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# ELECTROCHEMICAL BEHAVIOUR OF OMEPRAZOLE INTERACTING WITH MYCIN DERIVATIVES AND DOXYCYCLINE

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**Keywords:**

Drug-drug interaction, Omeprazole, Antibiotic, Binding constant

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**ABSTRACT:** The interaction of omeprazole with different types of antibiotics was investigated in biological buffer at physiological pH=7.4 by using electrochemical (cyclic and linear sweep voltammetry) method. The reduction processes of omeprazole in the absence of and in the presence of azithromycin, clarithromycin, roxithromycin and doxycyclline are irreversible. Omeprazole interacts in solution with antibiotics structures by a predominantly electrostatic mechanism. From electrochemical data, The 1:2, 1:1, 1:1 and 1:2 complexes of azithromycin-omeprazole, clarithromycin-omeprazole, roxithromycin-omeprazole and doxycycline-omeprazole are formed with the binding constants $\beta$ = 3.930 (±0.15), 0.985 (±0.02), 0.321 (±0.01) and 8.230 (±0.21) $\mu M^{-1}$ respectively. The results show that, the binding affinity of omeprazole increases in the sequence: roxithromycin > clarithromycin > azithromycin > doxycycline.

**INTRODUCTION:** Different types of antibiotics, macrolide, penicillin, tetracycline and 5-nitroimidazole derivatives, are used in combination with proton pump inhibitors especially omeprazole for triple and quadruple therapy for the cure of *Helicobacter pylori* infection in duodenal ulcer patients.[1-8] Omeprazole (OMZ), (*RS*)-5-methoxy-2-((4-methoxy-3,5-dimethylpyridin-2-yl) methyl sulfinyl)-1*H*-benzo[*d*] imidazole (**Scheme 1**) is a substituted benzimidazole compound and a prototype anti-secretory agent, being the first "proton pump inhibitor" widely used for the prophylaxis and treatment of gastro-duodenal ulcers and for the treatment of symptomatic gastro-oesophageal reflux.

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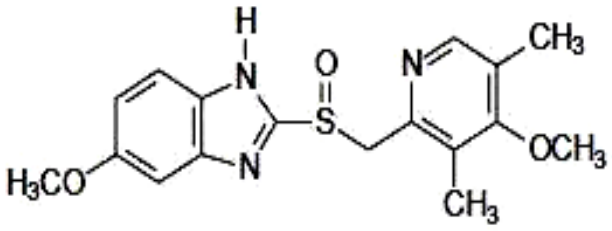
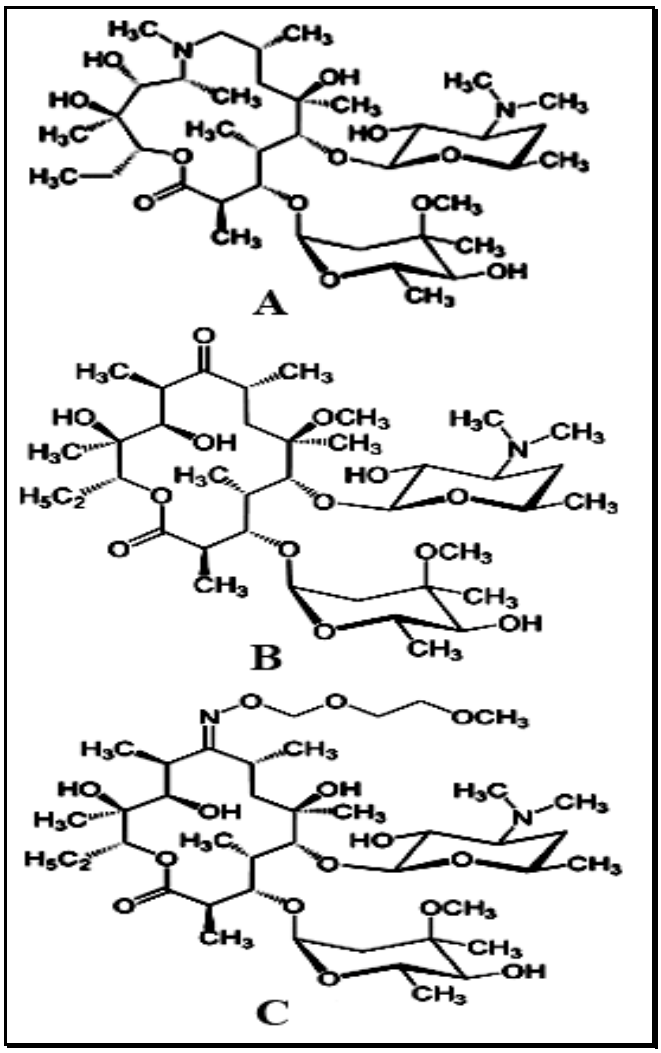
It acts by interacting with hydrogen/ potassium adenosine triphosphatase ($H^+/K^+$ ATPase) in the secretory membranes of the parietal cells and it is very effective in the treatment of Zollinger–Ellison syndrome.[9]




**SCHEME 1: THE STRUCTURE FORMULA OF OMEPRAZOLE**

Macrolides, including azithromycin (**Scheme 2A**), clarithromycin (**Scheme 2B**) and roxithromycin (**Scheme 2C**), belong to one of the most commonly used families of clinically important antibiotics which used to treat infections caused by gram-negative bacteria such as *Staphylococcus aureus*

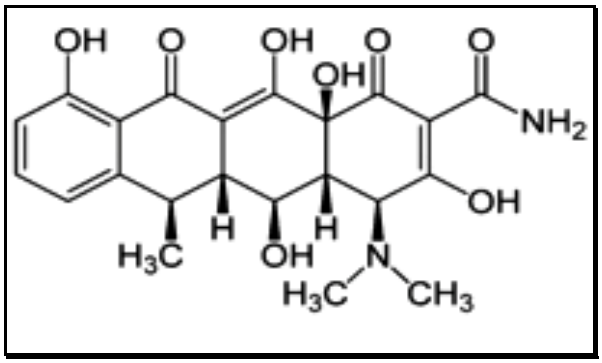
and *Streptococcus pneumonia*.[10] In general, the structures of the macrolide antibiotics contain a macrocyclic lactone and a neutral sugar moiety attached to the lactone. Another important structural characteristic is the presence of other sugar moiety containing a dimethylamine group which confers to the macrolides a basic behavior and makes them a potential n-electron donating substances.[11]




**SCHEME 2. THE STRUCTURE FORMULA OF A) AZITHROMYCIN, B) CLARITHROMYCIN AND C) ROXITHROMYCIN**

Penicillin, including amoxicillin, ampicillin and flucloxacillin, refers to a group of β-lactam antibiotics used in the treatment of bacterial infections caused by susceptible usually gram-positive, organisms.[12]

The tetracycline antibiotics, including doxycycline (**Scheme 3**), is active against a wide range of gram-positive and gram-negative bacteria, it is widely used in human and veterinary medicines as well as feed additives.[13]



**SCHEME 3. THE STRUCTURE FORMULA OF DOXYCYCLINE.**

Nitroimidazoles, including metronidazole and tinidazole, have been introduced as one of the most recognizable anti-microbial agents, regarding to their remarkable potency and relatively low toxicity. The members of this group have extremely useful clinical activity against anaerobic pathogens that include both gram-negative and gram-positive bacteria, in addition to the wide range of protozoans.[14]

Cephalosporins, including cefradine, ceftriaxone, ceftazidime, cefotaxime and cefoperazone, are penicillinase-resistant antibiotics with significant activity against both gram-positive and gram-negative bacteria. The key intermediate for semisynthetic production of a large number of cephalosporins is 7-aminocephalosporanic acid (7-ACA).[15]

Drug-drug interaction has become one of the major concerns not only for physician during the treatment of patients but also for pharmaceutical industries during the development of new drugs.[16]

Well-executed *in-vitro* studies can be used as a screening tool for further *in-vivo* assessment and can provide the basis for the design of subsequent *in-vivo* drug interaction studies.[17, 18] Recently, electrochemical investigation of drug–drug interactions can provide a useful complement to other methods and yield information about the mechanism of interaction.

Hence, this study was designed to study the *in - vitro* drug interaction of omeprazole with some

antibiotic mentioned above using linear sweep voltammetry and cyclic voltammetry in phosphate buffer at physiological pH=7.4.

## MATERIALS AND METHODS :

### Chemicals and Reagents

Omeprazole sodium (Sigma Chemical Co.) stock solution was prepared daily by dissolving it in bidistilled water at a concentration of [OMZ] = $1.00\times10^{-3}$ mol/L. Phosphate buffer (pH=7.4; 0.1 mol/L) was used as supporting electrolyte. Cefradine and ceftazidime are obtained from Orchid chemicals & pharmaceuticals Ltd (India). Cefoperazone, cefotaxime and ceftriaxone are obtained from Luna chemicals co., Ltd (China). Azithromycin and clarithromycin are obtained from Nexchem Ltd. (China). Roxithromycin, metronidazole, tinidazole and doxycycline hyclate are obtained from Cipla Ltd. (India). While amoxicillin trihydrate, ampicillin trihydrate and flucloxacillin sodium monohydrate are obtained from Ribbon pharmaceutical and chemical products co. (Italy). All pharmaceutical compounds were used without further purification.

### Instrumentation

Linear sweep voltammograms and cyclic voltammograms were obtained using an EG&G Princeton Applied Research Corporation (PAR) model 264A polarographic analyzer/stripping voltammeter, coupled with a PAR Model 303A, with a three-electrodes system consisting of a hanging mercury drop electrode (HMDE) as a working electrode, an Ag/AgCl sat'd KCl as a reference electrode and platinum wire as a counter electrode. The electrolytic cell is 10 ml. A PAR 305 stirrer is connected to the PAR 303A SMDE. A PAR model RE 0151 X-Y recorder is used to collect the experimental data.

The pH's is measured with Hanna microprocessor pH model 211.

### Procedure

The voltammetric measurements of each solution were carried out in a phosphate buffer pH=7.4 as supporting electrolyte. The accumulation potential of -0.45 V (vs. Ag/AgCl sat'd KCl) is chosen for electroanalytical process. The solutions were purged with nitrogen for 15 min before the commencement of the experiments and the purging time 30 s between each measurement. A nitrogen stream was blanketed over the solution during the recording of the voltammograms. A known volume of standard solution of analyte was added to the voltammetric cell deaerated and the linear sweep voltammograms was recorded at a scan rate 100 mV/s at room temperature (25±2°C).

## RESULTS AND DISCUSSION:

### Electrochemical behavior of omeprazole

Omeprazole is an electrochemically active drug with a sulfoxide group in its molecular structure, so it can be easily reduced at the Hg electrode. In our experiments, the cyclic voltammograms of omeprazole was recorded under the selected conditions and the result is shown in **Fig. 1**.

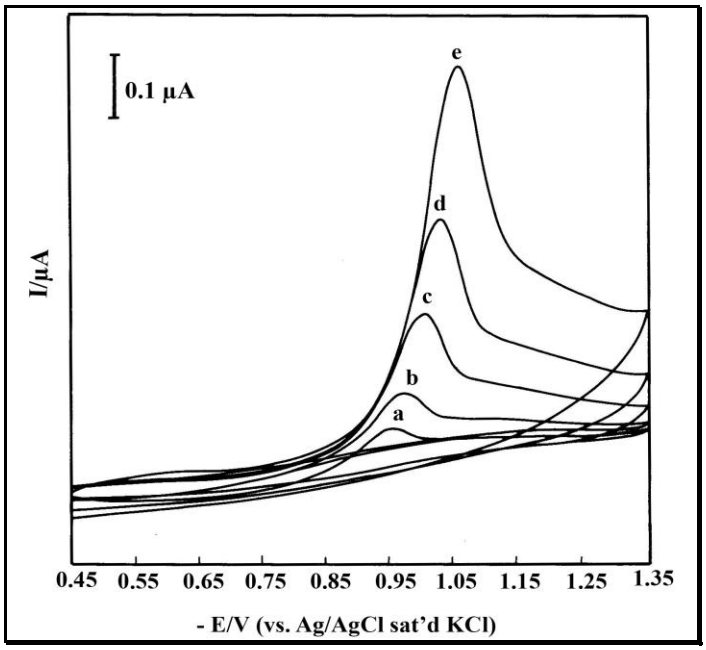



**FIG. 1: Cyclic voltammograms of $1.5\times10^{-6}$ mol/L omeprazole at various scan rates in 0.1 mol/L phosphate buffer solution pH=7.4, accumulation time 15 s scan rates: a) 10 b) 20 c) 50 d) 100 e) 200 $mVs^{-1}$.**

Omeprazole shows a reductive peak at -1.0 V and no oxidative peak, which indicates that the electrochemical behavior of omeprazole on the Hg electrode is irreversible. The proposed mechanism for omeprazole reduction, first a thioether is formed from the sulfoxide group with the consumption of two protons and two electrons transfer process, followed by the breaking of the C-S bond with consumption of two protons, two electrons transfer and 4- methoxy -2, 3, 5- trimethylpyridine and 2-mercapto -5- methoxybenzimidazole are formed.[19-22]

In our report, we have discussed the effect of accumulation potential, accumulation time, drop size, and scan rate. The chosen working conditions are: 0.1 mol/L phosphate buffer pH=7.4 is used as a supporting electrolyte, a potential of -0.45 V is adopted as the optimum accumulation potential, a time of 15 s is adopted as the accumulation time, drop size of medium, drop area 0.014 $cm^2$, scan rate for linear sweep voltammetry v = 100 $mVs^{-1}$.

The interaction of omeprazole with cefradine**,** ceftriaxone, ceftazidime, cefotaxime and cefoperazone cephalosporin antibiotic, amoxicillin, ampicillin and flucloxacillin penicillin antibiotics and metronidazole and tinidazole 5-nitroimidazole antibiotics is not observed under chosen conditions, while it is observed in cases of azithromycin, clarithromycin and roxithromycin macrolide antibiotics and doxycyclline tetracycline antibiotic, as will be described below.

**Electrochemical behavior of OMZ in the presence of antibiotics**

The electrochemical properties of azithromycin, clarithromycin, roxithromycin and doxycyclline on the mercury electrode have been studied. The azithromycin and roxithromycin are electrochemically inactive in the studied potential range, while clarithromycin is electrochemical active, yielding one peak due to the reduction of the carbonyl group in the C-9 position at -0.74 V.[23, 24] and also doxycycline is electrochemically active yielding two peak due to the reduction of the carbonyl group in the C-1 and C-11 positions at -1.2 and -1.33.[25]

When azithromycin, clarithromycin, roxithromycin and doxycyclline are individually added to the OMZ solution, significant decrease in peak current and slightly negative shift in peak potential of omeprazole is observed upon the individual addition of azithromycin, clarithromycin, roxithromycin and doxycyclline drugs. Furthermore, no new peaks are noticed in presence of azithromycin, clarithromycin, roxithromycin or doxycyclline in the same potential range.

**Fig. 2** displays linear sweep voltammograms of omeprazole in the absence and presence of roxithromycin at HMDE in phosphate buffer at physiological pH=7.4. On plotting the peak current ($i_p$) of omeprazole as a function of concentration of antibiotics (A, azithromycin, clarithromycin, roxithromycin and doxycyclline) as shown in **Fig. 3,** indicates that the decrease in peak current of omeprazole could be attributed to the formation of an electrochemically inactive omeprazole-azithromycin, clarithromycin, roxithromycin and doxycyclline complex.

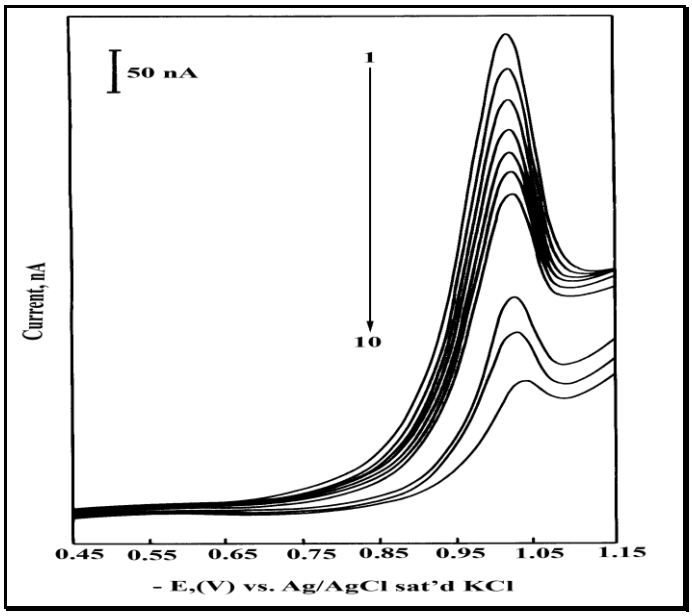



**FIG. 2: Linear sweep cathodic adsorptive stripping voltammograms of $1.5\times10^{-6}$ mol/L omeprazole in the absence (1) and presence of (2) 0.1 ; (3) 0.2; (4) 0.3; (5) 0.4; (6) 0.5; (7) 0.6; (8) 0.9; (9) 1.1; (10) $11.4\times10^{-6}$ mol/L roxithromycin in 0.1 mol/L phosphate buffer pH=7.4, scan rate 100 $mVs^{-1}$, accumulation time 15 s.**

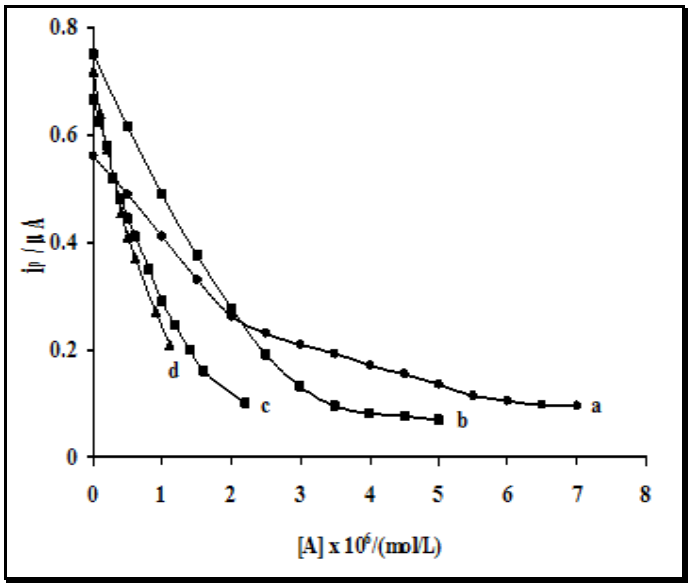



**FIG. 3: The dependence of peak currents of omeprazole on the concentration of azithromycin (a), doxycycline (b), clarithromycin (c)and roxithromycin (d). Other conditions were the same as in FIG. 2.**

This means that the omeprazole sulfoxide group, the redox-active moiety must bind tightly to azithromycin, clarithromycin, roxithromycin and doxycyclline molecules and then it loses its electroactivity.

The cyclic voltammetric (CV) behaviour of omeprazole in phosphate buffer pH=7.4, in the absence **(Fig. 1)** and the presence of azithromycin (**Fig. 4**), clarithromycin, roxithromycin and doxycyclline with scan rate varied from 10 to 200 $mVs^{-1}$, indicates that The reduction process of omeprazole showed only one cathodic peak in the absence and in the presence of azithromycin, clarithromycin, roxithromycin and doxycyclline.

On scanning in the positive direction, no oxidation peak is observed, indicating that the reduction processes of omeprazole in the absence and in the presence of azithromycin, clarithromycin, roxithromycin or doxycyclline are irreversible.

The CV experiments shows that both peak potential ($E_p$) and peak current ($i_p$) of omeprazole in absence and in presence of azithromycin, clarithromycin, roxithromycin and doxycyclline are dependent on the scan rate, v /$mVs^{-1}$.

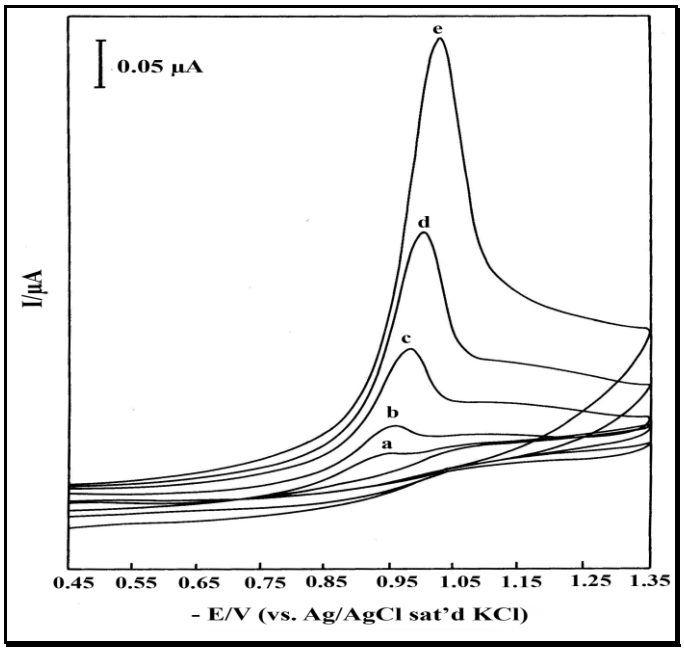



**Fig. 4: Cyclic voltammograms of $1.5\times10^{-6}$ mol/L omeprazole in presence of $3\times10^{-6}$ mol/L of azithromycin at various scan rates in 0.1 mol/L phosphate buffer solution pH=7.4, accumulation time 15 s scan rates: a) 10 b) 20 c) 50 d) 100 e) 200 $mVs^{-1}$.**

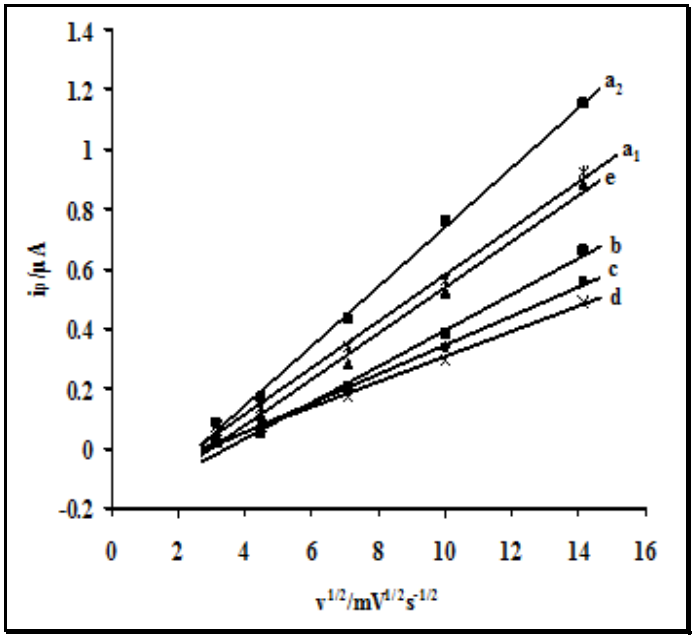



**FIG. 5: the relationship between $i_p$/µA and $v^{1/2}/mV^{-1/2}s^{-1/2}$ for $1.5\times10^{-6}$ and $1\times10^{-6}$ mol/L omeprazole in the ($a_1$ and $a_2$) absence and presence of $3\times10^{-6}$ mol/L azithromycin (b), $0.8\times10^{-6}$ mol/L clarithromycin (c) and $0.5\times10^{-6}$ mol/L roxithromycin (d) and presence of $3\times10^{-6}$ mol/L doxycycline (e) respectively**

According to the previous observations, it seems that the decrease in the peak current of omeprazole in presence of azithromycin, clarithromycin, roxithromycin and doxycyclline, which results in the considerable decrease in the apparent diffusion coefficient of omeprazole- azithromycin, clarithromycin, roxithromycin and doxycyclline complexes.

This is emphasized from the decrease in the slope of the linear plots of $i_p$/µA of omeprazole vs. $v^{1/2}/mV^{-1/2}s^{1/2}$ using CV in absence and in presence of azithromycin, clarithromycin, roxithromycin and doxycyclline as shown in **Fig. 5,** where the slope values are 0.0776±0.002, 0.0599±0.004, 0.0484±0.001 and 0.0422±0.001 µA $mV^{-1/2}s^{1/2}$ with correlation coefficient of lines are 0.9964, 0.9931, 0.9964 and 0.9977 in the absence ($1.5\times10^{-6}$mol/L omeprazole) and in the presence of $3\times10^{-6}$mol/L azithromycin, $0.8\times10^{-6}$ mol/L clarithromycin and $0.5\times10^{-6}$ mol/L roxithromycin respectively.

Where the slope values are 0.1073±0.003 and 0.0768±0.005 µA $mV^{-1/2}s^{1/2}$ with correlation coefficient of lines are 0.995 and 0.994 in the absence ($1x10^{-6}$ mol/L omeprazole) and the

presence of $3\times10^{-6}$ mol/L doxycycline respectively. From these values, the diffusion coefficient is calculated of free omeprazole and omeprazole-azithromycin, clarithromycin, roxithromycin and doxycyclline complexes. Where the diffusion coefficient ($D_f$) of the free omeprazole is found to be 2.335 ($\pm0.22$)$\times10^{-6}$ $cm^2s^{-1}$, whereas, $D_b$= 2.051($\pm0.13$ )$\times10^{-6}$, 1.844 ($\pm0.17$)$\times10^{-6}$ and 1.722 ($\pm0.21$)$\times10^{-6}$ $cm^2s^{-1}$ for bound omeprazole with azithromycin, clarithromycin and roxithromycin respectively, while the diffusion coefficient ($D_f$) of the free omeprazole is found to be 3.361 ($\pm0.32$)$\times10^{-6}$ $cm^2s^{-1}$, whereas $D_b$= 2.843 ($\pm0.27$)$\times10^{-6}$ $cm^2s^{-1}$ for bound omeprazole with doxycycline.

It can be seen that, the apparent diffusion coefficient of omeprazole-azithromycin, clarithromycin, roxithromycin and doxycyclline complexes are smaller than that of free omeprazole, indicating that the considerable decrease in the peak current of omeprazole observed upon addition of azithromycin, clarithromycin, roxithromycin and doxycyclline is due to the lower diffusion coefficient of omeprazole-azithromycin, clarithromycin, roxithromycin and doxycyclline complexes compared to that of the free omeprazole.

**Determination of the stoichiometry and binding constants**

To determine the composition of these supramolecular complexes and the binding constants, the method proposed by Li et al.[26-29] can be used. It is assumed that omeprazole and azithromycin, clarithromycin, roxithromycin and doxycyclline antibiotics (A) only produce a single complex A- nOMZ.

$$A + nOMZ \leftrightarrow A\text{-}nOMZ \quad (1)$$

The binding constant is

$$\beta = \frac{[A\text{-}nOMZ]}{[A][OMZ]^n} \quad (2)$$

and the following equations can be deduced:

$$\Delta i_{max} = K[A_t] \quad (3)$$

$$\Delta i = K[A\text{-}nOMZ] \quad (4)$$

$$[A] + [A\text{-}nOMZ] = [A_t] \quad (5)$$

$$\Delta i_{max} - \Delta i = K([A_t]-[A\text{-}nOMZ]) = K[A] \quad (6)$$

Introducing Equations 3–6 into Equation 2 leads to:

$$\log\left[\frac{\Delta i}{\Delta i_{max}-\Delta i}\right] = n\log(\beta) + n\log[OMZ] \quad (7)$$

Where $\Delta i$ is the peak current difference in the presence and absence of antibiotics, $\Delta i_{max}$ is the maximum peak current change. [$A_t$], [A-nOMZ], [A] and [OMZ] are referring to the total, drug-bound, free concentration of antibiotic in solution and concentration of omeprazole respectively. *K* is a constant value and n number of molecules of omeprazole bound to antibiotics.

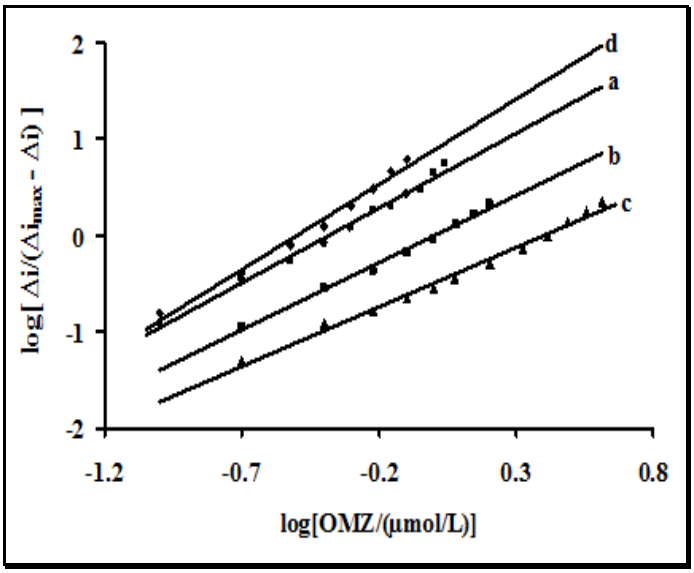



**FIG. 6: The relationship between $\log[\Delta i/(\Delta i_{max} - \Delta i)]$ and log [OMZ/(μmol/L)] in phosphate buffer of pH=7.4 solution containing azithromycin (a), clarithromycin (b), roxithromycin (c) and doxycycline (d).**

By keeping the concentration of each of azithromycin, clarithromycin, roxithromycin and doxycyclline at $1\times10^{-6}$ mol/L and varying the concentration of omeprazole, the plots of log [$\Delta i/(\Delta i_{max}-\Delta i)$] with log[OMZ/(μmol/L)] become linear, with slope equal to n and intercept equal to log $\beta$, as shown in **Fig. 6**.

From lines in **Fig. 6**, we obtain the following results: the number of molecule n = 2, 1, 1 and 2 of omeprazole bound to one molecule of azithromycin, clarithromycin, roxithromycin and doxycyclline respectively, where the binding constant $\beta$ = 3.930 ($\pm0.15$), 0.985 ($\pm0.02$), 0.321 ($\pm0.01$) and 8.230 ($\pm0.21$) $\mu M^{-1}$ for azithromycin, clarithromycin, roxithromycin and doxycyclline complexes with omeprazole respectively.

This indicate the formation of a 1:2, 1:1, 1:1 and 1:2 complexes of azithromycin, clarithromycin,

roxithromycin and doxycycline with omeprazole respectively.

**Discussion of the interaction mechanisms of omeprazole and antibiotics**

The electrochemical methods show that mixing azithromycin, clarithromycin, roxithromycin or doxycycline, the peak current of omeprazole decreases obviously, and no new peak is obtained, which means the antibiotics-nOMZ is formed. And the formation of antibiotics-nOMZ complex results in the negative shift of apparent standard potential of omeprazole which should be attributed to electrostatic interaction.[30-32]

The other evidence for electrostatic interaction is that azithromycin, clarithromycin, roxithromycin and doxycycline contains two tertiary amine groups, one tertiary amine group, one tertiary amine group and two amine groups, one primary amine group and one tertiary amine group, respectively which are protonated and positively charged in aqueous solution.[11]

However, omeprazole contains sulfoxide group which has an electrostatic aspect, resulting in significant dipolar character, with negative charge centered on oxygen and the positively charged sulfur atom.[33, 34]. So that it would be easy to bind together by electrostatic attraction to form a super-molecular complex. From the foregoing results, we suggested that, the most probable mechanism for the interaction of each of azithromycin, clarithromycin, roxithromycin and doxycycline with omeprazole under chosen conditions is electrostatic attractions.

**CONCLUSION:** The mechanism of the interaction between omeprazole and azithromycin, clarithromycin, roxithromycin and doxycycline is proposed to be the electrostatic mode. Occurrence of such interactions can impair the clinical efficacy of both drugs and reduce their bioavailability. Therefore it can be inferred that cautions should be exercised during administration of these drugs, although a detail *in vivo* experiment would be necessary to get a clear idea about the therapeutic properties of these drugs.

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