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International Journal of Pharmaceutical Research & Allied Sciences, 2020, 9(1):121-129

Research Article

ISSN : 2277-3657
CODEN(USA) : IJPRPM

Determination of the Stability Constants Comlexes of Metformin Hydrochloride With Cu(II), Cd(II) and Zn(II)

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ABSTRACT

In the present work, binary complexes of Copper(II), Cadmium(II) and Zinc(II) with metformin hydrochloride have been studied potentiometrically. Stability constants of binary complex systems have been estimated by the method proposed by Irving-Rossotti at 25ºC and 0.11M ionic strength (NaClO4) in aqueous solution. The conditional formation constants of the complexes formed between ligand and metal were calculated according to pH function. The maximum values of the conditional formation constants were found to be in accordance with the mixed metal-ligand complex formation constants in a given pH region. In addition to these, the molar fractions were calculated using the formation constants of the mixed metal-ligand complexes. As a result of the experimental study, the values of stability constants of metal-ligand complexes at 25ºCare as noted below: $logK_1$=8.45; $logK_2$=8.30 for Zn(II)-Metformin hydrochloride; $logK_1$=8.78 ; $logK_2$=8.00 for Cu(II)-Metformin hydrochloride: $logK_1$=8.18; $logK_2$=7.36 for Cd(II) – Metformin hydrochloride.

Key words: *Metformin hydrochloride, Zinc(II), Copper(II), Cadmium(II) and metal-ligand complex, stability constants.*

INTRODUCTION

Potentiometric titration method is one of the techniques used to determine stability constants because this method is based on a powerful and simple electroanalytical method. In addition, potentiometric operation provides advantages for instance low cost, fast response, simple instrumentation, low detection limit and dynamic ranges. At the same time, the potentiometry method requires compensation with constant ionic power to ensure that the activity coefficients remain constant for all species in the experimental working environment [1, 2]. Metal ions usually bind to ligands through selective and strong interactions. The strength and selectivity of metal ligand bonds depend on stability constants. The complex properties of an aqueous sample against metal ions are very important because they determine the distribution of metal ions between different species and hence their solubility, mobility and toxicity. The stability constants of the metal-ligand complexes obtained as a result of the interactive relation between drugs with metals are very useful in determining the mechanism of drugs. However, the interaction of metals and ligands in complex media controls the stability of metal complexes [3, 4].
Metformin is a drug synthesized to reduce blood sugar [5]. Metformin hydrochloride is chemically designated as 2-(N,N-dimethylcarbamimidoyl) guanidine which has the molecular formula as shown in Figure 1. Given the chemical structure of Metformin hydrochloride, there are primary, secondary and tertiary amino groups as donor centers. In addition to these, Metformin hydrochloride is highly soluble in water but has poor solubility in lipids. Hence, it is difficult to extract it from the aqueous plasma matrix [6-8].

Currently, metformin hydrochloride has been used as a hypoglycemic agent in people with type-2 diabetes [9, 10]. It has further potential advantages in patients with the metabolic syndrome where hyperinsulinaemia is present [11]. One of the known clinical advantage of metformin hydrochloride over sulfonylureas is that doses of metformin hydrochloride do not cause hypoglycemia. Metformin hydrochloride does not reduce blood glucose in non-diabetic people because it has direct helpful impact on serum lipoproteins and lipids [12].

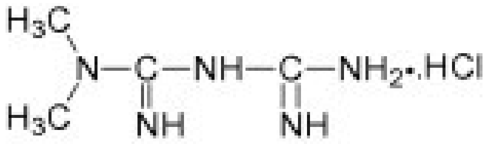

Figure 1. The chemical structure of Metformin HCI

EXPERIMENTAL

Reagents and chemicals

All other reagent used were analytical grade. Pure standard of metformin hydrochloride was purchased from Merck. Copper(II)nitrate trihydrate, cadmium(II)nitrate tetrahydrate and zinc(II)nitrate hexahydrate, perchloric acid ($HCIO_4$), 0.1 N sodium perchlorate (0.1 N $NaCIO_4$) and 0.1 N sodium hydroxide solution (0.1 N NaOH) reagent were obtained from Merck Chemical (Germany).

Preparation of standard stock and titration solutions

0.01 M Metformin hydrochloride (dissolved in water), 0.1000 N NaOH, 0.100 M $HClO_4$, 1.0 M $NaClO_4$, 0.01 M $Cu(NO_3)_2$, 0.01 M $Cd(NO_3)_2$and 0.01 M $Zn(NO_3)_2$solutions were prepared. The solutions for determination of protonation constants of metformin hydrochloride and metal ligand complexes were prepared as follows.

a) **$HCIO_4$:** 5 mL 0.100 M $HClO_4$ + 5.0 mL 1.0 M $NaClO_4$ were added and diluted to 50.0 mL by water.
b) **Metformin hydrochloride:** 5.0 mL 0.100 M HClO4 + 10.0 mL 0.0100 M Metformin hydrochloride + 5.0 mL 1.0 M NaClO4 were added and diluted to 50.0 mL by water.
c) **$HCIO_4$ + Metformin hydrochloride + Cu(II)**: 5.0 mL 0.100 M $HClO_4$ + 10.0 mL 0.0100 M Metformin hydrochloride + 5.0 mL 1.0 M $NaClO_4$ + 5.0 mL 0.0100 M Cu(II) were added and diluted to 50.0 mL by water.
d) **$HCIO_4$ + Metformin hydrochloride + Cd (II)**: 5.0 mL 0.100M $HClO_4$ + 10.0 mL 0.0100M Metformin hydrochloride + 5.0 mL 1.0 M $NaClO_4$ + 5.0 mL 0.0100 M Cd(II) were added and diluted to 50.0 mL by water .
e) **$HCIO_4$ + Metformin hydrochloride + Zn(II):** 10.0 mL 0.100M $HClO_4$ + 5.0 mL 0.0100M metformin hydrochloride + 5.0 mL 1.0 M $NaClO_4$ + 5.0 mL 0.0100 M Zn(II) were added and diluted to 50.0 mL by water.

The Determination of Protonation Constants

To determine the protonation constants, the mixture containing $HClO_4$ and ligand + $HClO_4$ solutions were titrated on the potentiometer device using NaOH (0.1N) (Figures. 2-4). Average $\bar{n}A$ values were calculated from the titration curves and for the calculation, the following equation was used.

$N_A = y + (v_1 – v_2) (N + E^0)/(V^0 + v_1) TL^0$

Where:

V^o	= volume at the beginning	: 50.0 mL
N	= normality of the base	: 0.100 N
TL^o	= total molar ligand concentration metformin hydrochloride	: $2.00.10^{-3}$ M

E° = concentration of acid : 0.0102 M

Y = the number of protons given for metformin hydrochloride : 0

The volumes of v_1 and v_2 were read from the titration chart which contain $HClO_4$ and ligand + $HClO_4$. $\bar{n}_A$ values at different pH values were determined using v_1 and v_2 volumes. Then, using these values, $\bar{n}_A$ = f (pH) was plotted. The protonation constants and the acidity constants of Metformin hydrochloride are outlined in Table 1.

The Determination of Stability Constants

The stability constants of the binary complexes were determined potentiometrically using Irving-Rossotti method. Therefore, the mixtures which contain some metal ions were titrated with standard 0.1 N sodium hydroxide solution in potentiometer device and the titration chart were plotted (Figures. 2-4). $\bar{n}L$ values were calculated using the equation given below. pL values were calculated using $\bar{n}L$ values to calculate the stability constants. The following equation was used to calculate $\bar{n}L$ values:

$$n_L = (v_3 - v_2) [N + E^0 + TL^0 (y - n_A)] / (V^0+v_2). n_A .TM^0$$

Where:

V°= volume at the beginning : 50.0 mL

N= normality of the base : 0.100 N

TL°= total molar ligand concentration : $2.00.10^{-3}$ M

E°= concentration of acid : $1.02.10^{-2}$ M

y= the number of protons given for Metformin hydrochloride : 0

TM°= total molar metal concentration : $1.00.10^{-3}$ M

The following equation was used to calculate pL values.

$$pL = \log \ (1+\beta_1[H+] + \beta_2[H+]^2) \ / TL^0 - n_L .TM^0$$

In order to establish stability constants of the mixed metal ligand complexes, Irving-Rossotti method was also used. The mixture of metals was consisted and ligand was titrated potentiometrically. The $\bar{n}_L$=f(p_L) graphs (Figures. 5-7) were plotted using $\bar{n}L$ and pL values which were calculated from titration curves. The separation among ($HClO_4$), ($HClO_4$) and ($HClO_4$ + L + M) plots in all potentiometric titration curves showed the formation of a mixed metal ligand complex (Figures 5-7). The approach of Irving-Rossotti to binary systems was applied for the mixed system. The results are summarized in Table 1.

$$M + L \rightleftharpoons ML$$

$$ML + L \rightleftharpoons ML_2$$

RESULTS AND DISCUSSION

In this experimental study, the conditional formation constants were calculated and these constants were found to be in agreement with the formation constants of mixed systems. However, this study describes the complexation formation between metformin hydrochloride with Cu(II), Cd(II) and Zn(II). This result affords us to find the stability constants of mixed metal-ligand complexes. The stability constants of Metformin hydrochloride-Cu(II), Metformin hydrochloride-Cd(II) and Metformin hydrochloride-Zn(II) complexes were determined in aquous solution by pH-metric titration. The conditional formation constants, namely the stability constants of metal-ligand complexes can also be calculated. The difference between the formation constants of mixed and binary complex systems is a parameter which characterizes the formation behaviour of mixed metal-ligand complexes.

These results would be helpful for studies related to understanding pharmaceutical action of guanidines. Cu(II) –Metformin hydrochloride, Zn(II) –Metformin hydrochloride, Cd(II) –Metformin hydrochloride systems are also in agreement with our observations systems.

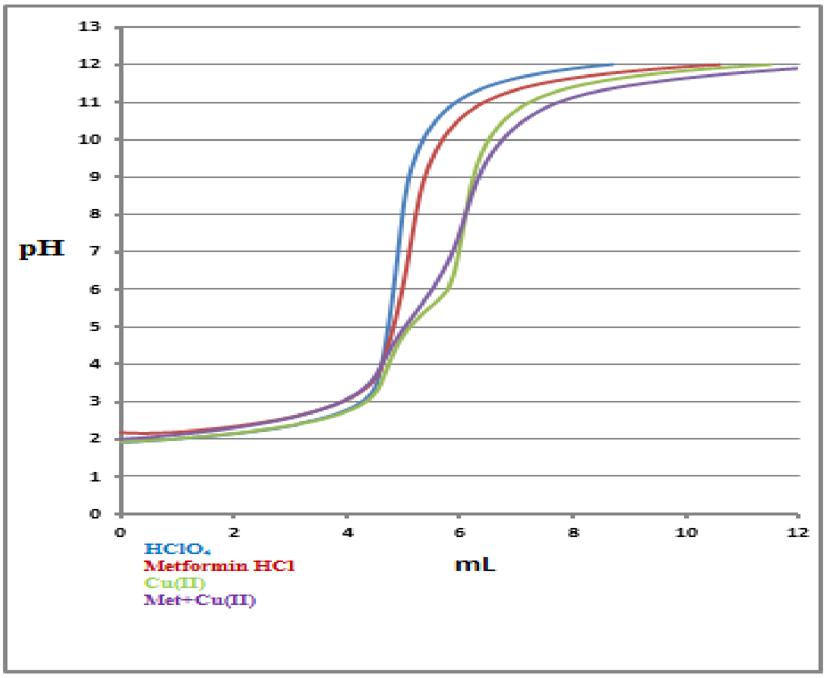

Figure 2. The potentiometric titration chart of metformin HCl - Copper (II) complex

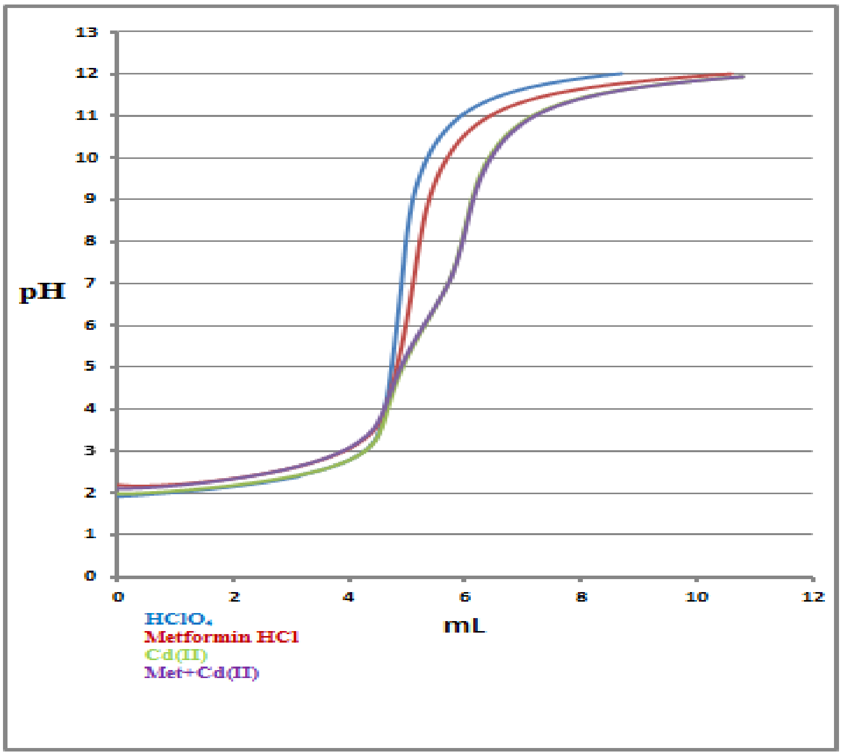

Figure 3. The potentiometric titration chart of metformin HCl - Cadmium (II) complex

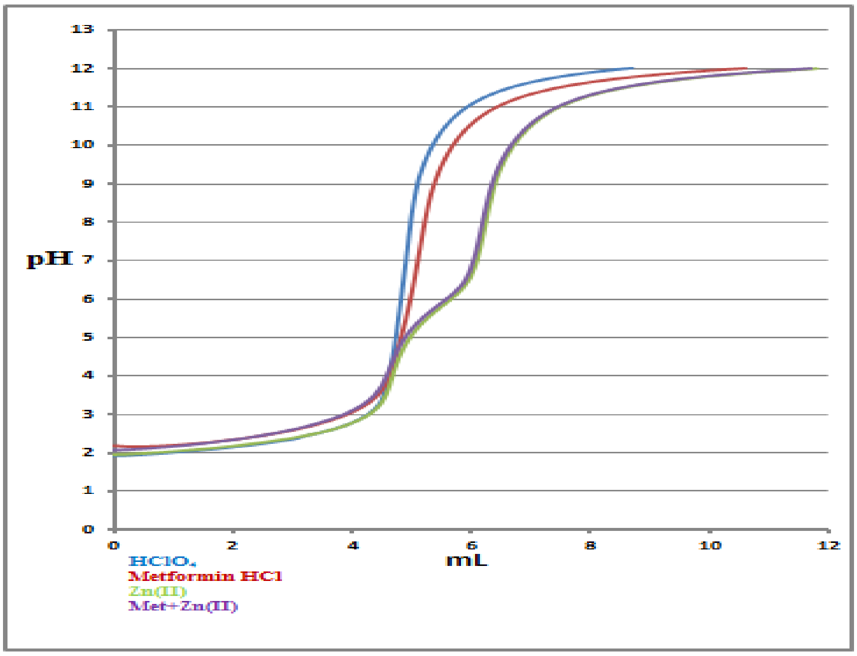

Figure 4. The potentiometric titration chart of metformin HCl - Zinc (II) complex

Table 1. The protonation constants of Metformin Hydrochloride

Metformin Hydrochloride	$\log K_1$=11,02	$\log K_2$=2,79

pL values were calculated using β values. The relation $\bar{n}_L$ = f (pL) was plotted using $\bar{n}_L$ and pL values which were calculated for each metal ion. The stability constants were determined from these graphs (Table 2).

Table 2. The stability constants of binary and ternary complexes

Ligand-Metal	**$\log K_1$**	**$\log K_2$**
Cu(II)-Metformin hydrochloride	8.78	8.00
Cd(II)-Metformin hydrochloride	8.18	7.36
Zn(II)-Metformin hydrochloride	8.45	8.30

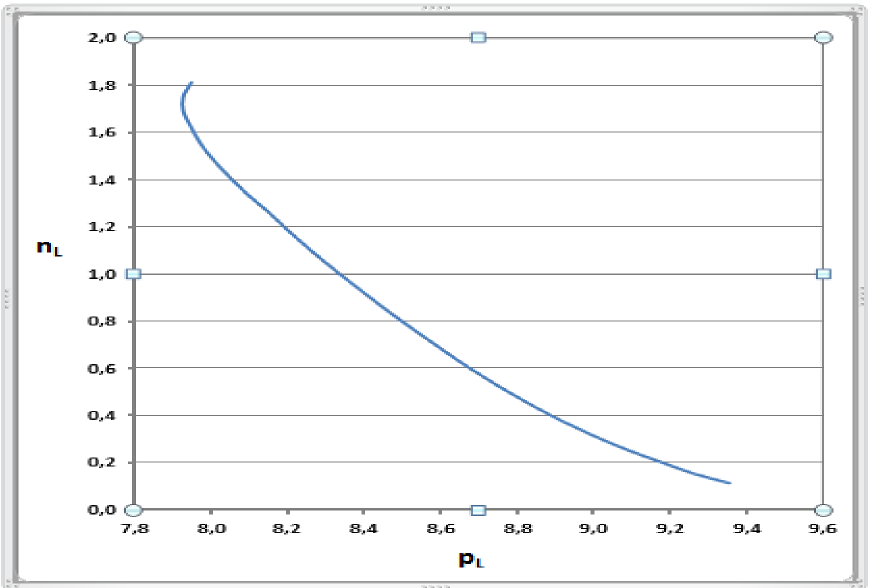

Figure 5. nL=f(pL) curve for Cu(II)-Metformin Hydrochloride

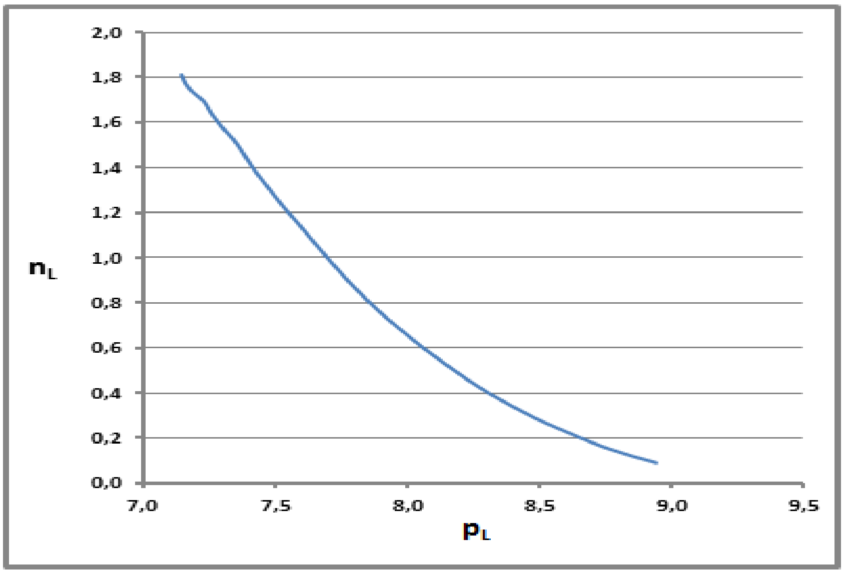

Figure 6. nL=f(pL) curves for Cd(II)-Metformin Hydrochloride

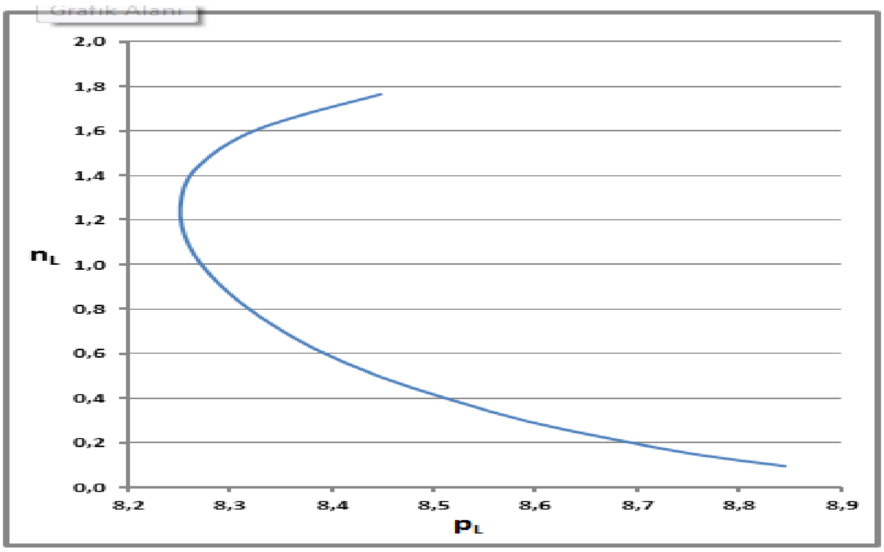

Figure 7. nL=f(pL) curves for Zn(II)-Metformin Hydrochloride

In addition, the conditional formation constants were calculated and were plotted as a function of pH (Figures. 8-10).

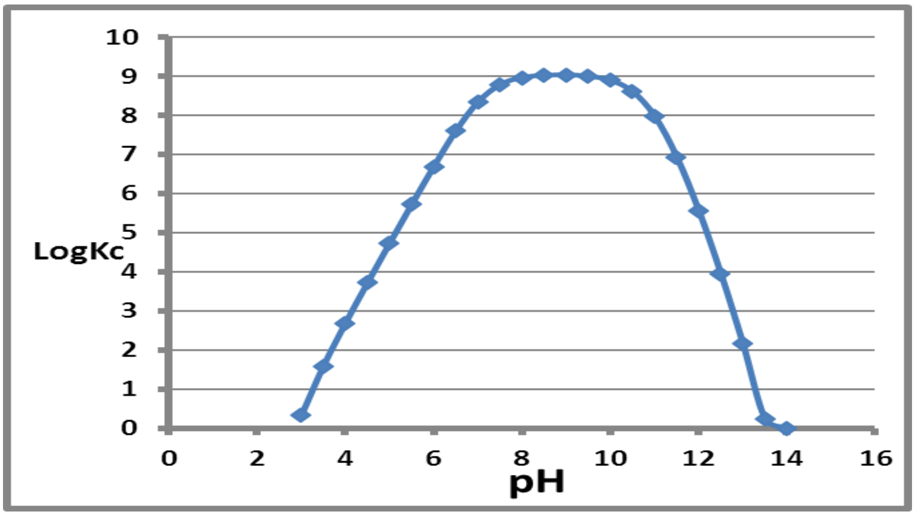

Figure 8. Conditional formation curve of Cu (II)-Metformin hydrochloride

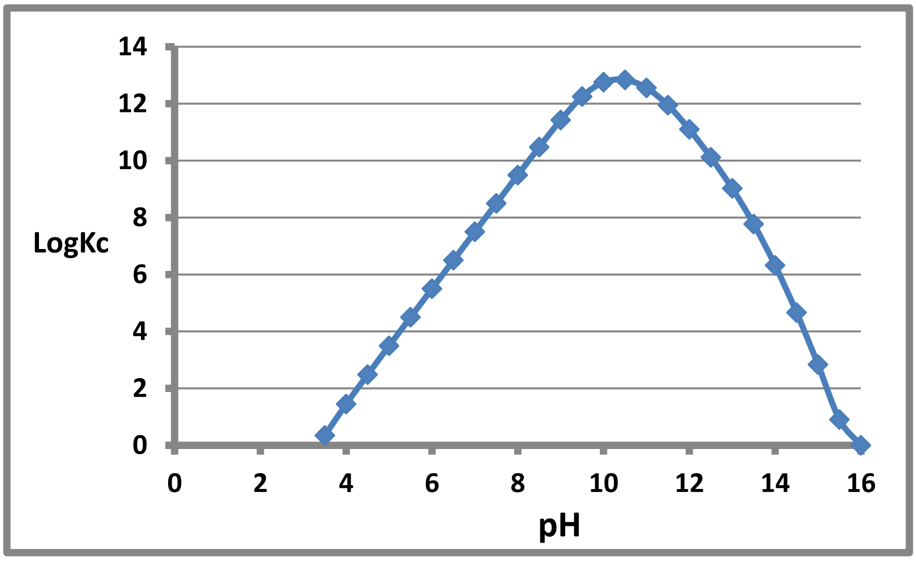

Figure 9. Conditional formation curve of Cd (II)-Metformin hydrochloride

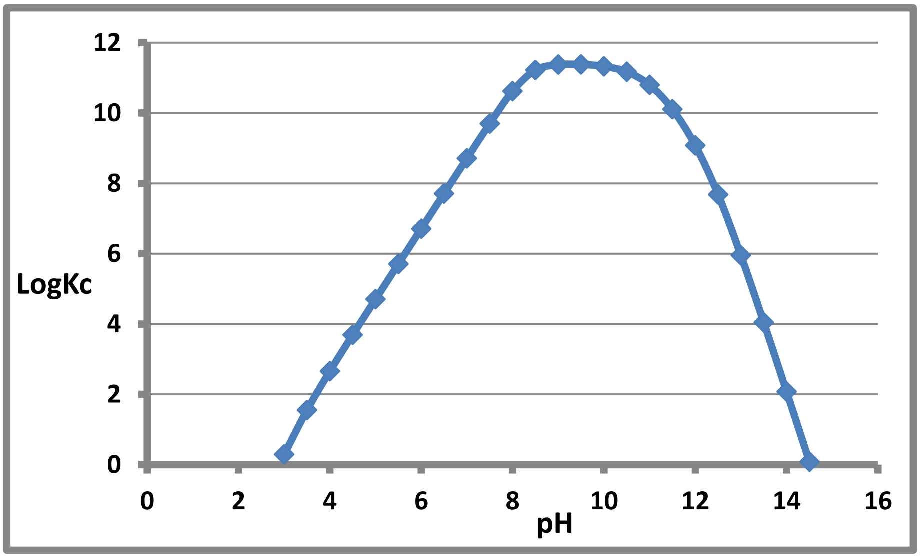

Figure 10. Conditional formation curve of Zn (II)-Metformin hydrochloride

The mole fractions of different species of mixed complexes were found by means of the calculated formation constants and were plotted as a function of pH (Figures. 11-13).

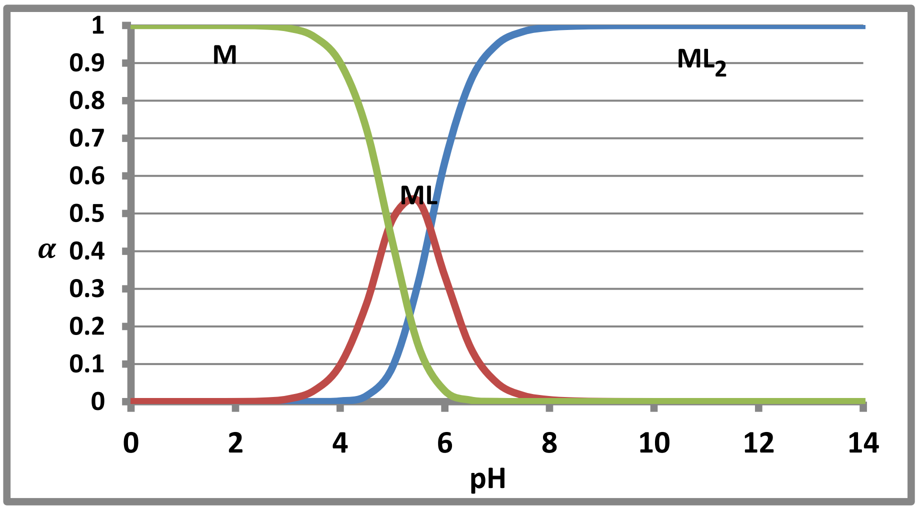

Figure 11. Mole fraction diagram of the Cu(II)-Metformin hydrochloride complex as a function of pH

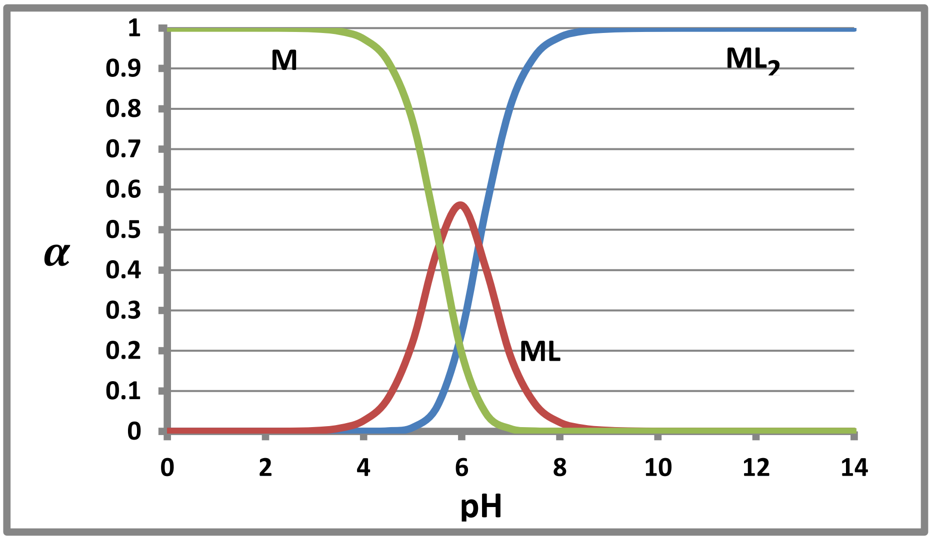

Figure 12. Mole fraction diagram of the Cd(II)-Metformin hydrochloride complex as a function of pH

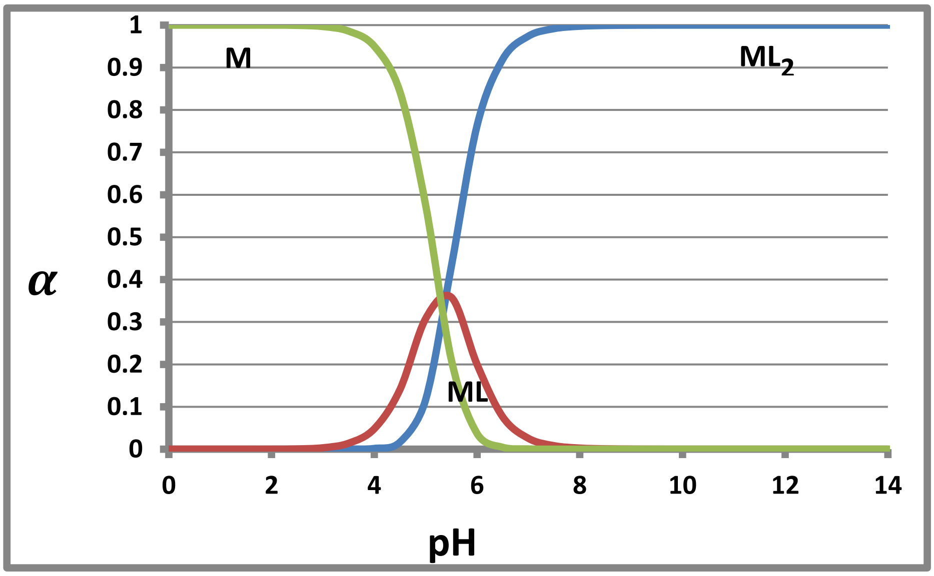

Figure 13. Mole fraction diagram of the Zn(II)-Metformin hydrochloride complex as a function of pH

CONCLUSION

As a summary, in our study we have determined the stability constants of binary complexes of Metformin hydrochloride and three metals (Cu(II), Cd(II) and Zn (II)). The conditional formation constants were calculated and these constants were found to be in agreement with the formation constants of mixed systems. Also mole fraction diagrams showed the formation of binary complexes.

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