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Original Research Article

Spectrophotometric Study of Complex Formations between Alprazolam and Some Transition Metal Ions in Non Aqueous Solution

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ABSTRACT

In this study, the complexation reaction between Alprazolam (ALP) and metal ions (Zn^{2+} , Ni^{2+} , Cu^{2+} and Co^{2+}) was investigated by using spectrophotometry in ethanol solvent. The stoichiometry of M^{+}/ALP complexes was calculated by applying the Job, molar ratio and Continuous Changes methods and the relevant diagrams were plotted for each metal ions in each method. The results show that the obtained complexes are 1:3. In the Continuous Changes method a defeat was observed at molar fraction of 0.66 for all complexes, which confirms complexes with 1:3 mole ratio. The formation constants of complexes were determined by using nonlinear least square method (KINFIT software) and it was concluded that the stability of complexes is varied in the order $\text{Cu}^{2+} > \text{Co}^{2+} > \text{Ni}^{2+} > \text{Zn}^{2+}$. Therefore, Cu is the strongest and Zn formed with Alprazolam ligand is the weakest complex.

Keywords: Spectrophotometric, Alprazolam, Metal ions, Stability, Complexation Reaction.

Introduction

Complex formation and the effect of solvent composition on sustainability and complex nature created has been considered in many studies. Researches shows that some drugs those contain metal complexes are more active [1]. Alprazolam as a benzodiazepine drug is included in the category of tranquillizer drugs [2, 3] and it is known with teriazole structure[4], high effectiveness and low toxicity. The alprazolam effects can be justified by the performance of the drug in the brain [5, 6]. Alprazolam has a poor solubility in water at physiological pH [7] so that after oral administration it is quickly absorbed and affects the membranes of nerve cells as a result, similar to the other benzodiazepines and benzodiazepine receptors, and increases login chloride in cells [8]. It is used to treat anxiety disorders and as an adjunctive treatment for depression[9]. It has been reported that complexes of copper (II) with alprazolam appears to be quite active, having a rapid onset of action and it also prolongs the duration as compared to that of alprazolam itself. [10]. Absorbance measurements based on UV (ultraviolet) and visible radiation have been widely used for identifying a large number of inorganic and organic species. Molecular absorption methods of UV or visible is most widely used among all quantitative analysis techniques and clinical chemical laboratories all around the world [11, 12]. One of the important branches in analytical chemistry is study of complex formation between a variety of ligands and cations in various solvents that can conduct an introduction to information new ligands with cations in the solution[13]. Spectroscopy is a valuable tool for obtaining complex combination of ions in solution and the complex formation constants[14]. To achieve this purpose, complex formation stoichiometric should be determined based on one of the following three methods:

- 1) Molar ratio method
- 2) Slope ratio method
- 3) Continuous changes method

In 2012, Hosseini and Nezhad-Ali studied the formation of a complex between iodoquinol and a number of metal complexes with spectrophotometry in binary solvent (ionic power = 0.1). The Mole ratio and Job methods confirmed complex with 1:1 ratio [15]. In 2010, Abdel-Latif & and Saber Mansour studied on the potentiometric and conductometry behaviours and thermodynamics of 3-methyl-1-phenyl complex. Their results showed that by increasing

temperature and solution, ionic power constant of complex formation dropped [16]. Afkhami et al. calculated the constant of formation complex between newly synthesized Schiff base and number of metal cations in chloroform and dichloromethane solvents. This drug as ligand can form complex through electron donor groups with transition metals. Stoichiometry of M_2L & ML was obtained for complex with the use of Rafa on the spectrophotometric data [17]. In 2012, Asadi et al. studied on the formation and thermodynamics of a complex between a number of Schiff base ligands and metal cations as electron acceptor. Their results showed that by increasing temperature, constant of complex formation dropped and Ni was the strongest complex[18].

In 2010, Tirmazi and heyyat studied the formation of a complex between Famotidine and nickel cation with spectrophotometry at a wavelength of 326 nm and different temperatures. The Mole ratio method confirmed complex with 1:4 (nickel: Famotidine) ratio [19].

In 2014, Laatikainen et al reported the formation of a complex between 2-amino methyl pyridine and Nickel cation at 22°C. Stoichiometry of ML , ML_2 & ML_3 was obtained for complex with the use of PLS, LS and Continuous changes methods [20].

In this study, the stability of the complex formed by ALP ion complexes with various metal ions that is used in non-aqueous solvents will be investigated by using Spectrophotometry method.

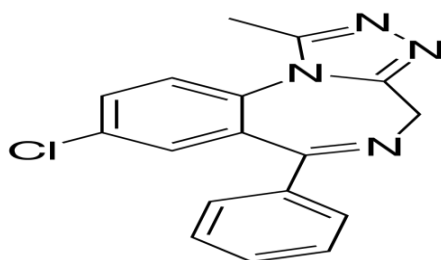


Figure1. Alprazolam structure

Experimental

General

The reagents, used are copper nitrate (99.5%, Merck), cobalt nitrate (99.5%, Merck), nickel nitrate (99.5%, Merck), zinc nitrate (99.5%, Merck), ethanol (96%, Merck), sodium dodecyl sulphate (SDS)(99.5%, Merck) for increasing dissolution rate of alprazolam, acetate buffer (pH= 5) for preventing pH changes. All the reagents were used as received without further purification. Visible and UV spectrophotometer Manufactured by Shimadzu Co, Model uv-2550 two rays equipped with Quartz cell were used to register the UV and visible spectrums.

Initially, the salts were dried since the experiments should be performed in a dry environment. Drying was performed with transferring the ligand (Alprazolam) to a desiccator containing phosphorus pentoxide which is connected to a vacuum. A solution of ligand with constant concentration (5×10^{-5} M), 1.5 ml SDS (5×10^{-4} M) and 1 ml acetate buffer was prepared in a balloon 10 ml. Furthermore, a solution of cations with concentration (8×10^{-5} M), 1.5 ml SDS (5×10^{-4} M) and 1 ml acetate buffer in balloon with 10 ml volume was prepared. After the addition of cations to the ligand, the absorption amount was measured after a short time that for equilibrium solution was approximately 5 minutes. In the continuous changes method a solution with the same concentration of the ligand and cations was prepared (5×10^{-5} M). Samples were prepared with different volumes of metal-ligand in a way that the final volume and total concentration were kept constant (2 ml). After equilibrium was reached, the absorption amount during the maximum wave of ligand was measured.

The solution of ligand with concentration 0.00005 M in ethanol, in the presence of buffer and SDS was prepared and the absorption amounts in the wavelength range of 200-350 nm spectrum were studied. Alprazolam has two maximum wavelengths in the range from 222 to 250 nm as shown in Fig 2.

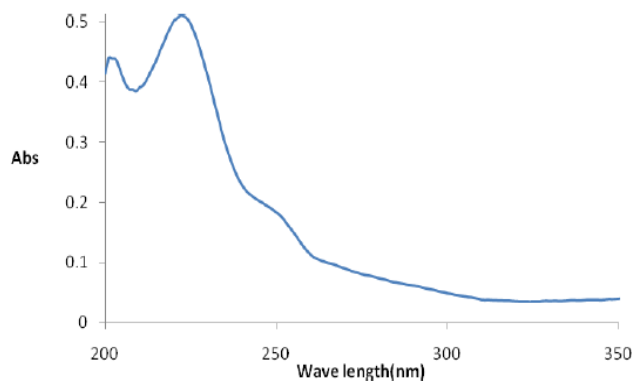


Figure2. The absorption spectrum of Alprazolam ligand

Results and discussion

Absorption spectrum of Alprazolam and the formation of complexes

To study the reaction between the ligand and the desired metal cations, the absorption spectrum of Ligand was measured in two cases: in the absence of metal cations and in the presence of metal cations. The obtained results are displayed in Figure 3. As it is seen, by increasing the metal cations, the absorption intensity decreased with a partial displacement or the formation of new absorption bands for complexes. The observed changes are evident for the formation of new species. Therefore, the comparison of alprazolam absorption of the two cases, shows that, in the presence of cations, the absorption at a wavelength of 200 nm increased from 4.2 to 7.2 while the maximum absorption in the absence of cations increased from 0.5 to 0.6. This increase is due to the presence of metallic cations. However, in both the cases, the alprazolam maximum absorption occurred in the wavelength of 200-250 nm.

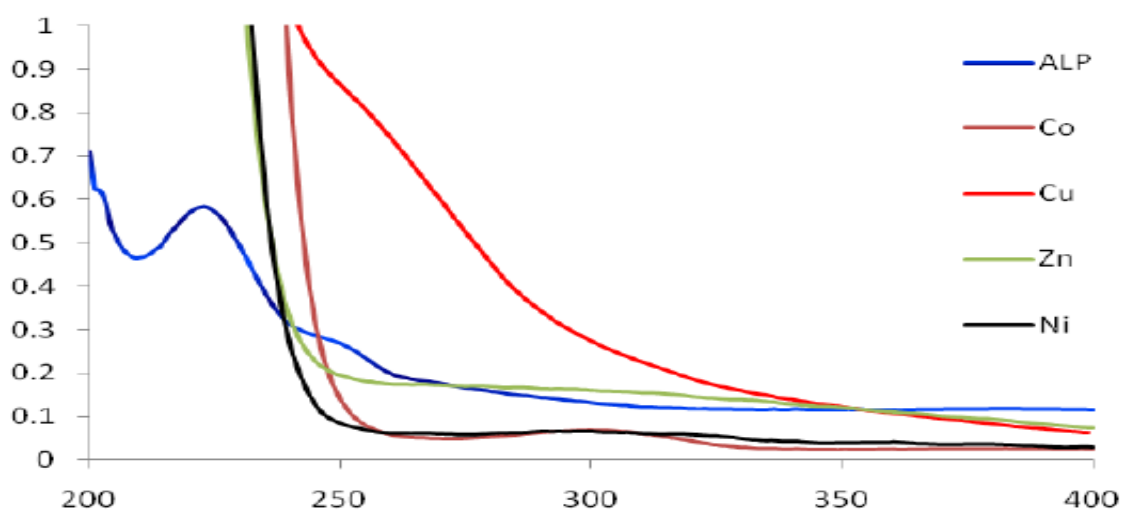


Figure3. The absorption spectrum of Alprazolam ligand (5×10^{-5} M) in the absence and presence metal cations

The determination of the [Ligand+metal cation] complex stoichiometry based on the molar ratio method

In the molar ratio method, a series of solutions should be provided in a way that the concentration of a reactant is constant (metal) while that of the other reactant is changed. Then,

the absorbance of each solution is determined and the absorption diagrams are plotted versus molar ratio of reactants[21]. In this study, two curves with different slopes were obtained the intersections of which shows Ligand to metal ratio. According to the plotted diagrams, the absorption amount decreases with increasing cation concentration.

In order to determine complex stoichiometry, the required solution was prepared according to the method described in the experimental section. First, the absorption amount of alprazolam solution was measured. Next, the cation solution was added slowly to the alprazolam solution at 25°C and when the equilibrium was achieved in the region of 200-400 nm, the absorption amount was measured and the absorbance values was read at each point in [Ligand] / [metal cation] molar ratio drawn. The considered molar ratios are shown in Table 1. In this study, four metal cations were used including copper, cobalt, nickel and zinc.

Table1. The molar ratio of Ligand and metal cation

[L]/[Cu ²⁺]	[L]/[Co ²⁺]	[L]/[Ni ²⁺]	[L]/[Zn ²⁺]	[L]/[Cu ²⁺]	[L]/[Co ²⁺]	[L]/[Ni ²⁺]	[L]/[Zn ²⁺]
0.42	0.42	0.42	0.42	2.54	2.54	2.54	2.54
0.87	0.87	0.87	0.87	3.01	3.01	3.01	3.01
1.02	1.02	1.02	1.02	3.24	3.24	3.24	3.24
1.12	1.12	1.12	1.12	3.55	3.55	3.55	3.55
1.47	1.47	1.47	1.47	3.88	3.88	3.88	3.88
1.64	1.64	1.64	1.64	4.03	4.03	4.03	4.03
2.01	2.01	2.01	2.01	2.54	2.54	2.54	2.54

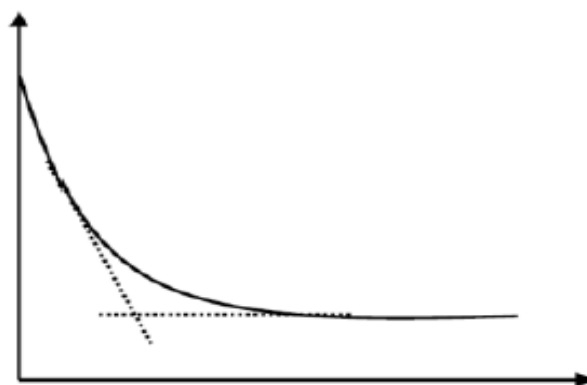


Figure4. molar ratio Method at a wavelength of titrant

In the $[L+Cu^{2+}]$ and $[L+Ni^{2+}]$ complexes the absorption increased by adding cation solution in wavelength range of 220-250 nm of ligand. In the $[L+Co^{2+}]$ complex, the absorption initially increased by the addition of cation solution while it decreased over time. In the $[L+Zn^{2+}]$ complex, the absorption decreased continuously by the addition of cation solution in the studied domain. The existence of isosbestic point and non-interference Indicates a complex with 1:3 molar ratio for $[L+Cu^{2+}]$ and $[L+Co^{2+}]$ systems at a wavelengths of 296 and 239 nm. however, The existence of isosbestic point and non-interference Indicates a complex with 1:3 molar ratio for $[L+Ni^{2+}]$ system at wavelengths of 242 & 254 nm and also for $[L+Zn^{2+}]$ system at a wavelength of 233 nm. The less curvature in the molar ratio diagram of $[L+Zn^{2+}]$ is an evident for the weak ligand complexes with these cations. It should be noted that, a wavelength the absorption of which depends only on the number of equivalent of two adsorbents is called as the isosbestic point [22].

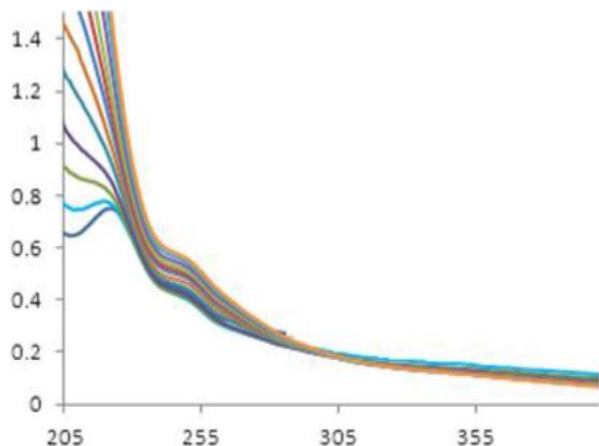


Figure5. The absorption spectrum of Alp in the presence adding of $[Cu^{2+}]$ solution by mentioned molar ratio

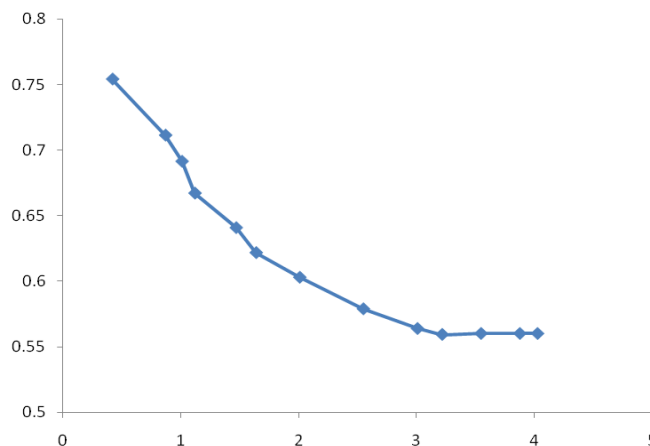


Figure6. Molar ratio curve for the system L + Cu

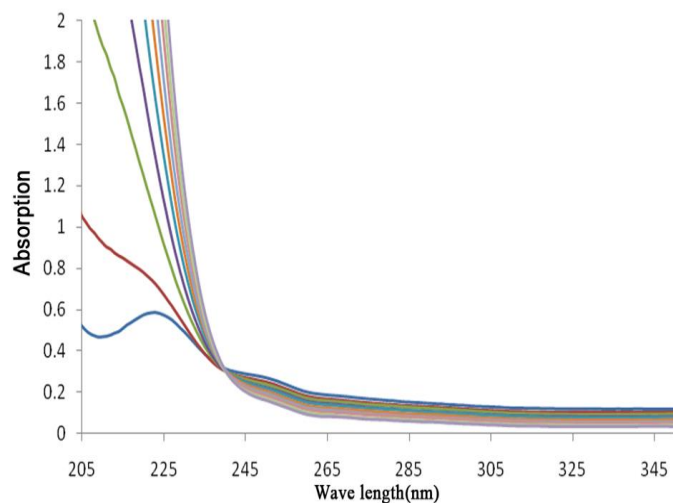


Figure7. The absorption spectrum of Alp in the presence adding of $[\text{Co}^{2+}]$ solution by mentioned molar ratio

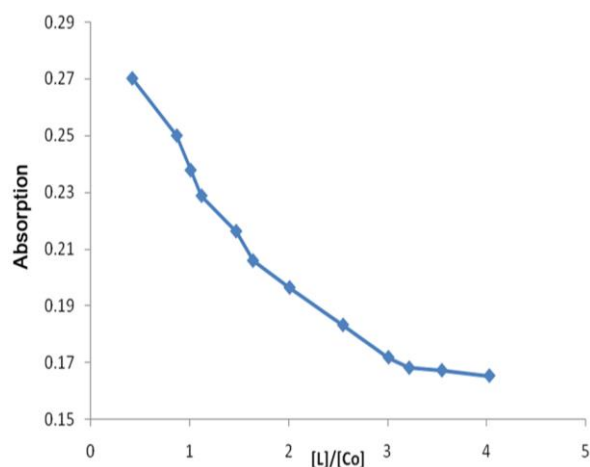


Figure8. Molar ratio curve for the system L + Co

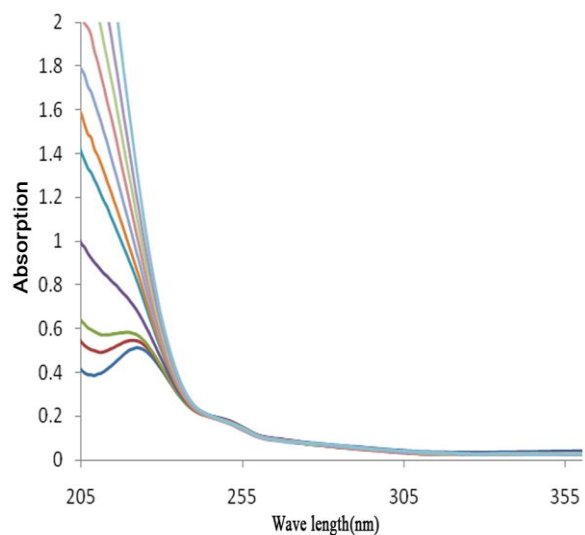


Figure9. The absorption spectrum of Alp in the presence adding of $[\text{Ni}^{2+}]$ solution by mentioned molar ratio

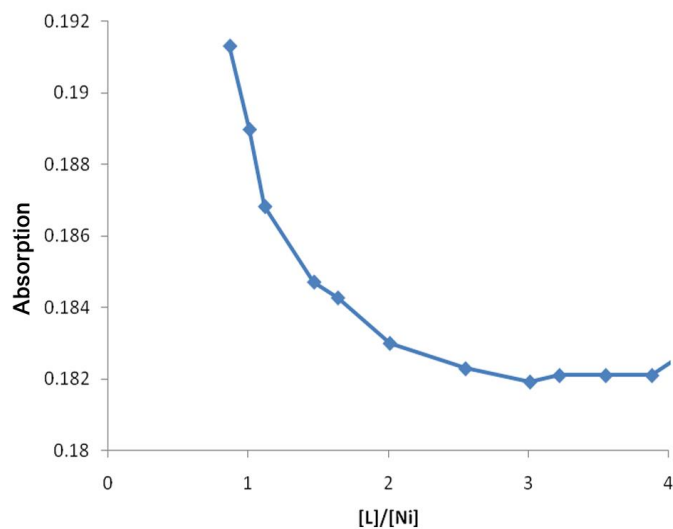


Figure10. Molar ratio curve for the system L + Ni

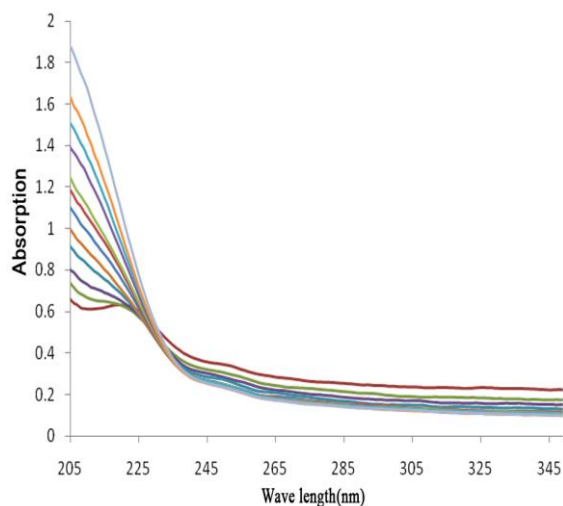


Figure11. The absorption spectrum of Alp in the presence adding of $[Zn^{2+}]$ solution by mentioned molar ratio

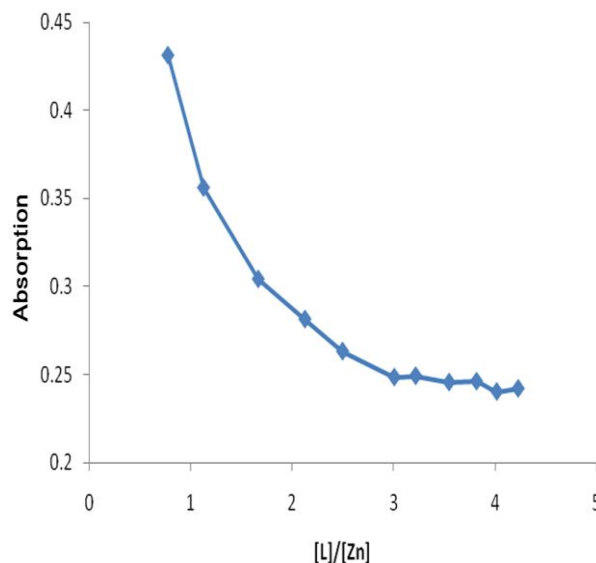


Figure12. Molar ratio curve for the system L + Zn

The determination of the ML_2^1 complex stoichiometry based on the continuous changes method

The theory of the continuous changes method was presented by Ostromisslensky Lenski [23] and Job [24]. As the complex stoichiometry of 1:3 is primarily confirmed in last Section, the continuous changes method is considered in this study. For this purpose, solutions were prepared with the same concentrations of ligand and copper, cobalt, nickel and zinc cations and the absorption amounts were measured in different molar fractions of cations. Then, the corrected absorption values were plotted versus molar fraction of copper, cobalt, nickel and zinc at the wavelength of each cations. The results of systems of ligand and bivalent metal cation are illustrated in Figure 13. The absorption diagram at the complex absorbed wavelength has a maximum and the maximum mole fraction in this figure shows complex composition. In the systems of $[L+Cu^{2+}]$, $[L+Co^{2+}]$, $[L+Ni^{+2}]$ and $[L+Zn^{2+}]$, the corrected absorption values were plotted versus molar fractions of copper, cobalt, nickel and zinc cations at the wavelength of 233,

¹ [Ligand + Bivalent metal cation]

250, 248 and 250 nm. According to Figures 14 -17, there is only one defeat on the curves in the mole fraction of 0.66. This is another evidence on the formation of a complex of 3:1 for the studied systems.

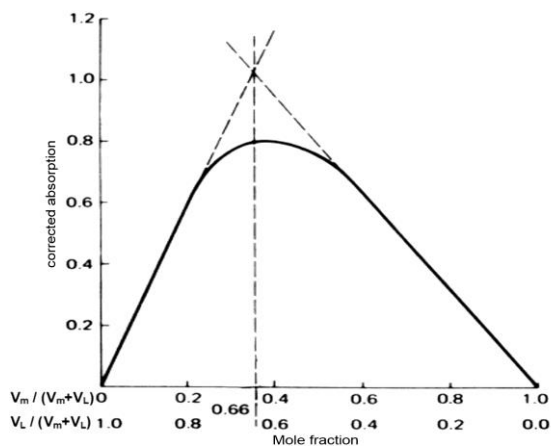


Figure13. continuous changes method diagram of ML_2 complex

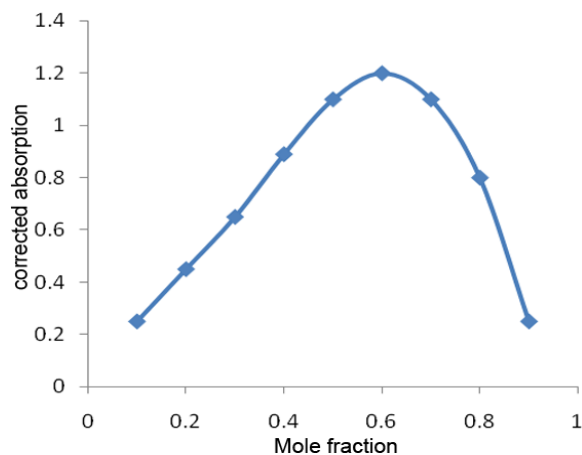


Figure14. continuous changes method diagram of $[L+Cu]$ system

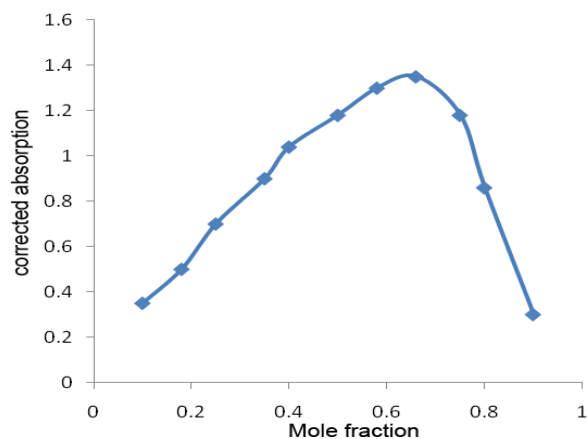


Figure15. continuous changes method diagram of $[L+Co]$ system

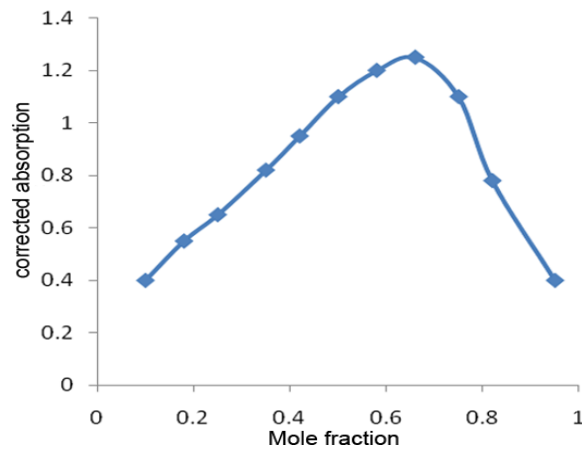


Figure16. continuous changes method diagram of $[L+Ni]$ system

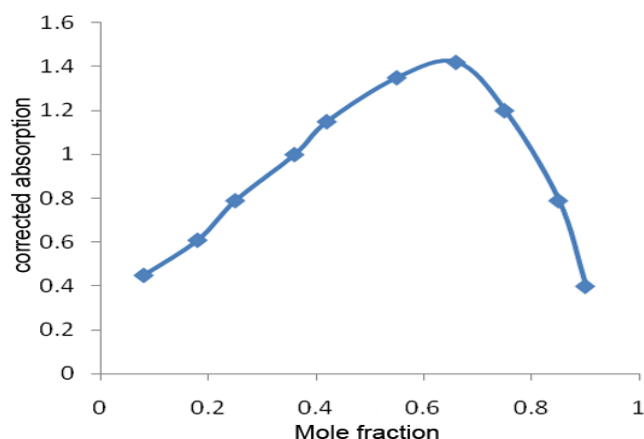


Figure17.continuous changes method diagram of [L+Zn]

The determination of the ML_2 formation constant of complexes

After measuring the absorbance values for different mole ratios at the wavelengths of the cations in last Section, the obtained values were fitted by using KINFIT curve fitting software (ver. 1.1.14, with GPL-2|GPL-3 licence) based on the nonlinear least squares method and the formation constants of complexes were calculated. The diagrams were plotted for ligand complexes with cobalt and zinc cations at the wavelength of 250 nm and for ligand complexes with copper and nickel cations at the wavelengths of 233 and 248 nm. The symbols (o), (\times) and (=) stand for the theoretical points, the experimental points and two modes equality, respectively. The constant values obtained through curve fitting for the resulting complexes of alprazolam are shown in Table 2. The formation constant of the complex (K_f) is calculated from the following formula: $K_f = [ML_2]/[M^{2+}][L]$ where, $[ML_2]$: is complex concentration, $[M^{2+}]$ is metal cation concentration, and $[L]$ is Ligand concentration.

Table2. The constant of complexes formation

M^{2+}	Cu^{2+}	Co^{2+}	Ni^{2+}	Zn^{2+}
Log K_f	13.39	13.26	13.14	13.09

Conclusion

The existence of isosbestic point in all the formed complexes and non-interference in them is evidence of the complex existence. By using the molar ratio method, weaker defeat is revealed in curves of Co, Ni, Zn with ligand compared to that of Cu. This indicates that the cited cation complexes are weaker than that of copper complex. The results of the curve fitting confirms this issue and according to the obtained values for the constants of complex formation, Cu was the strongest and Zn formed with ligand was the weakest complex. Stability of complexes is varied in the following order: $Cu^{2+} > Co^{2+} > Ni^{2+} > Zn^{2+}$. In the continuous changes method a defeat is observed at molar fraction of 0.66 for all complexes, which confirms complexes with 1:3 mole ratio.

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