRI, Lucknow

Table 3 : Analytical Data of Complexes

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		156^0C	52.71	3.05	11.05	—
2	$(C_{34}H_{42}N_6O_8S_2Co)$ (785.796)	Violet Pink	80	210^0C	51.96 (36.90)	4.87 (4.91)	10.69 (10.67)	7.49 (7.69)

Results and Discussion

Turner and Anderson2 have modified Job's method for the determination of stability constants. If the initial concentration of metallic ions and ligands are "a" and "b" respectively then stability constant "K" is given by the equation

$$K = \frac{X}{(a-x)(b-x)} \quad \ldots\ldots (1)$$

Where "x" is the concentration of the complex.[n]

If two solutions on the two curves have the same conductance then a1, a2 and b1, b2 represent the concentration of the metal and the ligand respectively for 2:1 complex. Thus, following equation can be derived from equation (1)

$$\frac{a2-a1}{a1-x} = \frac{b2-b1}{b1-x} \quad \ldots\ldots\ldots (2)$$

From fig 2 (a) and (b)

$a_1 = [(0.005 \times 1.6) / 12000] = 6.66 \times 10^{-7}$
$b_1 = [(0.005 \times 10.4 / 12000] = 4.33 \times 10^{-6}$
$a_2 = [(0.003 \times 2.2) / 12000] = 5.5 \times 10^{-7}$
$b_2 = [(0.003 \times 9.8 / 12000] = 2.45 \times 10^{-6} 5.5 \times 10^{-7}$

From equation 2, value of x comes out to be $x=4.79 \times 10^{-7}$

Thus, from equation 1

$K = 2.25 \times 10^{11}$
Log K = 11.3529
Free energy change ΔG can be calculated as
ΔG = -2.303 x RT log K
= -2.303 x 1.987 x 308.0 x 11.35
ΔG = -15.996 k Cal / mole

Table 4: Stability Constant, Free Energy Change, Molar Conductance and Magnetic- Moment Data of Complexes

S. No.	Composition of Complex (m-wt.)	Stability constant (L/mole)		Free Energy change -ΔF (Kcal/mole)	Molar conductance (ohm^{-1}cm^{2}mol^{-1})
		K	Log K		
1	($C_{34}H_{42}N_6O_8S_2Co$)	2.25 x 10^{11}	11.3529	15.996	9.34

Through this analysis, it has been observed that the formation of complex of Omeprazole with bivalent metal cations like Co(II) takes place in the ratio 2:1. The modified Job's method of continuous variation was used to calculate the stability constant of the complex and the free energy change. The value of free energy change is negative showing the feasibility of complex formation. The results are recorded in table 4. After determining the metal-ligand ratio, the stability constant and free energy changes, the complex was synthesized. These findings might be useful in the optimization of Omeprazole as lead for future development of anti-ulcerative drugs.

Conclusion

Through this work it has been ascertained that the drug omeprazole forms a complex in solution with bivalent cations like Co (II) in the ratio of 2:1. The stability constant of the complex and the free energy change values show the feasibility and stability of the formed complex.

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