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The Study of Chromium Metal complexes of Alfuzosin Drug with Some Important Amino Acids

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Abstract: *The study of pH metric determination of the stability constant of the ternary metal complexes of chromium(III) ion with the BPH drug Alfuzosin, which is used to treat the signs and symptoms of benign enlargement of the prostate and with some biologically important ligands such as amino acids has been performed in 80 percent (v/v) ethanol-water medium at 30°C and a fixed ionic strength of 0.1M $NaClO_4$.*

Keywords: Chromium Metal ion, Alfuzosin, Δlog K**,** BHP, ternary complexes, Relative Parameters $\beta_{111}\beta_{20}\beta_{02}K_DK_RK_r$ and ΔlogK.

I. INTRODUCTION

The medicine first used to treat BHP appears to be beneficial in the treatment of kidney stones. Commonly known as alfuzosin it is used in the treatment of benign prostatic hyperplasia. This belongs to a class of uroselective adrenergic receptor (α1a) antagonist quinazoline derivative.[1,2] It helps to relieve symptoms like difficulty in passing urine. However, it does not decrease the size of the prostate. Its IUPAC Name is N-[3-[(4-amino-6,7-dimethoxyquinazolin-2-yl)-methylamino]propyl] oxolane-2-carboxamide. This drug is marketed under various brand names such as Uroxatral and elsewhere under the tradenames xat, xatral, prostetrol and alfural.[3]

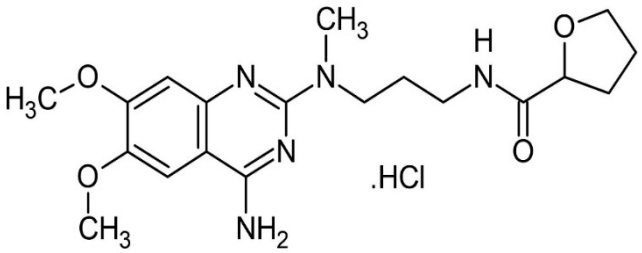

Figure. 1. Alfuzosin Hydrochloride (Uroxatral)

IUPAC Name - N-[3-[(4-amino-6,7-dimethoxyquinazolin-2-yl)-methylamino]propyl]oxolane-2-carboxamide[4]

As an antagonist of the α_1 adrenergic receptor, it works by relaxing the muscles in the prostate and bladder neck, making it easier to urinate. Alfuzosin was patented in 1978 and approved for medical use in 1988.[4] It was approved in the US for BPH in 2003. In 2017, it was the 266th most prescribed medication in the *United States*, with more than one million prescriptions.Formula$C_{19}H_{27}N_5O_4$ molar mass 389.456 g·mol^{-1} By selectively inhibiting alpha adrenergic receptors in the lower urinary tract, alfuzosin causes smooth muscle relaxation in the bladder neck and prostate, improving urine flow, thereby reducing BPH symptoms.[5] Additionally, alfuzosin reduces the vasoconstrictor effect of catecholamines (epinephrine and norepinephrine), leading to peripheral vasodilation.[6] This leads to a risk of postural hypotension/syncope, and prescribing information warns that caution should be exercised in patients who take nitrates, antihypertensives, or have experienced decreased blood pressure after using other medications.[7]

Chromium is also a transition series element having atomic number 29, an ultra-trace metal necessary for insulin potentiation on carbohydrate and lipid targets. chromium deficiency causes insulin resistance. Chromium is involved in lipid and protein metabolism. Glucose tolerance factor is a real insulin potentiator (GTF). Trivalent chromium is a component of glucose tolerance factor. Chrome is used to make steel and other alloys.[8,9]

Chrome plating, dyeing and pigment production, leather and wood preservation, and cooling tower water treatment all require chromium compounds (III or VI). Smaller amounts are utilized in drilling muds, textiles and copy machine

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toner. Chromium is found in rocks, animals, plants, soil, volcanic dust and gases. Cr^{3+} is an essential dietary element for optimal glucose, protein, and fat metabolism.[10]The biochemical reactions taking place in solutions include organic molecules with potential containing sites and also strongly coordinating transition metal ions.[11-15]This research looks at a few amino acids.[16-18] The current study looks at potentiometric research on Chromium (III) metal complexes with Benign Prostatic Hyperplasia Alfuzosin and amino acids in an ethanol-water medium with an ethanol-water content of 80 percent (v/v)[16,19,20]

II. MATERIAL METHODS

The potentiometric titration technique was employed to investigate ternary metal complexes, and the ligands Alfuzosin (D) and amino acids (R) were the titrating reagents in the titrations against the standard sodium hydroxide solution. Addition of 1M sodium perchlorate solution was used to preserve the solution's 0.1 M ionic strength. An inert atmosphere of 30°C was maintained by bubbling oxygen-free nitrogen gas through an electrode assembly to remove CO_2 from the solution. The titration of carbonate-free ethanol-water solution in 80 percent (v/v) ethanol-water was adjusted by the method of Vansittart and Hass in the investigation of ternary metal complexes.[16]

III. RESULTS AND DISCUSSION

Computational SCOGS were used to minimize the usual derivation of the formation constant of ternary complexes. The titration system is set up as follows.

The Calvin Bjerrum pH metric titration techniques which was modified by Irving Rossotti[21] were applied for the determination of the equilibrium constants of 1:1:1 ternary complexes.[22-24]Titration procedure involves following steps:

I	Free $HClO_4$ (A)
II	Free $HClO_4$ (A) + Alfuzosin (D)
III	Free $HClO_4$ (A) + Alfuzosin (D) + Chromium ion (M)
IV	Free $HClO_4$ (A) + Amino acids (R)
V	Free $HClO_4$ (A) + Amino acids (R) + Chromium ion (M)
VI	Free $HClO_4$ +Alfuzosin (D) + Amino acids (R)+ Chromium ion (M)

The metal ligand stability constant and proton ligand constant of Alfuzosin and amino acids with chromium (III) were determined in this study at 80 % (v/v) ethanol-water mixture at 30°C and ionic strength μ= 0.1 M $NaClO_4$ are shown in the table no. 1.

Ligands	**pK_1**	**pK_2**	**Chromium**	
			$Logk_1$	**$Logk_2$**
Alfuzosin	4.131	5.561	9.1757	-
Glycine	2.771	9.742	6.511	3.9398
Leucine	3.8108	10.341	7.7079	4.3502
Glutamic Acid	3.1362	5.8987	3.509	3.0419

Table 1: The proton ligand constant and metal ligand stability constant of drug Alfuzosin and amino acids with chromium (III)

The pK and logK value of drug here is important for the explanation of stability constant of Metal ligand ternary complexes.[24-26]The pH metric titrations curves for Cr(III)+D1 +R3 is represented in **Figure 2**.From this figure it is has been clearly found that the mixed ligand curve coincideswith the A+D1 curve up to pH ~2.8 after that point of pH it gets deviated. Thecomposite curve remains towards the left side of the mixed ligand complex curve.Divergence of the curve towards the x axis after pH~ 2.9. The mixed ligandstability constant of this complex is 12.61 which is found to be high. TheFormation of ternary 1:1:1 complex is confirmed by decrease in ternary complexcurve in comparison with binary complex curve Cr(III)+D1 and Cr(III)+R3. Theprimary ligand D1 and secondary ligand R3 both forms 1:1 and 1:2 complexes withChromium metal ion. The precipitation occurred at the higher values of the pHindicates that the complex formation is occurred in the higher pH region.Potentiometric titration in ternary systems reveals that the mixed ligand curve coincides with the A+D complex curve up to pH 2.9, beyond which it deviates. The theoretical composite curve continues to be to the left of the mixed ligand complex curve. The mixed ligand curve shifts towards the X-axis after pH~2.9 indicating the development of hydroxide species. Because the mixed ligand curve coincides with the

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titration curves of separate metal complexes, the creation of a 1:1:1 complex by involving progressive equilibrium is possible.

The principal ligand drug Alfuzosin forms 1:1 complex with Cr(III) , while the secondary ligand amino acid glycine forms 1:1 and 1:2 complexes of chromium(III). The percentage distribution curves of free metal decrease substantially with rising pH, as seen in the figure of percentage concentration species of Cr(III) - Alfuzosin –glycine, leucine and Glutamic acid. This shows that metal ions are involved in the complex building process. As a function of pH, the percentage concentration of free ligands Alfuzosin and glycine increases, which may be related to the dissociation of ligands present in the system.

From the Species distribution study by using SCOGS programme, species distribution curves were plotted as a function of pH at temperature 30 °C and μ= 0.1 M $NaClO_4$ to explain the equilibrium and evaluate the calculated stability constant of ternary complexes Cr(III) - Alfuzosin glycine. The concentration of Cr(III) – Alfuzosin –glycine increases from pH ~3.1 whereas the concentrations for the formation of D (Alfuzosin) and HR (Glycine) decrease continuously with increasing pH, indicating the formation of Cr(III)–Alfuzosin-glycine. This species concentration is steadily increasing, confirming the formation of ternary complexes.

Amino acids		β_{111}	β_{20}	β_{02}	K_D	K_R	K_r	**Δlog K**
Glycine	R_1	15.1445	9.9715	10.4570	7.1247	8.8977	2.1996	-0.8779
Leucine	R_2	15.3544	9.9715	12.0487	6.2145	7.6478	1.9623	1.4921
Glutamic acid	R_3	12.6154	9.9715	6.5454	3.5252	9.4745	2.4384	-0.3843

Table 2: Parameters determined based on equilibrium constant of mixed ligand complexes of Cr(III), Alfuzosin (D_1), Aminoacids (R) and pK/ logK of binary complexes at 30^0C and 0.1M ionic Strength $NaClO_4$ 80% (V/V) Ethanol-Water medium.

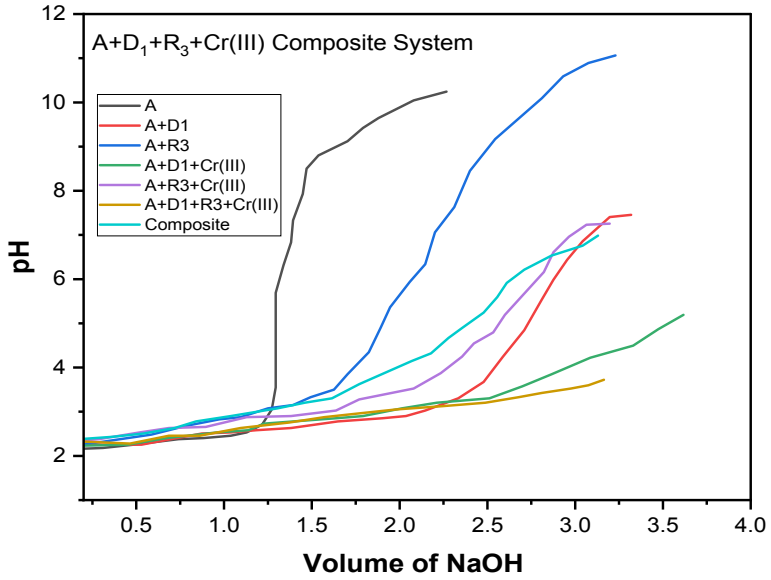

Figure 2: Potentiometric titration curves for A + D_1 + R_3 + Cr(III) + Composite.

IV. CONCLUSION

The ternary complex's ΔlogK value is greater than the statistically anticipated value, indicating that the formed complex is stable. Alfuzosin, the principal ligand, is a smaller molecule. As a result, the ΔlogK value is less negative. The electrostatic repulsion between the negative charges on Alfuzosin drug molecule and amino acids, according to Thompson and Lorass, causes ternary complexes to have a lower 1ogK value. Because the major ligand Alfuzosin coordinates with the metal ion in the low pH range and forms a 1: 1 complex in the current studies of ternary complexes, steric hindrance is the most critical aspect to consider.

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