

Research Article

Voltammetric assay of duloxetine hydrochloride at carbon-based electrode modified by titanium dioxide nanoparticles enriched with multi-walled carbon nanotubes

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Abstract

A rapid voltammetric method was introduced and validated to determine duloxetine hydrochloride (DUL) via a newly introduced electrochemical sensor. Cyclic and square wave voltammetry modes were used to investigate the electrochemistry of DUL. Several experimental parameters as pH, electrode modifiers, scan rate, and deposition time were investigated to establish the optimum parameters required for analysis. A linear response ranged from 3.0×10^{-6} to 2.0×10^{-4} mol L⁻¹ with a detection limit of 4.0×10^{-7} mol L⁻¹. The proposed method has been successfully applied to determine DUL in its active pharmaceutical preparation as well as spiked urine.

Introduction

Duloxetine hydrochloride (DUL), serotonin and norepinephrine reuptake inhibitor, is known as N-methyl-3-(naphthalen-1-yloxy)-3-(thiophene-2-yl) propan-1-amine hydrochloride (Figure 1). Serotonin and norepinephrine are the two neurotransmitters whose lack at synapses cause depression therefore this drug was initially used in the treatment of depressive and anxiety disorders [1], and also it was used to treat fibromyalgia and chronic musculoskeletal pain. The U.S. Food and Drug Administration (FDA) approved (DUL) to treat depression and diabetic polyneuropathy [2], anxiety disorder [3], fibromyalgia [4], and chronic musculoskeletal pain. DUL is used also in treatment of stress urinary incontinence [5,6].

One official analytical method was documented for determination of DUL in bulk [7]. Literature survey reveals variety of analytical methods including spectrophotometry [8-15], spectrofluorimetry [16], high-performance liquid chromatography [17-26], potentiometry [27,28], gas chromatography-mass spectrometry [29], capillary electrophoresis [30-32], and electrochemistry [33].

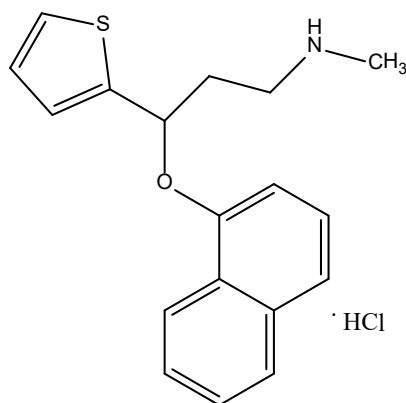


Figure 1. Chemical structure of DUL

Attention was directed recently to chemically modified electrodes due to their important effects in improving both peak potential and current. Electrode modification by different modifiers has been reported recently with improvement of sensitivity, selectivity, and detection limit [34-37].

In the presented work, a rapid, simple and non-expensive voltammetric technique is described for the determination of DUL in bulk, pharmaceutical preparation and urine at carbon paste electrode modified with titanium dioxide nanoparticles enhanced by multi-walled carbon nanotubes (TMCPE).

Materials and Methods

Materials and reagents

DUL was obtained from Eli Lilly (purity 99.99%, according to supplier certificate). Cymbalta hard gastro-resistant capsules (Batch No.C428554) labeled to contain 30 mg DUL per capsule, manufactured by Eli Lilly (Netherlands) were purchased from the local market. Britton-Robinson (BR) buffers ranged from pH 2.0 to 11.0 were prepared as described before [38], Graphite powder and paraffin oil, titanium (IV) oxide nano particles, (purity of 99.5%) and multiwalled carbon nanotubes (MWCNTs) (purity > 95%) were supplied from Sigma-Aldrich. 1.0×10^{-2} mol L⁻¹ of DUL in doubly distilled water was prepared.

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Instruments

Experiments were done utilizing Bio-logic Science Instruments Pvt. Ltd. (France) with EC-Lab software. A platinum wire (BASi model MW-1032, USA) and Ag/AgCl (3.0 mol L⁻¹ NaCl) (BASi model MW-2063, USA) were used as the auxiliary electrode and reference electrode, respectively. A JENWAY 3510 pH meter (Staffordshire, England) was utilized to adjust pH. Scanning electron microscope (SEM) measurements were done utilizing a JSM- 6700F scanning electron microscope (Japan Electro Company).

Modified electrode

Carbon paste electrode (CPE) and multiwalled carbon nanotubes modified carbon paste electrode (MCPE) were prepared as described before [39].

TMCPE 1% (w/w) was prepared by the same previous manner, but with addition of 10 mg MWCNTs and 10 mg titanium (IV) oxide nanoparticles to 980 mg graphite powder in ethyl ether with continuous stirring to make them homogenous and allowed to evaporate then mixed with a suitable amount of paraffin oil in a glassy mortar until a homogeneously prepared paste was resulted. The hole of the electrode was filled with the paste and smoothed on a filter paper until the shiny surface is appeared.

Procedures

Firstly, TMCPE was cycled in the potential range of (0-1.42 V) in BR buffer (pH 6.0) at a scan rate of 100 mVs⁻¹ for many times until a reproducible response was obtained. After that, a proper amount of DUL was added and cyclic voltammograms were recorded at the same potential range and scan rate. Square wave voltammograms were recorded from 0.2-1.6 V at a scan rate 100 mVs⁻¹.

Determination of DUL in bulk: Square wave voltammetry (SWV) was utilized to determine DUL in bulk. Aliquots of DUL (1.0 × 10⁻³ mol L⁻¹) were transferred using micropipette to 5.0 mL BR buffer (pH 6.0) in the electrolytic cell. Voltammetric analyses were done and square wave voltammograms were recorded at TMCPE. Calibration graphs were obtained by plotting the anodic peak current versus final concentration of DUL.

Determination of DUL in Capsules: Ten hard capsules of Cymbalta were open; their contents are collected, finely powdered and mixed well. Amount of the powder required to prepare 1.0 × 10⁻³ mol L⁻¹ DUL was added to volumetric flask (100 mL) containing 60 mL doubly distilled water. The flask was sonicated for 25 min and completed up to 100 mL with doubly distilled water, mixed well and filtered to remove all excipients. Aliquots of DUL were transferred to the cell and the procedure as for bulk was done.

Determination of DUL in Urine: Urine (1.0 mL) was added to BR buffer of pH 6.0 (9.0 mL) without any pre-treatment. Aliquots of DUL (1.0 × 10⁻³ mol L⁻¹) were transferred to the cell and the procedure as for bulk was done.

Results and Discussion

Electrochemistry of DUL

Figure 2A exhibits anodic peaks during the forward direction and there are no peaks during the reverse direction over the pH range (2.0-11.0), denoting to the irreversibility of DUL oxidation. The peak potential (E) has shifted less positively with increasing the pH denoting to participation of protons in the oxidation process. The peak potential varies as a function of pH in two linear parts (Figure 2B): the first one from pH 2.0 to 7.0 (E (V) = 1.282 - 0.009 pH, correlation coefficient (r²) = 0.9998) and the other from pH 8.0 to 11.0 (E (V) = 1.721 - 0.083 pH, r² = 0.9988). pH 6.0 displays the highest and well-defined oxidation peak current (I) of DUL (Figure 2C) that's why it was taken as the optimum pH for the rest of experiments.

Influence of electrode modifications

A comparison was done between CPE, MCPE and TMCPE by applying the recommended procedure on each electrode for DUL using cyclic voltammetry to determine the electrode of the highest response and consequently the highest sensitivity which is needed to complete the work. Figure 3 shows that the oxidation peak of DUL has the following values of current and potential for CPE (11.03 μA, 1.224 V), MCPE (12.37 μA, 1.194 V) and TMCPE (15.00 μA, 1.186 V), subsequently TMCPE was selected for subsequent experiments. Figure 4 shows that the surfaces of CPE and MCPE as separate layers and protrusions, respectively, while irregular surface as moon surface of TMCPE giving a high electro-active surface area of the electrode resulted in its higher response.

Influence of scan rate

Scan rate (v) effect on oxidation current of DUL (I) was studied in pH 6.0 (BR buffer) at TMCPE (Figure 5), from which we got a linear relationship between log I and log v. Linear relation was obtained and log I = -0.053 + 0.63 log v, r² = 0.9995. The slope was found to be 0.63 which indicates that the oxidation reaction taking place through diffusion-controlled process with some adsorption [40].

Figure 6 exhibits log E versus log v, an can be calculated from the slope of the relation (α is the transfer coefficient, n is the number of electrons) [41] based on Laviron equation $E = E^0 + 2.303RT/\alpha nF[\log RTK^0/\alpha nF + \log v]$, where F is the Faraday constant, R is the gas constant and T is the temperature.

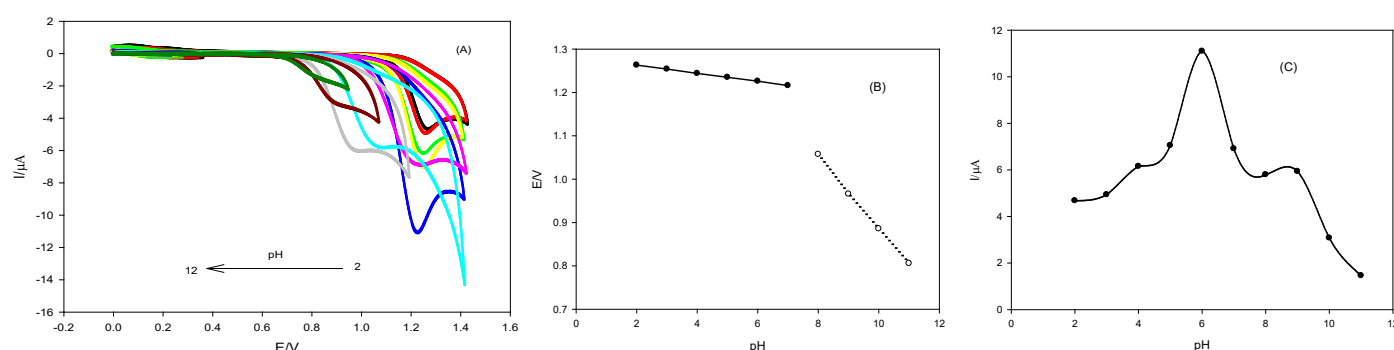


Figure 2. Cyclic voltammograms of DUL (1.0 × 10⁻³ mol L⁻¹) at CPE in different BR buffers. (A), Peak potential (B) and current (C) plots as a function of pH. Scan rate of 100 mV s⁻¹

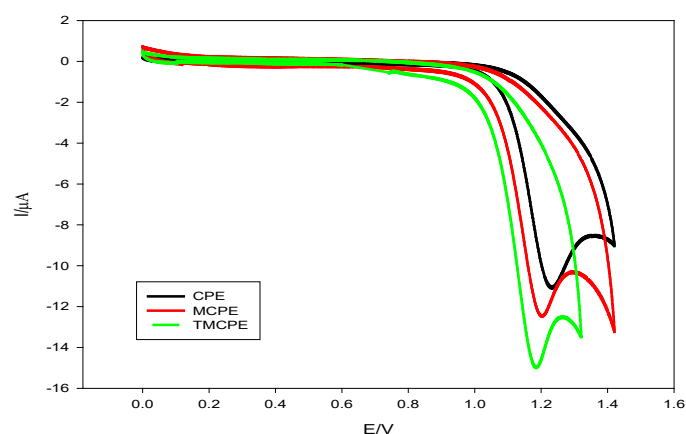


Figure 3. Cyclic voltammograms of DUL ($1.0 \times 10^{-3} \text{ mol L}^{-1}$) in BR buffer (pH 6.0) at different electrodes at a scan rate of 100 mVs^{-1}

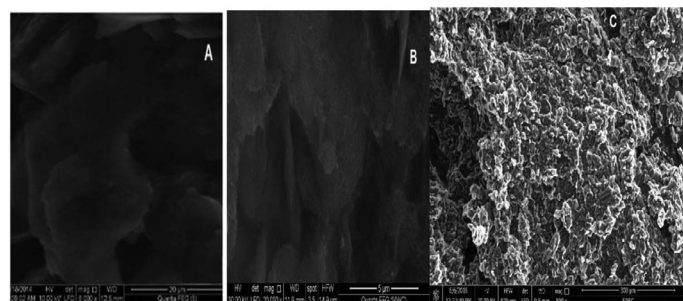


Figure 4. The pictures of SEM of CPE (A), MCPE (B) and TMCPE (C)

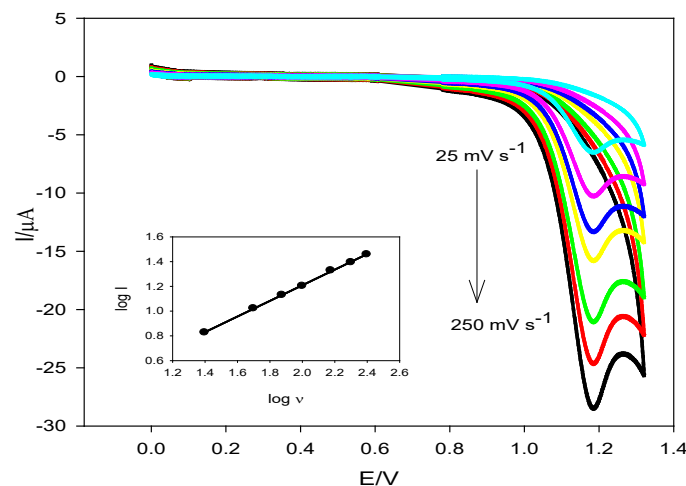


Figure 5. Cyclic voltammograms of DUL ($1.0 \times 10^{-3} \text{ mol L}^{-1}$) using different scan rates ($v = 25\text{--}250 \text{ mV s}^{-1}$) in pH 6.0 (BR buffer) at TMCPE. The inset: $\log I$ vs. $\log v$

In this case and from figure 6, the slope value is 0.057; an values were calculated to be 1.042. $\alpha \approx 0.5$, thus, $n \approx 2$ assured the suggested mechanism of oxidation of DUL (Scheme 1).

The diffusion coefficient (D_0) of DUL was calculated by Randles-Sevcik equation: $I = (2.99 \times 10^5) n A C_0 D_0^{1/2} v^{1/2}$ where A is the electrode surface area (cm^2) and C_0 is the concentration of DUL ($1.0 \times 10^{-3} \text{ mol L}^{-1}$) [42]. D_0 was found to be $1.76 \times 10^{-5} \text{ cm}^2 \text{ s}^{-1}$.

It is worthy to mention that the electro active surface area of TMCPE was calculated by Randles-Sevcik equation using $1.0 \text{ mmol L}^{-1} \text{ K}_3\text{Fe}(\text{CN})_6$ in $0.1 \text{ mol L}^{-1} \text{ KCl}$ (D_0 of $\text{K}_3\text{Fe}(\text{CN})_6$ is $7.6 \times 10^{-6} \text{ cm}^2$

s^{-1}) at TMCPE through applying different scan rates and found to be 0.115 cm^2 .

Deposition time

Deposition time (t) influences on the peak current of DUL at TMCPE (Figure 7). The current increases as deposition time increases reaching a steady state at 35 s but the broadness of the peak started to increase with increasing time after 5 s, so 5 s was taken as the optimum deposition time for subsequent measurements.

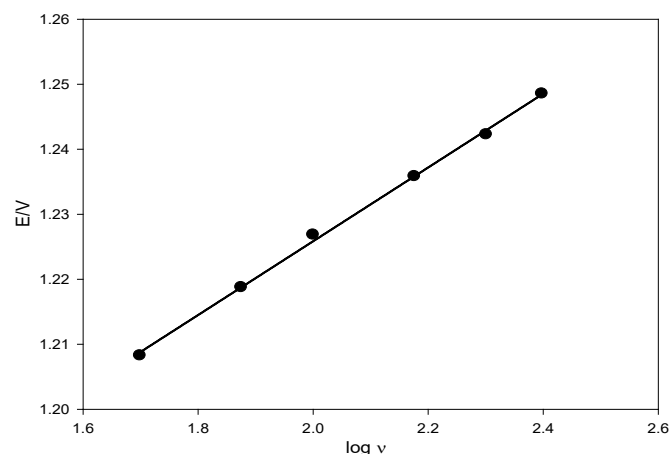


Figure 6. Relation between the oxidation peak potential of DUL versus logarithm of the scan rates

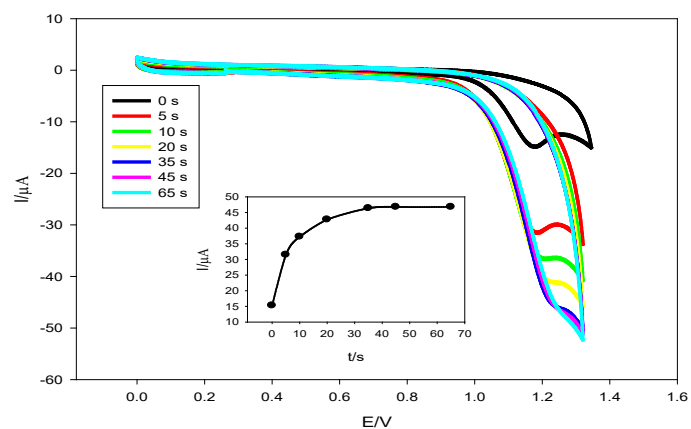
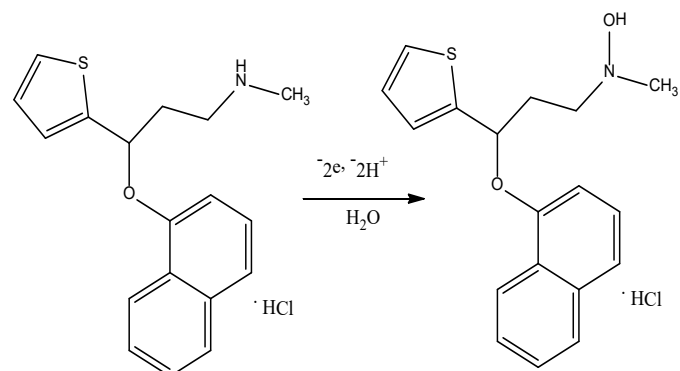


Figure 7. Cyclic voltammograms of DUL ($1.0 \times 10^{-3} \text{ mol L}^{-1}$) at TMCPE in pH 6.0 (BR buffer), $v = 100 \text{ mV s}^{-1}$. The inset: I versus t



Scheme 1. The suggested mechanism of oxidation of DUL

Validation

The presented method was validation according to the International Conference on Harmonization (ICH) Tripartite Guideline Q2 (R1) [43].

Determination of DUL: Figure 8 presents the linearity of DUL at TMCPE over the concentration ranges of 3.0×10^{-6} - 2.0×10^{-4} mol L⁻¹, $r^2 = 0.9996$. The regression data of this linear relation was tabulated and shown in Table 1.

The limit of detection (LOD) and of quantification (LOQ) for DUL were found to be 4.0×10^{-7} mol L⁻¹ and 1.33×10^{-6} mol L⁻¹, respectively. 5.96×10^{-6} mol L⁻¹ DUL (Five measurements) was used to determine repeatability of the suggested SWV method, recoveries range was (99.826% - 100.32%) and the relative standard deviation (RSD) was 1.95% indicating precision of the proposed method.

Robustness of the method using 1.38×10^{-5} mol L⁻¹ DUL solution was demonstrated by repeating experimental procedure several times but with making minor change in optimum experimental parameters such as changing buffer pH by ± 0.2 , v by ± 5 and t by 5 ± 1 . The RSD values were 0.743%, 0.688% and 0.858%, respectively. Therefore, the proposed method was unaffected by these minor changes.

Table 2 presents a comparison between the suggested method and the reported methods for DUL determination. The proposed method was found to be more sensitive than the reported spectrophotometric methods [10-14], and chromatographic methods [16-20].

Assay of DUL in dosage form: The ability of the proposed method in determining DUL in capsules without interference from the present excipients reflected and proved its selectivity. The determination of DUL in Cymbalta capsules using TMCP was done successfully using standard addition method. Neither sample pretreatment nor tedious extraction steps were required to be done before the experimental investigation. Known concentrations of DUL (2.99×10^{-6} , 2.91×10^{-5} , 6.54×10^{-5} , 9.91×10^{-5} and 1.30×10^{-4} mol L⁻¹) were added to sample solution (6.95×10^{-6} mol L⁻¹) as shown in table 3. The mean recovery and mean RSD were 100.198% and 0.2067%, respectively.

Assay of DUL in Urine: Figure 9 presents the calibration graph DUL in urine. Linearity ranged from 7.0×10^{-6} mol L⁻¹ to 1.1×10^{-4} mol L⁻¹, $r^2 = 0.9994$, LOD and LOQ were 6.9×10^{-6} mol L⁻¹ and 2.3×10^{-6} mol L⁻¹, respectively (Table 1).

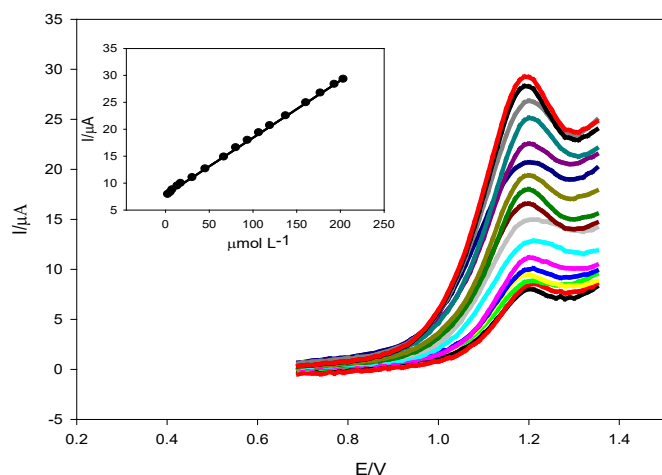


Figure 8. The influence of changing the concentration of DUL at TMCPE in pH 6.0 (BR buffer), $v = \text{mV s}^{-1}$. The inset: the peak current versus the concentration of DUL

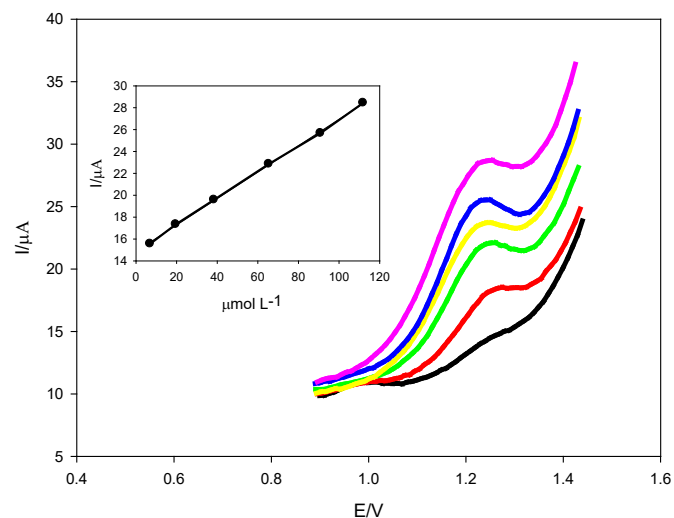


Figure 9. Square wave voltammogram of DUL spiked in urine at TMCPE in pH 6.0 (BR buffer). The inset: the peak current versus the concentration of DUL

Table 1. Parameters of the regression equations for quantitative determination of DUL in bulk and in human urine sample

Parameters	DUL	DUL in urine
Linearity (mol L ⁻¹)	3.0×10^{-6} - 2.0×10^{-4}	7.0×10^{-6} - 1.1×10^{-4}
Slope	0.106	0.121
Intercept	7.8	14.864
r^2	0.9996	0.9994
LOD (mol L ⁻¹)	4.0×10^{-7}	6.9×10^{-6}
LOQ (mol L ⁻¹)	1.33×10^{-6}	2.3×10^{-6}

Table 2. Comparison between suggested method and some methods to determine DUL in literature

Method	DUL linear range	Reference
Proposed voltammetry (mol L ⁻¹)	3.0×10^{-6} to 2.0×10^{-4}	This work
μg mL ⁻¹	(1.00-66.78)	
Spectrophotometry (μg mL ⁻¹)	5-30	[10]
	5-50	[11]
	10-50	[12]
	5-25	[13]
	2.5-25	[14]
Chromatography (μg mL ⁻¹)	20-120	[16]
	2-10	[17]
	30-90	[18]
	8-56	[19]
	20-120	[20]

Table 3. Determination of DUL in Cymbalta capsules

Drug	Added	Taken	Found	%Recovery
	2.99×10^{-6}		9.91×10^{-6}	100.10
	2.91×10^{-5}		3.56×10^{-5}	99.972
	6.54×10^{-5}	6.95×10^{-6}	7.16×10^{-5}	100.26
	9.91×10^{-5}		1.05×10^{-4}	100.14
	1.30×10^{-4}		1.36×10^{-4}	100.52
Mean ^a				100.198
SD ^b				0.2071
%RSD ^c				0.2067
SE ^d				0.0926

^aMean for five determinations.

^bSD is the standard deviation.

^cRSD = (SD/mean) \times 100.

^dSE is the standard error.

Conclusion

In the presented work, square wave voltammetric technique was utilized for fast and sensitive determination of DUL in bulk, capsules and urine through the oxidation of DUL at TMCPE. The presence of modifiers caused an increment in the peak current. SWV method has also been fully validated.

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