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Research Article

Characterization by Potentiometric Procedures of the Stability Constants of the Binary and Ternary Complexes of Cu(II) and Duloxetine Drug with Amino Acids

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Potentiometric titration method has been used to define stoichiometries and stability constants of ternary complexes of Cu(II) with duloxetine (D) and some selected amino acids (L). The protonation constants of the ligands and the stability constants of the binary and ternary complexes of Cu(II) with the ligands were calculated from the potentiometric data using the HYPERQUAD program. The formation constants of the complexes formed in aqueous solutions and their concentration distributions as a function of pH were evaluated at 25°C and ionic strength 0.10 mol·L^{-1} $NaNO_3$. Respective stabilities of ternary complexes have been determined compared with the corresponding binary complexes in terms of $\Delta\log K$ and %R.S. values. A novel binary and ternary duloxetine (D) drug with glycine and its Cu(II) complexes has been synthesized and characterized by several spectroscopic methods. Electronic spectra and magnetic susceptibility measurements reveal square planar geometry for both complexes. The elemental analyses and mass spectral data have justified the [Cu(D)(Gly)] and [Cu(D)Cl(H_2O)] composition of complexes, where D = duloxetine and Gly = glycine. The EPR spectra of Cu(II) complexes support the mononuclear structures. Thermal properties and decomposition kinetics of Cu(II) complexes are investigated.

1. Introduction

Drugs are naturally occurring or synthetic, which contain oxygen or sulfur or nitrogen atoms in their functional groups. They form complexes with metal ions either initially or after metabolic changes in the body to form stable five- or six-membered rings. The ever-increasing importance of ternary complexes especially those involving ligands containing functional groups identical with those present in enzymes, namely, -COOH, - NH_2, and -CONH, is obvious from the application of such complexes in many analytical and biological reactions [1]. Metal(II), ternary complexes with nitrogen- and oxygen-donor ligands acknowledged ample attention newly, as they may show remarkably high stability [2–4]. These complexes have recently been investigated as of their aptitude as a metal system for metal-protein complexes like metalloenzymes. Cu(II) amongst other transition metal ions delivers vigorous center in numerous enzymes. It looks consequently to be of substantial attention to demeanor numerous studies causing binary and ternary complexes of Cu(II) connecting the duloxetine drug (D) and certain amino acids.

Duloxetine is the most recent serotonin and norepinephrine reuptake inhibitor (SSNRI) drug introduced for the therapy of depression [5]. Duloxetine (D) (Figure 1) is chemically 2(+)-(S)-*N*-methyl-(gamma)-(1-naphthyloxy)-2-thiophenepropylamine. The metal complexes of drugs are found to be more potent than parent drugs [6–9]. The literature survey reveals that, over the last decade, there has been tremendous attention towards studies on metal complex formation using drugs as ligands [10–13]. The best known example of a small molecule metal-containing drug is cisplatin (*cis*-DDP), chemically (*cis*-[$PtCl_2(NH_3)_2$]. The anticancer activity of this complex arises due to the formation of another ternary complex in which two chloride ions are replaced by the N-7 guanines located adjacently on

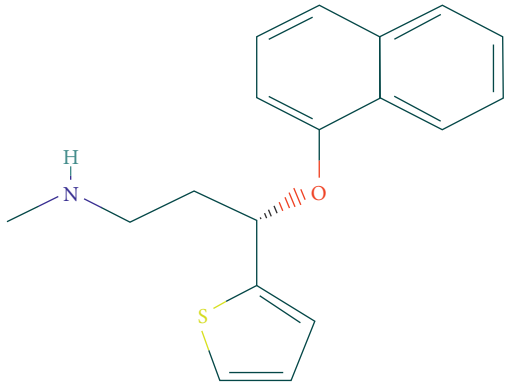


Figure 1: Chemical structure of duloxetine (D).

the DNA of the cancer cell [14]. Biological action of complexes is contingent on thermodynamic and kinetic properties. Lipophilicity of any drug upsurges due to chelate formation, and its action upsurges meaningfully due to operative penetrability of drug to its site of action [15, 16]. Interface of numerous metal ions with antibiotics can increase their activity as compared to free ligands. The present investigation describes the equilibria associated with the interaction of the Cu(II) ion with duloxetine drug (D) and some amino acids (L) in aqueous media at 25°C and ionic strength 0.10 mol·L^{-1} $NaNO_3$ using the potentiometric technique. The values of $\Delta\log K$ and percentage of relative stabilization (%R.S.) for the mixed-ligand complexes studied have been evaluated and discussed. Species distribution in solutions over varied levels of pH was assessed. Also, the synthesis and characterization of novel binary and ternary Cu(II) complexes are described.

2. Experimental

2.1. Materials. All chemicals used in this study were of the highest purity available and were used without any further purification. Duloxetine (D) and amino acids (glycine (Gly), alanine (Ala), β-phenylalanine (Phe), valine (Val), proline (Pro), threonine (Thr), lysine (Lys), histidine·HCl (Hisd), ornithine (Orn), and S-methylcysteine (Met) together with histamine·2HCl (Hist) and imidazole (Imz) were provided by Sigma Chemical Company. Stock solution of the copper used in the study was prepared from the nitrate salt of $Cu(NO_3)_2{\cdot}2H_2O$. This stock solution was acidified with HCl to prevent the hydrolysis of the metal. Carbonate-free NaOH (titrant) was prepared and standardized against a potassium hydrogen phthalate solution. Doubly distilled conductivity water was used for the preparation of all solutions. The elemental analyses (C, H, N, and S) of the Cu(II) complexes were performed by the microanalytical center, Cairo University, Giza, Egypt. Copper content was determined complexometrically by standard EDTA titration, and the Cl was tested gravimetrically using $AgNO_3$. The analyses were repeated twice to check the accuracy of the data. Electronic spectra of the complexes were recorded on a Shimadzu Model 1601 UV-visible Spectrophotometer. FTIR spectra were recorded on an FTIR-Shimadzu model IR-Affinity-1 spectrophotometer using KBr pellets. The mass spectra were recorded by the EI technique at 70 eV using MS-5988 GS-MS Hewlett–Packard instrument. Room temperature magnetic susceptibility measurements were carried out on a modified Gouy-type magnetic balance, Hertz SG8-5HJ. The room temperature molar conductivity of the complexes in DMSO solution (10^{-3} M) was measured using a deep vision 601 model digital conductometer. The X-band EPR spectrum was performed at LNT (77 K) using TCNE as the G-marker. X-ray diffraction (XRD) patterns of the samples were recorded with a Rigaku Geigerflex X-ray diffractometer. All the diffraction patterns were obtained by using Cu Kα_1 radiation, with a graphite monochromator at 5°/min scanning rate. SEM images were recorded in a Hitachi SEM analyzer.

2.2. Potentiometric Procedure and Measurements. Potentiometric titration was done at 25 ± 0.1°C through double-walled glass vessel (Griffin pH J-300-010G Digital pH meter was used). Electrode systems were calibrated via concentration scale, where pH must be unstated as of –log [H^+] through the course of study. Ionic strength remained constant (0.1 mol·L^{-1}), and this constant pH was achieved through $NaNO_3$ solution (40 ml used in each titration). pK_w of water was measured at 0.1 mol·L^{-1}, ionic strength to be 13.87 ± 0.05. Acid dissociation coefficients of ligand was measured potentiometrically through titration of ligand (40 ml) solution (1.25×10^{-3} mol·L^{-1}) with stable ionic strength, i.e., 0.1 mol·L^{-1}, accustomed with $NaNO_3$. Stock solutions used for titration in binary systems were primed with consecutive addition of celebrated volume of 1.25×10^{-3} mol·L^{-1} Cu(II) and D or L solution in 1 : 1, 1 : 2, and 1 : 3 metal to ligand molar ratio. Stability coefficients of the varied ligand complex were measured via titration by 40 ml of solution comprising Cu(II), D, and L, all levels (concentration) (1.25×10^{-3} mol·L^{-1}), and 0.1 mol·L^{-1} $NaNO_3$. Titration was done in the sanitized N_2 atmosphere through aqueous 0.05 mol·L^{-1} NaOH as the titrant.

2.3. Treatment of Potentiometric Data. Equilibrium reaction in the system was determined, which may be presented as generic expression:

$$l(\mathrm{M}) + p(\mathrm{D}) + q(\mathrm{L}) + r(\mathrm{H}) \rightleftharpoons \left[(\mathrm{M})_l(\mathrm{D})_p(\mathrm{L})_q(\mathrm{H})_r\right] \quad (1)$$

where l, p, q, and r are the numbers of copper(II) ion, duloxetine (D), amino acids (L), and proton, respectively, in the complex MlDpLqH.

This is being defined as follows:

$$\beta_{lpqr} = \frac{\left[\mathrm{M}_l\mathrm{D}_p\mathrm{L}_q\mathrm{H}_r\right]}{[\mathrm{M}]^l[\mathrm{D}]^p[\mathrm{L}]^q[\mathrm{H}]^r}. \quad (2)$$

Formation constant was calculated through the HYPERQUAD computer program [17]. Stoichiometry and stability constant of complexes formed were found through numerous composition models. Standard deviation was

used as an indication of existence of one species along with the suitability of the equilibrium model tested.

2.4. Distribution Speciation: pH Function. Speciation was calculated via the HYSS program [18], which plotted the distribution of species at series of complexes on the quantified pH range. This program used total concentrations of the metal and ligand as the input data along with the pH range, and equilibrium concentrations were computed by the best fit set of β values. Visual output may therefore deliver a graphic record of principal complex species at any specified pH particularly in the physiological range of pH.

2.5. Syntheses

2.5.1. Synthesis of [Cu(D)Cl(H_2O)]. The duloxetine drug (D) (2.23 g; 7.53 mmol) was dissolved in 20 mL of ethanol, and then 1.68 g (7.53 mmol) of $Cu(NO_3)_2{\cdot}2H_2O$ dissolved in 20 mL of ethanol was added dropwise, and the reaction mixture was stirred and heated at 50°C for 3 h. The solvent was allowed to evaporate slowly to produce a solid. The resultant product was collected by filtration and washed with ethanol and diethylether to get the pure complex.

Brown; yield, solid 83%; m.p.: >300°C; % found (calculated) [$C_{18}H_{20}ClCuNO_2S$ (M.Wt. = 413.4)]: C = 52.21 (52.30), H = 4.73 (4.88), N = 3.26 (3.39), Cl = 8.27 (8.57), S = 7.57 (7.75), and Cu = 15.32 (15.37); μ_{eff} (B.M.) = 1.78; Λ_m ($\Omega^{-1}{\cdot}mol^{-1}{\cdot}cm^2$) = 12.4; IR: ($\nu$, cm^{-1}) 3459 $(OH)_{water}$, 1824 (C-N), 720 $(C\text{-}S\text{-}C)_{thiophene\ ring}$, 931 and 863 ($H_2O$), 594 (M-S), 573 (M-Cl), 507 (M-O), and 474 (M-N).

2.5.2. Synthesis of [Cu(D)(Gly)]. An appropriate amount of $Cu(NO_3)_2{\cdot}2H_2O$ (1.68 g, 7.53 mmol) is dissolved in hot ethanol (20 mL), which was further mixed with a boiling ethanolic solution (20 mL) of duloxetine drug (D) (2.23 g, 7.53 mmol) followed by addition of glycine (Gly) (0.57 g, 7.53 mmol). The mixture was heated on a water bath for about 3 h and filtered. The filtrate was left to stand overnight, yielding shining deep brown crystals of the complex, which were filtered off. The resultant product was collected by filtration and washed with ethanol and diethylether to get the pure complex.

Deep brown; yield, solid 85%; m.p.: >300°C; % found (calculated) [$C_{20}H_{22}CuN_2O_3S$ (M.Wt. = 434.0)]: C = 55.29 (55.35), H = 4.93 (5.11), N = 6.37 (6.45), S = 7.24 (7.39), and Cu = 14.58 (14.64); μ_{eff} (B.M.) = 1.82; Λ_m ($\Omega^{-1}{\cdot}mol^{-1}{\cdot}cm^2$) = 10.3; IR: ($\nu$, cm^{-1}) 3159 (NH), 1824 (C-N), 1623 (C=O), 722 $(C\text{-}S\text{-}C)_{thiophene\ ring}$, 594 (M-S), 513 (M-O), and 478 (M-N).

3. Results and Discussion

3.1. Characterization of Solutions. Potentiometric titration data were used for protonation coefficients ($\log_{10} K_1$, $\log_{10} K_2$, and $\log_{10} K_3$) of all ligands, and formation coefficients of binary complexes were investigated by similar experimental circumstances of temperature and ionic strength for screening of ternary complexes. Results obtained are presented in Tables 1 and 2) and are in accordance with literature data [19].

3.1.1. Protonation Constant of Duloxetine (D). Duloxetine (D) contains as a minimum one site which may reversibly dissociate a proton (a hydrogen ion) to form negative-charged anion. Duloxetine may discharge one proton from the amine group. The pK_a value of the protonated drug is 9.34, which is predominantly existent in the ionized form at physiologic pH.

3.1.2. Binary Complex Formation Equilibria of Duloxetine (D). Titration of duloxetine was done in presence and absence of the Cu(II) ion. Titration curves of the Cu(D) complex are depressed from the free D curve, representing Cu(II) complex formation through protons displacement. Formation constant was measured by fitting potentiometric data based on probable composition models. The selected model with finest statistical fit was determined to consist of Cu(D) (duloxetine) (1100) and $Cu(D)_2$ (1200) complexes (Table 2). Stability coefficient of complexes was calculated by using the following equation:

$$\mathrm{Cu(II)} + \mathrm{D} \rightleftharpoons \mathrm{Cu(II)D} \quad \beta_1 = \beta^{\mathrm{Cu}}_{\mathrm{Cu(D)}} = \frac{[\mathrm{Cu(II)(D)}]}{[\mathrm{Cu(II)}][\mathrm{D}]}$$

$$\mathrm{Cu(II)} + 2\mathrm{D} \rightleftharpoons \mathrm{Cu(II)(D)_2} \quad \beta_2 = \beta^{\mathrm{Cu}}_{\mathrm{Cu(D)2}} = \frac{[\mathrm{Cu(II)(D)_2}]^2}{[\mathrm{Cu(II)}][\mathrm{D}]^2} \tag{3}$$

The concentration distribution diagram of Cu(II)-D systems is provided in Figure 2. Concentration of Cu(D) species upsurges with the growing pH, achieving a supreme (97.6%) at 8.8 pH. Furthermore, a growth in the pH level was escorted by reduction in the level of Cu(D) species and rise in level of $Cu(D)_2$ species.

3.1.3. Equilibria for Formation of Ternary Complex. Multiple equilibrium studies by pH-metric measurements in ternary copper(II) complexes with duloxetine (D) as the primary ligand and amino acids (L) as secondary ligands exhibited occurrence of [Cu(D)(L)], [Cu(D)(LH)], and [Cu(D)(LH-1)] ternary complex species. Stability coefficients of amino acid complexes are greater compared to those of the corresponding monodentate imidazole complex, reflecting that amino acids possibly organizes with Cu(D) as the bidentate ligand through amino and carboxylate groups, despite of the monodentate ligand. Constancy of the ternary complex containing glycine is advanced compared to those containing alanine. It is recommended that steric interference, initiated by manifestation of the methyl group on the carbon-containing amino group (alanine),is liable for low stability of its ternary complexes.

Value of the stability constant of the histidine complex was found higher as compared to α-amino acids and found in accordance with histamine (Table 3). These results indicated that histidine coordinated in histamine-like way. Histidine has shown to form protonated (1111) and deprotonated (1110) complex species.

Table 1: The protonation constants of the ligands at 25°C and 0.10 mol·L^{-1} ionic strength.

System	$\log_{10} K_1$	$\log_{10} K_2$	$\log_{10} K_3$
Duloxetine (D)	9.34 (0.01)		
Glycine (Gly)	9.61 (0.02)	2.48 (0.02)	
Alanine (Ala)	9.80 (0.01)	2.82 (0.03)	
Valine (Val)	9.68 (0.00)	2.50 (0.01)	
Proline (Pro)	10.65 (0.009)	2.53 (0.01)	
β-Phenylalanine (Phe)	9.20 (0.01)	2.61 (0.03)	
S-Methylcysteine (Met)	8.65 (0.02)		
Threonine (Thr)	9.06 (0.009)	2.01 (0.03)	
Ornithine (Orn)	10.58 (0.03)	8.99 (0.04)	1.55 (0.05)
Lysine (Lys)	10.44 (0.01)	9.22 (0.02)	
Histidine (Hisd)	9.48 (0.01)	6.28 (0.01)	2.16 (0.04)
Histamine (Hist)	9.88 (0.03)	6.06 (0.05)	
Imidazole (Imz)	7.06 (0.01)		

Standard deviations are given in parentheses.

Table 2: Stability coefficients of Cu(II) complexes of the binary system at 25°C and 0.10 mol·L^{-1} ionic strength.

Systems	l	p	q	r	$\log\beta^a$
Cu(II)-D	1	1	0	0	8.07 (0.003)
	1	2	0	0	12.65 (0.01)
Cu(II)-Gly	1	0	1	0	8.15 (0.02)
	1	0	2	0	14.89 (0.04)
Cu(II)-Ala	1	0	1	0	8.13 (0.03)
	1	0	2	0	14.77 (0.05)
Cu(II)-Val	1	0	1	0	8.11 (0.02)
	1	0	2	0	14.73 (0.03)
Cu^{II}-Prol	1	0	1	0	8.60 (0.03)
	1	0	2	0	15.97 (0.05)
Cu(II)-Phe	1	0	1	0	8.35 (0.02)
	1	0	2	0	14.25 (0.03)
Cu(II)-Met	1	0	1	0	8.10 (0.01)
	1	0	2	0	14.81 (0.02)
Cu(II)-Thr	1	0	1	0	8.34 (0.02)
	1	0	2	0	14.80 (0.04)
	1	0	1	−1	1.06 (0.01)
Cu(II)-Orn	1	0	1	0	11.85 (0.04)
	1	0	2	0	15.95 (0.07)
	1	0	1	1	19.69 (0.03)
Cu(II)-Lys	1	0	1	0	11.83 (0.02)
	1	0	2	0	15.12 (0.03)
	1	0	1	1	19.44 (0.02)
Cu(II)-Hisd	1	0	1	0	10.65 (0.01)
	1	0	2	0	18.68 (0.03)
	1	0	1	1	18.39 (0.02)
Cu(II)-Hist	1	0	1	0	9.39 (0.02)
	1	0	2	0	15.12 (0.05)
	1	0	1	1	17.34 (0.02)
Cu(II)-Imz	1	0	1	0	4.23 (0.01)
	1	0	2	0	7.57 (0.02)

Note: l, p, q, and r represent stoichiometric constants corresponding to Cu(II), D, L, and H^+, respectively. Coefficient −1 reflects proton loss.
[a]Standard deviation is presented in parentheses.

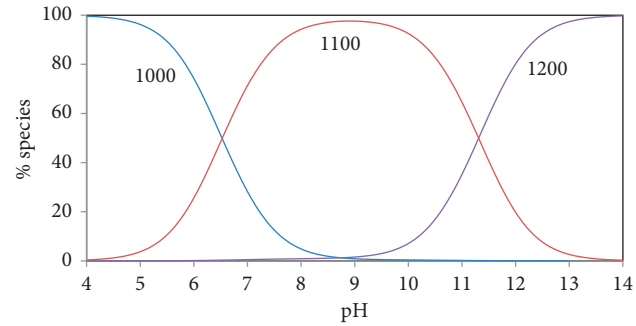


Figure 2: Concentration distribution of various species as a function of pH in the Cu-D binary system.

Ornithine and lysine can bind to the Cu(II) ion as α-amino acid (N and O-donor set) or by α- and ω-amino groups (N and N-donor set). Stability coefficients of ternary complexes (Table 3) are found to be higher compared to α-amino acids, reflecting that lysine and ornithine are ligating via two amino groups. Species distribution of ornithine is considered as representative amino acid and is provided in Figure 3. Protonated 1111 complex species are dominated by the formation degree accounting to 78% at 6.4 pH; on the other hand, deprotonated species 1110 gets extreme concentration of 33% at 8.6 pH. Consequently, species 1111 dominates in physiological range of pH.

In addition to the Cu(D)(L) complex threonine forms the Cu(D)(LH-1) species, which is formed via induced ionization of the β-alcohol group, as revealed in literature [20]. S-Methylcysteine exhibits lowest pK_a value, i.e., 8.65, among studied amino acids. This complex has greater stability coefficient compared to amino acids like glycine, which may be considered as proof that the sulfur atom contributes in the complex formation process.

$\log_{10} K^{Cu(D)}_{Cu(D)(L)}$ and $\log_{10} K^{Cu(L)}_{Cu(D)(L)}$ stability constants were compared with each other in order to decide which one of the ligands was contributing to the formation of the mixed ligand complexes and which one is acting as the primary or secondary ligand. For this purpose, the following equations were used:

$$\log_{10} K^{Cu(D)}_{Cu(D)(L)} = \log_{10} \beta^{Cu}_{Cu(D)(L)} - \log_{10} K^{Cu}_{Cu(D)},$$
$$\log_{10} K^{Cu(L)}_{Cu(D)(L)} = \log_{10} \beta^{Cu}_{Cu(D)(L)} - \log_{10} K^{Cu}_{Cu(L)}, \quad (4)$$

where $\log_{10} K^{Cu(D)}_{Cu(D)(L)}$ and $\log_{10} K^{Cu(L)}_{Cu(D)(L)}$ constants were calculated for each mixed ligand system, as shown in Table 3. It can be seen that the D drug acts as the primary ligand in all systems and amino acids act as the secondary ligands.

In order to characterize the stability of the mixed ligand [Cu(D)L], complexes with respect to the corresponding binary analogues can be expressed quantitatively in terms of $\Delta\log_{10} K$ and %R.S. The $\Delta\log_{10}$ values for ternary complexes are given by equation (6):

$$Cu(D) + Cu(L) \rightleftharpoons Cu(D)(L) + Cu \quad (5)$$

$$\Delta\log_{10} K = \log_{10} K^{Cu(D)}_{Cu(D)(L)} - \left(\log_{10} K^{Cu}_{Cu(D)} + \log_{10} K^{Cu}_{Cu(L)}\right). \quad (6)$$

Table 3: Formation coefficients of ternary complexes in Cu(II)-D-amino acids systems at 25°C and 0.10 mol·L^{-1} ionic strength.

System	l	p	q	r	$\log_{10}\beta^{a}$	$\log_{10} K^{Cu(D)}_{Cu(D)(L)}$	$\log_{10} K^{Cu(L)}_{Cu(D)(L)}$	$\Delta\log 10\ K$	%R.S.[b]
Cu(II)-D-Gly	1	1	1	0	17.32 (0.01)	9.25	9.17	1.1	13.50
Cu(II)-D-Ala	1	1	1	0	17.12 (0.02)	8.95	8.89	0.82	10.09
Cu(II)-D-Val	1	1	1	0	17.05 (0.01)	8.98	8.94	0.87	10.73
Cu(II)-D-Pro	1	1	1	0	17.61 (0.01)	9.54	9.01	0.04	10.93
Cu(II)-D-Phe	1	1	1	0	16.75 (0.02)	8.68	8.40	0.33	3.95
Cu(II)-D-Met	1	1	1	0	17.96 (0.02)	9.89	9.86	1.79	22.10
Cu(II)-D-Thr	1	1	1	0	17.56 (0.02)	9.49	9.22	1.15	13.64
	1	1	1	−1	2.62 (0.02)				
Cu(II)-D-Orn	1	1	1	0	20.30 (0.01)	12.23	8.45	0.38	3.21
	1	1	1	1	25.45 (0.01)				
Cu(II)-D-Lys	1	1	1	0	20.76 (0.03)	12.69	8.93	0.86	7.27
	1	1	1	1	24.88 (0.01)				
Cu(II)-D-Hisd	1	1	1	0	21.30 (0.01)	13.23	10.55	2.58	24.22
	1	1	1	1	26.01 (0.01)				
Cu(II)-D-Hist	1	1	1	0	20.90 (0.04)	12.83	11.51	3.44	36.63
	1	1	1	1	25.11 (0.02)				
Cu(II)-D-Imz	1	1	1	0	13.34 (0.002)	5.27	9.11	1.04	24.59

Note: l, p, q, and r represent stoichiometric constants corresponding to Cu(II), D, amino acids, and H^+, respectively. [a]Standard deviation is presented in parentheses. [b]Percentage of the relative stabilization value, and coefficient −1 designates proton loss.

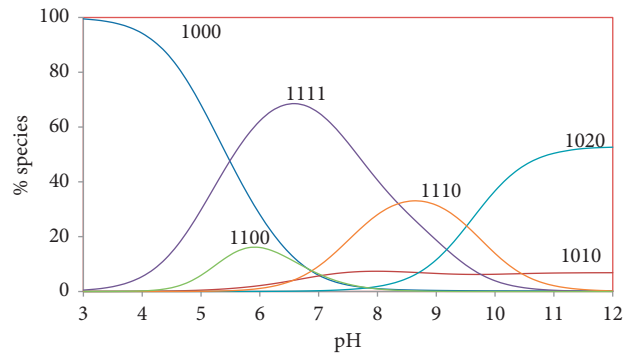


Figure 3: Concentration distribution of various species as a function of pH in the Cu-D: the ornithine ternary system.

Values of $\Delta\log_{10} K$ for the ternary complexes studied in this paper are positive and listed in Table 3. This means that that the amino acids form more stable complexes with Cu(D) than with the free Cu(II) ion. This fact may be taken as evidence for a stacking interaction between the drug and the amino acids.

Another parameter, which is percent relative stabilization (%R.S.) for quantifying the stability of a ternary complex, may be defined as follows:

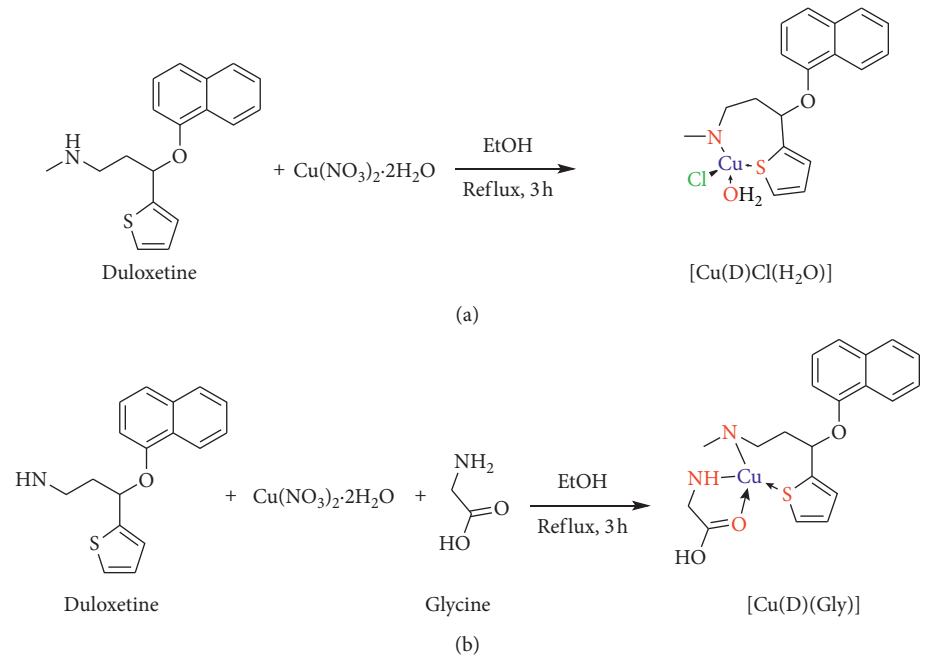
$$\%\,\text{R.S.} = \left\{ \frac{\log_{10} K^{Cu(D)}_{Cu(D)L} - \log_{10} K^{Cu}_{Cu(L)}}{\log_{10} K^{Cu}_{Cu(L)}} \right\} \times 100. \quad (7)$$

The values of %R.S. have been calculated (Table 3). For all systems, the parameter %R.S. is positive. This may be considered as evidence for the occurrence of enhanced stabilities. Positive values of %R.S. agree with the $\Delta\log K$ values.

3.2. Characterization of Solid Cu(II) Complexes. Complexes of Cu(II) have been synthesized according to Scheme 1. From the elemental analysis, it was found that the complexes have composition [Cu(D)Cl(H_2O)] and [Cu(D)(Gly)] where D = duloxetine and Gly = glycine. Complexes have been prepared to have a crystalline shape and are dried under vacuum and then subjected to elemental analyses. The elemental analyses result with molecular formulae, and some diverse physical properties such as melting points, colour, and percent yield were registered in the experimental part. It was found that the results obtained were compatible with the calculated results of suggested formulae. IR, UV-visible, mass, EPR spectra, magnetic moment, and thermal analysis have been used to confirm the structure of the complexes.

The measurements of conductivity for complexes were registered in the experimental part. From the results recorded, it was found that the molar conductance value of [Cu(D)Cl(H_2O)] and [Cu(D)(Gly)] chelate was 12.4 and 10.3 $\Omega^{-1}\cdot\text{mol}^{-1}\cdot\text{cm}^2$, respectively, which referred to the nonionic nature of both complexes [21].

From the result of IR spectra (Figure 4), it was observed that the υ(NH) stretching vibration of the imine nitrogen was found in the drug at 3248 cm^{-1}. But this band is absent in chelates. This was evidence of the participation of the imine nitrogen group in coordination [2]. The stretching band of C-S-C was appeared at 748 cm^{-1} in the duloxetine drug, but this band in complexes appeared at 720 and 722 cm^{-1} [22]. The changes indicated the participation of the sulfur atom in coordination to the metal ions [21, 22]. The bands at 931 and 864 cm^{-1} and 573 cm^{-1} were assigned to stretching vibration of coordinated water molecule and υ(M-Cl) mode, respectively, in the [Cu(D)Cl(H_2O)] complex. The bands at 833 cm^{-1} and 638 cm^{-1} appeared in the spectrum of the [Cu(D)Cl(H_2O)] complex which may be assigned to $\rho_r(H_2O)$ and $\rho_w(H_2O)$ [22]. Some new bands were present in the spectra of the complexes at wavenumbers 507 and 513 cm^{-1} which attributed to the υ(M-O) stretching vibrations. Other bands appeared at 474 and 478 cm^{-1} which attributed to the υ(M-N) mode [22]. The C=O band was



Scheme 1: Schematic syntheses of [Cu(D)Cl(H_2O)] and [Cu(D)(Gly)] complexes.

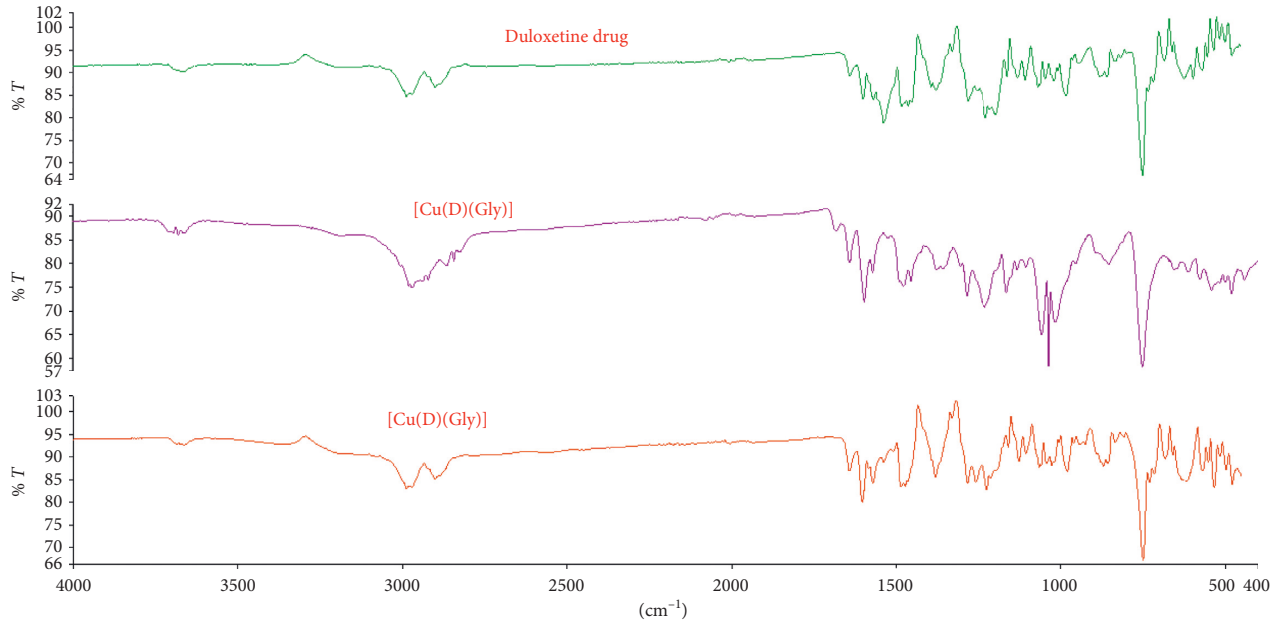


Figure 4: IR spectra of duloxetine drug and [Cu(D)Cl(H_2O)] and [Cu(D)(Gly)] complexes.

observed at 1656 cm^{-1}, but this band in the [Cu(D)(Gly)] complex was shifted to wavenumbers at 1623 cm^{-1}. Also, the band at 1376 and 1377 cm^{-1} in the both complexes is due to the $\upsilon(CH_3)$ frequency and is not affected upon complexation. Furthermore, the aliphatic protons are not greatly affected upon complexation [23].

The mass spectra of [Cu(D)Cl(H_2O)] and [Cu(D)(Gly)] complexes are presented in Figure 5. The molecular ions in the mass spectra were in agreement with the proposed molecular formula of the compounds. ESI-MS of the [Cu(D)Cl(H_2O)] and [Cu(D)(Gly)] complexes gave dominant *m/z* signals at 413.4 and 434.0 which corresponded to the calculated values of 413.4 and 434.0 and for copper and zinc complexes, respectively. Other signals were presumable due to unidentified fragments of the main compound. Furthermore, the results of the elemental analysis supported the proposed elemental composition of the compounds as their calculated and experimental values were close juxtaposition.

The EPR spectra of [Cu(D)Cl(H_2O)] and [Cu(D)(Gly)] complexes were recorded on the powder sample at room

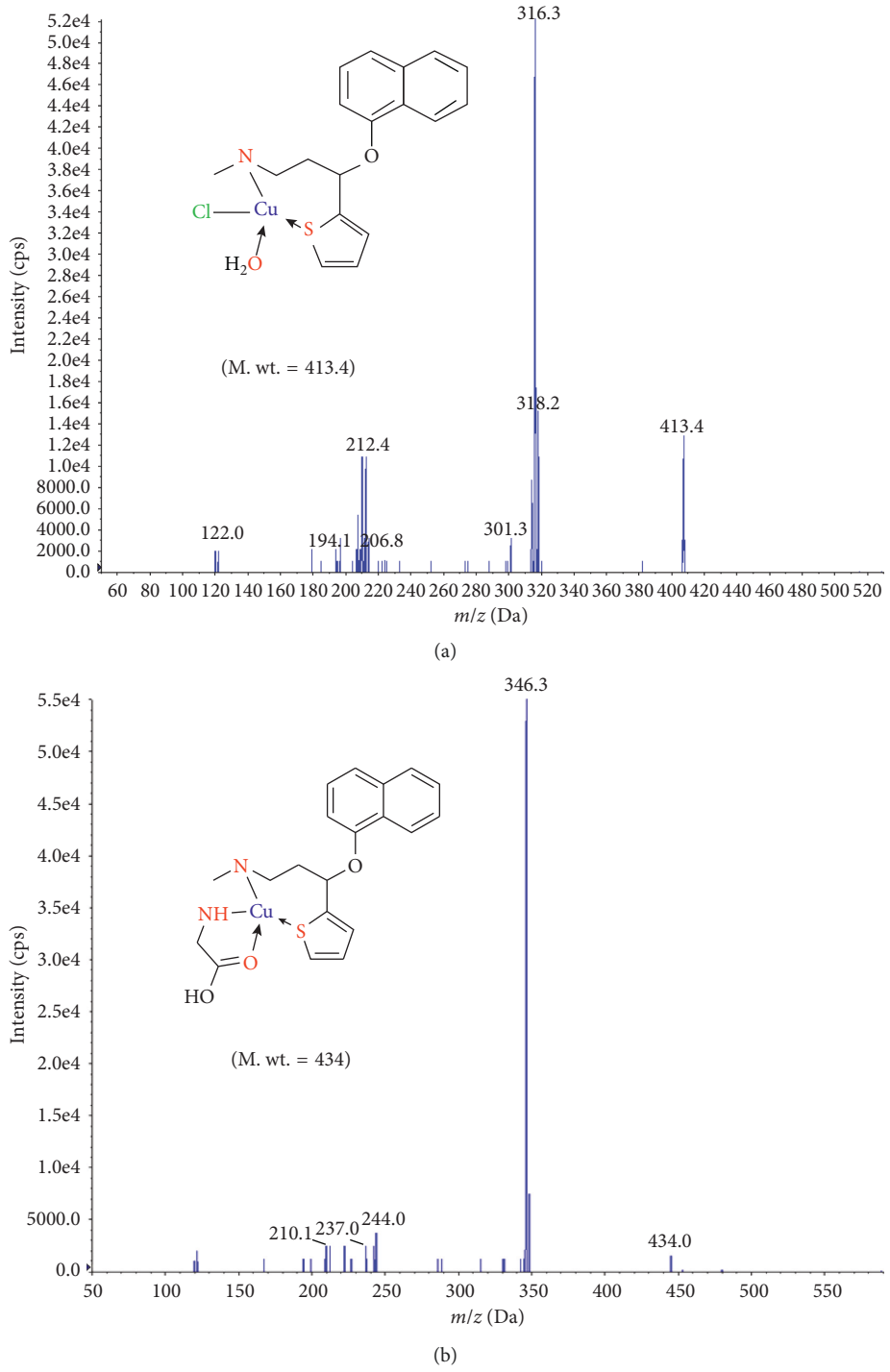


Figure 5: Mass spectra of (a) [Cu(D)Cl(H_2O)] complex and (b) [Cu(D)(Gly)] complex.

temperature (Figures 6(a) and 6(b)). The EPR spectra of those complexes were found to be axially symmetric with two g values, $g_\parallel = (2.22, 2.26)$, $g_\perp = (2.03, 2.05)$, respectively. The observed $g_\parallel$ values for these complexes are greater than g_e (2.0024), indicating that $(d_{x2-y2})^1$ is the ground state for Cu(II) ions configuration, i.e., $^4(a_{1g})^2(b_{2g})^2(b_{1g})^1$, which is characterized to square planar. The calculated g_{av} values (2.12, 2.14) and the observed $g_\parallel$ values (2.22, 2.26), which are <2.3, suggest the high covalent character of metal-ligand bond with distorted symmetry. In axial symmetry, $G = (g_\parallel - 2.0024)/(g_\perp - 2.0023)$, where G measures the exchange interaction between the metal centers in a polycrystalline solid. The calculated G values for [Cu(D)Cl(H_2O)] and [Cu(D)(Gly)] complexes are 3.13 and 3.31, respectively, suggesting the copper-copper exchange interaction in the solid complexes. These results are in agreement with the magnetic moment values for [Cu(D)Cl(H_2O)] and [Cu(D)(Gly)] complexes [23].

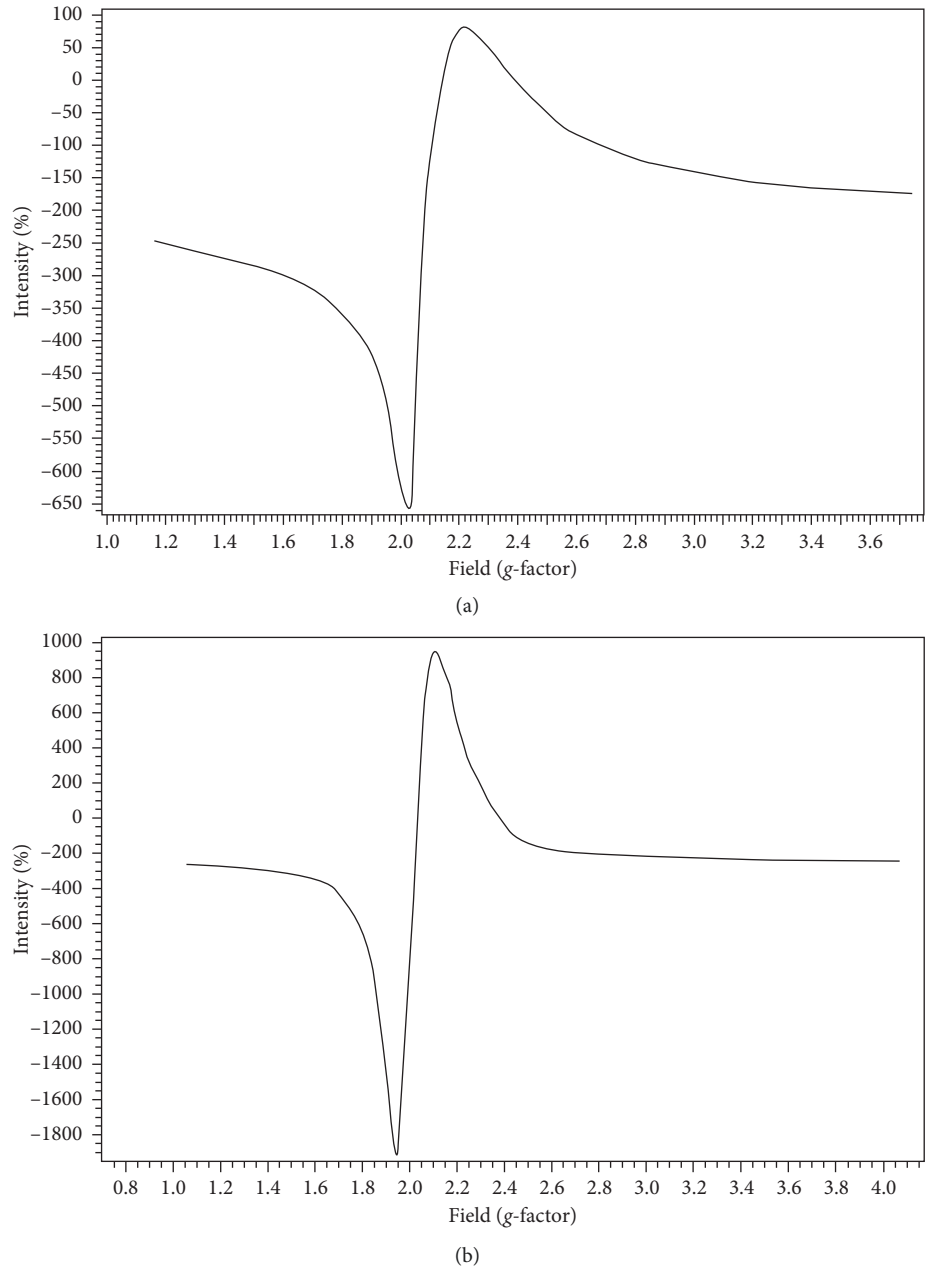


Figure 6: EPR spectra of complex [Cu(D)Cl(H_2O)] (a) and complex [Cu(D)(Gly)] (b).

Thermal behaviors of [Cu(D)Cl(H_2O)] and [Cu(D)(Gly)] complexes were investigated by TG/DTG/DTA/DSC techniques. The thermogravimetric analysis for the complexes was carried out within temperature ranging from room temperature to 735.9°C for [Cu(D)Cl(H_2O)] and [Cu(D)(Gly)] complexes. The TG/DTG curves of both complexes are given in Figure 7. [Cu(Dul)(Gly)] complex was stable up to 350°C as no mass loss was observed below 350°C, eliminating the possibility of water molecule outside or inside the coordination sphere. On the contrary, the [Cu(D)Cl(H_2O)] complex was stable up to 180°C as no mass loss was observed below 180°C, eliminating the possibility of the water molecule outside (hydrated water) the coordination sphere.

Coats–Redfern of a relationship [24] can be used to evaluate the parameter of the thermodynamic activation due to the decomposition of complexes, namely, activation energy (E^*), enthalpy (ΔH^*), entropy (ΔS^*), and Gibbs free energy (ΔG^*). The data of these parameters were registered in Table 4. From the data, it was found that E^* of decomposition has the range of 36.74–177.21 kJ·mol^{-1}. The value of E^* for [Cu(D)Cl(H2O)] complex is higher than that for [Cu(D)(Gly)] complex. On the contrary, the negative values of ΔS^* indicate a more ordered activated complex than the reactants or that the reactions are slow.

The observed magnetic moments for [Cu(D)Cl(H_2O)] and [Cu(D)(Gly)] complexes are generally diagnostic of the

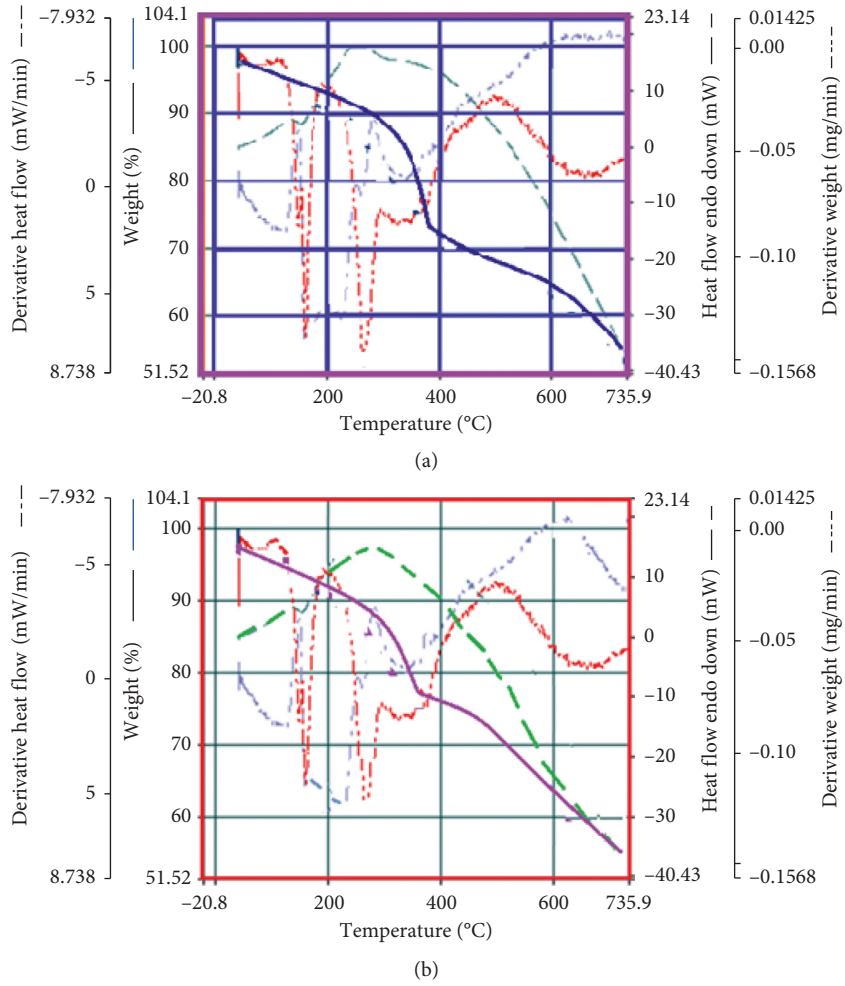


Figure 7: TGA/DTA/DTG spectra of complex [Cu(D)Cl(H_2O)] (a) and complex [Cu(D)(Gly)] (b).

coordination geometry about the metal ion. Room temperature magnetic moment of the [Cu(D)Cl(H_2O)] and [Cu(D)(Gly)] complexes is at 1.78 and 1.82 B.M., respectively, and these values are in tune with a high spin configuration and suggest square planar geometry for [Cu(D)Cl(H_2O)] and [Cu(D)(Gly)] complexes [25]. The electronic spectra of the [Cu(D)Cl(H_2O)] and [Cu(D)(Gly)] complexes (Figure 8) show three absorption bands in the range 14,684 and 15,642 ($\varepsilon = 83$ and 78 $L \cdot mol^{-1} \cdot cm^{-1}$) and 18,478 and 19,369 cm^{-1} ($\varepsilon = 108$ and 116 $L \cdot mol^{-1} \cdot cm^{-1}$) assignable to $^2B_1 \longrightarrow {}^2B_2$ $(dx^2 - y^2 \longrightarrow dzy)\nu^1$ and $^2B_1 \longrightarrow {}^2E$ $(dx^2 - y^2 \longrightarrow dzy,\ dyz)\nu^2$ transitions, respectively, which indicates the possibility of square planar geometry of the [Cu(D)Cl(H_2O)] and [Cu(D)(Gly)] complexes [26].

X-ray powder diffractograms of the [Cu(D)Cl(H_2O)] and [Cu(D)(Gly)] complexes have been given in Figure 9, and the observed diffraction data, i.e., d values, relative intensities, and 2θ (observed) of the [Cu(Gul)Cl(H_2O)] and [Cu(D)(Gly)] complexes, have been given in Table 5. Unit cell parameters were found by using trial-and-error methods as follows: the [Cu(D)(Gly)] complex is monoclinic with the unit cell parameters $\alpha = 90^\circ$, $\beta = 90^\circ$, $\gamma = 90^\circ$, $V = 810.30$ Å^3, $a = 6.364172$ Å, $b = 27.497931$ Å, and $c = 4.686936$ Å, and cell volume $V = 897.54$ Å^3. The other complex [Cu(D)(Gly)] is triclinic with the cell parameters for the [Cu(D)Cl(H_2O)] complex: $a = 7.0049$ Å, $b = 11.9422$ Å, $c = 5.6950$ Å, $\alpha = 103.539^\circ$, $\beta = 92.425^\circ$, and $\gamma = 90.875^\circ$, and cell volume, $V = 462.60$ Å^3; and for [Cu(D)(Gly)] complex: $a = 7.3043$ Å, $b = 14.8830$ Å, $c = 6.2792$ Å, $\alpha = 105.159^\circ$, $\beta = 92.591^\circ$, and $\gamma = 108.435^\circ$, and cell volume, $V = 624.53$ Å [27].

The nature of the ligand seems to bear key structural factors for the morphology of the agglomerates. Figure 10 shows the agglomerate particles of the complexes. For the [Cu(D)Cl(H_2O)] and [Cu(D)(Gly)] complexes, the agglomerates appear to be rod shaped which stack upon one another to give bigger agglomerates of the irregular shape. The average length of the bigger agglomerates varied in the range 3386 and 4972 nm while the width ranged from 556 to 1234 nm. The length and width of the smaller agglomerates varied from 500 to 1380 nm and 80–385 nm, respectively.

The molecular modeling calculations for [Cu(D)Cl(H_2O)] and [Cu(D)(Gly)] complexes were carried out using a Material Studio program that allows for rapid structure building, geometry optimization, and molecular display. Molecular mechanics calculate the steric energy,

Table 4: Kinetic parameters evaluated by Coats–Redfern equation.

Compound	Stage	Decomposition range (°C)	A (S^{-1})	E_a (kJ/mol)	ΔH (kJ/mol)	ΔS (kJ/mol K)	ΔG (kJ/mol)
[Cu(D)(H_2O)Cl]	1st	463	86.88×10^7	112.21	109.64	−0.033	154
	2nd	546	11.23×10^7	144.33	140.67	−0.068	187
	3rd	632	97.22×10^9	177.21	172.98	−0.094	247
[Cu(D)(Gly)]	1st	459	6.45×10^9	36.74	76.08	−0.032	158
	2nd	562	7.25×10^{10}	83.41	92.15	−0.073	195
	3rd	633	8.12×10^6	122.22	123.45	−0.095	192

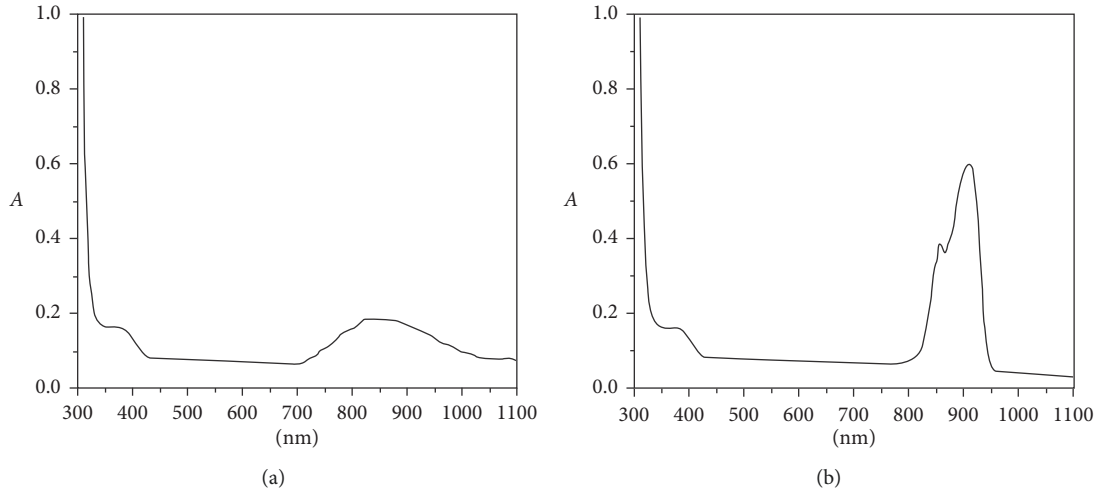


Figure 8: UV-Vis spectra of (a) [Cu(D)Cl(H_2O)] complex and (b) [Cu(D)(Gly)] complex.

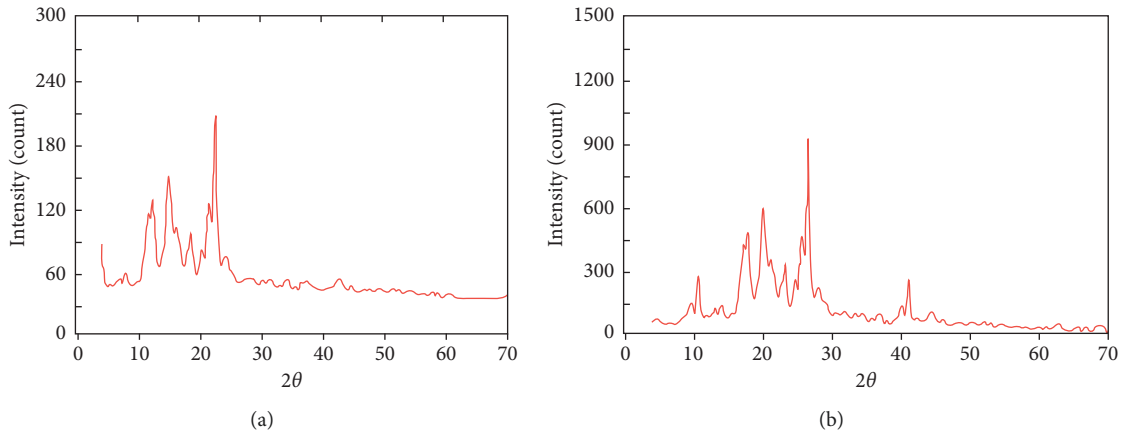


Figure 9: X-Ray powder diffraction patterns of (a) [Cu(D)Cl(H2O)] complex and (b) [Cu(D)(Gly)] complex.

which partition into stretching, bending, torsion, and nonbonded interactions for the molecules, and give a stable structure with least strain energy. Energy minimization was repeated several times to find the global minimum. The computational strategy in this study is to determine the minimum strain energy for [Cu(D)(H_2O)Cl] and [Cu(D)(Gly)] complexes, and the energy minimization values for square planar and without restricting the structure are almost equal, i.e., 4.93 and 32.87 kcal/mol, respectively. This supports square planar geometry for [Cu(D)(H_2O)Cl] and [Cu(D)(Gly)] complexes. Some important calculated bond length for the [Cu(Dul)(H_2O)Cl] complex is Cu_N, 1.814 Å; Cu_O_{water}, 1.793 Å and 1.773 Å; Cu_S, 2.814 Å; and Cu_Cl, 2.145 Å; and for [Cu(D)(Gly)] complex is Cu_N, 1.842 Å and 1.838 Å; Cu_O, 1.783 Å; and Cu_S, 2.834 Å [28]. The optimized structures of the [Cu(D)(H_2O)Cl]and [Cu(D)(Gly)] complexes are shown in Figures 11 and 12.

Table 5: X-ray powder diffraction data of [Cu(D)Cl(H_2O)] and [Cu(D)(Gly)] complexes.

D_{obs}	$2\theta_{obs}$	$2\theta_{calc}$	h	k	l
Complex [Cu(D)Cl(H_2O)]					
10.4422	8.546	8.499	0	0	1
9.2689	9.432	9.582	−2	0	1
8.4586	10.404	10.969	1	1	0
5.7841	16.902	16.8563	2	0	1
4.3596	19.299	19.458	2	1	0
4.2228	21.574	21.741	−2	1	2
3.7538	25.328	25.526	−5	0	3
3.2916	28.558	28.876	−6	0	3
2.7878	33.163	33.383	−1	2	1
2.9987	34.480	34.782	0	0	4
2.6327	36.819	36.465	2	1	3
2.4331	37.167	37.159	−8	0	2
2.3248	41.807	41.748	−8	1	4
2.1888	43.645	43.479	−6	2	3
2.1472	44.661	44.236	−2	2	4
Complex [Cu(D)(Gly)]					
9.8564	10.258	10.003	2	0	0
9.2583	11.458	11.256	0	0	1
7.1586	13.324	13.258	−2	0	1
6.2435	15.696	15.638	1	1	0
5.5686	17.252	17.583	−3	0	1
4.8517	19.918	19.899	1	1	1
4.2315	24.256	24.800	4	1	0
3.9898	25.633	25.385	−4	1	1
3.8465	27.363	27.159	−4	0	2
3.7258	34.208	34.851	7	0	0
3.6369	36.998	37.021	1	1	3
3.3458	38.995	39.433	2	2	2
3.1589	43.869	43.869	−2	2	3
3.0258	44.287	44.889	−8	1	2

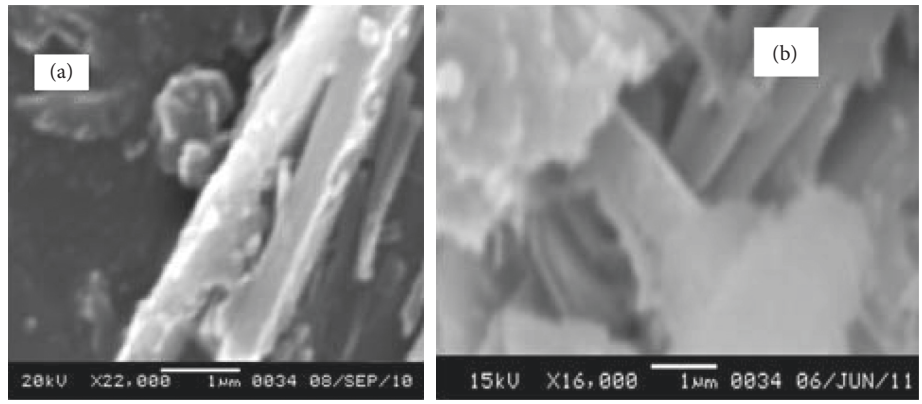


Figure 10: SEM image of (a) [Cu(D)Cl(H_2O)] complex and (b) [Cu(D)(Gly)] complex.

4. Conclusion

In summary, in our study, we have determined the stability constants of binary and ternary complexes of Cu(II) with duloxetine drug and some selected amino acids (L) at 25°C and ionic strength 0.10 mol·L^{-1} $NaNO_3$. The complexes stability constants ($\log_{10}\beta$), refined from the potentiometric data using the Hyperquad 2008 program, indicate that the ternary complexes are more stable than the binary complexes. Regarding the $\Delta\log_{10} K$ value computed for the mixed ligand complex systems, Cu(II)-D-Hisd ($\Delta\log_{10} K = 3.44$) had the highest values of stability. This, in turn, is in line with the stated order of stability. Duloxetine drug and complexes were characterized by using various techniques, i.e., elemental analysis, infrared, mass, molar conductance, magnetic moment, electronic spectra, and EPR. The analytical data show that the stoichiometry in complexes is 1 : 1 (D : Cu) and 1 : 1:1 (D : Cu : Gly). Tetra-coordinated square-planar geometry has been assigned for Cu(II) complexes

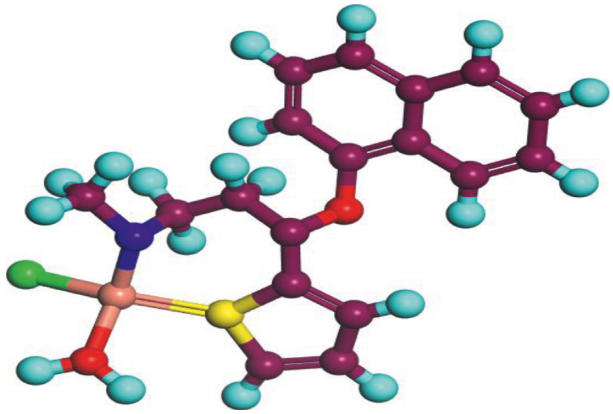


Figure 11: Molecular modeling of [Cu(D)(H_2O)Cl].

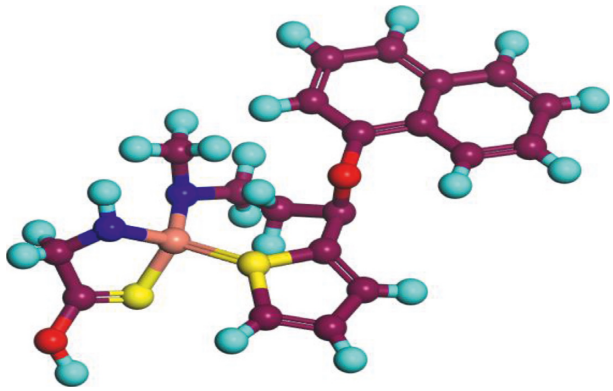


Figure 12: Molecular modeling of [Cu(D)(Gly)].

according to data obtained by the aforementioned techniques. Thermodynamic parameters (E, ΔS, ΔH, and ΔG) were calculated from TG curves dependent on the Coats–Redfern non-isothermal method.

Data Availability

The data used to support the findings of this study are available from the corresponding author upon request.

Conflicts of Interest

The authors declare that there are no conflicts of interest regarding the publication of this paper.

Acknowledgments

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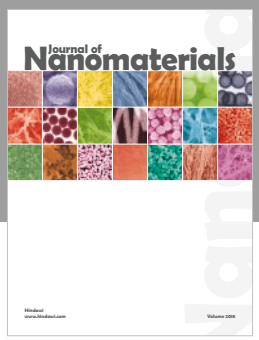

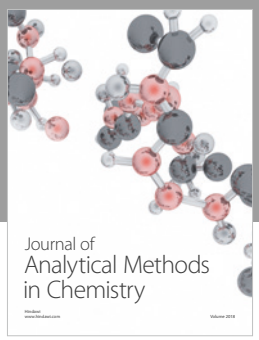

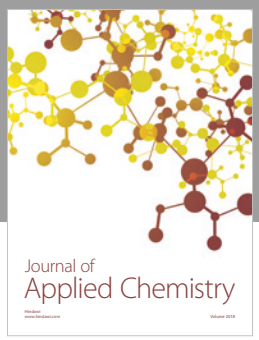

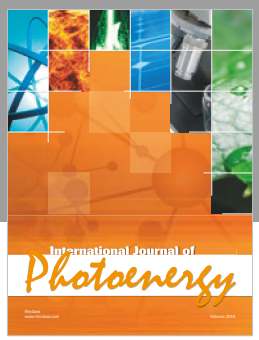

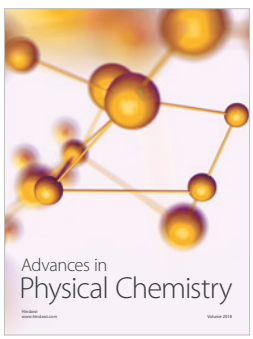

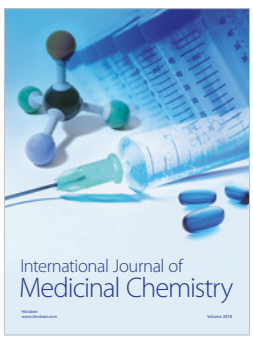

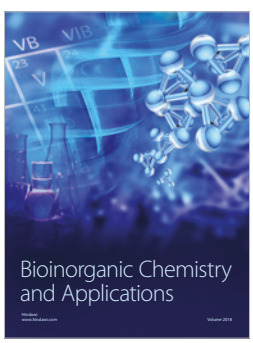

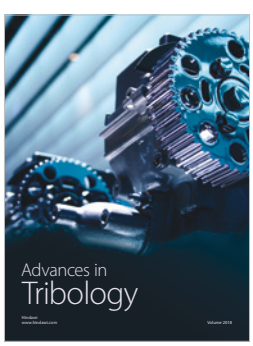

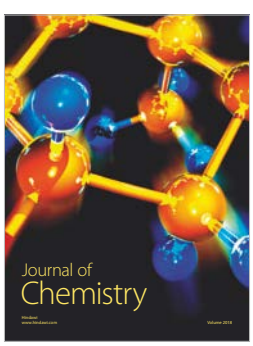

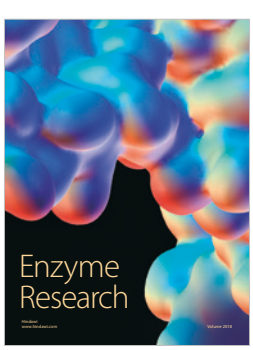

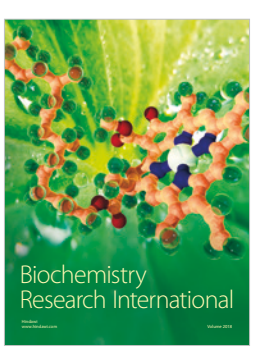

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