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Spectrophotometric and Cyclic Voltammetric Study of Interaction of Copper with Rizatriptan Benzoate

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ABSTRACT

Rizatriptan benzoate is a popular serotonin 5-HT1 receptor agonist triptan drug indicated for the acute treatment of migraine, a neurological disorder. Copper ion plays a key role in brain metabolism. Several neuro diseases are characterised by copper toxicity. The drug binds to copper acetate as revealed by UV and IR spectra. The triazole ring of the drug binds to copper. The cyclic voltammetric studies revealed that with increasing concentration of metal, the corresponding current increases. With increasing scan rate, the corresponding current increases linearly with the square root of the scan rate. This shows that the binding of the drug to the metal is diffusion controlled. The present study investigates the reaction of ascorbic acid with Copper-Rizatriptan complex at neutral pH. The mechanism of reversible formation of Cu(II)/Cu(I) is described based on absorption spectral data.

Keywords: Rizatriptan benzoate, Ascorbate cleavage, Cyclic voltammetric study, Spectrophotometric study

INTRODUCTION

Complexation of pharmaceuticals with metal ions has a variety of applications as it can affect the bio availability and stability of the medicinal compounds *in vivo*. Copper is an essential element in most of the metabolic activities of the human body as it plays diverse roles due to its existence in both reduced (Cu^{+}) state and oxidized (Cu^{2+}) state. A copper level in cerebrospinal fluid is extremely important to facilitate enzymatic defense mechanisms that prevent neuro degeneration [1] and neurogenic inflammation [2]. Its biological importance is also attributed to its ability to complex with medicinal compounds and affects its efficacy [3]. A wealth of literature is available documenting the potential benefits of Cu(II) for binding to biological organic molecules [4] and copper complexes being more effective than the drugs themselves [5]. There are numerous reports of Copper complexes of NSAIDS [6-10], amino acids [11], nucleobases [12], antibacterial agents [13], antitubercular drugs [14] and anticancer drugs [15].

Owing to the resemblance of biochemical reactions of complexes with electrochemical reactions, cyclic voltammetry has received much attention. It serves as a tool in investigating the redox behavior of the samples in a portable, faster and simpler method [16]. Recently, the interaction of hydantoin derivatives with CT-DNA [17], antitumor drugs with ds-DNA [18] is studied using cyclic voltammetry. However, no voltammetric investigation of the chelating properties of Cu with antimigraine drug like Rizatriptan benzoate has been reported so far. Antimigraine drugs work by activating 5-$HT_1\beta$ receptor leading to selective vasoconstriction of certain cranial extra cerebral blood vessel segments. Rizatriptan Benzoate (RTB) is a serotonin 5-HT1 receptor agonist triptan drug indicated for the acute treatment of migraine. Investigations have mainly focused on formulation and evaluation [19], synthesis [20] quantification [21] and mechanism of oxidation of rizatriptan [22] but interaction of this drug with copper ions is not reported in the literature.

Ascorbate is a water soluble antioxidant molecule playing a vital role in many pathological processes in the brain. Its capacity to bring variations in extracellular composition is exploited in treating neurological disorders [23] and cancer [24]. Chemically, L-Ascorbic acid is a mild reductant and is often acts as a reducing agent in biochemical reactions. One of the advantageous properties of ascorbic acid is that it acts as a pro-oxidant and also as an antioxidant. It is known that this cross over effect is a function of metal ion concentration and is exploited in the study of DNA-cleavage specificity in presence of Copper ion [25,26]. In the present study, the interaction of RTB with Cu is studied by voltammetric and absorption spectral techniques. The reaction of RTB-Cu complex with Ascorbic acid is being reported for the first time.

MATERIALS AND METHODS

Material

Analytical grade $CuSO_4.5H_2O$ and KCl were purchased from E Merck, Germany. Rizatriptan benzoate was obtained from Apotex India Pvt Ltd as a gift sample. $CuSO_4.5H_2O$ and KCl were dissolved in double distilled water to prepare millimolar solutions.

Instrumental

Three electrodes system consists of a GCE as the working electrode, Ag/AgCl (satd. KCl) as the reference electrode and platinum wire as the counter electrode was used. Cyclic voltammetric measurement was performed using Electrochemical Workstation (model CHI 660E, USA). FTIR spectra were recorded on a Shimadzu FT-IR-8400S instrument, using KBr pellets. UV measurements were performed on Shimadzu UV 2401 PC UV-visible spectrophotometer.

RESULTS AND DISCUSSION

Cyclic voltammetric response due to Cu(II)/Cu (I) couple was studied in the range of -0.6 to -0.6 V with an i_{pa}/i_{pc} ratio of 2.34 and a ΔEp value of 1.27 V at a scan rate of 0.1 Vs^{-1} in 0.1 M KCl. The redox process is assignable to the Cu (II)/Cu(I) couple in Figure 1.

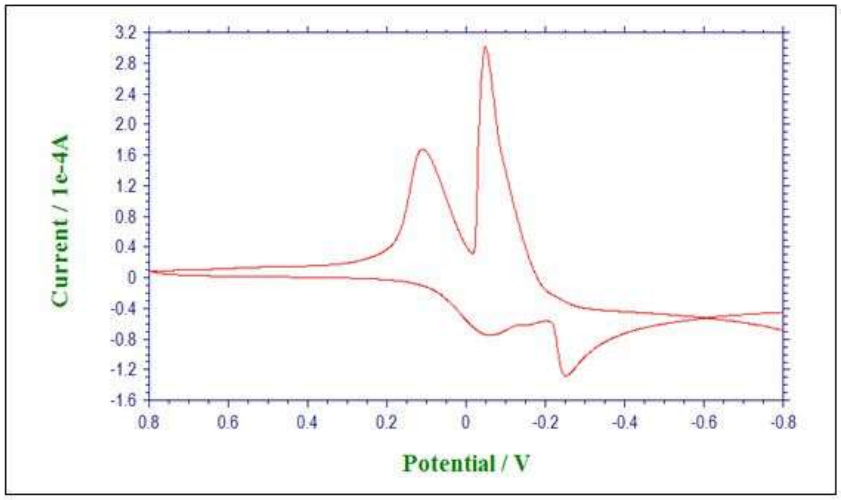


Figure 1: Cyclic voltammogram of 0.01 M in copper sulphate 0.1 M KCl

In the forward scan two anodic peaks ipa_1 and ipa_2 at -0.0518 V and 0.1114 V respectively and in the reverse scan two small cathodic peaks at ipc_1 and ipc_2 at -0.0597 V and -0.2517 V were observed resulting in a two electron reversible system. The first anodic peak corresponding to Cu^{2+} + e- → Cu^{+} (0.15 V). The first cathodic peak corresponding to Cu^{+} → Cu^{2+} + e-. The one-charged cuprum ions can undergo the disproportionation reaction: 2Cu (I) → Cu (II) + Cu (0).

The Cu(II) ions arising from the disproportionation can be reduced at more negative potentials than the reduction of Cu(II) diffusing from solution towards to electrode surface [27]. From Figure 2, it is observed that only one anodic peak at 1.3125 V is generated having a peak current of 3.3125 mA indicating that RTB is electro active compound and an irreversible system. It is apparent that window at which RTB shows electro activity is different from that of Cu^{2+}.

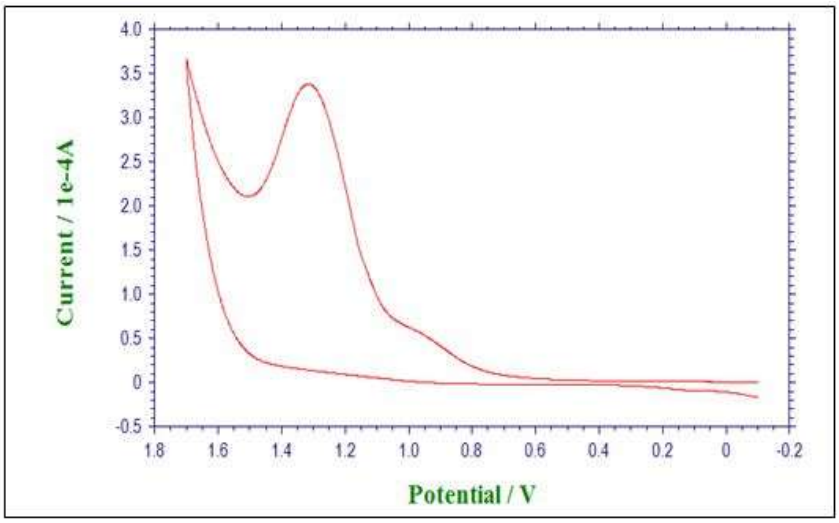


Figure 2: Cyclic voltammogram of 0.01 M in Rizatriptan benzoate in 0.1 M KCl

Voltammetric interaction of copper with RTB

The redox couple Cu (II) / Cu (I) was observed (Figure 3) in presence of 0.01 M RTB with 0.1 M KCl as a supporting electrolyte.

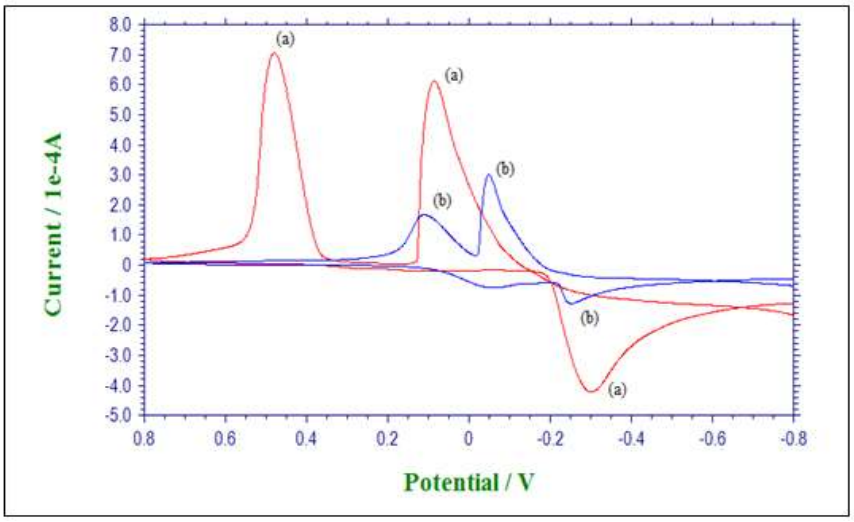


Figure 3: Cyclic voltammogram of (a) 0.01 M copper sulphate in presence of rizatriptan benzoate in 0.1 M KCl, (b) 0.01 M copper sulphate in 0.1 M KCl

The reversibility of the Cu(II)/Cu(I) redox process decreases due to associated RTB. The complex exhibits a quasi-reversible cyclic voltammetric response with ΔEp values in the range of 0.3894 Vs^{-1} at scan rate of 0.1 Vs^{-1} in 0.1 M KCl. A positive shift in potential is observed for the first anodic peak moving from -0.046 to 0.085 V with a corresponding cathodic peak from -0.254 to -0.307 V. A similar type of positive potential shift is observed for the second anodic peak from 0.111 to 0.479 Vs^{-1} with the disappearance of cathodic counterpart. The shift in peak potential Ep indicates the formation of complex.

The stability constant Kc and ΔG° for the complex is evaluated from the cyclic voltammetric data and gathered in Table 1, using the equation [28].

$$\text{Log Kc} = 0.434\ ZF/RT\Delta Ep \text{ and } \Delta G° = -2.303 \times 8.314 \times 298 \times \log Kc$$

Table 1: Stability constant Kc and ΔG° for the complex from the cyclic voltammetric data

Concentration of Cu in presence of 0.01 M RTB	E_a	I_a	E_c	I_c	ΔEp	K_c	ΔG°
0.01 M	0.0666	4.689	0.288	2.962	0.2214	30.549×10^{-6}	-42.70×10^{-3}
0.02 M	0.0851	6.095	0.3042	4.251	0.2190	25.292×10^{-6}	-42.24×10^{-3}

Variation of concentration of Cu^{2+}

Increase in concentrations of Cu^{2+} from 0.01 M to 0.02 M with a fixed concentration of RTB 0.01 M increases the peak current due to increasing movement of electrons indicating the complex formation Figure 4.

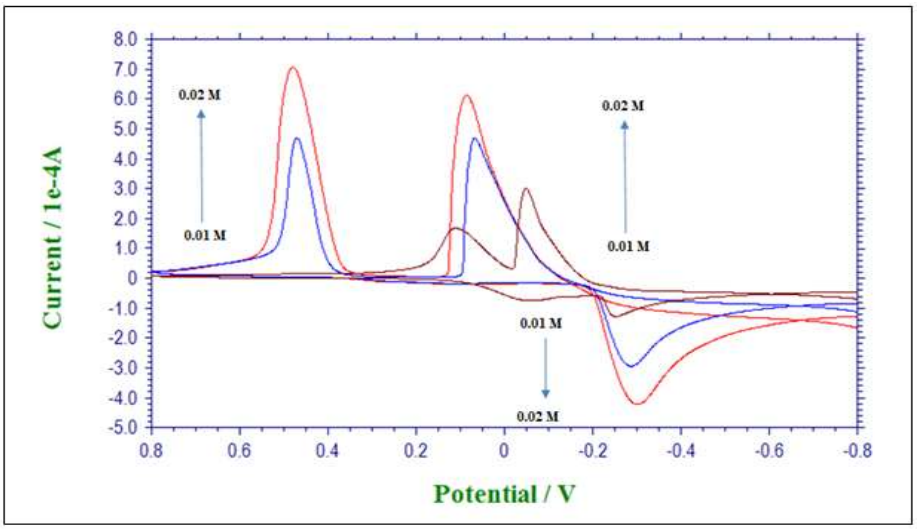


Figure 4: Cyclic voltammogram of 0.01 M and 0.02 M copper sulphate in presence of RTB in 0.1 M KCl

The first anodic peak current increases from 4.651 mA to 6.095 mA with the corresponding cathodic peak from 2.962 mA to -4.251 mA and a similar increase is observed for the second cathodic peak from 4.650 mA to 7.031 mA on increasing Cu^{2+} from 0.01 M to 0.02 M.

Variation of scan rate

To investigate the scan rate effect, a series of cyclic voltammogram of 0.02 M RTB in presence of 0.01 M Cu^{2+} in 0.1 M KCl at different scan rates were obtained and overlaid in Figure 5.

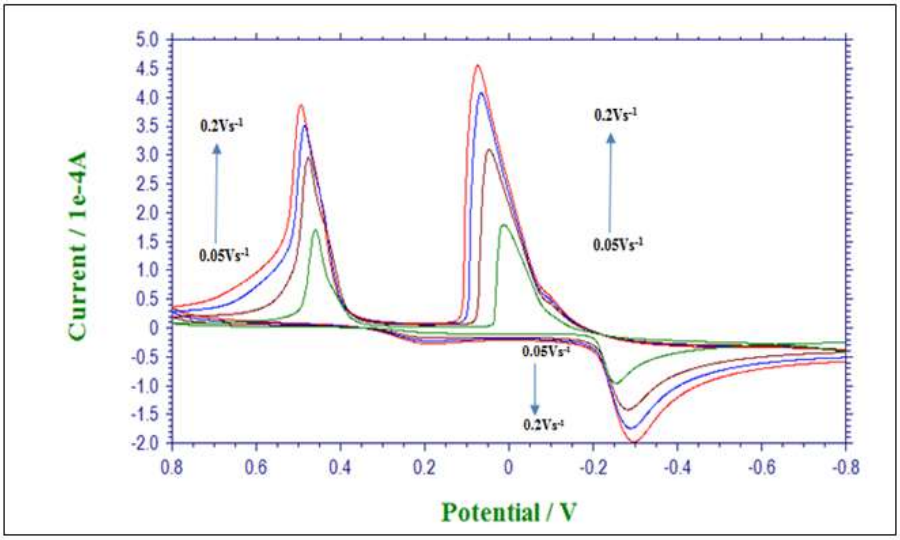


Figure 5: Cyclic voltammogram of 0.01 M copper sulphate in presence of RTB in 0.1 M KCl at different scan rates (0.05 Vs^{-1}, 0.1 Vs^{-1}, 0.15 Vs^{-1} and 0.2 Vs^{-1})

It can be seen that peak current of the complex increases while a minute potential shift is observed which may be explained by slower rate of formation of the stable complex. It is also observed that first and second anodic peaks shifts towards positive potential while the cathodic peak shifts negatively with increase in scan rate. This behaviour indicates that redox process is shifted from quasi-reversible to irreversible direction. The parameters are listed in Table 2.

Table 2: Current-potential data, peak potential separation, peak current ratio of the voltammogram of Cu-RTB complex in 0.1 M KCl

$V(s^{-1})$	$V^{1/2}$	E_{pa}	E_{pc}	i_{pc}	i_{pa}	ΔE_p	i_{pa1}/i_{pc}
0.05	0.2236	0.0141	0.2543	1.767	9.659	0.2402	0.1829
0.10	0.3162	0.0482	0.2805	3.070	1.428	0.2323	2.1498
0.15	0.3873	0.0666	0.2859	4.037	1.765	0.2293	2.2872
0.20	0.4472	0.0745	0.3017	4.542	1.995	0.2272	2.2766

V=scan rate, $V^{1/2}$=SQRT of scan rate, E_{pa}=Anodic peak potential, E_{pc}=Cathodic peak current, ipc=Cathodic peak current, i_{pa}=Anodic peak current

The plots of anodic and cathodic peak current *versus* square root of the scan rate depicts the comparison of the increasing and decreasing trends and suggest that the electrochemical process is diffusion controlled [29**]** Figures 6 and 7.

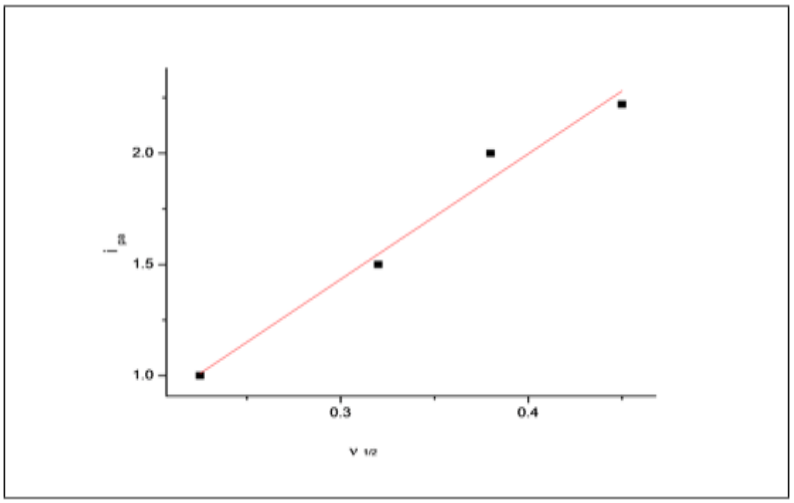


Figure 6: Plot of first cathodic peak current *vs.* square root of scan rate

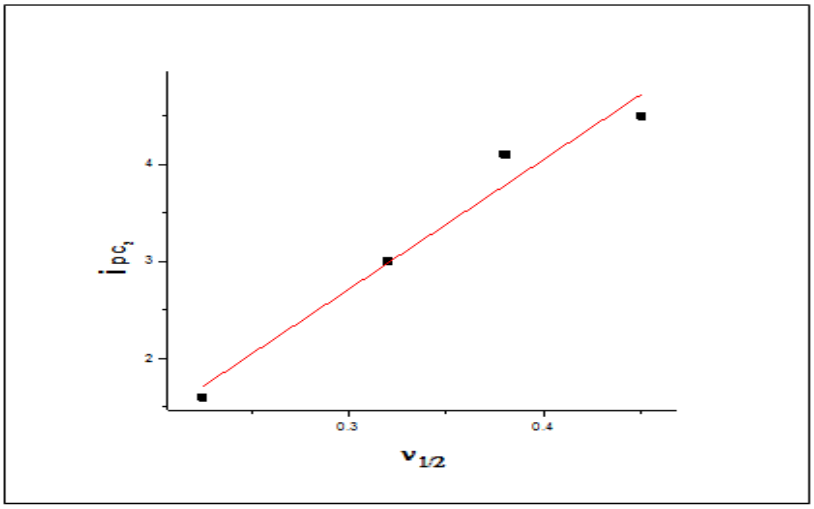


Figure 7: Plot of second cathodic current Vs square root of scan rate

The first anodic current increases from 1.788 mA to 4.520 mA and the second anodic current increase from 1.683 mA to 3.848 mA.

FTIR Spectra

A comparison of IR spectra of pure RTB in Figure 8 with IR spectra of Rizatriptan Benzoate-Cu complex in Figure 9 indicates a clear structural change. Most characteristic vibrational peaks in the region 1600 cm^{-1} to 500 cm^{-1} show reproducible changes after treating RTB with Cu.

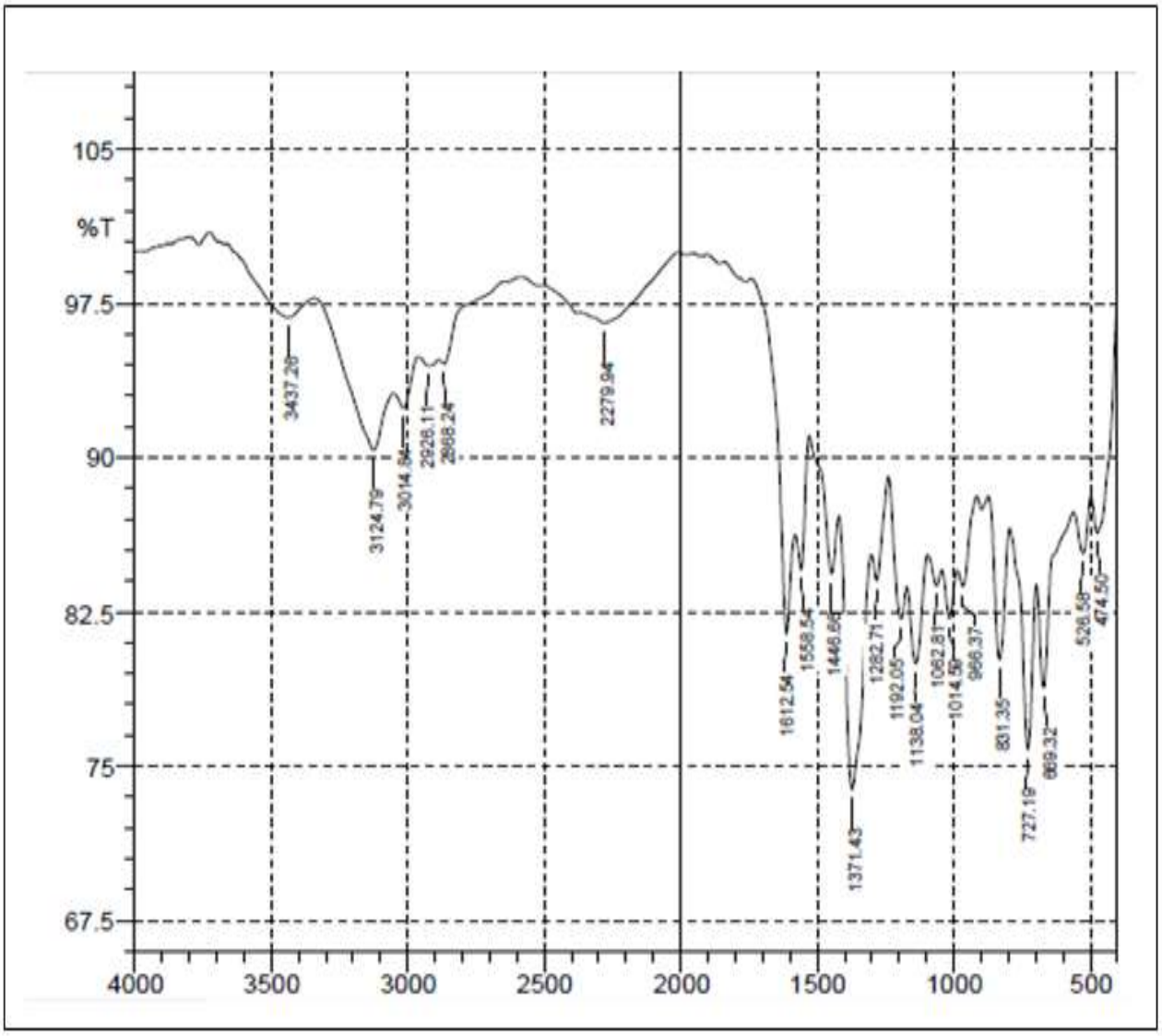


Figure 8: FTIR spectra of rizatriptan benzoate

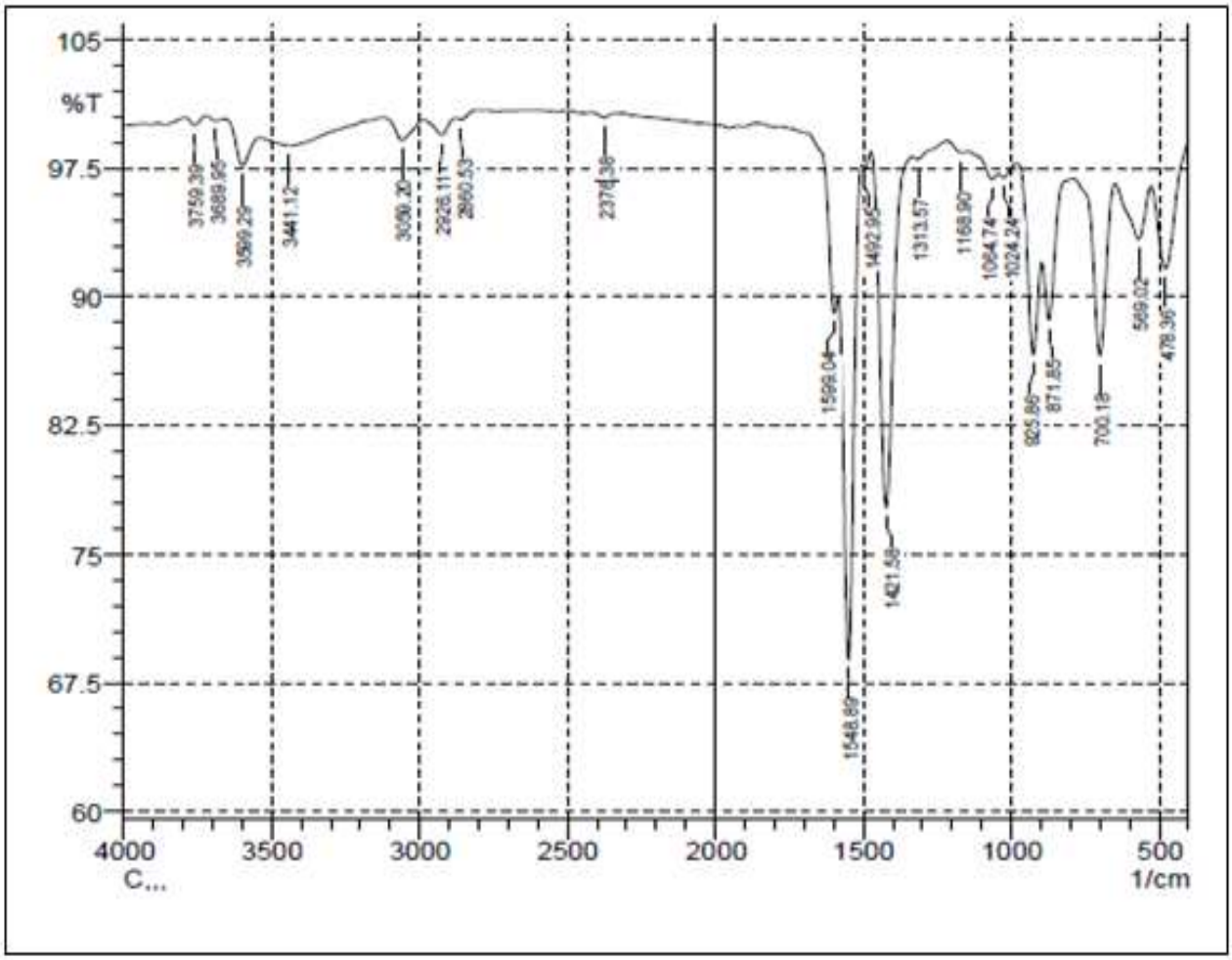


Figure 9: FTIR spectra of rizatriptan benzoate-Cu complex

The band in the pure RTB at 1612 cm^{-1} due to C=C stretch of aromatic ring, changes in frequency position to 1548 cm^{-1} and increases in intensity [30]. The band at 1371 cm^{-1} due to aromatic C-H stretching [31] shows a decrease in intensity and also a minor change to 1421 cm^{-1}. However, the band associated with aromatic C-H stretching at 2926 cm^{-1} and 2868 cm^{-1} show no major changes indicating no strong chemical interaction between aromatic ring and Cu. The band at 2279 cm^{-1} of C=N stretching in triazole ring moves to higher wavenumber of 2376 cm^{-1} suggesting the involvement of the triazole ring in complexation [32]. As a result of binding, a band at 3124 cm^{-1} caused by N-H stretch of aromatic 2° amine is shifted to 3599 cm^{-1}.

Ascorbate oxidation

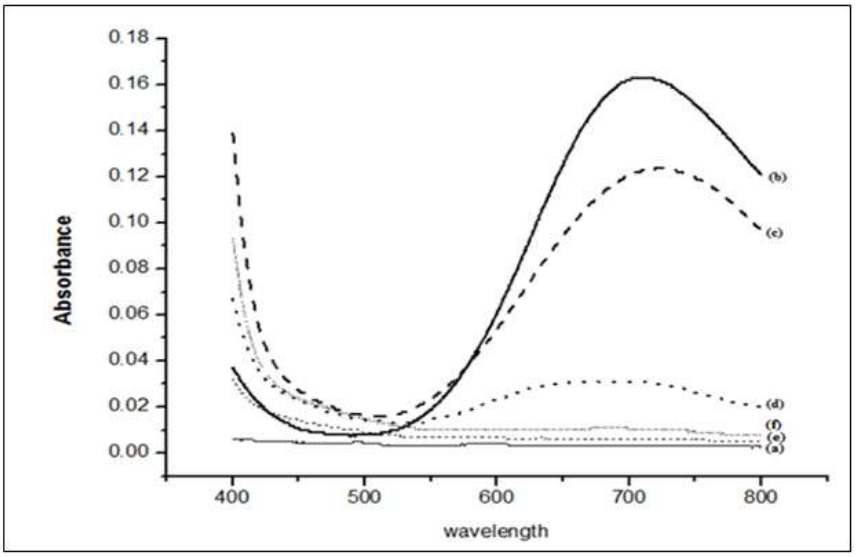


Figure 10: UV-Visible spectra of (a) RTB, (b) RTB+Cu, (c) RTB+Cu+AA at 5 min, (d) RTB+Cu+AA at 1 min, (e) RTB+Cu+AA, (f) RTB+Cu+AA at very high concentration

The association of RTB with Cu^{2+} was spectrophotometrically detected by ascorbylation *in vitro*, in Figure 10. RTB has bands in the 226 nm and 279 nm and shows no absorbance in the visible region (a), Addition of Cu –acetate to the drug in 1:2 ratio shifts the band at 776 to 710 nm (b). This indicates the binding of the ligand to Cu and formation of the new co-ordination environment around Cu^{2+}. The complex readily reacts with Ascorbic acid to form an unstable brown copper (I) species leading to the disappearance of the UV absorption peak (d).

Since, utilization of molecular oxygen and ascorbate is a function of concentration of Copper, Cu(I) species on exposure to air reacts with dioxygen and reverts to parent Cu(II) complex and the reaction, monitored by the UV-Visible spectrum shows a gradual conversion of the reduced species to the oxidized form (c), Scheme 1.

It is proposed that in Cu(II) → Cu(I) reduction of the complex Cu(II)-RTB could follow a multi-step processes with redox active intermediates that may be responsible for OH(·) radical production from H_2O_2 through a Fenton-like process [33].

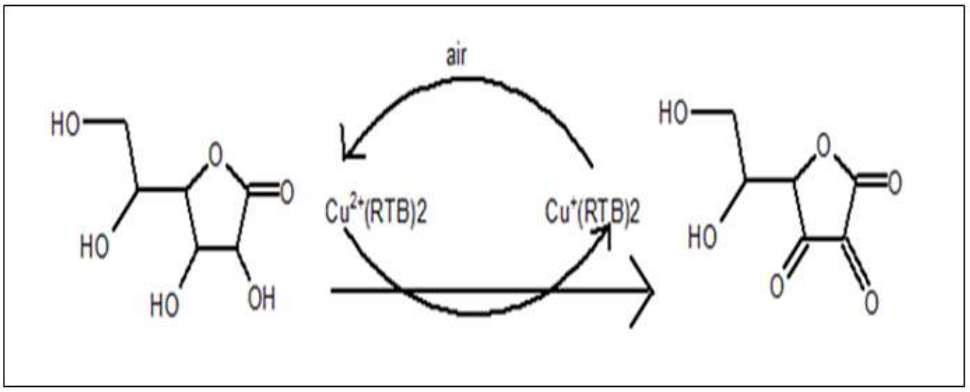
$$Cu^{2+}(RTB)_2 \rightarrow Cu^{+}(RTB)_2 \rightarrow O_2^{\bullet-} \rightarrow H_2O_2 \rightarrow 2HO\bullet$$

$$AscH^{-} + HO\bullet \rightarrow Asc\bullet- + H_2O$$

$$O^{2\bullet-}/HO_2\bullet + H_2O_2 \rightarrow O_2 + H_2O + HO\bullet$$

$$Cu^{2+}\text{-}RTB + O^{2\bullet-}/Asc$$

$$H\text{-} \rightarrow Cu^{2+}\text{-}RTB + O_2/Asc\bullet-$$



Scheme 1: Mechanism of reduction of the complex Cu (II)-RTB

CONCLUSIONS

This work indicates a strong interaction of Cu^{2+} with RTB in solution through the study of Cu^{2+}/Cu^{+} system in presence of RTB. The composition of the complexes in solution was determined voltammetrically and spectrophotometrically. Shift in peak position of $CuSO_4$ on addition of RTB suggests the formation of electrochemically active complex. The results suggest that the complexation is a diffusion controlled quasi irreversible process. The IR and UV-Visible data supports the formation of new species. *In-situ* absorption spectral studies of the reaction of ascorbic acid shows the formation of Cu^{+} species. The Cu^{+} reacts with molecular oxygen and Cu^{2+} complex is regenerated along with the formation of harmful hydroxyl radicals. This study highlights the toxic effects of RTB in presence of Copper and Ascorbic acid.

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REFERENCES

[1] C.W. Ritchie, AI. Bush, A. Mackinnon, *Arch Neurol.*, **2003**, 60(12), 1685-1691.
[2] D.M. McDonald, R.A. Mitchell, G. Gabella, A. Haskell, *J. Neurocytol*., **1988**, 17(5), 605-628.
[3] N. Farrell, *Catalysis by Metal Complexes*., **1989**, 11.
[4] J.J.R. Frausto da Silva, R.J.P. Williams, The Biological Chemistry of the Elements, Second Edition, 1991.
[5] C. Santini, M. Pellei, V. Gandin, M. Porchia, F. Tisato, C. Marzano, *Chem. Rev*., **2014**, 114(1), 815-862.
[6] L.O. Klotz, U. Weser, Kluwer Academic Publishers, Dordrecht, **1998**, 19.
[7] W. Hangarter, Humana Press, New Jersey, **1982**, 439.
[8] H.L. Regtop, J.R. Biffin, Divalent Metal Complexes of Indomethacin, Compositions and Medical Methods of use Thereof, US Patent Number-5310936, **1995**.
[9] H.L. Regtop, J.R. Biffin, Divalent Metal Salts of Indomethacin as Anti-inflammatory and Analgesic Agents, Patent number-WO 9014337 A1 901129, **1990**.
[10] B. Boettcher, W.R. Walker, M.W. Whitehouse, Complexes of Bivalent Copper and Compositions Containing NSAID Complexes, Patent Number AU 77-2584 19771128, CAN 92:58446, AN1980:58446, **1981**.
[11] M.A. Neelakantana, F. Rusalraja, J. Dharmarajaa, *Spectrochim. Acta A: Mol. Biomol. Spectrosc*., **2008**, 71(4), 1599-1609.
[12] Shouchunzhanga, Yangguangzhua, Chaotua, Haiyingweia, Z. Yanga, *J. Inorg. Biochem*., **2004**, 98(12), 2099-2110.

[13] Dilipkumarsaha, Udaysandbhor, K. Shirisha, Subhashpadhye, *Bioorg. Med. Chem. Lett*., **2004**, 14, 3027-3032.
[14] Jayendrapatole, Udaysandbhor, Subhashpadhye, D.N. Deobagkar, *Bioorg. Med. Chem. Lett*., **2003**, 13, 51-55.
[15] K.G. Daniela, P. Guptaa, R. Hope Harbachb, *Biochem. Pharmacol.*, **2004**, 67, 1139-1151.
[16] D.A. Qin, X.Q. Cai, Q. Miao, Z.H. Wang, M.L. Hu, *Int. J. Electrochem. Sci*., **2014**, 9, 1608-1620.
[17] A. Shah, E. Nosheen, S. Munir, A. Badshah, R. Qureshi, Z. Rehman, Muhammad, H. Hussain, *J. Photochem. Photobiol. B.*, **2013**, 120, 90-95.
[18] M.S. Ibrahim, *Analytica Chemical Acta*, **2001**, 443(1), 63-72.
[19] B. Haarika, P. Veerareddy, *Malaysian J. Pharm. Sci*., **2012**, 10(1), 45-60.
[20] Process for the large scale production of rizatriptan benzoate Patent number, WO 2007054979 A1, **2009**.
[21] S. Malini, Kalyan Raj, M.A. Veena, N. Nanda, *Int. Res. J. Pure Appl. Chem*., **2015**, 9(1), 1-11.
[22] S. Malini, Kalyan Raj, N. Nanda, *Int. J. Pharm. Sci. Rev. Res*., **2014**, 25(1), 290-294.
[23] H. Reiber, M. Ruff, *Clinica Chimica Acta*., **1993**, 217(2), 163-173.
[24] M.L. Heaney, J.R. Gardner, N. Karasavvas, D.W. Golde, *Cancer Res.*, **2005**, 68(19), 106-498.
[25] S.H. Chiou, W. Chang, *J. Biochem*., **1985**, 98(6), 1723-1726.
[26] H.A. Tajmir Riahi, *J. Inorg. Biochem*., **1991**, 44, 39-45.
[27] L. Trnkova, L. Zerzankova, F. Dycka, R. Mikelova, F. Jelen, *Sensors*., **2008**, 8(1), 429-444.
[28] N. Nanda, M. Tanu, S.M. Mayanna, *Int. J. Pharm. Tech. Res*., **1999**, 2(4), 2391-2402.
[29] S. Nandini, R. Siddappamanjunatha, S. Shanmugam, *J. Electroanal. Chem*., **2013**, 689, 233-242.
[30] N. Karaalii, E. Mentesei, *South African J. Chem.*, **2013**, 66, 72-76.
[31] D. Chavan Jyotsna, C. Doijad Rajendra, *Int. J. Pharm Tech. Res*., **2010**, 2(4), 2391-2402.
[32] P. Sudhir Kumar, J. Sahoo, *Orien. J. Chem*., **2014**, 30(1), 119-124.
[33] T. Prosdocimi, L. DeGioia, G. Zampella, L. Bertini, *J. Biol. Inorg. Chem*., **2016**, 21(2), 197-212.