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Stripping voltammetry of tinidazole in solubilized system and biological fluids

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ABSTRACT

The adsorptive voltammetric behaviour of tinidazole onto the HMDE was investigated and validated in solubilized system and biological fluids by CV, SWCAdSV and DPCAdSV. Addition of CTAB to the solution containing drug enhanced the peak current while anionic and non-ionic surfactants showed an opposite effect. The electrode process is irreversible and adsorption controlled. Various chemical and instrumental parameters affecting the monitored electroanalytical response were investigated and optimized for tinidazole determination. Under optimized conditions; the adsorptive stripping peak current is linear over the concentration range 7.0×10^{-9} to 6.2×10^{-7} mol/L with detection limit of 4.5×10^{-10} mol/L. The precision of the proposed method in terms of RSD is 1.2% and mean recovery of 100.01%. The applicability of proposed method is further extended to in vitro determination of the drug in biological fluids.

1. Introduction

The incidence of trichomonas infection among African women is increasing [1,2] and it is known that trichomoniasis facilitates the spread of HIV infection [3,4]. One of the commonest drugs used in the treatment of trichomoniasis is tinidazole [5,6]. Thus in order to authenticate the quality of tinidazole, an affordable, rapid and reproducible method of analysis is desirable. Recently, tinidazole (A) has been used against metronidazole-resistant trichomoniasis [7] and nonrecurrent bacterial vagnosis [8].

There are a few reports for the determination of the tinidazole in pharmaceutical dosage forms viz., Gas-liquid chromatography methods, spectrophtometric, absorptometric assay [9–12], thin layer chromatography (TLC) and high performance liquid chromatography [13]. Although Chromatographic methods offer required sensitivity and selectivity, but they needs sample clean-up, complicated extraction, tedious and time-consuming derivatization procedures, relatively heavy and expensive instrumentation which limit their use in quality control laboratories. Voltammetric methods have been found highly-sensitive, convenient and effective tool for the analysis of pharmaceuticals and biomolecules [14–36] owing to their simplicity, low cost and relatively short time analysis. Hence, voltammetric determination of tinidazole has been reported [37–39]; however, analysis in biological fluids and solubilized system is not carried out. Present voltammetric method in solubilized system lowers the detection limit upto nanogram level and makes it more sensitive than already reported methods.

The development of meaningful dissolution procedure for drug products with limited water solubility has been a great challenge to analysts [40–42]. It has been seen that surfactant play a very important role in electrode reactions, not only in solubilizing organic compounds [43,44] but also providing specific orientation of the molecules at the electrode interface. The aggregates of surfactants, such as micelles, liquid crystalline, vesicles etc. could enhance the stabilized content and the control release behaviour of drugs are widely studied as drug delivery systems [45,46].

2. Experimental

2.1. Materials and methods

Tinidazole (99% purity) was obtained from Cadila Pharmaceuticals Ltd., India and is used as received. Tablets containing tinidazole (*Tiniba*) labeled 500 mg was obtained from commercial sources. KCl (1.0 mol/L) solution was prepared in double distilled water and used as supporting electrolyte. A stock solution of tinidazole (1.0×10^{-3} mol/L) was prepared in DMF, CTAB, SDS and Tween-20. The solutions for recording voltammograms were prepared by mixing appropriate volume of stock solution, buffers and 1.0 mol/L KCl. All chemicals used were of analytical reagent grade quality and were obtained from Aldrich. All the glasswares were purchased from Borosil Glasswares Pvt. Ltd., India.

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2.2. Analytical procedure

2.2.1. Tiniba tablet solution

Ten tablets were weighed and the average mass per tablet was determined. A portion of the finely grounded material equivalent to 500 mg of tinidazole accurately weighed and transferred into the 100 mL calibrated flask containing 70 mL surfactant solution. The content of the flask was sonicated for about 15 min and then made up to the volume with the surfactant solution. An aliquot of the solution was then analyzed according to the proposed voltammetric procedure.

2.2.2. Serum and plasma analysis

Drug-free human blood obtained from healthy volunteers was centrifuged at 5000 rpm for 30 min to separate serum and plasma at room temperature. Separated serum and plasma samples were stored frozen until analysis. Then separated serum and plasma samples were treated with 1.0 mL of acetonitrile as protein denaturing and precipitating agent. After vortexing for 30 s, the serum and plasma samples were centrifuged for 10 min at 5000 rpm in order to eliminate serum and plasma protein residues. An aliquot of serum and plasma samples were fortified with tinidazole solution in CTAB to achieve a final concentration of 1.0×10^{-3} mol/L. Appropriate volumes of these spiked samples were transferred into the voltammetric cell containing phosphate buffer of pH 6.0. Quantification was performed by means of calibration curve method.

2.3. Instrumentation

Electrochemical measurements were performed using a μ-AUTOLAB TYPE III (Eco- Chemie B.V., Utrecht, The Netherlands) potentiostat-galvanostat with 757VA computrace software which is purchased from Metrohm India Ltd. The utilized electrodes are hanging mercury drop electrode (HMDE) as working electrode, Ag/AgCl (3.0 mol/L KCl) as reference electrode and a graphite rod as auxiliary electrode. All the solutions examined by electrochemical technique 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 pH-metric measurements were made on a Decibel DB-1011 digital pH meter fitted with a glass electrode and a saturated calomel electrode as reference, which was previously standardized with buffers of known pH.

3. Results and discussion

3.1. Tinidazole behaviour in solubilized system

The effect of different types of surfactants viz., cationic (CTAB), anionic (SDS), non-ionic (Tween-20) and DMF on the reduction of 1.5×10^{-8} mol/L tinidazole were investigated by the proposed voltammetric procedure. On comparing the voltammetric behaviour of tinidazole in DMF and in presence of surfactants, it is observed that tinidazole shows substantial increase in peak current and the limit of detection is found to be lower in CTAB (Fig. 1), while non-ionic and anionic surfactants showed an opposite effect. The reason for increase in voltammetric response is attributed due to adsorption of tinidazole on the electrode surface which leads to formation of self-micelle aggregate with the CTAB, which affects the mass transport. The adsorption of amphiphilic species on the electrode surface may result in changing the overpotential of the electrochemical process and rate of its corresponding charge transfer [47].

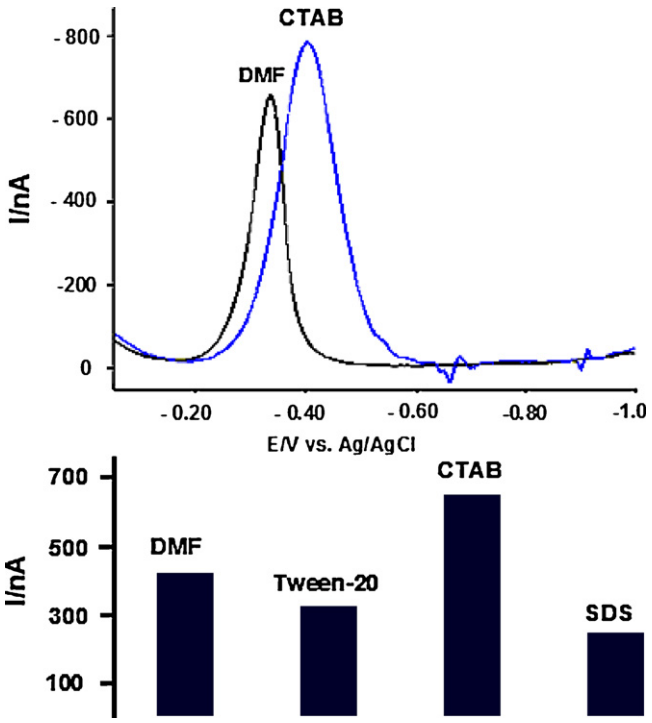

Fig. 1. Comparison of SWCAdSV peak current of 1.5×10^{-8} mol/L tinidazole in different surfactants and DMF.

3.2. Effect of CTAB concentration

The effect of CTAB concentration on the 1.2×10^{-6} mol/L tinidazole squarewave cathodic peak current is shown in Fig. 2. The cathodic peak current increases steadily in the beginning with increase in concentration of CTAB and reaches a maximum at 4.0×10^{-3} mol/L. It may be interpreted that the adsorption behaviour of CTAB changes from monomer adsorption to monolayer adsorption with increase in concentration of CTAB at the electrode surface. The CTAB concentration of 4.0×10^{-3} mol/L may have reached the critical micelle concentration (CMC), but the electrode process is cooperated by the adsorption and accumulation of CTAB. Another reason for the increase in peaks current may arise from the evidence given by Fuerstenau and co-workers [48–50] of the occurrence of lateral interactions in the adsorbing species. These workers concluded that once the adsorbed ions reach a certain critical concentration at the interface; they begin to asso-

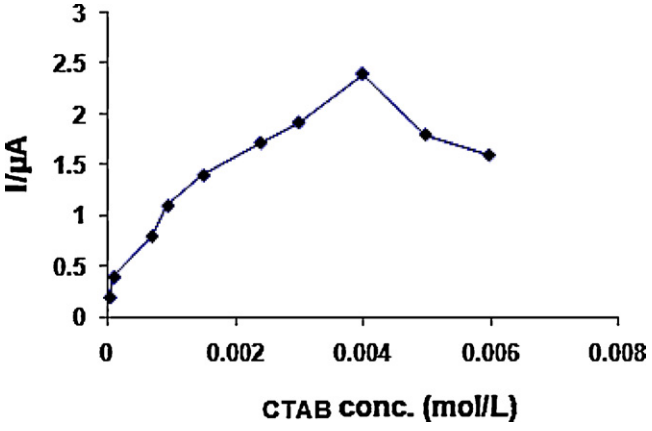

Fig. 2. Effect of CTAB concentration on SWCAdSV peak current of 1.2×10^{-6} mol/L tinidazole.

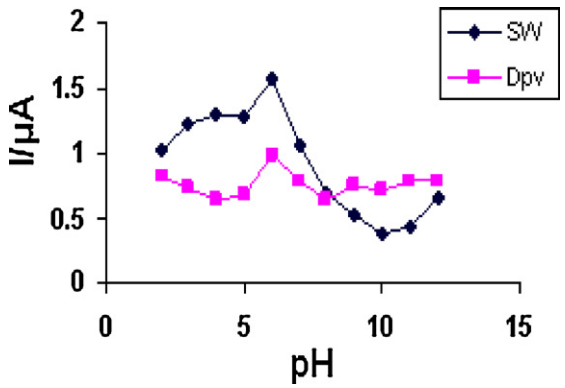

Fig. 3. Influence of pH on SWCAdSV peak current of 1.5×10^{-6} mol/L tinidazole in phosphate buffer (pH 2.4–12.0) after 200 s pre-concentration time; frequency (f) = 110 Hz, Δs = 10 mV and pulse amplitude = 50 mV at E_{acc} = −0.1 V.

ciate into two-dimensional patches of ions, which Fuerstenau et al. termed as 'hemimicelles.' However peak current decrease as further increase in CTAB concentration. It may be due to the micelle effect i.e., electron transfer between tinidazole and electrode surface would be inhibited by aggregates of micelles. Also the increase of hydrophobicity of the possible CTAB micelles might decrease the electron transfer rate constant which results in the decline of peak current at rather high CTAB concentration. Thus CTAB concentration of 4.0×10^{-3} mol/L can furthest enhances the electrochemical to maximum.

3.3. Effect of pH

Different experiments were carried out in various supporting buffers (phosphate, acetate, borate and citrate) at different pH values in order to assess their impact on the monitored electroanalytical signal. The best results with respect to sensitivity accompanied with sharper response were obtained with phosphate buffers. Therefore study was made in the pH range 2.4–12.0 in phosphate buffers at a target concentration of 1.2×10^{-6} mol/L aqueous tinidazole solution. With increase in pH, the peak potential shifted towards negative direction which indicating the existence of a protonation reaction coupled with the tinidazole reduction process.

The relation between E_p of the wave and pH of the medium over the range 2.4–12.0 may be expressed by the equations (i) and (ii):

$$\text{SWCAdSV; } E_p/V(\text{vs. Ag/AgCl}) = 0.0494 + 1.456\text{pH}, r^2 = 0.996 \quad \text{(i)}$$

$$\text{DPCAdSV; } E_p/V(\text{vs. Ag/AgCl}) = 0.0502 + 1.526\text{pH}, r^2 = 0.991 \quad \text{(ii)}$$

Linear pH dependence of the peak potential for reduction wave in the range 2.4–12.0 shows that protons participate directly in the reduction process.

As shown in Fig. 3, the height of the peak reaches a maximum at pH 6.0 and after that it decreases. Therefore, pH 6.0 was chosen as the optimum one for the determination of tinidazole.

3.4. Optimization of operational parameters

Stripping voltammetric procedure using SWCAdSV and DPCAdSV were used to optimize for determination of tinidazole in tablets and biological fluids. Both the techniques gave comparable results, but SWCAdSV has been chosen for optimizing the operational parameters. In order to obtain the maximum peak current, the optimum instrumental conditions such as pre-concentration time (t_{acc}), pre-concentration potential (E_{acc}), pulse amplitude (ΔE_{sw}), scan increment (Δs) and frequency (f) were examined using the selected waveforms.

The SWCAdSV peak current is linearly dependent on the frequency 40–140 Hz, while a well defined peak was observed at 110 HZ. A linear relationship was observed between the stripping peak current and frequency expressed as $i_p/\mu A = 0.0368\,(f) + 1.6332$, ($r^2 = 0.9946$). Although the response of tinidazole is increased with frequency, but above 110 Hz the peak current was obscured by a large residual current. Study of the effect of scan increment on adsorptive cathodic peak current of tinidazole revealed that the peak current enhanced upon the increase of scan increment (2–10 mV). A scan increment of 10 mV is preferable in the present study. At pulse amplitude 50 mV, the peak current was found to be much sharper and well defined. Thus the best peak definition was recorded using 100 Hz frequency, 10 mV scan increment and 50 mV pulse amplitude.

3.4.1. Effect of pre-concentration potential

Pre-concentration step is usually a simple and effective way to enhance the determining sensitivity. The influence of pre-concentration potential (E_{acc}) on the cathodic peak current (i_p) of 1.2×10^{-6} tinidazole was examined over the potential range −0.1 V to −1.2 V. The adsorbed species are most probably neutral molecules of drug species and the maximum peak current is achieved in the potential range of zero charge of mercury electrode. At more cathodic values, a decrease in peak current was observed indicating the drug is no longer strongly adsorbed at potentials where the mercury is negatively charged with respect to the zero charge potential. Thus maximum development of the peak current was achieved at −0.1 V. Hence, a pre-concentration potential of −0.1 V was used throughout the present study.

3.4.2. Effect of pre-concentration time

The effect of pre-concentration time for 1.2×10^{-6} mol/L tinidazole was investigated from 0 to 300 s. It was observed that peak current increases with increase in accumulation time up to 200 s indicating the enhancement of drug concentration at the electrode surface. Further increase in the accumulation time, the current first decreases and then tends to level off showing that the adsorptive equilibrium has reached. Above these times the peak currents are constant suggesting electrode surface saturation.

3.5. Validation of method

The analytical method was validated with respect to parameters such as limit of quantification (LOQ), limit of detection (LOD), precision, accuracy, selectivity, recovery, robustness and ruggedness [51–53].

3.5.1. Detection limit

Detection limit was calculated by equation LOD = 3 S.D./b, where S.D. is standard deviation of intercept and b is slope of the regression line. LOD for standard solution using SWCAdSV was found to be 4.5×10^{-10} mol/L. Analytical parameter for voltammetric determination of tinidazole using SWCAdSV and DPCAdSV methods has been tabulated in Table 1.

3.5.2. Quantification limit

The quantitation limit was examined by the equation LOQ = 10 S.D./b. The lower limit of quantitation for the standard solution was found to be 1.5×10^{-9} mol/L.

3.5.3. Accuracy and precision

The accuracy of the analysis was determined by calculating the percentage relative error between the measured mean concentration and the nominal concentration [54,55]. Precision of procedure was estimated by analyzing 0.1 μg/mL tinidazole solution for five

Table 1
Analytical parameters for voltammetric determination of tinidazole tablets, spiked serum and plasma samples using SWCAdSV and DPCAdSV.

SWCAdSV			
Parameter	Tablet	Serum	Plasma
Linearity range (mol/L)	7.0×10^{-9} to 6.2×10^{-7}	3.2×10^{-8} to 1.6×10^{-6}	3.2×10^{-8} to 1.6×10^{-6}
Slope (μA/mol/L)	3.0×10^{7}	3.0×10^{6}	3.0×10^{6}
Intercept (μA)	0.0001	0.6999	0.0398
LOD (mol/L)	4.5×10^{-10}	10.4×10^{-9}	12.0×10^{-9}
LOQ (mol/L)	1.5×10^{-9}	34.6×10^{-9}	4.0×10^{-8}
s_b[a]	0.0045	0.0104	0.0120
DPCAdSV			
Parameter	Tablet	Serum	Plasma
Linearity range (mol/L)	3.0×10^{-8} to 1.2×10^{-7}	3.2×10^{-8} to 1.6×10^{-6}	3.2×10^{-8} to 1.6×10^{-6}
Slope (μA/mol/L)	4.0×10^{6}	7.2×10^{5}	7.9×10^{5}
Intercept (μA)	0.0235	0.0364	0.0956
LOD (mol/L)	5.45×10^{-10}	32.5×10^{-9}	33.0×10^{-9}
LOQ (mol/L)	1.6×10^{-9}	10.8×10^{-8}	11.0×10^{-8}
s_b[a]	0.0066	0.0078	0.0087

[a] Standard deviation of the intercept of regression line.

times in four successive days using SWCAdSV and DPCAdSV methods. The percentage recoveries based on the average of five separate determinations are abridged in Table 2. The precision of the analysis was determined by calculating the relative standard deviation (% RSD) in biological fluids. The precision around the mean value should not exceed 15% of RSD. The results confirmed good accuracy and precision of proposed procedure for the determination of tinidazole.

3.5.4. Specificity and mean percentage recovery

Specificity of the drug in pharmaceutical formulation is examined in presence of some common excipients (e.g., cellulose, lactose, talc and magnesium stearate), added in the same ratio as in pharmaceutical formulation [56,57]. In order to evaluate the effect of presence of excipients on the proposed method, the standard addition method was applied. For this reason, appropriate volume of tinidazole tablet solution was added to the supporting electrolyte. After the voltammograms were recorded, known amounts of standard solution of tinidazole were added and voltammograms were recorded. The regression equations of standard addition methods were found to be $i_p/\mu A = (3.0 \times 10^7)$ Tindz. (mol/L) −0.0001; ($r^2 = 0.996$) and $i_p/\mu A = (2.98 \times 10^7)$ Tindz. (mol/L) −0.0005; ($r^2 = 0.998$) for SWCAdSV methods, respectively. There was no difference between the slopes of two methods between calibration curve and standard addition methods. The data showed that there was no interaction of excipients in the analysis of tinidazole in pharmaceutical formulation by the proposed method.

Table 2
Precision and accuracy for assay of tinidazole in tablets, spiked serum and plasman samples by SWCAdSV.

Nominal	Conc. (μg/mL)	[a]Found Conc. (μg/mL)	% Recovery	% RSD
Tablet	1.0	0.99	99.0	0.43
	2.0	2.02	101.0	0.85
	4.0	3.98	98.0	1.10
Serum	1.0	0.88	88.0	1.20
	2.0	1.89	94.5	0.98
	4.0	3.95	98.7	1.52
Plasma	1.0	0.84	84.0	1.23
	2.0	1.86	93.0	2.52
	4.0	3.87	96.7	1.36

[a] Average of five replicate measurements.

3.5.5. Robustness

The robustness was examined by evaluating the influence of small variation of some of the most important procedure variables including pre-concentration potential (E_{acc}) and pre-concentration time (t_{acc}). The obtained results provide an indication of the reliability of the proposed procedure for the assay of tinidazole and hence it can be considered robust.

3.5.6. Ruggedness

The ruggedness of the measurements is defined as the degree of reproducibility of results obtained by analysis of same sample under variety of normal test conditions such as different laboratories and different lot of reagents, under the same operational conditions at different elapsed time by two different analysts. The methods were found to be rugged with the results of variation coefficients 0.75 and 0.82% for SWCAdSV, 1.2 and 0.92% for DPCAdSV methods for first and second analysts, respectively. The results show no statistical differences between different analysts.

3.6. Cyclic voltammetric behaviour

Tinidazole in phosphate buffer pH 6.0 gives well defined single cathodic peak in potential range −0.3 to −0.6 V at all concentrations due to the reduction of $-NO_2$ group, which is not accompanied by corresponding anodic one indicates the irreversibility of reduction process. Also the peak potential shifts to more negative values on increasing the scan rate, confirms the irreversibility of the electrode process [58].

For finding the adsorptive character of the drug at HMDE a cyclic voltammogram (Fig. 4; curve 2) was recorded after 200 s preconcentration at −0.1 V and with 0 s (Fig. 4; curve 1) preconcentration time. The peak current (i_p) increases after preconcentration of the drug on the electrode surface for 200 s.

3.6.1. Effect of scan rate

According to the Randles–Seviek equation in a linear diffusion-controlled process $i_p \alpha \upsilon^{1/2}$; for the adsorptive process $i_p \alpha \upsilon$. The cathodic peak current is linearly proportional to scan rate confirms adsorption controlled behavoiur of tinidazole at HMDE (Fig. 5), which is expressed by the equation (iii) [59]:

$$i_p/\text{nA} = 0.0052\upsilon(\text{mV/s}) + 0.613,\ r^2 = 0.9984 \quad \text{(iii)}$$

The adsorption effect was also identified by a plot of $\log i_p$ vs. $\log \upsilon$ gives a straight line which can be expressed by the equation

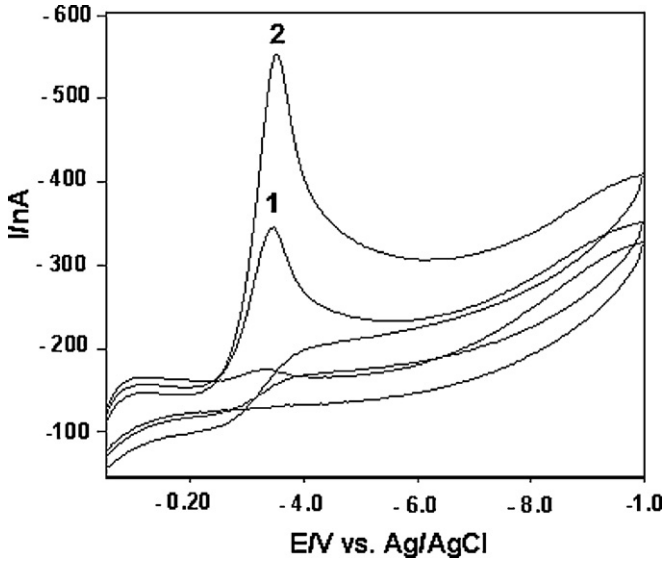

Fig. 4. Cyclic voltammograms of 1.5×10^{-8} mol/L tinidazole containing 4.0×10^{-3} mol/L CTAB in phosphate buffer (pH 6.0) at a scan rate of 100 mV/s, equilibrium time = 10 s. Curve (2) after preconcentration and (1) curve shows 0 s preconcentration.

(iv):

$$\log i_p/\text{nA} = 0.956 \log \upsilon(\text{mV/s}) - 1.228,\ r^2 = 0.9956 \quad \text{(iv)}$$

A slope of 0.95 which is close to the theoretical value of 1.0, indicate the adsorptive nature of the reduction process [60,61].

3.7. Analytical applications

The applicability of the proposed voltammetric procedure for the determination of tinidazole in tablets, serum and plasma was examined by measuring the stripping peak current as function of concentration of the bulk drug for at least three times under the optimized operational parameters.

3.7.1. Tinidazole assay in pharmaceutical dosage form

The proposed method was utilized for the determination of tinidazole in "*Tiniba*®" tablets as real pharmaceutical formulation.

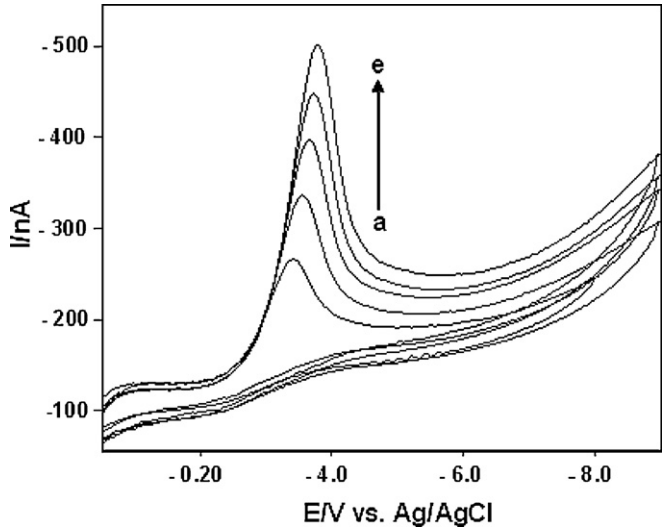

Fig. 5. Cyclic voltammograms of 1.5×10^{-6} mol/L tinidazole in 4.0×10^{-3} mol/L CTAB at different scan rates; (a)100 mV/s, (b) 200 mV/s, (c) 300 mV/s, (d) 400 mV/s, (e) 500 mV/s.

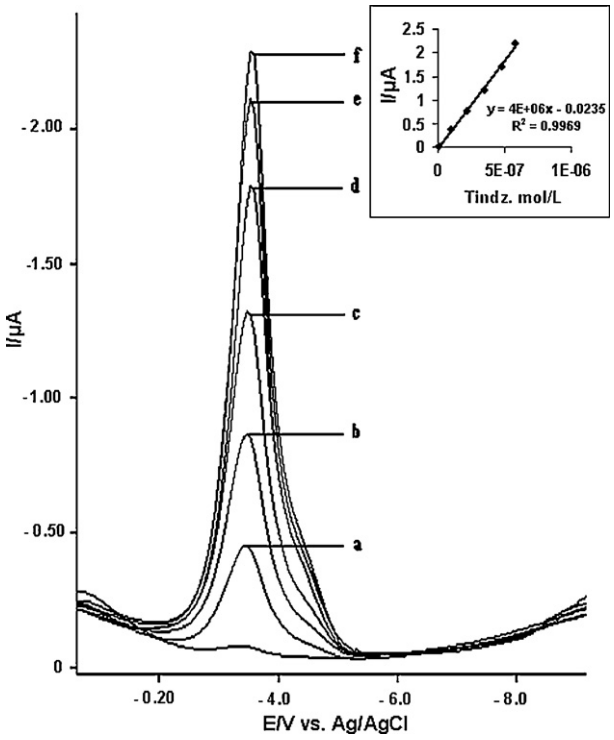

Fig. 6. The dependence of the SWCAdSV peak current of tinidazole in CTAB at different concentrations (a) 7.1×10^{-9} mol/L (b) 10.8×10^{-8} mol/L (c) 22.1×10^{-8} mol/L (d) 3.4×10^{-7} mol/L (e) 4.8×10^{-7} mol/L (f) 6.2×10^{-7} mol/L, $E_{acc} = -0.1$ V, $t_{acc} = 200$ s, frequency $f = 110$ Hz, pulse amplitude $\Delta E_{sw} = 50$ mV and scan increment $\Delta s = 10$ mV.

The dependence of stripping peak current on the concentration of the drug is linear over concentration range 7.0×10^{-9} to 6.2×10^{-7} mol/L for SWCAdSV and 3.0×10^{-8} to 1.2×10^{-7} mol/L for DPCAdSV respectively (Fig. 6). The calibration graph was represented by the equations (v) and (vi).

$$\text{DPCAdSV}: i_p/\mu\text{A} = (4.0 \times 10^6)\text{Tindz.(mol/L)} - (0.0235);\ r^2 = 0.998;\ n = 3 \quad \text{(v)}$$

$$\text{SWCAdSV}: i_p/\mu\text{A} = (3.0 \times 10^7)\text{Tindz.(mol/L)} - (0.0001);\ r^2 = 0.996;\ n = 3 \quad \text{(vi)}$$

The regression plots showed that there was a linear dependence of the current intensity on the concentration of tinidazole in both DPCAdSV and SWCAdSV modes over convenient range (Table 2).

3.7.2. Tinidazole assay in spiked biological fluids

The applicability of proposed procedure for the assay of tinidazole in spiked human biological fluids was tested. Fig. 7 illustrates the response of successive concentrations of tinidazole in spiked serum and plasma following its preconcentration onto the HMDE for 200 s. The variation of peak current with tinidazole concentration was studied in both serum and plasma samples. The concentration of tinidazole was linear over concentration range 3.2×10^{-8} to 1.6×10^{-6} mol/L by proposed procedure in plasma and serum samples according to equations (vii) to (x):

Serum

$$\text{DPCAdSV}: i_p/\text{nA} = (7.2 \times 10^5)\text{Tindz.(molL)} + (0.0364);\ r^2 = 0.999;\ n = 3 \quad \text{(vii)}$$

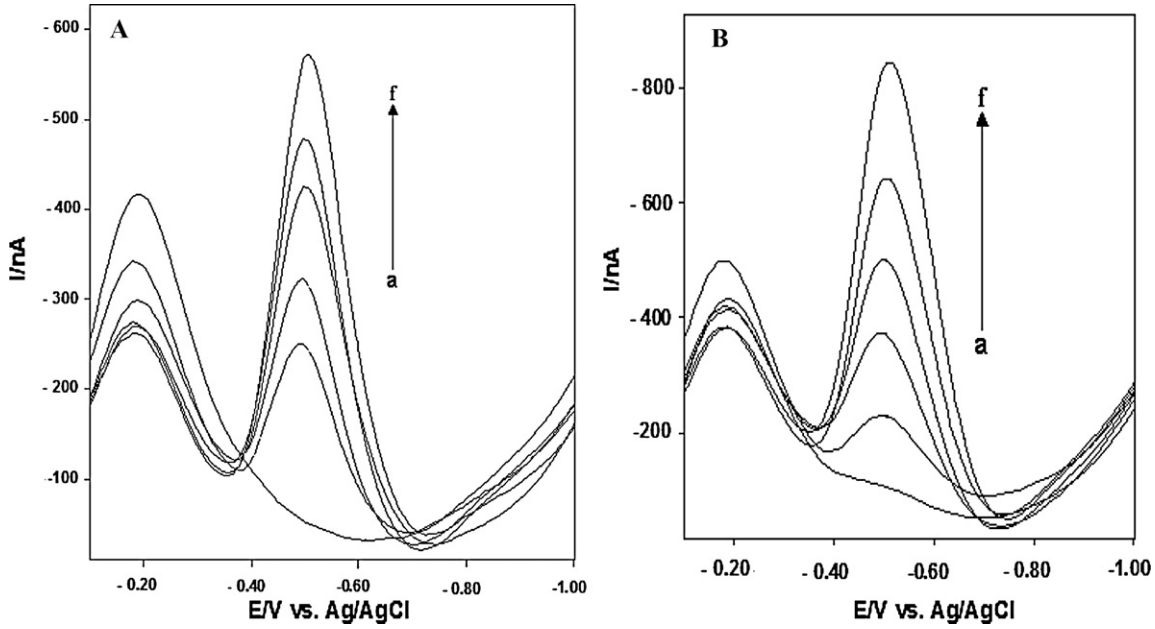

Fig. 7. SWCAdSV peak current of tinidazole in spiked (A) plasma and (B) serum sample (pH 6.0) at different concentrations, (a) 3.2×10^{-8} mol/L (b) 6.4×10^{-4} mol/L (c) 8.7×10^{-7} mol/L (d) 1.01×10^{-6} mol/L (e) 1.19×10^{-6} mol/L (*f*) 1.6×10^{-6} mol/L, $E_{acc} = -0.1$ V, $t_{acc} = 200$ s, $f = 110$ Hz, $\Delta E_{sw} = 50$ mV and $\Delta s = 10$ mV.

$$\text{SWCAdSV} : i_p/\mu\text{A} = (3.0 \times 10^6)\text{Tindz.(mol/L)} + (0.6999); r^2 = 0.998; n = 3 \quad \text{(viii)}$$

Plasma

$$\text{DPCAdSV} : i_p/\text{nA} = (7.9 \times 10^5)\text{Tindz.(mol/L)} + (0.0956); r^2 = 0.995; n = 3 \quad \text{(ix)}$$

$$\text{SWCAdSV} : i_p/\text{nA} = (3.0 \times 10^6)\text{Tindz.(mol/L)} + (0.0398); r^2 = 0.999; n = 3 \quad \text{(x)}$$

Quantifications were performed by means of the calibration curve method from the related calibration equation. The LOD and LOQ values were calculated based on peak current and are tabulated in Table 2.

3.8. Comparison of the sensitivity of proposed method and other previously reported methods

Table 3 compares the detection limit of the proposed method with the other reported methods [37,39]. It is clear from the table that stripping method is more sensitive as compared to previously reported methods. The data in Table 3 reveal that the detection limit of the proposed method is lower than all previous reported methods.

Table 3
Comparison of the detection limit of the proposed method with the other reported methods.

Electrochemical method at SWNTs	1.0×10^{-8} mol/L	[37]
Voltammetry at Poly(carmine) film electrode	5.0×10^{-8} mol/L	[39]
Voltammetry in solubilized system	4.5×10^{-10} mol/L	Present work

4. Conclusion

The proposed cathodic adsorptive stripping voltammetric procedure can be successfully applied for determination of tinidazole in pharmaceutical formulation and biological fluids. The method involves direct dissolution of pharmaceutical tablets in supporting electrolyte containing surfactant solutions, allows a fast and reproducible determination of this compound with no interference from ingredients present. The present method is found to be practically rapid, convenient, accurate, low cost and precise. Determination of drug in presence of surfactants provides new medium for study of interaction of drugs with biological membranes, because surfactants interacts with adsorbing membranes enhancing permeability of dissolved drugs. As applied to serum and plasma samples, these methods have the advantage that no prior extraction procedure is required prior to the analysis. The developed method with the detection limit of 4.5×10^{-10} mol/L in presence of CTAB is more sensitive than already reported analytical methods. The method could possibly be adopted for the pharmacokinetic studies as well as for quality control laboratories.

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