STUDY OF TRANSITION METAL-DRUGS COMPLEXES IN MIXED SOLVENT BY P^H – METRIC METHOD.

J. P. Nehete[1], A. N. Sonar[2], G. P. Waghulade[3], S. N. Vaishnav[4]

1,4 . Department of Chemistry, S.V. P. Arts & Science College, Ainpur (India)
E-mail: jayantnehete@gmail.com
2. Department of Chemistry, Shri V. S. Naik College, Raver (India)
3. Department of Chemistry, DDN Bhole College, Bhusawal (India)

.

ABSTRACT
The interaction of transition metal ions with substituted heterocyclic drug Clarithromycin has been investigated in 70% ethanol-water mixture at 0.1 M ionic strength and 303 K by potentiometric titration. The data obtained is used to estimate the values of proton-ligand stability constant (pK) and metal-ligand stability constant (log K). It is observed that the metal ions form 1:1 and 1:2 complexes with substituted heterocyclic drug.
Keyword: Stability constant, substituted heterocyclic drug.

INTRODUCTION

The studies of metal-ligand complexes in solution of a number of metal ions with carboxylic acids, oximes, phenols etc. would be interesting which throw light on the mode of storage and transport f metal ion in the biological kingdom. The selected substituted heterocyclic drug Clarithromycin is an antibiotic and used to treat various bacterial infections[1]. Numerous researchers [2-5] have studied the formation and stability constant of metal complexes with transition metals. Pandhare [6] have been investigated the study of stability constant of transition metal complexes with 7-Hydroxy Flavones at 30°C in 50 % (V/V) dioxane - water medium and 0.1 M ionic strength. Azharuddin [7] has been investigated the stability constants of binary complexes of some rare earth and nuclear metal ions with some peptides at 0.1 M ionic strength pH-metrically. It is observed that there is formation of 1:1 and 1:2 complexes between metal ions and ligand. Pawar [8] has been studied the determination of stability constants of the complexes of some peptides with d block metal ions in ethanol-water mixtures at 300 K at 0.1 M constant ionic strength pH-metrically. Ebru Mavloglu et al have studied the stability constant of Ni (II), Co (II) ,Cu (II) and Zn (II) complexes of hypoxynthine at physiological condition by potentiometric method [9]. Vyas et. al. have determined the stability constant of binary complexes of d_{10} metal ions Cu (II), Ni (II), Co (II) and Mn (II) with substituted derivatives of coumarin by using Irving –Rossoti method at constant temperature 303 K and 0.1 M ionic strength [10]. After review of literature survey the detail study of complex under identical set of experimental condition is still lacking. It was thought of interest to study the chelating properties of substituted

heterocyclic drugs under suitable condition with lanthanide by pH metrically.

EXPERIMENTAL

Determination of stability constants:

The pH measurements were carried out with equip-tronic EQ-610 pH meter (accuracy ± 0.01 units) using combine glass electrode at 303 K. Pure transition metal nitrates and sulphates (99.9% Pure) were used. All metal nitrates and sulphates available from Sigma Aldrich Chem. Co., U.S.A. Metal solution was prepared in triply distill water and concentration was estimated by standard method. The solution of drug was prepared in solvent .The pH metric reading in 70% ethanol-water mixture were converted to $[H^+]$ value by applying the correction proposed by Van Uitert Haas [11]. The ethanol was purified by the method described by Vogel [12]. The overall ionic strength of solution was constant maintains by adding $NaClO_4$. All the solutions were titrated with standard carbonate free NaOH (0.2 N) solution at constant ionic strength (0.1 M). The titration was carried out in double wall glass jacketed titration cell connect to the constant temperature circulating bath. The temperature of reaction cell is constant by circulating water from Thermostat (0.1^0C). The experimental procedure involved pH metric titrations of solutions of –

1. Free HClO4 (A)
2. Free HClO4 + Ligand (A+L)
3. Free HClO4 + Ligand +Metal ion (A+L+M)

Data obtained from each titration is plotted as pH Vs volume of NaOH added and corresponding volume at successive pH for each set is determined and calculated.

RESULTS AND DISCUSSION

Proton-ligand stability constant (pK)

Substituted heterocyclic drugs may be ionized as acid having replaceable H^+ ion from ^-OH group. Therefore it is represented as HL,

$$HL \longrightarrow H^+ + L^-$$

he titration data used to construct the curves between volume of NaOH and P^H. They are called acid-ligand titration curves. It is observed from titration curves for all systems ligand start deviating from the free acid curves at P^H =3.5 and deviating continuously up to P^H =12.0. The deviation shows that dissociation of proton in substituted drugs.

The average number of proton associated with the ligand (n_A) was determined from free acid (A) and acid - ligand (A+L) titration curves employing the equation of Irving and Rossotti [13].

$$\overline{n_A} = \gamma - \frac{(V_2 - V_1)(E^0 + N)}{(V_0 + V_1) T^0_L}$$

Where,

V_0 = Initial volume of solution

V_1 =Volume of alkali required during free acid titration.

V_2 = Volume of alkali required during free acid + ligand titration.

N = Normality of sodium hydroxide.

E^0 = Concentration of mineral acid $(HClO_4)$

γ = Number of replaceable hydrogen ion.

T^0_L = Concentration of ligand

The P^K values were determined from formation curves (n_A V/s P^H) by noting the P^H at which n_A=0.5 (half integral method). The accurate values of pK were calculated by point wise calculations which are presented in table-1.

Table-1: Determination of proton-ligand stability constant (pK) of substituted heterocyclic drugs at 0.1 M ionic strength.

System	pK Values	
	Half integral	Point wise calculation
Clarithromycin	8.55	8.95

Metal-ligand stability constant (Log k)

Metal-ligand stability constant of metal chelates with some substituted heterocyclic drug were determined by employing Bjerrum Calvin P^H metric titration method as adopted by Irving and Rossotti. The values of metal ligand stability constant ($\log K_1$ and $\log K_2$) were determined from formation curves (n V/s P^H) by using half integral method. The accurate values were calculated by point wise calculations which are presented in table-2.

Table-2: Determination of metal-ligand stability constant (log K) metal ion with Clarithromycin at 0.1 M ionic strength.

System	Log k_1	Log k_2	Log k_1 – Log k_2	Log k_1 / Log k_2
Ni (II) -Ligand	6.90	4.35	2.55	1.5862
Cu (II) -Ligand	6.85	4.54	2.31	1.5088
Zn (II)-Ligand	6.60	4.28	2.32	1.5420
Fe (II) -Ligand	6.75	4.15	2.60	1.6265
Mg (II) -Ligand	6.60	4.15	2.45	1.5903

CONCLUSION

The result shows the ratio of Log k_1 / Log k_2 is positive and greater than one in all cases. The higher value of ratio (Log k_1 / Log k_2) indicates more stable stepwise complex formation takes place. This implies that there is little or no steric hindrance to the addition of secondary ligand molecule. The difference between log K_1 and log K_2 was sufficiently large indicates the stepwise formation of 1:1 and 1:2 complexes.

REFERENCES

[1] The American society of Health system pharmacists, 4 Sept. 2015
[2] N.Turkes, R.Aydin and V. Ozer, *Truk. J. Chem*., 23, 1999, 139.
[3] P. D. Sawalakhe and M. L. Narwade, *J. Ind. Chem*. Soc., 73, 1996, 347.
[4] M. L. Narwade, V. S. Jamode, and S. K. Gudadhe, Stability constant of Co(II), Ni(II) and Cu(II) chelate with some substituted Pyrazolines, *Acta. Ciencia Indica,* XIc, 1985, 234.

[5] R. D. Talele, A. N. Sonar and N. S. Pawar, *Journal of Medicinal Chemistry and Drug Discovery*, 1(2), 2016, 426-433.

[6] G. R. Pandhare and V. M. Shinde *Int. J. Chem. Phy. Sci.*, 4 (special issue), 2015, 1-6.

[7] Q. S. Azharuddin, *Der Chemica Sinica*, 3(5), 2012, 1289-1292.

[8] R. B. Pawar, *Online International Interdisciplinary Research Journal*, 2(3), 2012, 35-39.

[9] E. Mavioglu, S.Arzik and A. S.celebi, *JFS*, 27, 2004, 1.

[10] K. B. Vyas, G. R. Jani and M. V. Hathi, *E-J Chem*, 6(4), 2009, 112.

[11] L. G.Van, Vitert and C. Haas, *J. Am. Chem. Soc.,* 75, 1953, 451.

[12] Vogel's "A Text Book of Practical Organic Chemistry" V[th] edition, Longman Scientific and Technical, John Willey and Sons, New York, 1989, 401.

[13] H.S. Irving and H.S. Rossotti, *J. Chem. Society,* 1953, 3397.