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Study of Ni^{2+}- Famotidine Complexes by Polarography

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ABSTRACT

The interaction between Famotidine and Ni^{2+} was investigated using direct current polarography. The polarographic technique was used to determine the Kinetic parameters (K_{0fh}, αn) and thermodynamic parameters such as enthalpy change ($\Delta H^{\#}$), free energy change ($\Delta G^{\#}$) and entropy change ($\Delta S^{\#}$) of Ni^{2+} complexes with Famotidine. The electrode processes were irreversible and diffusion controlled.

INTRODUCTION

Famotidine (Fig. 1) is pale yellowish white, crystalline powder. It is sensitive to light, freely soluble in dimethylformamide and in glacial acetic acid, slightly soluble in methanol, very slightly soluble in water, practically insoluble in acetone, in alcohol, in chloroform, in ether and in ethyl acetate.

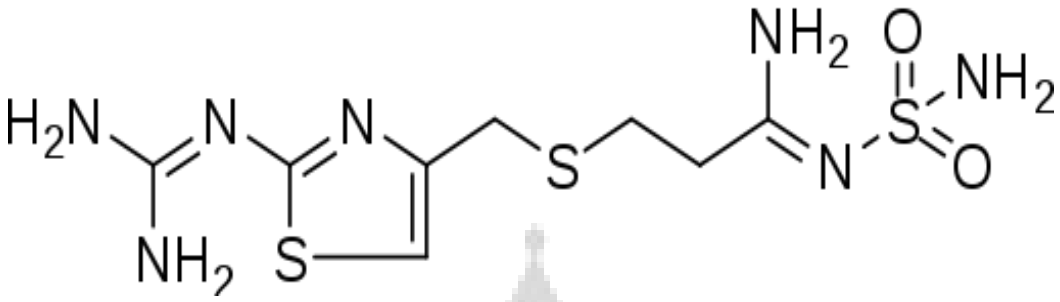

Fig. 1: 3-([2-(diaminomethyleneamino)thiazol- 4-yl]methylthio)- N'-sulfamoylpropanimidamide

Famotidine, a competitive histamine H_2-receptor antagonist, is used to treat gastrointestinal disorders such as gastric or duodenal ulcer, gastroesophageal reflux disease, and pathological hypersecretory conditions. Famotidine inhibits many of the isoenzymes of the hepatic CYP450 enzyme system. Other actions of Famotidine include an increase in gastric bacterial flora such as nitrate-reducing organisms. Famotidine is given to surgery patients before operations to prevent postoperative nausea and to reduce the risk of aspiration pneumonitis. Famotidine is also given to some patients who take NSAIDs, to prevent peptic ulcers[1]. It serves as an alternative to proton pump inhibitors[2]. Famotidine has also been used in combination with an H1 antagonist to treat and prevent urticaria caused by an acute allergic reaction[3]. It has been found to decrease the debilitating effects of chronic heart failure by blocking histamine[4].

Famotidine has been studied and determined by several procedures/techniques including spectrophotometric/spectrophotometry[5-8], Spectrofluorimetry[9], Colorimetry[10], Potentiometry[11-12], HPLC[13-15]. Many electrochemical procedures have been reported for the determination of Famotidine. Famotidine has been determined in different samples by different techniques such as Square wave adsorptive stripping voltammetric[16-18], Square Wave Voltammetry[19], DPP[20] and others[21-22]. Study of Famotidine complexes have been done with some metals[23-24].

Here attempts have been made to study the electroreduction of various complexes of famotidine in various experimental conditions using direct current polarography.

Nickel[25] is metallic element which is required in rare forms of life. As for most metals, the toxicity of nickel depends on the route of exposure and the solubility of the nickel compound[26]. In short and long term studies of animal administered various soluble nickel salts orally, nickel was found primarily in the kidneys. The relative tissue concentrations were kidneys > lungs> liver >heart> testes[27-28]. Oral administration of Ni^{2+} found to accumulate higher in the spinal cord than in the cerebellum or frontal cortex[29]. Pulmonary absorption is the major route of concern for nickel induced toxicity. Nickel may be absorbed as the soluble nickel ion (Ni^{2+}) while sparingly soluble nickel compounds may be phagocytized. So it becomes necessary to study Nickel-Famotidine complexes.

Nickel-Famotidine complex has been studied earlier by spectophotometry[30] and potentiometry[31-32], but unfortunately its kinetic and thermodynamic parameters are not determined. Here attempts have made to determine these parameters.

MATERIALS & METHODS

Apparatus

The digital D. C. Polarograph (CL-357) of Elico Limited was used to record current-voltage data. This equipment has the three electrode assembly, dropping mercury electrode as working electrode, calomel as reference electrode and platinum electrode as counter electrode. The current responses and applied potential were recorded at scan rate 150 mV/min. Dropping mercury electrode had the characteristics m = 2.422 mg/sec, t = 2.5 sec and h = 60 cm.

The Elico digital pH meter model 111E was used to measure the pH of the analytes.

Proposed Procedure

The general procedure used to produce DC polarograms was as follows:

An aliquot (10 ml) of experimental solution which contains drug (Famotidine), metal solution, supporting electrolyte/buffer, Triton-X-100 (Maxima Suppresser) and water was placed in a dry, clean polarographic cell and deoxygenated with nitrogen for 15 min. The current-voltage values were measured manually.

The negative potential was applied to the working electrode with 150 mV/min span rate and 100 nA/div sensitivity of current measurement. After the background polarogram had been obtained, aliquots of the required amounts of Famotidine solution were added.

Reagents

Famotidine was obtained from Panchseel Organics Ltd., Mumbai, Maharashtra, India**.** Famotidine was dissolved in water. All solutions were prepared freshly with triple distilled water and analytical reagent grade chemicals (MERCK).

Analytical grade salts of Nickel Nitrate [$NiNO_3$], Zinc Sulphate [$ZnSO_4$], Lead Nitrate [$PbNO_3$], and Cadmium Acetate [$Cd(CH_3COO^-)_2$] of strength 2.5×10^{-2} M were used for present study. Aqueous buffers of different pH were prepared. pH was adjusted by 0.1 M HCl and 0.1 M NaOH. 1.0 M KNO_3 was used as supporting electrolyte for $NiNO_3$, $ZnSO_4$ & $PbNO_3$ and 1.0 M Acetate Buffer (pH = 4.37) for $Cd(CH_3COO^-)_2$**.** All solutions were prepared in triple distilled water. Triton X-100 (0.001%) was used to suppress polarographic maxima. The depolariser (metal) and ligand (drug) were taken in different ratio.

RESULTS AND DISCUSSION

Pure Ni(II) gave a well defined wave in 0.1 M KNO_3 with $E_{1/2}$ = – 0.995 volts vs S.C.E. Addition of famotidine to Ni(II) shifts its half wave potential towards negative direction and decreases the diffusion current with increasing concentration of ligand (drug) too. This clearly indicates complex formation between metal and drug. Ni(II) undergoes $2e^-$ reduction at d.m.e. Reduction is found to be irreversible and diffusion controlled.

The plots of log [i/(id-i)] vs $E_{d.e.}$ were linear with slope values much higher than expected for reversible reaction, which suggest that electrode reaction is irreversible. Nickel – Famotidine complex have been studied in 40 % and 60 % methanol medium. Further, complexation of famotidine with Ni(II) has also been studied at different pH values and at different temperatures Kinetic parameters (K^o_{fh}, αn) are calculated by using Meites-Israel and Gaur-Bhargava methods in different experimental conditions. Polarographic characteristics and kinetic parameters are summarised in Table 1 to 4.

Table 1. Effect of pH on Nickel-Famotidine System

Famotidine Conc. = 3.32×10^{-3}

Triton-X-100 = 0.001%

Temperature = 298 ± 1K

pH (±0.01)	$E_{½}$ v. vs S.C.E.	I_d (100nA)	D (cm^2 sec^{-1})	αn (M.I.)	αn (G.B.)	K^o_{fh} (M.I.) (cm sec^{-1})	K^o_{fh} (G.B.) (cm sec^{-1})
6.18	-1.023	9.8	0.9898	0.4889	0.5336	1.63×10^{-9}	3.73×10^{-10}
7.55	-1.121	9.2	0.8723	0.4952	0.5404	1.80×10^{-10}	3.40×10^{-11}
8.73	-1.234	8.5	0.7446	0.5273	0.5755	4.03×10^{-12}	5.40×10^{-13}
9.65	-1.291	7.9	0.6432	0.5460	0.5959	4.53×10^{-13}	5.01×10^{-14}
10.85	-1.334	7.4	0.5644	0.5557	0.6065	1.03×10^{-13}	9.99×10^{-15}

Table 2. Effect of ligand concentration on the half wave potential of Ni(II) in 40% Ethanol medium

pH = 8.73

Triton-X-100 = 0.001%

Temperature = 298 ± 1K

Conc. (M)	E ½ (Volt)	$I_d \times 100$ nA	D (cm^2 sec^{-1})	Slope (V)	αn (M.I.) (V)	αn (G.B.) (V)	K^ofh (M.I.) (cm sec^{-1})	K^ofh (G.B.) (cm sec^{-1})
1.32×10^{-3}	-1.002	9.3	5.5720	0.0992	0.5459	0.5957	6.25×10^{-10}	1.21×10^{-10}
2.65×10^{-3}	-1.004	8.7	1.2190	0.1020	0.5309	0.5794	5.03×10^{-10}	1.03×10^{-10}
3.98×10^{-3}	-1.006	8.2	0.4813	0.1046	0.5177	0.5650	5.08×10^{-10}	1.09×10^{-10}
5.31×10^{-3}	-1.010	7.6	0.2325	0.1071	0.5059	0.5521	5.19×10^{-10}	1.15×10^{-10}
6.64×10^{-3}	-1.014	7.0	0.1262	0.1136	0.4769	0.5204	1.11×10^{-09}	2.73×10^{-10}
7.96×10^{-3}	-1.016	6.5	0.0756	0.1186	0.4568	0.4985	1.84×10^{-09}	4.85×10^{-10}
9.29×10^{-3}	-1.063	6.0	0.0473	0.1295	0.4185	0.4567	3.07×10^{-09}	8.70×10^{-10}
10.62×10^{-3}	-1.067	5.6	0.0315	0.1361	0.3982	0.4346	5.46×10^{-09}	1.67×10^{-09}

Table 3. Effect of ligand concentration on the half wave potential of Ni(II) in 60% Ethanol medium

pH = 8.73

Triton-X-100 = 0.001%

Temperature = 298 ± 1K

Conc. (M)	E ½ (Volt)	I_d × 100 nA	D (cm^2 sec^{-1})	Slope (V)	αn (M.I.) (V)	αn (G.B.) (V)	K^o_{fh} (M.I.) (cm sec^{-1})	K^o_{fh} (G.B.) (cm sec^{-1})
1.32×10^{-3}	-1.000	8.9	5.1030	0.0984	0.5504	0.6006	5.24×10^{-10}	1.00×10^{-10}
2.65×10^{-3}	-1.008	8.4	1.1364	0.1083	0.5004	0.5461	1.48×10^{-09}	3.34×10^{-10}
3.98×10^{-3}	-1.013	8.0	0.4581	0.1098	0.4936	0.5387	1.12×10^{-09}	2.57×10^{-10}
5.31×10^{-3}	-1.017	7.4	0.2204	0.1146	0.4729	0.5161	1.63×10^{-09}	4.02×10^{-10}
6.64×10^{-3}	-1.024	6.8	0.1191	0.1197	0.4524	0.4938	2.37×10^{-09}	6.27×10^{-10}
7.96×10^{-3}	-1.035	6.3	0.0710	0.1273	0.4257	0.4646	4.43×10^{-09}	1.27×10^{-09}
9.29×10^{-3}	-1.043	5.8	0.0442	0.1346	0.4026	0.4394	7.82×10^{-09}	2.42×10^{-09}
10.62×10^{-3}	-1.057	5.5	0.0304	0.1465	0.3699	0.4037	2.00×10^{-08}	6.90×10^{-09}

Table 4. Effect of temperature on Nickel-Famotidine System

pH = 8.73

Famotidine Conc. = 3.32×10^{-3}

Triton-X-100 = 0.001%

Temp. (°C)	$E_{½}$ (V)	I_d (100 nA)	D (cm^2 sec^{-1})	αn (M.I.)	αn (G.B.)	K^o_{fh} (M.I.) (cm sec^{-1})	K^o_{fh} (G.B.) (cm sec^{-1})
20	-1.003	8.0	0.6597	0.4524	0.4938	8.09×10^{-09}	2.18×10^{-09}
25	-1.006	8.5	0.7447	0.5264	0.5745	4.50×10^{-10}	9.27×10^{-11}
30	-1.005	9.3	0.8915	0.5578	0.6088	1.47×10^{-10}	2.71×10^{-11}
35	-1.007	10.0	1.0307	0.6058	0.6611	2.31×10^{-11}	3.58×10^{-12}
40	-1.008	10.7	1.1801	0.6557	0.7156	3.40×10^{-12}	4.39×10^{-13}

Further, thermodynamic parameters ($\Delta Hp^{\#}$, $\Delta Hv^{\#}$, $\Delta G^{\#}$, $\Delta S^{\#}$) have been reported in Table 5. The enthalpy of activation at constant pressure ($\Delta Hp^{\#}$) has been calculated by substituting the value of slope of the plot (log K^{0}_{fh} v/s 1/T) in the Vant Hoff equation.

$$\Delta Hp^{\#} = 2.303R \times \text{Slope}$$

Where R= Gas constant

The value of slope comes out to be 14.763×10^{3}.

$$\Delta Hp^{\#} = \Delta Hv^{\#} + RT$$

From this relation $\Delta Hv^{\#}$ (enthalpy change of activation at constant volume) was evaluated, the activation free energy change ($\Delta G^{\#}$) was determined using the relationship.

$$K^{0}_{fh} = (KT/h)r_o\exp(-\Delta G^{\#}/RT)$$

Where K = Boltzmann constant,

h = Plank's constant,

r_o = mean distance between depolarized ions in the bulk solution,

R = Gas constant,

T = absolute temperature.

In general value of r_o is taken as 2×10^{-8} cm [33]. The entropy of activation ($\Delta S^{\#}$) was calculated using following equation;

$$\Delta S^{\#} = (\Delta Hv^{\#} - \Delta G^{\#})/T$$

The plot of log K^{0}_{fh} vs. 1/T is found to be linear from the slope of which the values of $\Delta Hp^{\#}$, $\Delta Hv^{\#}$, $\Delta G^{\#}$ and $\Delta S^{\#}$ have been evaluated and presented in Table 5.

Table 5. Thermodynamic parameters at different temperatures

Temp. (^{o}C)	$\Delta H_P^{\neq}$ (J/Mole)	$\Delta H_V^{\neq}$ (J/Mole)	$\Delta G^{\neq}$ (J/Mole)	$\Delta S^{\neq}$ (J/Kelvin)
20	28.2669×10^{4}	28.0233×10^{4}	63.0143×10^{3}	7.4136×10^{2}
25	28.2669×10^{4}	28.0191×10^{4}	71.3252×10^{3}	7.0089×10^{2}
30	28.2669×10^{4}	28.0150×10^{4}	75.3941×10^{3}	6.7576×10^{2}
35	28.2669×10^{4}	28.0108×10^{4}	81.4433×10^{3}	6.4501×10^{2}
40	28.2669×10^{4}	28.0067×10^{4}	87.8184×10^{3}	6.1421×10^{2}

CONCLUSION

From the values reported in table 1 and 4, it can be concluded that values of id and D decreases with increase in the concentration of complexing agent (drug). Further, values of K^{o}_{fh} i.e. formal forward rate constant, calculated by Meites-Israel and Gaur-Bhargava's methods, increases with increasing concentration of drug which indicates increase of reversibility. Further, when complexation was carried out at different pH and different temperatures, values of K^{o}_{fh} decrease with increasing pH and temperature separately hence reversibility decreases or irreversibility increases with increasing pH and temperature.

A perusal of the values of various quantities presents in Table 5 show that activation free energy change ($\Delta G^{\#}$) is positive at all the temperatures suggesting the non spontaneous nature of electrode process. Positive value of $\Delta S^{\#}$ suggests that formation of activated state is accompanied by increase of entropy.

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