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Potentiometric studies on the stability constants of some drugs with copper (II), chromium (III) AND calcium (II) metal ions in 80% (V/V) ethanol-water medium

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Abstract
The stability constants for the Copper (II), Chromium (III) and Calcium (II) ions with drugs such as dapsone, furosemide and ciprofloxacine have been studied using pH-measurements in 80% (v/v) ethanol-water medium. The value of proton-ligand stability constants and metal- ligand stability constants are calculated. The stability of the chromium (III) complexes is greater than that of copper (II) and calcium (II) complexes.

Keywords: Proton, ligand, stability constant, copper, chromium, calcium complexes

Introduction
Majority of diseases are caused by microorganism [1]. It is necessary to kill and remove the microorganism from daily need articles and foodstuff. When such organism enters in a body, they multiply fastly, weakened the body defense factor and causes a disease. A substance used for cure of an ailment or alleviation of symptoms is called drug or medicine. Several types of drugs [2] such as antileprotic, high-ceiling diuretics, antibacterial etc. and their metal complexes have special importance in bio-chemical systems. Some metal ions present in biological fluids e.g. copper, chromium and calcium are energy sources of life. The protonation study of drugs [3] in aqueous medium is already done by several peoples. Little information is known about the stability constant of drug and metal complexes in non-aqueous and ethanol-water mixed solvents, with respect to their protonation and stability constants or solvation properties [2,3,4] *In vivo* reactions were considered to take place in aqueous medium. Recently it has been observed that solvent such as ethanol is a good media for *in vivo* reaction [5]. The study on proton-ligand and metal ligand stability constants of drugs complexes in ethanol-water medium will useful for understanding of drugs intake in living organisms.
In present work, the proton ligand stability constant and stability constant of drugs with copper (II), chromium (III) and calcium (II) metals have been studied potentiometrically in 80% (v/v) ethanol-water mixture.

Materials and Methods
Drugs samples of dapsone, furosemide and ciprofloxacine in pure form were obtained from pharma industries and used as received. Ethanol was purified as described in literature [6] Double distilled water was used for the preparation of both ethanol-water mixtures and stock solution of drugs.
All chemicals used were AR grade. $NaClO_4$ (0.1M) and NaOH solution was prepared in carbon dioxide free double distilled water. $HClO_4$ Reidal (Germany) was used for the preparation of the stock solutions of copper (II), chromium (III) and calcium (II) to prevent hydrolysis.
All pH metric titrations were carried out at 27 °C in an inert atmosphere by bubbling oxygen free nitrogen gas through an assembly containing the electrodes in order to prevent atmospheric oxidation using carbonate free NaOH. The pH of the solution measured using.
Elico model L1-120 Digital pH meter and Elico (pH-13) type Ek-62A glass electrode. Following three solutions were titrated separately against standard carbonate free NaOH.
1. Free $HClO_4$
2. Free $HClO_4$ + Ligand (drug)
3. 3. Free $HClO_4$ + Ligand (drug) + Metal ion

For the determination of the proton-ligand stability constants, stock solutions of free perchloric acid, drug and sodium perchlorate were taken in a 50 mL volumetric flask, followed by ethanol to obtain solutions of the desired concentration and percentage of ethanol. The contents were diluted upto the mark. Aliquots of 50 mL were transferred to the pH metric cell and titrated against standard NaOH solution.

For the determination of metal-ligand stability constants of drug with metal ions suitable amount of metal ion, drug and perchloric acid stock solutions was taken into pH metric cell and titrated against NaOH solution until a precipitate was just observed in titration cell. At this point titration was stopped. During each titration ionic strength of solution was maintained by adding 0.1 M NaClO4. pH meter readings were after taken every fixed interval until stable values were obtained. pH meter readings in 80% (v/v) ethanol-water were corrected [7].

Proton-ligand stability constant and metal-ligand stability constant of drugs-metal ion complexes were calculated with the help of computational programme, to minimize the standard deviation.

Results and Discussion

The proton-ligand stability constants of dapsone, furosemide and ciprofloxacine and the metal-liagnd stability constants of their copper (II), chromium (III) and calcium (II) determined in 80% (v/v) ethanol - water mixture at 27 °C and ionic strength μ = 0.1 M (NaClO4). are given in Table-1.

Table 1: Proton ligand and metal – ligand stability constant of Cu (II), Cr (II), Ca (II)

Drugs	pK			Metal ions		
	pK_1	pK_2		Cu^{+2}	Cr^{+3}	Ca^{+2}
Dapsone	3.1237	-	log k_1	5.2139	5.9640	-
			log k_2	-	-	-
			log β	5.2139	5.9640	-
Furosemide	5.6315	-	log k_1	2.8575	2.8937	2.8400
			log k_2	-	-	-
			log β	2.8575	2.8937	2.8400
Ciprofloxacine	8.0016	9.3549	log k_1	-	10.1320	5.4170
			log k_2	-	-	-
			log β	-	10.1320	5.4170

The basicities of the ligand have been measured in terms of their proton-ligand stability constant. The determination of proton-ligand stability constant of the ligand is a prerequisite for the evaluation of metal-ligand stability constant. Hence, proton-ligand stability constants of the ligands have been determined pH metric titration technique [8].

The titration curve for dapsone show buffer region in pH < 3, furosemide pH < 6 and ciprofloxacine pH > 7. The release of proton in the lower buffer region indicate the dissociation of proton from protonated nitrogen atom. From the acid and ligand titration curves the value of nA have been calculated using and further by computational programme [10].

The n A values range between 0.1 and 1 for dapsone and furosemide indicating the liberation of one proton and 0.1 and 2 for ciprofloxacine indicating the liberation of two proton. The pK value for dapsone, furosemide and ciprofloxacine was determined pH meterically. The dissociation of proton from carboxylic group for furosemide as shown below.

The pK value of dapsone is found to be lower as compared to the pK value of other drugs. The lower pK value of dapsone is explained on the basis of the more electronegative oxygen atom of SO_2 attached to ring having a loan pair of electron, increases the electron density of $–NH_2$ which affect the deprotonation of NH_2 group, therefore dapsone is weak basic [9].

The pK value of furosemide is slightly greater than dapsone. The reason is that in furosemide the more electronegative oxygen atom in pyrrole ring having loan pair of electrons, increases the electron density of NH group which reduce the deprotonation of -NH group and makes the ligand more basic than dapsone.

The pK values of ciprofloxacine are found to be greater than dapsone and furosemide. This can be explained on the basis of the strong + mesomeric effect [14] of oxygen atom with its loan pair of electrons. This trend in basicity can be attributed to the intrinsic nature of the basic site and intermolecular hydrogen bonding Thus the order of pK values of the ligands as follow, shows the good agreement with pK value in aqueous medium [10-14].

Ciprofloxacine > Furosemide > Dapsone

pH decreases, if a neutral metal ion solution is added to the ligand solution. The metal-ligand titration curve lies below the pure ligand titration curve. The pH of complex formation is much below than the pH of metal ion hydrolysis. These features of the pH metric studies confirm the formation of complexes by all the metal ions with drugs.

The metal ligand formation curve data for dapsone, furosemide and ciprofloxacine with copper (II), chromium (III) and calcium (II) indicates that the in values range between 0.2 to 0.8. This suggests that metal ions form 1:1 complex [15] with drugs in solution. Study of log k value is evaluated by the computational technique are in good agreement with each binary formation constants so obtained are presented in Tabled. The order of log k 1 > log(k) 2 is commonly observed. The reason is statistical effect, statistically coordination of a second molecule is difficult when compared to the first due to availability of a smaller number of coordinating sites on the metal ion for the second ligand. The standard deviation for various metal-ligand system is within 0.036.

The ligand dapsone, furosemide and ciprofloxacine contain different coordinating sites. The release of proton in the pH range of above ligands in the present investigation indicate that -OH group is participating in bonding with metal ion. It confirmed that these ligand act as oxygen donors. The persual of the stability data reveals that the overall stabilities with respect to ligand lie in the order in accordance with

their relative basicities are shown below
Ciprofloxacine > Furosemide > Dapsone have proposed a relation between the stability of the complexes and basicity of the ligand by the equation [15].

Logk = a pK + b

The relation graph shows a straight line and the value of slope should be unity for a series of closely related ligand. In the present study such relationship does not exists since the drugs used are of diverse in nature.
The stability constant of metal-ligands such as dapsone, furosemide and ciprofloxacine show the good agreement with Irving-William order of stability constant [16].
Ca (II) < Cu (II) < Cr (III).
The comparison between the stability constant of Ca (II) and Cu (II) with ligands, indicate that the weakly basic copper [9] forms stronger complex than strongly basic calcium. It suggests that strength of bonding in these complexes depends on the ability of the metal to form homopolar bond between the metal and ligand. Another reason for the higher stability constant of copper is that, copper has single 'S' electron outside the filled third shell. The filled 'd' electrons are involved in metallic bonding. This factor too much more noble character of copper, to make compounds more covalent [17] Cu^{+2} greatest lattice and solvation energies, hence higher stability constant for Cu^{+2} ion is observed.
Furosemide and ciprofloxacine interact with metal ions Cu(II) and Cr(III) form normal (ML) and Bis binary (ML_2) complexes,[18,19] These ligands form complexes with Cu(II) and Cr(III) due formation stable five membered chelate ring, but observed that Cr(III) form more stable five membered ring with these ligand than Cu(Pi) because of higher charge on metal ion and small size [9].
The study shows that Ca_2 form complex with furosemide and ciprofloxacine but not with dapsone. The reason is calcium is strongly basic metal forming weakest chelates. This suggest that strength of bonding in these chelates depends on the ability of the metal to form the homopolar bonds between the metal and ligand [9].
Dapsone form stable complexes with Cu (II) and Cr (III) but the complex with Cr (III) is more stable than Cu (II), because of higher on metal and small size.

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