Formation of Alkaline Earth and Transition Metal Complexes with Efavirenz Drug in Ethanol-Water Media

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Abstract:

The stability constant of Efavirenz drug with alkaline earth metal ions Mg(II), Ca(II) and transition metal ions Fe(III), Cu(II) were investigate using pH metric 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 constants (log K) 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+}**

Keywords: Stability Constant, alkaline earth metal, transition metal, Efavirenz, pH metry.

Introduction:

Coordination compound containing one metal and one ligand is known as binary complex. Metal complexes with various ligand shows their contribution in the field of pollution control, medicine, industries, analytical chemistry, pharmacology, pathology biochemistry, metallurgy etc. The stability of metal complexes with medicinal drugs plays a major role in the biological and chemical activity. 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. 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. For the present investigation, we selected Efavirenz drug. Efavirenz is a non-nucleoside reverse transcriptase inhibitor (NNRTI) and is used as a part of highly active anti-retroviral therapy (HAART) for the treatment of human immunodeficiency virus (HIV-1). Both nucleoside and non-nucleoside RTIs inhibit the same target. The reverse transcriptase enzyme transcribes viral RNA into DNA. Unlike nucleoside RTIs, which bind at the enzyme's active site, NNRTIs bind within a pocket, termed the NNRTI pocket. Efavirenz is not effective against HIV-2, as the pocket of the HIV-2 reverse transcriptase has a different structure, which confers intrinsic resistance to the NNRTI class. It is never used alone and is always given in combination with other drugs. It is a white to slightly pink crystalline powder and it is soluble in various organic solvents but practically insoluble in water. It is chemically (4*S*)-6-chloro -(cyclopropylethynyl)-1, 4-dihydro-4- (trifluoromethyl) - 2H-3, 1-benzoxazin-2-one.Efavirenz activity is mediated predominantly by non-competitive inhibition of HIV-1 RT. The toxicity of EFV is central nervous system (CNS) side-effects. The EFV-associated CNS side-effects typically resolve after two to four weeks. However, in some cases they can persist for months or not resolve at all. Thus, EFV should be avoided in patients with a history of psychiatric illness.

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 Efavirenz drug with 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:

Efavirenz drug 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) $HClO_4$+ Efavirenz (A+ L)

(C) $HClO_4$+ Efavirenz + 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 50 ml with double distilled water and the reaction solution were pH meterically titrated against the standard alkali at temperature 27 ^{0}C.

Result and Discussion:

Drug Efavirenz is non-nucleoside, reverse transcriptase inhibitor. The structural of drug shows one secondary amine group and one carbonyl group. The drug efavirenz gives only one pKa value. The protonation constant of drug obtained under experimental condition is 10.7206. This pKa value can be assigned to secondary amine group in the basic range. The proton ligand stability constant (pKa) of Efavirenz drug is determined by point wise calculation method as suggested by Irving and Rossoti. Metal ligand stability constant (logK) transition metal ions with Efavirenz 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 Efavirenz 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.

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

pKa	logK	Fe^{3+}	Cu^{2+}	Mg^{2+}	Ca^{2+}
10.7206	$logK_1$	11.2450	7.0282	3.7182	2.8045
	$logK_2$	11.0221	6.8544	2.9312	2.4620
	log β	22.2671	13.8826	6.6494	5.2665

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

pKa	logK	Fe^{3+}	Cu^{2+}	Mg^{2+}	Ca^{2+}
10.7206	$logK_1$	12.0561	8.2540	3.9535	2.9732
	$logK_2$	- - - -	- - - -	- - - -	- - - -
	log β	12.0561	8.2540	3.9535	2.9732

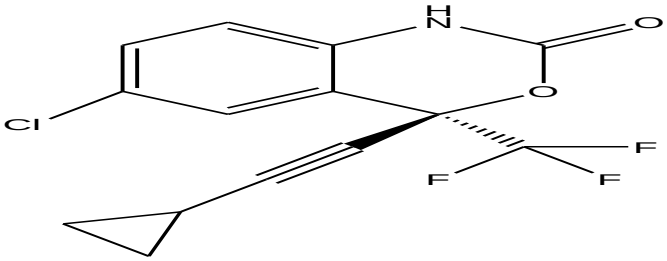

Figure 1: Efavirenz (molecular formula is $C_{14}H_9ClF_3NO_2$)

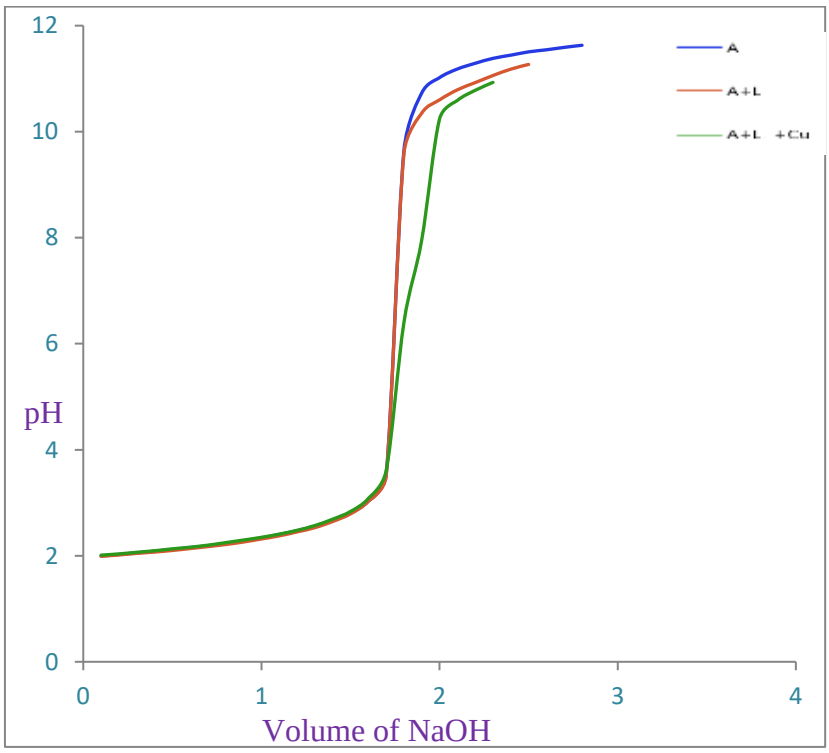

Figure 2: The pH metric titration curve for Cu (II)- Efavirenz

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