Research Article

CYCLIC VOLTAMMETRIC STUDIES OF THE INTERACTION OF RIZATRIPTAN BENZOATE WITH COPPER IN AQUEOUS SOLUTION

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Article Received on: 07/09/17 Approved for publication: 12/10/17

DOI: 10.7897/2230-8407.0810192

ABSTRACT

The interaction of copper with Rizatriptan benzoate has been studied using cyclic voltammetric technique in the potential range -0.8 to 8.0 V with three electrodes system of a Glassy carbon electrode as the working electrode, Ag/AgCl (satd. KCl) as the reference electrode and platinum wire as the counter electrode in 0.1 M KCl as the supporting electrolyte. The voltammetric patterns reveals that with increasing concentration of metal the corresponding current increases and with increasing scan rate, the corresponding current increases linearly with the square root of the scan rate indicating that the binding of the drug to the metal is diffusion controlled. Stability constant K_c and thermodynamic parameter ΔG is evaluated. As revealed by UV spectrophotometry, the metal to drug ratio is 1:2 and IR spectra shows that the triazole ring of the drug binds to copper.

Keywords: Rizatriptan benzoate, 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. Copper levels in cerebrospinal fluid is extremely important to facilitate enzymatic defence mechanisms that prevent neuro degeneration¹ and neurogenic inflammation². Its biological importance is also attributed to its ability to complex with medicinal compounds and affect its efficacy³. A wealth of literature is available documenting the potential benefits of Cu (II) for binding to biological organic molecules⁴ and copper complexes being more effective than the drugs themselves⁵. There are numerous reports of Copper complexes of NSAIDS⁶⁻¹⁰, amino acids¹¹, nucleobase¹², antibacterial agents¹³, anti-tubercular drugs¹⁴ and anticancer drugs¹⁵.

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 method¹⁶. Recently, the interaction of hydantoin derivatives with CT-DNA¹⁷, antitumor drugs with ds-DNA¹⁸ is studied using cyclic voltammetry.

Antimigraine drugs work by activating 5-HT₁ β 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, evaluation¹⁹, synthesis²⁰ quantification²¹ and

mechanism of oxidation of Rizatriptan²². However, Voltammetric studies of interaction of this drug with copper ions is not reported in the literature. Hence, in the present study, the voltammetric behaviour of Rizatriptan in the presence and absence of Cu(II) ions is reported.

MATERIALS AND METHODS

Analytical grade $\text{CuSO}_4 \cdot 5\text{H}_2\text{O}$ and KCl were purchased from E.Merck, Germany. Rizatriptan benzoate was obtained from Apotex India pvt Ltd as a gift sample. $\text{CuSO}_4 \cdot 5\text{H}_2\text{O}$ 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 spectrophotometer²³.

RESULTS AND DISCUSSION

Cyclic voltammetric response due to Cu (II)/Cu (I) couple was studied in the range of -0.8 to -0.8 V with an ipa/ipc ratio of 2.34 and a ΔE_p value of 1.27V 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. In the forward scan two anodic peaks ipa₁ and ipa₂ at -

0.0518 V and 0.1114V respectively and in the reverse scan two small cathodic peaks at ip_{c1} and ip_{c2} at -0.0597 V and -0.2517 V were observed resulting in a two-electron reversible system. The one-charged cuprum ions can undergo the disproportionation reaction: $2Cu(I) \rightarrow Cu(II) + Cu(0)$.

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 surface²⁴.

Rizatriptan Benzoate is electro inactive in the range -0.8 to -0.8 V with 0.1 M KCl as the supporting electrolyte. However, from Figure 2, it is observed that only one anodic peak at 1.3125 V is generated having a peak current of 3.3125mA indicating that RTB is electroactive compound and an irreversible system. It is apparent that window at which RTB shows electroactivity is different from that of Cu^{2+} and is inactive in the range -0.8 to +0.8 V.

Voltammetric interaction of Copper with RTB

The redox couple Cu (II) / Cu (I) was observed in presence of 0.01M RTB with 0.1 M KCl as a supporting electrolyte Figure 3. The reversibility of the Cu (II) / Cu (I) redox process changes due to the associated RTB. A positive shift in potential is observed for the first anodic peak moving from -0.046 to 0.085V with a corresponding cathodic peak showing a negative shift from -0.254 to -0.307V. A similar type of positive potential shift is observed for the second anodic peak from 0.111 to 0.479Vs-1 with the disappearance of cathodic counterpart. The shift in peak potential E_p indicates an association of Cu with RTB.

The stability constant K_c and ΔG° for the complex is evaluated from the cyclic voltammetric data and gathered in Table 1, using the equation²⁵

$$\log K_c = 0.434 ZF/RT\Delta E_p \text{ and } \Delta G^\circ = -2.303 \times 8.314 \times 298 \times \log K_c$$

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

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

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

TABLE 1: STABILITY CONSTANT K_c AND ΔG° FOR THE COMPLEX FROM THE CYCLIC VOLTAMMETRIC DATA

Concentration of Cu in presence of 0.01M RTB	E_a	I_a	E_c	I_c	ΔE_p	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 0.01M to 0.02M with a fixed concentration of RTB 0.01M in Figure 4 shows an increasing increasing movement of electrons indicating the complex formation. The first anodic peak current increases from 4.651mA to 6.095mA with the corresponding cathodic peak from 2.962mA to -4.251mA and a similar increase is observed for the

second cathodic peak from 4.650mA to 7.031mA on increasing Cu^{2+} from 0.01M to 0.02M.

Variation of scan rate

To investigate the scan rate effect, a series of cyclic voltammograms of 0.02M RTB in presence of 0.01M Cu^{2+} in 0.1M KCl at different scan rates from 0.05 to 0.2Vs⁻¹ were obtained and is overlaid in Figure 5.

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 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.

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

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

TABLE 2: CURRENT-POTENTIAL DATA, PEAK POTENTIAL SEPARATION, PEAK CURRENT RATIO OF THE VOLTAMMOGRAMS OF CU- RTB COMPLEX IN 0.1M KCL

Scan rate	$v^{1/2}$	Ea		Ia		Ec		Ic	
		Ea ₁	Ea ₂	Ia ₁	Ia ₂	Ec ₁	Ec ₂	Ic ₁	Ic ₂
0.05	0.2236	0.011	0.458	1.788	1.683	-	0.2569	-	9.440
0.15	0.3162	0.045	0.477	3.070	2.923	-	0.2859	-	1.428
0.20	0.3873	0.064	0.484	4.037	3.491	-	0.2884	-	1.765
0.25	0.4472	0.074	0.492	4.520	3.848	-	0.2991	-	1.995

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 first, second anodic and second cathodic peak current versus square root of the scan rate depicts the increasing trend and suggests that the electrochemical process is diffusion controlled²⁶ Figure 6-8. The first anodic current increases from 1.788 mA to 4.520mA and the second anodic current increase from 1.683mA to 3.848mA.

Figure 6: Plot of second cathodic peak current Vs square root of scan rate

Figure 7: Plot of first anodic peak current Vs square root of scan rate

Figure 8: Plot of second anodic current Vs square root of scan rate

FTIR spectra

A comparison of IR spectra of pure RTB in Figure 9 with IR spectra of Rizatriptan Benzoate-Cu complex in Figure 10 indicates a clear structural change. Most characteristic vibrational peaks in the region 1600cm⁻¹ to 500cm⁻¹ show reproducible changes after treating RTB with Cu. The band in the pure RTB at 1612cm⁻¹ due to C=C stretch of aromatic ring, changes in frequency position to 1548cm⁻¹ and increases in intensity²⁷. The band at 1371cm⁻¹ due to aromatic C-H stretching²⁸ shows a decrease in intensity and a minor change to 1421cm⁻¹. However, the band associated with aromatic C-H stretching at 2926cm⁻¹ and 2868cm⁻¹ show no major changes indicating no strong chemical interaction between aromatic ring and Cu. The band at 2279cm⁻¹ of C=N stretching in triazole ring moves to higher wavenumber of 2376cm⁻¹ suggesting the involvement of the triazole ring in complexation²⁹. As a result of binding, a band at 3124cm⁻¹ caused by N-H stretch of aromatic 2° amine is shifted to 3599cm⁻¹.

Figure 9: FTIR spectra of Rizatriptan Benzoate

Figure 10: FTIR spectra of Rizatriptan Benzoate-Cu complex

CONCLUSION

This work indicates a strong interaction of Cu^{2+} with RTB in solution through the study of $\text{Cu}^{2+}/\text{Cu}^+$ system in presence of RTB. The composition of the complexes in solution was determined voltammetrically. 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.

ACKNOWLEDGMENTS

One of the authors (Malini. S) is thankful to Dr. Ananth Raj, HOD Department of Chemistry, DSCE for his support and encouragement and BMS College of Engineering for providing the electrochemical workstation.

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Cite this article as:

Malini S. *et al.* Cyclic voltammetric studies of the interaction of rizatriptan benzoate with copper in aqueous solution. *Int. Res. J. Pharm.* 2017;8(10):117-121 <http://dx.doi.org/10.7897/2230-8407.0810192>

Source of support: Nil, Conflict of interest: None Declared

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