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Conductometric Determination of Stability Constants of Cu–fluconazole and Cu-metformin

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ABSTRACT
Monovariation method was used to determine the M-L ratio of fluconazole (flz) and metformin (met) complexes of Cu. The stability constant of the formed complexes was calculated by conductance measurement using method of continuous variations. Thereafter, the Gibb's free energy for the formation of Cu: flz and Cu: met complexes were evaluated accordingly. The conductometric titrations was carried out at 25 ℃. Data after the analysis showed the formation of 1:1 [M: L] ratio between Cu: flz and Cu: met; with stability constant of 3.39 and 2.25, respectively. The free energy change, -4.62 and -3.07 $kCalmol^{-1}$ was obtained for Cu-flz and Cu-met, respectively. The negative values of ΔG means that the complexes formation process is spontaneous. This work has strongly revalidated previous claims and can be used in exploring more potential applications and enhancement of these drugs' efficacies.

Keywords:
Stability Constants, Conductometry, Turner Method, Drug

INTRODUCTION

The interaction between metal and ligand is a fundamental aspect of coordination chemistry, with significant implications in pharmacology and drug development (Abdullahi et al., 2025). In this context, the thermodynamic stability constant (K) serves as a critical parameter for assessing the strength of the interaction between a metal ion and a ligand, particularly in the case of drug-metal complexes. A high metal-ligand thermodynamic stability constant indicates a strong and stable interaction, which can be vital for the efficacy and safety of metal-based drugs. Several factors that affect the stability of metal complexes include; nature of central metal ion and ligand, chelating effect, nature of solvents, etc (Meraj et al., 2024).In addition, the thermodynamic stability constant, often denoted as K or K_f, quantifies the stability of a metal-ligand complex in solution. A higher value of K implies a more favorable formation of the complex, meaning that once the complex is formed, it is less likely to dissociate back into its constituent parts.

Furthermore, a high stability constant indicates that the metal-ligand complex is resistant to dissociation in biological systems, which can enhance the bioavailability of the drug. This stability ensures that the therapeutic metal remains active in the presence of competing ions and biomolecules, leading to improved pharmacokinetics and bioactivity (Meraj et al., 2024). Many metal-based drugs, such as cisplatin and its derivatives, exploit the stability of metal-ligand interactions to target specific biomolecules, including DNA.

A stable metal-ligand complex can facilitate selective binding to target sites, enhancing therapeutic efficacy while minimizing side effect (Karges et al., 2021)(Yan et al., 2024). This selectivity is particularly crucial in cancer therapy, where minimizing damage to healthy cells is essential. The stability of metal-ligand complexes can also mitigate toxicity concerns associated with free metal ions. Unbound metal ions may exhibit toxic effects due to their reactivity and ability to interact with a wide range of biological molecules. By forming stable complexes, the bioavailability of free metal ions is reduced, which can lead to safer therapeutic profiles(Flora & Pachauri, 2010)(Gulcin & Alwasel, 2022).Understanding the thermodynamic stability of metal-ligand interactions can guide in drug design. Researchers can optimize ligands to achieve higher stability constants, enhancing the performance of metal-based therapeutics. For instance, modifications to ligand structures can be made to improve their chelating ability, leading to stronger complexes and more effective drugs(Awasthi et al., 2019)(Law, 2024).

In general, techniques like pH-metry, potentiometry, conductometry, polarography, spectrophotometry, ion exchange etc are used for the complexometric study - as build up to determination of stability constant (Asemave, 2024; Asemave et al., 2023; Burghate et al., 2015). In all these methods, conductometry technique is considered as a more accurate because its viability at very low solution concentrations where the interactions between cation and anion are known to be very small.

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More so, conductometry is a highly sensitive and inexpensive technique with a simple experimental arrangement (Rawate, 2018; Sonar, 2016) The electrical current in a chemical cell is carried out by the ionic entities in the solution conductometrically. The ease with which current is conducted through a solution is essentially depended upon the amounts and type of ions in the solution. During progress of a conductometric titration changes in the conductivity of the solution usually occur. Therefore, at the end point involving neutralization/ precipitation reaction the conductivity of the solution will be minimum. The equivalence point may be located graphically by plotting the change in conductance as a function of the volume of titrant added (Ghara et al., 2017). Therefore, the aim of this work was to investigate the conductometric thermodynamic stability constants of Cu-flz and Cu-met complexes.

MATERIALS AND METHODS

All chemicals used were of analytical grade. Pure sample of flz and met were obtained from reliable pharmaceutical company. $CuSO_4.5H_2O$ (Merck), ethanol and distilled water were of analytical grade. The conductance measurement was performed by conductivity meter.

Methods

Conductometric titrations for detection of Metal-Ligand ratio (Monovariant method)

The conductometric titrations for detection of Metal-Ligand ratio (Monovariant method) was carried out as previously reported (Burghate et al., 2015; Nair, 2013; Rawate, 2018; Smita, 2012; Wacker & Seubert, 2014). Solution of drug (flz/ met) having strength 0.01 M was prepared. Similarly, 0.02 M of metal salt was prepared and these stock solutions were suitably diluted as and when required. 5 mL of drug solution (0.01 M) was diluted to 50 mL in a beaker and kept at thermostatic bath at 25 ℃ (ligand solution). This was titrated conductometrically against 0.02 M metal salt solution taken in a burette. Conductance was recorded after every addition of 0.5 mL of metal salt solution with constant stirring at constant temperature. Volume corrections were applied as: Conductance = $\frac{V+v}{V} \times Observed\ Conductance$; where V = initial volume of ligand solution and v = volume of metal solution added.

Modified Job's Method of Continuous Variation

Again, modified Job's Method of Continuous Variation was adopted (Burghate et al., 2015; Nair, 2013) for the determination of the composition. Equimolar solutions of ligand and metal were prepared and three series C_1, C_2, C_3 of solutions were made. In set C_1 metal salt solution was filled with volume 0mL to 20 mL and total volume was made to 20 mL in each. Similarly, in C_2 ligand solution was filled and set C_3 was prepared by mixing metal salt solution from 0 mL to 20 mL and ligand solution from 20 mL to 0 mL.

Conductance was recorded for each solution. Change (Δ) in conductance was calculated as "C_1+C_2-C_3". Graphs were plotted between corrected conductance and mole metal-ligand ratio. The composition was determined from the equivalence point in the graph.

Determination of the stability constant of the M-L complex

For the determination of the M-L stability constants, Turner and Anderson's Modified Job's Method were used (Burghate et al., 2015; Ghara et al., 2017; Smita, 2012). Suppose the initial concentration of metal ion was 'a' and that of ligand was 'b' then the stability constant 'K' is given by (see equation 1); where K = conditional stability constant; x = concentration of complex. Therefore, x was determined (hence the M-L stability constant) by the operations as presented in equations 2 and 3. From equation 2, a_1 and b_1 are concentrations of metal ion and ligand before dilution; a_2 and b_2 are concentrations of metal ion and ligand after dilution. Hence, x was calculated by the aid of equation (3) using the appropriate values of a_1, a_2, b_1, and b_2 respectively.

$$K = \frac{x}{(a-x)(b-x)}\ ; \quad (1)$$

$$\frac{a_2-a_1}{a_1-x} = \frac{b_1-b_2}{b_2-x}; \quad (2)$$

$$x = \frac{a_2b_2-a_1b_1}{(a_2-a_1)+(b_2-b_1)} \quad (3)$$

Determination of thermodynamic Paramaters

On the basis of log K values, free energy change of the system was determined by using the following equation; ΔG = -2.303RT log K; where, R = Gas constant & T = absolute temperature, ΔG ($JK^{-1}mol^{-1}$) (Ghara et al., 2017; Rawate, 2018).

RESULTS AND DISCUSSION

Results from the Monovariant Method

The results for the conductometric titrations of Cu and flz/ met are presented in Figure 1 (for Cu-flz) & Figure 2 (for Cu-met). Two slopes were drawn from each of the plots and the intersect signifies the point of equivalence. In general, the conductivity was observed to increase with increasing concentration. This happened because of increase in the number of ions per unit volume of the solution (Burghate et al., 2015; Gopalan & Ramalingam, 2001).

Therefore, the determination of metal-ligand ratio (Cu: flz/met) - stoichiometric analysis - was carried out as: $V_1S_1 = V_2S_2$ (where V_1 = initial volume of the ligand, 50 mL, V_2= volume of metal added, 3 mL, S_1 = strength of ligand, 0.001 M and S_2 = strength of complex (Burghate et al., 2015; Ghara et al., 2017; Smita, 2012). Therefore,

$$S2 = \frac{50 \times 0.001}{3} = 0.0167 \sim 0.02$$

Hence the metal ligand ratio is 0.02: 0.02 = 1: 1.

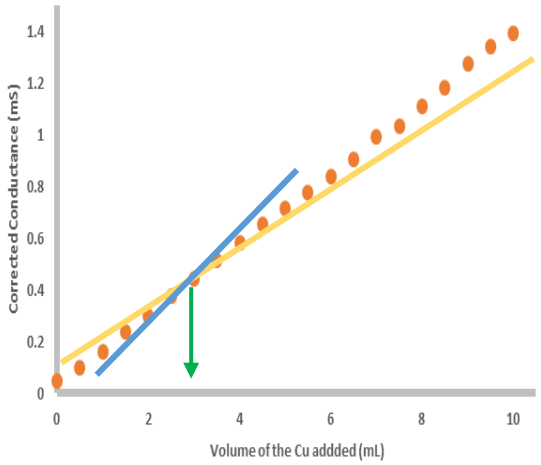

Figure 1: Corrected conductance between Cu and flz, [Cu] = 0.02 M and [flz] = 0.001 M

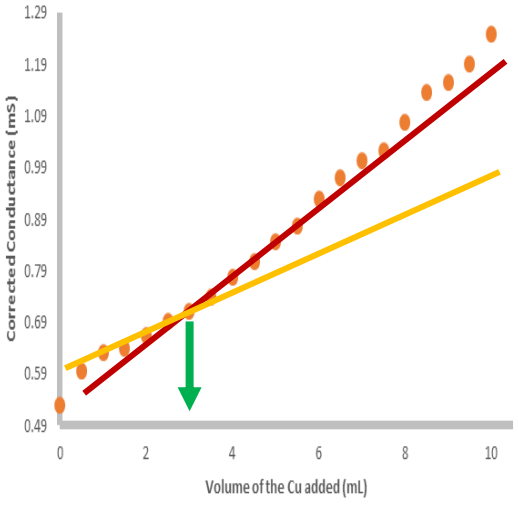

Figure 2: Corrected conductance between Cu and met, [Cu] = 0.02 M and [met] = 0.001 M

Results of the Modified Job's Method of Continuous variation

The results for the modified Job's method of continuous variation are given in Tables 1-4; Tables 1 & 2 are for Cu: flz at 0.01 M and 0.005 M, respectively. Then Tables 3 & 4 represents the results of Cu: met at 0.01 M and 0.005 M respectively. Again, the curves implied that the equivalent points occurred at the M-L ratio of 10: 10, hence the stoichiometry is 1: 1 as earlier observed (Rawate, 2018). The results here conforms to the formation of complex of Schiff base with Cu, which also takes place in the ratio 1:1 by using the monovariant method (Ghara et al., 2017). Again, this stoichiometry agrees to the formation of complex of amyloride with Pb with a the ratio 1:1 (Nair, 2013). More so, the formation of complex of N- benzothiazole-2-yl-3,5- disubstituted pyrazoline with Co, Ni, Cu take place in 1:1 ratio (Burghate et al., 2015); just as the conductance study of the interaction between Cu-rifampicin in aqueous medium at 303 K resulted into 1:1 complex (Rawate, 2018).

Table 1: Modified Job's Method of Continuous Variation, [Cu] = [flz] = 0.01 M

S/No	M - L ratio	Δ Cond. ($C_1+C_2-C_3$)	Corrected Conduct. (mS)
1	2:18	0.27	0.297
2	4:16	0.27	**0.351**
3	6:14	0.27	0.378
4	8:12	0.34	0.476
5	10:10	0.40	0.600
6	12:8	0.36	0.576
7	16:4	0.32	0.544
8	18:2	0.22	0.396

Table 2: Modified Job's Method of Continuous Variation, [Cu] = [flz] = 0.005 M

S/No	M-L ratio	Δ cond. ($C_1+C_2-C_3$)	Corrected Cond. (mS)
1	2:18	0.12	0.132
2	4:16	0.06	0.072
3	6:14	0.10	**0.130**
4	8:12	0.10	0.140
5	10:10	0.11	0.165
6	12:8	0.06	0.096
7	16:4	0.02	0.036
8	18:2	-0.01	-0.018

Table 3: Modified Job's Method of Continuous Variation, [Cu] = [met] = 0.01 M

S/No	M-L ratio	Δ cond. ($C_1+C_2-C_3$)	Corrected Cond. (mS)
1	2:18	0.18	**0.198**
2	4:16	0.10	0.126
3	6:14	0.20	0.260
4	8:12	0.40	0.560
5	10:10	0.42	0.630
6	12:8	0.38	0.620
7	14:6	0.35	0.600
8	16:4	0.05	0.090
9	18:2	-0.05	-0.095

Table 4: Modified Job's Method of Continuous Variation, [Cu] = [met] = 0.005 M

S/No	M-L ratio	Δ cond. (C_1+C_2 – C_3)	Corrected Cond. (mS)
1	2:18	0.08	0.088
2	4:16	0.03	0.036
3	6:14	0.08	0.104
4	8:12	0.09	**0.126**
5	10:10	0.09	0.140
6	12:8	0.07	0.120
7	14:6	0.05	0.085
8	16:4	0.03	0.054
9	18:2	-0.05	-0.095

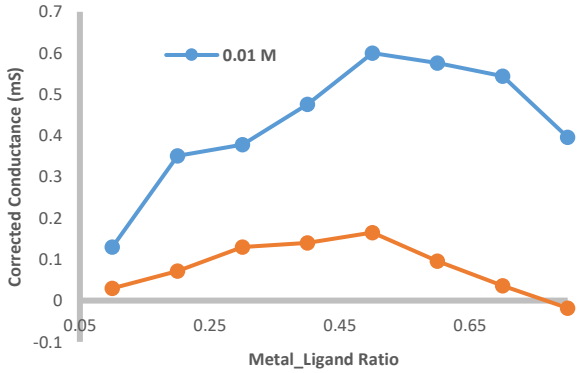

Figure 3: Plot for estimation of Cu: flz complex composition and stability constant

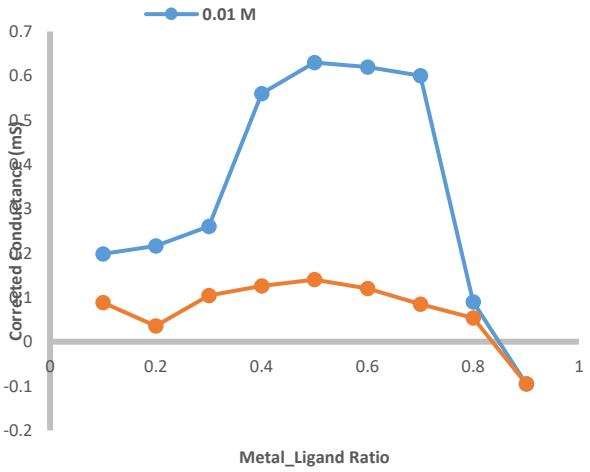

Figure4: Plot for estimation of Cu: met complex composition and stability constant

Results for stability constants

The stability constants were determined as follows as they similarly report in the literature (Ghara et al., 2017; Rawate, 2018). For Cu-flz we have: a_1 = (4× 0.01)/20 = 0.002; b_1 = (16×0.01)/20 = 0.008; a_2 = (6×0.005)/20 = 0.0015; and b_2 = (14×0.005)/20 = 0.0035. Thus, x = 0.00215. whereas, for Cu-met: a_1 = (2×0.01)/20 = 0.001; b_1 = (18×0.01)/20 = 0.009; a_2 = (8×0.005)/20 = 0.002; and b_2 = (12×0.005)/20 = 0.003. Thus, x = 0.001. Hence K (as described in Equation 1) was determined for Cu-flz and Cu-met, respectively. More so, free energies change (G= -2.303 RT log K) were obtained. The formation constants (K) and the free energy change are given in the Table 5.

Parameters	Cu-flz	Cu-met
K	2450.14	178.57
LogK	3.39	2.25
ΔG (kCalmol^{-1})	-4.62	-3.07

Table 5: Conductometric formation constant of Cu-flz and Cu-met complexes

Our results of the formation constant and the free energy change totally tally with the following reports. Data from the modified Job's method of continuous variation was used to calculate the stability constant (log K= 3.00) of the Pb-amyloride complex with the free energy change, -4.134 Kcal/mol. The value of free energy change is negative showing the feasibility of complex formation (Nair, 2013). LogK = 4.1668 was found for the complex Cu-Schiff base (Ghara et al., 2017). Analogously, the free energy change of Cu-rifampicin and other complexes had negative values of ΔG implying the complex formation process is spontaneous (Rawate, 2018; Sonar, 2016).

This research has much import in exploring the optimization and diversification of drug use. The battle against antimicrobial resistance (AMR) requires a multi-faceted approach. While the development of new therapeutics remains essential, repurposing existing drugs and harnessing the antimicrobial properties of metal ions/ metal-drug complexes offer promising and complementary strategies. Therefore, drug repurposing alongside the therapeutic use of metal ions/ metal-drug complexes, offers a viable path forward in our ongoing fight against the rise of superbugs and the threat they pose to global health.

CONCLUSION

This work showed that the stoichiometries of Cu: flz and Cu: met are 1: 1. Meanwhile, the formation constants of the complexes, Cu: flz and Cu: met obtained are 3.39 and 2.25, respectively. Conductometric technique was used. It was observed that the free energy change is -4.62 and -3.07 kCalmol^{-1} for Cu-flz and Cu-met, respectively. Thus, Cu-flz has higher formation constant and free energy than the Cu-met complex. This work has strongly revalidated

previous claims and can be used in exploring more potential applications and enhancement of these drugs' effectiveness.

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