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Interaction of Manganese(II) with Proton Pump Inhibitor at Different pH: A Cyclic Voltammetric Study

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Abstract

The electrochemistry of Mn^{2+} at different pH (3.5-4.5) in acetate buffer solution has been investigated, using cyclic voltammetric method at glassy carbon electrode (GCE). Cyclic voltammograms (CVs) of Mn^{2+} show two cathodic and an anodic peaks over the entire investigated pH. The CVs of Mn^{2+} has also been performed in presence of proton pump inhibitors (PPIs) such as omeprazole, pantoprazole, esomeprazole and rabeprazole to elucidate the interaction of Mn^{2+} with the PPIs in acetate buffer solution. At the studied pH, a reasonably strong interaction was observed between Mn^{2+} and PPIs at different molar ratio of Mn^{2+} ion and PPIs. However, maximum interaction has been found at 1:2 molar ratio of Mn^{2+} and PPIs. This indicates the most suitable condition for the interaction between Mn^{2+} and PPIs. These results could allow insight into the interactions of metal ions with the PPIs.

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

I. Introduction

A potential class of drugs with an excellent safety profile, proton pump inhibitors (PPIs) is widely used for the treatment of gastric-ulcer diseases[1-4]. PPIs are used comprehensively for the treatment of gastric acid-related disorders because they can produce a greater degree and longer duration of gastric acid suppression and thus, better healing rates, than histamine H_2 receptor antagonists[5-10]. PPIs are the most probable inhibitors of gastric acid secretion with a prospective to increase intragastric pH by several units, as well as hydrogen ion concentration by several hundred to thousand fold[11]. PPIs are substituted benzimidazoles and are lipophilic weak bases that cross the parietal cell membrane and enter the acidic parietal cell canaliculus[12]. 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[13]. 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[14]. Gastric nitrate rendering bacteria levels increase, as do carcinogenic nitrosamines in gastric juice. A pH of less than 3.8 allows gastric bacterial overgrowth[15]. 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, manganese and molybdenum. Most of the first row transition metals are important for enzymes[16]. They have one or both of two important properties: (i) some of them can be easily changed their oxidation state, (ii) acting as critical redox couples e.g. Fe(II)/Fe(III). 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 reactions[17]. Several studies on the synthesis, characterization and applications of Mn^{2+}-PPIs complexes has been reported elsewhere [12,18,19].

The cyclic voltammetric study of various metal ions in presence of ligand has been investigated in our laboratory and reported in detail[20,21]. We have therefore, started a wide ranging electrochemical studies of metal complexes of PPIs using cyclic voltammetry. In the present paper we report a study of the electrochemical interaction of Mn^{2+} 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).

II. Experimental

Materials and Methods

Analar grade manganese(II) perchlorate ($Mn(ClO_4)_2 . xH_2O$) 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 acetic 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 (CH Instruments Inc., USA; Model CHI 620D).

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Preparation of various solutions

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. Stock solution of 1.0 mM Mn^{2+} was prepared with analytical grade hydrated manganese(II) perchlorate salt with acetate buffer 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. The metal-ligand solutions for complexation reaction were prepared by mixing of identical 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

In the present work glassy carbon electrode (GCE) was used as 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.

III. Results and Discussion

Electrochemical redox behavior of Mn^{2+} 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. The results are described below.

Cyclic voltammetry of Mn^{2+} in acetate buffer solution

Cyclic voltammetric study of 1.0 mM Mn^{2+} in acetate buffer solution at different pH values was investigated at GCE within the potential window of +1200 to -1200 mV. Fig. 1(a), shows a CV of 1.0 mM Mn^{2+} in acetate buffer solution with scan rate of 100 mVs^{-1} at pH 4.0. In the forward scan two cathodic peak, i_{pc1} at about 475.90 mV and i_{pc2} at about -798.4 mV and in the reverse scan an anodic peak, i_{pa1} at about 994.80 mV were observed. The cathodic peaks result from the reduction of Mn^{2+} to Mn^+ and Mn^+ to Mn, and the anodic peak is for the oxidation of Mn to Mn^{2+}. The above result suggests that at pH 4.0 Mn^{2+} undergoes single step two-electron transfer redox reaction which is in good agreement with the previous work [Radhi *et al*., 2010]. The possible mechanism of the redox reaction is as follows:

For reduction half-reaction
$Mn^{2+} + e \rightarrow Mn^+$
$Mn^+ + e \rightarrow Mn$
For oxidation half-reaction
$Mn \rightarrow Mn^{2+} + 2e$

Effect of scan rate: The effect of the scan rate on the electrochemical response of Mn^{2+} under the identical condition (1.0 mM Mn^{2+} at pH 4.0) was examined by taking the CVs of Mn^{2+} with scan rate of 25, 75, 100, 125, 175 and 200 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_{pa1}/i_{pc1} is about (1.074-1.376). It is found that the peak current ratio was increased with the increasing of scan rate. Also the peak potential separation, ΔE_p is in between (357.10-570.40) mV. It is also increased with the variation of scan rate. These suggest that the redox couple Mn^{2+}/Mn^+ follows a 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.

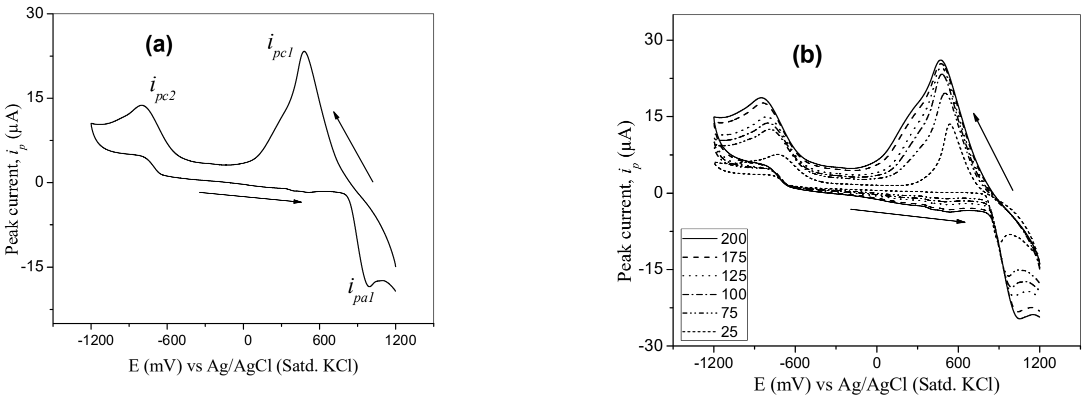

Fig. 1. (a) CV of 1.0 mM Mn^{2+} in acetate buffer solution at pH 4.0 with scan rate of 100 mVs^{-1} and (b) CVs of 1.0 mM Mn^{2+} at various scan rate: 25 (semi das), 75 (dash dot dot), 100 (das dot), 125 (dot), 175 (dash) and 200 (solid) mVs^{-1} at GCE.

In Fig. 2(a), it is apparent that the peak current for the electrochemical redox reaction of Mn^{2+} 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. 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 also suggest that the redox process is quasi-reversible reaction rather than a reversible reaction.

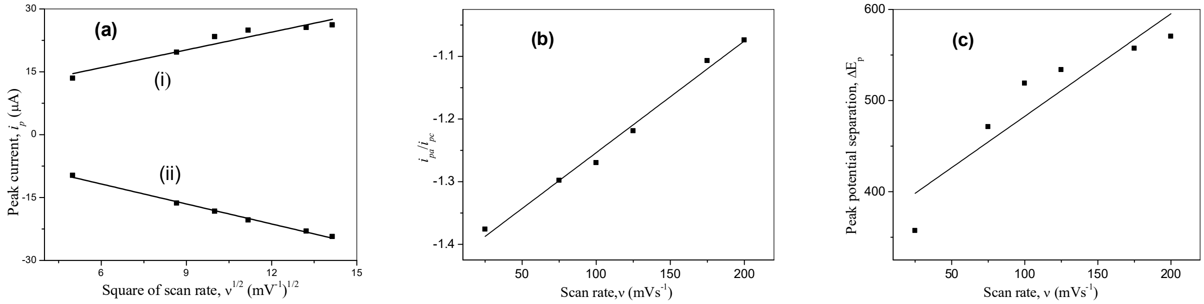

Fig. 2. (a) Plots of cathodic peak current (i) and anodic peak current (ii) as a function of square root of scan rate, (b) Peak current ratio (i_{pa1}/i_{pc1}) dependence on scan rate and (c) A plot of peak potential separation with scan rate for 1.0 mM Mn^{2+} at pH 4.0.

Effect of pH on the cyclic voltammograms of Mn^{2+}

The effect of pH (pH 3.5, 4.0 and 4.5) on the CVs of the redox reaction of Mn^{2+} in acetate buffer solution has been investigated as shown in Fig. 3. It is found that with the increase of pH intense cathodic peaks and distinguishable anodic peak are found. The data from the voltammograms are shown in Table 1.

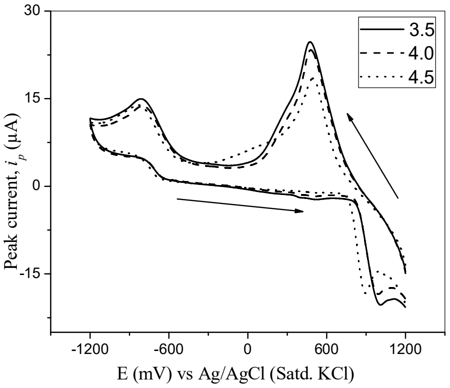

Fig. 3. CVs of 1.0 mM Mn^{2+} in acetate buffer solution at pH 3.5 (solid), pH 4.0 (dash) and pH 4.5 (dot).

Table 1. Peak potential and peak current for the voltammograms obtained from Mn^{2+} at different pH.

pH	Peak current, i_p μA			Peak potential, E_p mV			PPS mV
	i_{pc1}	i_{pc2}	i_{pa1} (-)	E_{pc1}	E_{pc2} (-)	E_{pa1}	$\Delta E=E_{pa1}-E_{pc1}$
3.5	24.66	14.83	20.31	467.80	817.3	1005.40	537.60
4.0	23.19	13.75	18.43	476.50	798.4	987.80	511.30
4.5	18.49	13.84	18.22	491.20	829.8	893.80	893.80

PPS = Peak potential separation

Cyclic voltammetry of Mn^{2+} in presence of omeprazole (Ome)

The electrochemical studies of the interaction of Mn^{2+} with Ome in acetate buffer at pH 3.5, 4.0 and 4.5 have been carried out. The cyclic voltammograms recorded for Mn^{2+}, and Mn^{2+} in presence of various molar concentrations of Ome (molar ratios of Mn^{2+}/Ome.; 1:1, 1:2, 1:3 and 1:4) are shown in Fig. 4. The voltammogram recorded for each ratio of Mn^{2+} and Ome, the peak current for both anodic and cathodic peaks decreased than those for free Mn^{2+}. Moreover, it is apparently found that the anodic peak and the cathodic peak are disappeared for different ratio at aforementioned three pH. The results suggest that there is an interaction between Mn^{2+} and Ome. It is obvious that a strong interaction occurs at 1:2 molar ratio of Mn^{2+} and Ome. However Ome showed small hump at acidic medium.

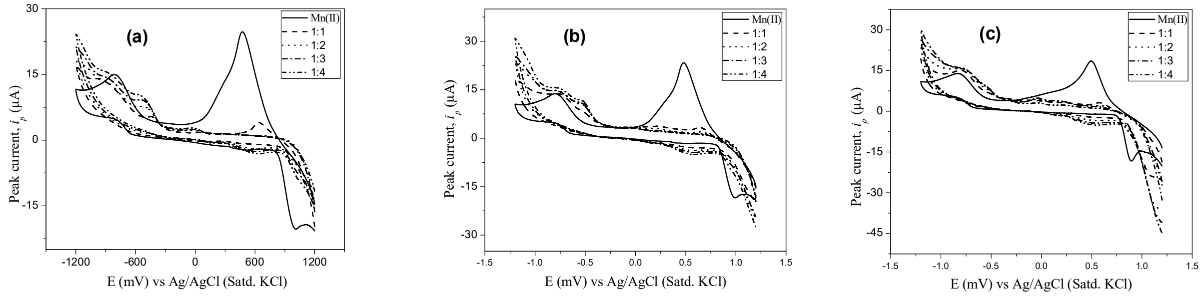

Fig. 4. CVs of Mn^{2+} (solid), and Mn^{2+}/Ome with different ratio (i) 1:1 (dash), (ii) 1:2 (dot), (iii) 1:3 (dash dot), and (iv) 1:4 (dash dot dot) in acetate buffer solution at (a) pH 3.5, (b) pH 4.0 and (c) pH 4.5.

Cyclic voltammetry of Mn^{2+} in presence of pantoprazole (Pan)

The electrochemical studies of the interaction of Mn^{2+} with Pan in acetate buffer at pH 3.5, 4.0 and 4.5 have been performed. The CVs recorded for Mn^{2+}, and Mn^{2+} in presence of various molar concentrations of Pan (identical molar ratio as before) are shown in Fig. 5. The voltammogram recorded for each ratio of Mn^{2+} and Pan, the peak current for both anodic and cathodic peak decreased than those for free Mn^{2+}. Additionally, it is apparently found that the anodic peak and the cathodic peak are disappeared for different ratio at pH 3.5, pH 4.0 and pH 4.5. The results suggest that there is an interaction between Mn^{2+} and Pan and a strong interaction occurs at 1:2 molar ratio of Mn^{2+} and Pan.

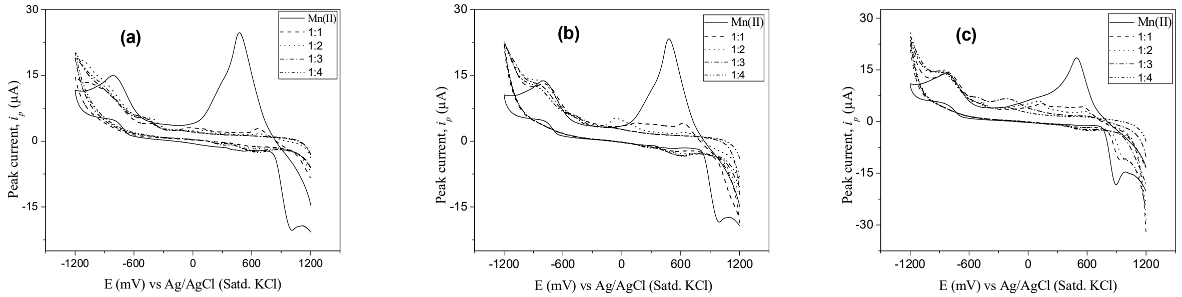

Fig. 5. CVs of Mn^{2+} (solid), and Mn^{2+}/Pan with different ratio (i) 1:1 (dash), (ii) 1:2 (dot), (iii) 1:3 (dash dot), and (iv) 1:4 (dash dot dot) in acetate buffer solution at (a) pH 3.5, (b) pH 4.0 and (c) pH 4.5.

Cyclic voltammetry of Mn^{2+} in presence of esomeprazole (Eso)

The electrochemical study of the interaction of Mn^{2+} with Eso in acetate buffer solution at pH 3.5, 4.0 and 4.5 has been carried out. The CVs recorded for Mn^{2+}, and Mn^{2+} in presence of various molar concentrations of Eso (mentioned previously) are shown in Fig. 6. The voltammogram recorded for each ratio of Mn^{2+} and Eso, the peak current for both anodic and cathodic peak decreased than those for free Mn^{2+}.

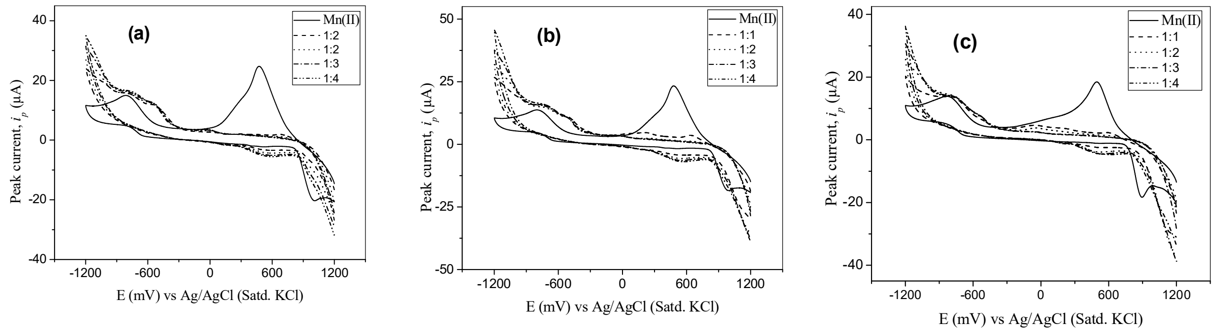

Fig. 6. CVs of Mn^{2+} (solid), and Mn^{2+}/Eso with different ratio (i) 1:1 (dash), (ii) 1:2 (dot), (iii) 1:3 (dash dot), and (iv) 1:4 (dash dot dot) in acetate buffer solution at (a) pH 3.5, (b) pH 4.0 and (c) pH 4.5.

In addition to that, it is apparently found that the anodic peak and the cathodic peak are disappeared for different ratio at aforementioned three pH. The results suggest that there is an interaction between Mn^{2+} and Eso and it is obvious that a strong interaction occurs at 1:2 molar ratio of Mn^{2+} and Eso.

Cyclic voltammetry of Mn^{2+} in presence of rabeprazole (Rab)

The electrochemical study of the interaction of Mn^{2+} with Rab in acetate buffer at pH 3.5, 4.0 and 4.5 has been carried out. The recorded CVs for Mn^{2+} and Mn^{2+} in presence of various molar concentrations of Rab (molar ratios of Mn^{2+} /Rab; 1:1, 1:2, 1:3 and 1:4) are shown in Fig. 7.

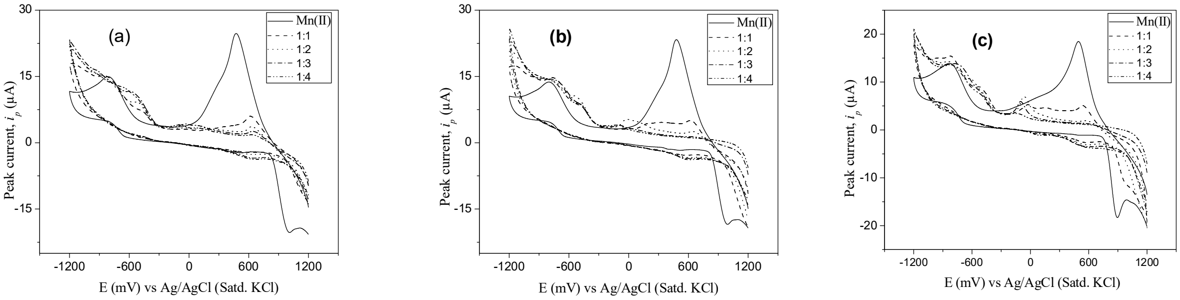

Fig. 7. CVs of Mn^{2+} (solid), and Mn^{2+}/Rab with different ratio (i) 1:1 (dash), (ii) 1:2 (dot), (iii) 1:3 (dash dot) and (iv) 1:4 (dash dot dot) in acetate buffer solution at (a) pH 3.5, (b) pH 4.0 and (c) pH 4.5.

The voltammogram recorded for each ratio of Mn^{2+} and Rab, the peak current for both anodic and cathodic peak decreased compared to those for free Mn^{2+}. Moreover, it is apparently found that the anodic peak and the cathodic peak are disappeared for different ratio at aforementioned three pH. The results suggest that there is an interaction between Mn^{2+} and Rab. From the Fig. 7, it is obvious that a strong interaction occurs at 1:2 molar ratio of Mn^{2+} and Rab.

IV. Conclusions

The interactions between Mn^{2+} and the proton pump inhibitors (PPIs) such as omeprazole, pantoprazole, esomeprazole and rabeprazole in acetate buffer solution has been investigated at various pH (3.5, 4.0 and 4.5) employing cyclic voltammetric technique at glassy carbon electrode. The CV of Mn^{2+} shows two cathodic peaks and an intense anodic peak in the studied pH. The peak potential separation and peak current ratio revealed that the redox process follows quasi-reversible reaction path. The effect of pH on the redox behavior of Mn^{2+} showed that with the increase of solution pH, the peak current increased. In presence of omeprazole for Mn^{2+}, the anodic peak current decreased compared to solely Mn^{2+}. However, the cathodic peak was completely disappeared. Moreover, anodic peak shifted significantly towards positive direction. This is an indication of strong interaction of Mn^{2+} and omeprazole. The maximum interaction is found at 1:2 molar ratio of Mn^{2+} and omeprazole at studied pH. Almost identical behavior was observed for the electrochemical interaction of Mn^{2+} and other PPIs. The electrochemical study of the interactions between metal ions and PPIs would provide important information for the technological application of PPIs in human body.

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