**Determination of Stability Constant of Zinc (II)-Famotidine Complex in Pharmaceutical Formulation by DPP**

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**ABSTRACT**

The stability constant for Zinc (II) - famotidine complex was investigated using differential pulse polarography. The molar reactivity of the reaction between Zn (II) -FMTDN was studied using the molar ratio method where, precise determination of the structure of the complex was accomplished by varying the concentration of famotidine with constant equimolar concentration of Zn (II). A sharp inflection point is obtained at a mole fraction of 0.5 indicating the formation of 1:1 complex. The stability constant of the Zn (II) – FMTDN complex has been determined by classical method of Lingane. He reported a derived equation describing a shift in half-wave potential as a function of the excess of a ligand at a fixed pH. Thus the value of log \(\beta\) has been found to be 7.93 for Zn (II) – FMTDN Complex.

**Keywords**: Stability constant, Famotidine, polarography.

**I. INTRODUCTION**

Stability constants are fundamental for understanding the behaviour of metal ions in aqueous solution. Such understanding is important in wide variety of areas such as metal ions in biology, biomedical applications, and metal ions in the environment, pollution, analytical chemistry, geochemistry, food chemistry, extraction metallurgy and photography\(^1\). Both plants and animals contain significant quantities of both metal ions and ligands. Some of the essential metal ions are Na, K, Mg, Ca, Fe, Cu, Zn, etc. These metal ions can interact with different ligands found in human serum, such as \(\text{H}_2\text{O}, \text{OH}^-, \text{Cl}^-, \text{HCO}_3^-, \text{SO}_4^{2-}, \text{F}^-, \text{Br}^-, \text{I}^-, \text{proteins, carbohydrates and carboxylic acids, nucleic acids, lipids and steroids}\(^2\). Stability constants of
complexes also have an important role in the design of drugs for alleviation of metal poisoning.3

Famotidine (FAM) (Fig. 1) is chemically 3-[[2-[(Aminoiminomethyl) amino] -4thiazolyl] methyl] thio]-N-(aminosulfonyl) propanimidamide. It is commonly used in the treatment of peptic ulcer disease and gastro oesophageal-reflux disease. Famotidine is histamine H2-receptor antagonist which blocks the action of histamine on stomach cells and reduces acid production. Famotidine anti-ulcerogenic drug is a very potent chelating agent and its effective coordination to metal ion may have significant biological implications.4

Zinc is also the most important essential trace element. It is known that there are about 300 enzymes in which zinc present in their active sites and plays an important role as structural ions. Zinc presents in all body tissues and fluids. It is necessary to maintain normal physiological and biochemical functions of cell. It is present in metalloenzyme superoxide dismutase, alkaline phosphatase, alcohol dehydrogenase, and DNA and RNA polymerases. Zinc ion strongly interacts with nitrogen and oxygen and forms complexes with appropriate ligands. Some of these complexes exhibit antifungal activity.5 Some zinc containing macrocyclic compounds are very important as lipophilic carriers for anti-HIV medicines. Free zinc ion in solution is highly toxic to plants, invertebrates and even vertebrate fish.6

No one has described the stability constants of the metal- famotidine complexes by DPP. In view of this, we have proposed to undertake studies on the, investigation of the affinity and thermodynamics interaction of famotidine drugs with zinc metal by determining their stability.

II. MATERIALS AND METHOD

A. Chemicals

Analytical reagent grade famotidine was used for the preparation of solutions in HCl using double distilled water. The purity of reference standards was 99.9%. All other reagents employed were of analytical grade and used without further purification.

B. DPP studies of metal - famotidine complex

To measure the complexation of Zn (II) with famotidine, the electrochemical cell was assembled with 10 mL of sodium acetate buffer having pH 5.00 ±0.10, containing 0.1M KCl in deionized water. Then, the solution was cleaned thoroughly with pure nitrogen for 10 minutes. The polarograms were recorded in the following order: pure supporting electrolyte, after Metal (II) addition, and after addition of each aliquot of famotidine.

III. DETERMINATION OF STOICHIOMETRY OF COMPLEX BY DPP

A. Mole ratio

Accurate amounts of the metal salts Zn (II) and the famotidine were taken to prepare respective solutions in deionized distilled water. Different aliquots of ligand solution were
added in 1x $10^{-4}$ M metal solution and volume was kept constant for all. The peak current was recorded at its peak potential, while temperature was maintained at 25±1 °C.15.

**B. Slope ratio**

For this method the working solution was such that the sequence of the complex solution was split in two halves. In one half volume of 1x$10^{-3}$ M Zn (II) was kept constant, while varying the volume of 1x$10^{-3}$ M famotidine, and in the other half of the samples sequence, famotidine was kept constant, with variable concentration of metal. The complex samples were scanned by DPP at the respective Ep and the recorded peak current was plotted versus concentration of varying species. Slope of each straight line was evaluated. The ratio of the slopes helped to establish the stoichiometry of the Zn-famotidine complex.

**C. Job’s plot**

The solutions were prepared by mixing metal and famotidine solution by continuous increase of one ingredient with the similar decrease of second ingredient. Peak current (Ip) of all samples was recorded at its peak potential (Ep) and by plotting graph between metal composition and respective peak current, stoichiometry was determined.

**IV. INSTRUMENTATION**

For DPP measurements, a polarographic analyzer model CL-362 supplied by an Elico Ltd, Hyderabad was used. A dropping mercury as a working electrode, saturated calomel as reference and platinum wire as auxiliary electrodes were used. UV-VIS spectrophotometer, PerkinElmer Lambda 25, in 1 cm quartz cell was used for Spectrophotometric analysis. All measurements were made at room temperature. The pH measurements were carried out with the help of Elico pH meter.

**V. RESULTS AND DISCUSSION**

**A. Determination of stoichiometry of complex by Job’s plot**

The solutions were prepared by mixing metal and ligand solution by continuous increase of one ingredient with the similar decrease of second ingredient. Peak current of all samples was recorded at its peak potential and by plotting graph between metal composition and respective peak current, stoichiometry was determined.

The plots of Ip against the mole ratio of Zn (II) complex with famotidine, suggest a mole ratio of 1:1 for Zn (II)-FMTDN.

The molar reactivity of the reaction between Zn (II) -FMTDN was studied using the molar ratio method where, precise determination of the structure of the complex was accomplished by varying the concentration of famotidine with constant equimolar concentration of Zn (II). A sharp inflection point is obtained at a mole fraction of 0.5 indicating the formation of 1:1 complex. The presence of amino, amido, and thioether groups in the

structure of famotidine causes this drug to possess chelating properties, and it may interact very effectively with the essential metal ions present in blood plasma and different tissues.\(^7\)

**B. Properties of the Complex**

The reaction of famotidine with Zn (II) was investigated at pH 5.0 buffer solutions, at three temperatures 35°C. The absorption spectra were recorded over the voltage range of -0.200 V to –1600V. It was found that famotidine with Zn (II) formed a water soluble complex. The Zn-complex gave a peak at -1.362V peak potential and was used for the analytical measurements.

In solution, zinc was present as zinc (II) aquo-complex. Water behaves as a weak field ligand so zinc (II) aquo-complex which can be easily replaced by famotidine, to form stable complex ML. Concentration effects of zinc on the formation of complex Zn-FMTDN complex showed that a two-fold mole ratio of reagent to analyte is necessary for maximum complex formation. Metal ion binding is not able to change some conformational features of famotidine, which could be biologically an important factor.\(^8,9\)

**C. Determination of half wave potential of Zn (II) with Famotidine**

A 1×10⁻3 M Zn (II) solution in 1.0 M KCl has been used to obtain polarograms of Zn (II). This showed an Ep at 1.670 v vs. SCE for zinc (Fig.1). Polarographic study was done on Zn (II) with various concentration of famotidine. The polarogram (Fig.2 and Fig. 3) showed the peak potentials shifted towards more negative value with increasing concentration of ligand indicating complex formation and the peak current was found to decrease regularly with increase of famotidine concentration as shown in Table 1 (Fig.4).

**Table 1. Experimental Data of Zn (II) – FMTDN complex by Continuous Variation Method**

<table>
<thead>
<tr>
<th>Sr.No</th>
<th>Metal Zn Conc. (×10⁻⁴ moles)</th>
<th>Ligand Conc. (×10⁻⁴ moles)</th>
<th>XZn</th>
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<th>Ep</th>
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Table 2: Experimental Data of Zn (II) – FMTDN Complex by Mole Ratio Method

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</table>

Figure 1: Determination of half wave potential of Zn (II) with famotidine

Figure 2: DPP of Zn (II) – FMTDN complex by Mole Ratio Method
D. Determination of stability constant Zn (II) – FMTDN

The stability constant of the Zn (II) – FMTDN has been determined by classical method of Lingane.
The following Lingane equation has been used to calculate the stability constant of the complex studied.

\[ E = E_M - E_c = \frac{0.0592}{n} \log_{10} \beta_{MLj} + \frac{0.0592}{n} \log_{10}[L]^j \]

Where \( E_M \) and \( E_c \) are the peak potentials of the free metal ion and the complexed metal ion, respectively, \([L]\) is the free ligand concentration and \( j \) is the number of ligands in a complex \( MLj \). Thus the value of \( \log \beta \) has been found to be 7.93 for Zn (II) – FMTDN. Differential pulse Polarographic data of Zn (II) – FMTDN Complex is given in Table-2.

VI. CONCLUSION

The molar reactivity of the reaction between Zn (II) -FMTDN was studied using the molar ratio method where, precise determination of the structure of the complex was accomplished by varying the concentration of famotidine with constant equimolar concentration of Zn (II). A sharp inflection point is obtained at a mole fraction of 0.5 indicating the formation of 1:1 complex. The stability constant of the Zn (II) – FMTDN complex has been determined by classical method of Lingane. He reported a derived equation describing a shift in half-wave potential as a function of the excess of a ligand at a fixed pH. Thus the value of \( \log \beta \) has been found to be 7.93 for Zn (II) – FMTDN.

REFERENCES