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POTENTIOMETRIC STUDY ON COMPLEXES OF METFORMIN DRUG WITH Mg(II) AND Ca(II) METAL IONS IN ETHANOL-WATER MEDIA

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Abstract: *The stability constant of Metformin Hydrochloride (MTF) drug with alkaline earth metal ions Mg(II)and Ca(II) using a pH metric titration technique in 20% (v/v) ethanol-water mixture at 25°C temperatures and at an ionic strength of 0.1M $NaClO_4$ were investigated. The method of Calvin and Bjerrum as adopted by Irving and Rossotti has been employed to determine metal-ligand stability constant logK values. It is observed that alkaline earth metal ion forms 1:1 and 1:2 complexes. The trend in the formation constants follows the order:* ***Mg^{2+}> Ca^{2+}***
Keywords: *Stability Constant, alkaline earth metal, Metformin Hydrochloride drug, pH meter.*

INTRODUCTION

Alkaline earth metal complexes play an important role in biological activity of drugs. The stability of metal complexes with medicinal drugs plays a major role in the biological and chemical activity. Metal complexes are widely used in various fields, such as biological processes, pharmaceuticals, separation techniques, analytical processes etc. Potentiometric titration is accepted as a powerful and simple electro analytical technique for determination of stability constants. The determination of stability constants is an important process for many branches of chemistry.

In recent years, there has been an increased interest in the study of the alkaline earth metal complexes. Most of the s-block elements form complexes. Mg(II) ions form complexes with several enzymes which are essential for energy release. They are also important for transmission of impulses along the nerve fibres. Ca(II) is important in bone, teeth and blood clotting. It maintains the regular breathing of hearts, contraction of muscles[1]. There are different kinds of ligand used for complexation. For the present investigation, we have selected Metformin (MTF) drug. Metformin Hydrochlorid (MTF) [1,1dimethylbiguanidehydro chloride] is an antidiabetic drug and biguanide antihyperglycemic agent used for treating non-insulin-dependent diabetes mellitus. The IUPAC name of MTF is 3-(diaminomethylene)-1, 1-dimethylguanidine hydrochloride.

The structure of MTF is

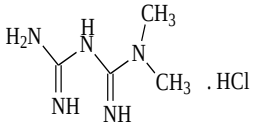

Figure 1. Metformin Hydrochloride

The physical properties of MTF are given in the following table.

Table 1. Physical properties of MTF

1	Molecular formula	$C_4H_{12}ClN_5$
2	Molecular weight	165.625g/mol
3	Phase	Solid (at STP)
4	Melting Point	224.5°C
5	Refractivity	56.642
6	Polarizability	13.427
7	Water solubility	1.38e-02gm/lit

MTF improves glycemic control by decreasing hepatic glucose production, decreasing glucose absorption and increasing insulin-mediated glucose

uptake. MTF is the only oral antihyperglycemic agent that is not associated with weight gain. MTF decreases fasting plasma glucose, postprandial blood glucose and glycosolated hemoglobin levels, which are reflective of the last 8-10 weeks of glucose control. MTF may also have a positive effect on lipid levels.

After a review of literature survey[2-4] and in continuation of our earlier work with complexation of Metformin drug[5-7]. It was thought of interest to study the complexes of Metformin drug with alkaline earth metal ions Mg^{2+} and Ca^{2+} using the pH metric titration technique in 20% (v/v) ethanol-water media at constant ionic strength of 0.1M $NaClO_4$.

EXPERIMENTAL SECTION:

All the chemicals used were of AR Grade. The pure drug Metformin Hydrochloride (MTF) obtained as a gift sample from a reputed pharmaceutical industry & is soluble in double distilled water. 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 HClO4. The metal salt solutions were also standardized using EDTA titration8. All the measurements were made at 25°C in 20% (v/v) ethanol-water mixture at constant ionic strength of 0.1M NaClO4. The water thermostat Fisher Scientific Isotemperature Refrigerated Circulator model 9000 accurate to ± 0.1°C was used to maintain the temperature constant. The solutions were equilibrated in the thermostat for about 15 minutes before titration. The pH measurement was 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.

The following sets of solutions were prepared (total volume 50 ml) and titrated pH metrically against standard NaOH solution at temperature 25 °C.

I) Free $HClO_4$ (A)

II) Free $HClO_4$ (A) + MTF (L)

III) Free $HClO_4$ (A) + MTF (L) + Metal solution (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.

Table 2. Proton-ligand and metal-ligand stability constant of Metformin drug

Metal ion	*Proton-ligand Stability constant*	*Metal-ligand stability constant*		
		$logK_1$	$logK_2$	$log\beta$
Mg(II)	$pK_1 = 2.905$	5.21	4.25	9.46
Ca(II)	$pK_2 = 11.101$	4.62	3.64	8.26

RESULTS AND DISCUSSION:

The results obtained are analysed by the computer programme and the stability constant values are calculated. ***Metformin hydrochloride*** contains one primary, three secondary and one tertiary –N atom. Out of three secondary amino groups, two are having C=N bond. Hence the electrons present on these N atoms may experiences the force of repulsion due to delocalized π^- electrons. One secondary amino group is attached to two carbon atom by single bond. Hence, it might be expected that protonation may be taking place at primary NH_2 group as well as at =NH group easily, rather than NH-group. This results in two pKa values 2.905 and 11.101. The pKa in the basic range is due to the presence of $–NH_2$, whereas, the pKa in the acidic range might be due to steric hindrance and lesser case of electron pair from –NH-group. The complex formation capacity of MTF drug is much more due to the presence of one free primary amino group and two terminal =NH group[9].

The proton ligand stability constant pKa of MTF drug is determined by point wise calculation method and half integral method as suggested by Irving and Rossoti. Metal ligand stability constant logK of alkaline earth metal Mg^{2+} and Ca^{2+} ions with MTF drug are calculated by point wise and half integral method of Calvin and Bjerrum as adopted by Irving and Rossotti have been employed. Since we got $\overline{n}_A$ between 0.2 to 0.8 and 1.2 to 1.8 indicating 1:1 and 1:2 complex formations. The order of stability constants for these alkaline earth metal complexes was as follows: $\mathbf{Mg^{2+} > Ca^{2+}}$

CONCLUSIONS

The alkaline earth metal ion forms 1:1 and 1:2 complexes with Metformin drug. The metal-ligand stability constants for Magnesium complexes are more stable than Calcium complexes. $\mathbf{Mg^{2+} > Ca^{2+}}$

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