Colloids and Surfaces A: Physicochem. Eng. Aspects 337 (2009) 74–79

Contents lists available at ScienceDirect

Colloids and Surfaces A: Physicochemical and Engineering Aspects

journal homepage: www.elsevier.com/locate/colsurfa

# Effect of surfactant on voltammetric behaviour of ornidazole

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ARTICLE INFO

*Article history:*
Received 19 June 2008
Received in revised form
24 November 2008
Accepted 28 November 2008
Available online 6 December 2008

*Keywords:*
Ornidazole
Solubilized systems
Pharmaceutical formulation
Surfactant
Voltammetry

ABSTRACT

The objective of the present work is to develop a voltammetric method for the determination of ornidazole in pharmaceutical formulations and it also deals with the beneficial use of surfactants in the catalysis of electrode reactions. The proposed method is rapid and sensitive for the qualitative and quantitative analysis of ornidazole in solubilized systems. The voltammetric behaviour of ornidazole has been studied in different surfactant media viz., anionic, cationic, non-ionic surfactants over the pH range 2.5 to 12.0 in phosphate buffer (0.2 M). Addition of non-ionic surfactant (Tween 20) to the ornidazole containing electrolyte enhanced the reduction current signal while the anionic surfactant sodium lauryl sulphate and cationic surfactant cetyltrimethylammonium bromide showed a small enhancement in peak current. The mechanism of reduction has been postulated on the basis of controlled potential electrolysis, coulometry and spectral analysis. The reduction process is irreversible and was diffusion controlled. Analytical method with adequate precise and accuracy was developed for the determination of ornidazole with linear concentration range $4.0 \times 10^{-3}$ to $4.0 \times 10^{-6}$ mol $L^{-1}$. The lower limit of quantification (LOQ) and the lower limit of detection (LOD) were found to be $1.2 \times 10^{-6}$ and $3.6 \times 10^{-7}$ mol $L^{-1}$ respectively. The analysis of ornidazole in its pharmaceutical formulation exhibited the mean recovery of 98% for the reduction peak.



## 1. Introduction

Nitrohomocycles and nitroheterocycles constitute a large group of drugs, with antibacterial, antiprotozoan and anticancer activities involving the reduction of nitro group [1]. Nitroimidazole derivatives posses toxic selectivities to anaerobic microorganism[2]. The derivatives contain 5-imidazole nucleus with substituents at the N1 position of the heterocyclic aromatic ring. The selective action of these drugs depends on the standard potential of the nitro compounds/anion radical system $R–NO_2/R–NO_2$. In view of the similarities between electrochemical and enzymatic reactions [3], elucidation of the mechanism of the electroreduction of these compounds is of great biological interest.

Ornidazole 1[(2-hydroxyethyl) chloromethyl]-2-methyl-5-nitro-1H-imidazole (Scheme 1) is used in the treatment of hepatic and intestinal amoebiasis, giardiasis, trichomoniasis of the urogenital tract and bacterial vaginosis. In vivo, any amino metabolite of such drugs has not yet been detected in free form. It seems that their cytotoxicity is not due to the final reduction products, but due to the formation of a unstable intermediate, possibly an anion radical, at a lower reduction level than would correspond to a complete reduction [4]. Studies of the mechanism of action of nitroimidazoles showed that the reduction pathway is more complex than is usually postulated for the elecroreduction of aromatic nitro compounds[5]. For these reasons, elucidation of the mechanism of electroreduction of ornidazole and related compounds is of biological interest.

Very few electrochemical studies have been made on this compound. Sankar and Reddy [6] reported that ornidazole produces a single cathodic peak at dropping mercury electrode. Lopez Fonseca et al. [7] discussed the electrochemistry of ornidazole by normal pulse polarography. Studies of the electroreduction of ornidazole have been also limited only to its voltammetric investigation in non aqueous media [8,9]. Barety et al. [10] studied the electro reduction of nitroimidazole derivatives in dimethyl sulphoxide where a radical anion is formed in a first electron uptake at the platinum rotating disc electrode. Some other techniques including spectrophotometric [11], HPLC with UV–vis detection [12], flow injection chemical luminescence [13], have been reported for the determination of ornidazole in pharmaceutical and biological fluids. The above mentioned methods suffer from poor sensitivity and detection limit. The ornidazole molecule has electro active group but nothing appears to have been published concerning its electrochemical behaviour in presence of surface active agents. There are certain advantages associated with this method such as dissolution, high selectivity, no interference from other active compounds present in commercial dosage form. The development of meaningful dissolution procedure for drug products with limited water solubility has been a great challenge to analyst [14–16]. It has been seen that surfactant

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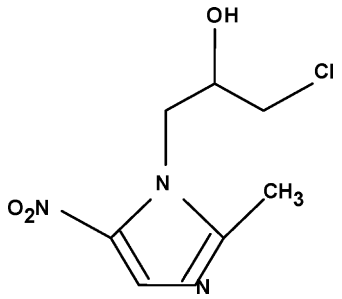
doi:10.1016/j.colsurfa.2008.11.054




**Scheme 1.** Structural formula of ornidazole.

play a very important role in electrode reactions, not only in solubilizing [17–19] organic compounds but also by providing specific orientation of the molecules at the electrode interface. Surfactants [20] are included as excipients in many drug formulations, with the objective of improving dissolution rate and increasing drug solubility. These aims are based on the ability of surfactants to reduce interfacial tension and contact angle between solid particles and aqueous media, thus improving drug wettability and increasing surface availability for the drug dissolution.

Aqueous micellar solutions are surfactant based self organized systems [21] that can be used as less hazardous and versatile substitutes for organic solvent in voltammetry, HPLC separation [22] and in electrochemical analysis [23,24]. The amphiphilic structure of surfactants and their assembly in aqueous solution provides a multifunctional environment for the solubilization and partitioning of aqueous soluble and insoluble compounds.

In the present study, the effect of the changing the charge of the surfactant used, namely anionic, non-ionic, cationic, its concentrations with the solution pH and concentration of analyte on the voltammetric response of this drug has been studied. The purpose of the present voltammetric studies have been to study the redox behaviour of ornidazole by employing different voltammetric techniques and to establish the methodology for there determination in presence of surfactants by using differential pulse polarography and cyclic voltammetry in bulk form and its pharmaceutical formulations.

## 2. Experimental

### 2.1. Reagents and materials

Ornidazole (99% pure) was a gift from Aristo pharmaceuticals (India). Tablet containing ornidazole (Ornida-500) labeled 500 mg. were obtained from commercial sources. Potassium chloride (1.0 M) solution was prepared in distilled water and used as supporting electrolyte. A stock solution of ornidazole $2.0 \times 10^{-2}$ M was prepared in different percentage of Tween-20 and acetonitrile solution. The solutions for recording voltammograms were prepared by mixing appropriate volume of stock solutions and buffers of varying pH. A series of phosphate buffers in the range of 2.5–12.0 were prepared.

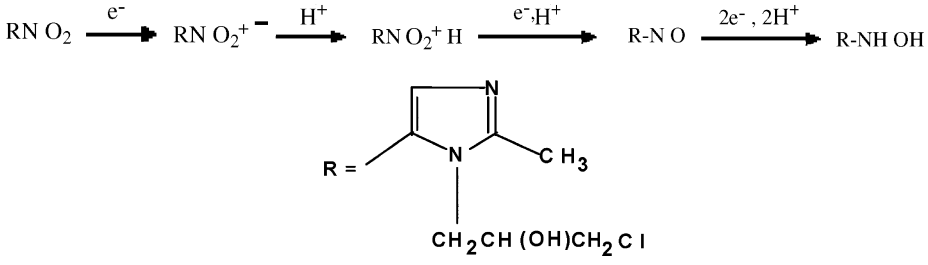
### 2.2. Instrumentation

The differential pulse polarographic (DPP) measurements were carried out using ELICO CL 362 Polarographic analyzer. The drop time of 1 s was electronically controlled using a 663 VA stand from the company. The polarograms were recorded using a potential rate of 100 mV $s^{-1}$. A three electrode system composed of a dropping mercury electrode (DME), saturated calomel electrode (SCE) as reference electrode and platinum wire as an auxillary electrode was used. The solutions were purged with pure nitrogen gas for 10 min and then polarographed at ambient temperature.

Cyclic voltammetric experiments were performed using EG & G PAR Model 273 A Potentiostat controlled by 270/250 electrochemistry software 4.30. A three electrode system was composed of a glassy carbon, working electrode ($\varphi$ = 2 mm EG &G/PAR), Ag/AgCl reference electrode and platinum wire as an auxillary electrode. To provide a reproducible active surface and improve the sensitivity and resolution of the voltammetric peaks, the working electrode was polished with 0.5 μm alumina powder on a polishing cloth prior to each electrochemical measurement. Then it was thoroughly rinsed with methanol and double distilled water and gently dried with a tissue paper. The electrode cleaning procedure required only 2 min. All the solutions examined by electrochemical techniques were purged for 10 min with purified nitrogen gas after which a continuous stream of nitrogen was passed over the solutions during the measurements. All measurements were carried out at room temperature (25 ± 0.1 °C). The pH metric studies were carried out on Decible, Db-1011 digital pH meter fitted with a glass electrode and saturated calomel electrode as a reference electrode, which was previously calibrated with buffer of known pH.

### 2.3. Procedure

The amount of Ornidazole present in each tablet was 500 mg. Excipients such as microcrystalline cellulose; lactose and titanium dioxide were added to dosage forms. The mass of ten tablets was determined and finely powdered, and then the required amount of sample to prepare a solution of $1 \times 10^{-3}$ M was transferred into a 50 mL of standard flasks. After that 40 mL of Tween 20, cetrmide and sodium lauryl sulphate (0.1% by weight) were added separately to each flask to dissolve the active material. The contents of flasks were stirred magnetically for 30 min and then diluted to volume with same solvents. After dilution the solutions were centrifuged. An aliquot of the supernatant liquid was then transferred into a calibrated flask and a series of dilutions were prepared with phosphate buffers in pH range 2.5–12.0 and mixed 1.0 mL potassium chloride as supporting electrolyte. The contents of the drug in pharmaceutical formulation were determined using calibration graph.




**Scheme 2.** Reduction mechanism of ornidazole.

## 3. Results and discussion

### 3.1. Differential pulse polarographic behaviour

The voltammetric behaviour of ornidazole was examined in solubilized systems in pH range 2.5–12.0 employing DC, DPP and CV techniques. The effect of different surfactants was examined and it was found that ornidazole with neutral surfactant (Tween 20) leads to the maximum increase in peak current (Fig. 1). The reason for the increase in peak current may arise from the evidence given by Fuerstenau et al., of the occurrence of lateral interaction in the adsorbing species. These workers concluded that once the adsorbed ions reach a certain critical concentration at the interface; they begin to associate into two dimensional patches of ions, which Fuerstenau et al. termed as "hemi micelles" [25–27]. The ornidazole molecules which are essentially non polar, as is observed by its low solubility in water, are attracted to non polar region of these hemi micelles, which are oriented towards the electrode surface. Thus more ornidazole molecules reach to the electrode surface as a consequence of which there is a rise in peak height. Electrochemical parameters of ornidazole determined at DME in solubilized systems are shown in Table 1.

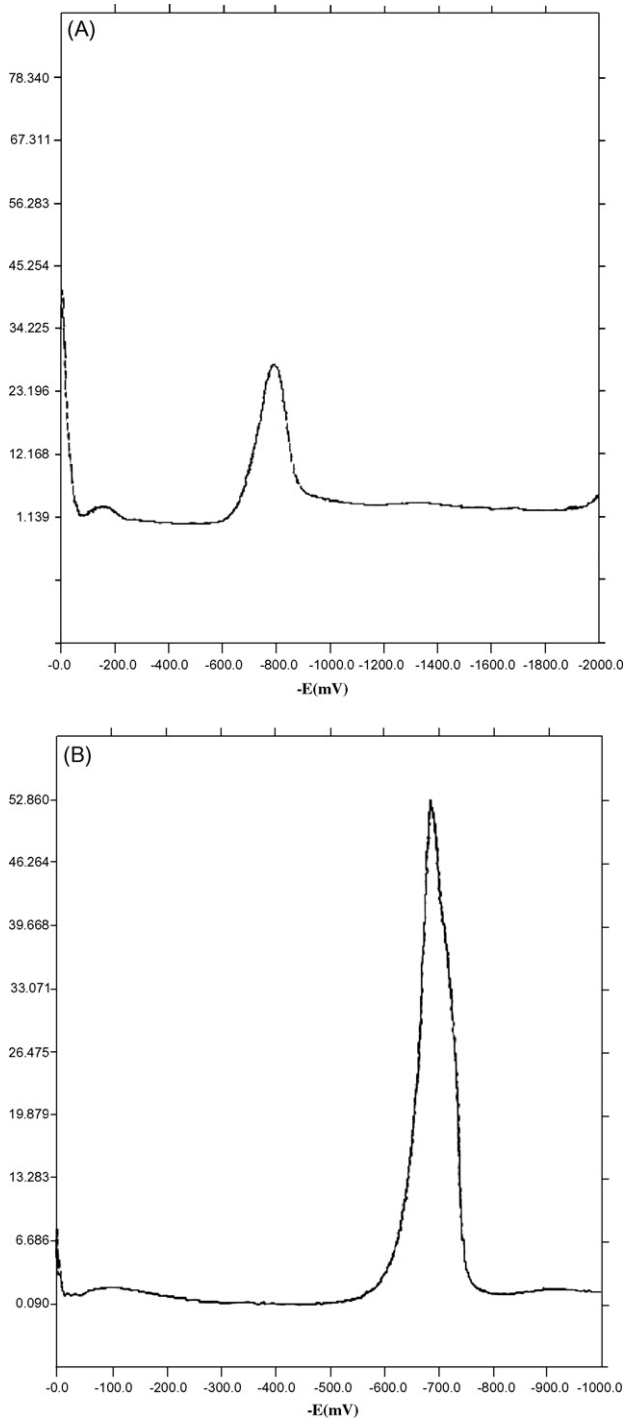



**Fig. 1.** Differential pulse polarograms of $2.0 \times 10^{-3}$ M ornidazole solution in phosphate buffer 9.5, pulse amplitude 100 mV $s^{-1}$ (A) without addition of $4.67 \times 10^{-4}$ mol $L^{-1}$ Tween-20 (B) after addition of $4.67 \times 10^{-4}$ mol $L^{-1}$ Tween-20 showing enhancement in peak current.

**Table 1**
Electrochemical parameters of ornidazole in solubilized Systems.

| Electrolyte (B-R Buffer pH 5) | $E_{pc}$ (mV) (vs. Ag/AgCl) | $i_{pc}$ (μA) |
|---|---|---|
| $2.0 \times 10^{-3}$ mol $L^{-1}$ ornidazole + $4.67 \times 10^{-4}$ mol $L^{-1}$ Tween 20 | 720.0 | 51.95 |
| $2.0 \times 10^{-3}$ mol $L^{-1}$ ornidazole + $2.97 \times 10^{-4}$ mol $L^{-1}$ cetrimide | 980.0 | 33.65 |
| $2.0 \times 10^{-3}$ mol $L^{-1}$ ornidazole + $3.46 \times 10^{-4}$ mol $L^{-1}$ sodium lauryl sulphate | 820.0 | 37.08 |

The effect of surfactants on the peak height of poorly soluble drugs can also be explained by the fact that the amphiphilic structure of surfactants and their assembly in aqueous solution provides a multifunctional environment for the solubilization and partitioning of aqueous soluble and insoluble compounds [28]. Micellar assemblies have the ability to dissolve significant amounts of different types of water insoluble redox active probes that can be electrochemically studied at suitable electrodes. Aqueous micellar solutions are surfactant based organized systems that can be used as less hazardous and versatile substitutes for organic solvent in voltammetry, HPLC separation and in catalysis.

The voltammetric behaviour of ornidazole with different concentration of Tween 20 was examined and it was found that ornidazole with $4.67 \times 10^{-4}$ mol $L^{-1}$ Tween-20 solution gave single, well defined reduction peak with maximum peak height. Further increase of surfactant concentration causes a drop in peak height and wave is drown out. The drop in peak current with increased concentration of Tween-20 is due to micelle formation, resulting in partition of the drug between the aqueous phase and micelle, i.e. it get entrapped in the insulated hydrophobic environment of the micelle and than diffuse along with the micelle, which leads to drop in peak current [29].

The shape and characteristics of all voltammograms were strongly depend on various electrolyte and the pH of the medium. Britton-Robinson, acetate and phosphate buffer were used and the best result with sharper response were obtained with phosphate buffer. Ornidazole exhibited a single, well defined cathodic peak over the entire pH range 2.5–12.0. The peak shift to more negative potential as pH increases, indicating the participation of protons in electrode process. Fig. 2 represents the influence of pH on peak current. The effect of pH on the polarograms of ornidazole leads to the conclusion that basic medium is suitable for analytical studies. The absolute values of $i_p$ where peak shape is well defined, passes through a maximum at pH 9.5.

On the basis of the electrochemical reduction of ornidazole, an analytical method has been developed for the determination of the drug. A linear relationship between peak current and ornidazole concentration was observed in the concentration range $2.0 \times 10^{-3}$ to $4.0 \times 10^{-6}$ and $4.0 \times 10^{-3}$ to $0.13 \times 10^{-3}$ M in Tween 20 and acetonitrile respectively. On comparing the polarographic behaviour

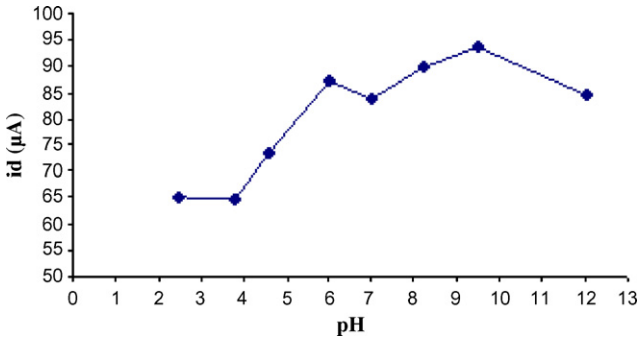



**Fig. 2.** Plot of $i_d$ vs. pH of ornidazole at conc. $4.0 \times 10^{-3}$ M, pulse amplitude 100 mV $s^{-1}$ in $4.67 \times 10^{-4}$ mol $L^{-1}$ Tween 20.

of ornidazole in acetonitrile and in the presence of surfactant it is observed that ornidazole shows increase in peak current and the limit of detection is also found to be lower in Tween 20 in comparison with acetonitrile, used as a solvent under same experimental conditions. The linear regression equation is expressed as [$i_p$ (μA) = $2.3536 \times 10^4$ C (mol $L^{-1}$) + 5.255 A] for cathodic peak in Tween 20, where $i_p$ is peak current in μA and C is the concentration in mol $L^{-1}$ with good correlation ($r^2$ = 0.9926). Fig. 3 shows the linear relationship between peak current and ornidazole concentration. The peak height also increased linearly in both bulk and pharmaceutical formulation with pulse amplitude from 5 to 100 mV $s^{-1}$. According to international conference on Harmonization (ICH) guidelines [30] the following expression is used to evaluate LOD and LOQ.

A. Sensitivity/detection limit

The detection limit was calculated by the equation LOD = 3S.D./*b*, where S.D. is the standard deviation of the intercept and b is the slope of the regression line. The calculated detection limit for the standard solution was $3.6 \times 10^{-7}$ mol $L^{-1}$ or 0.07 μg $mL^{-1}$.

B. Quantitation limit

The quantitation limit was examined by the equation LOQ = 10S.D./*b*. The lower limit of quantitation for the standard solution was found to be $1.2 \times 10^{-6}$ mol $L^{-1}$ or 0.26 μg $mL^{-1}$.

C. Specificity

Specificity is the ability of the method to measure the analytical response in the presence of all potential impurities. For the specificity test, voltammograms of the standard solutions of tablet excipients (starch, gelatin, lactose, and magnesium stearate) were recorded under selected conditions. The response of the analyte in this mixture was compared with the response of pure nitrofurantoin. It was found that assay results were not changed.

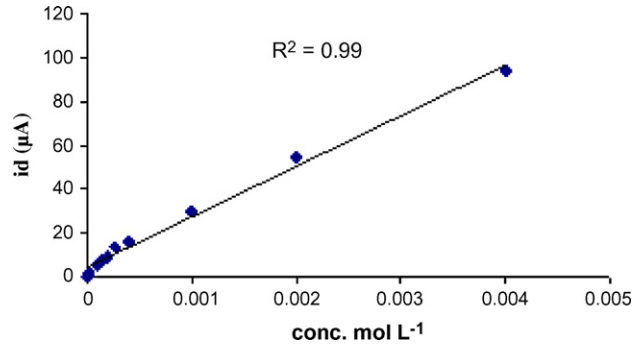



**Fig. 3.** Plot of $i_d$ vs. conc. of ornidazole at, pulse amplitude 100 mV $s^{-1}$, pH 9.5 in $4.67 \times 10^{-4}$ mol $L^{-1}$ Tween 20.

**Table 2**
Analytical parameters for voltammetric determination of ornidazole.

| Parameters | DPP | |
|---|---|---|
| | Solvent | Surfactant (Tween 20) |
| Concentration range (mol $L^{-1}$) | $4.0 \times 10^{-3}$ to $0.13 \times 10^{-3}$ | $2.0 \times 10^{-3}$ to $4.0 \times 10^{-6}$ |
| Measured Potential (mV) | −780 | −726 |
| LOD (μg/mL) | 0.1 | 0.07 |
| LOQ (μg/mL) | 0.34 | 0.26 |
| Correlation coefficient ($r^2$) | 0.995 | 0.992 |
| Intercept (μA) | 0.508 | 5.255 |
| Slope (μA/μg ml) | $9.1 \times 10^3$ | $2.35 \times 10^4$ |
| % Recovery | 99 | 98 |
| Applications | Tablets | Tablets |

D. Stability

In this study, irbesartan stock solutions were kept in the dark at +4 °C for 1 month and were analyzed at different times (every day). It has been seen that repeatable peak currents of ornidazole stock solution occurred up to 15 days and after that the peak current decreased significantly. So the solutions were found to be stable for 15 days.

Analytical parameters for voltammetric determination of ornidazole using differential pulse polarography are tabulated in Table 2.

### 3.2. Cyclic voltammetry of ornidazole in presence and absence of surfactant

Reversibility of the reduction process was studied at cyclic voltammetry with glassy carbon-working electrode, Ag/AgCl reference and platinum wire as an auxiliary electrode. Ornidazole exhibited single cathodic peak in the pH range 2.5–12.0, while no anodic peak was observed in reverse scan, indicating irreversible nature of the electrode process. The absolute values of $i_p$ where peak shaped is well defined, passes through a maximum at pH 5 in both Tween 20 and acetonitrile. In cyclic voltammetry a linear relationship between peak current and ornidazole concentration was observed in the concentration range $4.0 \times 10^{-3}$ to $3 \times 10^{-5}$ and $4.0 \times 10^{-3}$ to $0.13 \times 10^{-3}$ mol $L^{-1}$ in Tween 20 and acetonitrile respectively and the cathodic peak potential shifted towards more negative potential with increasing scan rate from 20 to 250 mV$s^{-1}$. Fig. 4 shows the cyclic voltammograms of ornidazole in Tween 20 and acetonitrile solution at different scan rate with pH 5.

On subsequent scans, the peak height decreased gradually and peak move to less potential. On comparing the voltammograms it can be observed that the cathodic current is dependent upon the percentage of Tween 20 suggesting the formation of ion-pair that anchor onto the surface of the electrode that should posses some hydrophobic character. As the sweep rate is increased from 50 to 100 mV $s^{-1}$ at a fixed concentration of Tween 20; (i) the peak potential shift cathodically, (ii) the peak current function, $i_p/AC\nu^{1/2}$ exhibits almost constancy. A linear Randles-Seveik plot, i.e., a plot of $i_p$ vs. $\nu^{1/2}$ (Fig. 5) was obtained, according to the following linear regression equation:

$$i_p\,(\mu A) = 0.0816\nu^{1/2}\,(\mathrm{mV\,s^{-1}}) + 1.2013 \qquad r^2 = 0.99,$$

which indicates that diffusion is the means of mass transport. The finding was further confirmed by plotting $\log i_p$ vs. $\log \nu$; a straight line was observed which can be expressed by the equation: $\log i_p$ (μA) = 0.4152 + 1.396 $\log \nu$ (V $s^{-1}$); $r^2$ = 0.991 with slope

**Table 3**
Statistics and performance characteristics of the analytical method from the calibration data set.

| Standard | | | | Tablet | | | |
|---|---|---|---|---|---|---|---|
| $I$ (μA) | $(x-\bar{x})^2$ | $E$ (mV) | $(x-\bar{x})^2$ | $I$ (μA) | $(x-\bar{x})^2$ | $E$ (mV) | $(x-\bar{x})^2$ |
| 61.9500 | 0.000108 | −720 | 3.24 | 60.5300 | 0.0236 | −702 | 0.36 |
| 61.7700 | 0.006084 | −714 | 17.64 | 60.9800 | 0.0877 | −702 | 0.36 |
| 61.6600 | 0.035344 | −719 | 0.64 | 60.5387 | 0.0210 | −704 | 1.96 |
| 61.8700 | 0.000484 | −718 | 0.04 | 60.8400 | 0.0244 | −703 | 0.16 |
| 61.9900 | 0.020164 | −720 | 3.24 | 60.5300 | 0.0236 | −702 | 0.36 |
| $\sum x$ | $\sum (x-x)^2$ | $\sum x$ | $\sum (x-x)^2$ | $\sum x$ | $\sum (x-x)^2$ | $\sum x$ | $\sum (x-x)^2$ |
| 61.8480 | 0.062184 | −718.2 | 24.80 | 60.6837 | 0.180329 | −702.6 | 3.20 |
| R.S.D. = 0.1246 | | R.S.D. = 2.4899 | | R.S.D. = 0.2123 | | R.S.D. = 0.8944 | |
| C.V = 0.20 | | C.V. = 0.34 | | C.V. = 0.34 | | C.V. = 0.12 | |

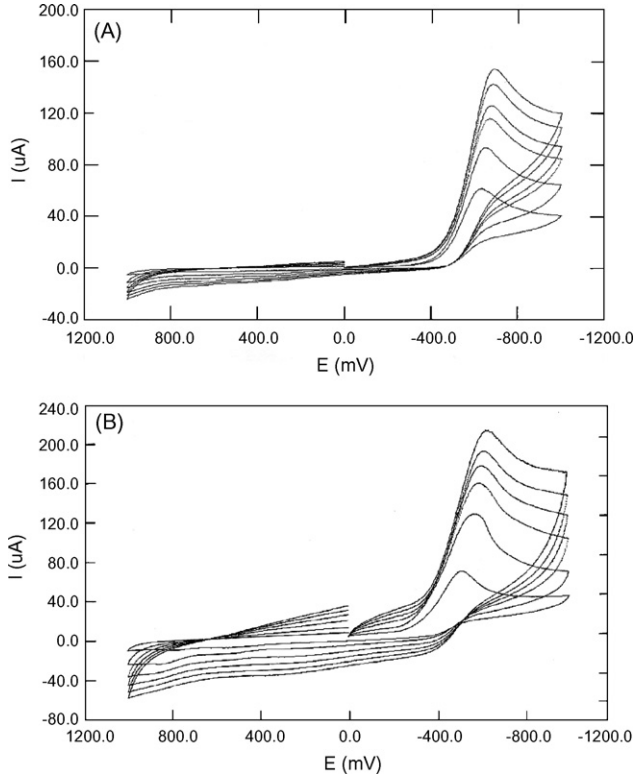



**Fig. 4.** Cyclic voltammograms of $4.0 \times 10^{-3}$ M ornidazole with different scan rates (A) in acetonitrile and (B) in presence of $4.67 \times 10^{-4}$ mol $L^{-1}$ Tween 20, pH 5.1.

of 0.41 which is closed to 0.5. The shift in $E_p$ with pH towards more negative potential was also observed. This pH dependence of $E_p$ suggests that participation of proton in rate determining step.

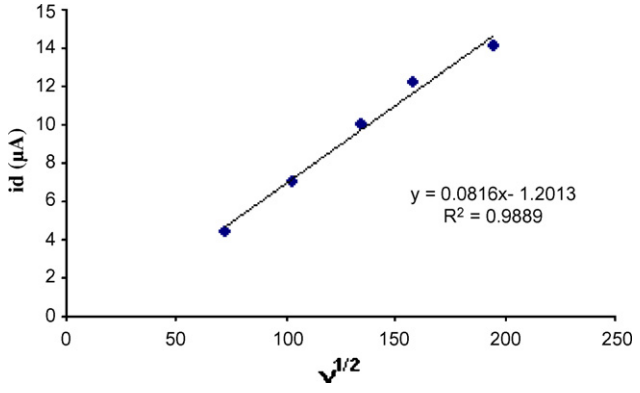



**Fig. 5.** Plot of $i_d$ vs. $v^{1/2}$ of ornidazole at conc. $4.0 \times 10^{-3}$ M, pH 5.1 in $4.67 \times 10^{-4}$ mol $L^{-1}$ Tween 20.

### 3.3. Controlled potential electrolysis and coulometry

Controlled potential coulometry was employed for determining number of electrons ($n$) transferred in electrode process. Number of electrons $n$, were calculated from the charge consumed by the desired concentration of ornidazole. The charge consumed was determined in acidic medium. For this purpose 2 mL of $2.0 \times 10^{-3}$ M solution of the electroactive species was placed in the cell and electrolysis was carried out at a potential −1.0 to +1.0 V against Ag/AgCl reference electrode. During the electrolysis, solutions were continuously stirred and purged with nitrogen. Number of electrons n was calculated using the equation $Q = nFN$, where $Q$ is the charge in coulombs, $F$ is the Faraday constant, and $N$ is the number of moles of substrate. Millicoulometry was also employed to find the number of electrons involved in the electrode process using the method of De Vries and Kroon and were found to be four for $-NO_2$ grouping for ornidazole.

## 4. Reaction mechanism

On the basis of DC, DPP, CV, coulometry, chromatographic and spectral studies following ECE type mechanism may be postulated for the reduction of ornidazole (Scheme 2).

## 5. Analysis of drug in pharmaceutical formulation

The applicability of the proposed voltammetric method for the sample dosage forms was examined by analyzing Ornida −500 mg tablet. The amount of the compound in the tablets was calculated by standard addition method. The accurate and precise results obtained for the formulation ornidazole was found to be in good agreement with that of the drug taken from formulations. The effect of excipients on the polarographic response of ornidazole was studied using the above process and it was found that, they did not interfere with assay. Therefore, the proposed method can be used as selective method of analysis. In order to validate and to obtain the precision and accuracy of the developed method, recovery studies have been carried out at different concentration levels. The performance data of the proposed method have been tabulated in Table 3.

## 6. Conclusion

The proposed study provides a sensitive and selective method of ornidazole analysis in solubilized systems that was developed in this work allows quantitative determination of the drug in pharmaceutical dosage form. The analytical results obtained by DPP and CV are adequately accurate and precise and are in good agreement with those obtained by other techniques. The developed method with detection limit of $3.6 \times 10^{-7}$ mol $L^{-1}$ is more sensitive to already reported different spectroscopic and chromatographic methods and the main advantage of this new method is the use

of less hazardous surfactant media in place of organic solvents. This method have higher sensitivity and because of the possibility of higher sample dilution, less influence of matrix effects. Consequently the proposed method has a high potential of a good analytical alternative for determining ornidazole in pharmaceutical formulations.

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