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Thermodynamic studies of transition metal complexes with Metformin Hydrochloride drug in 20 % (v/v) ethanol-water mixture

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ABSTRACT

pH metry is one of the most convenient and successful technique employed for metal complex equilibrium measurements. In the present work we investigate the stability constant of Metformin Hydrochloride drug with transition metal ions Fe(III),Co(II),Ni(II),Cu(II),Zn(II) &Cd(II) using P^H metric technique in 20%(v/v) ethanol-water mixture at 298K,308K ,318K and at an ionic strength of 0.1M $NaClO_4$. The method of Calvin and Bjerrum as modified by Irving and Rossotti has been employed to determine metal-ligand stability constant (logK) values. It is observed that a transition metal ion forms 1:1 and 1:2 complexes. The thermodynamic parameter ΔG, ΔH and ΔS were calculated from values of stability constant at different temperatures. The formations of metal complexes were found to be spontaneous and exothermic in nature.

Keywords: P^H metry, Stability Constant, transition metal, Metformin Hydrochloride drug, thermodynamic parameter.

INTRODUCTION

Drugs have various functional groups present in its structure, which can bind to metal ions present in human body [1].Metal complexes of drugs are found to be more potent than parent drugs [2].Chemistry of drugs attracts many researchers because of its application in medicinal study. The stability of metal complexes with medicinal drugs play a major role in the biological & chemical activity [3, 4] Metal Complexes are widely used in various fields, such as biological processes pharmaceuticals, separation techniques, analytical processes etc. [5] Most of the d-block elements form complexes. There are different kinds of ligand used for complexation. For the present investigation, we selected antidiabetic drug Metformin Hydrochloride .Metformin Hydrochloride [1,1dimethyl biguanidehydrochloride] is a hypoglycemic agent having molecular formula $C_4H_{12}ClN_5$ and IUPAC name 3-(diaminomethylene)-1, 1- dimethylguanidine hydrochloride.

The physical properties of medicinal drug Metformin Hydrochloride is as shown below. Molecular weight = 165.625g/mol

Phase = solid (at STP)
M.P. = 224.5°c
Refractivity = 56.642

Polarizability = 13.427
Solubility = freely soluble in water, solubility = 1.38e-02gm/lit

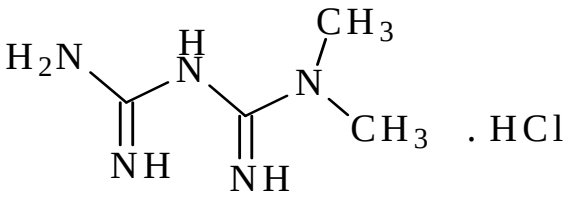

Fig1: Metformin Hydrochloride ($C_4H_{12}ClN_5$)

Metformin hydrochloride is a biguanide antihyperglycemic agent used for treating non-insulin-dependent diabetes mellitus [NIDDM]. It improves glycemic control by decreasing hepatic glucose production, decreasing glucose absorption and increasing insulin-mediated glucose uptake. Metformin hydrochloride is the only oral antihyperglycemic agent that is not associated with weight gain. Metformin hydrochloride decreases fasting plasma glucose, postprandial blood glucose and glycosolated hemoglobin [HbA1c] levels, which are reflective of the last 8-10 weeks of glucose control. Metformin hydrochloride may also have a positive effect on lipid levels. [6, 7]

Literature survey reveals that many researchers [8-16] use medicinal drug/Schiff bases as a ligand, but very few were investigated thermodynamic stability constant and thermodynamic parameters ΔG, ΔH and ΔS of complexes at different temperature range.

The detail study of complex under identical set of experimental condition is still lacking. Therefore we decide to study the effect of temperature on thermodynamic parameters ΔG, ΔH and ΔS of complexes of Metformin Hydrochloride drug with transition metal ions Fe(III),Co(II),Ni(II),Cu(II),Zn(II)&Cd(II) using pH metrically in 20% (v/v) ethanol-water mixture at constant ionic strength of 0.1M $NaClO_4$.

MATERIALS AND METHODS

The ligand Metformin Hydrochloride is soluble in double distilled water. NaOH, $NaClO_4$,$HClO_4$ & metal salts were of AR grade .The solutions used in the potentiometric titration were prepared in double distilled water. The NaOH solution was standardized against oxalic acid solution (0.1M) and standard alkali solution was again used for standardization of $HClO_4$. The metal salt solutions were also standardized using EDTA titration.[17] All the measurements were made at 298 K,308K &318K in 20% (V/V) ethanol-water mixture at constant ionic strength of 0.1M $NaClO_4$.The thermostat model SL-131 (Adar Dutt and co(India) pvt.ltd. Mumbai) was used to maintain the temp constant. The pH measurement were made using a digital pH meter model Elico L1-120 in Conjunction with a glass and reference calomel electrode (reading accuracy ±0.01 pH units) the instrument was calibrated at pH 4.00 ,7.00 and 9.18 using the standard buffer solutions .

Potentiometric procedure:
For evaluating the protonation constant of the ligand & the formation constant of the complexes in 20 %(v/v) ethanol-water mixture with different metal ions we prepare the following sets of solutions.

(A) $HClO_4$ (A)
(B)$HClO_4$+ Metformin Hydrochloride (A+ L)
(C)$HClO_4$+ Metformin Hydrochloride + Metal (A+ L+ M)

The above mentioned sets prepared by keeping M: L ratio, the concentration of perchloric acid & sodium perchlorate (0.1M) were kept constant for all sets. The volume of every mixture was made up to 50 ml with double distilled water and the reaction solution were potentiometerically titrated against the standard alkali at temp 298K, 308K&318K.

Determination of the Thermodynamic parameters:-
The thermodynamic parameters such as Gibb's free energy, entropy change and enthalpy change for formation of complexes were determined. The change in free energy of the ligands is calculated by using following equation.

$\Delta G = - 2.303\ RT\ \log K$ (1)

The change in enthalpy (ΔH) is calculated by plotting 1/ T vs. logK. The equation utilized for the calculation of changes in enthalpy is as [18]

$\text{Slope} = - \Delta H / 2.303\ R$ (2)

The evaluation of changes in entropy (ΔS) is done by the following equation.

$\Delta S = (\Delta H - \Delta G) / T$ (3)

Table-1 Proton-ligand& metal-ligand stability constant of Metformin Hydrochloride drug at 0.1M ionic strength in 20% (v/v) ethanol-water mixture

Temp	pK	logK	Fe(III)	Co(II)	Ni(II)	Cu(II)	Zn(II)	Cd(II)
298K	pK_1=2.9052	$logK_1$	11.872	5.233	5.532	8.595	6.444	5.337
	pK_2=11.100	logK	10.446	4.336	4.619	6.354	5.193	4.456
308K	pK_1=2.6184	$logK_1$	11.558	5.092	5.391	8.452	6.302	5.196
	pK_2=10.958	$logK_2$	10.229	4.199	4.471	6.105	5.077	4.310
318K	pK_1=2.3459	$logK_1$	11.310	4.989	5.216	8.322	6.201	5.084
	pK_2=10.856	$logK_2$	10.069	4.105	4.349	5.973	4.976	4.200

Table-2 Thermodynamic parameters of Metformin Hydrochloride complexes formation with transition metal ions at 0.1M ionic strength in 20% (v/v) ethanol-water mixture.

Metals	ΔG(KJ/mol)			ΔH(KJ/mol)	ΔS(J/mol)		
	298K	308K	318K		298K	308K	318K
Fe(III)	$-\Delta G_1$ =67.74	68.16	68.86	$-\Delta H_1$= 51.137	ΔS_1 = 55.72	55.27	55.75
	$-\Delta G_2$ =59.60	60.32	61.30	$-\Delta H_2$= 34.209	ΔS_2 = 85.20	84.79	85.21
Co(II)	$-\Delta G_1$= 29.85	30.02	30.38	$-\Delta H_1$= 22.099	ΔS_1 = 26.03	25.73	26.04
	$-\Delta G_2$= 24.74	24.76	24.99	$-\Delta H_2$= 21.034	ΔS_2 = 12.44	12.10	12.45
Ni(II)	$-\Delta G_1$ =31.56	31.79	31.76	$-\Delta H_1$= 28.541	ΔS_1 = 10.14	10.55	10.12
	$-\Delta G_2$=26.35	26.36	26.48	$-\Delta H_2$= 24.426	ΔS_2 = 6.463	6.300	6.460
Cu(II)	$-\Delta G_1$ =49.04	49.84	50.67	$-\Delta H_1$= 24.779	ΔS_1 = 81.41	81.36	81.41
	$-\Delta G_2$ =36.25	36.00	36.37	$-\Delta H_2$= 34.678	ΔS_2 = 5.288	4.301	5.322
Zn(II)	$-\Delta G_1$ =36.76	37.16	37.75	$-\Delta H_1$= 22.084	ΔS_1 = 49.27	48.96	49.28
	$-\Delta G_2$ =29.62	29.93	30.29	$-\Delta H_2$= 19.701	ΔS_2 = 33.30	33.23	33.32
Cd(II)	$-\Delta G_1$ =30.43	30.64	30.95	$-\Delta H_1$= 22.935	ΔS_1 = 25.23	25.02	25.22
	$-\Delta G_2$ =25.42	25.41	25.57	$-\Delta H_2$= 23.258	ΔS_2 = 7.277	7.012	7.280

RESULTS AND DISCUSSION

Proton ligand stability constants (pK) of Metformin Hydrochloride drug is determined by point wise calculation method as suggested by Irving & Rossoti. Metal ligand stability constant (logk) transition metal ions with Metformin Hydrochloride drug (ligand) were calculated by point wise and half integral method of Calvin and Bjerrum as modified by Irving and Rossotti has been employed .For the present investigation we have studied the stability constants of divalent transition metal ions except Fe which is in trivalent state. Since we got $\bar{n}A$ between 0.2 to 0.8 and 1.2 to 1.8 indicating 1:1 and 1:2 Complex formations. The proton-ligand stability constants values decreases with increase in temperature for all systems. This suggested that liberation of protons becomes easier at higher temperature. The values of metal-ligand stability constant decreases with increase in temperature. This suggests that the complex formation is exothermic and favorable at lower temperature. The negative values of ΔH and ΔG of complex formation indicates the complex formation process is spontaneous. [19] All the metal complexes are accompanied by negative enthalpy (ΔH) changes suggesting that the metal-ligand bonds are fairly strong. Positive entropy changes accompanying a given reaction are due to the release of bound water molecules from the metal chelates .During formation of metal chelates, water molecules from the primary hydrationc sphere of the metal ion are displaced by the chelating ligand.Thus there is an increase in the number of particles in the system i.e. Randomness of the system increases. [20] The order of stability constants for these metal complexes was as follows:

Fe^{3+} > Cu^{2+} > Zn^{2+} > Ni^{2+} > Cd^{2+} > Co^{2+}

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