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Voltammetric study of the interaction of Cu(II) with proton pump inhibitor at different pH

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Abstract

The electrochemical redox behavior of transition metal ion, Cu(II) at different pH in acetate buffer solution has been investigated using cyclic voltammetric method at glassy carbon electrode (GCE). Cyclic voltammograms of Cu(II) show two cathodic and an anodic peaks those remain identical at various pH. The cyclic voltammetric response of the metal ion has been observed in presence of proton pump inhibitors (PPIs) such as omeprazole, pantoprazole, esomeprazole and rabeprazole at various proportions of metal ion and PPIs. The nature of cyclic voltammograms of Cu(II) has been changed dramatically in presence of the PPIs due to the strong interaction between metal ion and PPIs. Almost similar interaction was noticed for all the PPIs. However, the maximum interaction was found at 1:2 molar ratio of Cu(II) and PPIs. The result could provide deep insight into the interaction between various metal ions and the PPIs that have been taken quite regularly in human body.

Keywords: Transition metal ions; Proton pump inhibitors; Cyclic voltammetry; Glassy carbon electrode; Acetate buffer

Introduction

Proton pump inhibitors (PPIs) comprise a class of drugs with an excellent safety profile are widely used for the treatment of acid-peptic diseases. They are used extensively for the treatment of gastric acid-related disorders because they produce a greater degree and longer duration of gastric acid suppression and, thus, better healing rates, than histamine H_2 receptor antagonists (Blume *et al.*, 2006, Horn *et al.* 2000, Welage *et al.*, 2000, *Gerson et al.*, 2001, Sibbing *et al.*, 2009, and Stone, 2009). PPIs are the most potent inhibitors of gastric acid secretion, with a potential to increase intragastric pH by several units, as well as hydrogen ion concentration by several hundred to thousand fold (McColl, 2009). PPIs are substituted benzimidazoles and are lipophilic weak bases that cross the parietal cell membrane and enter the acidic parietal cell canaliculus (Malik *et al.*, 2010). In this acidic environment, the PPIs become protonated producing the activated sulphonamide from the drug that binds covalently with the H^+, K^+ -ATPase enzyme resulting in irreversible inhibition of acid secretion by the proton pump. This enzyme is responsible for hydrogen ion secretion in exchange for potassium ions in the gastric lumen (Sheen *et al.*, 2011). As a result, PPIs can modify the bioavailability and absorption of essential vitamins and minerals both in the stomach and duodenum, which may also affect more distal absorption. PPIs act by irreversibly blocking the H^+/K^+ adenosine triphosphatase enzyme system of the gastric parietal cells (Zajac *et al.*, 2013). Gastric nitrate rendering bacteria levels increase, as do carcinogenic nitrosamines in gastric juice. A pH of less than 3.8 allows gastric bacterial overgrowth (Theisen *et al.*, 2000 and Stein *et al.*, 1998).The proton pump is the terminal stage in gastric acid secretion, being directly responsible for secreting H^+ ions into the gastric lumen, making it an ideal target for inhibiting acid secretion. Several transition elements are important to the chemistry of living systems, the most familiar examples being iron, cobalt, copper, and molybdenum. Most of the first row transition metals are important for enzymes (Dlouhy *et al.*). They have one or both of two important properties: (i) some readily change oxidation state, (ii) acting as critical redox couples. Several have high charge density, making them good candidates for reaction centers. Iron is by far the most widespread and important transition metal that has a function in living systems; proteins containing iron participate in two main processes, oxygen transport and electron transfer

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reactions (Finney *et al.*, 2003). Cu(II) is able to bind to several electron donor groups (Gebhard *et al.*, 2001 and Maliki *et al.*, 2012) can thus irreversibly inhibit their function (Eichhorn, 1975). The interaction between metal ions and PPIs has been studied electrochemically by synthesizing metal-ion-PPIs complex (Ghandour *et al.,* 2015). However, direct electrochemical study of metal ions in presence of PPIs in solution has been rarely reported.

The cyclic voltammetric study of various metal ions in presence of ligand has been investigated in our laboratory and reported in detail (Shaikh *et al.*, 2005 and 2006). Cyclic voltammetric method has been chosen for this present study because of its potential ability in investigating the redox behavior of electroactive species. We have therefore, started a wide ranging electrochemical studies of metal complexes of PPIs using cyclic voltammetry. Here we report a study of the electrochemical interaction of transition metal ion Cu(II) (copper perchlorate $Cu(ClO_4)_2.6H_2O$) and PPIs such as omeprazole (Ome), pantoprazole (Pan), esomeprazole (Eso) and rabeprazole (Rab) in acetate buffer solution at various pH (3.5, 4.0 and 4.5).

Materials and methods

Analar grade copper perchlorate ($Cu(ClO_4)_2.6H_2O$) has been purchased from Sigma-Aldrich and used without further purification. Analytical Grade omeprazole, pantoprazole, esomeprazole and rabeprazole of Sigma-Aldrich were used in this study. For the preparation of acetate buffer solution, extra pure acidic acid (BDH, England) and sodium acetate (Merck Germany) were procured and used without further treatment. Sodium hydroxide (Merck, Germany) was used as it is available for maintaining the pH of the solution. All aqueous solutions were prepared in deionized water. The experiments were carried out at room temperature.

A three electrode electrochemical cell consisted of a working electrode (Glassy carbon electrode), a reference electrode (Ag/AgCl (satd. KCl)) and a counter electrode (Pt wire) was used in this study. Cyclic voltammetric measurement was performed using computerized electrochemical workstation (Model CHI 620D, CHI Instruments Inc., USA).

Preparation of various solutions

Preparation of buffer solution: The acetate buffer used in this study was prepared by mixing requisite volume of 0.1 M sodium acetate ($CH_3COONa.3H_2O$) and 0.1 M acetic acid (CH_3COOH) solution. For the preparation of the 0.1M $CH_3COONa.3H_2O$ and 0.1M CH_3COOH solutions, 50% ethanol-water was used as solvent. By the addition of 0.1 M sodium hydroxide (NaOH), the desired pH (3.5, 4.0 and 4.5) was adjusted.

Preparation of Metal solution: Stock solution of 1.0 mM Cu(II) was prepared with analytical grade copper(II) perchlorate hexahydrate salt respectively with acetate buffer solution.

Preparation of PPIs solution: Four different concentrations (1.0 mM, 2.0 mM, 3.0 mM and 4.0 mM) of omeprazole, pantoprazole sodium, esomeprazole magnesium and rabeprazole sodium solutions were prepared by using acetate buffer solution.

Preparation of different Metal-ligand (PPIs) solutions: The metal-ligand solutions for complexation reaction were prepared by mixing of same amount (volume/volume) of metal and ligand solution to achieve 1:1, 1:2, 1:3 and 1:4 (metal-ligand) ratios at desired pH.

Preparation of Working Electrode

This electrode preparation includes the polishing and conditioning of the electrode. At the beginning of each experiment, the working electrode was polished with alumina slurry (a few amount of alumina polishing powder of particle size 0.3 micron and a few drops of water) on the surface of water resistant polishing cloth. Then it was rinsed with plenty of de-ionized water and the whitish alumina was wiped off with a clean tissue paper. First of all, the cell was filled with desired volume of the experimental solution and the Teflon cap was placed on the cell. Then three electrodes were inserted in the solution.

Results and discussion

Electrochemical redox behavior of Cu(II) in acetate buffer solution and their interaction with proton pump inhibitors (PPIs) such as omeprazole, pantoprazole, esomeprazole and rabeprazole were performed at GCE at various molar ratio and different scan rate. The effect of pH such as 3.5, 4.0 and 4.5 in acetate buffer solution was also examined in this study.

Cyclic voltammetric investigation of Cu(II) and its interaction with PPIs

Cyclic voltammetric studies of Cu(II) in acetate buffer solution: Cyclic voltammetric study of 1.0 mM Cu(II) in acetate buffer solution at different pH value was investigated at GCE within the potential window of +1200 to -800 mV. Fig. 1(a) shows a CV of 1.0 mM Cu(II) in acetate buffer

solution with scan rate of 100 mVs^{-1} at pH 3.5. In the forward scan two cathodic peaks, i_{pc1} and i_{pc2} at about -219.2 mV and 415.3 mV and in the reverse scan an anodic peak, i_{pa2} at about 446.3 mV were observed. The cathodic peaks result from the reduction of Cu(II) to Cu(I) and Cu(I) to Cu(0), and the only an anodic peak is for the oxidation of Cu(0) to Cu(II). The possible mechanism of the redox reaction is as follows:

For reduction half-reaction: $Cu(II) + e^- \rightarrow Cu(I)$

$Cu(I) + e^- \rightarrow Cu(0)$

For oxidation half-reaction: $Cu(0) \rightarrow Cu(II) + 2e^-$

Effect of scan rate: The effect of the scan rate on the electrochemical response of Cu(II) under the identical condition (1.0 mM Cu(II) at pH 3.5) was examined by taking the CV of Cu(II) with scan rate of 25, 50, 75, 100 and 125 mVs^{-1} as shown in Fig. 1(b). With the increasing of scan rate, the cathodic and anodic peak current increased. The observation suggests that the electrode process is diffusion controlled in acetate buffer medium. The ratio of the oxidation peak current and its corresponding reduction counterpart i_{pa}/i_{pc} is about (1.4686-1.7886). It is found that the peak current ratio is increased with the increasing of scan rate. Also the peak potential separation, ΔE_p is in between (614.9-896.9 mV). It is increased with the variation of scan rate. These suggest that the redox process is quasi-reversible reaction rather than a reversible reaction. Moreover, the shifting of the peak potential at various scan rates indicates quasi-reversibility of the redox process, which is also characterized by the shape and separation of the cathodic and anodic peak.

In addition to that the cathodic peaks are slightly shifted towards negative potential while the anodic peaks are moved a little towards positive potential with scan rate. This observation indicates that there is a tendency of the redox process shifted from quasi-reversible to irreversible direction.

In Fig. 2(a), it is apparent that the peak current for the electrochemical redox reaction of Cu(II) has linear relation with square root of scan rate. This observation is again in favor of the fact that the electrode process is diffusion controlled with no adsorption on the electrode surface. The ratio of the oxidation peak current and its corresponding reduction counterpart has a linear relation with scan rate (Fig. 2(b)). Also the peak potential separation, ΔE_p is linearly increased with scan rate (Fig 2(c)). These results suggest that the redox process is a quasi-reversible reaction rather than a reversible reaction.

Effect of pH on the cyclic voltammograms of Cu(II): The effect of pH (3.5, 4.0 and 4.5) on the CVs of the redox reaction of Cu(II) in acetate buffer solution has been investigated as shown in Fig. 3. It is found that with the increase of pH a distinguishable cathodic peak and intense anodic peak are found. The data from the voltammograms are shown in Table I.

Cyclic voltammetric response of PPIs: Cyclic voltammetric response of Ome, Pan, Eso and Rab were recorded in acetate buffer solution in identical condition as for metal ions. In this condition except Ome and Rab, PPIs showed no significant peak. Ome and Rab showed a cathodic and an anodic peaks at -383.6, 433.0 mV and 209.9, 100.6 mV. Except Ome and Rab the other PPIs has no significant contribution to the faradic current in the CVs of Cu (II).

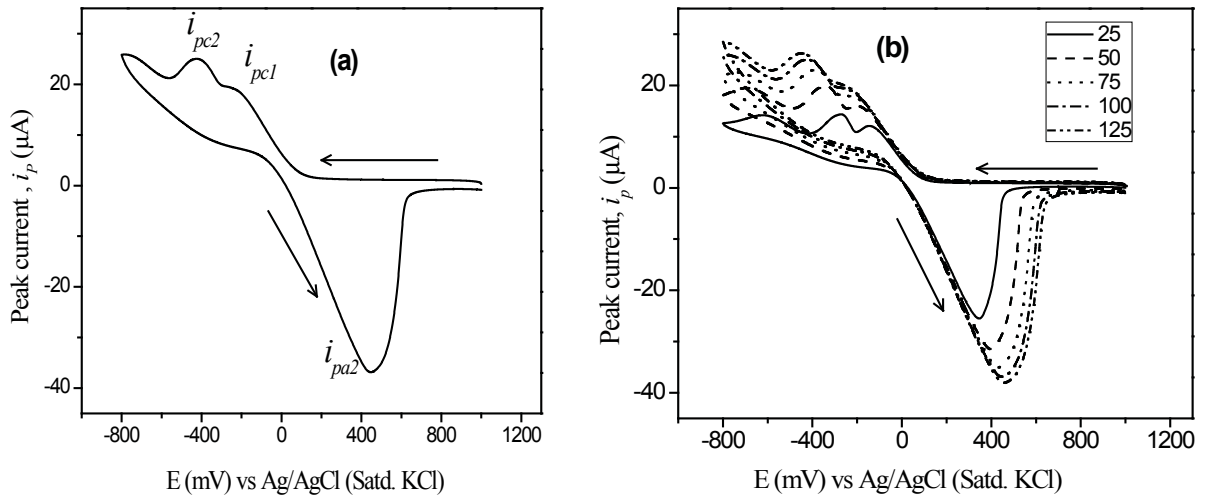

Fig. 1. (a) CV of 1.0 mM Cu(II) in acetate buffer solution at pH 3.5 with scan rate of 100 mVs^{-1} and (b) CVs of 1.0 mM Cu(II) at various scan rate: 25 (solid), 50 (dash), 75 (dot), 100 (dash dot), and 125 (dash dot dot) mVs^{-1} at GCE.

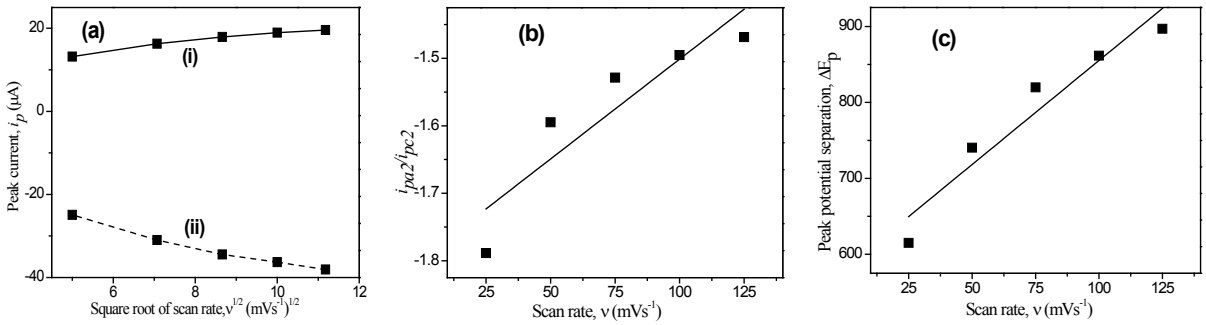

Fig. 2. (a) Plots of cathodic peak current (i) and anodic peak current (ii) as a function of square root of scan rate, (b) Peak current ratio (i_{pa2}/i_{pc2}) dependence on scan rate and (c) A plot of peak potential separation with scan rate for 1.0 mM Cu(II) at pH 3.5.

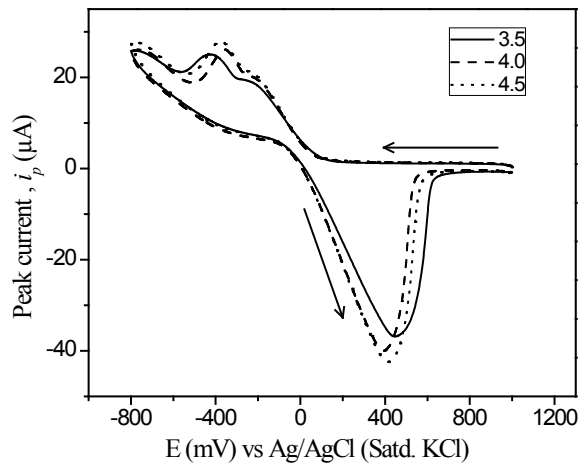

Fig. 3. CVs of 1.0 mM Cu(II) in acetate buffer solution at pH 3.5 (solid), pH 4.0 (dash) and pH 4.5 (dot).

Cyclic voltammetric studies of Cu(II) in presence of Omeprazole (Ome): The electrochemical studies of the interaction of Cu(II) with Ome in acetate buffer solution at pH 3.5, 4.0 and 4.5 has been carried out. The cyclic voltammograms recorded for Cu(II), and Cu(II) in presence of various molar concentrations of Ome (molar ratios of Cu(II)/Ome; 1:1, 1:2, 1:3 and 1:4) are shown in Fig. 4. The voltammogram recorded for each ratio of Cu(II) and Ome, the peak current for both anodic and cathodic peak decreases than those for free Cu(II). Moreover it is apparently found that the cathodic peaks shifted significantly towards negative direction and almost disappeared while the anodic peaks are shifted towards positive direction for different ratio at studied pH. The results suggest that there is an interaction between Cu(II) and Ome. From the Fig. 4, it is obvious that a strong interaction occurs at 1:2 molar ratio of Cu(II) and Ome which is a good agreement with previous studies (Ghandour *et al.*, 2015).

Table I. Peak potential and peak current for the voltammogram obtained from Cu(II) at different pH.

Solution pH	Peak current, i_p, (μA)		Peak potential, E$_p$, (mV)		Peak potential separation, $\Delta E = E_{pa} - E_{pc}$ (mV)
	i_{pc}	i_{pa} (-)	E_{pc} (-)	E_{pa}	
3.5	24.75	37.01	415.3	446.3	861.6
4.0	26.01	40.16	360.3	391.4	751.7
4.5	27.81	42.45	377.8	413.4	791.2

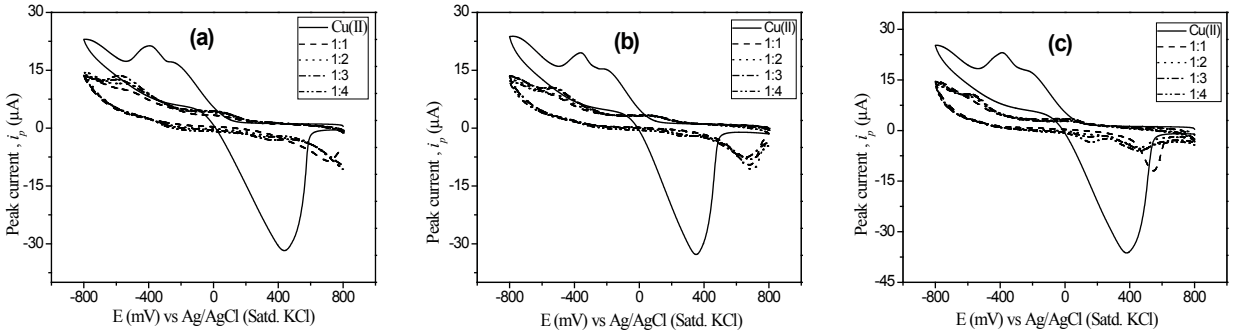

Fig. 4. CVs of Cu(II) (solid), and Cu(II)/Ome with different ratio (i) 1:1 (dash), (ii) 1:2 (dot), (iii) 1:3 (dash dot), and (iv) 1:4 (dash dot dot) in acetate buffer solution at (a) pH 3.5, (b) pH 4.0 and (c) pH 4.5.

Similar behavior was also observed in the interaction of Cu(II) and Ome at pH 4.0 and 4.5. A strong interaction was taken place at 1:2 ratio of Cu(II) and Ome. However, in more acidic medium (pH 3.5 and 4.0) Ome showed greater peak current compared to less acidic medium due to the protonation of Ome which is facilitated in more acidic medium than less acidic medium (McColl *et.al.*, 2009).

Cyclic voltammetric studies of Cu(II) in presence of Pantoprazole (Pan): The electrochemical studies of the interaction of Cu(II) with Pan in acetate buffer at pH 3.5, 4.0 and 4.5 has been carried out. The CVs recorded for Cu(II), and Cu(II) in presence of various molar concentrations of Pan (molar ratios of Cu(II)/Pan; 1:1, 1:2, 1:3 and 1:4) are shown in Fig. 5. The CV recorded for each ratio of Cu(II) and Pan, the peak current for both anodic and cathodic peak decreases than those for free Cu(II). Moreover it is apparently found that the cathodic peaks almost disappeared while the anodic peaks are shifted towards positive direction for different ratio at all pH. The results suggest that there is an interaction between Cu(II) and Pan. It is obvious that a strong interaction occurs at 1:2 molar ratio of Cu(II) and Pan.

Similar behavior was also observed in the interaction of Cu(II) and Pan at pH 4.0 and 4.5 and the strong interaction was occurred at 1:2 ratio of Cu(II) and Pan.

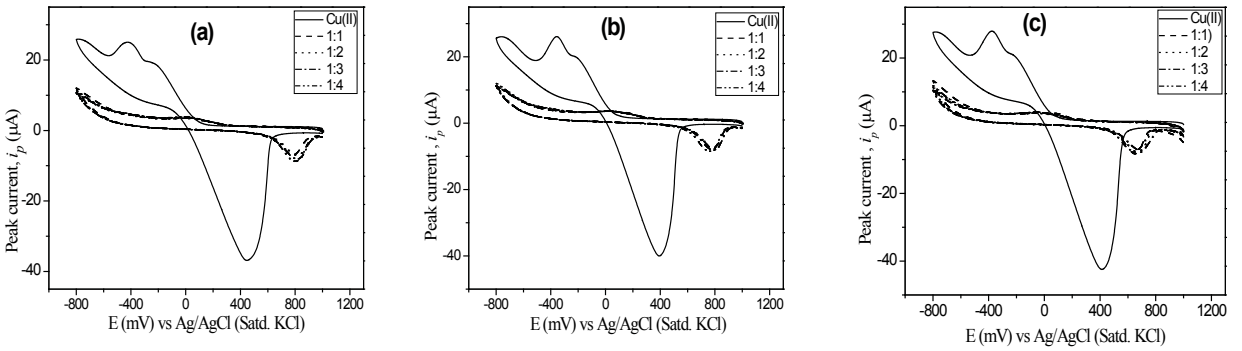

Fig. 5. CVs of Cu(II) (solid), and Cu(II)/Pan with different ratio (i) 1:1 (dash), (ii) 1:2 (dot), (iii) 1:3 (dash dot), and (iv) 1:4 (dash dot dot) in acetate buffer solution at (a) pH 3.5, (b) pH 4.0 and (c) pH 4.5.

Cyclic voltammetric studies of Cu(II) in presence of Esomeprazole (Eso): The electrochemical studies of the interaction of Cu(II) with Eso in acetate buffer at pH 3.5, 4.0 and 4.5 has been performed. The CVs recorded for

Cu(II), and Cu(II) in presence of various molar concentrations of Eso (molar ratios of Cu(II)/Eso; 1:1, 1:2, 1:3 and 1:4) are shown in Fig. 6.

The voltammogram recorded for each ratio of Cu(II) and Eso, the peak current for both anodic and cathodic peak decreases than those for free Cu(II). Moreover it is apparently found that the cathodic peaks shifted slightly towards negative direction and almost disappeared while the anodic peak was shifted towards positive direction for different ratio at studied pH. The results suggest that there is an interaction between Cu(II) and Eso and the strong interaction occurred at 1:2 molar ratio of Cu(II) and Eso.

Similar behavior was also observed in the interaction of Cu(II) and Eso at pH 4.0 and 4.5 and strong reaction was taken place at 1:2 ratio of Cu(II) and Eso.

Cyclic voltammetric studies of Cu(II) in presence of Rabeprazole (Rab): The electrochemical studies of the interaction of Cu(II) with Rab in acetate buffer at pH 3.5, 4.0 and 4.5 has been carried out. The CVs recorded for Cu(II), and Cu(II) in presence of various molar concentration of Rab (molar ratios of Cu(II)/Rab; 1:1, 1:2, 1:3 and 1:4) are shown in Fig. 7. The voltammogram recorded for each ratio of Cu(II) and Rab., the peak current for both anodic and cathodic peak decreases than those for free Cu(II). Moreover it is apparently found that the cathodic peaks were almost disappeared while the anodic peaks are shifted towards positive direction for different ratio at every pH. The results suggest that there is an interaction between Cu(II) and Rab and it is obvious that a strong interaction occurred at 1:2 molar ratio of Cu(II) and Rab.

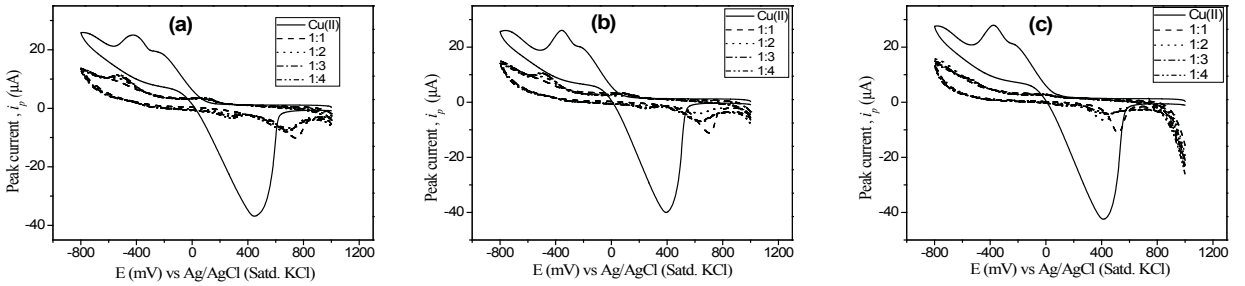

Fig. 6. CVs of Cu(II) (solid), and Cu(II)/Eso with different ratio (i) 1:1 (dash), (ii) 1:2 (dot), (iii) 1:3 (dash dot), and (iv) 1:4 (dash dot dot) in acetate buffer solution at (a) pH 3.5, (b) pH 4.0 and (c) pH 4.5.

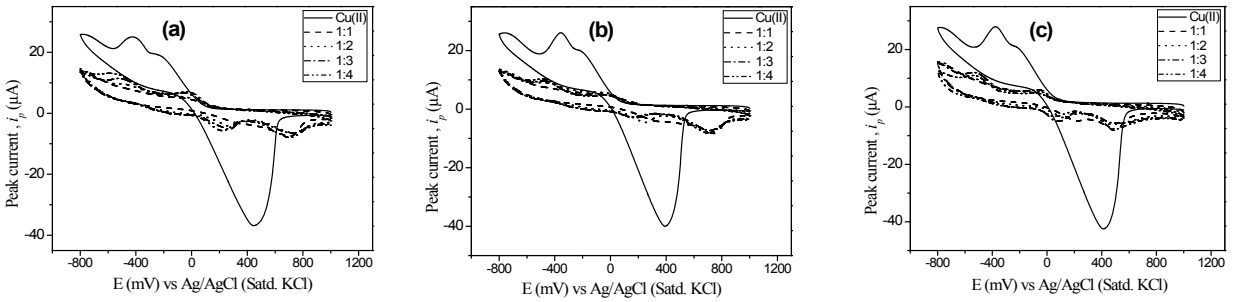

Fig. 7. CVs of Cu(II) (solid), and Cu(II)/Rab with different ratio (i) 1:1 (dash), (ii) 1:2 (dot), (iii) 1:3 (dash dot), and (iv) 1:4 (dash dot dot) in acetate buffer solution at (a) pH 3.5, (b) pH 4.0 and (c) pH 4.5

Similar behavior was also observed in the interaction of Cu(II) and Rab at pH 4.0 and 4.5 and it was observed that at 1:2 ratio of Cu(II) and Rab a strong interaction was occurred. Rab showed greater peak current compared to less acidic medium due to the protonation of Rab which is facilitated in more acidic medium than less acidic medium (McColl *et. al.*, 2009).

Conclusions

Voltammetric studies on redox reaction of Cu(II) and Cu(II) in presence of proton pump inhibitors (PPIs) such as omeprazole, pantoprazole, esomeprazole and rabeprazole in acetate buffer were studied at various pH (3.5, 4.0 and 4.5) at GCE. The CV of Cu(II) shows two cathodic peaks and an intense anodic peak in the studied pH. The peak potential separation and peak current ratio reveal that the redox process follows quasi-reversible reaction path. The electrode processes are diffusion controlled as indicated by linear behavior of i_p vs. $v^{1/2}$. The effect of pH on the redox behavior of Cu(II) revealed that with the increase of solution pH, the peak current increased. In presence of omeprazole for Cu(II), the anodic peak current decreased compared to solely Cu(II). However, the cathodic peak was completely disappeared. Moreover, anodic peak shifted significantly towards positive direction. This is an indication of strong interaction of Cu(II) and omeprazole. The maximum interaction is found at 1:2 ratio of Cu(II) and omeprazole at studied pH. Almost identical behavior was observed for the electrochemical interaction of Cu(II) and other PPIs.

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