International Journal of Basic and Applied Chemical Sciences ISSN: 2277-2073 (Online)
An Online International Journal Available at http://www.cibtech.org/jcs.htm
2012 Vol. 2 (3) July-September pp.7-9/Nehete et al.
Research Article

STUDIES OF STABILITIES OF MONTELUKAST COMPLEXES WITH METAL IONS IN MIXED SOLVENT AT 0.02 M IONIC STRENGTH AND 303K BY POTENTIOMETRIC METHOD

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ABSTRACT
The interaction of metal ions with substituted heterocyclic drug has been investigated in 70% ethanol-water mixture at 0.02 M ionic strength and 303K by potentiometric titration. The data obtained is used to estimate the values of proton-ligand stability constant (pK) and metal-ligand stability constant (logK). It is observed that the metal ions form 1:1 and 1:2 complexes with substituted heterocyclic drug.

Key Words: *Stability Constant, Substituted Heterocyclic Drug*

INTRODUCTION
Montelukast is beneficial for the treatment of asthma, seasonal allergies. Naciye *et al.,* (1999) have studied the stabilities of complexes of Sc (II), Y (II) with catechol derivative at 0.1M ionic strength. Sawalakhe and Narwade (1996) have investigated the stability constant of transition and rare earth metal ions with substituted β-diketones. Shangguan *et al.,* (2001) have studied the protonation constant of new macro cyclic dinucleating ligand in aqueous medium. Mavioglu *et al.,* (2004) have studied the stability constant of Lanthanide complexes with Iminodiacetic Acid in Water and Dioxane-Water mixtures by potentiometric methods. Vyas *et al.,* (2009) 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 30^0C and 0.1M ionic strength Vyas *et al.,* (2009). 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.

MATERIALS AND METHODS
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 Temperature range from 303 K -318K. Pure rare earth nitrates (99.9% Pure) were used. All metal nitrates available from Sigma Aldrich Chem. Co., U.S.A. Metal nitrate 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 *et al.,* (1953). The ethanol was purified by the method described by Vogel *et al.,* (1975). The overall ionic strength of solution was constant maintains by adding $NaClO_4$. All the solutions were titrated with standard carbonate free NaOH (0.2N) solution at constant ionic strength (0.02M). 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

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

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

The 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 = 2.5 and deviating continuously up to P^H = 11. 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 and acid - ligand titration curves employing the equation of Irving and Rossotti (1953).

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. 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 some substituted heterocyclic drugs at 0.02 M ionic strength.

System	Constant pK	
Montelukast	Half Integral	Point Wise Calculation
	9.80	9.76

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 formation of chelate between metal ions with some substituted heterocyclic drug were indicated by the significant separation starting from P^H =2.5 for all complexes.

Table 2: Determination of metal-ligand stability constant (logK) rare earth metals with Montelukast at 0.02 M ionic strength.

System	$Logk_1$	$Logk_2$	$Logk_1 - Logk_2$	$Logk_1 / Logk_2$
Ni (II) -Ligand-1	7.85	5.05	2.80	1.5544
Cu (II) -Ligand-1	7.07	4.06	3.01	1.7413
Zn (II) -Ligand-1	7.26	4.62	2.64	1.5714
Mg (II) -Ligand-1	7.26	4.48	2.78	1.6205
Ce (III) - Ligand-1	6.93	4.06	2.87	1.7068
Gd (III) - Ligand-1	7.26	4.15	3.11	1.7493

The result shows the ratio of $Logk_1 / Logk_2$ is positive and greater than one in all cases. This implies that there is little or no steric hindrance to the addition of secondary ligand molecule. The difference between $logK_1$ and $logK_2$ was more than 2.5 indicating the simultaneous formation of 1:1 and 1:2 complexes.

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