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CONTENTS OF PART - II

22. Potentiometric Investigation of Complexation of Lisinopril Drugwith Transition Metal Ions in Mixed Solvent Media

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Abstract:

In the present work we investigate the stability constant of Lisinopril hydrochloride drug with transition metal ions Co, Ni, Cu, Zn, and Cd using potentiometric titration technique in 20%(v/v) ethanol-water mixture at 27 °C temperature and at an ionic strength of 0.1M $NaClO_4$.{Metal to ligand ratio=1:5& 1:1}The method of Calvin and Bjerrum as adopted by Irving and Rossotti has been employed to determine proton ligand (pKa) and metal-ligand stability constant (logK) values. It is observed that a transition metal ion forms 1:1 and 1:2 complexes.

Keywords : Stability Constant, transition metal ions, Lisinopril drug, Potentiometric.

Introduction

Metal complexes are widely used in various fields, such as biological processes pharmaceuticals, separation techniques, analytical processes etc.To understand the complex formation ability of the ligands and the activity of complexes, it is essential to have the knowledge about solution equilibria involved in the reactions. The extent to which the ligand binds to metal ions is normally expressed in terms of stability. Potentiometric titration is accepted as a powerfuland simple electro analytical technique for determination of stability constants. Most of thed-block elements form complexes. There are different kinds of ligand used for complexation. For the present investigation, we selectedLisinopril hydrochloride (2S)-1-[(2S)-6-amino-2-{[(1S)-1-carboxy-3 phenylpropyl] amino}hexanoyl] pyrrolidine-2-carboxylic acid is an angiotension-converting enzyme (ACE) inhibitor), the enzyme responsible for the conversion of angiotensin I (ATI) to angiotensin II (ATII). It is antihypertensive agent and cardiotonic agent. It is used for the treatment of hypertension and symptomatic congestive heart failure. It may be used to slow the progression of renal disease in hypertensive patients with diabetes mellitus. Historically, lisinopril

was the third ACE inhibitor (after captopril and enalapril) and was introduced into therapy in the early 1990.

The physical properties of medicinal drug Lisinopril Hydrochloride are shown below:

Sr .No.	Physical property	Value
1	Molecular weight	441.98 g/mol
2	Phase	Solid (at STP)
3	Melting point	148 °C
4	Boiling Point	666.4 °C
5	Density	1.251 g/cm^3
6	Colour	White
7	Solubility	Soluble in water

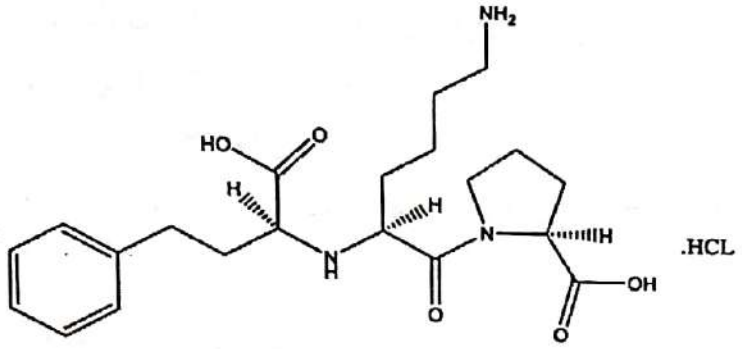

Figure 1: Lisinopril hydrochloride(molecular formula $C_{21}H_{32}N_3O_5Cl$)

After a review of literature survey and in continuation of our earlier work with complexation of medicinal drugs[1-22], we have carried out a solution study on the complexationof Lisinoprilhydrochloride drug with transition metal ions Co^{2+}, Ni^{2+}, Cu^{2+}, Zn^{2+} and Cd^{2+}using pH metrically in 20% (v/v)ethanol-water mixture at constant ionic strength of 0.1M $NaClO_4$.

Experimental Section: I. Materials and Solution. The ligand Lisinopril hydrochloride is soluble in 20% (v/v) ethanol-water mixture. NaOH, $NaClO_4$,$HClO_4$ and metal salts were of AR grade.The solutions used in the pH metric 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 $HClO_4$. The metal salt solutions were also standardized using EDTA titration. All the measurements were made at 27 ^{0}Cin 20%(V/V) ethanol-water mixture at constant ionic strength of 0.1M $NaClO_4$.The thermostat model SL-131 was used to maintain the temperature constant. The pH measurement were 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 .

II. Potentiometric procedure. For evaluating the protonation constant of the ligand and the formation constant of the complexes in 20 %(v/v) ethanol-water mixture with different metal ions we prepare the following sets of solutions.

(A) $HClO_4$ (A)

(B) $HClO_4$+Lisinopril (A+ L)

(C) $HClO_4$+ Lisinopril + Metal (A+ L+ M)

The above mentioned sets prepared by keeping M: Lratio, the concentration of perchloric acid and sodium perchlorate (0.1M) were kept constant for all sets. The volume of every mixture was made up to 50ml with double distilled water and the reaction solution were potentiometerically titrated against the standard alkali at temperature27 ^{0}C.

Table 1. Proton-ligand and metal-ligand stability constant of Lisinopril drugin 20 % (v/v) ethanol-water medium (Metal to ligand ratio=1:5)

pKa	logK	Co^{2+}	Ni^{2+}	Cu^{2+}	Zn^{2+}	Cd^{2+}
pK_1= 3.3231	$logK_1$	4.4357	4.7358	7.7686	3.4064	3.8847
pK_2 =7.5482	$logK_2$	3.1107	---	4.5350	2.8612	---
	$log\beta$	7.5464	4.7358	12.303	6.2676	3.8847

Table 2. Proton-ligand and metal-ligand stability constant of Lisinoprildrugin 20 % (v/v) ethanol-water medium (Metal to ligand ratio=1:1)

pKa	logK	Co^{2+}	Ni^{2+}	Cu^{2+}	Zn^{2+}	Cd^{2+}
pK_1= 3.3231	$logK_1$	3.8393	5.0993	6.7643	4.1102	3.7549
pK_2 =7.5482	$logK_2$	---	---	---	---	---
	$log\,\beta$	3.8393	5.0993	6.7643	4.1102	3.7549

Result and Discussion

Lisinopril hydrochlorideis antihypertensive drug having chemical formula $C_{21}H_{32}N_3O_5C$ Its structural form shows two -COOH groups, one primary amine and one secondary amin groups. Apart from this it also contains one ketonic group and one nitrogen in pentacyclic rin Out of all these functional groups, primary amine and -COOH groups are dominating because th

are present in free state. This result into two pKa values 3.3231 and 7.5482. The pKa in the acidic range might be due to -COOH group and pKa in the basic range is due to presence of $-NH_2$ group. The low value of pk_2 might be because of $-NH_2$ group attached to long alkyl chain. The secondary amine and ketonic group does not participate in the process of protonation. This may be due to bulky group/ring present near to it and may be due to steric hindrance. The proton ligand stability constant (pKa) of Lisinopril drug is determined by point wise calculation method as suggested by Irving andRossoti. Metal ligand stability constant (logK) transition metal ions with Lisinopril drug (ligand) were calculated by point wise and half integral method of Calvin and Bjerrum as adopted by Irving and Rossotti has been employed.For the present investigation we have studied the stability constant of divalent transition metal ions. Since we got $\bar{n}_A$ 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 metal complexes was as follows:

$Cu^{2+} > Co^{2+} > Zn^{2+} > Ni^{2+} > Cd^{2+}$ {*Metal to ligand ratio=1:5*}**and**

$Cu^{2+} > Ni^{2+} > Zn^{2+} > Co^{2+} > Cd^{2+}$ {*Metal to ligand ratio=1:1*}

The above stabilities of metal complexes with ligand are similar to the observations made by several research workers and are in accordance with Irving and Williams order. In the present metal ions, Copper has available d orbital with low energy hence show maximum stability whereas it decreases in zinc complexes due to the lack of vacant d orbital having low energy. This natural order is particularly valid for nitrogen and oxygen donor ligands, irrespective of nature of ligands. Similarly extra stability of Cu (II) complex is attributed to unique electronic configuration of Cu (II) and John-Teller effect. The low value of logK for Cd (II) indicates that their complexes may not be planar.

Conclusion

In the present investigation, stability constants of transition metal complexes with Lisinopril Hydrochloride drug at 1:5 and 1:1 metal-ligand ratio were studied at 27 ^{0}C. It is found that stability constant of transition metal complexes when metal-ligand ratio 1:5 is greater than those of transition metal complexes when metal-ligand ratio is 1:1. This indicates that at higher concentration of ligand more stable complexes are formed.

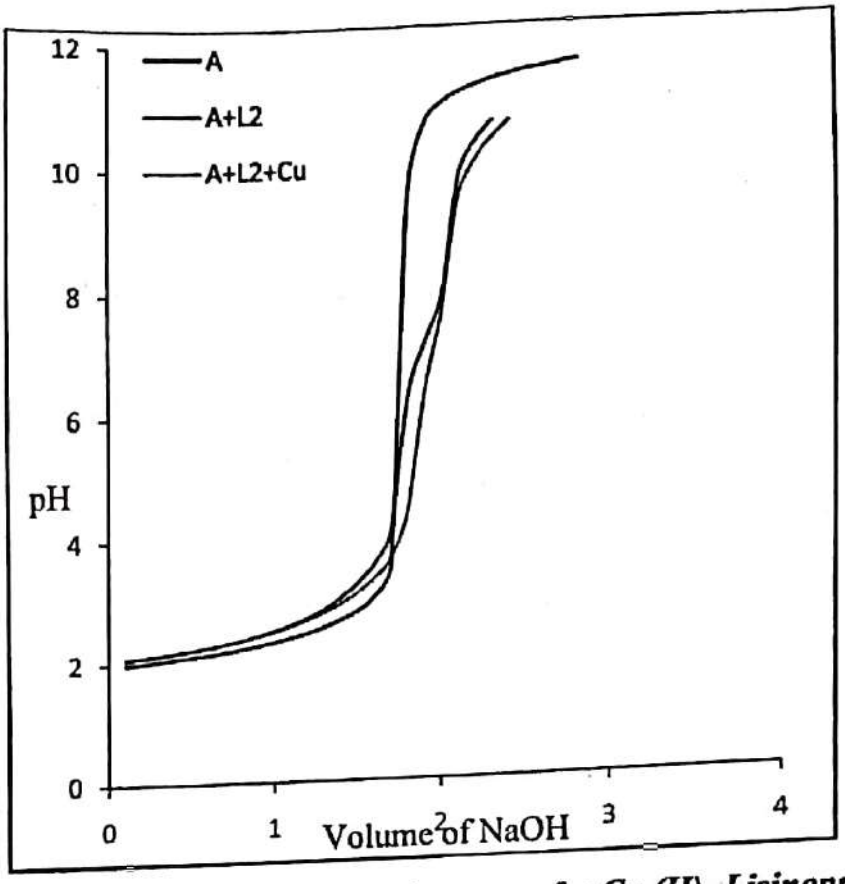

Figure 2: The pH metric titration curve for Cu (II)- Lisinopril

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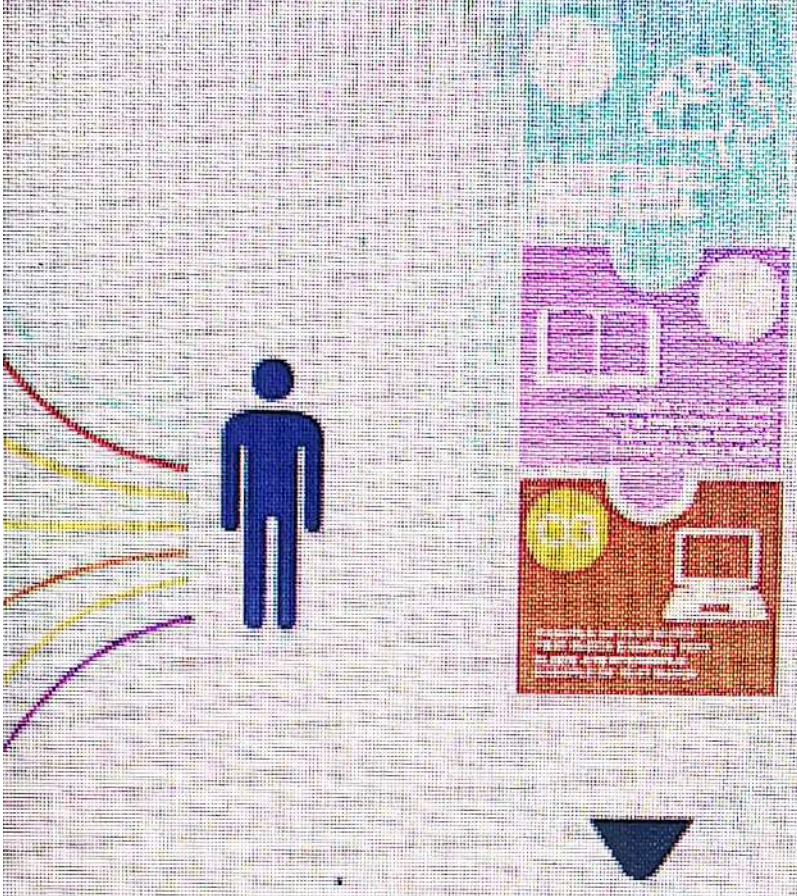

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