International Journal of ChemTech Research
CODEN (USA): IJCRGG ISSN : 0974-4290
Vol.4, No.1, pp 190-197, Jan-Mar 2012

Electrochemical Study of Cd^{+2}-Theophylline Complex

Yogesh Kumar*, Sharda, Mahipat Singh, and Rajayashree Pandey*†

*†Lab No. 303, Electrochemical Laboratory, Department of Chemistry, University of Rajasthan, Jaipur-302055, Rajasthan, India.

*Corres.authors: yogesh.kmar@yahoo.com**
rajayashree@yahoo.com†*

Abstract: The interaction between Theophylline and Cd^{2+} was investigated using direct current polarography. The polarographic technique was used to determine the stability constants and thermodynamic parameters such as enthalpy change (ΔH), free energy change (ΔG) and entropy change (ΔS) of Cd^{2+} complexes with Theophylline at pH-5 in 0.5M acetate buffer. The study was carried out at two different temperatures 20 °C and 30 °C. Cd^{2+}-Theophylline complexes were formed in 1:1, 1:2 and 1:3 ratios. The electrode processes were reversible and diffusion controlled.
Key words: stability constant, thermodynamic parameters, Cd^{2+}–Theophylline system.

Introduction

Theophylline is widely used as a bronchodilator for the treatment of bronchial asthma and neonatal apnea.[1] Its primary mode of action is inhibiting phosphodiesterase, thus causing relaxation of the bronchiole walls. Theophylline also exerts excitatory influences on the skeletal muscle, gastric secretion, kidneys and fatty acid metabolism in addition to inhibitory effects on smooth muscle. It is well known that excessive administration of Theophylline occasionally produces serious toxicity, including vomiting, tachycardia, and central nervous system excitation including seizures.[2-3] Furthermore, Theophylline has biological importance which can be used in anticancer drugs.[4-7] The purines includes theophylline, theobromine and caffeine constitute an important class of anti-inflammatory agents.[8] Theophylline has biological importance as it is structurally related to nucleic acids components.[9] Thus it can be used as a drug in therapy for respiratory such as COPD or asthma under a variety of brand names and anticancer drugs. A few metal-theophylline complexes have shown significant antitumor activity.[10] The anion derived from theophylline has often been used as a model ligand in studying the interaction with metal ions.[11]

Cadmium has very toxic biological effects at concentrations smaller than almost any commonly found mineral. Ingestion of any significant amount of cadmium causes immediate poisoning and damage to the liver and the kidneys. Inhalation of cadmium dust causes problems for the respiratory tract as well as for the kidneys, eventually death may follow.[12] Cd^{2+} is the most toxic element in the environment to which industrial civilization has exposed itself. In human beings, the concentration of Cd^{2+} increases, and they suffer from several diseases.[13] The concentration of Cd^{2+} in blood and serum can be reduced by ligand therapy[14]; therefore, the study of Cd^{2+} complexes with Theophylline has great importance.

New mixed ligand complexes were synthesized between theophylline and cyanate to give complexes with general formula $[M(Tp)_4Y_2]$ where Tp= theophylline, Y= cyanate ion and M=Co(II), Ni(II),Cu(II), Zn(II) and Cd(II).[15] The interaction

between three purine alkaloids (caffeine, theophylline, and theobromine) and human serum albumin (HSA) was investigated using UV/VIS absorption, circular dichroism (CD), fluorescence,
synchronous fluorescence, and three-dimensional fluorescence spectra techniques. The binding study of Theophylline with HSA has toxicological and medical importance.[16] The interactions of caffeine and theophylline with divalent cadmium, mercury, strontium and barium ions were studied in aqueous solution and physiological pH.[17]
A large number of pharmaceuticals can be reduced or oxidized in the available potential range and their waves can be used in their determination. It seems that often the therapeutical activity is paralleled by electrochemical reactivity. Pharmaceutical companies will use, whenever possible, officially approved methods of analysis. In the past, some polarographic analytical procedures were listed in numerous Pharmacopoeias. It should be a goal of electroanalytical chemists around the world to have them listed again. The lower costs, faster results, and the possibility for quickly detecting mishandlings by technicians, are powerful arguments.[18]
In this work, we demonstrated the binding of Theophylline and Cd^{2+} and the thermodynamics of their interaction. In order to attain these objectives, we planned to carry out detailed investigation of Theophylline and Cd^{2+} using Direct current Polarography.

Procedure

The general procedure for D.C. polarography is as follows-
A 10 ml of experimental solution was placed in a polarographic cell and deoxygenated with nitrogen for 15 min. The cell was placed in the thermostat and the capillary was inserted in solution. The current voltage curves were measured manually. Polarographic experiments were carried out with Elico D.C. recording polarograph CL 357. The current voltage measurements were performed with three electrode assembly, a dropping mercury electrode as working electrode, calomel as reference electrode and platinum electrode as counter electrode. A digital pH meter model 111 E was used for measuring the pH of the analytes. The potential was applied to the working electrode with 150 mV/min span rate and 100 nA/div. sensitivity of current measurement. The dropping mercury electrode had the following characteristics- m = 2.420 mg/sec, t = 3.6 sec, h = 60 cm.

Reagents

All the solutions were prepared from doubly distilled water and analytical reagent grade chemicals (MERCK).
Theophylline {Sidmak Laboratories (India)} solution was prepared freshly every 5 days.
$Cd(CH_3COO)_2.2H_2O$ used was of analytical reagent grade.
0.5M Acetate buffer (pH-5) has been used as supporting electrolyte. Triton X-100 (0.001%) was used to suppress polarographic maxima.

Table -1: Polarographic data and *Fj (X)* values of Cd^{2+}–Theophylline system.
$Cd^{2+} = 1.25 \times 10^{-2}$ M, 0.5M Acetate buffer(pH-5), T = 20 °C
$E_{1/2}$ (Cd^{2+}) = –0.64277volts vs. S.C.E

[X]	i_d ×100 nA	-Ec V	$-\Delta E_{1/2}$ = Ec-Em	FoX	$F_1X\times10^2$	$F_2X\times10^4$	$F_3X\times10^7$
0.001250	3.4	0.64400	0.00123	1.13	1.08	7.02	2.82
0.001563	3.3	0.64531	0.00254	1.30	1.90	10.89	4.73
0.001875	3.2	0.64673	0.00396	1.50	2.65	13.06	5.10
0.002188	3.1	0.64803	0.00526	1.71	3.26	13.98	4.79
0.002500	3.0	0.64968	0.00691	2.02	4.07	15.47	4.79
0.002813	2.9	0.65104	0.00827	2.32	4.71	16.03	4.45

Where
i_d = Diffusion current
$\Delta E_{1/2}$ = Difference in $E_{1/2}$ of $Cd^{2+}$and Cd^{2+}-Theophylline complex.
Em = Half wave potential of Cd^{2+} ion.
Ec = Half wave potential of Cd^{2+}-Theophylline complex

Table -2: Polarographic data and *Fj (X)* values of Cd^{2+}–Theophylline system.
Cd^{2+} = 1.25 × 10^{-2} M , 0.5M Acetate buffer(pH-5), T = 30 °C
$E_{1/2}$ (Cd^{2+}) = –0.63795 volts vs. S.C.E

[X]	Id×100 nA	$-E_{1/2}$ c V	$-\Delta E_{1/2}$ = Ec-Em	FoX	$F_1X\times10^2$	$F_2X\times10^4$	$F_3X\times10^7$
0.00125	3.8	0.63883	0.00088	1.10	0.78	3.07	0.85
0.001563	3.7	0.63975	0.00180	1.21	1.34	6.04	2.58
0.001875	3.6	0.64073	0.00278	1.34	1.82	7.55	2.96
0.002188	3.5	0.64178	0.00383	1.50	2.26	8.50	2.97
0.0025	3.4	0.64281	0.00486	1.66	2.66	9.03	2.81
0.002813	3.3	0.64407	0.00612	1.89	3.16	9.81	2.78

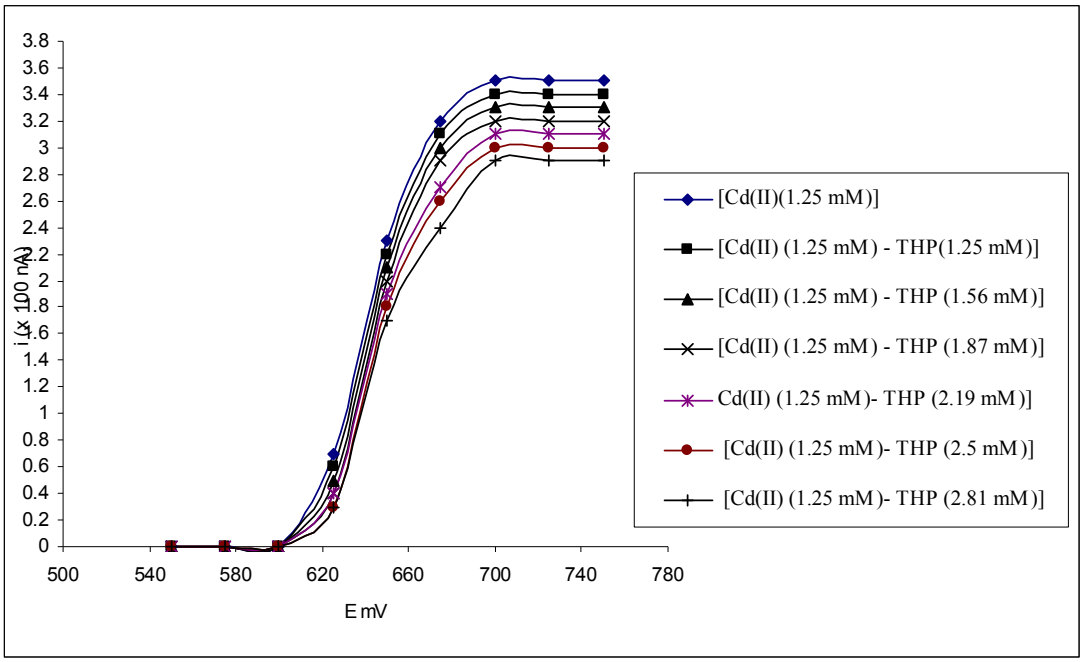

Fig. 1.A

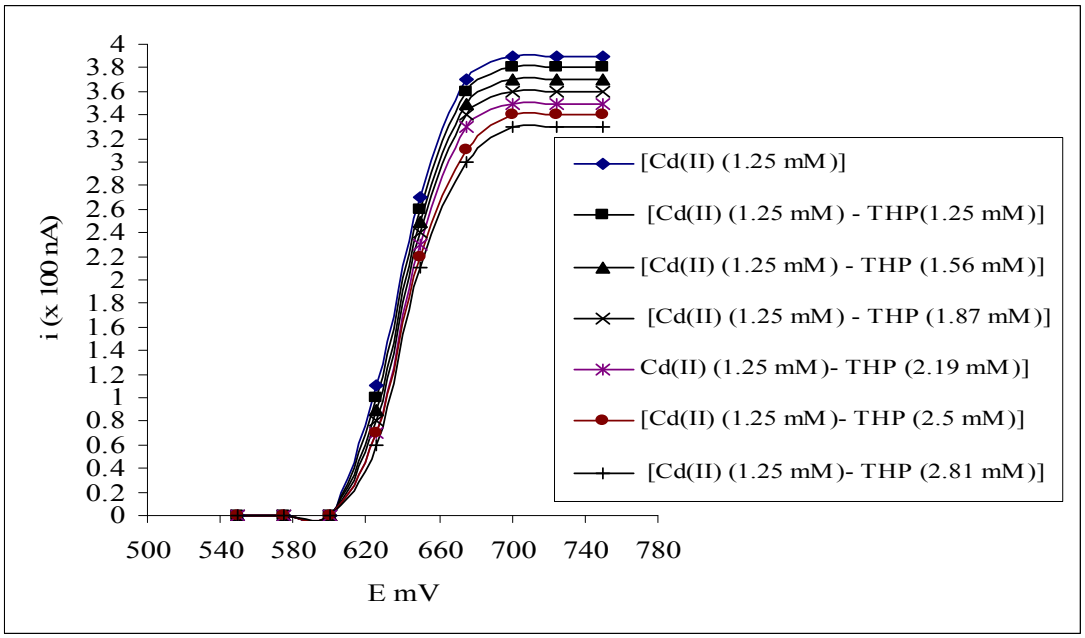

Fig. 1.B
Fig. 1. (A & B) Polarograms of Cd^{2+} - Theophylline system at 20 °C and 30 °C respectively.

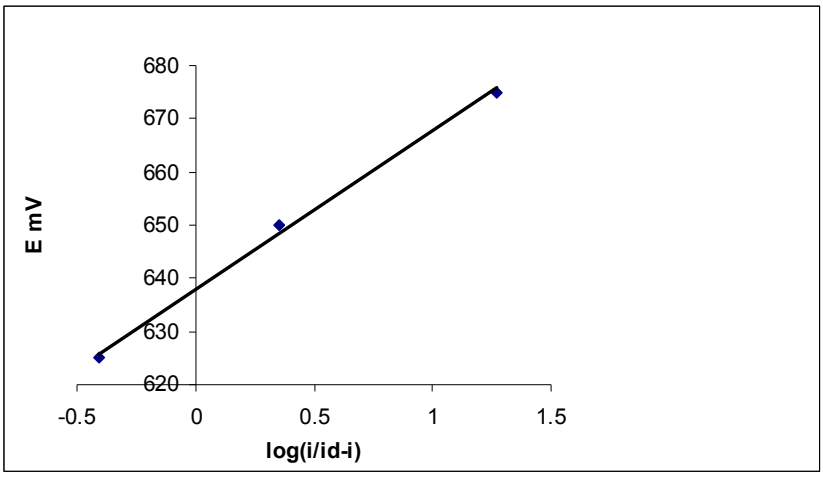

Fig. 2.A

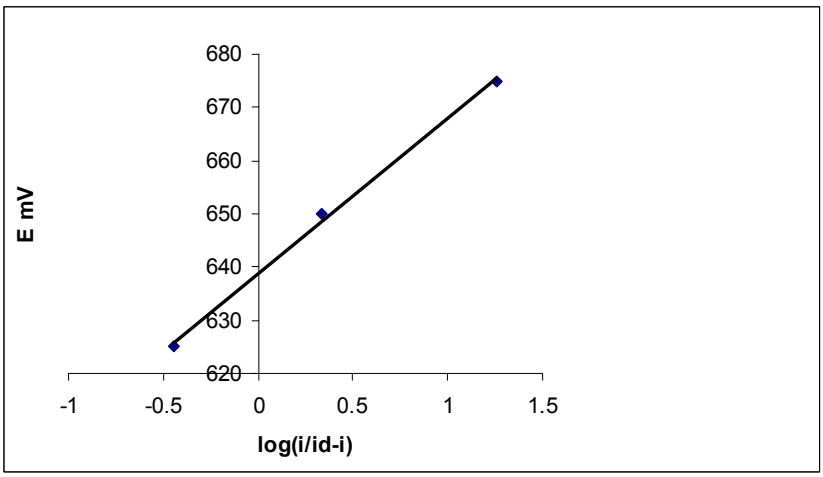

Fig. 2.B

Fig. 2.(A & B) plot E vs. log(i/i_d-i) at 30 °C

Where [Cd^{2+}] = 1.25 × 10^{-3} M and [Cd^{2+} – Theophylline system] = 1.25 × 10^{-3} M in Fig. 2.A & 2.B respectively.

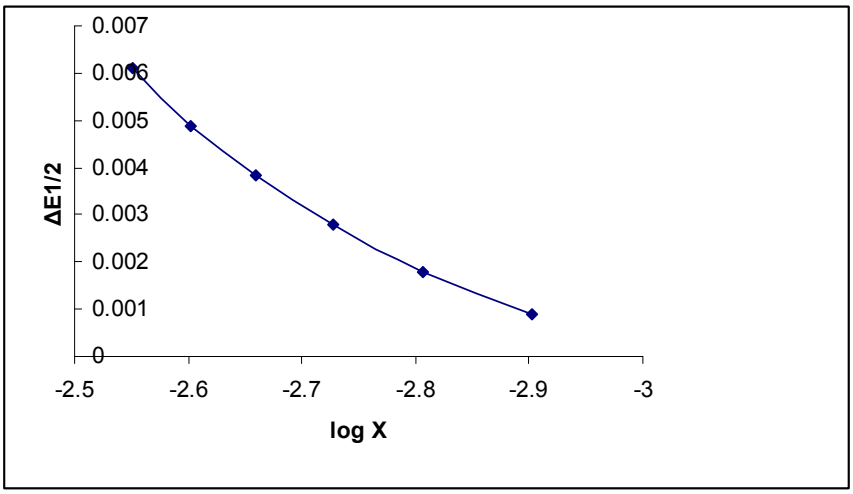

Fig 3. plot $\Delta E_{1/2}$ vs. log[concentration]

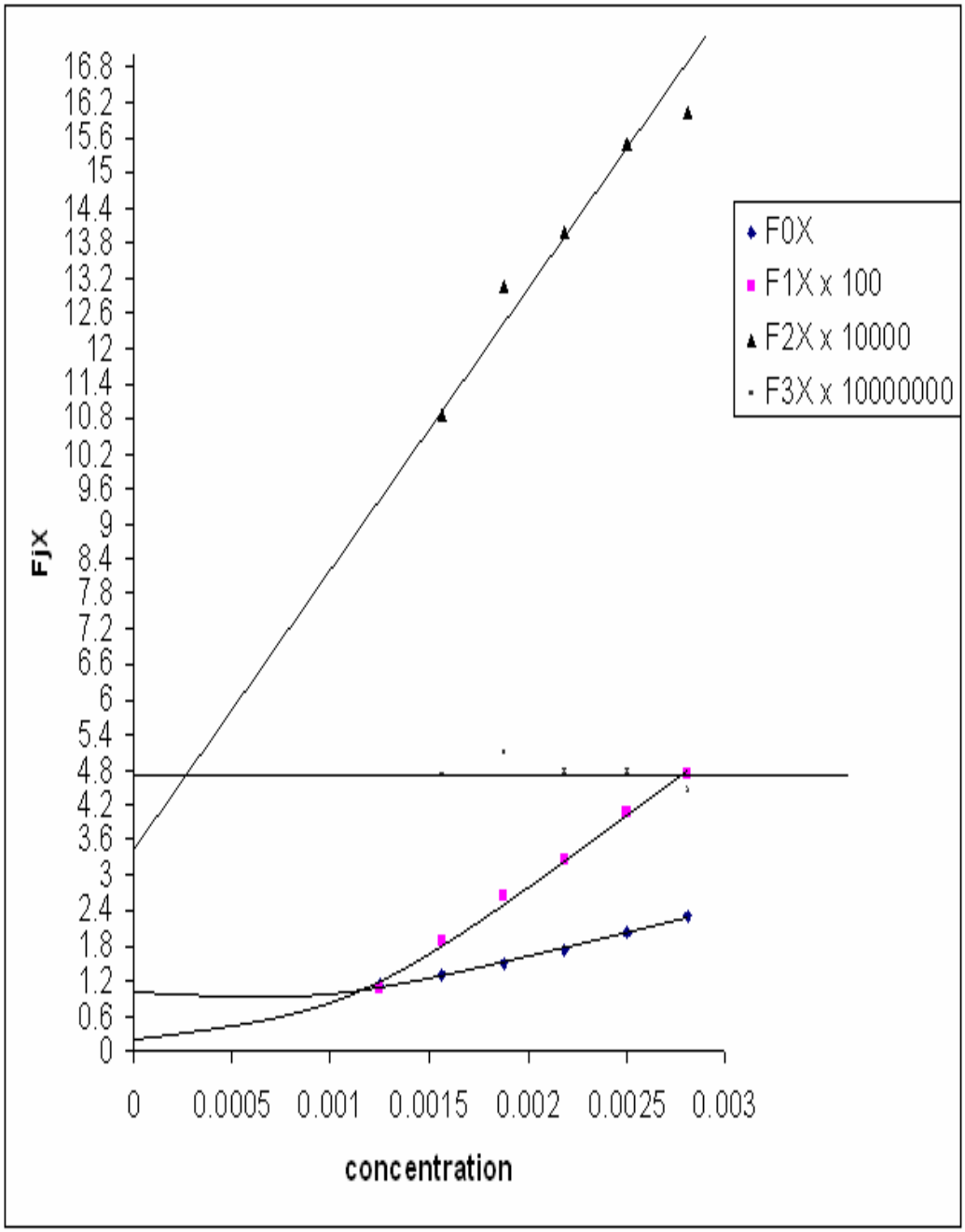

Fig. 4 Fj (X) values of Cd^{2+}–Theophylline system at T = 20 °C

Results and Discussion

A well-defined two-electron reversible reduction and diffusion controlled wave Cd^{2+} was observed in acetate buffer at pH-5. The value of $E_{1/2}$ reversible for Cd^{2+}, was –0.640 mV vs. SCE. The nature of the C–V curve of Cd^{2+} complexes with Theophylline was also reversible and diffusion-controlled.

When aqueous solution of Theophylline is added, half wave potential shifts towards more negative direction i.e. towards more cathodic value, the difference being related to the free energy of dissociation of complex[19] and diffusion current decreases which suggests complex formation. The complex ion formed is of much larger size as compared to the aquo metal ion hence there is the low value of diffusion currents with the increase of ligand concentration. (Fig. 1.A & 1.B)

The slope values of the plots of $\log(i/i_d-i)$ vs. E mV are found in the range 30±2 mV suggesting the reversible nature of electrode reaction. (Fig. 2.A & 2.B)

If several complexes are formed in solution, the dependence of the half-wave potential for the

reduction of the complex forming metal on the logarithm of the activity of the ligand will no longer be linear. In this case the plot of $\Delta E_{1/2}$ against log [X] consists either of several linear sections (in accordance with the number of complexes formed, whose formation constants differ fairly appreciably) or of a smooth curve which is convex with respect to the abscissa axis, (with increase of the activity of the ligand, complexes with a larger coordination number are formed and the slope of the plot increases). The smooth curve is obtained when the stability constants of the complexes do not differ very markedly and the regions of their existence overlap.[20] (Fig 3)

The Deford and Hume method[21] confirmed the formation of 1:1, 1:2 and 1:3 complexes of Cd^{2+} with Theophylline. Complexation has been carried out at two (20°C and 30°C) temperatures. At 20°C more shifts in half wave potential was observed. The temperature coefficient of the half wave potential is between -0.517 to -0.697 mV/degree so the system is reversible.[22] The plots of *Fj (X)* vs. X (where X is the concentration of Theophylline in mole/liter) are given in (Fig. 4 & 5) and results are summarized in tables 1 & 2 at 20°C & 30°C respectively.

Fig. 4 & 5 illustrates plots of the functions *Fj (X)* for the Cd^{2+}-Theophylline system. Evidently three complexes are formed in this system: $Cd(THP)^{+2}$, $Cd(THP)_2^{+2}$ and $Cd(THP)_3^{+2}$. From the plots of *Fj (X)* vs. X values of β_1, β_2 and β_3 have been evaluated. Value of intercept gives the value of β, where as value of logβ represents the stability constant. More will be the value of stability constant more will be stability.(Table 3)

As shown in (Table 3) stability constant values decreases in 1:2 and 1:3 ratio with increases in temperature suggesting more stability of Cd^{2+}-Theophylline complexes at 20^0C in comparison to that of at 30^0C.

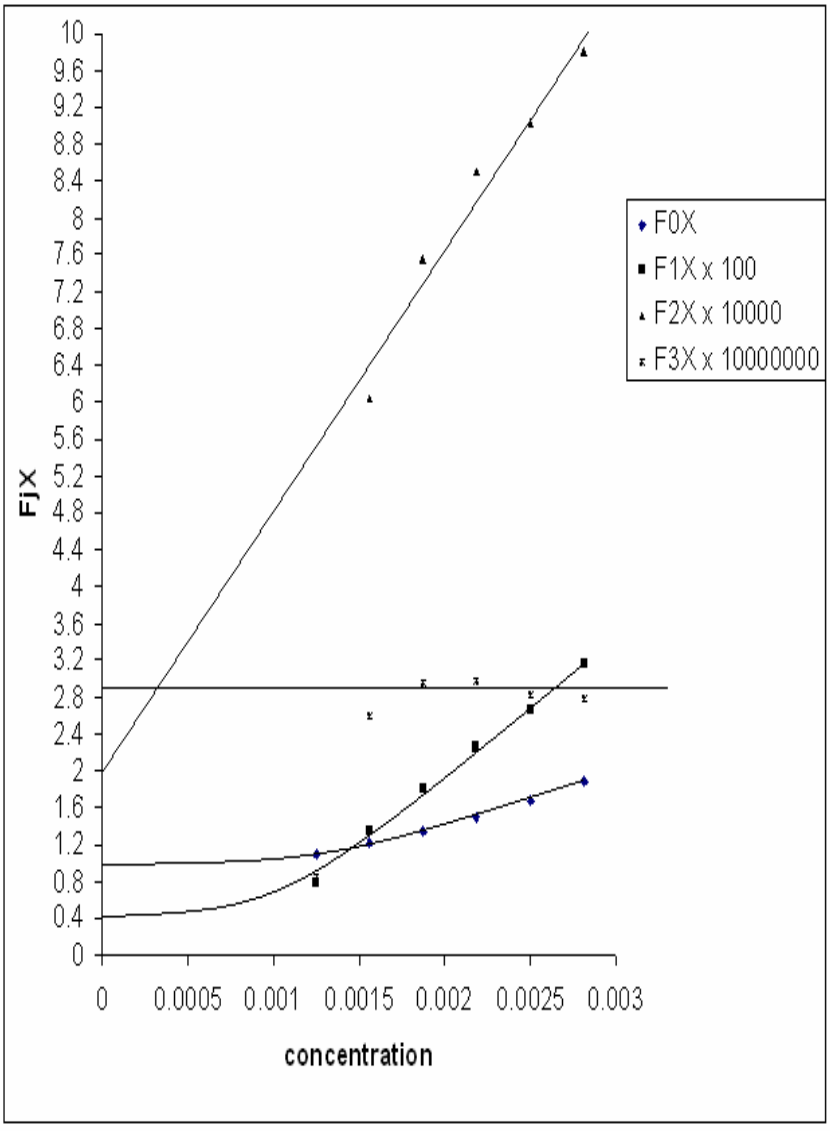

Fig. 5 Fj (X) values of Cd^{2+}–Theophylline system at T = 30 °C

Table -3: Stability constant of Cd^{2+}–Theophylline system.

System	Ratio	T = 20 °C		T = 30 °C	
		β	log β	β	log β
$Cd(THP)^{+2}$	1:1	β1 =20	1.301	β1 =40	1.602
$Cd(THP)_2^{+2}$	1:2	β2 =3.5 ×10^4	4.544	β2 =2×10^4	4.300
$Cd(THP)_3^{+2}$	1:3	β3 =4.75×10^7	7.677	β3 =2.9×10^7	7.462

Table -4: Thermodynamic parameters of Cd^{2+}–Theophylline system at 20 °C and 30 °C.

System	Ratio	Thermodynamic parameters		
		ΔG	ΔH	ΔS
$Cd(THP)^{+2}$	1:1	-7298.9	51171.00886	199.5561
$Cd(THP)_2^{+2}$	1:2	-25492.7	-41313.16587	-53.9946
$Cd(THP)_3^{+2}$	1:3	-43067.1	-36427.34214	22.66134

Thermodynamic parameters

The thermodynamic parameters[23-24] such as free energy change (ΔG), enthalpy change (ΔH), and entropy change (ΔS) of interaction are important to interpret the binding mode [25]. The kind of complex species that can be measured with a mercury electrode depends on thermodynamic aspect.[26] Experiments were carried out at 20 °C and 30 °C, since Theophylline does not undergo any gross structural change in this temperature range. The values of thermodynamic parameters of the complexes are given in (Table 4).

From Table 4, it can be seen that the negative value for ΔG indicates the spontaneity of the binding of Theophylline with Cd^{2+}. The more negative value for ΔG in case of 1:3 complexes shows that deriving tendency of complexation reaction increases from left to right and reaction tend to proceed spontaneously. The value of ΔH suggests that Cd^{2+}–Theophylline system in ratio 1:1 is endothermic while ratio 1:2 and 1:3 is exothermic in nature. It means greater the amount of heat released in reaction, more stable are the reaction products. The negative value of ΔS in 1:2 ratio corresponds to a more ordered activated complex and this implies a small value of the steric factor. Positive value of entropy in ratio 1:1 and 1:3 reveals the formation of comparatively disordered complex.[27-28]

Conclusion

It is clear from the study that the shift of $E_{1/2}$ becomes more negative on increasing the concentration of Theophylline to Cd^{2+}, which confirms complex formation. Cd^{2+} formed 1:1, 1: 2 and 1: 3 complexes. The values of their stability constants varied from 1.301 to
7.677 and confirmed that Theophylline in combination could be effective against Cd^{2+} toxicity. The stability constants (log β) and thermodynamic parameters such as free energy change (ΔG), enthalpy change (ΔH) and entropy change (ΔS) of Cd^{2+} complexes with Theophylline was determined by employing the polarographic technique (0.5M) Acetate buffer at pH-5 at 25 °C and 35 °C.

Acknowledgement

The authors are thankful to the Head of Department of Chemistry, University of Rajasthan, Jaipur for providing the laboratory facilities and CSIR, New Delhi for providing the JRF.

References

1. P. Gaudreault and J.Guay Med. Toxicol.,1(1986) 169–191.
2. W.A. Auritt, S.J. MeGeady and H.C. Mansmann,, J. Allergy Clin. Immunol., 75(1985) 731–735.
3. M. Hirose, H. Yokoyama and K. Iinuma, Brain Dev., 26(2004) 448–452.
4. N. Shohreh, S. Abolfazl, Z. Shokrollah and D. Maryam, J. Biomol. Struct. Dyn., 21(2003) 2.
5. V. Francesco, A. Rao Ole, A. Kalpit, A. Julie and D. M. F. V. Aalten, Chemistry and biology, 12(2005) 973-980.
6. P. Jacek, G. Anna, U. Katarzyna, O. Jakub, C. Agata and W. Grzegorz, Acta Biochim. Pol., 52(4)(2005) 923-926.
7. M. Kiriaki, F. Duclerc, Parra Maria José A. Oliveira Oscar V. Bustillos and Ademar B.

Lugão, International Nuclear Atlantic Conference-INAC,Santos. SP. Brazil, September 30 to October 5. Associação Brasileira De Energia Nuclear–ABEN, 2007, ISBN: 978-85-99141-02-1.

8. S. S. Marwaha, J. Kaur and G. S. Sodhi, Met Based Drugs, 2(1)(1995) 13–17.
9. S. Nafisi, A. S. Sadjadi, S. S. Zadeh and M. Damerchelli, J. Biomol. Struct. Dyn., 21(2003) 2.
10. L. David, O. Cozar, E. Forizs, C. Craciun, D. Ristoiu and C. Balan Spectrochim. Acta, Part A, 55(1999) 2559–2564.
11. H. A. Neville, G. A. Trevor, R. H. John, F. K. Gregory and Ian, J. M., J.C.S. chem. Comm., (1979) 324-326.
12. R. Zevenhoven and P. Kilpinen, TKK, Espoo, 2001.
13. J. Harte, C. Holdren, R. Schneider and C. Shirtley, Toxics A to Z: A Guide to Everyday Pollution Hazards. University of California Press, 1991.
14. U. Gubrelay, R. Mathur and S. J. Flora, Ind J. Pharmacol, 30(1998) 209-17.
15. S. A. Shaker and Y. Farina, Modern applied science, 3(2009).
16. H.-M. Zhang, T.-T.Chen, Q.-H. Zhou and Y.-Q. Wang J. Mol. Struct., 938(2009) 221–228.
17. N. Shohreh, S. A. Seyed, Z. S. Shokrollah and D. Maryam, J. Biomol. Struct. Dyn., 21(2) (2003) 289-296.
18. P. Zuman, Review Acta Chim.Slov.56(2009) 18–29.
19. L. Meites, Polarographic techniques. Brooklyn, New York, 1964, pp.290.
20. E.A. Mambetkaziev and S.I. Zhdanov, Russ. Chem. Rev., 1980, 49 (4), Translated from Uspekhi Khimii, 49(1980) 588-617.
21. D. Deford and D. N. Hume, J. Am. Chem. Soc., 73(1951) 5321.
22. L. Meites,"Polarographic techniques", Brooklyn, New York, 1964, pp.288.
23. F. Khanam, l. Tantuvay, J.Pharm.Biomed. Anal., 27(2002) 933-944.
24. S. N. Chadar, F. Khan and S. Sharma, chemija, 19(2008) 1–6.
25. P.D. Ross and S. Subramanian, Biochemistry, 20(1981) 3096–3102.
26. A. E. Martell and M. Calvin Chemistry of Metal Chelate Compounds. Prentice-Hall Inc., New York, 1952.
27. K. Saini, H.P.Gupta and R.S. Pandey,J.Indian Chem. Soc., 83(2006) 495-496.
28. R. Kumar and G. Veerabhadram, Bulletin of Pure & Applied Sciences-Chemistry, (25C) 2006.

*****