Studies on Stability and Configurational Changes of Nickel and Copper Ethambutol Dihydrochloride and Metformin Hydrochloride in both Cationic and Anionic Surfactants

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ABSTRACT: *Present paper investigates and discusses formation and stability of two metal drug complexes under various external conditions and also results of kinetic investigation under changing pH as well as with various additives and solvent compositions in order to determine its configurational alterations. These studies are important from the view point of application of the metal-drug complexes under changing human abdominal environment. Two drugs namely Ethambutol dihydrochloride and Metformin hydrochloride used for tuberculosis and diabetic treatment , the most prevalent diseases in tropical countries, have been chosen for present studies.*

I. INTRODUCTION

Metallic elements play a crucial role in living systems [1]. A characteristic of metals is that they easily lose electrons from the elemental or metallic state to form positively charged ions which tend to be soluble in biological fluids. It is in this cationic form that metals play their role in biology. Whereas metal ions are electron deficient, most biological molecules such as protein and DNA are electron rich. The attraction between these opposing charges leads to the general tendency of metal ions to bind to and interact with biological molecules. It is not surprising therefore that natural evolution has incorporated many metals into essential biological functions. A natural question therefore arises that whether metal ions can be incorporated into life saving and other essential drugs and in doing so whether the metal complexes thus formed can act as potential clinical agents with enhanced activity.

The present work deals with studies on complex formation properties of two widely prescribed antituberculosis (ethambutol dihydrochloride EB) and antidiabetic (metformin hydrochloride MF) drugs. The metal ions chosen for the purpose are bivalent copper and nickel. The choice of metal ions rests on their availability and more so on their importance in physiological system. Recently it has been found that the course of action of ethambutol in physiological systems involves formation of chelate complexes with bivalent cations [2]. Restriction of the visual field and loss of colour discrimination which result from prolonged use of ethambutol have been attributed to the progressive depletion of copper and zinc in the human system [3]. Evidently the bivalent trace metal ions present in body system play a significant role for effective antitubercular activity.

II. EXPERIMENTAL

Chemical used are of analar grade. Estimation of Cu^{2+} and Ni^{2+} ion have been done by complexometric titration with ethylenediaminetetraacetic acid (disodium salt) [4]. Analytical studies include C, N, H estimation, spectral measurement (UV-visible, IR, NMR) and pH-metric studies. Purity of metal drug complexes were checked by the method of thin layer chromatography.

Dissociation constant of the drug hydrochloride and the thermodynamic stability of their metal complexes with Cu(II) and Ni(II) have been determined by pH–metric study. The hydrogen in concentration is measured with a Systronics Model 335 pH-meter having glass/calomel electrodes and temperature probe. The electrodes are maintained at a constant temperature of $30 \pm 0.1^{o}C$. The pH-meter is calibrated directly in terms of hydrogen ion concentration at specific ionic strength (0.1 or 0.05 mol dm^{-3} potassium nitrate) using saturated potassium hydrogen phthalate at pH 3.55 and 0.05 mol dm^{-3} borax at 9.2 pH. All studies are carried out at $30^{o}C$ in an inert atmosphere using standard KOH solution at constant ionic strength. For the evaluation of stability constant of the metal complexes, different molar proportions of metal : drug have been used for titration. The findings of pH-metric study are supplemented by UV-visible spectra of the drugs and their complexes with Cu(II) and Ni(ii) recorded by Shimadzu UV-1700A spectrophotometer having thermostatic attachment. Data from IR and NMR spectroscopic studies are also used for the purpose. Micellar effect on thermodynamic

stability and spectral properties of the metal-drug complexes have been evaluated by conducting the same studies with CTAB and SDS.

Kinetics of the dissociation reaction of nickel ethambutol complex (Ni-EB) has been studied spectrophotometrically by measuring the decrease in absorbance at 480nm as a function of time. The spectral measurements are carried out using Shimadzu UV-1700 spectrophotometer. Preliminary investigation indicated that the reaction is susceptible to light. Hence all experiments have been carried out in amber coloured bottles covered with black paper so as to cut off light as far as possible. The dissociation reaction is studied under varying conditions of pH, solvent composition, amount of additive (NaCl) and temperature. A Remi Cryastat Model No. 397 LAG is used to maintain the temperature of the reaction mixture at the desired value. Kinetic runs are also carried out at different initial concentration of $[Ni-EB]_T$, keeping the pH, ionic strength, solvent composition and temperature constant. The rate constant values are obtained using the first order rate equation and from the slope of the plot of $\ell n\, (A_t - A_\infty)$ vs time (A_t and A_∞ were the absorbance values of Ni – EB complex at time 't' and at infinite time respectively).

III.   RESULT AND DISCUSSION

Characterisation of the drugs, viz., ethambutol dihydrochloride and metformin hydrochloride as well as (their Cu(II) and Ni(II) complexes) has been done through routine analytical methods like solubility, melting point, C, H, N analysis & IR & UV- Visible spectral studies. These results are shown in Table-1, 2, and 3.

Table-1: Physical properties

Compound	Colour	Solubility	Melting point
EB 2HCl	White	Soluble in water, dimethyl sulphoxide and glycol	$202\pm1.5\ ^0C$
MF HCl	Off-white	More soluble in water less soluble in ethanol	$228\ ^0C$
Cu(II)-EB	Deep blue in colour	Highly soluble in both water and ethanol	$120\ ^0C$
Ni(II)-(EB)$_2$	Greenish blue in colour	Highly soluble in water and ethanol	_
Cu(II)-(MF)$_2$	Pale pink colour	Sparingly soluble in water and ethanol	$260 \pm 1\ ^0C$
Ni(II)-(MF)$_2$	Light yellow colour	Sparingly soluble in water and ethanol	_

Table-2:   C H N analysis of metal drug complexes

Compound	%C	%H	%N
Cu(II)-EB	34.01	7.31	7.27
Ni(II)-(EB)$_2$	35.84	7.19	8.91
Cu(II)-(MF)$_2$	21.18	4.47	38.78

Table-3: IR Study of the metal drug complexes

| Compound	Major peaks
EB 2HCl	$3503\ cm^{-1}$(O-H stretching) $2986\ cm^{-1}$(N-H stretching) $1640\ cm^{-1}$(C-N stretching) $1400\ cm^{-1}$(N-H bending) $955\ cm^{-1}$(C-H bending)
MF HCl	$3150\text{-}3100\ cm^{-1}$, $1580\ cm^{-1}$(N-H bending) $1620\ cm^{-1}$,$1063\ cm^{-1}$, $935\ cm^{-1}$(C-N stretching) $745\ cm^{-1}$(C-H bending)
Cu(II)-EB	$2966\text{-}2935\ cm^{-1}$(N-H stretching) $2085\ cm^{-1}$(M-N stretching) $<1640\ cm^{-1}$(C-N stretching)
Cu(II)-(MF)$_2$	$3159\text{-}3111\ cm^{-1}$,$1589\ cm^{-1}$(N-H bending) $1637\ cm^{-1}$(C-N stretching)

The dissociation constants of the drug hydrochlorides and thermodynamic stability constants values of the metal drug complexes have been evaluated by pH-metric technique. For example, for Cu(II)-ethambutol (EB), the various complex formation equilibria are described by equation 1-3

$$H_2A^{2+} \overset{K_1}{\rightleftharpoons} HA^+ + H^+ \tag{1}$$

$$HA^+ \overset{K_2}{\rightleftharpoons} A^+ + H^+ \tag{2}$$

$$CU^{2+} + A \overset{K_2}{\rightleftharpoons} CuA^{2+} \tag{3}$$

Where the first two equations represent the acid dissociation equilibria for ethambutol dihydrochloride. From a number of pH-metric experiments, taking different molar properties of Cu(II) : EB, the complex has been determined as 1:1 [5,6]. This has been subsequently confirmed by spectral studies (Table -4). Moreover, the $[Cu(EB)]^+$ complex has a single peak in the visible region (Fig. 1) due to $E_g \rightarrow T_{2g}$ transition. The peak, however, changes shape, increases in intensity and shifts to lower wavelength side with gradual increases in pH. In fact there is a blue shift from 690nm at pH 4.31 to 620nm at pH 9.7 where the peak position remains finally unaltered with further increase in pH up to 11.4. Clearly, base hydrolysis at high pH is ruled out. Also enhanced complex formation with increase in pH is indicated. On the basis of ligand field theory, the gradual blue shift from 690nm to 620nm with increasing pH indicates that the donor atoms in the high pH region exert higher ligand field strength. From the study of a large number of Cu-N complexes it has been concluded that those having absorbance values above 600nm are attributed either to (2N, 2O) or (4) donors in the equatorial position [7-12]. On this basis it may be said that the $[Cu(EB)]^{2+}$ complex of the present study has two N and two O donors occupying the equatorial sites with solvent interaction in the apical position. The two N-donors are from the two amino groups in the EB molecule and the two O donors are form the solvent molecules. There is no precipitation throughout the entire pH range of study [12]. Again there is only one isobestic point in the spectra at different pH (Fig.1) which indicates presence of two species throughout the complex formation [13] process. Based on all the above information a plausible planar structure has been proposed for $[Cu(EB)]^{2+}$. Although like copper, nickel, also forms at high pH square planer complex with EB, here the pH-metric and spectrophotometric studies are consistent with a bis-complex formation of the type $[Ni(EB)_2]^{2+}$. So an additional equilibrium step here (in addition to equation 1-3) is

$$NiA^{2+} + A \overset{K_4}{\rightleftharpoons} [NiA_2]^{2+} \tag{4}$$

Ni(II) complexes of polyamine ligands are known [14-17] to produce in solution an equilibrium mixture of octahedral, paramagnetic and square planar, diamagnetic NiA_2^{2+} complex ('A' being a diamine ligand).

$$\text{Ni } A_2 (H_2O)_2^{2+} \rightleftharpoons \text{Ni } A_2^{2+} + 2H_2O \tag{5}$$
$$\text{(Octahedral)} \qquad\qquad \text{(Planar)}$$
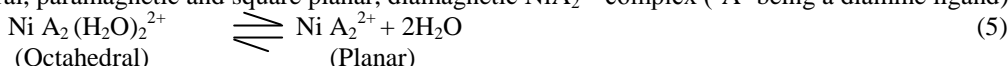
Similar behaviour was also observed in the present study where the peak at 610 nm ($^3A_{2g} \rightarrow {}^3T_{1g}(F)$) prominent up to pH 8.92, shifts to 480 nm at pH 11.0 ($^1A_{1g} \rightarrow {}^1E_g$). The complex is predominantly bluish green in colour up to pH 8.92 whereas at and above pH 11.0, the orange–red square planar $Ni(EB)_2^{2+}$ is virtually the only Ni(II) species present. In the intermediate range of pH between 8.92 to 11.0, both the species exist in sizable amounts. Thus with increase in pH, the $\in_{610}$ gradually falls while that at 480 nm increases (Fig.2). Several factors like [OH⁻], added electrolyte, temperature are known to affect [5] the octahedral-planar conversion. Although the octahedral configuration seems to be the favoured one due to additional energy release when two extra ligands are coordinated, but John-Teller distortion as well as ligand geometry may push the equilibrium to the right. In the present study, the orange-red planar complex formed is found to be highly unstable and slowly hydrolyses to from the bluish-green octahedral complex on standing with accompanying decrease in pH. A detail kinetic study of the configurational conversion is described later. The effect of electrolyte NaCl on the absorbance value at 480nm (Fig.3) at pH 11.05 ± 0.04 indicate a linear increase in $\in_{480}$ values with increase in [NaCl]. This is explained by the fact that the ions of the electrolyte compete for the water molecules released during configurational transition [17] and thereby enhance the formation of the square planar species $[Ni(EB)_2]^{2+}$. Returning again to the octahedral Ni(II)-EB complex, at low pH (~910), it is charecterised by three peaks at 980nm ($A_{2g}(F) \rightarrow {}^3T_{2g}(F)$), 610nm ($^3A_{2g}(F) \rightarrow {}^3T_{1g}(P)$). Using these transitions, the Racah Parameter (B) and the Dq values have been evaluated as 1020.4 and 761.5 cm⁻¹ respectively. Considerable reduction in B value compared to that of $Ni(H_2O)_6^{2+}$ (B = 953 cm⁻¹), is attributed to a certain degree of covalency of the metal-ligand bond causing the delocalisation of metal ion electron density into the ligand. The 10Dq value for Cu(II)-EB complex for the single $E_g \rightarrow T_{2g}$ transition has also been evaluated as 16129 cm⁻¹, in agreement with the literature value [5].

Metformin hydrochloride is a monobasic acid and hence its deprotonation step occurs as in equation 2. Similar to Ni(II)-EB system, both Cu(II) and Ni(II) form bis-complex of the type $M[(MF)_2]^{2+}$ where M is the bivalent metal ion and MF is the drug molecule metformin. This has been established from both pH-metric and spectral studies. Cu(II)-MF mono complex is faint blue in colour with λ_{max} at 740nm. The very low intense peak virtually remains unaltered but gradually loses intensity with increasing pH. At high pH (>6.0), the peak which appears at 640nm shows regular blue shift and gains in intensity so that at pH 10.20, the λ_{max} is at 527nm with $\in=88.2$ mol^{-1} dm^3 cm^{-1}. The entire visible spectrum (Fig. 4) for Cu(II)-MF system at different pH has two isobestic points and hence three Cu(II) species exists in solution. In conjunction with pH-metric studies these are identified as Cu(II), $[Cu(MF)]^{2+}$ and $[Cu(MF)_2]^{2+}$, the last one being pale pink in colour with low solubility in water. Spectral and pH-metric studies for Ni(II)-MF system reveal that upto pH 7, complex formation is negligible. At low pH (<9.0) the green coloured complex formed due to $^3A_{2g} \rightarrow \, ^3T_{1g}$ transition (octahedral field) changes to yellow complex due to $^1A_{1g} \rightarrow \, ^1E_g$ transition (S.P. field) when the pH is increased beyond 9.0. The low pH peak at 620nm has the characteristic of tetragonally distorted pseudo octahedral Ni(II) complex [18] and is assigned to the mono complex $[Ni(MF)]^{2+}$. The peak at high pH (≥ 9) is due to singlet ground state planar Ni(II) complex [19] and is presumably due to $[Ni(MF)_2]^{2+}$. Present result from pH-metric study are in accordance with above findings.

Table 4: Absorbance values of Cu (II) - EB complex at different molar proportions of   [Cu^{2+}] : [EB]. Stock [Cu^{2+}] = 0.02, [EB] = 0.02 mol dm^{-3}, Total volume = 20 ml, Temp. 30°C, Solvent = 50% (v/v) dioxane - water.

Volume of Cu^{+2}, ml	Volume of EB, ml	[Cu(II)]/[EB]	A$_{650}$	Total molar concentration, mol dm^{-3}
1.0	9.0	0.111	0.055	0.2
2.0	8.0	0.250	0.172	0.2
3.0	7.0	0.429	0.285	0.2
4.0	6.0	0.666	0.425	0.2
5.0	5.0	1.000	0.510	0.2
6.0	4.0	1.500	0.165	0.2
7.0	3.0	2.330	0.085	0.2
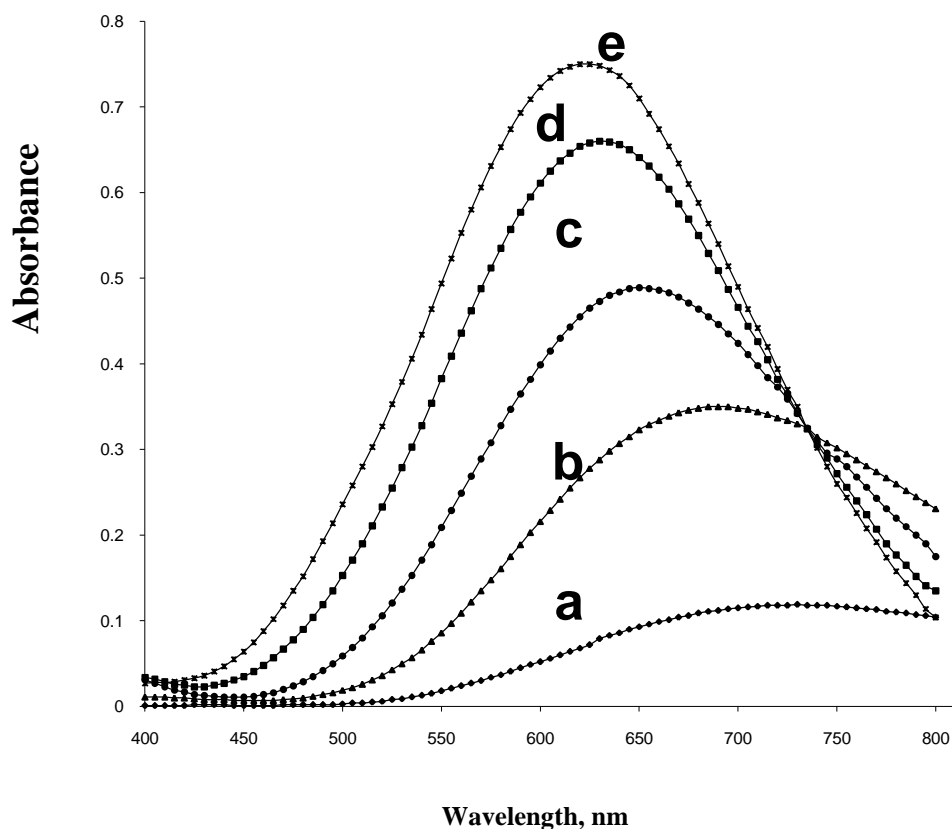
Fig 1: **Spectrophotometric curves for Cu-Ethambutol system. Temp. 30°C, I = 0.1 mol dm^{-3}, total volume 20 ml, [Cu^{+2}] = 0.005 mol dm^{-3}, [EB] = 0.1 mol dm^{-3}. pH at a = 3.00, b = 4.31, c = 6.57, d = 7.89 and e = 11.37.**

Spectrophotometric curves for Ni-Ethambutol system at different pH.Temp. 30^{0}C, I = 0.1 mol dm^{-1}, total volume 14.4 ml, [Ni^{+2}] = 0.0174 mol dm^3, [EB] = 0.0347 mol dm^3, pH at a = 4.02, b = 8.92, c = 9.60, d = 10.80, e = 11.00. Curve a refers to Ni^{+2} solution of strength 0.219 dm^3 having pH 4.02.
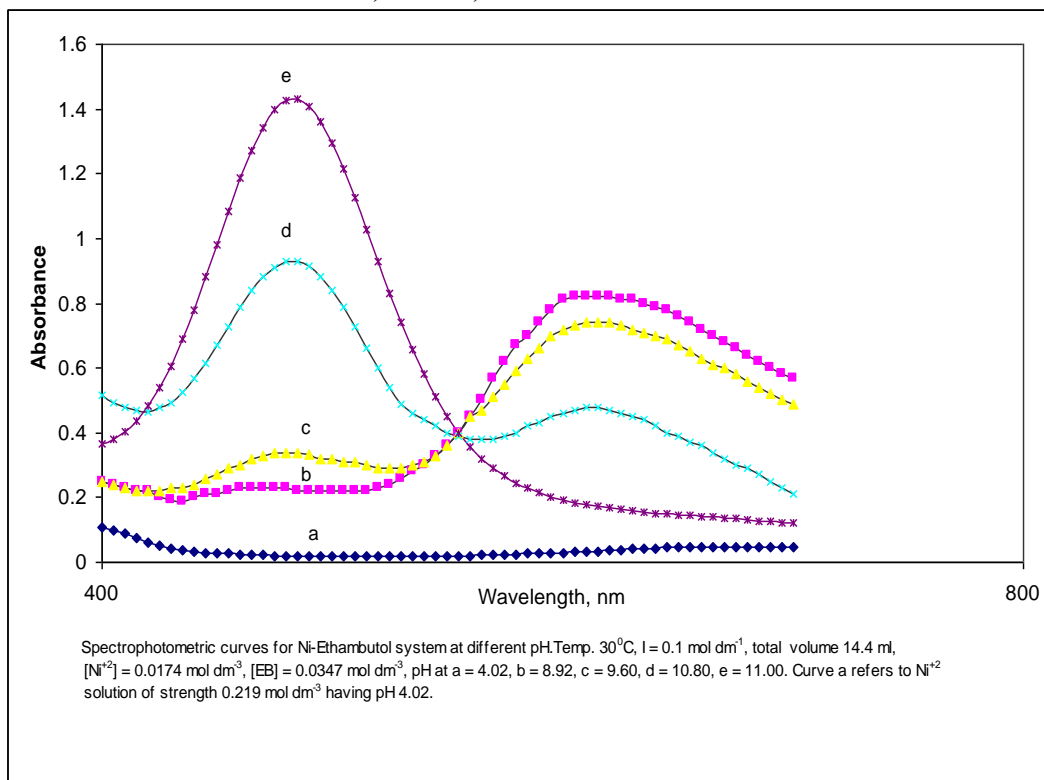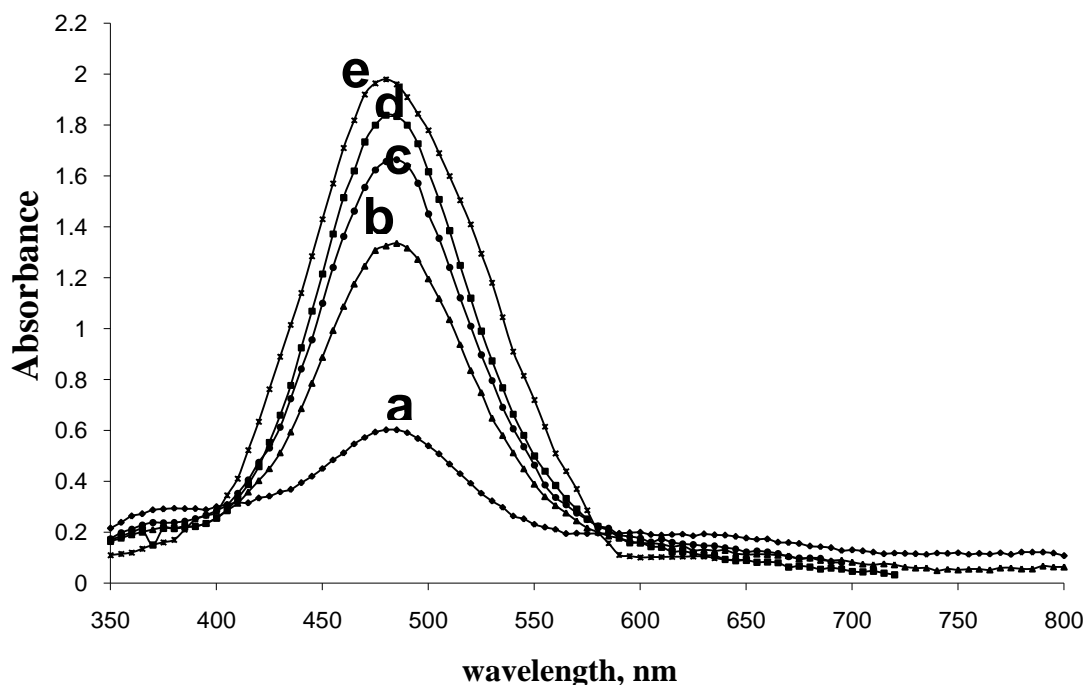
Fig 2:

Fig 3: **Spectra of Ni(II) - EB complex in presence of NaCl. Temp. 30°C, I = 0.1 mol dm^{-3}, total volume 10 ml, [Ni- EB] = 0.1 mol dm^{-3}. [NaCl] at a = 0, b = 0.5, c = 1.0, d = 2.0 and e = 3.0 mol dm^{-3}.**
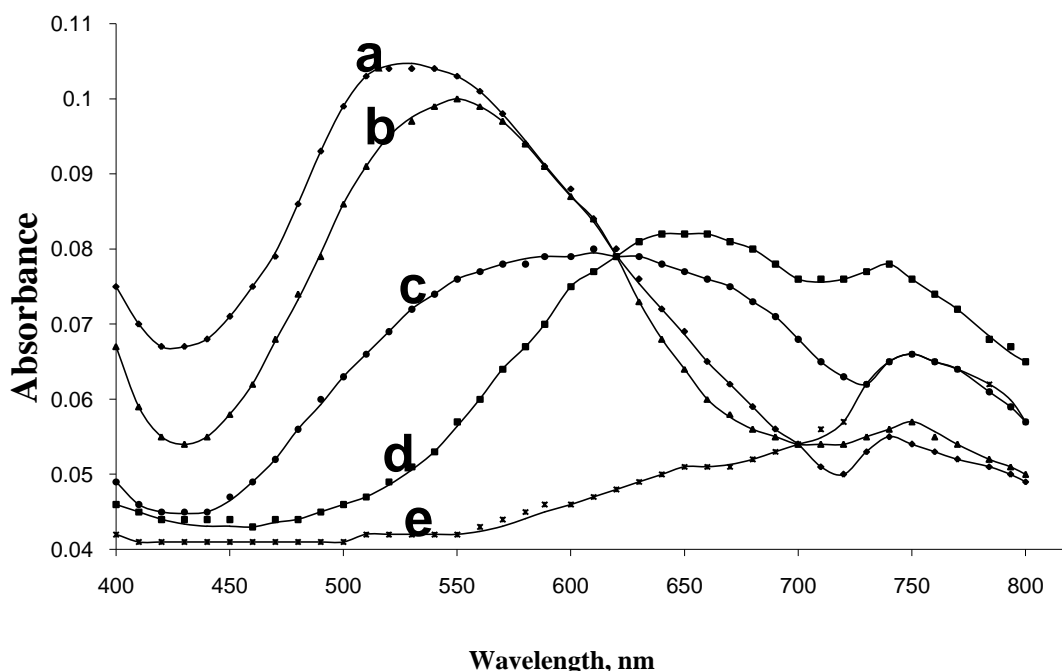
Wavelength, nm

Fig. 4: Specrophotometric curves for Cu-Metformin system at different pH. Temp. 30°C, I=0.1 mol dm^{-3}, total volume 40 ml, [Cu^{+2}] = 0.1 mol dm^{-3}, [Metformin] = 0.05 mol dm^{-3}, pH at a = 0.20, b = 9.22, c = 7.43, d = 5.98, e = 4.49.

Determination of various equilibrium constants which include acid dissociation constants of the ligands as well as the stability constants of the metal complexes formed was carried out by Standard literature procedure [20-21] and [22-24]. For the present study involving four complex formation systems , two each of Cu(II) and Ni(II), the titration data are analysed for several metal complex species with p=1, q=0, -1, -2 and r = 1, 2 in the general equation

$$pM + qH + rA \rightleftharpoons M_p H_q A_r \qquad (6)$$

(p, q and r are the stoichiometric quantities of M, H and A respectively)

$$\beta_{pqr} = [M_p H_q A_r] / [M]^p [H]^q [A]^r \qquad (7)$$

Dissociation constants determined by above means tally well with the literature value as shown in Table 5 and 6.

Table-5 :   Dissociation constant of drugs.

Drug	Method	This study		Literature value [33]	
		pk$_1$	pk$_2$	pk$_1$	pk$_2$
EB.2HCl	C & M	6.10	9.15	5.78	9.10
	I & R	6.00	9.13	--	--
MET.HCl	C & M	--	11.25	--	--
	I & R	2.97	11.61	2.80	11.50

Table 6: Stability constant values of mono and bis-complexes of Cu(II) and Ni(II) with ethambutol or metformin at 30°C.

Complexes	log K$_1$	log K$_2$
[Cu(EB)4H$_2$O]$^{2+}$	9.87	--
[Ni(EB)$_2$2H$_2$O]$^{2+}$	6.84	3.58
Cu(Met)$_2$]$^{2+}$	9.27	7.96
Ni(Met)$_2$2H$_2$O]$^{2+}$	5.88	3.86

Next the micellar effect on drug dissociation constant as well as their complex formation properties with Cu(II) and Ni(II) was investigated. In this study it was found that in the SDS micellar medium the dissociation constant values of the drug hydrochlorides decrease to a considerable extent whereas the reverse

occurs in CTAB micellar medium. In fact the log K value decreases by more than two units in SDS micellar medium. The decrease is attributed to the stabilisation of the protonated ethambutol species (of ethambutol dihydrochloride) on the negative charged micellar, surface [25-26]. On the other hand the CTAB micelles have positive surface charge and so negative ions or neutral molecules are stabilised on the micellar surface. Moreover, CTAB facilitates dissociation of the weak acid presumably due to strong affinity of the counter ion Br^- towards the proton attached to the ethambutol molecule. As a result the dissociation constant values increase. In both the SDS and CTAB micellar media, the dissociation constant values show a nonlinear trend with variation in [surfactant]. The non-linear trend of the dissociation constant values with variation in [surfactant] is attributed to the lowering of dielectric constant [27] in such media which stabilises the protonated species and thereby opposes the effects from electrostatic forces.

The stability of the complex in micellar medium has the order SDS >> aqueous > CTAB. Thus relative to aqueous medium, complex formation is enhanced in the anionic surfactant medium largely due to electrostatic effect. The reaction occurs in the region of the micellar surface and the catalytic effect resides on the concentrative effect of the micelle surface on the reagents. The various equilibrium constants which include constant values the dissociation of the drug hydrochlorides and the stability constant value of the metal complexes are listed in Tables 7and 8.

Table-7 : Variation of pK values of ethambutol dihydrochloride and metformin hydrochloride with change in surfactant concentration.

Medium	Concentration $\times 10^3$, mol dm^{-3}	EB. 2 HCl		MF. HCl
		pK$_1$	pK$_2$	pK$_1$
Water	--	6.10	9.15	11.25
CTAB	0.5	6.07	9.11	11.30
	1.0	6.00	9.02	11.23
	1.5	5.84	8.89	11.07
	2.0	6.20	9.46	11.00
	2.5	6.03	9.07	11.02
SDS	5.0	8.38	10.61	11.68
	10.0	8.58	10.78	11.71
	15.0	8.62	10.83	11.76
	20.0	8.53	10.70	11.85
	25.0	8.69	10.89	11.91

Table-8: Stability constant values of mono and bis complexes of Cu(II) and Ni(II) with EB.2 HCl and MF.HCl in SDS and CTAB micellar medium. All measurements are done at 30°C.

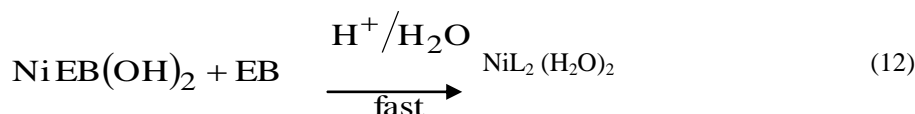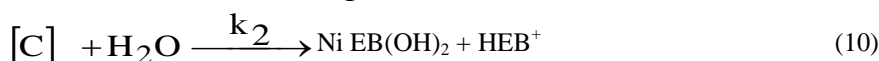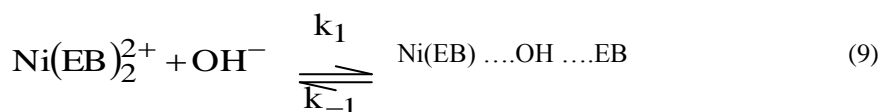| Complex	Medium	log K$_1$	log K$_2$
$[Cu(EB)4H_2O]^{2+}$	Water	9.87	--
	SDS	13.74	--
	CTAB	8.90	--
$[Ni(EB)_2 2H_2O]^{2+}$	Water	6.84	3.58
	SDS	8.41	5.45
	CTAB	6.02	2.90
$[Cu(MF)_2]^{2+}$	Water	9.27	7.96
	SDS	10.30	8.90
	CTAB	8.04	7.99
$[Ni(MF)_2 2H_2O]^{2+}$	Water	5.88	3.86
	SDS	6.95	5.05
	CTAB	5.50	4.99

The configurational conversion of Ni(II)-EB complex from planar to octahedral was next investigated through kinetic studies. For this purpose, the reactions were studied under pseudo-first order conditions with $[Ni(EB)_2]^{2+} >> [OH^-]$. The disappearance kinetics of the orange-red $Ni(EB)_2^{2+}$ complex formed at high pH was monitored spectrophotometrically by measuring its absorbance at 480nm. Stock solution of the orange-red Ni(II)-EB complex was used within a 24 hours of the experiments. Reaction parameters like $[Ni(EB)_2]^{2+}$, pH, solvent composition, additional electrolyte were varied one at a time keeping the other variables constants. Kinetic data were analysed using the rate law

$$-\frac{d[Ni(EB)_2]^{2+}}{dt} = k_{obs}[Ni(EB)_2]^{2+} \tag{8}$$

Accordingly, the plot of log A_t vs time yielded the first order rate constant (k_{obs}). Table 9 lists the k_{obs} values under various reaction conditions. Results obtained by such kinetic studies may be summarised as follows

(a)   The k_{obs} values are almost constant on varying the $[Ni(EB)_2]^{2+}$ from 3.46 to 11.52×10^{-3} mol dm^{-3}, showing first order dependence of the rate on substrate concentration.

(b)   With increase in pH the rate constant values increase though not linearly. The plot of $1/k_{obs}$ vs $1/[OH^-]$ (Fig. 5) is linear with positive intercept. This indicates intermediate complex formation with the substrate.

(c)   The conversion reaction carried out in different solvent media indicates that the k_{obs} values increase systematically with decrease in dielectric constant of the medium. Obviously oppositely charged ions are involved in the formation of the intermediate complex.

(d)   Added electrolytes like NaCl retard the rate of conversion from planar to octahedral configuration. The k_{obs} values are inversely proportional to its concentration.

Based on the above findings the mechanism for the planar to octahedral conversion reaction may be represented as follows :

$$Ni(EB)_2^{2+} + OH^- \underset{k_{-1}}{\overset{k_1}{\rightleftharpoons}} Ni(EB)....OH....EB \tag{9}$$

$$[C] + H_2O \xrightarrow{k_2} Ni\,EB(OH)_2 + HEB^+ \tag{10}$$

$$HEB^+ \overset{k_2}{\rightleftharpoons} H^+ + EB \tag{11}$$

$$Ni\,EB(OH)_2 + EB \xrightarrow[\text{fast}]{H^+/H_2O} NiL_2\,(H_2O)_2 \tag{12}$$

Steady state condition is applied for the formation of the intermediate complex [C] and the rate equation is solved accordingly. This leads to the final expression for rate constant as

$$k_{obs} = \frac{k_1 k_2 [OH^-]}{(k_{-1} + k_2)\left\{1 + (k_1/k_{-1})[OH^-]\right\}} \tag{13}$$

Equation 13 together with the rate mechanism explain the observed kinetic features viz., first order dependence on $[Ni(EB)_2]^{2+}$, dependence of complex concentration on $[OH^-]$ and inverse dependence on the dielectric constant of the medium. In the event $k_{-1} \ll k_2$, equation 13 becomes

$$\frac{1}{k_{obs}} = \frac{1}{k_1[OH^-]} + \frac{K}{k_1} \tag{14}$$

so that the plot of $1/k_{obs}$ vs $[OH^-]$ is a straight line whose slope and intercept values yields micro rate constants values as $k_1 = 0.4071$, $k_2 = 3.396 \times 10^{-3}$ and k_{-1} -5.714×10^{-5} mol^{-1} dm^2 sec^{-1}. Using these values in equation 12, the k_{obs} values are calculated at various $[OH^-]$ and are presented in Table 10. The excellent agreement between the observed and calculated rate constant values confirms the proposed rate mechanism.

Table 9 : Rate constant values for the configurational conversion of nickel ethambutol $\left(Ni\,L_2^{2+}\right)$ complex from planar to octahedral. Temp. 30°C, Stock $\left(Ni\,L_2^{2+}\right)$ = 0.242 mol dm^{-3}, [KOH]=0.5 mol dm^{-3} Total volume = 10.5. Condition of experimentsare as described in Section 2.3. In column three dielectric constant values are given in parantheses.

$\left[\mathrm{Ni\ L}_2^{2+}\right] \times 10^3$ $\mathrm{mol\ dm}^{-3}$	pH	Medium and dielectric constant	[NaCl] mol dm^{-3}	$K_{obs} \times 10^5$ sec^{-1}
3.46	10.80	Aqueous-100%	0	4.45
4.62				4.03
5.76				4.90
6.91				4.53
8.07				5.76
9.22				4.80
11.52				3.78
3.46	10.15		0	2.85
	10.37			
	10.54			
	10.72			
	11.10			
	11.36			
	11.60			
3.46	11.60	Water – methanol 88.75% - 11.25% (13.38)	0	14.0
		75% - 25% (67.07)		17.5
		54% - 35% (62.48)		18.3
		50% - 50% (55.59)		29.0
3.46	11.60	0	0	6.06
			2.50	5.00
			4.16	3.80
			5.00	2.60
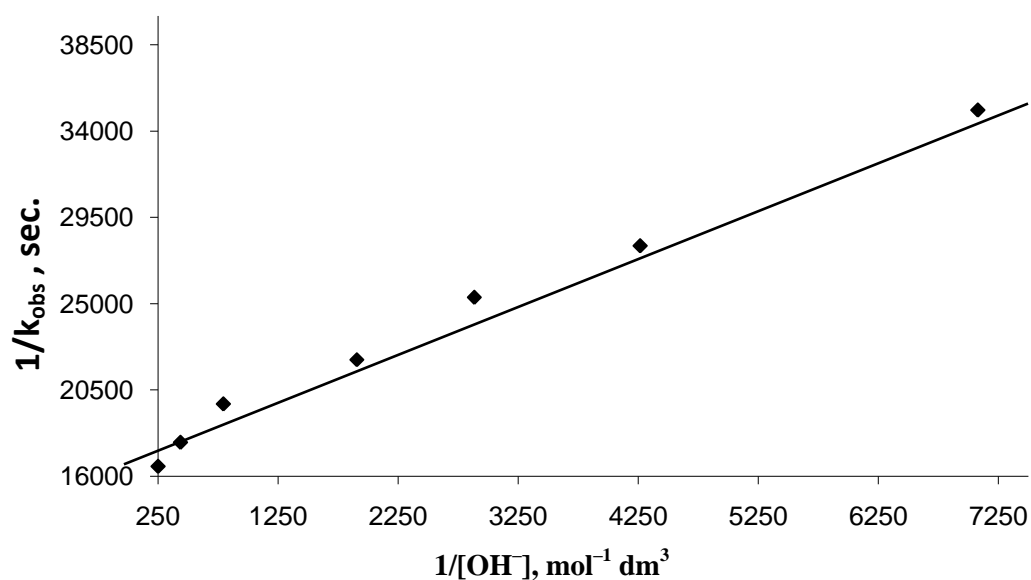
Fig.5: Plot of 1/k$_{obs}$ vs 1/[OH$^-$] for planar-octahedral conversion of $\mathrm{Ni(EB)}_2^{2+}$ complex, temp. = 30°C and $\left[\mathrm{NiL}_2^{2+}\right]$ = 3.63 × 10^{-3} mol dm^{-3}.

Table-10: Observed and calculated rate constant values as a function of pH for alkaline hydrolysis of planar NiL_2^{2+}.

pH	$10^5 \times k_{obs}$, sec^{-1}	$10^5 \times k_{cal}^*$, sec^{-1}
10.15	2.85	2.82
10.35	3.57	3.45
10.54	3.95	4.00
10.72	4.53	4.43
11.10	5.06	5.06
11.36	5.36	5.30
11.60	5.63	5.40

Micellar effect on the kinetics of configurational conversion of $Ni(EB)_2^{2+}$ from planar to octahedral configuration constitutes the final part of the present study. Aqueous micelles are known to influence reaction rates and equilibria including those of coordination compounds [28-33]. The cationic surfactant of CTAB is chosen for the study. The constant values at different concentrations of CTAB from 3.7×10^{-3} to 2.22×10^{-2} mol dm^{-3} (Table 11) indicate almost ten fold increase in k_{obs} compared to that in aqueous medium. Spectral studies corroborate the findings that the conversion reaction is accelerated in CTAB micellar medium. The enhancement in k_{obs} values can be explained on the basis of concentration effect and/or dielectric constant of the micellar medium. Concentration effect necessitates the reactant and/or product molecules to accumulate in the some volume around the micellar surface. This in turn necessitates the substrate $[Ni(EB)_2]^{2+}$ to be either anionic or at least neutral. Existence of such anionic/neutral amide complexes of Ni(II) have earlier been established [12-34] and involve the following equilibria for its formation

$$Ni(EB)_2^{2+} \rightleftharpoons Ni(EB)_2 H_{-1}^+ + H^+ \qquad (15)$$

$$Ni(EB)_2 H_{-1}^+ \rightleftharpoons Ni(EB)_2 H_{-2} + H^+ \qquad (16)$$
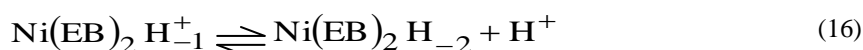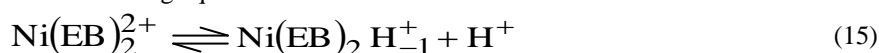
Alternatively, the effective dielectric constant on the micellar surface of CTAB has been established [27-35] and this lowering in dielectric constant increased the rate of reaction and hence the constant.

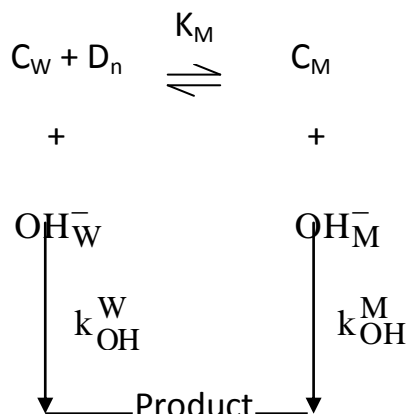**Table-11: Rate constant values at different concentration of CTAB micellar medium.**
Temp. = 30°C, pH = 11.60 ± 0.05, [Ni – EB] = 9.26×10^{-3} mol dm^{-3}.

$[CTAB] \times 10^{-3}$ mol dm^{-3}	$k_{obs} \times 10^{-4}$ sec
2.222	6.25
1.852	6.00
1.700	5.8
1.481	5.75
1.250	5.5
1.111	5.16
0.920	4.60
0.740	4.22
0.560	4.00
0.370	3.30

The mechanism for rate enhancement in micellar medium can be explained by assuming that the partitioning of [OH$^-$] between the aqueous and micellar pseudo-phase is controlled by pseudo-phase ion-exchange equilibrium [36]

$$OH_M^- + Br_W^- \xrightleftharpoons{K_{Br}^{OH}} OH_W^- + Br_M^- \qquad (17)$$
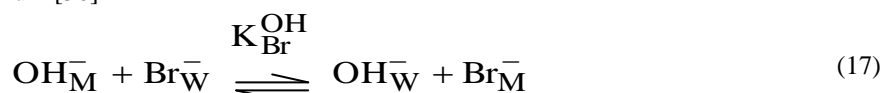
The scheme of reaction proposed to interpret the rate data in presence of CTAB is as follows

$$C_W + D_n \underset{\rightleftharpoons}{\overset{K_M}{}} C_M$$

$$+ \qquad\qquad +$$

$$OH_W^- \qquad\qquad OH_M^-$$

$$\downarrow k_{OH}^W \qquad\qquad \downarrow k_{OH}^M$$

$$\longmapsto Product \longmapsto$$

The rate equation has the final rate expression

$$k_\psi = \frac{k_\psi^o + \left[\left(k_{OH}^M \, K_M - k_{OH}^W\right)m_{OH}^S - k_\psi^w K_M\right][D_n]}{1 + K_M[D_n]}$$

which rearranges to

$$\frac{1}{k_\psi - k_\psi^0} = \frac{1}{p} \times \frac{1}{[D_n]} + \frac{K_M}{[P]} \qquad\qquad (18)$$

Here $P = \left(k_{OH}^M \, K_M - k_{OH}^W\right)m_{OH}^s - k_\psi^W \, K_M$

k_ψ = rate constant in micellar medium

k_ψ^o = rate constant in water

$[D_n] = [CTAB]_T - CmC.$

The plot of $1/k_\psi - k_\psi^o$ vs $1/[D_n]$ is a straight line from which the binding constant K_M is calculated as (intercept/slope) and is found to be equal to 29.52.

4. CONCLUSION

Dissociation of the drug studied decreases in presence of anionic surfactant, in other words such medium favours protonation of the drug. Stability constant values of the metal drug complexes increases with increase in concentration of the anionic surfactant while cationic surfactants retard the stability of the drug metal complex. However at very high pH (>11) the cationic surfactant CTAB constantly favours the formation of nickel-ethambutol complex. This reversal trend is explained by further deprotonation of nickel-ethambutol complex to form anionic species. The configurational change from planar to octahedral geometry, in case of nickel-ethambutol complex is favoured in the cationic surfactant CTAB.

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