EQUILIBRIUM STUDIES IN TERNARY COMPLEXES OF METFORMIN- CHROMIUM (III) AND AMINO ACIDS pH METRICALLY

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Abstract : The present study describes the formation of the Chromium [Cr^{3+}] complexes of Metformin. The properties of the complexes were investigated by measuring the pH values. This is of special interest, owing to their enhanced biological activities. A stability constant of the Ternary complexes formed between the Chromium metal and the anti-diabetic drug Metformin with some biologically important amino acids has been studied using PH Meter at constant ionic strength of 0.1 N $NaClO_4$. A Chromium (III) complex has been characterized while it's Binary Studies, this and further the interaction of binary complexes with the important amino acids in the ternary equilibrium. The stability constants of ternary systems as shown by the experimental data. The results showed that the Chromium complexes were formed with the Metformin ligand; thereby, this complex clearly shows a positive synergistic effect. Furthermore, the ternary Chromium complex has been found to show low stability constant values indicating less stability of the ternary complexes than that of the binary complexes.

Keywords - Stability Constants, Ternary Complex, Metformin, Chromium (III).

I. INTRODUCTION

Diabetes is a metabolic syndrome which was characterized by hyperglycemia and glycosuria resulting from the defect in the secretion or the action of insulin, or both of them [1,2]. Some metal complexes ororgano-metallic compounds have been used in medicine for long time. Supplement containing metal ions was needed for a person with type 2 diabetes mellitus, according to its important role in glucose metabolism[3]. Metformin, the most common prescribed oral medication in type 2 diabetes, lowers HbA1caround 1.5%, rarely causes hypoglycemia (compared with insulin or sulfonylureas), has relatively few contraindications, its adverse effect sare generally tolerable, did not cause weight gain, was cheap, and was highly acceptable among patients [4]. Metformin exerts it was mainan the hyperglycemic effects through activation of AMP-activated protein kinase, resulting in reduced hepatic gluconeogenesis [5]. In addition, Moderate improvements in lipid profile and weight reduction have been reported with metformin use. Metformin hydrochloride decreases fasting plasma glucose, postprandial blood glucose and glycosylated 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]

Chromium is required ultra-trace metal and needed for potentiating of insulin action on carbohydrate and lipids; active as a bioorganic chromium complex. Insulin resistance is caused due to chromium deficiency. Chromium has its role in carbohydrate, lipid and protein metabolism. It is a true potentiator of insulin and is known as glucose tolerance factor (GTF) [8, 9]. Chromium (III) is essential to normal glucose, protein, and fat metabolism and is thus an essential diet element. The body has several systems for reducing chromium (VI) to chromium (III). This chromium (VI) detoxification leads to increased levels of chromium (III) [10]. As chromium promotes the action of insulin for blood glucose level in one of the study it is revealed that chromium may be used to cure diabetes 2 but not always beneficial blind use of it may lead to toxification [11]. As the amino acids are the essential part of the proteins it will be worth considering them as one of the ligand.

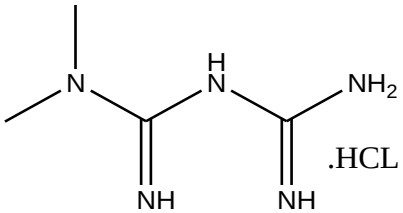


fig.1 structure of the Drug metformin hydrocloride

II. MATERIAL AND METHODS

All chemicals and solvents used for synthesis were commercially available, reagent grade and were used without further purification. Solvents and starting materials were supplied by Sigma Aldrich or Merck Chemical Companies and used without further purification. The concentration of metal ions was determined by the standard procedures [12].Amino acids from Merck (Germany) and H.D. Fine (India) were made by dissolving A.R. grade sample in 80% (V/V) ethanol – water medium. Solution of the Drug Metformin was prepared by dissolving sample as received in 80% (V/V) ethanol-water medium. Drugs samples in pure form were obtained from pharmacy industries. The Methodology were used in the study of ternary metal complexes by the potentiometric titration technique, involves the titrations of carbonate free solution against Standard sodium hydroxide, where drug Metformin (D) and amino acids (R) are the ligands. The ionic strength of the solutions was maintained constant i.e. 0.1 M by adding appropriate amount of 1M sodium per chlorate solution. The metal solution of 0.02 Molar concentrations and that of the ligand with 0.01 Molar concentrations was prepared by taking nitrates of the metal and recrystallized drug respectively. The titrations were carried out at 27 ^{0}Cin and inert Atmosphere by bubbling oxygen free nitrogen gas through an assembly containing the electrode to expel out CO_2. The experimental procedure, in the study of ternary metal complexes by the potentiometric titration technique, involves the titration of carbonate free solution of in 80 % (V/V) Ethanol-Water, were corrected by method of Vansittart and Hass. The formation constant of ternary complexes were determined by computational programmed SCOGS to minimize the Standard derivation. The different systems of Acid, Acid –ligand, Acid –ligand –Metal and Acid-ligand-Metal-Amino –acid have studied by potentiometric titrations against standard NaOH. The dissociation of the species in the aqueous equilibrium is as follows.

I	Free $HClO_4$ (A)
II	Free $HClO_4$ (A) + MET (D)
III	Free $HClO_4$ (A) + MET (D) + Chromium ion (M)
IV	Free $HClO_4$ (A) + Amino acids (R)
V	Free $HClO_4$ (A) + Amino acids (R) + Chromium ion (M)
VI	Free $HClO_4$ (A) + MET (D) + Amino acids (R) + Chromium ion (M)

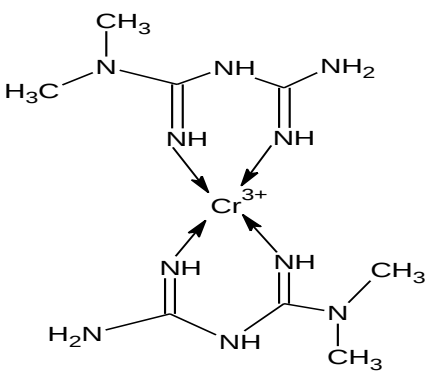
III. RESULT AND DISCUSSION

Binary Complexes: In this study, Chromium (III) was used to react with Metformin and obtained the following results. This was found in accordance to the results obtained in one of the earlier study [13].The proton ligand constant and metal ligand stability constant of drug Metformin and amino acids with Chromium (III) determined in 80 % (v/v) ethanol-water mixture at 27°C and ionic strength μ= 0.1 M $NaCl0_4$ are given in Table No.1.

Table No.1

Legands	pK_1	pK_2	Chromium	
			$Logk_1$	$Logk_2$
Metformin	3.1165	11.0262		
Glycine	2.77000	9.74000	6.5110	3.9398
Leucine	3.81000	10.34000	7.7079	4.3502
Glutamine	3.01000	9.28000	7.2510	6.0820
Glutamic acid	3.13600	5.89870	3.5090	3.0419
Methionine	3.12000	9.60000	3.0998	-
Phenyl alanine	3.14000	9.30000	6.4405	5.3615
Valine	3.21000	9.80240	5.6119	3.6000

The proposed structure of the binary complex formed here can be represented as



1. Chromium (II) complex with the MetforminHCl.

3.2. Ternary complexes: The potentiometric titration, ternary systems of Glycine shows that the mixed ligand curve coincide with A+D complex curve up to the pH ~ 2.3 and after this pH, it deviates. Theoretical composite curve remains toward left of the mixed ligand complex curve. After pH ~ 2.9, the mixed ligand curve drifts towards X-axis, indicating the formation of hydroxide species. Since the mixed ligand curve coincide with individual metal complex titration curves, the formation of 1:1:1 complex by involving stepwise equilibrium. The primary ligand drug Metformin form 1:2 and secondary ligand i.e. amino-acid form 1:1 and 1:2 complexes while leucine forms 1:1 complexes with Cr (III). It is evident from the figure of percentage concentration species of all the Cr (III)-Metformin-Glycine -system that the percentage distribution curves of free metal decreases sharply with increase in the pH this indicates involvement of metal ion in the complex formation process. (fig. 1 and fig. 2)

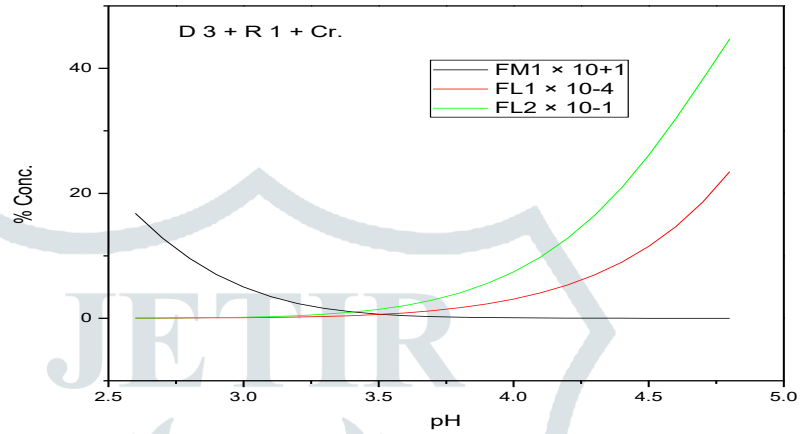


Fig.1 Percentage distribution of free metal, Drug and Amino acid for Metformin - Glycine – Chromium system

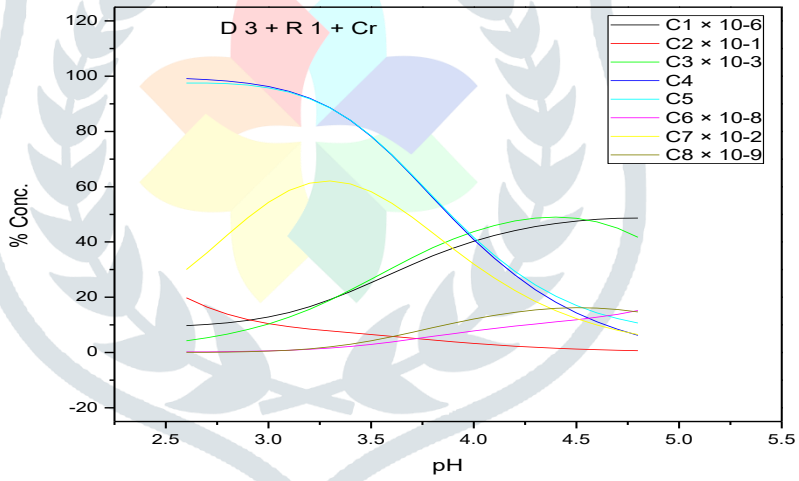


Fig.2 Percentage distribution curve of Metformin - Glycine – Chromium system

Here following types of concentration species are found to be distributed.

$$C1 = H2D \rightleftharpoons DH + H$$

$$C2 = HD \rightleftharpoons D + H$$

$$C3 = H2R \rightleftharpoons HR + H$$

$$C4 = HR \rightleftharpoons R + H$$

$$C5 = M+R \rightleftharpoons MR$$

$$C6 = MR + R \rightleftharpoons MR2$$

$$C7 = M+D \rightleftharpoons MD$$

$$C8 = MD + D \rightleftharpoons MD2$$

$$C9 = M+R+D \rightleftharpoons MRD$$

3.3The stability constant of ternary complexes: The relative stabilities of the binary and ternary complexes are quantitatively expressed in tern of β_{11}, β_{02}, β_{02}, K_D, K_R, K_r and ΔlogK value which are represented in table II.

Parameters based on some relationship between the formation of ternary complexes of Chromium (III) metal ion with Metformin in the presence of amino acids (1:1:1) system at temp = 27^{0}C and μ = 0.1 M $NaClO_4$ Medium = 80% (V/V) Ethanol-Water are given in table no. 2

Table No. 2.

Amino Acids	β_{11}	β_{20}	β_{02}	K_D	K_R	K_r	ΔlogK
Glycine	17.0035	23.5231	10.4498	4.9953	10.4935	1.176181	-1.5147
Leucine	19.7152	23.5231	12.0581	7.707	12.0073	1.370342	-0.0009
Glutamine	17.9721	23.5231	13.3331	5.9639	10.7211	1.029845	-1.2871
Glutamic acid	15.5096	23.5231	6.5506	3.5014	12.0009	1.561081	-0.0073
Methionine	14.6068	23.5231	3.0998	2.5986	11.507	2.926051	-0.5012
Phenyl alanine	16.6987	23.5231	11.802	4.6905	10.2582	1.00442	-1.75
Valine	16.6836	23.5231	9.2119	4.6754	11.0717	1.284505	-0.9365

IV. CONCLUSION

The Comparison of β_{11} with β_{20} and β_{02} of this system show that preferential formation of ternary complexes over binary complex of primary as well as secondary ligand. The positive value of K_D & K_R indicates higher stability of ternary complexes with respect to that of primary as well as secondary ligands. The K_r value of this complex is positive but lower one which indicates higher stability of Binary complexes of all the system. The ΔlogK value of this system is lower than the statistically expected value showing the unstabilized nature of the ternary complexes therefore its ΔlogK value is negative. Here we have studied the equilibrium constants of the complexes in the solution equilibrium of Metformin drug and Chromium (III) complex containing amino acids. The Stability order of the complexes in this case was found to be

Metformin = Leucine > Glutamic acid > Methionine > Vaine > Glutamine > Glycine > Phenyl alanine

V. ACKNOWLEDGMENT

The authors are very much thankful to the Principal of K.K.M College Manwath for his cooperation to carry out the research.

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