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Competition of Chromium on Iron binding sites in the biological system

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ABSTRACT
Hexavalent chromium is mutagenic and neurotoxic. Trivalent Chromium is involved in the enzymes of glucose metabolism. Chromium is generally found in +3 oxidation state and sometimes it competes for the binding sites of iron in the biological system, when the concentration of chromium exceeds above the normal, it inhibits the absorption of iron and iron deficiency leads diseases such as anemia, tinnitus and depression. Salicylicdhydroxamic acid a hydroxamate type siderophore is used as a drug in the chelation therapy of iron overload patients. The complex formation of Cr(III) and Fe(III) with salicyclic hydroxamate were studied potentiometrically at different temperatures and data was subjected to computer programs. The stability constant (log beta values and thermodynamic stabilities were calculated. It was found that salicyclic hydroxamate forms 1:1 complex at pH 3 and 1:2 complex at pH 4 with Cr(III) and Fe(III), respectively. The stability constant (Log beta and thermodynamic stabilities of Cr(III) Salicyclic hydroxamate complexes are close to Fe(III) Salicyclic hydroxamate complexes. It was observed from the stability constant values that after chelating therapy the concentration of chromium become low and deficiency symptoms appear resulting diabetes.

Keywords: Salicyclic hydroxamic acid, iron overload, stability constants

1. INTRODUCTION
Chromium is an essential element in the physiological system. It is involved in carbohydrate, lipid and protein metabolism. It plays an important role in serum cholesterol hemostasis[1]. It has been proposed that chromium forms essential part of the glucose tolerance factor which together with insulin is responsible for controlling the clearance of glucose from the bloodstream[2]. Bovine colostrums contain a biologically active low molecular weight chromium binding substance. It contains aspartic acid, glutamic acid, glycine and cysteine[3]. The compounds of Cr(VI) have hepatotoxic, nephrotoxic, mutagenic and carcinogenic effects[4]. Among trace metals iron is a essential nutrient for micro organism as well as for other organisms because of its varied functions in biological redox process[5,6]. But iron can be toxic when in excess. Iron can increase the capacity of transferrin and ferritin. This condition is known as iron overload[7]. There are many natural mechanism for solubilization or removal of iron, for example, the microorganism utilize a well define iron acquisition strategy which includes the production of low molecular weight chelating agents called siderophores to solubilze and transport ferric ions in aqueous medium[8]. These siderophores are better chelators for Fe(III) than Fe(II). The stability contants for the ferric siderophore complexes are extremely high (Kf= 10^{36} -10^{55}), with Fe(II) it is very low (Kf=10^{8})[9,10]. For the treatment of iron overload the salicylhydroxamate appear to be more selective as its stability constant for Fe(III) complex is several orders of magnitude greater than those for other useful metal ions complexes. Desferrioxamine mesylate a linear trihyroxamic acid natural siderophore produce by norcardia and streptomyces have been used for the treatment of iron overload[11]. This research work established the stability constant, thermodynamic stabilities and spectrophotometric studies of Chromium and Iron chelating drug complexes i.e. salicylichydroxamic acid.

2. EXPERIMENTAL
All reagents were of AR grade. Solutions were made in deionized water free from CO_2. For all pH measurement Orion pH meter model SA 720 was used. A 0.05 M solution of potassium hydrogen pthalate which has pH value 4.01 at 25°C was used to calibrate the pH meter along with the standard buffer solution made from BDH standard chemicals. For potentiometric titrations a double walled glass cell was used. The temperature of the cell was kept constant throughout the experiment by circulating water. All the titrations were done at different temperatures i.e. 30°C, 35°C, 40°C 45°C and 50°C. 20 ml of 0.01 M metal ion solution mixed with 20 ml of 0.01 M salicyhydroxamic acid solution and titrated with 0.1 M NaOH solution. The change in pH was noted with the small increment (0.05 ml) of base. The solution was stirred with magnetic stirrer constantly. For each metal salicylhydroxamic acid solution i.e. Fe(III) and Cr(III), these titrations were performed twice to minimize the probable error.

2.1 *spectrophotometric Analysis*
Spectrophotometric measurements, spectra were recorded on Shimadzu UV 160 A Spectrophotometer. The absorbance peak of the compound at diferent pH was scanned. (Spectra enclosed)

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2.2 *Determination of log beta values through potentiometric and spectrophotometric method*

The data obtained from pH titrations was utilized for the calculation of log beta values. For this purpose computer program BEST was used. Data files FOR004.DAT was prepared for each titration. Calculated beta values were refined several times, till the $beta_{fit}$ values reduced up to 0.04. The data file of this program required the following information

1. Total volume of the solution.
2. Molarity of the base used for pH titration.
3. Change in pH after each step.
4. No. of millimole of metal ions present in the solution
5. No. of millimole of ligand present in the solution.

The whole calculations in this program was based upon the expected beta values for each species present in the solution by refining these values to get sigmafit values, the significance of $beta_{fit}$ was reflected on accuracy of K values. The K values of the complexes at different temperature was used to calculate the thermodynamics values of complexes.

3. RESULT AND DISCUSSION

The potentiometric titration data for salicylhydroxamic acid and its Cr(III) and Fe(III) complexes were analyzed by the computer program. The log β values and thermodynamic stability of Cr(III) and Fe(III) complexes are shown in Table 1 & 2. It was found that like other hydroxamic acids, salicyl hydroxamic acid forms stepwise complexes, one at pH 3 and other at pH 4. iron and chromium both showed the three stages of the complexation. Each resulted into highly stable complexes, the third one is at pH 6, either 1:3 or the ligands may behave as tridentate ligand, i.e. in addition to the bidentate hydroxamate function the -OH attached directly at o-position becomes capable of binding Fe(III)[12]. A chelating agent to be effective in removing a toxic metal from the body, it must satisfied second law of thermodynamic that is the free energy change for the transfer of metal ions from the binding sites to the chelating drug must be negative. To achieve this requirement, stability constant between the toxic metal and chelating drug must be greater than that of the competing ligands with the metal concerned[13]. The ionic radii of Fe(III) is very much close to Cr(III). Therefore the thermodynamic stabilities and log beta values for Fe(III) complexes and Cr(III) complexes are surprisingly close. From the observed data, it is suggested that for the treatment of iron over load in beta thelesemic patients on hydroxamate based drugs Cr(III) equilibrium may also be disturbed and leads to chromium deficiency symptoms resulting in deficiency diseases.

When excess chromium is deposited in the body the toxicity of this metal ion causes electrolytic disturbances, deposition of excesses metal in different vital organs, alteration in membrane permeability and interference in the enzymatic processes[14].

The persons who are suffering with toxicity need effective chelation therapy. The siderophores has been used for the clearance of iron in iron overload patients but chelators are nonspecific and may chelate essential metal ions which are vital for the body functions. Such interactions are determined by the relative affinities of the toxic metal and the essential metal for the chelator. Metal containing compounds have been used not only as biological probes but also as diagnostic and therapeutic pharmaceuticals.

Table-1: Log β values of Cr(iii) and Fe(iii) hydroxamate siderphore at different temperature calculated by computer program

Cr(III)	**30 °C**	**35 °C**	**40 °C**	**45 °C**	**50°C**
Log β 110	8.6	8.8	9.15	9.50	9.95
Log β 210	12.66	12.9	13.20	13.5	13.70
Log β 310	14.99	14.66	14.75	15.10	15.50
Fe(III)					
Log β 110	14.8	15.12	15.52	15.95	16.60
Log β 210	24.0	24.5	24.75	24.9	25.1
Log β 310	31.0	31.25	31.7	32.0	32.15

Table-2: Entropy and Enthalpy values of Cr(iii) and Fe(iii) hydroxamate siderophore complexes

	$-\Delta H$	**ΔS**	**$-\Delta H_2$**	**ΔS_2**	**$-\Delta H_3$**	**ΔS_3**
Cr(III)	11.35	410	8.5	300	5.10	100
Fe(III)	11.75	480	8.45	325	5.5	115

Units for ΔH = k J $MOLE^{-1}$
Units for ΔS = J K^{-1} $MOLE^{-1}$

Some metal ions are recognized as nutrients for animals and plant life they are essential at low level but toxic at high level. This is typical behavior of many substances in the aquatic environment. Some of the heavy metals are among the most harmful elemental pollutants and are of particular concern because of their toxicities to humans[15]. These elements in general are transition metals and some of the representative elements such as lead and tin. In the lower right hand corner of the periodic table heavy metals include essential elements like iron as well as toxic metals like cadmium and mercury. Most of them have tremendous affinity for sulphur and disrupt enzymes functions by forming bonds with sulphur groups in enzymes. Protein carboxylic acid and amino groups are also chemically bounded by heavy metals. Chromium, iron, copper, lead and mercury ions bind to the cell membranes, hindering transport process through the cell wall[16]. Metal ions are present in the body in biological system in a definite concentration.

When becomes low deficiency diseases occur , when it becomes high toxic effect .The aim of our research work what will be the effect of this drug on Chromium tri positive concentration during chelation therapy. It may be calculated by comparison with log β values of tri positive Cr ions. Fe^{+3} showed high stability constant and thermodynamic stabilities values and form complex first then Cr, so the concentration of Cr becomes low and leaves to abnormal metabolism of carbohydrates result in diabetes mellitus.

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