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Complexation of some metal ions with metformin hydrochloride in acidic aqueous solutions

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ABSTRACT

Potentiometric determination of stability constant was used for the simultaneous equilibrium study of transition metal ions with metformin hydrochloride. The ionic strength was maintained using KNO_3 and metal to ligand ratio was 1 : 1 , 1 : 2, 1 : 5 and 2 : 3. The stability constant values were compaired. For all metal ions stability constant values was maximum for 1 : 5 and minimum for 2 : 3 molar ratio.

Key words: Metformin HCl, Potentiometric studies, complexation, Stability Constants, Calvin-Bjerrum Method.

INTRODUCTION

Metal complexes are having wide applications including medicinal, biological, metallurgy, painting pigments etc. therefore much more work is done on the complexations, particularly solution state study is carried out by earlier researchers [1-4] pH metry being the most widely used method for determination of stability constant, so we have used this technique. The potentiometric study offer several advantages such as speed, low cost, ease of preparation, simple instrumentation, relatively fast response, very low detections limit, wide dynamic ranges and reasonable selectivity. The potentiometery may be considered as the most accurate technique for the evaluation of complex equilibrium constants. These technique requires the selection of medium with the constant ionic strength in order to ensure that the activity coefficients remain constant for all the species within the experimental condition. To maintain ionic strength constant, KCl, KNO_3, NaCl, $NaNO_3$, $NaClO_4$ etc. are used. We used KNO_3 to maintain ionic strength.

Now a days more emphasis is given on the complexations of medicinal drug with transition and inner transition metal.[4] For present study we selected metformin HCl, as a ligand. Metformin, an antihyperglycemic agents, is eliminated by tabular secretion in addition toglomerular filtrations in the human kindney.

EXPERIMENTAL

All chemicals used were of the A.R. or extra pure grade. Determination of the pKa values of the 1 : 1 and 1 : 2 and K_{ml} complexes were carried out by potentiometric titration against standard 0.1 N sodium hydroxide solution using pH meter as follows: The metal nitrate and p-aminobenzoic acid in the molar ratios 1 : 1, 1 : 2, 1 :5 and 2 :3 were mixed together in a beaker, 5 ml of HNO_3 (0.1N)

and 5 mL of 1 M KNO_3 was added, the solution was made to 50 mL and titrated against 0.1 N NaOH. The pKa values were then calculated using computer programme.

All the other solutions were also prepared in doubly distilled water. The pH measurements were carried out on ELICO digital model LI-122 pH meter (accuracy ± 0,01 pH unit) with a combined electrode type CL-51 having pH range 0-14 and temperature range 20 –100 ^{0}C. The method of Calvin-Bjerrum as modified by Irving and Rossotti was used to obtain log K_1^H and log K_1^M values[2].

RESULTS AND DISCUSSION

Glucophage (metformin hydrochloride tablets) are oral antihyperglycemic drugs used in the management of type II diabetes. Metformin HCl is a white to off-white crystalline compound with a molecular formula of $C_4 H_{11} N_5$ HCl and a molecular weight of 165.63. The structural formula is as shown.

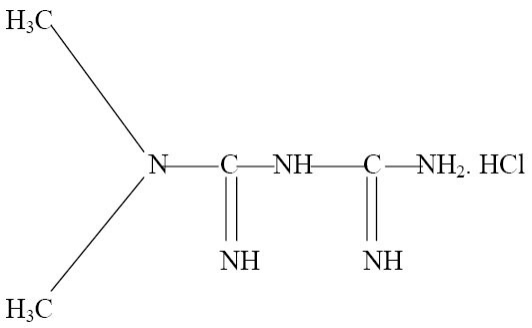

Table 1: Metal-ligand stability constants

Metals	M : L ratios			
	1 : 1	**1 : 2**	**1 : 5**	**2 : 3**
Ni	12.00949	09.81115	12.32391	08.40635
Co	09.88007	11.53687	12.25277	08.72034
Mg	11.61063	12.33035	12.94623	11.14190
Fe	02.61388	02.82353	12.86263	02.58296
Cu	11.371163	07.711005	12.67773	01.80516

Table 2 : Trends in stability constant with respect to metal

1 : 1	Ni > Mg > Cu > Co > Fe
1 : 2	Mg > Co > Ni > Cu > Fe
1 : 5	Mg > Fe > Cu > Ni > Co
2 : 3	Mg > Co > Ni > Fe > Cu

Metformin HCl is freely soluble in water and is practically insoluble in acetone, ether and chloroform. It is the only oral antidiabetic approved by FDA and EMEA for children above 10 years of age.

The structure of biguanide in solution is

Table 3: Trends in stability constant with respect to M : L ratio

S.No	Metals	Ratios
1	Ni	1: 5 > 1 : 1 > 1: 2 > 2 : 3
2	Co	1: 5 > 1 : 2 > 1 : 1 > 2 : 3
3	Mg	1: 5 > 1 : 2 > 1 : 1 > 2 : 3
4	Fe	1: 5 > 1 : 2 > 1 : 1 > 2 : 3
5	Cu	1: 5 > 1 : 1 > 1 : 2 > 2 : 3

pH-dependent because of the strong basic character of the polar guanidine moiety. This results in its metal complexes also being pH –dependent in solution. Like biguanide, metformin (1,1- dimethyl biguanide, MET) exists in various forms: diprotonated $(H_2MET)^{2+}$ in strong acidic solution, monoprotonated $(HMET)^{+}$ in weak acid, MET in neutral and deprotonated $(MET)^{-}$ in strong alkali solution[8]

In the present work, a pH-metric investigation of metal-ligand stability constant has been studied, the metal-ligand ratio was 1 : 1 , 1 : 2, 1 : 5 & 2 :3 , the stability constant values are given in table No.1. The analysis of results indicate following trends.

The results indicate that Mg is having maximum stability constant as compared to other metals except 1 : 1 complexes in which Ni is having maximum stability. The lowest stability is observed in case of 1 : 1 & 1 : 2 for Fe and in the case of 1 : 5 & 2 : 3,The lowest is for Co & Cu respectively. The trends are shown in table 2 .

When the stability constants are arranged according to their metal to ligand ratio we observed that Ni and Cu is having same trends where as Co, Mg and Fe is showing similar trends hence we can divide this into two groups. The trends are shown in table No.3.

The high values of metal-ligand complexes between Fe and boric acid are also observed by earlier researcher.[9] The higher values for stability constant of Ni with cysteine & Schiff base is also reported by Fatima S. M. Hassan [10].

The difference between above work and our work is that we have selected medicinal drug metformin HCl and the ionic strength was mentioned by using KNO_3. The stability constant depends on experimental condition, nature of ligand and nature of metal atom. The order obtained can be correlated with atomic size / ionic size of metal, its capacity to accept a lone pair of electron and availability of empty **d** orbitals. In all cases we observe that when ligand is five times more than metal, the stability is more. This indicates that at higher concentration of ligand more laible complexes are formed. The lowest stability for all metal complexes observed in 2 : 3 ratio, which indicate insufficient concentration of ligand.

The ligand metformin has one free primary amino group and two terminal =NH group. Hence the complex formation capacity of this drug is much more. From this discussion, we conclude that as the ligand concentration is increased stability is increased. Secondly compaired to transition metal metformin interact more with Mg^{2+} ion. This interaction can be attributed to electrostatic interaction or polar interaction rather than covalent or co-ordinate interactions.

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REFERENCES

1. N.G.Palaskar, Sanjay Ubale, Mazhar Farooqui, Milind Ubale, Sandeep Kotharkar, *Asian J. Chem*. **14**(2): 1086-1088 (2002).
2. Farooque Basheer Ansari, Fauzia Mansoor, S. H. Quadri, *Int. J. Chem. Sci.:* **6**(**2**): 873-877 (2008).
3. Ayesha Durrani, Mazhar Farooqui, Ahmed Zaheer, *Transation of the SAEST* **41**: 28-29 (2006).
4. Magre B. K. , Farooqui M. N., Ubale M.B., *Nat Acad Sci Lat*., **31**(11-12): 353-355 (2008).
5. V.T. Chaudhari, Mazhar Farooqui, *J. Indian Chem. Soc*. **86**: 166-167 (2009).

6. Ayesha Javaid, Ruqaiya Hasan, Asma Zaiband, Shama Masroor, *Pak. J. Pharma Sci.,* **20**(**1**): 67-71 (2007).
7. Bentefit, G. Morgant, B. Viossat, S. Leonce, N.Guilband, A. Pierre, G. Atassi and Nguyen Huy. Dung., *J. of Inorganic Bio-Chemistry,* **68**(**1**): 53-59 (1997).
8. Miaoli Zhu, Liping Lu, Pin Yang and Xianglin Jin*, Acta Cryst* **E58**: 272-274 (2002).
9. G. N. Mukherjee and Ansuman Das , *Proc Indian Acad Sci*. (*Chem Sci*.), **114**(3): 163-174 (2002).
10. Fatma S. M. Hassan *, The Arabian J. Sci. and Engg*., 30, (**IA**) (2005).