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Effect of Methyldopa an antihypertensive medicine, on bioavailability of some metals of biological interest

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Abstract: - Hypertension has become a common phenomenon. Primary factors are fast going life and tensions to keep pace with it. All these factors accounts towards heavy Antihypertensive drugs usage worldwide. The excess intake of these drugs may cause many abnormalities. Methyldopa is an antihypertensive drug, and shows strong interaction with metals. Interactions of methyldopa with some biologically important metals i.e. iron, copper, cobalt, nickel and zinc was studied by potentiometric method. Theoretical stability constant values were calculated using potentiometric titration curves and were refined through computer program "BEST". The stoichiometry of the studied complexes was found ML_2 through potentiometric method. $Log\beta_2$ values were obtained 10.0, 8.10, 8.02, 10.0, 10.0 and 9.50 for Fe(II)-Methyldopa, Fe(III)-Methyldopa, Cu(II)-Methyldopa, Co(II)-Methyldopa, Ni(II)-Methyldopa and Zn(II)-Methyldopa complexes respectively.

Keywords: Potentiometric Titrations, Stability Constant, Metals, Methyldopa.

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Introduction:

Metals play a vital role in a living system. It has been found that the activity of the biometals is very often attained through the formation of complexes with different bioligands, where the thermodynamic and kinetic properties of the complexes govern the mode of biological action. The catalytic roles, selectivity and specificity depend significantly on the properties of coordination compounds [1-2].

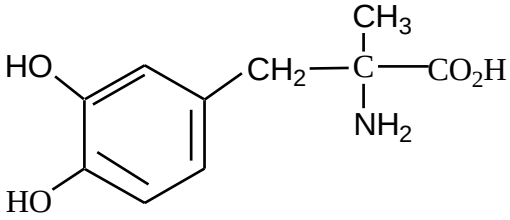
It has been found that some metallo-elements play a significant role in the regulation and control of essential biological processes. Usually they perform the functions of participants, mediators and regulators bound in complexes with proper bioligands [3-4]. Any change in their concentration through complexation, can affect strongly such basic properties as bonding, mobilization and transmembrane transportation as well as the properties of the ligands coordinated with them. In this way it is possible to shift the very delicate balance of the biometals in the organism known as biometal homeostasis, which determines to a great extent their biological functions [5].

On the other hand many substances introduced in the organism as food ingredients and especially as drugs or different biostimulators, represent mono- or polydentate ligands, capable of coordinating some of the biometals, and thus altering their homeostasis. On these grounds at least part of the biological and pharmacological effects of such agents can be understood and used for different purposes [6].

Methyldopa or alpha-methyldopa is a centrally acting anti adrenergic antagonist for antihypertensive medication. It is the most prescribed drug during pregnancy. It is available with brand names Aldomet, Apo-Methyldopa, Dopamet, and Novomedopa etc.

Methyldopa is a white to yellowish white, odorless fine powder, and is soluble in water. It is effective when used alone or with other high blood pressure medications .

It is the L-isomer of alpha-methyldopa, having chemical name levo-3-(3,4-dihydroxyphenyl)-2-methylalanine [7-9]. Its empirical formula is $C_{10}H_{13}NO_4$, with a molecular mass of 211.22, and its structural formula is;



Experimental:

Materials

All the chemicals used were of analytical grade, and employed without further purification. All the volumetric glassware used was

of standard quality. Special care was taken to wash them thoroughly before use. For potentiometric study, CO_2 free water was prepared by boiling distilled deionized water for 10 minutes and then cooled it in airtight flask. All the solutions were prepared in distilled deionized water, freed from CO_2 by boiling for 10-15 minutes.

Fe(III) solution was prepared by dissolving a known amount of $FeCl_3.6H_2O$ in 1M HCl. This solution was standardized by Spectrophotometric method using 1,10-phenanthroline as colouring reagent ($\varepsilon = 1.011x10^4$) at $\lambda = 510nm$ [10] .The acid concentration was determined by titrating against standard NaOH. Fe(II) solution was prepared by dissolving 0.3921g Ferrous ammonium sulphate. 0.01M Cu(II) solution was prepared by dissolving 0.0170g $CuCl_2.2H_2O$ in 100 mL of 0.1 M HCl. A 0.01M solution of Co(II) was prepared by dissolving 0.2379g of $CoCl_2.6H_2O$ in 100 mL 0.1 M HCl. The prepared solution was standardized by EDTA using xylenol orange indicator. A 0.01M solution of Ni(II) was prepared by dissolving 0.2377g of $NiSO_4.6H_2O$ in 100 mL 0.1 M HCl. The solution was standardized by standard EDTA solution using murexide as indicator. 0.01M Zn(II) solution was prepared by dissolving 0.2875g of $ZnSO_4.7H_2O$ in 100 mL 0.1 M HCl. Zinc solution was standardized by EDTA solution using solochrome black indicator . Fresh solution of Methyldopa was prepared each time by dissolving 0.0211g methyldopa in 100 mL of water to make 0.01M solution.

Potentiometric Titration

The potentiometric titration was performed in potentiometric titration cell (Figure 1). Titration of methyldopa was performed in order to compare it with titration curves of methyldopa metal complexes. 20 mL of 0.001M-methyldopa solution was taken, and final volume was made up to 40.0 mL accurately with calibrated pipette. The temperature was controlled by circulating water, through a thermostat, at 25 ^{o}C. Standard base was added in sufficiently small increments of 0.05 mL (with the help of micropipette) and after each increment pH of the reaction mixture was recorded till pH was not affected by further addition of standard NaOH. pH values were plotted against volume of standard NaOH added. For potentiometric titration of Fe(II)-Methyldopa complex, equimolar solutions of both metal and ligand were taken. 20 mL of 0.001 M solution of Fe(II) was mixed with 20 ml of methyldopa solution. This solution was titrated in the potentiometric titration cell. Standard base was added in sufficiently small increments of 0.05mL (with the help of micropipette) and after each increment, pH of the reaction mixture was recorded till pH was not affected by further addition of standard NaOH. pH values were plotted against volume of standard NaOH added. Potentiometric titrations of Fe(III)-Methyldopa, Cu(II)-Methyldopa, Co(II)-Methyldopa, Ni(II)-Methyldopa and Zn(II)-Methyldopa were performed in the same manner like the titration of Fe(II)-Methyldopa.

Stability Constant Determination

Theoretical pH values were calculated for all the complexes. The values of stability constants of all the complexes were computed from computer program BEST, and species distribution curves were also plotted.

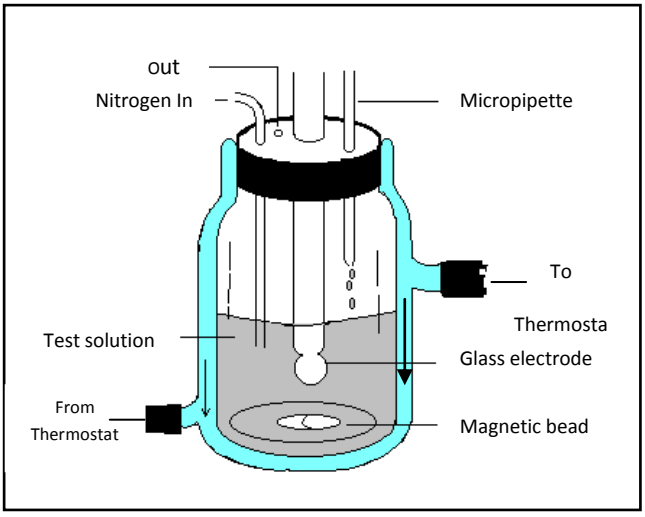


Figure 1: Cell used for potentiometric titration

Results and Discussion:

Complexation of methyldopa with different metals was studied by potentiometric method. The shapes of the potentiometric titration curves were used to study the protonation of the ligand and complexation properties. As a reference, potentiometric titration of Methyldopa was performed initially. The titration curve showed one break, and the pK_a for this curve was found to be 9.30, which is in agreement with the literature value [11] (Figure 2).

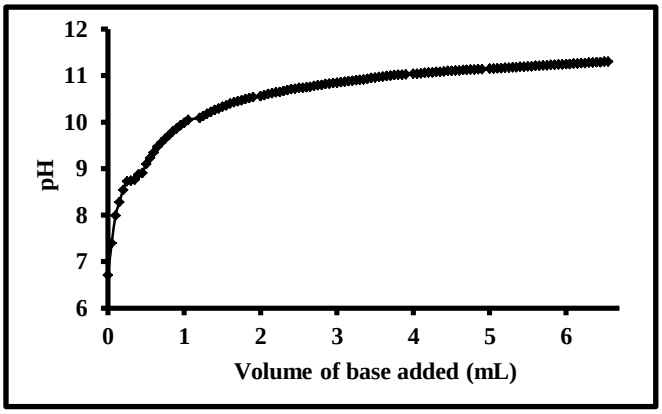


Figure 2: Potentiometric Titration of Methyldopa

Titrations were performed with iron, copper, cobalt, nickel and zinc -methyldopa complexes, in order to find out the stability constants and numbers of species existing in solution.

Titration of Fe(II)-Methyldopa complex in 1:1 metal to ligand ratio was performed. There was a prominant decrease in the pH of the complex, showing that complexation had taken place after the release of proton.The titration curve also shows two depressions near pH 6.0 and 9.0, indicating the formation of two types of species. The first species formed between the pH range of 4-6 . While the second species exists between pH range of 6-9 (Figure 3). The stability constant values for Fe(II)-methyldopa complex were determined from the data of potentiometric titration, using computer program 'BEST'. Theoratical β values were calculated for Fe(II)-Methyldopa complex, from the potentiometric titration curve. An input data file "FOR004.DAT" was written and with the help of various options of the program, obtained σ_{fit} value was refined which was found to be 0.019 ± 0.001. Logβ_1 and logβ_2

values were obtained for Fe(II)-Methyldopa complex by this program (Table 1). Program 'BEST' also calculates the species distribution at different pH of the titration. These results are generally obtained in terms of mole fraction species with respect to pH. Species distribution at different pH was calculated, and finally their diagrame was drawn (Figure 4).

Potentiometric titration of Fe(III)-Methyldopa was performed by taking metal and ligand in 1:1 molar ratio (Figure 3). Depression in the titration curve of complex as compared to the titration curve of ligand was very prominent, which showed a stable complex formation between metal and ligand. The decrease in pH after complex formation suggested that deprotonation of ligand taking place after complex formation. The titration curve showed two prominent breaks near pH 3.5 and 6, suggesting the formation of two types of species. Both species are being formed in enough concentration with high stability (Figure 4, Table 1).

Table 1: Stability constant values of Metal-Methyldopa complexes calculated by "BEST"

S.No	Complex	σ_{fit}	Logβ_1	Logβ_2
1	Fe(II)-Methyldopa	0.019 ± 0.001	7.50	10.0
2	Fe(III)-Methyldopa	0.033 ± 0.001	5.00	8.10
3	Cu(II)- Methyldopa	0.032 ± 0.001	5.00	8.02
4	Co(II)- Methyldopa	0.010 ± 0.001	7.00	10.0
5	Ni(II)- Methyldopa	0.040 ± 0.001	6.04	10.0
6	Zn(II)- Methyldopa	0.018 ± 0.001	7.00	9.50

Titration of Cu(II)-Methyldopa complex in 1:1 metal to ligand ratio was performed. pH decreased after complex formation, suggesting that complexation was taking place after removal of protons from the ligand (Figure 3). Depression in the titration curve of complex as compared to the titration curve of ligand showed a strong complex formation. The titration curve was showing a small twist between pH 4.0 and 5.5, then a second very prominent twist between pH 6-10. It shows that the first species exists in a low concentration with less stability , then the second species is forming with high stability (Figure 4, Table 1).

Titration of Co(II)-Methyldopa complex in 1:1 metal to ligand ratio was performed (Figure 3). There is a small difference present between the pH of ligand and complex, showing a weak complex formation. The titration curve showing that two types of species were forming in very low concentration. The first species was forming between pH 6-8, while the other species was forming between pH 9-10 (Figure 4). The stability constant values for Co(II)-methyldopa complex were determined from the data of potentiometric titration, using computer program 'BEST'.

Titration of Ni(II)-Methyldopa complex in 1:1 metal to ligand ratio was performed. There is less difference between the pH of complex and ligand (Figure 3). It shows a weak complex formation. The titration curve showed the formation of two types of species in vey low concentration. The first species was forming between pH 6-8, while the second species formed between pH 9-10. (Figure 4). The stability constant values for Ni(II)-methyldopa complex were determined from the data of potentiometric titration, using computer program 'BEST'. Logβ_1 and logβ_2 values were obtained for Ni(II)-Methyldopa complex by this program (Table 1). Species distribution at different pH was also calculated by this program, and finally their diagrame was drawn (Figure 4).

Titration of Zn(II)-Methyldopa complex in 1:1 metal to ligand ratio was performed. Titration curve showed a weak complex formation (Figure 3). The titration curve showed the formation of two types of species. One species was formed in low concentration with low stability between pH 6-8. The other species was formed with high stability between pH 8-10 (Figure 4).

The stability constant values for Zn(II)-methyldopa complex were determined from the data of potentiometric titration, using computer program 'BEST'. Logβ_1 and logβ_2 values were obtained for Zn(II)-Mthyldopa complex by this program (Table 1). Species distribution at different pH was also calculated, and finally their diagrame was drawn (Figure 4).

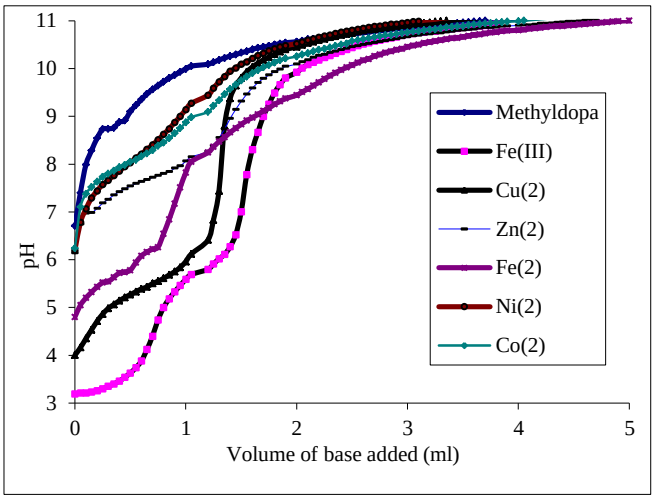


Figure 3: Potentiometric titration curves of Methyldopa metal complexes

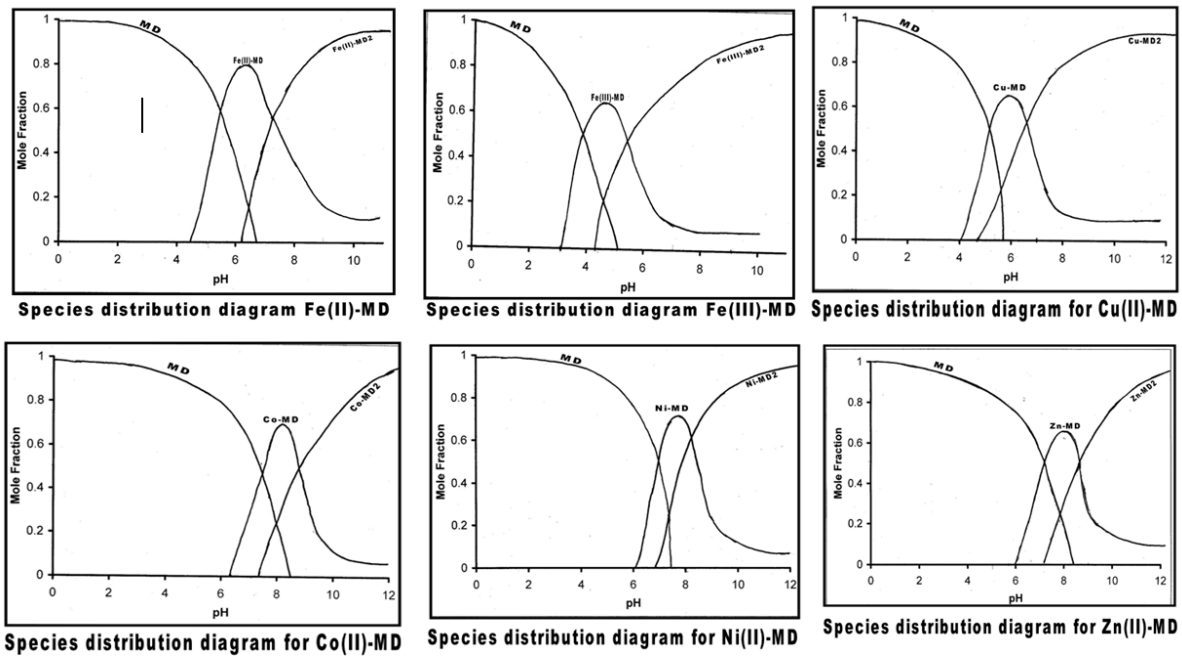


Figure 4: Species Distribution Diagrams of Metal-Methyldopa Complexes

Conclusion:

There may be many interactions of Methyldopa in the human body, but our study was limited to the interaction and complexation of this drug with bioavailable metals. It is a catecholic drug with oxygen as donor atom. Metal complexes of essential elements Iron (Ferrous and Ferric), Copper, Nickle, Cobalt and Zinc are formed with antihypertensive drug α-methyldopa. Stability constant values of these complexes shows strong interaction of this drugs with biologically important metals. This drug does not work as reducing agent. Therefore when ferric reacts with this drug it remain trivalent with log β_1 5.0 and log β_2 8.1. Ferrous on the other hand has high stability than Fe(III) having log β_1 7.5 and log β_2 10.0. All other metals have lower stability constants than ferrous. Therefore continuous use of methyldopa may results in iron deficiency. But if iron is in +3 state then it may not compete for zinc in the system as zinc has higher stability constants than ferric state of iron.This interaction affect on the biological properties of these metals and medicine as well.

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