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Lalasaheb Kashid
Department of Chemistry,
9 LG \ D 3 U D W L V K W K D Q • V \$ U W V
Science and Commerce College,
Baramati, Pune, Maharashtra,
India

Dnyaneshwar Gharbude
Department of Chemistry,
9 LG \ D 3 U D W L V K W K D Q • V \$ U W V
Science and Commerce College,
Baramati, Pune, Maharashtra,
India

Corresponding Author:
Lalasaheb Kashid
Department of Chemistry,
9 LG \ D 3 U D W L V K W K D Q • V \$ U W V
Science and Commerce College,
Baramati, Pune, Maharashtra,
India

Electrochemical profiling and analytical method validation of bismuth subsalicylate in marketed pharmaceutical formulation via cyclic voltammetry

Lalasaheb Kashid and Dnyaneshwar Gharbude

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Abstract

Bismuth subsalicylate (BSS) is a metallopharmaceutical drug commonly used as an antidiarrheal agent. Traditional analytical methods for metallopharmaceutical often require long analysis times, high reagent use, and costly equipment. To address these issues, a cyclic voltammetry (CV) method was developed for BSS determination. The measurements used a potentiostat with a glassy carbon electrode (GCE) and Britton-Robinson Buffer (0.04 M, pH 9.0) as the supporting electrolyte. A platinum auxiliary electrode and Ag/AgCl (3 M KCl) as the reference electrode, completed the setup. BSS showed an irreversible redox reaction at the GCE. Optimal CV parameters included a scan rate of 0.05 V/s and potential range from -0.1 to 1.5 V. The method showed linearity from 2 to 18 ppm with an R^2 of 0.997. Limits of detection and quantification were 0.159 ppm and 0.483 ppm, respectively. Tablet D Q D O \ V L V J D Y H U H F R Y H U L H V Z L W K P H D Q F R Q W H Q W 7 1 6 H U method is precise, reproducible, and complies with ICH guidelines, making it suitable for routine BSS drug analysis.

Keywords: Bismuth subsalicylate, method validation, cyclic voltammetry, britton robinson buffer

1. Introduction

Bismuth subsalicylate (BSS), chemically known as basic bismuth salicylate, is an active pharmaceutical ingredient widely utilized for the treatment of gastrointestinal disorders such as diarrhea, indigestion, heartburn, and nausea. As a non-systemic medication with antimicrobial and anti-inflammatory properties, BSS plays a vital role in managing infections such as *Helicobacter pylori* and acute diarrhea syndromes. Despite its therapeutic importance, challenges persist in accurately and reliably quantifying BSS in pharmaceutical formulations due to its sparing solubility, complexation behavior, and hydrolysis in aqueous environments^[7, 8]. Traditional analytical approaches for BSS determination, including spectrophotometry, high-performance liquid chromatography (HPLC), atomic absorption spectroscopy, and gravimetric techniques, have been widely employed, but these often require extensive sample preparation, costly reagents, and lack the sensitivity required for trace-level quantification^[9-11]. These limitations have stimulated interest in the development of alternative methodologies that are both rapid and cost-effective. Electroanalytical techniques such as voltammetry and polarography have emerged as powerful tools for pharmaceutical analysis, offering advantages such as high sensitivity, selectivity, low detection limits, and minimal sample pretreatment^[12-14]. In particular, methods like cyclic voltammetry (CV), square wave voltammetry (SWV), and differential pulse voltammetry (DPV) have demonstrated considerable promise in the quantification of metal-containing drugs and complex organometallic compounds^[15, 16]. The electrochemical behavior of bismuth compounds is especially suited for such analysis due to their well-defined redox properties and affinity for ligand coordination^[17]. Furthermore, regulatory authorities such as the International Conference on Harmonization (ICH) have emphasized the critical need for method validation in pharmaceutical quality control to ensure accuracy, precision, linearity, specificity, robustness, and reproducibility^[18]. Therefore, validated electroanalytical methods are essential for routine quality assurance and regulatory compliance in pharmaceutical industries^[19].

Given the pharmacological relevance of BSS and the pH and E_p vs. pH were plotted to evaluate pH-dependent necessity for robust analytical methods, the present study electrochemical behavior.

aims to develop and validate an electroanalytical method for

the quantification of BSS in commercial formulations using

differential pulse voltammetry. The study also seeks to After identifying the optimal pH, WKH H I I H F W R I V F D explore the redox behavior of BSS under various was examined in the range of 3- P 9 V 7 K H L Q I O X H physicochemical conditions, thereby providing a scan rate on peak resolution and signal intensity was comprehensive understanding of its electrochemical profile. assessed while other parameters were held constant.

This approach offers potential for routine monitoring of BSS

content in pharmaceutical preparations with greater speed 2.4.3. Repetitive Cycles

sensitivity, and operational simplicity^[9].

Using a 12-ppm solution of Bismuth Subsalicylate, repetitive CV cycles (4 cycles) were conducted at a scan rate R I P 9 V & K D Q J H V L Q , S D Q G (S Z L were monitored to evaluate the electrochemical stability and

2. Materials and Methods

2.1. Chemicals

AR-grade Bismuth Subsalicylate (99.9%) was used in HCl adsorption behavior of the analyte.

with doubly distilled water. Other chemicals were of AR

grade and locally sourced. Britton-Robinson (0.04 M, pH 2- 3. Results and Discussions

11), carbonate (0.04 M, pH 9-12), and phosphate (0.04 M) 3.1. Effect of Supporting Electrolytes

buffers were prepared using standard procedures with The choice of supporting electrolyte significantly influences the electrochemical response by affecting cell resistance and ion migration. The electrochemical behavior of Bismuth

2.2. Instrumentation

Electrochemical studies were conducted on a Phadke STAT (GCE) using cyclic voltammetry in various buffers (BRB,

S R W H Q W L R V 3 W D W R Z L W R I W (Z D U H X N o s p o t e , D a c e t a t e , U r a t e , U r o n a t e ; p H 1 - 1 0) and electrolytes electrode setup: GCE (working), Ag/AgCl.KCl (reference), + 1 2 x + & O 2 y . 1 2 x \$ P R Q R o b i n s o n V H and Pt wire (auxiliary). All experiments were performed at buffer (BRB) at pH 9.0 provided the highest anodic peak

& S + Z D V U H F R U G H G X V L Q J D o r e n O U p a R = S + P H W H b j \$ D W 0 . 4 5 6 0 V , indicating optimal sensitivity. Thus, BRB pH 9.0 was selected as the optimal supporting electrolyte for further

2.3. Electrochemical Analysis

Voltammograms of Bismuth Subsalicylate were recorded studies.

using cyclic voltammetry (CV) in unstirred solutions.

Initially, blank voltammograms were obtained using the 3.2. Electrochemical characterization of BSS

supporting electrolyte alone, following purging with The electrochemical characterization of Bismuth nitrogen gas (99.9%) for 20 minutes to remove dissolved Subsalicylate (BSS) by cyclic voltammetry reveals a redox oxygen. Subsequently, the analyte solution was examined ne K D Q L V P L Q Y R O Y L Q J E R W K % L æ p L under identical experimental conditions. Prior to each ligand. In aqueous solution, BSS partially dissociates, measurement, the working electrode surface was carefully U H O H D V L Q J % L æ p D Q G V - B a o z a f a D , D W H renewed and polished to ensure reproducibility and 1986). During the cathodic scan, a diffusion-controlled reduction peak appears due to the three-electron reduction of % L æ p W R H O H P H Q W D O E L V P X W K % L relationship between peak current and the square root of the scan rate (Bard and Faulkner, 2001). On the reverse scan, a corresponding anodic peak confirms partial reoxidation of concentrations. Background voltammograms were first % L h E D F N W R % L æ p : D Q J \$ W P I recorded under the following conditions: Init E = - 9 an irreversible anodic peak is observed, attributed to the + L J K (9 / R Z 9 , Q L W 3 1 3 6 I R D I Q G D W L R Q R I W K H V O H o u r o u p O n d a h ¶ V 9 V 6 H J P H Q W V 6 D P S O H , Q u i n h y d r o Q u i n h y d r o B e s t e r e z S H a n a l , 2 0 0 4) . This 7 L P H V D Q G 6 H Q V L W L Y L W \ o s i d a t i o n i s p H - d e p e n d e n t , w i t h p e a k p o t e n t i a l s h i f t i n g A standard cyclic voltammetry procedure was employed, negatively with increasing pH, suggesting a proton-coupled and the peak current (I_p) and peak potential (E_p) were electron transfer mechanism (Zhou et al., 2010). U H F R U G H G) R U R S W L P L J D W L R Q H S G K L S D L L R D Q P H O V H U ¶ V R P S I O H H ¶ D W R Q Q , S E H W Z and E_p was studied by varying one parameter at a time influence peak shape and position (Stumm and Morgan, 1996). These findings are consistent with standard electrochemical behavior reported in the literature for metal-ligand systems and support a dual redox mechanism for BSS. These processes are strongly influenced by pH, scan rate, and complexation, aligning with established electrochemical principles and published experimental data.

2.4. Method Optimization

Optimization of the cyclic voltammetry (CV) parameters for scan rate (Bard and Faulkner, 2001). On the reverse scan, a Bismuth Subsalicylate was performed using two different corresponding anodic peak confirms partial reoxidation of concentrations. Background voltammograms were first % L h E D F N W R % L æ p : D Q J \$ W P I recorded under the following conditions: Init E = - 9 an irreversible anodic peak is observed, attributed to the + L J K (9 / R Z 9 , Q L W 3 1 3 6 I R D I Q G D W L R Q R I W K H V O H o u r o u p O n d a h ¶ V 9 V 6 H J P H Q W V 6 D P S O H , Q u i n h y d r o Q u i n h y d r o B e s t e r e z S H a n a l , 2 0 0 4) . This 7 L P H V D Q G 6 H Q V L W L Y L W \ o s i d a t i o n i s p H - d e p e n d e n t , w i t h p e a k p o t e n t i a l s h i f t i n g A standard cyclic voltammetry procedure was employed, negatively with increasing pH, suggesting a proton-coupled and the peak current (I_p) and peak potential (E_p) were electron transfer mechanism (Zhou et al., 2010). U H F R U G H G) R U R S W L P L J D W L R Q H S G K L S D L L R D Q P H O V H U ¶ V R P S I O H H ¶ D W R Q Q , S E H W Z and E_p was studied by varying one parameter at a time influence peak shape and position (Stumm and Morgan, 1996). These findings are consistent with standard electrochemical behavior reported in the literature for metal-ligand systems and support a dual redox mechanism for BSS. These processes are strongly influenced by pH, scan rate, and complexation, aligning with established electrochemical principles and published experimental data.

2.4.1. Effect of pH

The influence of pH (2-10) on I_p and E_p was studied using BSS. These processes are strongly influenced by pH, scan buffer solutions and supporting electrolytes. Graphs of I_p vs. rate, and complexation, aligning with established electrochemical principles and published experimental data.

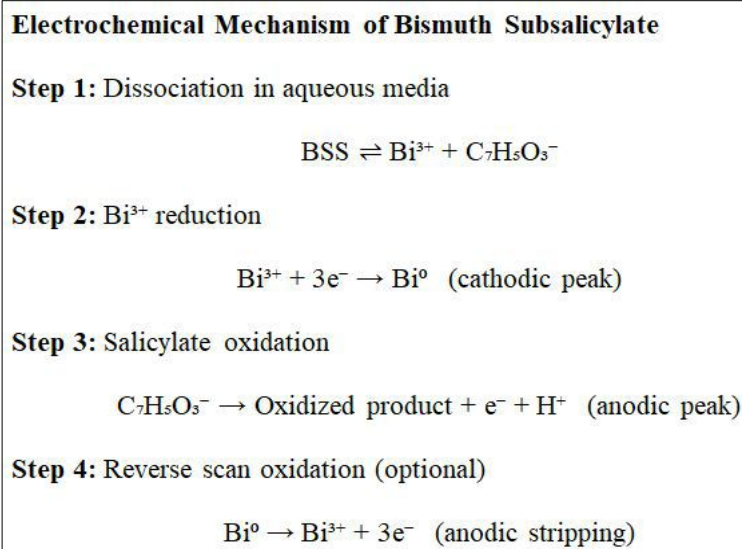


Fig 1: Electrochemical Mechanism of BSS

3.3. Effect of Solution pH

The electrochemical response of Bismuth Subsalicylate values with increasing pH, suggesting proton involvement in (BSS) was studied at a glassy carbon electrode in Britton-Robinson buffer (BRB) across pH 3-10. The peak current increased with rising pH, reaching a maximum at pH 9.0, $E_{\text{pa}} \text{ (V)} = 0.037 - 0.00950 \text{ (S + 5)}$ which was chosen for further studies. The anodic peak $E_{\text{pc}} \text{ (V)} = 0.661 - 0.068 \text{ (S + 5)}$

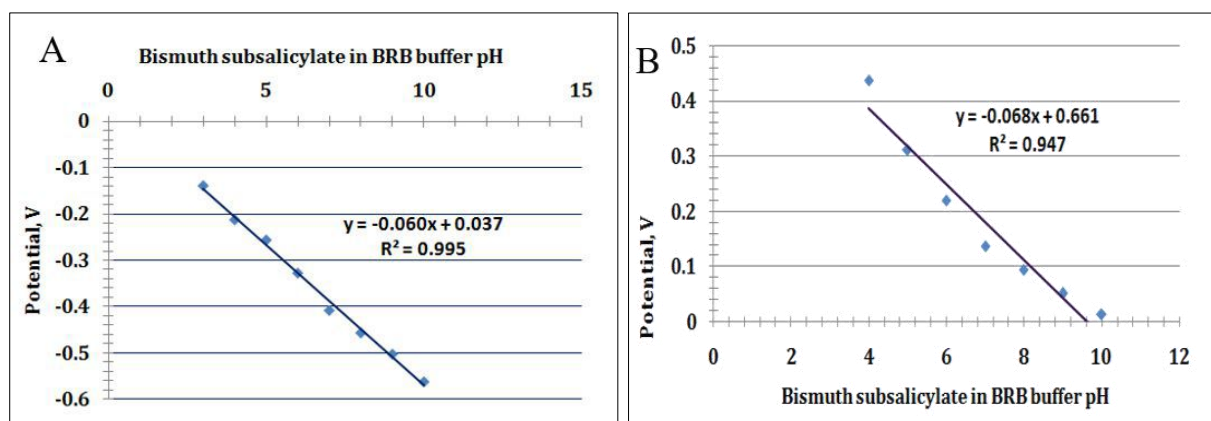
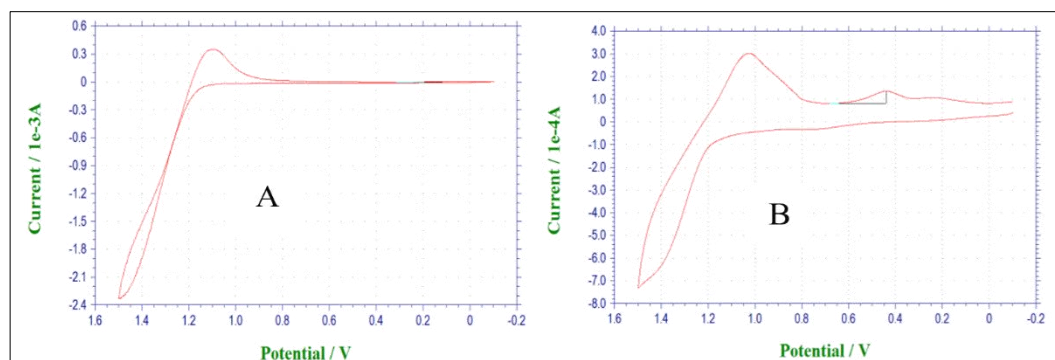


Fig 2: Effect of pH on (A) anodic potential (B) cathodic potential of bismuth subsalicylate in BRB buffer, as a supporting electrolyte.

The linear shift of peak potential with pH, as BSS closely matches the theoretical Nernst value of 59 mV/pH (at 25°C), supports this interpretation and confirms the involvement of one proton per electron equal number of protons and electrons. This suggests a proton-coupled electron transfer (PCET) mechanism during the oxidation of the salicylate moiety, likely the phenolic -



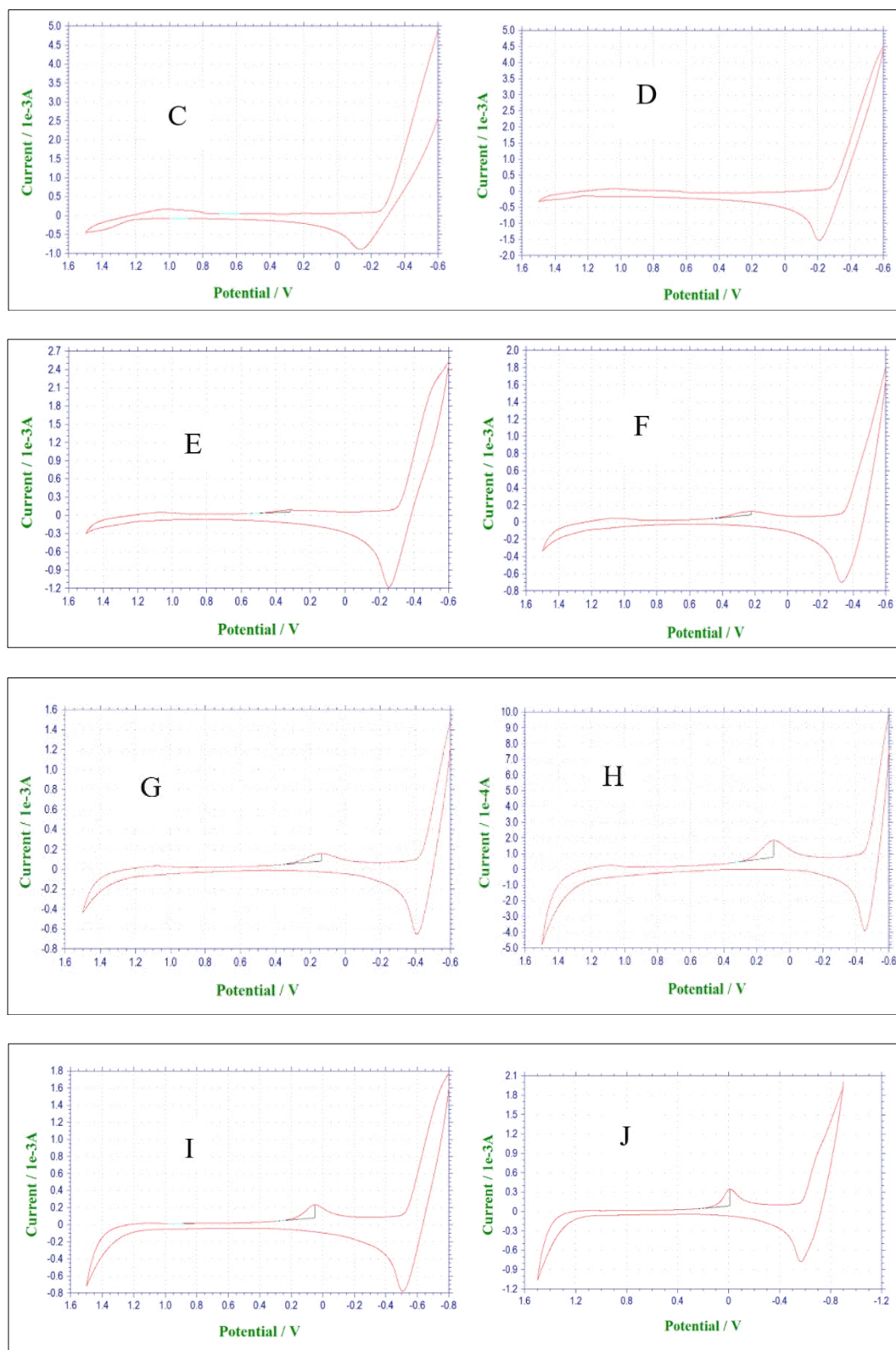


Fig 3: Cyclic voltammograms of Bismuth Subsalicylate recorded in Britton-Robinson buffer (BRB) at different pH values: (A) pH 1.0, (B) pH 2.0, (C) pH 3.0, (D) pH 4.0, (E) pH 5.0, (F) pH 6.0, (G) pH 7.0, (H) pH 8.0, (I) pH 9.0, and (J) pH 10.0.

3.4. Method Validation

3.4.1. Linearity

The linearity of the developed electroanalytical method for indicating a strong linear relationship between analyte concentration and electrochemical response. To quantify the determination of bismuth subsalicylate was evaluated using cyclic voltammetry (CV). Standard solutions were prepared to obtain concentrations ranging from 2 to 18 ppm. For each concentration, cyclic voltammograms were recorded, and the anodic peak current was measured at the characteristic potential, as shown in Figure 4A. A gradual and consistent increase in anodic peak current was observed with rising concentrations of bismuth subsalicylate, and the resulting plot, illustrated in Figure 4B, exhibited excellent linearity across the studied range. The linear

regression equation obtained was $y=0.470x+2.098$, with a and accurate electrochemical response across the tested correlation coefficient (R^2) of 0.997, confirming a strong concentration range, validating its effectiveness for correlation between current and concentration. These results quantitative analysis of bismuth subsalicylate. demonstrate that the method provides a reliable, sensitive,

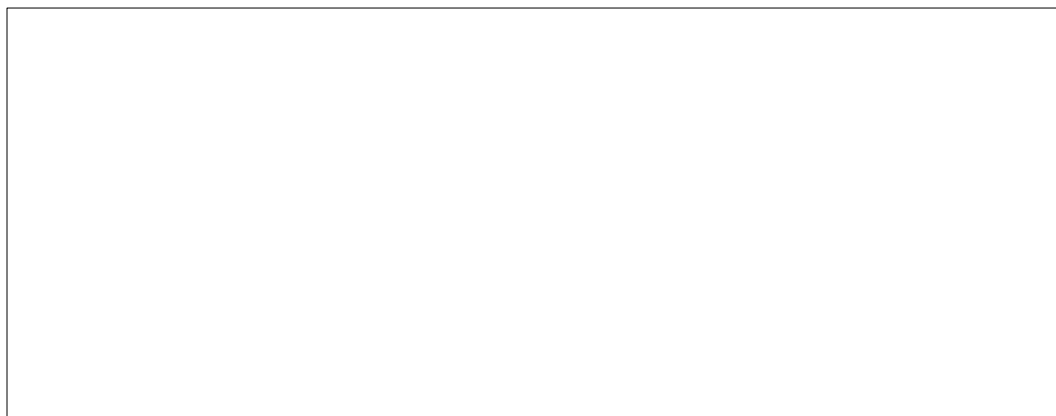


Fig 4: (A) Cyclic voltammograms and (B) calibration curve showing the linear increase in anodic peak current with increasing concentrations of BSS in BRB, pH 9.0.

3.4.2. Precision

The precision of the developed cyclic voltammetry (CV) excellent repeatability. Interday precision was assessed by method for the determination of bismuth subsalicylate was analyzing the same concentration over three different days evaluated through both intraday (repeatability) and interday by two different analysts as illustrated in figure 5. The (intermediate precision) studies. For intraday precision, a resulting %RSD was 0.31%, which is well within the ppm solution of bismuth subsalicylate in BRB buffer (pH acceptable limit of less than 2%, confirming the high 9.0) was analyzed six times within a single day. The peak precision and reliability of the proposed CV method (Table currents obtained were consistent, and the relative standard deviation (%RSD) was calculated to be 0.43%, indicating

Table 1: Results of Intraday and Interday precision for bismuth subsalicylate

[BSS] (ppm)	Intraday precision Ipa (A)	Interday precision Ipa (A)			Average %RSD
		Day 1	Day 2	Day 3	
12.0	7.767	7.767	7.737	7.797	0.3100
12.0	7.797	7.797	7.787	7.758	
12.0	7.709	7.709	7.795	7.785	
12.0	7.747	7.747	7.777	7.759	
12.0	7.797	7.797	7.798	7.771	
12.0	7.759	7.759	7.764	7.787	
%RSD	0.4300	0.4300	0.3000	0.2100	

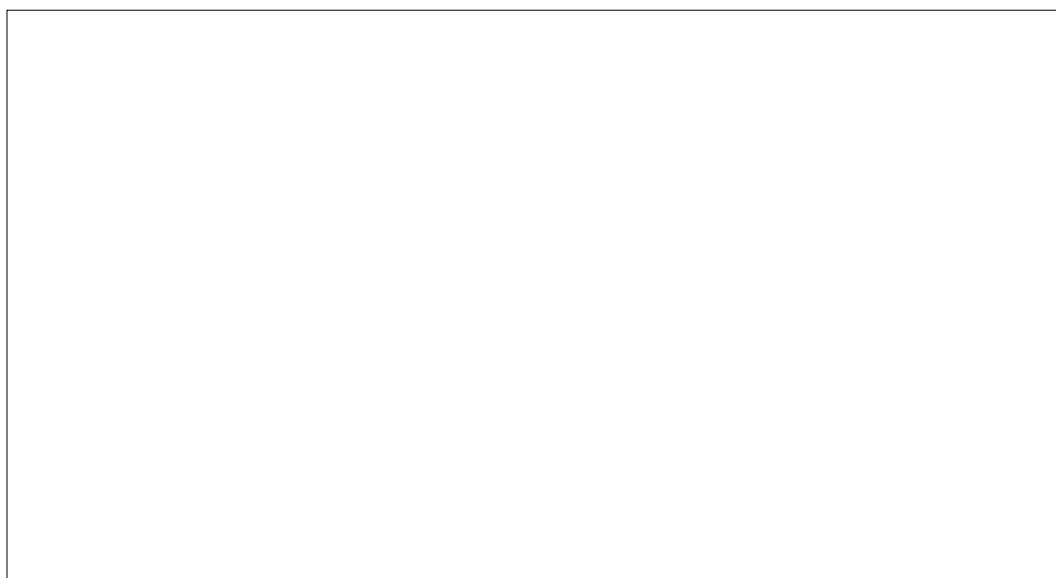


Fig 5: Interday study of BSS in BRB, pH 9.0

3.4.3. Accuracy

bismuth subsalicylate is summarized in Table 2. The results of the proposed method was evaluated through how good recoveries in the range of 98.19-100.87 % using recovery studies by spiking the sample with known amounts cyclic voltammetry (CV) indicating that method is accurate. of pure bismuth subsalicylate. Solutions were prepared in However, the CV method was found to be more precise, as triplicate at three concentration levels, and the percentage the relative standard deviation (%RSD) for both intraday recovery was calculated using the regression equation and interday measurements was consistently below 2%, derived from the calibration curve. The recovery data for satisfying the precision criteria.

Table 2: Results of Accuracy for bismuth subsalicylate

Amount added (ppm)	Peak Current (A)	Amount found (ppm)	% Recovery	% Recovery – SD (RDS)
6.0	4.839	5.8319	97.199	98.191 – 1.3952 (1.42%)
6.0	4.912	5.9872	99.787	
6.0	4.850	5.8553	97.589	
12.0	7.828	12.1915	101.596	100.87 – 0.9855 (0.977%)
12.0	7.724	11.9702	99.7520	
12.0	7.810	12.1532	101.277	
18.0	10.63	18.1532	100.851	99.787 – 1.4526 (1.46%)
18.0	10.59	18.0681	100.378	
18.0	10.40	17.6638	98.1320	



Fig 6: Recovery studies of bismuth subsalicylate at (A) 6.00 ppm, (B) 12.00 ppm, and (C) 18.00 ppm by cyclic voltammetry in BRB buffer (pH 9.0). Conditions: Init E = -0.1 V, High E = 1.5 V, Low E = -0.1 V, Scan rate = 0.05 V/s, 2 segments, 0.001 V interval, sensitivity = 0.01 A/V.

3.4.4. Limit of Detection and Limit of Quantification

The Limit of Detection (LOD) is the lowest concentration of analyte that can be reliably detected, while the Limit of Quantification (LOQ) is the lowest concentration that can be quantitatively determined with acceptable precision and accuracy. These parameters were calculated using the following equations

to be 0.159 ppm and 0.4829 ppm, respectively. These values demonstrate the high sensitivity of the method, making it suitable for detecting and quantifying bismuth subsalicylate at low concentrations.

$$\text{LOD} = (3.3 \text{ SD}) / m$$

$$\text{LOQ} = (10 \text{ SD}) / m$$

Where SD is the standard deviation of the y-intercept, and m is the slope of the calibration curve. For the cyclic voltammetry (CV) method, the LOD and LOQ were found in Table 3.

Table 3: Summary of the CV developed method

Parameter	Values	Parameter	Values
Absorption maximum / Anodic Peak potential	-0.005 V	Standard deviation	0.0227
Beer's law range	2-18 ppm	Accuracy (%)	98.19-100.87%
Correlation coefficient	0.997	Precision (%RSD)	1.13%
Regression equation	$y = 0.470x + 2.098$	LOD (ppm)	0.1590
Slope	0.470	LOQ (ppm)	0.4829
Intercept	2.098	Solvent system pH	9.0

3.5.6. Application of Method

Three marketed formulations containing bismuth subsalicylate were analyzed using the proposed method, and quantitative determination of bismuth subsalicylate in commercially available fixed-dose tablet formulations. The results are summarized in Table 4.

Table 4: Determination of Bismuth Subsalicylate in Pharmaceutical Tablets

Tablet Sample	Label Claim (mg)	Mean Content (%) – SD
Bismatrol	262 mg	99.79 – 1.91
Diotame	262 mg/15 ml	98.46 – 2.11
Pepto Bismol	262 mg/15 ml	97.13 – 1.82

The bismuth subsalicylate content in each sample was calculated using the peak current values and the regression equations derived from the calibration curve. The mean assay values for all three products were found to be in close agreement with the labelled amounts, indicating the reliability and accuracy of the developed method. These results confirm that the method is suitable for routine quality control analysis of bismuth subsalicylate in fixed-dose formulations.

4. Conclusion

Cyclic voltammetry (CV) is a widely employed electroanalytical technique for investigating redox processes and elucidating electrode reaction mechanisms. In this study, CV was utilized for the qualitative and quantitative determination of bismuth subsalicylate, a metallopharmaceutical compound, in both standard solutions and pharmaceutical formulations. The compound exhibited a completely irreversible redox behavior at a glassy carbon electrode in Britton-Robinson Buffer (BRB). Optimized CV conditions included a scan rate of 0.05 V/s and a potential window ranging from -0.1 V to +1.5 V. The peak potential remained constant at approximately -0.005 V, indicating stable and reproducible electrochemical behavior. A linear calibration curve was obtained with a correlation coefficient (R^2) of 0.997, demonstrating excellent linearity. The limit of detection (LOD) and limit of quantification (LOQ) were found to be 0.1590 ppm and 0.4829 ppm, respectively. The procedure was validated in accordance with ICH guidelines for accuracy, precision, and robustness. Statistical evaluations confirmed the reliability and reproducibility of the method. Overall, cyclic voltammetry offers a simple, rapid, and highly effective analytical approach for the determination of bismuth subsalicylate, making it well-suited for routine quality control in pharmaceutical applications.

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