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COMPLEXATION OF LISINOPRIL DRUG WITH ALKALINE EARTH AND TRANSITION METAL IONS IN MIXED SOLVENT MEDIA

RAMESH WARE[1], M.A. SAKHARE[2], SHAUKAT PATEL[3], SHAILENDRASINGH THAKUR*[1]

[1]Department of Chemistry, Milliya College, Beed. [2]Department of Chemistry, Balbhim College, Beed. [3]Department of Chemistry, Adarsh College, Omerga. Email: svthakur1972@gmail.com

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ABSTRACT

Objective: To investigate the stability constant of Lisinopril hydrochloride drug with alkaline earth metal ions Mg(II), Ca(II) and transition metal ions Fe(III), Cu(II) using potentiometric titration technique in 20%(v/v) ethanol-water mixture at 27 °C temperature and at an ionic strength of 0.1M $NaClO_4$.

Materials and Methods: 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. 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 pH measurement were made using a digital pH meter.

Results: 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 alkaline earth metal & transition metal ion forms 1:1 and 1:2 complexes. The order of stability constants for these metal complexes was as: **Fe^{3+} > Cu^{2+} > Mg^{2+} > Ca^{2+}**

Conclusion: The stability constants of trivalent Fe show maximum stability whereas divalent Ca shows minimum stability.

Keywords: - Stability Constant, alkaline earth metal, transition metal, Lisinopril drug.

INTRODUCTION

Potentiometric titration is accepted as a powerful and simple electro analytical technique for determination of stability constants. Most of the s-block and d-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. There are different kinds of ligand used for complexation. In the present investigation, we selected Lisinopril 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.

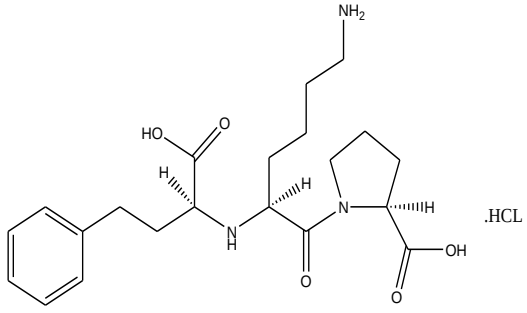

Fig1: ***Lisinopril hydrochloride (molecular formula $C_{21}H_{32}N_3O_5Cl$)***

After a review of literature survey and in continuation of our earlier work with complexation of medicinal drugs[1-10], we have carried out a solution study on the complexation of Lisinopril drug with alkaline earth metal ions Mg^{2+}, Ca^{2+} and transition metal ions Fe^{3+}, Cu^{2+} using pH metrically in 20% (v/v) ethanol-water mixture at constant ionic strength of 0.1M $NaClO_4$.

MATERIALS AND METHODS

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}C in 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 .

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: L ratio, 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 temperature 27 ^{0}C.

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

pKa	logK	Fe^{3+}	Cu^{2+}	Mg^{2+}	Ca^{2+}
pK_1= 3.3231	$logK_1$	8.2393	6.7643	3.1102	2.6549
pK_2 =7.5482	$logK_2$	- - -	- - -	- - -	- - -
	$log\ \beta$	8.2393	6.7643	3.1102	2.6549

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

pKa	logK	Fe^{3+}	Cu^{2+}	Mg^{2+}	Ca^{2+}
pK_1= 3.3231	$logK_1$	9.1369	7.7686	2.8302	2.9848
pK_2 = 7.5482	$logK_2$	7.0314	4.535	2.6612	---
	$log\beta$	16.1683	12.3036	5.4914	2.9848

RESULT AND DISCUSSION

Lisinopril hydrochloride is antihypertensive drug having chemical formula $C_{21}H_{32}N_3O_5Cl$. Its structural form shows two -COOH groups, one primary amine and one secondary amine groups. Apart from this it also contains one ketonic group and one nitrogen in pentacyclic ring. Out of all these functional groups, primary amine and -COOH groups are dominating because they 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 and Rossoti. Metal ligand stability constant (logK) of alkaline earth metal ions and 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. The order of stability constants for these metal complexes was as follows:

$Fe^{3+} > Cu^{2+} > Mg^{2+} > Ca^{2+}$ {*Metal to ligand ratio=1:5*} and
$Fe^{3+} > Cu^{2+} > Mg^{2+} > Ca^{2+}$ {*Metal to ligand ratio=1:1*}

CONCLUSION

In the present investigation, stability constants of alkaline earth metal and 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 metal complexes when metal-ligand ratio 1:5 is greater than those of metal complexes when metal-ligand ratio is 1:1. **This indicates that at higher concentration of ligand more stable complexes are formed.** The stability constants of trivalent Fe show maximum stability whereas divalent Ca shows minimum stability.

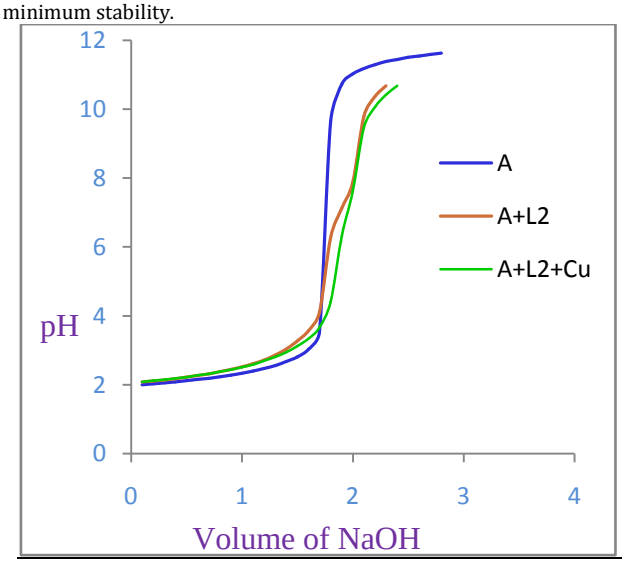

Fig2: The pH metric titration curve for Cu (II)- Lisinopril

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