Chemistry Research Journal, 2019, 4(1):149-154

Available online www.chemrj.org

Research Article

ISSN: 2455-8990
CODEN(USA): CRJHA5

Copper (II) Metal Complexes with Benign Prostatic Hyperplasia (BPH) Drug Tamsulosin and Biological Important Ligands in 80% Ethanol –Water Mixture: A Potentiometric Studies

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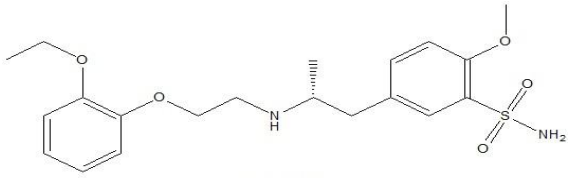
Abstract The stability constant of ternary metal complexes of Copper (II) ion with BPH Drug Tamsulosin marketed as FLOMAX^R and some biological important ligands such as amino acids have been determined potentiometricaly in 80 % (v/v) ethanol-water medium at 27°C and fixed ionic strength 0.1M $NaClO_4$ by computational program SCOG.

Keywords Tamsulosin, Δlog K**,** BHP, ternary complexes

Introduction

The Drug Tamsulosin is available in market by name Flomax^R used for the treatment of symptomatic Benign Prostatic Hyperplasia, helps with Passage of Kidney stone [1-2] and for the Urinary retentions also used for the treatment of acute urinary retention. Though the drug preliminarily used to treat BHP however appears to be useful for the kidney stone of the order 4 mm to 10 mm size [3].



tamsulosin

This drug is alpha blocker and bladder neck muscle fibers is relaxed by its use and make prostate easier to urinate. Tamsulosin is used to treat men who have symptoms of an enlarged prostate gland, which is also known as benign enlargement of the prostate (Benign Prostatic Hyperplasia or BPH). Benign enlargement of the prostate is a problem that can occur in men as they get older. The prostate gland is located below the bladder. As the prostate gland becomes enlarged some muscles in that gland may become hard and get in the way of the tube that take urine from the bladder, which can cause problems in urinating, such as a need to urinate often, a weak stream when urinating, or a feeling of not being able to empty the bladder completely as it is a Alpha adrenergic receptor antagonist. The absorption, excretion and metabolism of tamsulosin hydrochloride (TMS), a potent α_1-adrenoceptor blocking agent, were studied in four healthy male subjects after a single oral administration of C-TMS at a dose of 0.2 mg. Unchanged TMS and 11 metabolites in 0-24 h urine samples were quantified. TMS accounted for 8·7% of the dose. Extensive excretion of the sulphate of the *o*-deethylatedmetabolite (M-1-Sul) and *o*-ethoxyphenoxy acetic acid (AM-1) was seen, accounting for

15.7 and 7.5% of the dose respectively [4] therefore it is clear that this drug excretes to level good and thus it may become possible along with that it may take out certain excess amount of the metals from the body.

The metal ions are integral parts of enzymes and play an important role in the biological system, such as to trigger a reaction, control reaction mechanism, stabilize protein structure, maintain structure of cell walls etc. Latest information indicates regulation of metabolism and growth of animal cell is dependent upon the mobilization of divalent and trivalent metal ions.

Copper is a transition metal ion are integral parts of enzymes and play an important role in the biological system, such as to trigger a reaction, control reaction mechanism, stabilize protein structure, maintain structure of cell walls etc. Latest information indicates regulation of metabolism and growth of animal cell is dependent upon the mobilization of divalent and trivalent metal ions. It is widely distributed throughout the body [5]. The identification of mammalian homologues of these proteins reveal a remarkable structural and functional conservation of copper metabolism between bacteria, yeast and humans. Furthermore, studies on the function and localization of the products of the Menkes and Wilson's disease genes, which are defective in patients afflicted with these diseases, have provided valuable insight into the mechanisms of copper balance and their role in maintaining appropriate copper distribution in mammals [6]. Copper (Cu) is an essential trace element required for survival by all organisms from bacterial cells to humans. All amino acids are polymer and regarded as building block of protein. Some amino acids are studied in this research [7]. Present investigation deals with the potentiometric studies on copper (II) metal complexes with Benign Prostatic Hypeplasia Tamsulosin and amino acids in 80% (v/v) ethanol-water medium.

Materials and Methods

The nitrates of copper, of A.R. grade were obtained from Doodle (India). Metal ion was used in the form of their perchlorates to avoid the possibility of complex formation with anions. The perchlorates were prepared from the corresponding nitrates [8]. The concentration of metal ions was estimated by the standard procedures [9-11]. Sodium perchlorate (E. Merck) was dissolved in carbon dioxide free distilled water.

The solution of sodium hydroxide was also prepared in carbonate free distilled water by allowing the solution to stand for a long time till any carbonate if present precipitated. The solution was used as titrant for the potentiometric titration. As a routine, the solution was standardized at least once every day by titrating with standard oxalic acid solution. Perchloric acid of Reidal (Germany) was used for the preparation of the stock solution. Its exact normality was obtained by titrating it conductometrically using standard sodium hydroxide solution. Amino acids from Merck (Germany) and Fluka (Germany) were prepared by dissolving A.R. grade sample in 80% (v/v) ethanol – water medium.

Solution of the Drug Tamsulosin were prepared by dissolving sample as received in 80% (v/v) ethanol-water medium. Drugs samples in pure form were obtained from pharmacy industries.

The Methodology were used in the study of ternary metal complexes by the potentiometric titration technique, involves the titrations of carbonate free solution of against standard sodium hydroxide, where drug Tamsulosin (D) and amino acids (R) are the ligands.

The ionic strength of the solutions was maintained constant i.e. 0.1 M by adding appropriate amount of 1M sodium perchlorate solution. The titrations were carried out at 27^0C in an inert atmosphere by bubbling oxygen free nitrogen gas through an assembly containing the electrode to expel out CO_2.The experimental procedure, in the study of ternary metal complexes by the potentiometric titration technique, involves the titration of carbonate free solution of in 80 % (v/v) ethanol-water, were corrected by method of Vansittart and Hass. The formation constant of ternary complexes were determined by computational programmed SCOGS to minimize the standard derivation. The system taken for the titration are set as follows:

I	Free $HClO_4$ (A)			
II	Free $HClO_4$ (A) +		Tamsulosin (D)	
III	Free $HClO_4$	(A) +	Tamsulosin (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 $HClO_4$	(A) +	Tamsulosin (D) + Amino acids (R)+ Copper ion (M)

Result and Discussions

a. Binary metal complexes

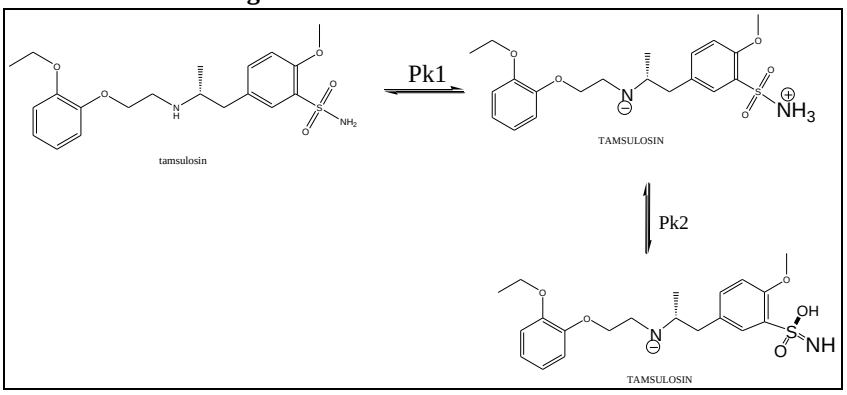
The proton ligand constant and metal ligand stability constant of drug tamsulosin and amino acids with copper (II) determined in 80 % (v/v) ethanol-water mixture at 27°C and ionic strength μ= 0.1 M $NaClO_4$ are shown in the table no. 1.

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

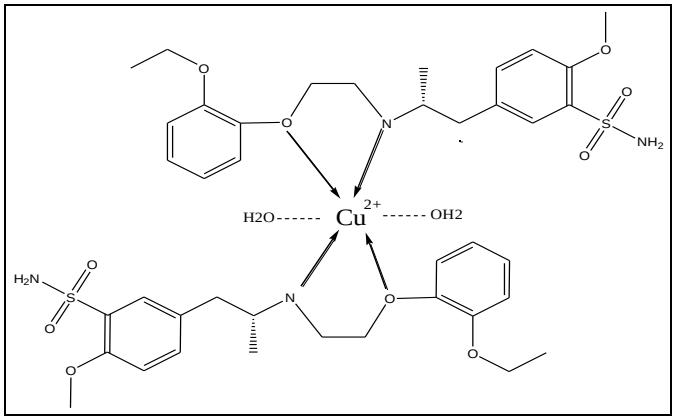
Ligands	**pK_1**	**pK_2**	**Copper**	
			Log k_1	**Log k_2**
Tamsulosin	2.5444	5.9636	6.6043	-
Glycine	2.7700	9.740	6.510	3.940
Leucine	3.8100	10.340	7.708	4.350
Glutamine	3.0100	9.280	9.400	7.890
Valine	3.2100	9.802	10.010	8.480
Methionine	3.1200	9.600	9.640	8.670

The pK and logK value of drug here is important for the explanation of stability constant of Metal ligand ternary complexes [18]

Proton Dissociation Scheme for Free Ligand Tamsulosin



Proposed Structure of Cu(II) Tamsulosin Complex



b. Ternary metal complexes

The potentiometric titration, ternary systems shows that the mixed ligand curve coincide with A+D complex curve up to the pH ~ 2.5 and after this pH, it deviates. Theoretical composite curve remains toward left of the mixed ligand complex curve. After pH ~ 2.5, the mixed ligand curve drifts towards X-axis, indicating the formation of hydroxide species. Since the mixed ligand curve coincide with individual metal complex titration curves, the formation of 1:1:1 complex by involving stepwise equilibrium.

The primary ligand drug Tamsulosin form 1:1 and secondary ligand amino acid glycine form 1:1 and 1:2 complexes with Cu (II). It is evident from the figure of percentage concentration species of Cu (II) - Tamsulosin–glycine, leucine, glutamine, valine and methionine systems that the percentage distribution curves of free metal decreases sharply with increasing pH. This indicates involvement of metal ion in the complex formation process. Percentage concentration of free ligands Tamsulosin and glycine increases and this increase may be due to the dissociation of ligand present in the system, as a function of pH.

Species distribution studies

To explain the equilibrium and evaluate the calculated stability constant of ternary complexes Cu (II) - Tamsulosin - glycine, species distribution curves have been plotted as a function of pH at temperature 27 °C and μ = 0.1 M $NaClO_4$ by using SCOG programme. It can be seen that, the concentration of Cu (II) - Tamsulosin–glycine increases from pH~2.6 whereas the concentration for the formation of D (Tamsulosin) and HR (Glycine) show continuous decrease with increasing pH which indicates the formation of Cu(II)-Tamsulosin-glycine. The concentration of this species continuously increases; confirm the formation of ternary complexes.

It can be observed that the concentration of Cu (II)-Tamsulosin amino acids such as glycine increases from pH 4.5 where as that of leucine, glutamine, valine and methionine from 5.9, 4.0, 2.5, 3.9 respectively. The concentration for the formation of D (drug Tamsulosin) and HR (glycine amino acid) represented by C_1 and C_2 show continuous decrease with increasing pH which indicates the formation of Cu (II) - drug (D)- amino acid(R) such as glycine, leucine, glutamine, valine and metheinine represented by $C_{7.}$ The concentration continuously increases; confirm the formation of ternary complexes.

From the SCOG distribution curve it is concluded that the formation of ternary complex started only after the metal primary ligand complex has attained its maximum concentration. This indicate that metal primary ligand complex Cu (II)- Tamsulosin is formed first then the secondary ligands such as glycine, leucine, glutamine, valine and methionine coordinated to it, resulting the formation of ternary complex. Ternary complexes with glycine, tryptophan, leucine and glutamic acid show the following types of the concentration species distribution

$C_1 = HD \rightleftharpoons D + H$

$C_2 = H_2R \rightleftharpoons HR + H$

$C_3 = HR \rightleftharpoons R + H$

$C_4 = M + R \rightleftharpoons MR$

$C5 = MR + R \rightleftharpoons MR_2$

$C_6 = M + D \rightleftharpoons MD$

$C_7 = M + D + R \rightleftharpoons MDR$

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

Moreover the maximum percentage of the formation of ternary complexes is more than that of the Cu (II) amino acids and Cu (II) Tamsulosin binary complex, this indicates that the stabilization of ternary complex.

The stability constant of ternary complexes.

The relative stabilities of the binary and ternary complexes are quantitatively expressed in tern of β_{11}, β_{20}, β_{02}, K_D, K_R, K_r and ΔlogK value which are represented in table 2.

For the system ligand which form both 1: 1 and 1:2 binary complexes. The magnitude of the constant is the measure of stability of mixed ligand complexes. Water and Ka calculated statistically expected value 0.6 log units by considering with probabilities for a variety of reason discussed by Sigel. ΔlogK value can be calculated by using first or second approach. The calculated ΔlogK values for all systems are given in table II.

The Comparison of β_{11} with β_{20} and β_{02} of this system show that preferential formation of ternary complexes over binary complex of primary as well as secondary ligand. The considerably positive value of K_D & K_R indicates high stability of ternary complexes with respect to that of primary as well as secondary ligands. The K_r value of this complex is positive but the magnitude is smaller which indicates lower stability of ternary complexes.

Results of the present investigations show that the stability constant of ternary complexes formed are fairly stable. The negative ΔlogK value of this system in case of ternary system of Valine indicates that the ternary complex is less stable than the binary 1:1 copper –Tamsulosin & metal-amino acids complex. This is in accordance with statistical considerations. The negative value of ΔlogK does not mean that the complex is not formed. The negative value may be due to the higher stability of its binary complexes, reduced number of coordination sites, steric hindrance [12-15]. Electronic consideration [16-17] difference in bond type, geometrical structure etc.

Parameters based on some relationship between the formation of ternary complexes of Copper (II) metal ion with Tamsulosin in the presence of Amino acids (1:1:1) system at temp = 27^0c μ = 0.1 m $naclo_4$ medium = 80% (v/v) ethanol-water are given in table no. 2

Table 2

Amino acids	β_{11}	B_{20}	B_{02}	K_D	K_R	K_r	ΔlogK
Glycine	17.2843	6.6043	18.6599	10.680	7.6044	2.4242	1.0001
Leucine	14.6757	6.6043	8.0703	8.0714	6.6054	4.0409	0.0011
Glutamine	16.5050	6.6043	17.29	9.9007	7.1050	2.3856	0.5007
Valine	15.1147	6.6043	18.49	8.5104	5.1047	1.8708	- 1.4996
Methionine	16.7438	6.6043	18.31	10.1395	7.1038	2.3184	0.4995

Conclusion

The ΔlogK value of this system is higher than the statistically expected value showing the stabilized nature of the ternary complex. The primary ligand Tamsulosin having smaller size.

Therefore its ΔlogK value is less negative Thompson & Lorass pointed out that more negative 1ogK value of ternary complexes is due to the electrostatic repulsion between the negative charges on Tamsulosin & amino acids. Steric hindrance consideration is the most important factor because in the present studies of ternary complex, primary ligand Tamsulosin coordinates with the metal ion in the lower pH range and form 1: 1 complex. In solution, ternary complex forms as the titration curve run below the Cu (II)-Tamsulosin titration curve. So, it is evident that the entry of the secondary ligand amino acids faces steric hindrance due to bigger size of the Cu (II)-Tamsulosin complex as compared to aqua ion, which tries to restrict the entry of the secondary ligand in the coordination sphere of the Cu (II) metal ion & thus reduces the stability of ternary complexes. The order of stability of ternary complexes of Cu (II) with respect of secondary ligand for respective primary ligands is Tamsulosin = glycine >giutamine>Methionine>leucine>valine

Acknowledgement

The authors are very much thankful to the Head, Department of Chemistry Dr. K. G. Huge, Dr. B. S. Munde, Principal K.K.M. College Manwat and Principal, Dnyanopasak College Parbhani for providing necessary facilities at Department Chemistry Research Center. One of the author is very much thankful to UGC-WRO Pune for the financial support through MRP-47-606/13 (WRO)

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