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ORIGINAL ARTICLE **OPEN ACCESS**

A Potentiometric Metal Complexation Study of Drug Alfuzosin with Copper (II) Ion

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ABSTRACT
Potentiometric determination of the stability constant of the ternary metal complexes of Copper (II) ion with the BPH drug Alfuzosin, sold under the brand names UroxatralAlfman, Alfugress, etc and 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 $NaClO_4$. Treatment of benign prostatic hyperplasia with this drug (BPH). It relaxes the muscles of the prostate and the bladder neck, making it easier to urinate, as an antagonist of the adrenergic α-1 receptor.
Keywords : *Alfuzosin, Δlog K, BHP, ternary complexes.*
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INTRODUCTION

The post-synaptic alpha 1 adrenoreceptors found in the prostate, bladder base, bladder neck, prostatic capsule, and the prostatic urethra are selectively blocked by alfuzosin. Lower urinary tract alpha adrenergic receptors are specifically targeted by alfuzosin. UroxatralAlfman, Alfugress, and other Alfuzosin-based medications are used to treat symptomatic Benign Prostatic Hyperplasia, as well as for the treatment of acute urinary retention [1, 2]. The medicine first used to treat BHP appears to be beneficial in the treatment of kidney stones in the range of 4 mm to 10 mm in size [2].

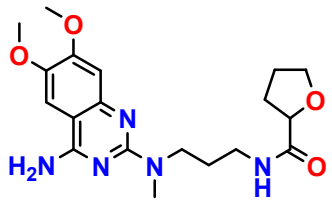


Figure 1 Alfuzosin(Uroxatral)

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

The drug alfuzosinis an alpha blocker, which relaxes the bladder neck muscle fibres and makes it easier to pee, making it more comfortable. Men with symptoms of an enlarged prostate gland, also known as benign prostatic hyperplasia (BPH), can use alfuzosin to alleviate their symptoms (Benign Prostatic Hyperplasia or BPH). Benign prostatic hyperplasia (BPH) is a common ailment among men as they age. Below the bladder, the prostate gland is situated. In men with prostate cancer, enlarged muscles in the gland may become stiff and block the tube that carries urine from the bladder, resulting in a need to urinate frequently, poor urination flow, or a feeling that the bladder has not been entirely emptied. Absorption, excretion, and metabolism were examined in four healthy male participants after taking Alfuzosin hydrochloride (Uroxatral) at a 0.2 mg dose orally once a day for two weeks. M-1-Sul (o-deethylatedmetabolite sulphate) and AM-1 (o-ethoxyphenyl acetic acid sulphate) were excreted in large amounts, accounting for 15.7 and 7.5 percent of the total dose respectively [3]. This drug therefore excretes to a good degree, making it feasible to remove some extra metals from the body along with it. Methyl-ion-containing enzymes provide multiple functions, including catalysing reaction mechanisms and stabilising protein structure as well as helping to keep cell walls and other structural elements in good shape. Animal cell metabolism and growth are regulated by the mobilisation of divalent and trivalent

metal ions, according to the most recent research. Copper is a transition metal ion that is found in enzymes and serves a variety of functions in the biological system, including triggering reactions, controlling reaction mechanisms, stabilising protein structure, and maintaining cell wall integrity. According to recent findings, the mobilisation of divalent and trivalent metal ions is required for the regulation of animal cell metabolism and growth. It is found in abundance throughout the body [4, 5]. Furthermore, research into the function and localization of the mechanisms of copper balance and their role in maintaining appropriate copper distribution in mammals [6-9]. Copper (Cu) is a trace element that all species, from bacteria to people, require for living. All amino acids are polymers and are considered protein building blocks. This research looks at a few amino acids [0-12]. The current study looks at potentiometric research on copper (II) 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) [13].

MATERIAL AND METHODS

Badar Chemicals supplied the A.R.-grade copper nitrates (India). Perchlorates of metal ions were employed to avoid the formation of complexes with anions. The equivalent nitrates were used to make the perchlorates [14]. The conventional methodologies for estimating metal ion concentrations were used [15-18]. Sodium perchlorate (E. Merck) was dissolved in carbon dioxide free distilled water. Solution of sodium hydroxide in carbonate free distilled water was also prepared by leaving the solution to remain for a long period until any carbonate precipitated. The potentiometric titration was carried out using the solution as a titrant. Every day, the solution was titrated with a normal oxalic acid solution to maintain its consistency. For the stock solution, Reidal (Germany) perchloric acid was employed. Conductometric titration of sodium hydroxide solution was used to determine its exact normalcy. Dissolving A.R. grade sample in 80% (v/v) ethanol – water medium yielded Merck (Germany) and Fluka (Germany) amino acids. An ethanol-water mixture of 80 percent (v/v) ethanol was used to dissolve the drug Alfuzosin. Drug samples in their purest form were obtained as gift samples. 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. Computational SCOGS were used to minimise the usual derivation of the formation constant of ternary complexes. The titration system is set up as follows.

PROCEDURE OF TITRATION

The Calvin Bjerrum pH metric titration techniques which was modified by Irving Rossotti were applied for the determination of the equilibrium constants of 1:1:1 ternary complexes [32, 33]. Titration procedure involves following steps:

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

RESULT AND DISCUSSION

3.1. Binary metal complexes

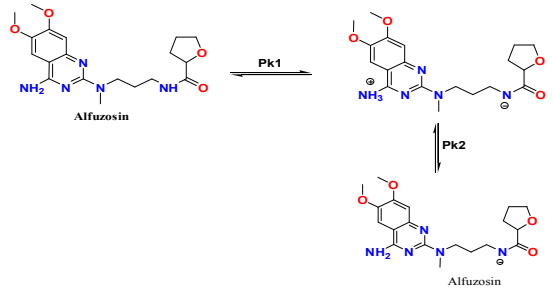
The metal ligand stability constant and proton ligand constant of Alfuzosin and amino acids with copper (II) were determined in this study at 80 % (v/v) ethanol-water mixture at 30°C and ionic strength μ= 0.1 M $NaClO_4$ are shown in the table no. 1.

Ligands	pK_1	pK_2	Copper	
			Log k_1	Log k_2
Alfuzosin	2.6121	5.7626	6.7161	-
Glycine	2.73	2.73	2.73	2.73
Leucine	9.71	9.71	9.71	9.71
Glutamine	9.89	9.89	9.89	9.89
Valine	8.71	8.71	8.71	8.71
Methionine	3.71	3.71	3.71	3.71

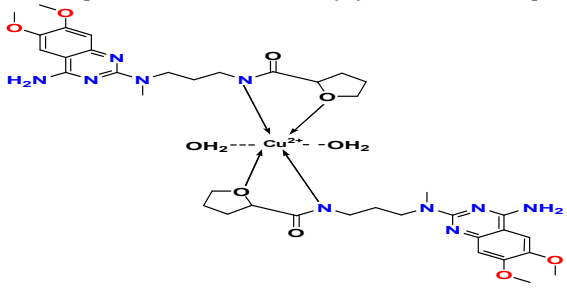
Table 1: The proton ligand constant and metal ligand stability constant of drug Alfuzosin and amino acids with copper (II)

The pK and logK value of drug here is important for the explanation of stability constant of Metal ligand ternary complexes [16, 19].

3.2.Dissociation of Protons Scheme for Free Ligand Alfuzosin



3.3. Proposed Structure of Cu(II) AlfuzosinComplex



3.4. Ternary metal complexes

Potentiometric titration in ternary systems reveals that the mixed ligand curve coincides with the A+D complex curve up to pH 2.5, 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 2.5, indicating the development of hydroxide species. Because the mixed ligand curve coincides with the 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 Cu, while the secondary ligand amino acid glycine forms 1:1 and 1:2 complexes (II). The percentage distribution curves of free metal decrease substantially with rising pH, as seen in the figure of percentage concentration species of Cu (II) - Alfuzosin –glycine, leucine, glutamine, valine, and methionine systems. 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.

Species distribution studies

Using the SCOGS programme, species distribution curves were plotted as a function of pH at temperature 27 °C and μ= 0.1 M $NaClO_4$ to explain the equilibrium and evaluate the calculated stability constant of ternary complexes Cu (II) - Alfuzosin glycine. The concentration of Cu (II) – Alfuzosin –glycine increases from pH2.6, whereas the concentrations for the formation of D (Alfuzosin) and HR (Glycine) decrease continuously with increasing pH, indicating the formation of Cu(II) – Alfuzosin-glycine. This species' concentration is steadily increasing, confirming the formation of ternary complexes. Percentage distribution of the species formed during the formation of mixed ligand complex in the system Cu (II) + D1+ R given in figure number 2 and free metal system is shown in figure 3 as given below.

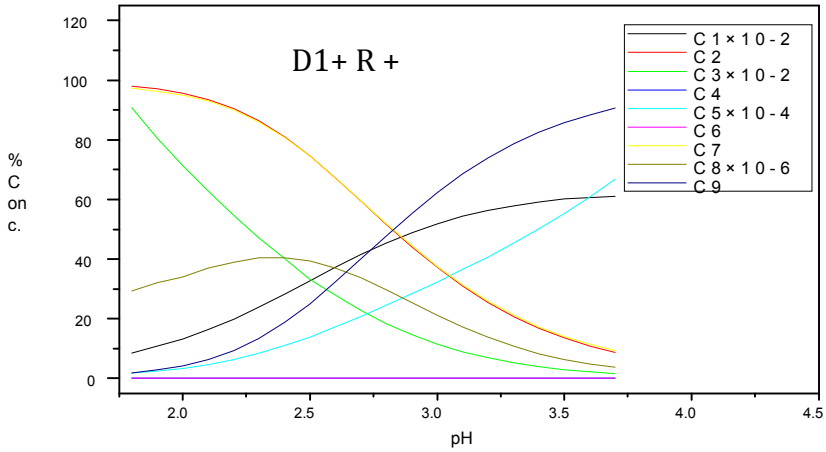


Figure 2 :Percentage distribution of the species formed during the formation of mixed ligand complex in the system Cu (II) + D1+ R.

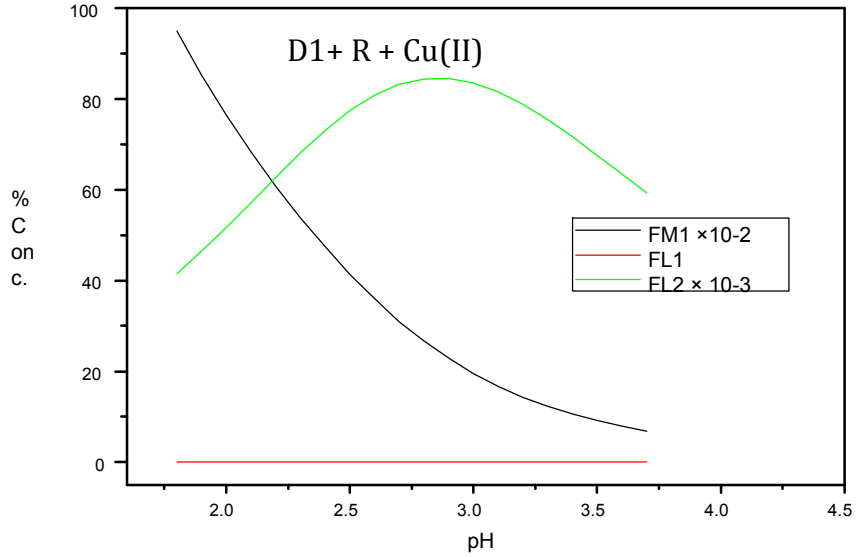


Figure 3 : Percentage distribution of free metal Cu(II), free ligand (D1) and free ligand (R7) of mixed ligand complex in the system Cu(II) + D1 + R7.

The concentration of Cu (II)-Alfuzosin amino acids such as glycine increases from pH 4.5, but that of leucine, glutamine, valine, and methionine decreases from 5.9, 4.0, 2.5, and 3.9, respectively. C1 and C2 represent the concentrations for the formation of D (drug Alfuzosin) and HR (glycine amino acid), which show a continuous decrease with increasing pH, indicating the formation of Cu (II) - drug (D)-amino acid(R) such as glycine, leucine, glutamine, valine, and methionine represented by C7. The concentration steadily rises, confirming the production of ternary complexes [20]. According to the SCOG distribution curve, the formation of ternary complexes began only after the metal main ligand complex had reached its maximum concentration. This indicates that the metal primary ligand complex Cu (II)- Alfuzosin is produced first, followed by secondary ligands such as glycine, leucine, glutamine, valine, and methionine, leading in the formation of ternary complex. Ternary complexes with glycine, tryptophan, leucine, and glutamic acid have the concentration species distributions shown below.

$$C1 = HD \rightleftharpoons D+H$$
$$C2 = H_2R \rightleftharpoons HR+H$$
$$C3 = HR \rightleftharpoons R+H$$
$$C4 = M+R \rightleftharpoons MR$$
$$C5 = MR+R \rightleftharpoons MR_2$$
$$C6 = M+D \rightleftharpoons MD$$
$$C7 = MD+R \rightleftharpoons MDR$$

Where M = Copper, R = Amino acids & D = drug Alfuzosin.

Furthermore, the highest percentage of ternary complex formation is greater than that of Cu (II) amino acids and Cu (II) Alfuzosin binary complex, indicating that ternary complex stabilisation occurs.

The stability constant of ternary complexes.

The relative stabilities of binary and ternary complexes are stated quantitatively in tern of β_{11}, β_{20}, β_{02}, K_D, K_R, K_r and ΔlogK value which are represented in table 2. With 1:1 and 1:2 ratios for the system ligand, which forms binary complexes. The magnitude of the constant represents the stability of mixed ligand complexes. Water and K_a derived a statistically anticipated value of 0.6 log units by calculating probabilities for the reasons given by Sigel. The logK value can be determined using either the first or second approach. Table II shows the calculated logK values for all systems. The comparison of 11 with 20 and 02 of this system shows that ternary complexes develop preferentially over binary complexes of primary and secondary ligands. The significantly positive value of K_D& K_R suggests that ternary complexes are more stable than primary and secondary ligands. This complex's Kr value is positive, but its magnitude is smaller, indicating that ternary complexes are less stable. The current analyses demonstrate that the stability constants of the produced ternary complexes are fairly stable. In the case of the ternary system of Valine, the negative logK value implies that the ternary complex is less stable than the binary 1:1 copper –Alfuzosin& metal-amino acids combination. This is consistent with statistical considerations. A negative logK value does not imply that the complex is not produced. The negative value could be attributed to the increased stability of its binary complexes, a smaller number of coordination sites, and steric hindrance [4, 21, 22]..Differences in bond type, geometrical structure, and other electronic considerations [23-25]. On the basis parameters of some relationship between the formation of ternary complexes of Copper (II) metal ion with Alfuzosin in the presence of Amino acids (1:1:1) system at temp = 27 ^{0} C μ = 0.1 m $NaClO_4$ medium = 80 percent (v/v) ethanol-water are given in table no. 2

Table 2 :formation of ternary complexes of Copper (II) metal ion with Alfuzosin Drug

AMINO ACIDS	β_{11}	β_{20}	β_{02}	K_D	K_R	K_r	Δlog K
GLYCINE	18.2143	6.7047	18.2457	10.751	7.6021	2.41244	0.9713
LEUCINE	14.6021	6.5021	8.0644	8.0845	6.6124	4.012454	0.0017
GLUTAMINE	16.5614	6.2421	17.392	9.8097	7.1151	2.374452	0.5021
VALINE	15.2545	6.6124	18.510	8.6124	5.1014	1.575244	-1.5144
METHIONINE	16.75124	6.6144	18.421	10.1245	7.1145	2.24577	0.5002

CONCLUSION

The ternary complex's ΔlogK value is greater than the statistically anticipated value, indicating that it 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 Alfuzosindrug 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. In solution, ternary complexes develop when the Cu (II)-Alfuzosin titration curve is run below it. As a result, the secondary ligand amino acids face steric hindrance due to the larger size of the Cu (II)-Alfuzosin complex compared to the aqua ion, which tries to restrict the secondary ligand's entry into the coordination sphere of the Cu (II) metal ion, reducing the stability of ternary complexes. Alfuzosin = glycine >glutamine>Methionine>leucine>valine is the order of stability of ternary Cu (II) complexes with respect to secondary ligand for respective primary ligands.

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