

Novel Approach for the Cyclic Voltammetric Determination of an Antidepressant Drug (Dosulepin) in Pharmaceutical Formulations

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ABSTRACT

Background: This research was focused on the development of a quick, simple, precise, and cost-effective voltammetric method for quantifying dosulepin. **Materials and Methods:** The antidepressant drug (dosulepin) was assessed in pharmaceutical formulations using square wave voltammetric (SWV) and Differential pulse voltammetric (DPV) techniques at a glassy carbon potentiometric working electrodes (GCE). **Results:** Dosulepin demonstrated a single clear and sharp cathodic peak in the applied potential -0.7 to -0.75 V versus Ag/AgCl/KCl reference electrode. Results from cyclic voltammetry, DPV, and SWV revealed one reduction wave with a peak potential of -0.7 V at pH 7. The proposed method's excellent sensitivity was demonstrated by the obtained LOD of 7.686×10^{-9} mol L⁻¹ and a LOQ of 2.589×10^{-7} mol L⁻¹ bulk were by applying Differential Pulse Voltammetry method. On other hand a LOD of 1.735×10^{-7} mol L⁻¹ and

a LOQ of 5.785×10^{-7} mol L⁻¹ bulk dosulepin were achieved by applying the Square Wave Voltammetry method. **Conclusion:** The suggested methods might be recommended for usage in quantitative detection, product testing, and research laboratories.

Keywords: DPV, SWV, GCE and Drug formulations.

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INTRODUCTION

Dosulepin an antidepressant drug may enhance the effects of alcohol, and this combination has been linked to at least one fatality.¹⁻³ Dosulepin can inhibit the antihypertensive effects of guanethidine and other adrenergic neuron blockers.⁴ Dosulepin's sympatho-mimetic effects might be amplified by sympatho-mimetics. Dosulepin's anticholinergic and antihistamine properties may enhance the effects of anticholinergic and antihistamine drugs, thus these combinations are not recommended. Diuretics may increase the effects of dosulepin on postural hypotension. Dosulepin's propensity to lower the seizure threshold may impair the effectiveness of anticonvulsants.^{5,6} Dosulepin is quickly absorbed from the gastrointestinal tract and substantially metabolized in the liver on first-pass into its main active metabolite, northiaden (desmethyl dosulepin). Within 2-3 hr of oral treatment, plasma concentrations range from 30.4 mg/mL to 278.8 mg/mL. It passes through the placenta and the blood-brain barrier and is disseminated in breast milk. It binds to plasma proteins 84 percent of the time and has a half-life of 51 hr in the body. When using dosulepin for the first time, many people encounter moderate, temporary side effects. Dry mouth, metallic taste, constipation, big bowel motions, and impaired eyesight are some of the symptoms. Heart palpitations, trouble urinating, tremors, low blood pressure (particularly if you get up quickly), sexual issues, sweating, and sensitivity to sunlight are all possible adverse effects.⁷⁻¹⁰ The chemical structure of dosulepin Hydrochloride is shown in scheme-I. Because of the similarities of electrochemical with biological mechanisms, it may be believed that the oxidation/reduction mechanisms occurring at the electrode and also in the human body follow similar principles. Cyclic voltammetry can be used to analyze biologically significant compounds electro-analytically in attempt to decide the molecule in various ways.¹¹⁻¹³ As a well-known and valuable medication, it has sparked a lot of analytical interest, and various techniques have been reported for evaluating it in pharmaceutical preparations or biological fluids. Due

to the great sensitivity and simplicity of voltammetric methods, as well as a dearth of published data on dosulepin's electrochemical activity, this research focused on its voltammetric behavior. Electrochemical techniques not only offer a unique perspective on drug quantification, but they may also offer the finest solutions to a range of pharmaceutical analytical problems. Electroanalytical techniques have proven to be sensitive and reliable for assessing in untreated materials, despite their relatively simple and affordable apparatus and quick analysis time.¹⁴⁻¹⁶ The current work provided a completely validated, simple, quick, and more sensitive technology for investigating dosulepin in pharmaceutical formulations using DPV and SWV at the GCE. The method has the advantage of not necessitating any sample processing or time-consuming extraction processes before the drug assay. To the best of our knowledge, hardly a study on the evaluation of dosulepin drug in pharmaceutical preparations utilizing a GCE as working electrode has been published. Thus, this paper offers a cyclic voltammetric analysis of dosulepin's electrochemical behaviour in pharmaceutical tablets employing GCE.

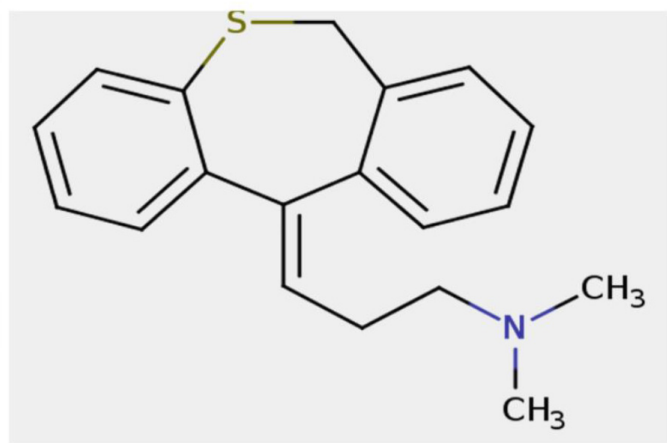
MATERIALS AND METHODS

Reagents and Materials

Sun Pharma India Limited provided the dosulepin, that was not purified before usage. In distilled water, a standard stock solution of bulk dosulepin (1×10^{-3} mol L⁻¹) was produced and kept at 4°C until analysis. Two dosulepin tablet samples were measured and processed into a powder form in a mortar. A 100 mg dosulepin component was weighed carefully and inserted in a 10 ml measuring flask with 8 ml DMSO. Before adding DMSO to bring it up to volume, the contents of the flask were repeatedly stirred for 10 min. The solution was then filtered using 0.45 mm pore size Whatman filter paper. Daily, bulk dosulepin samples (1×10^{-7} to 1×10^{-4} mol L⁻¹) were produced by diluting the normal bulk dosulepin

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Scheme 1: Chemical Structure of Dosulepin.

solution with distilled water immediately before use. A series BR buffer having pH values varying from 4-13 was created as a supporting electrolyte.

Instrumentation

A Model DY2100 Series Potentiostat was used for electrochemical procedures, as well as an auto-linked PC with software applications is used for comprehensive control of the study, documentation, and medication. The working electrode was activated glassy carbon, whereas the reference electrode was Ag/AgCl (3 M KCl) and the Pt wire electrode is used as an auxiliary electrode. A magnetic stirrer and a mixing bar provided convective transport during the pre-concentration step. The pH levels of the investigated solutions were determined using a digital pH meter (CHINO-DB-1011). The reference electrodes of the digital pH meter were a glass electrode and a calomel electrode that had been standardized utilizing buffers solutions of known pH.

Pre-treatment of the Glassy Carbon Electrode

Prior to experiments, with a CHI polishing kit the working GCE electrode was refined to a perfect shine and thoroughly cleaned with double distilled water.

General Analytical Procedure

Prior to analysis, 10 ml of the entire solution, comprising the BR buffer solution and the requisite quantity of dosulepin bulk sample, was placed in the electrochemical cell and ran through a purified deoxygenated N_2 flow for 10 min to remove the oxygen gas. The electrochemical preprocessing was always carried out in the same solution as the measurement. While the solution was agitated at 2000 rpm, dosulepin was accumulated at the working electrode for a predetermined amount of time. After a delay, SWV stripping in the cathodic path from potential range of 0.0 to 1.0 V versus an Ag/AgCl/KCl reference electrode at room temperature was conducted. Under identical settings, voltammetric measurements of differential pulses and square waves were performed. The calibration plot and the internal standard techniques were used to quantify dosulepin. The reversibility of the dosulepin drug reduction process was investigated using cyclic voltammetry methods.

RESULTS

Dosulepin's antidepressant drug electrochemical behavior on a GCE working electrode was studied using cyclic voltammetry (CV), DPV, and

SWV techniques. At all electrolytic concentrations, dosulepin generated a distinct and clear reduction signal in BR buffer solution.

Cyclic Voltammetric Studies

In the applied potential of -0.7 to -0.75 V against Ag/AgCl/KCl reference electrode, dosulepin displayed one clear and very well cathodic signal. pH was controlled using a variety of buffers, including Britton Robinson buffer. The experiment was carried out at a pH of 4-13 with a dosulepin solution concentration of 2 g/ml. CV, DPV, and SWV measurements at pH 7 indicated a single reduction pulse with a maximum potential of -0.7 V. The effect of scan rate (ν) on the peak current at cathode (i_p) and peak potential (V) was investigated using a solution of varying concentrations such as 1×10^{-5} mole L^{-1} , 2×10^{-5} mole L^{-1} , 3.0×10^{-5} mole L^{-1} , 4×10^{-5} mole L^{-1} , and 5.0×10^{-5} mole L^{-1} . The cyclic voltammograms (CV) were recorded at 5, 10, 20, 50, and 100 mVs^{-1} scan rates. On cyclic voltammograms, Figure 1 displays a clearly apparent drop peak at -0.7 V. A straight line was obtained when the peak potential ($-E_p$) was evaluated against by the logarithm of scan rate ($\log \nu$) at a certain concentration at pH 7 shown in Figure 2. When peak current (i_p) is compared against with the square root of scan rates ($\nu^{1/2}$) as shown in Figure 3, a straight line is formed. A perfect slope (Figure 4) of 0.262 was obtained by plotting the log of peak current ($\log i_p$) vs log of scan rate ($\log \nu$). The influence of scan rate on cyclic voltammetric parameters of dosulepin with the concentration $1 \times 10^{-5} mol L^{-1}$ and at pH 7 were given in Table 1. At 20 mV/sec , the effect of concentration on dosulepin cyclic voltammetric parameters was measured. At pH 7, several concentrations of dosulepin (1×10^{-5} to 6×10^{-5} mole L^{-1}) were used to determine the scan rate. The influence of dosulepin concentrations on the pattern of cyclic voltammogram is depicted in Figure 5. A straight line emerged from a graph of peak current (i_p) vs. concentration (C_0) for dosulepin sample in Figure 6. Table 2 showed the influence of concentration on the cyclic voltammetric characteristics of dosulepin at a scan rate of 20 mV/sec .

Analyses of Dosulepin in Pharmaceuticals

DPV, SWV and GCE have been employed to produce cyclic voltammograms of dosulepin sample (in bulk) with in Britton Robinson (BR) buffer solution at nearly neutral pH to improve the trace identification of drug.

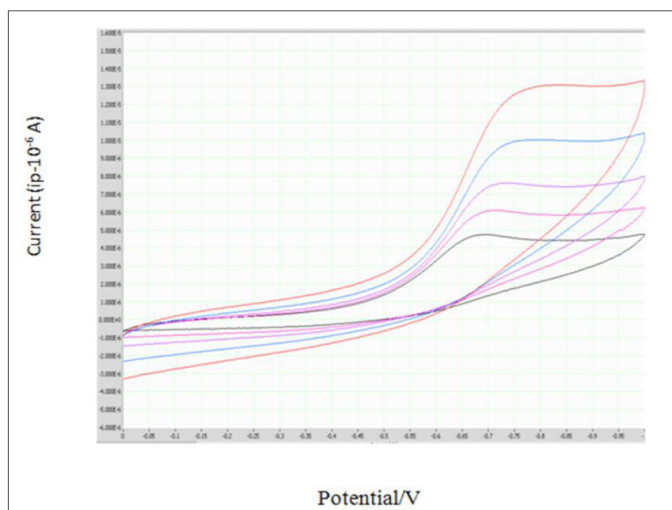


Figure 1: Cyclic voltammograms of $1 \times 10^{-5} mol L^{-1}$ Dosulepin in BR buffer pH 7 at different scan rates: (a) 5 mVs^{-1} (b) 10 mVs^{-1} (c) 20 mVs^{-1} (d) 50 mVs^{-1} (e) 100 mVs^{-1}

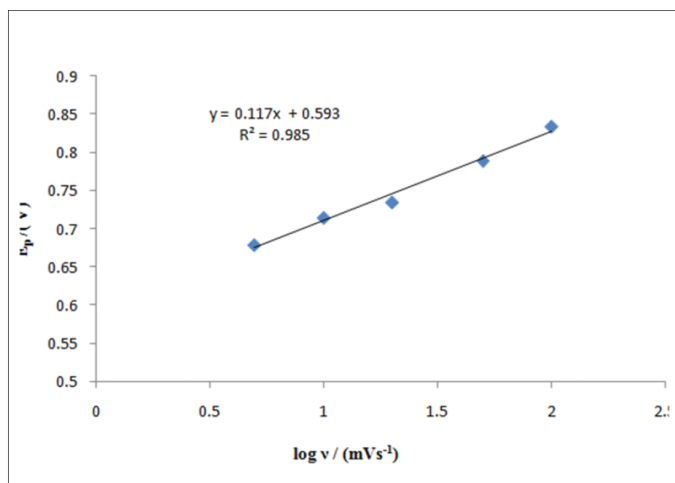


Figure 2: Plot of peak potential ($-E_p$) vs logarithm of scan rate ($\log v$) for the cyclic voltammograms of $1 \times 10^{-5} \text{ mol L}^{-1}$ Dosulepin in BR buffer at pH 7.

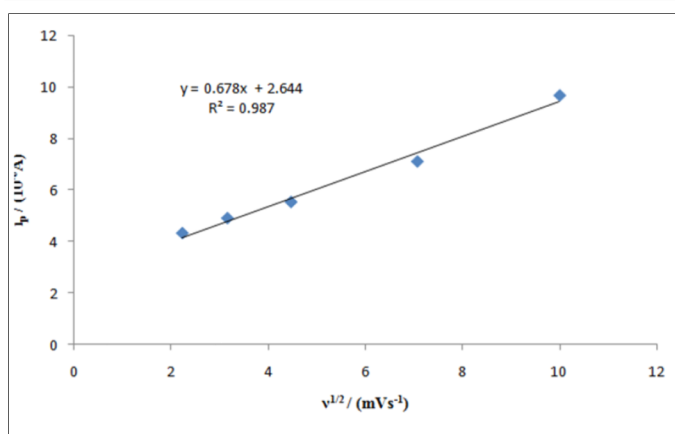


Figure 3: Plot of peak current (i_p) vs square root of scan rates ($v^{1/2}$) for the cyclic voltammograms of $1 \times 10^{-5} \text{ mol L}^{-1}$ Dosulepin in BR buffer at pH 7.

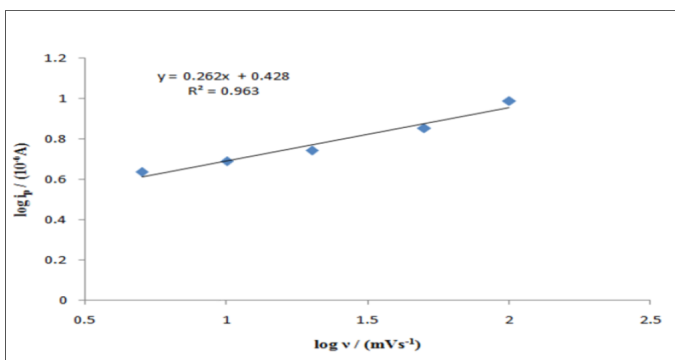


Figure 4: Plot of logarithm of peak current ($\log i_p$) vs logarithm of scan rate ($\log v$) for the cyclic voltammograms of $1 \times 10^{-5} \text{ mol L}^{-1}$ Dosulepin in BR buffer at pH 7.

Differential Pulse Voltammetry (DPV) Method

The GCE has established the best pulse-height scan rate and pre-concentration parameters for measuring bulk dosulepin employing

Table 1: Effect of scan rate on cyclic voltammetric parameters of Dosulepin at pH 7 (concentration $1 \times 10^{-5} \text{ mol L}^{-1}$).

S. No.	SR(v) (mV/sec)	I_p (V/2) (mV/2)	log.SR (mV/sec)	$-E_p$ (V)	$-E_{p/2}$ (V)	I_p (10^{-6} A)	$\log I_p$ (10^{-6} A)	αn_a
1.	5	1.9284	0.69897	0.679	0.630	4.312	0.6346	0.987
2.	10	1.5467	1	0.714	0.666	4.891	0.689398	1.012
3.	20	1.2352	1.30103	0.734	0.691	5.524	0.742254	1.135
4.	50	1.0042	1.69897	0.789	0.738	7.101	0.85132	0.937
5.	100	0.9676	2	0.834	0.780	9.676	0.985696	0.998

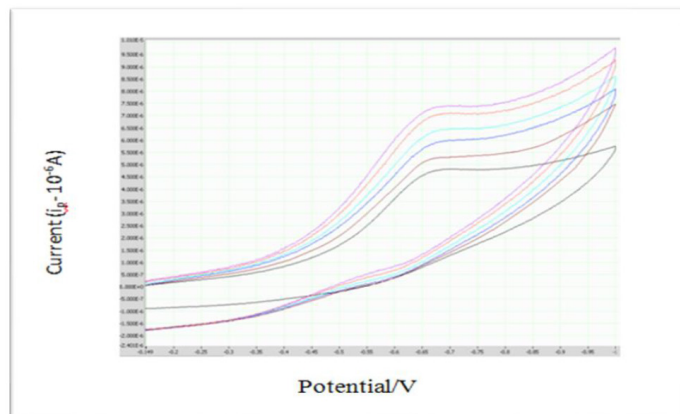


Figure 5: Cyclic voltammograms of Dosulepin in BR buffer of pH 7 at scan rate 20 mVs^{-1} in different concentrations: (a) $1 \times 10^{-5} \text{ mol L}^{-1}$ (b) $2 \times 10^{-5} \text{ mol L}^{-1}$ (c) $3 \times 10^{-5} \text{ mol L}^{-1}$ (d) $4 \times 10^{-5} \text{ mol L}^{-1}$ (e) $5 \times 10^{-5} \text{ mol L}^{-1}$ (f) $6 \times 10^{-5} \text{ mol L}^{-1}$.

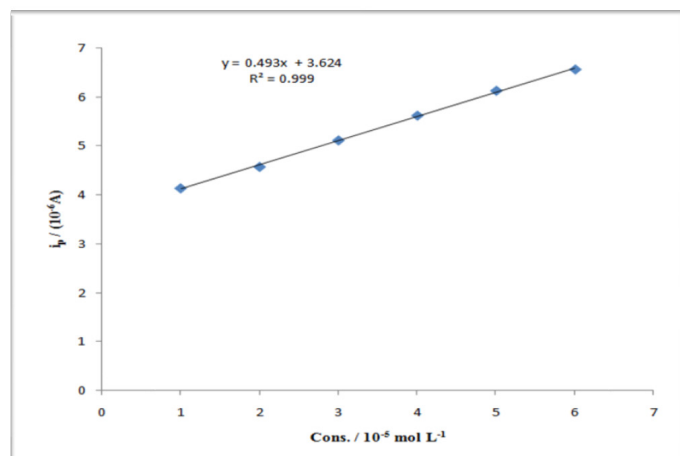


Figure 6: plot of peak current (i_p) vs concentration (C_o) for the cyclic voltammograms of Dosulepin in BR buffer of pH 7 at scan rate 20 mVs^{-1} .

differential pulse voltammetry (DPV) (Table 3). Voltammograms collected under optimum conditions are shown in Figure 7.

Square Wave Voltammetry (SWV) Method

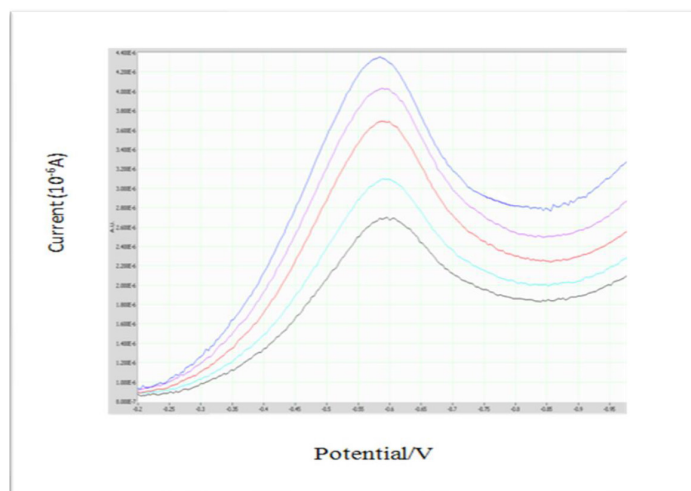
The GCE discovered the optimal operational configuration of pulse-height scan rate as well as pre-concentration variables for estimating bulk dosulepin utilizing square wave voltammetry (SWV) (Table 4), and obtained SWV voltammograms at neutral pH are displayed in Figure 8.

Table 2: Effect of concentration on cyclic voltammetric parameters of Dosulepin at 20 mV/sec. Scan rate.

S. No.	Concentration (mol L ⁻¹)	-E _p (V)	-E _{p/2} (V)	I _p (10 ⁻⁶ A)
1.	1.0x10 ⁻⁵	0.700	0.651	4.134
2.	2.0 x10 ⁻⁵	0.714	0.666	4.57
3.	3.0x10 ⁻⁵	0.717	0.674	5.109
4.	4.0x10 ⁻⁵	0.729	0.678	5.614
5.	5.0x10 ⁻⁵	0.743	0.695	6.122
6.	6.0x10 ⁻⁵	0.758	0.712	6.554

Table 3: The optimized experimental parameters of DPV procedure for the determination of Dosulepin.

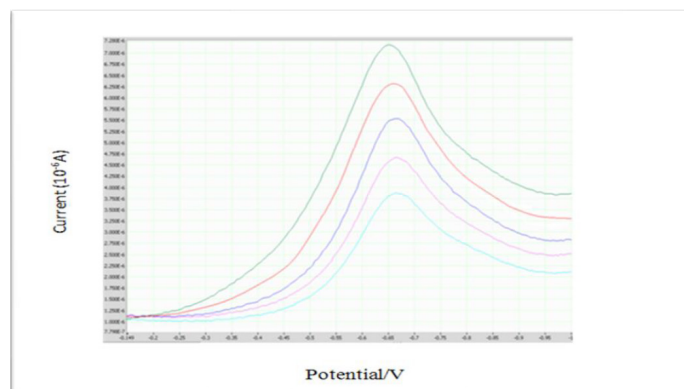
Variable	Optimized Value
pH	7
Buffer Type	BR Buffer
Strength of the buffer (M)	0.1
Temperature (°C)	25±1
Initial potential (V)	0.0
Final potential (V)	-1
Scan increment (V)	0.004
Pulse amplitude (V)	0.025
Frequency (Hz)	15

**Figure 7:** The DP-voltammograms for increased concentrations of Dosulepin in bulk samples in BR buffer of pH 7. (a) 1x10⁻⁶mol L⁻¹ (b) 1.2x10⁻⁶mol L⁻¹ (c) 1.4x10⁻⁶mol L⁻¹ (d) 1.6x10⁻⁶mol L⁻¹ (e) 1.8x10⁻⁶mol L⁻¹.

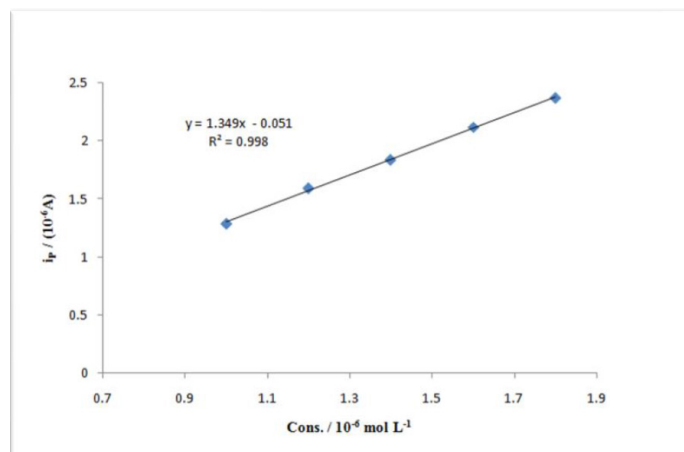
Using the DPV technique, a LOD of 7.686 x10⁻⁸mol L⁻¹ and a LOQ of 2.589x10⁻⁷mol L⁻¹ bulk were obtained. Using the specified SWV technique, however, a LOD of 1.735x10⁻⁷mol L⁻¹ and a LOQ of 5.785x10⁻⁷mol L⁻¹ bulk dosulepin were obtained (Table 5). It also showed the detection limits as well as the results of the statistical analysis of the experimental data, including intercepts, slopes and correlation coefficients procured by the linear least-squares treatment of the findings, and also the standard deviation (SD) of the intercept (S) on the ordinate. Figure 9 depicted a plot of *i_p* vs concentrations derived from DPS voltammograms, while Figure 10 depicted a plot of *i_p* versus concentrations derived from SWS voltammograms. The application of the Voltammetric determination of dosulepin drug, pharmaceutical form using DPV and SWV Modes were given in Table 4. The voltammetric determination of Dosulepin drug in

Table 4: The optimized experimental conditions of SWV procedure for the determination of Dosulepin.

Variable	Optimized Value
pH	7
Buffer Type	BR Buffer
Strength of the buffer (M)	0.1
Temperature (°C)	25±1
Initial potential (V)	0.0
Final potential (V)	-1
Scan increment (V)	0.004
Pulse Width (s)	0.2
Sample Width(s)	0.0

**Figure 8:** The SW-voltammograms for increased concentrations of Dosulepin bulk samples in BR buffer of pH 7. (a) 1x10⁻⁶mol L⁻¹ (b) 1.2x10⁻⁶mol L⁻¹ (c) 1.4x10⁻⁶mol L⁻¹ (d) 1.6x10⁻⁶mol L⁻¹ (e) 1.8x10⁻⁶mol L⁻¹.**Table 5:** Voltammetric determination of Dosulepin in bulk form using DPV and SWV Modes.

Techniques	DPV	SWV
Linearity range (mol L ⁻¹)	1x10 ⁻⁶ - 1x10 ⁻⁵	1x10 ⁻⁶ - 1x10 ⁻⁵
Slope (A/M)	1.349x10 ⁻⁶	2.725 x10 ⁻⁶
Intercept (μA)	-0.051	-0.325
Correlation Coefficient (r ²)	0.998	0.997
LOD (mol L ⁻¹)	7.686 x10 ⁻⁸	1.735 x10 ⁻⁷
LOQ (mol L ⁻¹)	2.589 x10 ⁻⁷	5.785 x10 ⁻⁷

**Figure 9:** Plot of peak current (*i_p*) vs concentrations of Dosulepin in BR buffer of pH 7 bulk samples from DP-voltammograms.

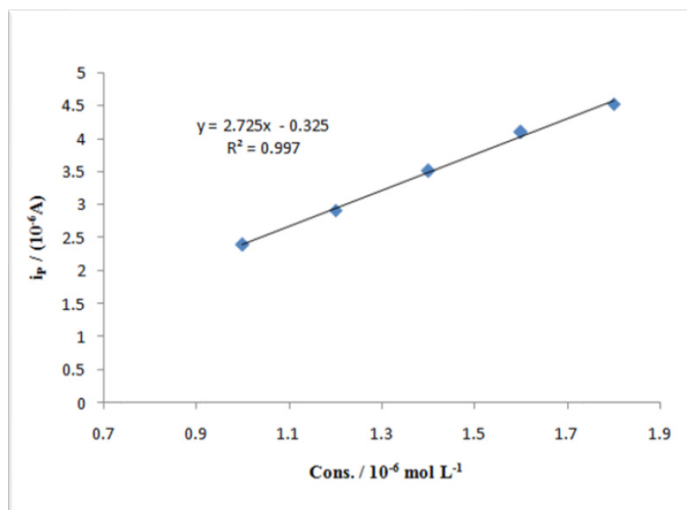


Figure 10: Plot of peak current (i_p) vs concentrations of Dosulepin in BR buffer of pH 7 bulk samples from SW-Voltammograms.

Table 6: Application of the Voltammetric determination of Dosulepin drug, pharmaceutical form using DPV and SWV Modes.

Techniques	DPV	SWV
Added ($\mu\text{mol L}^{-1}$)	2	2
	4	4
	6	6
	8	8
	10	10
	12	12
	14	14
Found ($\mu\text{mol L}^{-1}$)	2.04	1.98
	3.96	3.84
	5.88	5.92
	8.12	8.04
	10.04	9.96
	11.92	12.04
	13.84	14.08
N	3	3
Average recovery %	102	99
	99	96
	98	98.66
	101.5	100.5
	100.4	99.6
	99.33	100.33
	98.85	100.57
Mean	99.86	99.23
S.D.	1.475	1.610
RSD %	1.489	1.634

pharmaceutical formulation using DPV and SWV Modes is shown in Table 6.

DISCUSSION

The anodic direction revealed no peak within reversed scans of a cyclic voltammetric investigation, suggesting that such electrochemical reaction is irreversible. As the scan rate has increased, the peak potential

drifted toward greater negative Figures, illustrating the irreversible characteristics of the reduction reaction. The Britton Robinson (BR) buffer produced significant results in terms of sensitivity as well as a faster response with respect to pH. There were no peaks on the reverse scan, demonstrating the reversibility of the electrode processes shown in Figure 1. The Randel Sevcik equation depicts the correlation between the cathodic peak current $i_p/10^{-6}\text{A}$, the diffusion coefficient of the ionic species, $D_0/\text{cm}^2\text{s}^{-1}$, and the scan rate, v/mVs^{-1} .¹⁷⁻²¹

$$i_p = 2.99 \times 10^5 n (\alpha n_\alpha)^{1/2} A C D_0^{1/2} v^{1/2} \quad \dots (1)$$

Where n represents the total number of electrons transferred in reduction, α is the transfer coefficient, A is the actual surface area of the GCE (cm^2), and C_0 is the concentration of the ionic species (m mole dm^{-3}). The transfer coefficient for an irreversible process can be computed from:

$$(E_p - E_{p/2}) = 47.7/n\alpha \quad \dots (2)$$

$E_{p/2}$ is the potential of the electrochemical process when the current is half of its maximum. A detailed assessment of data on the influence of scan rate found that the association is linear up to the scan rate (v). This illustrates that charge transfer is regulated by partial diffusion and that aggregate adsorption at the surface of GCE is also conceivable. For a totally irreversible electrode process, the relationship between peak potential (E_p) and scan rate (v) is as follows:

$$E_p = \frac{2.303RT}{\alpha nF} \log \frac{RTKf}{\alpha nF} - \frac{2.303RT}{\alpha nF} \log v \quad \dots (3)$$

In Figure 2 a straight line was seen when maximum potential ($-E_p$) was evaluated against log of scan rate ($\log v$) at a given concentration at neutral pH, shown in the below expression.

$$E_p (v) = 0.117(\log v) + 0.593, (r^2 = 0.985) \quad \dots (4)$$

The influence of square root of scan rate ($v^{1/2}$) on peak current (i_p) was explored under the aforementioned experimental settings. The scan rate was increased from 5 to 100 mV/s at a constant dosulepin dosage, and the following findings were made: (a) the peak potential (E_p) altered cathodically, (ii) the peak current (i_p) steadily rose, and (iii) $i_p/ACv^{1/2}$ which represented the peak current function exhibited near-constancy.²²⁻²⁸ Peak current (i_p) is displayed against by the square root of scan rates ($v^{1/2}$) (Figure 3), yielding a straight line that may be described by the equation.

$$i_p (10^{-6} \text{A}) = 0.678v^{1/2} (\text{mV/s})^{1/2} + 2.644 (r^2 = 0.987) \quad \dots (5)$$

Figure 4 showed that the slope of the graph achieved is smaller than the projected value of 0.5 for optimal solution species association. The limited inclusion of diffusive drug molecules in the electrode interaction of adsorbed drug molecules may explain the lower experiment slope (0.262) given in Figure 4.²⁹ Diffusion governs the entire electrochemical process, with dosulepin drug molecules adsorbed on the surface of GCE. All of these characteristics pointed to the electrode process being diffusion-controlled (Table 1). Figure 5 showed how varying dosulepin concentrations affected the intensity of the peak current (i_p). According to the Randles – Sevcik equation, peak current (i_p) is proportional to concentration (C_0). A straight line emerges from a plotting graph of Dosulepin peak current (i_p) vs. Dosulepin concentration (C_0) shown in Figure 6.

$$i_p (10^{-6} \text{A}) = 0.493 \times C_0 (10^{-5} \text{mol L}^{-1}) + 3.624, (r^2 = 0.999) \quad \dots (6)$$

Validation of the DPV and SWV methods

The recommended technique for assaying the drug at trace levels was evaluated using the following criteria:

Limit of Detection and Limit of Quantification

Dosulepin's limits of detection (LOD) and limits of quantification (LOQ) were obtained using the formulas below.^{30,31}

$$\text{LOD} = 3s/b \quad \dots(7)$$

$$\text{LOQ} = 10s/b \quad \dots(8)$$

where s represent the intercept's standard deviation and b represents the calibration curve's slope. Using five duplicate tests of bulk dosulepin reference solutions, the repeatability, accuracy, and precision of data obtained using the stated stripping voltammetric procedures were studied.

The results of DPV showed (Table 5) that the outlined stripping voltammetric techniques for assaying dosulepin in pharmaceuticals were reliable

Linearity

The efficacy of the suggested DPV and SWV processes as electroanalytical techniques for dosulepin determination was evaluated at least three times under optimal operating circumstances to determine the stripped peak current (i_p) as a function of bulk drug concentration. The peak current (i_p) versus concentration calibration plot (Figures 9 and 10) in SWV and DPV was shown to be linear in the range 1×10^{-6} to $1 \times 10^{-5} \text{ mol L}^{-1}$. Here is the linear regression equation:

For DPV;

$$i_p (10^{-6} \text{ A}) = 1349 \times 10^{-6} (\text{mol L}^{-1}) - 0.051 ; r^2 = 0.998 \quad \dots(9)$$

For SWV;

$$i_p (10^{-6} \text{ A}) = 2.725 \times 10^{-6} (\text{mol L}^{-1}) - 0.325 ; r^2 = 0.997 \quad \dots(10)$$

The regression graphs demonstrated that the current intensity is linearly proportional to the concentration throughout the entire range in both DPV and SWV modes. The results of the correlation coefficient clearly show the calibration graphs' good linearity and the experimental points' minimal scattering.

CONCLUSION

For the first time, the electrochemical behavior of dosulepin by using GCE was established and investigated. At negative potentials, dosulepin is irrevocably decreased. This work demonstrates that dosulepin concentration in pharmaceuticals may be measured using DPV and SWV techniques based on their reduction reaction on GCE in BR buffer solution. This characteristic offers a convenient tool for detecting and quantifying chemicals in drugs at low concentrations. The methods provided in this paper might be useful in trace analysis, quality assurance, and diagnostic centers.

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CONFLICT OF INTEREST

The authors declare that there is no conflict of interest.

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