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HYDROPHOBIC INTERACTION β -CYCLODEXTRIN -DRUG INCLUSION COMPLEX - CATALYTIC EFFECT OF Cu (II) .

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ABSTRACT

The effect of β-Cyclodextrin with copper (II) catalyst on the oxidation of glutamine (drug) by PMS in acetic acid -sodium acetate buffer medium at 308K by kinetics studied. The phase solubility analysis was conducted the solubility of drug and β-cyclodextrin with copper (II) aqueous solutions and for calculating the correspondent thermodynamic parameters: free energy of activation (ΔS^0) and enthalpy of activation (ΔH^0) obtained as positively and entropy of activation (ΔG^0) as negatively. It provides inclusion complex of the guest (drug) inside the cavity of host (β-Cyclodextrin) due to this hydrophobic interaction was confirmed by UV-Visible absorption studies to determine the stability constant using a modified Benesi-Hildebrand equation. The stability constant values of glutamine are 87.57 L/mol. The limit of detection (LOD) and limit of quantification (LOQ) were found to be 0.29 LM^{-1} and 0.90 LM^{-1} respectively. The method has been successfully applied to the determination of pharmaceutical formulation with good accuracy of drug delivery.

KEYWORDS: copper (II), glutamine (drug), peroxomonosulphate (PMS), β-cyclodextrin (BCD), inclusion complex, kinetics: mechanism, Phase solubility studies

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INTRODUCTION

Kinetic studies and mechanism on the permanganic oxidation of L-Glutamine in strong acid medium in the presence and absence of Silver (I) was reported[1] nd oxidation of 3-methylindole by peroxomonosulphate using ethanol medium[2]. The decomposition of oxone has been influenced by pH when catalysed by transition metal ions [3-6] . In this transition metal ions of Ag, V, Fe, Ru, Mn etc. are reported to act as catalyst for some of the α – amino acid oxidation[7-10]. Cyclodextrins (CD), which are cyclic oligomers of α-D- glucopyranose, have a well-defined cavity [11]. These are containing six, seven or eight glucopyranose units (a, ß or γ respectively) obtained by the enzymatic degradation of starch [12]. Out of the three parent cyclodextrins, ß-cyclodextrin (ß-CD) appears most useful as a pharmaceutical complexing agent because of its complexing ability, low cost and other properties[13] . These cyclodextrins are hydrophilic molecules outside and hydrophobic inside which allows forming inclusion complexes with the majority of hydrophobic molecules[14]. They form inclusion complexes with a wide variety of species in aqueous solution[15]. The inclusion of some pharmaceutically related molecules, such as 1,4-benzoquinone (BQ), 9,10anthraquinone (AQ), anthracene (AN), acridine (AC), phenothiazine (PT) and thianthrene (TH) within cyclodextrin has been investigated using an electrochemical method[16]. Analysts have used this property of CDs, and a lot of methods based on the fluorescence of inclusion complexes with CDs have been proposed for the determination of several pharmaceutical drugs, pesticides, and metal ions[17-18]. In present work, phase solubility analysis was conducted the solubility of drug and β-cyclodextrin with copper (II) aqueous solutions and for calculating the correspondent thermodynamic parameters involved in the complex formation.

MATERIALS AND METHODS

2.1 Materials

β- Cyclodextrin was purchased from SD-Fine chemicals, India. Glutamine was obtained from Merck, India, and used as received. PMS was obtained from Aldrich, USA, and the purity of the sample was found to be 98% when tested by iodometric estimation and hence used without further purification. PMS solution was freshly prepared every day, stored in a blackened vessel to prevent photodecomposition, and standardized iodometrically. Acetic acid (E Merck, India Ltd.) was distilled and a stock solution of 8N acetic acid was prepared and standardized using sodium hydroxide (E Merck, India Ltd.). 4N acetic acid was prepared from the stock solution and used to make the buffer solution. A fresh solution of 2.5×10^{-3} mol dm^3 copper sulphate pentahydrate, (E Merck) was prepared by dissolving the appropriate amount of $CuSO_4.5H_2O$ with the addition of known volume of 4N acetic acid and made up to 100 ml in a standard measuring flask by using double distilled water. Analar grade solvents such as acetonitrile and 2-methyl-2-propanol were distilled and used for the reactions.

2.2 Methods

2.2.1 Kinetic Measurements

The kinetics studies of effect of β– cyclodextrin on the oxidation of glutamine by PMS, in the presence of Cu (II) catalyst in acetic acid–sodium acetate buffered medium (pH 3.6-5.2) at 308K was studied under pseudo first order conditions i.e., [amino acid] >> [PMS] at various time intervals. A known volume of PMS solution, thermostated at the desired temperature, was pipette out into the reaction mixture and simultaneously a timer was started. Consumption of PMS in this reaction mixture was monitored by iodometric method. The rate of the reaction followed first-order kinetics as shown (Fig.1).

2.2.2. Phase solubility studies

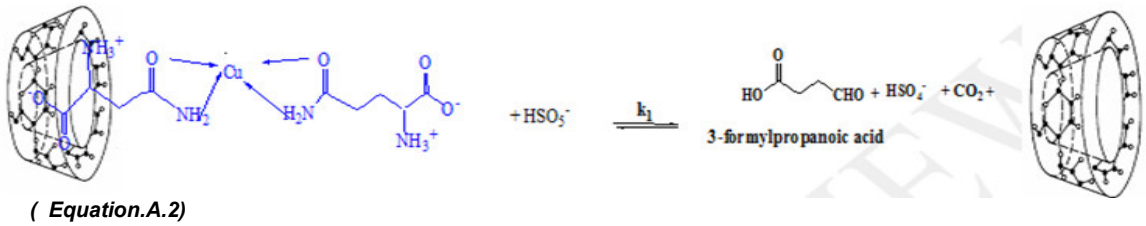
Phase solubility studies were carried out according to the method described by [Higuchi et al.,1965]. An excess amount of drug was mixed in an aqueous solution containing increasing amounts of the β–cyclodextrin was calculated the correspondent thermodynamic parameters involved in the complex formation at different temperature 30^0C, 35^0C, 40^0 C and 45^0C. The stability constants K_C were calculated from the straight-line portion of the phase solubility diagram according to the Higuchi-Connors equation [Higuchi et al., 1965] with slope less than unity, would be observed and the stability constant (KL) of the complex can be calculated from the slope and the intrinsic solubility ($S_0$1:1) of the drug in the aqueous complexation media (i.e. drug solubility when no cyclodextrin is present):

$$K_c = \text{slope} / (\text{Intercept} \times (1\text{-slope})$$

Equation(A.1) (1)

2.2.3 Stoichiometry and Product Analysis

The reaction mixture containing a large excess of β-cyclodextrin, PMS over drug in the presence of Cu (II) catalyst in acetic acid- sodium acetate buffer was kept for 48 h in a blackened vessel at room temperature. The organic layer was separated, dried and given for IR analysis.The stoichiometry of the reactions were determined for the reaction mixtures containing a large excess of [PMS], [β-cyclodextrin] over [drug] in the presence of the of Cu (II) catalyst .Then the reaction mixture was kept for 48 h and the unconsumed PMS was estimated iodometrically. Corrections for the self-decomposition of PMS were made from the value obtained from the control experiments. The observed stoichiometry of the reaction in the mixture of β-cyclodextrin and drug: PMS was 1:1due to the presence of Cu (II) catalyst. This is clearly indicate that the formation of inclusion complex. The special characteristic of Cyclodextrins is the ability to form an inclusion complex having apolar nature[19].



(Equation.A.2)

2.2.4Spectral Analysis

The reaction mixture was scanned in the ultraviolet and visible regions on a Perkin Elmer LS 25 UV spectrophotometer to unravel the intermediate formed during the course of the reaction. The absorption spectra were used to confirm the formation of inclusion complex. The reaction mixture of β-cyclodextrin in acetic acid - sodium acetate buffered medium by adding drug in the presence of Copper (II) ions.

2.2.5 ESR spectral analysis

The reaction mixture was scanned in the electron spin resonance spectrometer on a Varian E-112 EPR Spectrometer, Microwave power: 20 micro Watt at ambient temperature (DPPH :'G' Value = 2.00232, Magnetic field strength:3300 G) to unravel the free radical intermediate formed during the course of the reaction.

RESULTS AND DISCUSSION

3.1 Effect of [drug] on k_{obs}

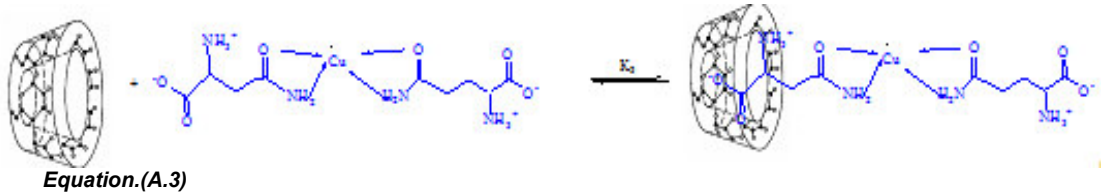
The values of k_{obs} were calculated for different concentrations of amino acids, by keeping the parameters at constant values. Perusal of the kinetic results showed that the rate constant increased with increase in [drug] (Table 1). Further, the plots of k_{obs} vs. [drug] were linear (Fig. 2). This result indicated the first order dependence of rate on drug. The positive intercept obtained in the above plots revealed that the reaction proceeded in two steps: one dependent on [drug] and the other independent of [drug]. The drug independent step was due to the self-decomposition of PMS under the experimental conditions employed in this study[20].

3.2 Effect of pH on k_{obs}

In the pH variation, the k_{obs} values increased with increase in pH values in all the drug. The plot of k_{obs} vs. $[H^+]$ gave a straight line with a positive intercept. (Fig. 3) The positive intercept obtained in the above plot revealed that the oxidation reaction proceeded in two steps - one dependent on the $[H^+]$ and the other independent of $[H^+]$ in presence of copper (II)) catalyst[22].

3.3 EFFECT OF [β-CYCLODEXTRIN] ON k_{obs}

The values of k_{obs} were calculated for different quantities of β-cyclodextrin by keeping the parameters at constant values at 308K. The rate of the reaction increased with increase in [β-cyclodextrin] in all the drug (Table 4.4) . The plot k_{obs} vs. [β-cyclodextrin] were linear with positive intercepts in all the drug. (Figure 4.3) This linear plot clearly indicates that the formation of inclusion complex of various drug with β-cyclodextrin. The mode of inclusion of Pickric acid into ß –CD cavity[23]



Equation.(A.3)

3.4 Effect of [Cu (II)] on k_{obs}

The effect of [copper (II)] on k_{obs} was calculated by determining the values of k_{obs} at different concentrations of [copper (II)] ions, by keeping the other parameters at constant values. The kinetic results showed that the rate of a reaction increased with increase in [copper (II)] catalyst. (Table 1)[21]. The plots of k_{obs} vs [copper (II)] catalyst were linear with positive intercepts (Figure 5).

3.5 Phase solubility studies

Higuchi and Connors [Higuchi et al.,1965] have classified complexes based on their effect on drug Solubility and it is indicated by the phase-solubility profiles. A-type phase-solubility profiles are obtained when the solubility of the drug increases with increasing ligand (cyclodextrin) concentration. The complex is first order with respect to ligand. [Tommasini et al.,2004] suggesting the formation of 1:1 complexes. The phase solubility data made at different temperatures allowed to obtain additional information such as the thermodynamic parameters involved in the formation of the complex.

The integrated form of the Van't Hoff equation enables the calculation of the enthalpy (ΔH^0) and of entropy changes (ΔS^0), depending on the variations of the stability constants with temperature [Cooper et al.,1978]. The *Kc* values plotted in a Van't Hoff plot are shown in Figure 6.

$$\text{Ln } Kc = -\Delta H/RT + \Delta S/R$$

(Equation.A.4)

3.6 hermodynamics Values of the Inclusion complex

The thermodynamic parameters ($\Delta H°$, $\Delta S°$, $\Delta G°$ and E_a**)** for the formation of inclusion complex were determined from the temperature dependence of the plot of log k_2 vs. 1/T (Arrhenius plot) (Figure6). The corresponding enthalpy and entropy values were obtained from the slope and intercept, respectively. ΔG^0 was obtained according to the equation: $\Delta G^0 = \Delta H^0 - T\Delta S^0$ The results are shown in Table 1.The stability constant of the complexes of arginine with the β-cyclodextrin at different temperature (30^0 C, 35^0 C, 40^0 C and 45^0 C)

are shown in Table 1 The thermodynamic parameters: enthalpy changes (ΔH^0) and entropy changes (ΔS^0) of the binding reaction are important to confirm the force of interactions of drug with β-cyclodextrin (Equation A.3). Four driving forces for the inclusion of cyclodextrins with substrates were proposed, including hydrogen bonding between the hydroxyl groups of cyclodextrins and the guest molecules, van der Waals interactions between host and guest molecules, hydrophobic interaction, and the release of 'high-energy water' molecules from the cavities of β-cyclodextrins to the bulk water. Hydrophobic interaction involves favorable positive entropy together with a slightly positive enthalpy change (Table 1), whereas the other forces involve negative ΔH^0 and ΔS^0[24-25] Upon complexation both positive enthalpic and positive entropic values are obtained, indicating that this inclusion is mainly entropically driven one. As discussed above, ΔG^0 obtained are negative (Table 2), which indicated that the inclusion process proceeded spontaneously at this experimental condition. The use of cyclodextrins is one of the pharmaceutical strategies available to circumvent these drawbacks, as they can be used as complexing agents to increase the aqueous solubility of hydrophobic drugs and to increase their bioavailability and stability[26-28] was calculated through enthalpy and entropy changes, shows the spontaneous formation of VAL:ß-CD inclusion complex in aqueous solution [Uekama et al., 1998, Karathanos et al.,2007, Davies et al.,1996,]. The positive ΔH^0 together with positive $\Delta S\circ$ suggested that the inclusion process is an enthalpy controlled process in the case of the drug in the presence of copper.[29- 32]

3.7 Determination of stability constant by UV-Visible spectral analysis

Absorption spectra were used to confirm the formation of inclusion complex between drug and β-cyclodextrin. The values of stability constant were calculated by varying [drug], keeping the other parameters as constant. The concentrations of β-cyclodextrin and copper (II) catalyst have been assigned as 500 mg and concentrations of L-drug have been assigned as 50 mg. There was a linearly decrease in the absorbance with the successive addition of [drug] (0,5ml,1ml,1.5ml,2.0ml) (Fig 8.0) There was also shift in the λ_{max} from 215nm to 213nm whereas, intensity of the inclusion complex gets decreased at all points of wavelength due to the interaction of β- cyclodextrin and drug. It indicates that the solubility of drug increases upon forming the inclusion complex. A very good linear relationship was obtained for 1/A vs. [1/ β-CD] (Fig 9.0). The stability constant value of drug was $89.57M^{-1}$. The stoichiometry ratio for the inclusion complex formation between drug and β- cyclodextrin is 1:1.

3.8 ESR spectrum analysis

EPR spectrum of the mixture containing drug in the presence of copper(II) ions, showed five signals which corresponded to the formation of (copper(II)-drug- β-cyclodextrin) complex. In order to study whether copper(II) ions reacted directly with PMS, an EPR spectrum of copper(II) ions in acetate buffer with PMS was taken. It showed only four signals, ruling out the possibility of the formation of hydroxyl radical or any other radical. (Fig.10)

3.9 VALIDATION OF THE METHODS

3.9.1 Limit of detection.

The LODs value and LOQ values for the inclusion complex are 0.29 LM^{-1} and 0.90 LM^{-1}

3.9.2 Recovery of drug

To a fixed amount of the β- cyclodextrin in the dosage form, pure drug was added at different concentration and the stability constant was found by the proposed methods. The recovery was calculated by comparing the stability constant with those of the pure drug. It is a very good accuracy Table 2

3.9.3 Selectivity

The effect of the presence of common excipients such as; β- cyclodextrin and Cu (II) was studied. It was found that no interference was introduced by any of them and it acts as a catalyst.

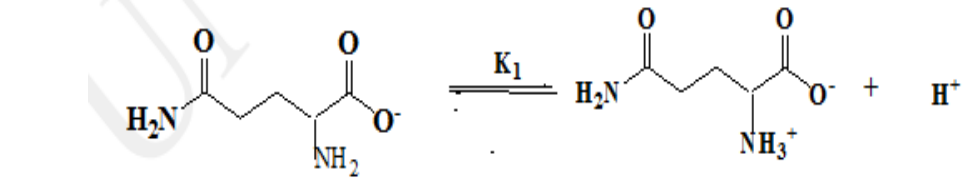
3.9.4 Applications of the methods

In order to study the validity of the proposed method, the pharmaceutical dosage forms (glutamine) was subjected to the analysis of their β- cyclodextrin content by the proposed method. Indicate the high accuracy of the proposed method for the determination of the studied drug. In addition to the catalyst we add Cu (II) ions which are responsible for greater importance in terms of the rate constant value, thermodynamic parameter and stability constant values for advantages of this method. The same phenomenon has been observed .

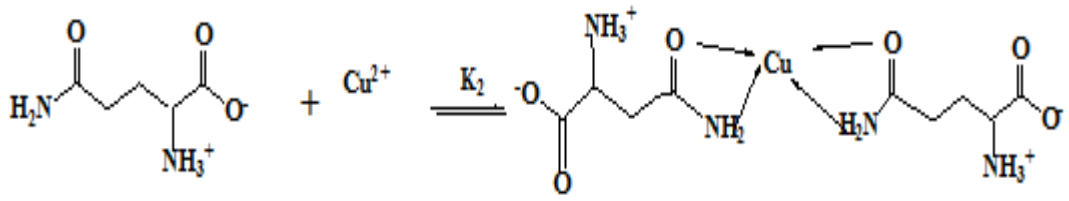
CONCLUSION

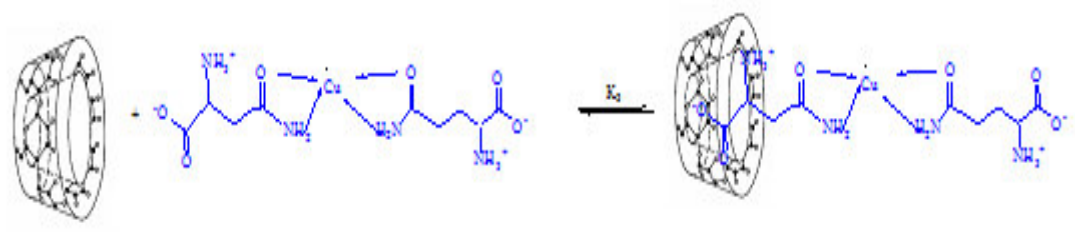
Catalytic effect of Cu (II) with β-cyclodextrin catalyst oxidation of drug by peroxomonosulphate (PMS) was studied in acetic acid -sodium acetate buffer medium at 308K. The rate of the reaction increases predomentally when Cu is added with β-cyclodextrin catalyst. Hence, the various concentration of drug, pH, β-CD and Cu (II) catalyst the rate of the reaction increases linearly. On the other hand the variation of PMS, sodium acetate, ionic strength and solvent polarity had negligible effect on the rate of the reaction .The stability constant values are 89.57 LM^{-1} (Table 3). The observed stoichiometry of the reaction in the mixture of β-cyclodextrin with Cu (II) and drug: PMS was 1:1. Which shows that the formation of inclusion complex. These inclusions were favored through entropy and enthalpy changes were calculated by thermodynamic parameters. The limit of detection (LOD) and limit of quantification (LOQ) was calculated and this method has been successfully applied to the determination of pharmaceutical formulation with good accuracy of drug delivery and pharmaceutical industry due to their use as complexing agent to increase the aqueous solubility of poor soluble drugs and to increase their bioavailability and stability. $\Delta G\circ$ obtained are also negative. It indicated that the inclusion process proceeded spontaneously at experimental temperature. Here the detailed mechanism for the Cu (II) catalyzed reaction pathway was given in Scheme 1.

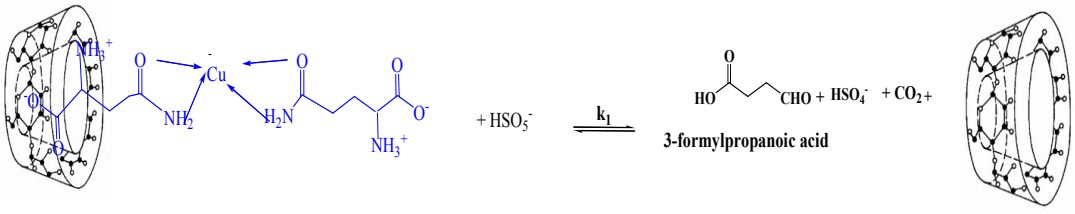
Scheme 1



Glutamine







$$2HSO_5^- \xrightarrow{k_2} 2HSO_4^- + O_2$$

$$\frac{-d[HSO_5^-]}{dt} = k_1[\text{complex}][HSO_5^-] + k_2[HSO_5^-]$$

$$= \frac{k_1K_1K_2K_3[\text{Glutamine}][Cu^{2+}][\beta\text{–CD}][HSO_5^-]}{K_1 + [H^+]} + k_2[HSO_5^-]$$

$$k_{obs} = \frac{k_1K_1K_2K_3[\text{Glutamine}][Cu^{2+}][\beta\text{–CD}]}{K_1 + [H^+]} + K_2$$

Since $K_1 << [H^+]$

$$\text{Hence } k_{obs} = \frac{k_1K_1K_2K_3[\text{Glutamine}][Cu^{2+}][\beta\text{-CD}]}{[H^+]} + K_2$$

Table 1

Effect of varying concentrations on the reaction rate at 308K

10^3 x [PMS] (mol dm^{-3})	10^2 x [drug] (mol dm^{-3})	10^2 x [sodium acetate] (mol dm^{-3})	pH± 0.1	β-cyclodextrine (gram)	10^{-3} x [Cu(II)] mol dm^{-3}	10^4x k_{obs} (s^{-1})	Temperature (K)
1.93	5.00	8.50	4.0	0.3	2.50	2.80	308
3.86	5.00	8.50	4.0	0.3	2.50	2.80	308
5.79	5.00	8.50	4.0	0.3	2.50	2.79	308
7.72	5.00	8.50	4.0	0.3	2.50	2.78	308
3.86	0.025	8.50	4.0	0.3	2.50	1.96	308
3.86	0.0375	8.50	4.0	0.3	2.50	2.80	308
3.86	0.05	8.50	4.0	0.3	2.50	3.34	308
3.86	0.0625	8.50	4.0	0.3	2.50	3.73	308
3.86	5.00	2.13	4.0	0.3	2.50	0.575	308
3.86	5.00	4.25	4.0	0.3	2.50	0.575	308
3.86	5.00	6.38	4.0	0.3	2.50	0.575	308
3.86	5.00	10.63	4.0	0.3	2.50	0.575	308
3.86	5.00	8.50	3.6	0.3	2.50	1.343	308
3.86	5.00	8.50	4.0	0.3	2.50	2.80	308
3.86	5.00	8.50	4.4	0.3	2.50	3.53	308
3.86	5.00	8.50	4.8	0.3	2.50	4.99	308
3.86	5.00	8.50	4.0	0.1	2.50	2.533	308
3.86	5.00	8.50	4.0	0.2	2.50	2.648	308
3.86	5.00	8.50	4.0	0.3	2.50	2.801	308
3.86	5.00	8.50	4.0	0.5	2.50	3.147	308
3.86	5.00	8.50	4.0	0.7	2.50	3.416	308
3.86	5.00	8.50	4.0	1.0	2.50	4.91	308
3.86	5.00	8.50	4.0	1.5	2.50	5.57	308
3.86	5.00	8.50	4.0	0.3	2.50.	2.80	308
3.86	5.00	8.50	4.0	0.3	5.00.	3.53	308
3.86	5.00	8.50	4.0	0.3	7.5	3.73	308
3.86	5.00	8.50	4.0	0.3	10.0	4.01	308
3.86	5.00	8.50	4.0	0.3	2.50	0.7676	303
3.86	5.00	8.50	4.0	0.3	2.50	2.80	308
3.86	5.00	8.50	4.0	0.3	2.50	3.201	314
3.86	5.00	8.50	4.0	0.3	2.50	3.917	318

Table 2

Thermodynamic parameters for the oxidation of drug in the presence of copper (II) ions at 308 K

Glutamine	ΔH^0 KJ mol^{-1}	ΔS^0 J $K^{-1}mol^{-1}$	ΔG^0 kJ mol^{-1}
Drug	68.79	37.41	-11.45

Table 3

Stability constant values of drug with various concentration of β-Cyclodextrin catalyst in the presence of Cu (II)

Stability constant values	89.57 LM^{-1}
Drug	Glutamine

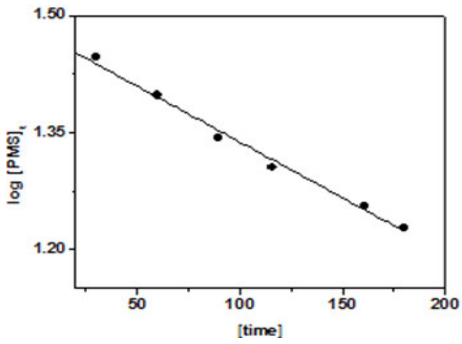


Figure 1

Plot of log $[PMS]_t$ vs. time

drug] = 5 x 10^{-2} M; [sodium acetate] = 8.5 x 10^{-2} M: $[H^+]$ = 5 x 10^{-1} M
[copper (II)] = 2.5 x 10^{-3} M; [β-cyclodextrin] = 0.3g; Temperature=308 K.

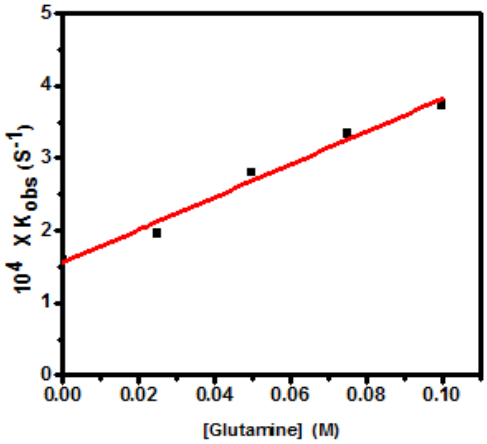


Figure 2
Plot of k_{obs} vs. [drug]
[sodium acetate] = 8.5 x 10^{-2} M: [H^+] = 5 x 10^{-1} M
[copper (II)] = 2.5 x 10^{-3} M; [β-cyclodextrin] = 0.3g;
[PMS] = 3.90 x 10^{-3} M; Temperature=308 K.

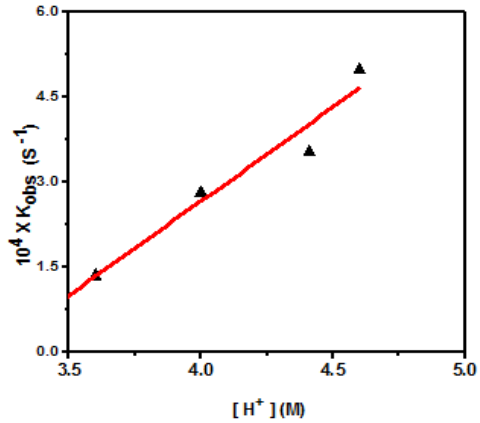


Figure 3
Plot of k_{obs} Vs. pH

[drug] = 5 x 10^{-2} M; [copper (II)] = 2.5 x 10^{-3} M;
[β-cyclodextrin] = 0.3g; [PMS] = 3.90 x 10^{-3} M; Temperature=308 K.

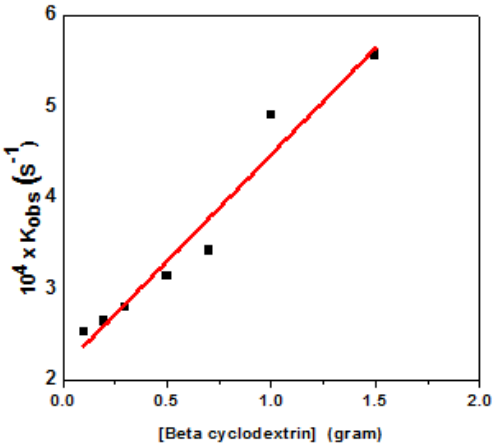


Figure 4
Plot of k_{obs} vs. [β-CD]

[drug] = 5 x 10^{-2} M; [sodium acetate] = 8.5 x 10^{-2} M: [H^+] = 5 x 10^{-1} M
[copper (II)] = 2.5 x 10^{-3} M; [PMS] = 3.90 x 10^{-3} M; Temperature=308 K.

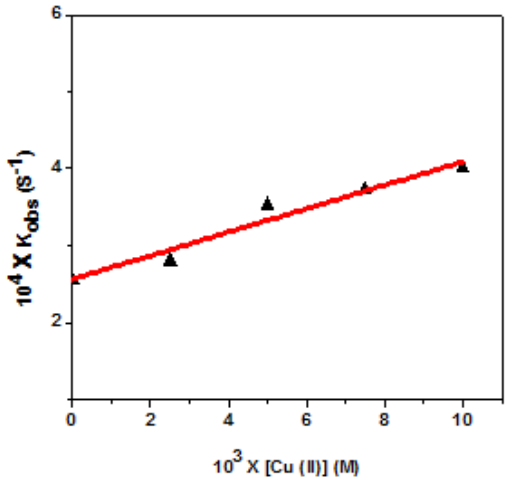


Figure 5

Plot of k_{obs} vs. [Cu (II)] of drug

[drug] = 5 x 10^{-2} M; [sodium acetate] = 8.5 x 10^{-2} M: [H^+] = 5 x 10^{-1} M
[PMS] = 3.90 x 10^{-3} M; Temperature=308 K.

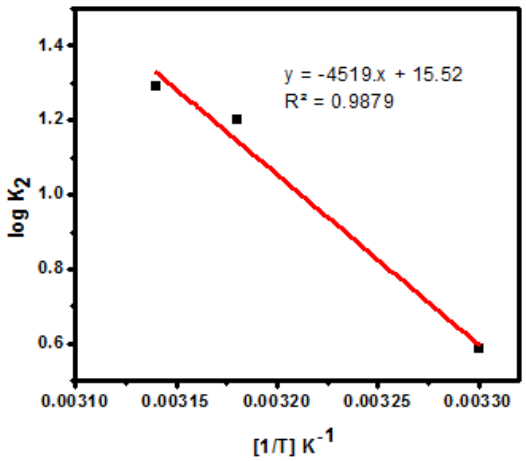


Figure 6

Van't Hoff plot of the formation of the complex between drug and β-cyclodextrin.

[drug] = 5 x 10^{-2} M; [sodium acetate] = 8.5 x 10^{-2} M: [H^+] = 5 x 10^{-1} M
[copper (II)] = 2.5 x 10^{-3} M; [PMS] = 3.90 x 10^{-3} M; [β-cyclodextrin] = 50mg

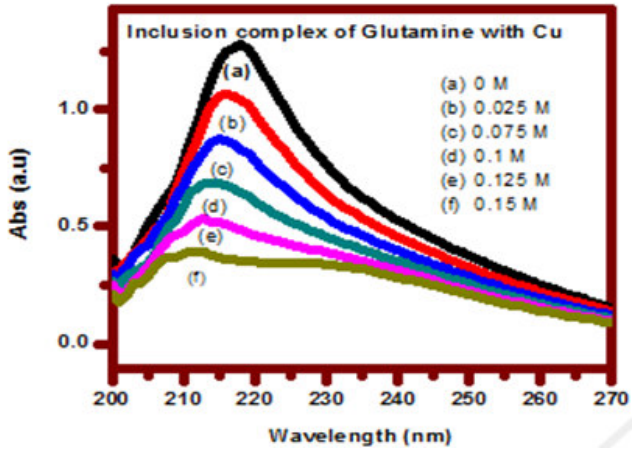


Figure 7

Absorption spectra of [drug] with β-CD in presence of copper (II) ions

[drug] = 5 x 10^{-2} M; [sodium acetate] = 8.5 x 10^{-2} M: [H^+] = 5 x 10^{-1} M
[copper (II)] = 2.5 x 10^{-3} M; [PMS] = 3.90 x 10^{-3} M; Temperature=308 K.
[β-cyclodextrin] = 50mg

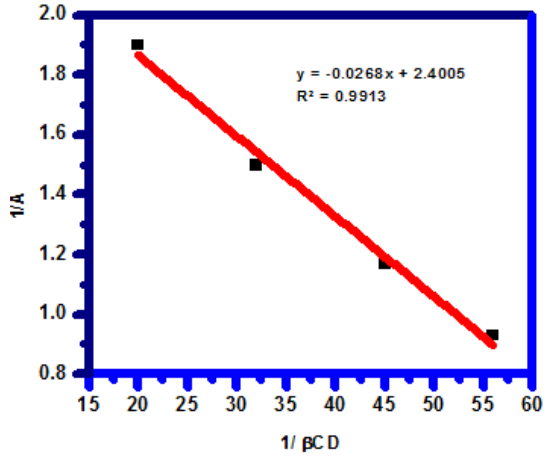


Figure 8
Reciprocal plot for 1/A against 1/β–CD of drug inclusion complex

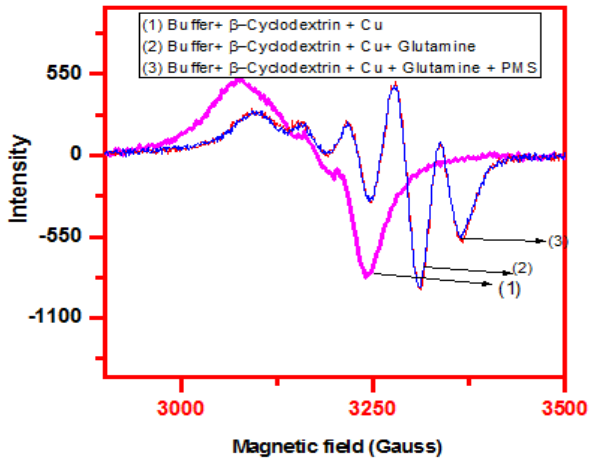


Figure 9
EPR spectra of the drug reaction mixture of in the presence of copper (II) ions
[drug] = 5 x 10^{-2} M; [sodium acetate] = 8.5 x 10^{-2} M: [H^+] = 5 x 10^{-1} M ;
[β-cyclodextrin] = 50mg; [copper (II)] = 2.5 x 10^{-3} M; [PMS] = 3.90 x 10^{-3} M;
Temperature=308 K.

CONFLICT OF INTEREST

All the authors are fully aware of the submission and agree to its submission for publication.

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