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REDUCTION OF FAMOTIDINE AT A MERCURY ELECTRODE USING SQUARE-WAVE VOLTAMMETRY

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Abstract

Famotidine is an electroactive and a surface-active compound which can be irreversibly reduced at a mercury electrode in moderate acidic media at the potential of about -1.20 V vs Ag/AgCl (KCl sat.). Square-wave voltammetry of this reaction can be utilised for a quantitative determination of the drug.

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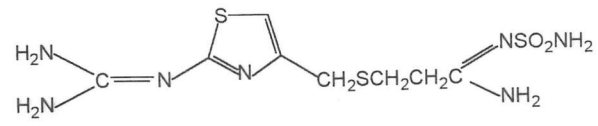
Introduction

Famotidine is a very effective drug which has been frequently used in the therapy of gastrointestinal ulcers [1-3]



It was recently reported by Squella at al. [4] that famotidine can be irreversibly oxidized on a glassy-carbon electrode and a method for its electroanalytical determination in pharmaceutical preparations has been proposed. We now demonstrate that famotidine can be reduced on a HMD electrode in an acidic medium. Additionally, it was found that famotidine molecules can be adsorbed on the mercury surface, prior to the redox reaction that takes place. Upon this feature of the redox mechanism of famotidine at the mercury electrode, an adsorptive stripping electroanalytical method for its quantitative determination is proposed. In comparison with solid electrodes, the mercury electrode is fairly more suitable for analytical application due to its renewable surface and low sensitivity to the contamination by the adsorbed products of a redox reaction.

Experimental

Famotidine (N-sulfamyl-3-[(2-guanidinethiazol-4-il)methyl-thio] propionamide) ("Henkel KGaA"), KNO_3, H_2SO_4 and CH_3OH (Merck, analytical grade) were used as received. Water was doubly distilled. A stock solution with concentration of famotidine of 0.01 mol/l was prepared in 96 % methanol. Supporting electrolyte was 1 mol/l KNO_3 and in order to achieve a low pH value of the supporting electrolyte solution, a certain amount of 1 mol/l H_2SO_4 solution was added. Voltammetric measurements were performed with a multimode polarograph PAR 384B and PAR 303A Static Mercury Drop Electrode Assembly (Princeton Applied Research). The auxiliary electrode was a Pt wire and Ag/AgCl (KCl-saturated) was the reference electrode. The surface area of the working mercury drop electrode was $S = 0.015\ cm^2$. All the measurements were performed at room temperature. Extra pure nitrogen was purged through the solutions for 8 minutes prior to each measurement and a nitrogen blanket was maintained thereafter.

Results and Discussion

In moderate acidic medium (pH 2) famotidine undergoes totally irreversible reduction at a mercury electrode within the potential range from -1.15 to -1.30 V as it is indicated by the cyclic and square-wave voltammograms which are shown in Fig. 1.

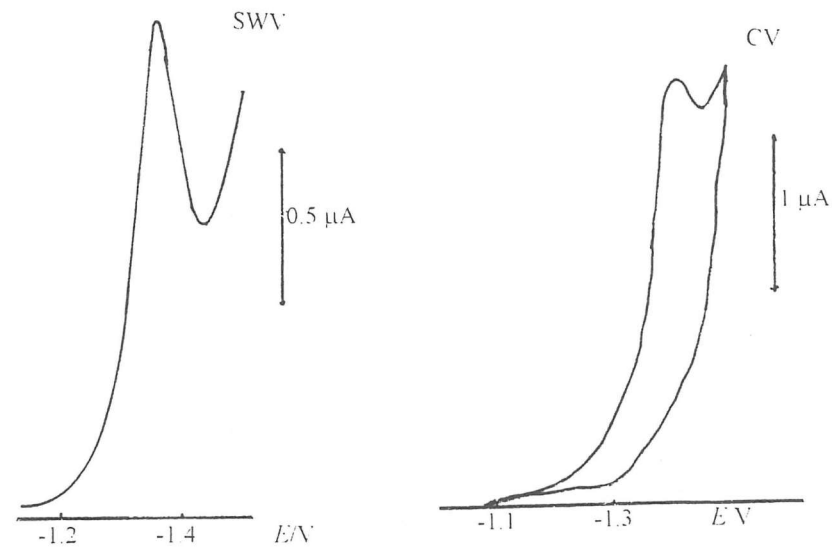


Fig. 1 Square-wave and cyclic voltammogram of 1.5×10^{-4} mol/l famotidine in 1 mol/l KNO_3 buffered to pH 2 on a hanging mercury drop electrode. Sweep rate of 0.2 V/s for CV voltammetry; f = 40 Hz, E_{sw} = 2 mV and dE = 2 mV for SW voltammetry.

The SW peak currents and peak potentials are pH dependent. The peak potentials are shifted in negative direction with the increase of pH, while the peak currents are markedly diminished (Table 1). Therefore, the most suitable conditions for measurements of famotidine lay in the pH range of 1 to 2.

Table 1. Dependence of the SW response of famotidine on the pH of the medium. Concentration of famotidine of 5×10^{-5} mol/l, frequency f = 50 Hz , amplitude E_{sw} = 10 mV and scan increment dE = 2 mV

pH	$-E_p$/V	I_p/μA
1.5	1.154	2.415
2.0	1.200	2.180
2.8	1.234	2.010
3.8	1.224	0.196
4.5	1.196	0.087

The SW response also depends on the concentration of famotidine. As can be seen from the Fig. 2, the peak current is linearly dependent on the concentration of famotidine within the concentration range of 5×10^{-5} - 8×10^{-4} mol/l. Moreover, the concentration of famotidine markedly affects the shape of the SW voltammograms.

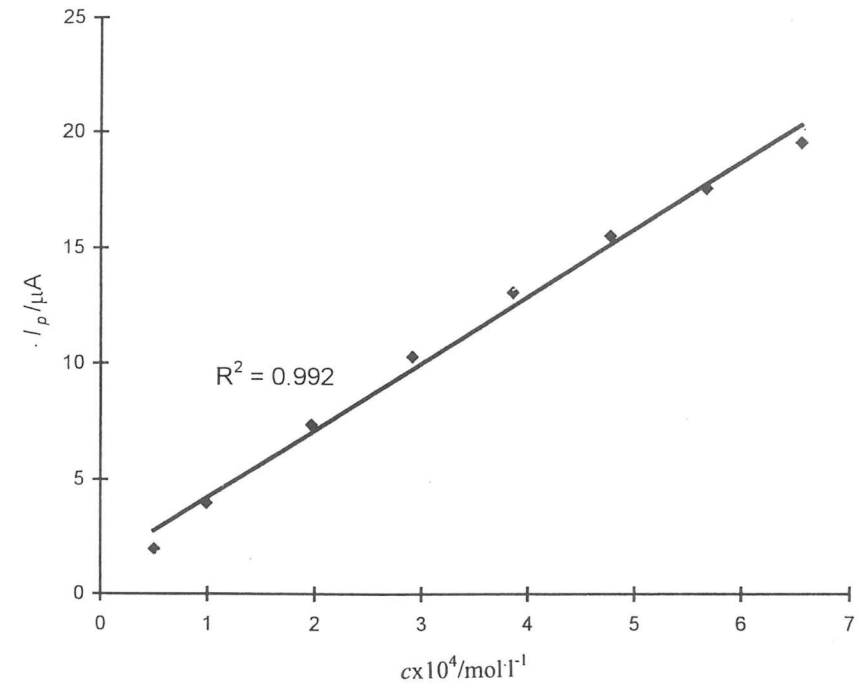


Fig. 2 Dependence of the SW peak currents on the famotidine concentration in 1 mol/l KNO_3 with pH 2, f = 50 Hz, E_{sw} = 10 mV and dE = 2 mV.

As can be seen from Fig. 3, an increase of the concentration of famotidine is accompanied by the enhancement of hydrogen evolution together with a shift of the H^+ reduction peak to more positive potentials. Literature data confirmed that redox reaction of hydrogen ion at various electrodes can be catalyzed by the presence of weak organic bases [5] and famotidine can be included in this type of organic compounds. A similar effect was previously observed by A. Webber at all. in the investigation of cimetidine [6]. Interestingly, cymetidine and famotidine have similar pharmacological and physiological activities. It should, however, be pointed out that the ability of famotidine to catalyze the redox reduction of hydrogen ions has negative consequences from an analytical point of view. Indeed, at famotidine concentrations higher than $8x10^{-4}$ mol/l, these two redox processes occur at rather close potential and cannot be separated.

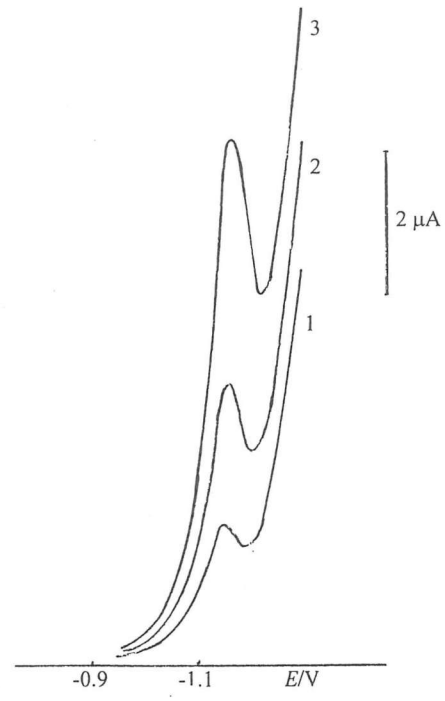


Fig. 3. SW voltammograms of $5x10^{-5}$ mol/l (1), $1x10^{-4}$ mol/l (2) and $2x10^{-4}$ mol/l (3) famotidine solutions.-For other parameters see caption in Fig. 2.

In order to achieve the best defined SW response of famotidine which could be useful for analytical purposes an optimization of the instrumental parameters such as frequency f, amplitude E_{sw} and scan increment dE of the SW signal was attempted. An increase of these parameters resulted in an enhanced peak current for famotidine. The peak potentials are shifted towards negative values upon increasing the frequency, while increasing the amplitude of the SW signal, produced the opposite effect. In addition, the SW peak of famotidine becomes wider upon increasing both frequency and amplitude. For instance, if the amplitude was larger that 50 mV, the SW peak became rather broad, and unsuitable for analytical purposes. It should also be noticed, that all these instrumental parameters affected the current for the reduction of hydrogen ions. Hence, the separation between the peak potential for famotidine and that for hydrogen evolution diminished with the increase of these parameters. From the analytical point of view, the best response (maximal value of the relation $I_p/E_{p/2}$) was achieved with 50 Hz frequency, 10 mV amplitude and 2 mV scan increment.

Famotidine is both an electroactive and a surface active compound. The dependence of the SW peak currents on the accumulation time is presented in Fig. 4. It is obvious that above 60 s accumulation time, the peak currents remain almost constant indicating that the electrode surface is saturated with adsorbed material.

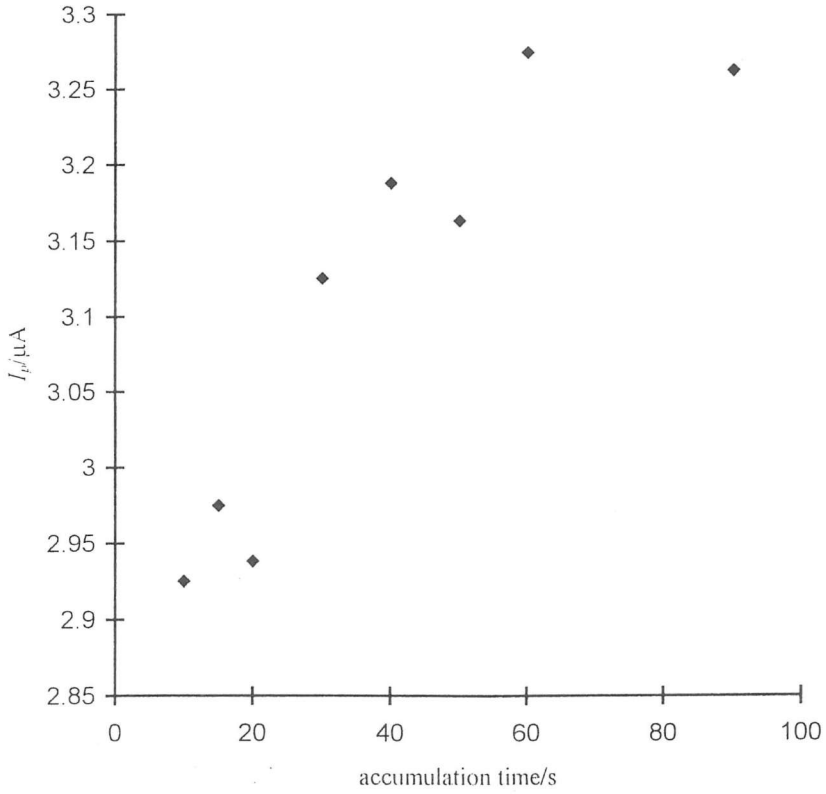
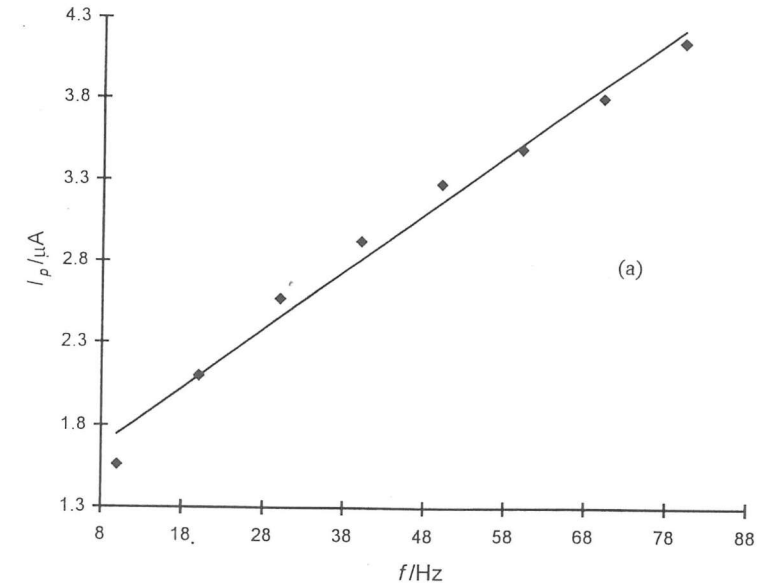


Fig. 4 Dependence of the SW peak currents of famotidine on the adsorptive accumulation time in unstirred solutions; accumulation potential of -0.80 V and concentration of famotidine of $5x10^{-5}$ mol/l. For other parameters see caption in Fig. 2.

Besides, the linear dependence of the peak current on the SW frequency and amplitude (Fig. 5), are consistent with the theory of the SW voltammetry of surface redox processes [7]. All these results, indicate that the redox process of famotidine at mercury electrode was preceded by its adsorption onto the electrode surface.



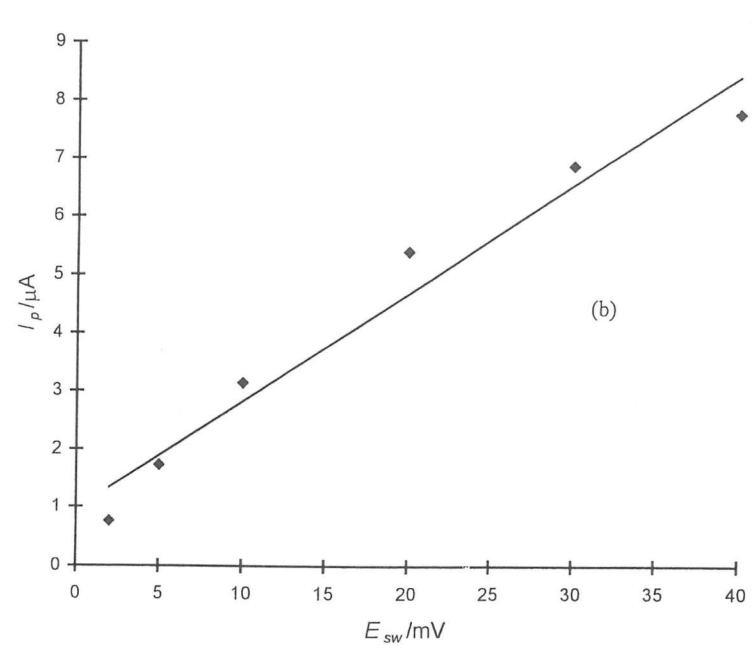


Fig. 5 Dependence of the SW peak currents of famotidine on the SW frequency (a) and SW amplitude (b) in unstirred solutions. Accumulation time of 30 s, accumulation potential of -0.80 V and concentration of famotidine of $5x10^{-5}$ mol/l. For other parameters see caption in Fig. 2.

According to theoretical predictions [7], the product αn can be calculated from the half-width of the SW peak by using equation (1) [7]. In the case of famotidine, the average half-width of its SW peak is 123 ± 10 mV. Using this data the product αn = 0,52 ± 0.04 has been estimated.

$$\Delta E_{p/2} = (63.5 \pm 0.5)/\alpha n \qquad (1)$$

Adsorption ability of famotidine can be useful for its determination in trace level. Concentrations of famotidine at submicromolar level can be measured by adsorptive accumulation intensified by mechanical stirring of the solutions. However, the larger the amount of the adsorbed molecules of famotidine onto the electrode surface, the stronger the effect on the reduction current of the hydrogen ions. For instance, if the concentration of famotidine is of about $5x10^{-5}$ mol/l and accumulation time longer than 100 s, these two competitive processes are overlapped. So far, it is obvious that the potential difference between these two processes appears to be the main limitation of the voltammetric method for determination of famotidine with SW voltammetry.

The refered potential separation can be improved by adding a certain amount of methanol to the solution. The effect of methanol on the SW response of famotidine is presented in the Fig. 6. It can be seen that the larger the amount of methanol, the better the peak of famotidine is defined. However, methanol adsorbs on the mercury electrode itself, which results in a decrease of the peak currents of famotidine. For instance, when the amount of methanol is larger than 20 % (volummetric part), the peak currents of famotidine proportionally decrease with accumulation time. It was found that 10 % of methanol in the electrolyte solution provides the best conditions for determination of famotidine.

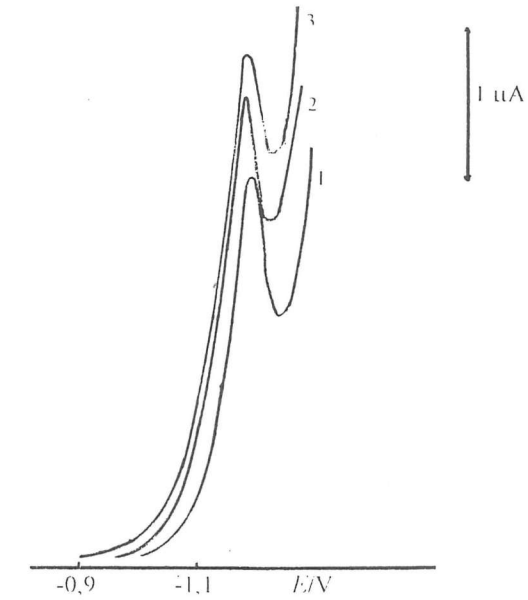


Fig. 6 SW voltammograms of $5x10^{-5}$ mol/l famotidine recorded in the presence of 20 % (1) and 10% (2) of methanol and without methanol (3) in unstirred solutions. Accumulation time of 30 s and accumulation potential of -0.80 V. For other parameters see caption in Fig. 2.

The amount of famotidine at submicromolar level ($5x10^{-7}$ mol/l) was measured with adsorptive accumulation performed by mechanical stirring of the solutions for 30 s and in the presence of methanol. The dependence of the peak currents on the concentration of famotidine in the range of $5x10^{-7}$ - $5x10^{-6}$ mol/l is presented in the Fig. 7. If the concentration of famotidine was in the range of $6x10^{-6}$ and $5x10^{-5}$ mol/l, 30 s accumulation time, without stirring of the solutions, provided sufficient sensitivity. Above this concentration range, famotidine could be measured without applying any accumulation time.

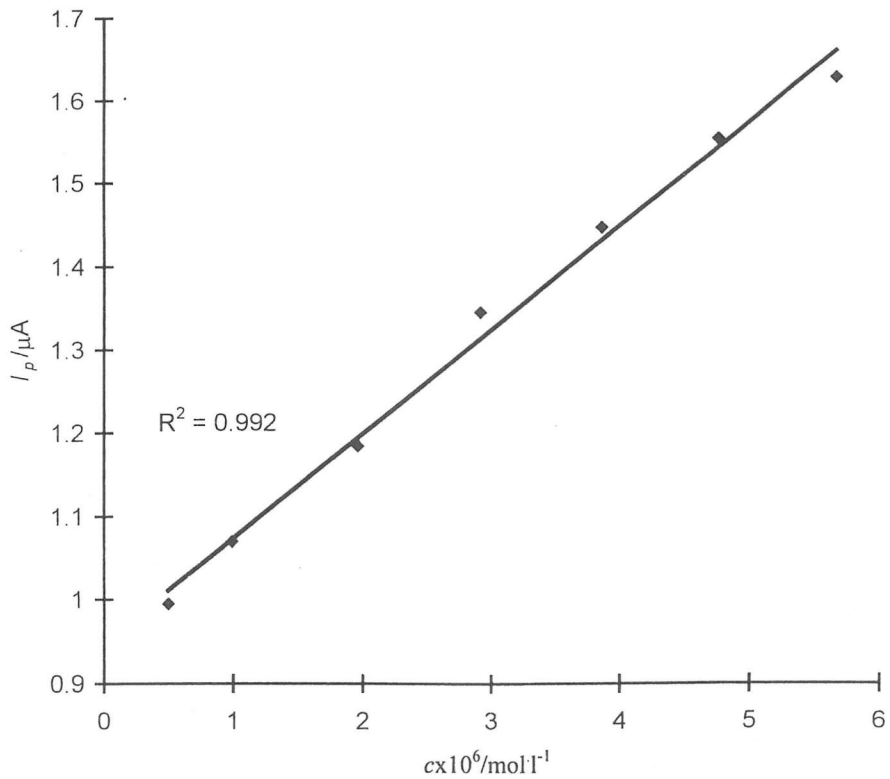


Fig. 7 Dependence of the SW peak currents on the famotidine concentration. Accumulation time of 30 s and accumulation potential of -0.80 V in 1 mol/l KNO_3 with 0.1 volummetric part of methanol in a stirred solution. For other parameters see caption in Fig. 2.

According to the literature data, a double bond R-CH=NH is reducible to R-CH_2-NH_2 at -1.20 V vs. SCE on the mercury electrode in Britton-Robinson buffer pH 3 [8-10]. The cleavage of Ar-SO_2-NH_2 bonds occurs between-1.6 V and -1.8 V vs. SCE in aqueous electrolyte solutions buffered to pH 9. The products are ArH, HSO_3^- and NH_4^+ [11]. The sulfide linkage -CH_2-S-CH_2- is not reducible in aqueous solutions [12]. However, the exact characterization of famotidine reduction process was not possible without the isolation of the reaction products.

Conclusion

Famotidine is both an electroactive and a surface active compound. It can be adsorbed at the HMD electrode surface and irreversibly reduced within the potential range of -1.15 to -1.30 V vs Ag/AgCl depending on the pH of the medium. This electrode reaction has been explored for determination of famotidine by square-wave voltammetry. The best voltammetric response was obtained in acidic medium (pH 2) with frequency f = 50 Hz, amplitude E_{sw} = 10 mV and scan increment dE = 2 mV.

Hydrogen evolution, which starts at a potential close to that of famotidine reduction, is catalysed by the presence of famotidine molecules at the electrode surface. Under certain experimental conditions these two competitive redox reactions can be overlapped which is a limitation of the presented voltammetric method. This disadvantage can be partially eliminated by adding methanol to the supporting electrolyte solution. Hence, the determination of famotidine at submicromolar concentration level ($5x10^{-7}$ - $5x10^{-6}$ mol/l) is possible in a 10 % (volummetric parts) solution of methanol in 1 mol/l KNO_3, with adsorptive accumulation performed by mechanical stirring of the solutions for 30 s.

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