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Adsorptive stripping voltammetric behavior and determination of anticholinergic agent oxybutynin chloride on a mercury electrode

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Abstract

Oxybutynin chloride is an antispasmodic, anticholinergic agent indicated for the treatment of overactive bladder with symptoms of urge urinary incontinence, urgency, and frequency. Its electrochemical behavior in phosphate buffers of pH range 2–10 at a hanging mercury drop electrode has been investigated using cyclic voltammetry, differential pulse cathodic adsorptive stripping voltammetry (DPCAdSV), and squarewave cathodic adsorptive stripping voltammetry (SWCAdSV). Voltammograms of the drug in phosphate buffer of pH 2–10 exhibited a single two-electron wave and it may be attributed to the reduction of the –C≡C– center. Based on the high adsorptive character of oxybutynin chloride onto the mercury electrode, a validated direct squarewave cathodic adsorptive stripping voltammetric and differential pulse cathodic adsorptive stripping voltammetric procedure has been developed for the determination of drug in bulk form and pharmaceutical formulation. The proposed SWCAdS and DPCAdS voltammetric methods allow quantitation over the range 1–18 and 1–17.6 μg mL^{-1} with detection limits of 0.1 and 0.23 μg mL^{-1}, respectively. Precision and accuracy were also checked and were within the limits.

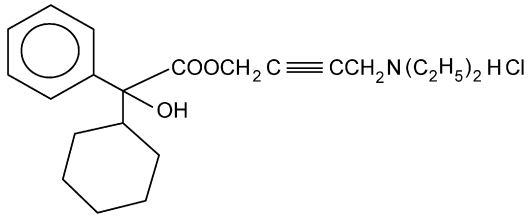
Keywords: Oxybutynin chloride; Adsorptive stripping voltammetry; Mercury electrode; Pharmaceutical formulation; SWCAdSV; DPCAdSV

1. Introduction

Urinary incontinence is one of the most common chronic medical conditions seen in primary care practice. It is more prevalent than diabetes, Alzheimer's diseases, and many other conditions that receive considerably more attention. Incontinence is an expensive problem, generating more costs each year than coronary artery bypass surgery and renal dialysis combined [1].

Urinary incontinence is often encountered by many people and the condition is particularly common in the elderly. A large postal survey in the UK has shown the incidence of urinary incontinence in the over 65 age group to be more than 15% for men and 25% for women [2]. Oxybutynin chloride (α-cyclohexyl-α-hydroxybenzenacetic acid-4-(diethylamino)-2-butynyl esters) (Scheme 1) an anticholinergic agents is a tertiary amine that mainly acts as a direct smooth muscle relaxant and displays weak antimuscarinic activity [3,4]. It has been shown to improve the symptoms of frequency and urgency in urinary incontinence in patients with detrusor instability associated with an increase in functional bladder capacity [5].

Oxybutynin chloride is the subject of a monograph in the US Pharmacopoeia USP [6]. The USP [6], on the other hand, described chromatographic methods for both the drug and its formulations. A survey of the literature revealed that few methods have been reported for its determination in biological fluids and pharmaceutical formulations using LC-ESI/MS/MS [7], GC-MS [8–12], HPLC [13,14], ion pair liquid chromatography



Scheme 1.

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[15], and radio receptor assay [16], but there was no electrochemical study on hanging mercury drop or solid electrodes published yet. Furthermore, the methods developed for oxybutynin chloride demand expensive equipment and could not be available in many laboratories.

In the last decades modern electrochemical techniques [17,18] such as differential pulse polarography (DPP) [19–21], adsorptive stripping voltammetry (AdSV) [22–28], and differential pulse voltammetry (DPV) [29,30] have been widely applied for the determination of pharmaceuticals. Furthermore, determination of oxybutynin chloride using an electrochemical method, especially stripping analysis, is yet to be reported.

This work aimed to study the voltammetric behavior and reduction mechanism of oxybutynin chloride, owing to the high sensitivity and simplicity of the voltammetric techniques and lack of literature data on the electrochemical behavior of oxybutynin chloride in pharmaceuticals employing differential pulse cathodic adsorptive stripping voltammetry and squarewave cathodic adsorptive stripping voltammetry at a hanging mercury drop electrode. The procedures did not require sample pretreatment or any time-consuming extraction step prior to drug assay.

2. Experimental

2.1. Reagents and materials

Oxybutynin chloride (99% pure) was a gift from Sunpharma Pharmaceuticals, Mumbai (India). Tablets containing oxybutynin chloride (Tropan) labeled 5 mg were obtained from commercial sources. A stock solution of oxybutynin 1 mg mL^{-1} was prepared by direct dissolution in dimethylformamide (DMF). The solution for recording voltammograms was prepared by mixing appropriate volumes of stock solution and buffer of varying pH. Phosphate buffers in the pH range 2–12.0 were prepared in ultrapure deionized water by adding suitable amounts of 85% H_3PO_4, KH_2PO_4, Na_2HPO_4, and Na_3PO_4 to obtain buffers in the pH range 2.0–12.0. The final volume of all buffer solutions was 200 mL, and the ionic strength was 0.2 [31] and was used as supporting electrolyte. The ionic strength was maintained by 1 M KCl. All chemicals used were of analytical reagent grade quality (Merck and Sigma) and were employed without further purification. High-purity water was obtained from Millipore (Milford, MA) Milli-Q Plus system.

2.2. Instrumentation

Electrochemical measurements were performed using a μAutolab type III (Eco-Chemie B.V., Utrecht, The Netherlands) potentiostat-galvanostat with 757VA Computrace software. The utilized electrodes were hanging mercury drop electrode (HMDE) as working electrode, Ag/AgCl (3 M KCl) as reference electrode, and a graphite rod as auxiliary electrode. The electrochemical cell was a Metrohm 663 VA stand. Controlled potential coulometric experiments were carried out using an Autolab Potentiostat/Galvanostat PGSTAT Metrohm 663 VA stand as electrochemical cell, fitted with a PC provided with the appropriate GPES 4.2 (General Purpose Electrochemical Software) software. Coulometric experiments were performed in the potentiostatic mode using Pt foil with large surface area as working electrode and a Pt wire, counterelectrode. All the solutions examined by the 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. Ready made precoated TLC silica gel-coated plates from E Merck, Germany, were used for TLC separation and the solvent system was DMF:water (15:1). The IR spectrum of solid complex was recorded using KBr pellets on a Shimadzu, Japan, and Prestige IR 20 Model IR spectrophotometer.

2.3. Procedure

Oxybutynin chloride determination was performed on commercially available tablet dosage form Tropan. The amount of oxybutynin chloride present in each tablet was 5 mg. Excipients such as cellulose acetate, hypromellose, lactose, magnesium stearate, polyethylene glycol, polyethylene oxide, titanium dioxide, polysorbate 80, sodium chloride, and butylated hydroxytoluene were added to the dosage form. Twenty tablets were weighted accurately and crushed to a fine powder. A sufficient amount of powder for preparing a stock solution of 1.0 mg mL^{-1} was weighed and transferred into 25 mL volumetric flask and completed to volume with dimethylformamide. The content of the flask was sonicated for 30 min to provide complete dissolution and then completed to volume with the same solvent and centrifuged. An aliquot of the supernatant liquid was then transferred into a calibrated flask and a series of dilutions (1 to 18 μg mL^{-1}) were prepared with phosphate buffers at pH 2–10 and mixed with 1 mL KCl as supporting electrolyte having 50% DMF and then transferred to a volumetric cell and the desire waveform was recorded in the range −0.05 to −1.0 V. The drug content per tablet was determined referring to the related regression equations.

3. Results and discussion

3.1. Electrochemical behavior of oxybutynin chloride at HMDE

In order to understand the electrochemical process occurring on HMDE cyclic voltammetry, differential pulse adsorptive cathodic stripping voltammetry and squarewave adsorptive cathodic stripping voltammetry were carried out. In all electrochemical methods oxybutynin chloride gave one well-defined reduction peak in the mix aqueous solution which is attributed to the reduction of unsaturated –C≡C– bonds.

3.1.1. Cyclic voltammetric behavior

The reversibility of the reduction process was investigated by using cyclic voltammetry. The cyclic voltammogram of oxybutynin chloride 6.0 μg mL^{-1} in phosphate buffers (pH 2–10) containing 50% DMF at the hanging mercury drop electrode (HMDE) exhibits a single well-defined peak in the potential

range −0.45 to −0.55 V, at all concentrations due to the reduction of the –C≡C– groups. The peak potential shifted to a more negative value on the increase of the scan rate, confirming the irreversible nature of the reduction process. For a totally irreversible electrode reaction, the relationship between the peak potential (E_p) and the scan rate (υ) is expressed as [32]

$$E_p = (2.303RT\alpha n_a F)\log(RTK_f/\alpha n_a F) - (2.303RT\alpha n_a F)\log\upsilon.$$

A straight line observed when E_p is plotted against log υ at a particular concentration in pH 4 can be expressed by

$$y(E_p) = -0.042(\log\upsilon) - 0.44\times10^{-6}, \quad r^2 = 0.995.$$

From the slope of the straight line ($\Delta E/\Delta\log\upsilon$), the αn_a value is calculated by using the expression $\Delta E/\Delta\log\upsilon = -30/\alpha n_a$. The αn_a value is found to be 1.6 and is taken for further calculation for the number of electrons transferred. Fractional α values confirm the irreversible reduction of oxybutynin chloride. Moreover, the αn_a value and the number of protons corresponding to the rate-determining step were calculated at different pH values. In the pH range 2–7, αn_a was found to be 1.96 ± 0.37 which is close to the value obtained above. Using the following expression $\Delta E_{1/2}/\Delta\text{pH}\ 0.059/\alpha n_a$, p was found to be 1.81 ± 0.23.

For finding the adsorptive character of the drug at HMDE a cyclic voltammogram (Fig. 1, curve 1) was recorded after 60 s preconcentration at −0.1 V and its second cycle at the same mercury drop (Fig. 1, curve 2), dotted cyclic voltammetric curve, shows zero preconcentration. A maximum developed peak current (i_p) was achieved after preconcentration of the drug on to the electrode surface for 800 s (Fig. 2).

This behavior confirmed the adsorptive character of the drug at the mercury surface. The adsorption effect was also identified by a plot of $\log i_p$ vs $\log\upsilon$ giving a straight line which can be expressed by the equation: $\log i_p(\mu A) = -76.070 + 0.904\log\upsilon$ (V s^{-1}). A slope close to 1.0 shows that the compound was adsorbed on the electrode surface.

3.1.2. Effect of pH

The shape and characteristics of all voltammograms were strongly dependent on various electrolyte and pH of the medium. Britton–Robinson, acetate, borate, citrate, and phosphate buffer were used in the study and the best results with respect to sensitivity accompanied with sharper response were obtained with phosphate buffer (0.2 M). Stripping peak potential shifted toward more negative potential with increase in pH, indicating involvement of hydrogen ions in the electrode process. Variation of stripping peak potential of oxybutynin chloride as a function of pH (2.0–10) employing different voltammetric modes can be expressed by the following equations: cyclic voltammetry, $E_p = -161-59$ pH vs Ag/AgCl, $r = 0.991$ ($n = 7$); differential pulse adsorptive stripping voltammetry, $E_p = -156-54$ pH vs Ag/AgCl, $r = 0.99$ ($n = 7$); squarewave adsorptive stripping voltammetry, $E_p = -169-58$ pH vs Ag/AgCl, $r = 0.992$ ($n = 7$). Studies for the dependence of stripping peak on pH for CV, DPCAdSV, and SWCAdSV

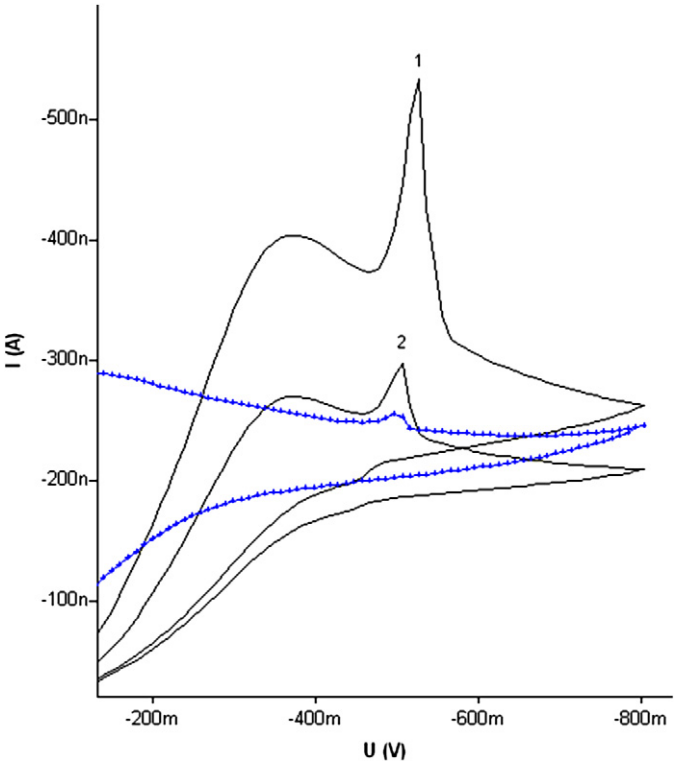

Fig. 1. Cyclic voltammograms for concentration 6.0 μg mL^{-1} oxybutynin chloride in phosphate buffer (pH 4) containing 50% DMF at a scan rate of 100 mV s^{-1}, equilibrium time = 10 s. (1) After 60 s preconcentration at −0.1 V and (2) its second cycle at the same mercury drop; dotted curve shows 0 s preconcentration.

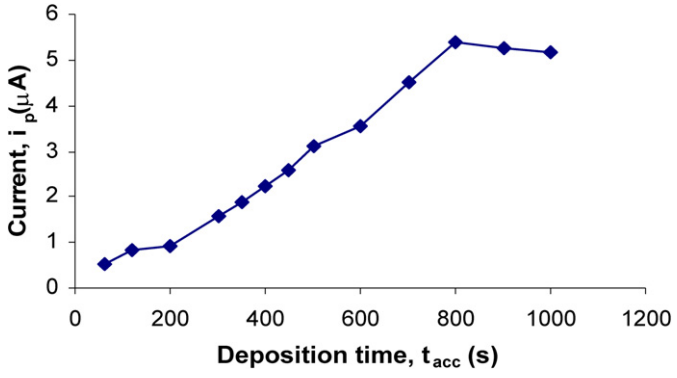

Fig. 2. Effect of the accumulation time (t_{acc}) on the squarewave peak current (i_p) for 1.0 μg mL^{-1} oxybutynin chloride in phosphate buffer (pH 4) containing 50% DMF; $E_{acc} = -0.1$ V; equilibrium time = 10 s; frequency $f = 50$ Hz; $\Delta s = 10$; and pulse amplitude $\Delta E_{sw} = 50$ mV.

(Fig. 3) were carried out to determine whether the electro-active species participate in equilibria involving protons directly and to obtain the pH range for maximum signal. Sharp response and better peak shape with maximum current were observed at pH 4 so this pH value was chosen as the working pH for further studies.

3.1.3. Controlled potential coulometric behavior

By using controlled potential coulometry, the number of electrons transferred, n values were calculated from the charge

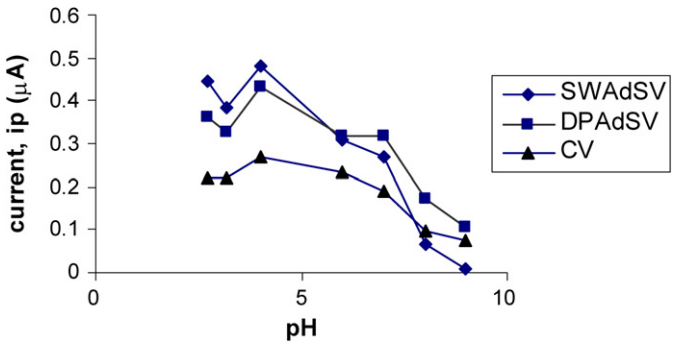

Fig. 3. The dependence of the squarewave adsorptive cathodic stripping voltammetric, differential pulse adsorptive cathodic stripping voltammetric, and cyclic voltammetric current (i_p) on phosphate buffer pH (2–10).

consumed by 6 μg mL^{-1} concentration of oxybutynin chloride. The charge consumed was determined in acidic medium. For this purpose 2 mL of 6 μg mL^{-1} solution of the electroactive species was placed in the cell and electrolysis was carried out at a potential −0.5 to −0.7 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 charge in coulombs, F is Faraday's constant, and N is number of moles of the substrate. The value is found to be two for the cathodic peak of the compound oxybutynin chloride in acidic medium.

Cyclic voltammograms of oxybutynin chloride just before and after electrolysis were taken and compared. The appearance of a small cathodic peak at -1.0 ± 0.2 V confirms the presence of –C=C– and this cathodic wave has been assigned to the reduction of the olefinic bond [33]. Before and after the electrolysis the products were also analyzed by IR spectrometry. The presence of peak in the range of 1649.14–1670.35 cm^{-1} in the product confirmed the reduction of the –C≡C– to –C=C– group. Voltammetric studies in conjunction with coulometry and TLC results confirm the formation of only one product. In the electrolyzed product only one product having R_f different from oxybutynin chloride was observed, indicating the formation of only one new product.

3.1.4. Optimization of operational parameters

Variation of the stripping voltammetric peak current of oxybutynin in phosphate buffer of pH 4 at HMDE was investigated using squarewave and differential pulse modes. Both techniques gave comparable results but squarewave cathodic adsorptive stripping voltammetry has been chosen as it is more sensitive than the other one but both techniques require some parameter adjustment. The important instrumental variables such as accumulation time (t_{acc}), accumulation potential (E_{acc}), pulse amplitude (ΔE_{sw}), scan increment (Δs), and frequency (f) were examined using the selected waveform.

The squarewave cathodic adsorptive stripping peak height for 1.0 μg mL^{-1} oxybutynin chloride depends strongly on the accumulation time, suggesting an effective adsorption of oxybutynin chloride on the HMDE. The peak current increased linearly with the increase of accumulation time up to 800 s and then the peak current leveled off (Fig. 2). This behavior may be attributed to the complete coverage of the mercury electrode surface with the drug species. Thus considerable increase in sensitivity can be achieved by application of adsorptive stripping voltammetric determination of oxybutynin chloride. But an accumulation time of 60 s was selected as an optimum in order to shorten analysis time as different concentrations of oxybutynin chloride lower than 18.0 μg mL^{-1} can be determined using this selected accumulation time. Furthermore, the longer the accumulation time the higher the efficiency of accumulation. When the accumulation time is longer than 60 s the peak current changes very slowly. Obviously the choice of preconcentration period required compromise between sensitivity and speed that is why in our work an accumulation time of 60 s was choosen.

The influence of accumulation potential (E_{acc}) on the cathodic peak current (i_p) of oxybutynin chloride was also examined over the potential range −0.05 to −0.9 V. Maximum development of the peak current was achieved at −0.1 V. Hence, an accumulation potential of −0.1 V was used throughout the present study. At more cathodic values a decrease in peak current was observed, indicating that the drug is no longer strongly adsorbed at potentials where the mercury is negatively charged with respect to the point of zero charge potential. The other dependencies were therefore measured at a potential of accumulation of −0.1 V.

Frequency was varied from 5 to 100 Hz using a scan increment of 10 mV, pulse amplitude of 50 mV, and 60 s accumulation time. A linear relationship was obtained between the peak current and the frequency of the signal up to 50 Hz. It was chosen to improve the sensitivity without any distortion of the peak or the baseline.

Study of the effect of scan increment on adsorptive cathodic peak current of the drug in phosphate pH 4 revealed that the peak current enhanced on the increase of scan increment (2–10 mV). A scan increment of 10 mV was preferable in the present study. At pulse amplitude 50 mV, the peak current was found to be much more sharp and defined.

The influence of the surface area of the working mercury electrode on the peak was also studied. As expected, an increase of the electrode surface area generated a higher peak current so a mercury drop of a large area (0.026 cm^2) was considered in the present study. The influence of the rest time was also considered and a time period of 10 s was chosen. Accordingly, the optimized operational conditions of the proposed stripping procedure were phosphate buffer at pH 4, $E_{acc} = -0.1$ V, $t_{acc} =$ 60 s, $f = 50$ Hz, $\Delta s = 10$ mV, $\Delta E_{sw} = 50$ mV, stirring rate = 2000 rpm, rest time = 10 s, and surface area of mercury drop = 0.026 cm^2.

3.2. Validation of the proposed method

The method was tested for linearity, specificity, precision and reproducibility. By using the above voltammetric modes, linear regression equations were obtained. Statistical evaluation of the regression lines regarding the standard deviation of residuals ($S_{y/x}$), standard deviation of the intercept (S_a) and standard deviation of the slope (S_b) is given in Table 1. The

Table 1
Analytical parameters for voltammetric determination of oxybutynin chloride using SWCAdSV and DPCAdSV modes

Parameter	SWCAdSV	DPCAdSV
Concentration range (μg mL^{-1})	1–18	1–17.6
LOD (μg mL^{-1})	0.1	0.23
LOQ (μg mL^{-1})	0.34	0.76
Mean found (%)	99.6	99.35
Correlation coefficient (r^2)	0.999	0.998
Slope (μA μg^{-1} mL^{-1})	8.62×10^{-6}	6.5×10^{-6}
Intercept (μA)	1.42×10^{-6}	1.12×10^{-6}
$S_{y/x}$[a]	5.2×10^{-5}	7.0×10^{-5}
S_a[b]	4×10^{-3}	5×10^{-3}
S_b[c]	3×10^{-5}	5×10^{-5}
%Error[d]	0.7	0.79
Applications	Tablets	Tablets

[a] $S_{y/x}$, is the standard deviation of the residuals.
[b] S_a, standard deviation of the intercept of regression line.
[c] S_b, standard deviation of the slope of regression line.
[d] % Error, $\%R{\cdot}\mathrm{SD}/\sqrt{n}$.

Table 2
Stripping voltammetric determination of oxybutynin chloride in Tropan tablets using SWCAdSV mode

Sample	Added amount (μg)	Amount found (μg)	Percentage recovery
Intraday precision	1.0	0.98	98.0
	1.0	0.986	98.6
	1.0	0.985	98.5
	1.0	0.992	99.2
Mean ± SD			98.57 ± 0.426
Interday precision	1.0	1.02	102
	1.0	0.981	98.1
	1.0	0.985	98.5
	1.0	0.993	99.3
Mean ± SD			99.475 ± 1.54

small figures point out the scattering and good linearity of the calibration graph. The intraday and interday precision on four successive days was evaluated through replicate analysis of Tropan tablets with 1 μg with percentage recoveries based on the average of four separate determinations, abridged in Table 2.

3.3. Robustness

The robustness was examined by evaluating the influence of small variation of some of the most important procedure variables including pH, preconcentration potential (E_{acc}), and preconcentration time (t_{acc}). The obtained result provided an indication of the reliability of the proposed procedure for the assay of oxybutynin chloride and hence it can be considered robust. The obtained mean percentage recoveries (Table 3) based on the average of five replicate measurements were not significantly affected within the studied range of variations of some operational parameters, and consequently the proposed procedure can be considered robust.

Table 3
Influence of variation of some of the operational parameters of the proposed procedure on the mean percentage recovery of 1.0 μg mL^{-1} bulk oxybutynin chloride; frequency, $f = 50$ Hz, and scan increment, $\Delta s = 10$ mV

Variables	Condition	(%)$R \pm$ SD ($n = 3$)
(i) pH		
3.8	$t_{acc} = 60$ s	99.3 ± 0.5
4.0	$E_{acc} = -0.1$ V	99.2 ± 0.24
4.2		98.4 ± 0.7
(ii) E_{acc} (V)		
−0.08	pH 4.0	99.4 ± 0.36
−0.10	$t_{acc} = 60$ s	99.7 ± 0.23
−0.12		98.6 ± 0.45
(iii) t_{acc} (s)		
58	pH 4.0	99.3 ± 0.6
60	$E_{acc} = -0.1$ V	98.0 ± 0.25
62		99.4 ± 0.35

Table 4
Quantification of oxybutynin chloride in Tropan tablets by the proposed SWCAdS voltammetric procedure

Concentration added[a] (μg)	Concentration found[a] (μg)	%R	%$R{\cdot}$SD
1.0	0.99	99.0	1.2
3.0	2.96	98.6	0.9
5.0	5.10	100.2	0.9
8.0	7.97	99.6	0.7
11.0	11.05	100.4	1.1

[a] Average of five replicate measurements.

3.4. Ruggedness

The ruggedness test of the analytical assay method is defined as degree of reproducibility of assay results obtained by the successful applications of the assay over time and multiple laboratories and analysts. Two analysts analyzed the same standard with SWCAdSV and DPCAdSV methods using the same instrument. The methods were found to be rugged with the results of variation coefficients 0.83 and 0.73% for SWCAdSV, and 0.95 and 1.2% for DPCAdSV methods for first and second analysts, respectively. The results show no statistical differences between different analysts.

3.5. Applications

The proposed procedure was applied to the analysis of Tropan tablets. The precision was estimated for 1.0–11.0 μg of the drug using the calibration graph and standard addition method. Representative voltammograms are shown in Fig. 4. The obtained mean percentage recoveries (%R) and the relative standard deviations (%$R{\cdot}$SD) based on the average of five replicate measurements were found to be 98.6–100.2 and 0.9–1.2, respectively (Table 4). The procedure did not require any time-consuming extraction steps prior to the assay of the drug.

4. Conclusion

The electrode reaction pathway at the hanging mercury drop electrode in phosphate buffers 2.0–10.0 has been elucidated.

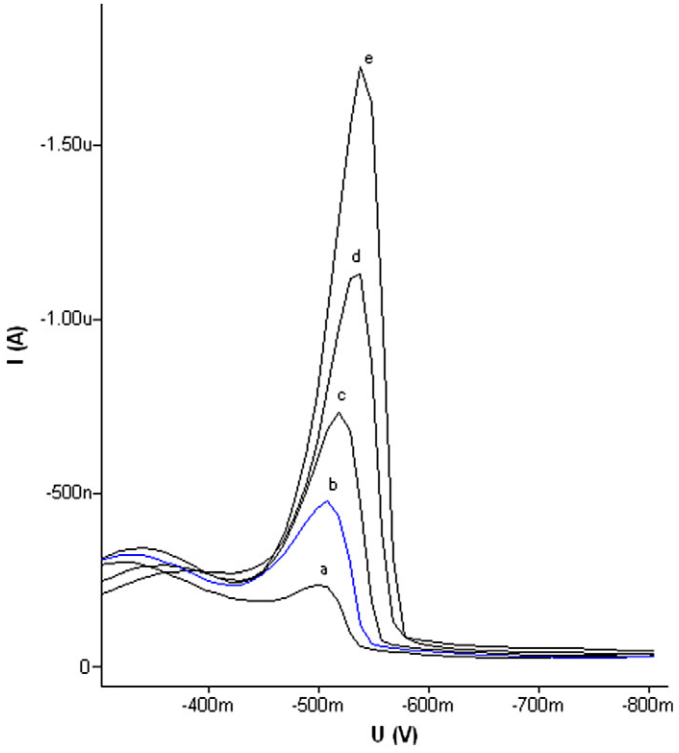

Fig. 4. The dependence of the SWCAdS voltammetric current for oxybutynin chloride at different concentrations; phosphate buffer, pH 4 (0.2 M), $E_{acc} = -0.1$ V, $t_{acc} = 60$ s, frequency $f = 50$ Hz, pulse amplitude $\Delta E_{sw} = 50$ mV, and scan increment $\Delta s = 10$ mV. (a) 1.0 μg, (b) 3.0 μg, (c) 5.0 μg, (d) 8.0 μg, and (e) 11.0 μg.

The electrochemical reduction of oxybutynin chloride under the conditions described in this work is an irreversible process controlled by adsorption. The validated SWCAdS and DPCAdS voltammetric procedure could be used successfully to determine oxybutynin chloride in bulk form and pharmaceutical formulation. In these methods, a high percentage of recovery shows that the compounds are almost completely extracted from tablet formulations and the results indicate that the developed method can be used to quantify oxybutynin chloride without interference from other ingredients. Furthermore, in an earlier HPLC method [18] of determination of oxybutynin chloride in dosage form a lower limit of detection was found to be 0.5 μg mL^{-1} but in the present developed method it could be estimated up to a level of 0.1 μg mL^{-1} (SWCAdSV) and 0.23 μg mL^{-1} (DPCAdSV) using a 60 s preconcentration time. By applying a higher preconcentration time onto the mercury electrode we can quantify up to nanogram levels. The proposed methods have distinct advantages over other existing methods regarding sensitivity, time savings, and minimum detectability. In addition no sophisticated instrumentation is required. Consequently, the proposed methods have the potential of a good analytical alternative for determining oxybutynin chloride in pharmaceutical formulations.

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