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Eco-friendly differential pulse voltammetric determination of benzydamine hydrochloride using a gold nanoparticles-modified carbon paste electrode

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A differential pulse voltammetric (DPV) method is presented for the determination of benzydamine hydrochloride (BZ) in bulk powder, mouthwash, and artificial saliva matrices. This work represents the first application of DPV for the electrochemical determination of BZ. The method employs a carbon paste electrode (CPE) modified with electrodeposited gold nanoparticles (Au-NPs) through a chronoamperometric step, which significantly enhances the oxidation peak current for BZ within the potential window of 0.0 to 1.6 V. The variables, most significantly the pH and scan rate, affecting the voltammetric response were systematically optimized. Under the optimized conditions, the proposed sensor exhibited a linear response over the concentration range of 1.00–10.00 μM with a limit of detection (LOD) of 0.1024 μM. Validation in accordance with the ICH guidelines confirmed satisfactory accuracy and precision. The applicability of the developed method was further verified through the successful quantification of BZ in mouthwash formulations and artificial saliva samples. The proposed DPV approach provides a complementary analytical alternative rather than a replacement, which was evidenced by comparison with the reported electrochemical methods. In addition, the environmental and practical performance of the method was assessed using established greenness and applicability metrics, confirming that the proposed approach combines analytical effectiveness with a low environmental burden and favorable practical characteristics.

1. Introduction

Voltammetry has gained considerable significance as an electrochemical technique,[1] particularly in pharmaceutical analysis for determining organic and inorganic compounds, owing to its numerous analytical merits. These include high sensitivity and selectivity, a wide quantitative range, and reduced susceptibility to matrix effects. Common techniques for pharmaceutical determination include high-performance liquid chromatography (HPLC) and spectrophotometry.[2] However, these methods often require expensive equipment, lengthy analysis times, and large amounts of organic solvents and present less sensitive results. In contrast, voltammetric techniques offer advantages such as rapid analysis, high sensitivity, minimal sample preparation requirements, and environmental friendliness. From a practical standpoint, voltammetric methods also provide operational simplicity, low energy consumption, and overall cost-effectiveness.[3–9]

The successful application of voltammetric methods with such advantages heavily depends on the choice and modification of appropriate working electrodes. Carbon paste electrodes (CPEs) are commonly employed in electroanalysis as the working electrode due to their various advantages, including low cost, ease of fabrication and surface renewal, and favorable conductivity. However, two significant limitations of unmodified CPEs are their susceptibility to surface fouling and lack of inherent selectivity, often leading to overlapped voltammetric responses and diminished analytical performance. To overcome these drawbacks, chemical modification is strategically employed to create selectively enhanced surfaces, particularly through the development of chemically modified carbon paste electrodes (CMCPEs).

Chemically modified carbon paste electrodes (CMCPEs) incorporate various adsorptive and conductive nanomaterials,[10] including metal nanoparticles, carbon nanotubes, and graphene, as modifiers. These materials function by improving the adsorption and electron transfer kinetics of target analytes. The

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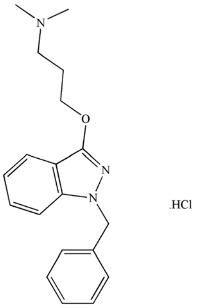


Fig. 1 Chemical structure of benzydamine hydrochloride ($C_{19}H_{23}N_3$-O·HCl); molecular weight = 345.9 g.

resulting CMCPEs offer superior analytical capabilities, like enhanced sensitivity and selectivity, and lower detection limits, which are attributed to the large surface areas of the modifiers, fast mass transport, and catalytic properties. This approach tailors electrode surfaces for specific applications, making CMCPEs powerful tools in modern electroanalysis.[3,4,7,11]

Among the various nanomaterials available, gold nanoparticles (Au-NPs) stand out as particularly promising nanomaterials for fabricating electrochemical sensors, owing to their remarkable biocompatibility, effective conductivity, and electrocatalytic and chemical properties.[4,7,12] Their unique characteristics make them well-suited for detecting pharmaceutical compounds, including the non-steroidal anti-inflammatory drug (NSAID) discussed below.

Benzydamine hydrochloride (BZ) (Fig. 1) is a topical and systemic NSAID with analgesic properties.[13] BZ is an official drug with the chemical name 3-(1-benzylindazol-3-yloxy) propyldimethylamine hydrochloride.[14] It is commonly formulated as a 0.15% mouthwash or oromucosal spray for oropharyngeal inflammation treatment.[13]

Several analytical methods have been reported for BZ determination, comprising spectrophotometry,[15–18] chemometry,[19] HPLC,[17,20–24] UPLC coupled with tandem mass spectrometry,[25] GC,[26–28] TLC,[29] gravimetry,[30] and electrochemistry.[31–37] The aim of this research is to establish a reliable and highly sensitive differential pulse voltammetric (DPV) method for BZ determination in its pure form, mouthwash, and artificial saliva, and to critically evaluate its analytical performance in comparison with existing potentiometric techniques and the reported amperometric method,[37] with emphasis on sensitivity, detection limit, selectivity, and practical applicability. Additionally, a thorough sustainability assessment was conducted using different tools, allowing comparison with the reported ones. These tools include Analytical Eco-Scale (AES),[38] Green Analytical Procedure Index (GAPI),[39] Analytical Greenness (AGREE) metric,[40] Red-Green-Blue model (RGB12),[41] and Blue Applicability Grade Index (BAGI).[42]

2. Experimental

2.1. Materials and reagents

The pure standard BZ was obtained from Amoun Pharmaceutical Company, El-Obour City, Cairo, Egypt. Its purity was 100.51% ± 1.382% according to the reported method.[24] Tantum Verde® (batch no. 2209038) labelled to contain 0.15% of BZ was purchased from the local market.

Graphite powder, paraffin oil, phosphoric acid, acetic acid, and chloroauric acid ($HAuCl_4$) were bought from Sigma-Aldrich (Darmstadt, Germany).

Concentrated sulphuric acid (H_2SO_4), sodium hydroxide (NaOH), boric acid (H_3BO_3), potassium chloride (KCl), sodium chloride (NaCl), calcium chloride ($CaCl_2$), magnesium chloride ($MgCl_2$), sodium phosphate (Na_3PO_4), and sodium bicarbonate ($NaHCO_3$) were purchased from El-Nasr Pharmaceutical Chemical Company (Cairo, Egypt).

The following preparation details are listed in the SI: 0.01 M H_2SO_4 used as the supporting electrolyte, the Britton–Robinson buffer (BRB) solution used for the pH study, 0.2 M sodium hydroxide used for the pH adjustment of BRB, 0.1 M KCl, and 5.00×10^{-4} M $HAuCl_4$ solution prepared for electrode modification, and artificial saliva.[43]

2.2. Apparatus

Electrochemical measurements were carried out using a Metrohm Autolab PGSTAT204 potentiostat/galvanostat (Netherlands) controlled using the NOVA 1.11.2 software. A three-electrode cell, comprising a Ag/AgCl reference electrode, a platinum wire counter electrode, and Au-NPs/CPE as the working electrode, was employed. The working electrode, a CPE (model MF-2010) from BASi (Indiana, USA), has a Teflon body with a diameter of 2.87 mm, 1 mm deep cavity at one end and a central copper wire for electrical connection. A pH glass electrode (Jenway, UK) was employed for pH measurements. The morphology and distribution of the Au-NPs on the screen-printed electrode (SPE) surface were evaluated using a scanning electron microscope (SEM) (Quanta FEG 250) from Thermo Fisher Scientific (Massachusetts, USA).

2.3. Procedure

2.3.1. Standard solutions of BZ. The stock standard solution of BZ (10^{-2} M) was prepared by dissolving 86.5 mg of BZ in 0.01 M H_2SO_4 in a 25-mL volumetric flask and then diluting to the mark with the same solvent. The working standard solutions for BZ (1.00–10.00 μM) were prepared by the dilution of the stock standard solution in a series of 25-mL measuring flasks with 0.01 M H_2SO_4 to the required concentrations.

2.3.2. Working electrode preparation. A homogeneous paste for the CPE was made by thoroughly mixing 995 mg graphite powder with 0.4 mL paraffin oil using a mortar and pestle. A part of this paste was then packed into the hollow part of a Teflon piston holder (electrode frame) with an electrical wire providing direct contact with the potentiostat and smoothed on clean paper to achieve a glossy surface.

2.3.3. Electrodeposition of Au-NPs on CPE. Following an established procedure by Afkhami *et al.*[3] and Soliman *et al.*,[7] for the modification of the CPE surface by Au-NPs, a chronoamperometric technique was employed for gold electrodeposition from a 5.00×10^{-4} M $HAuCl_4$ solution containing 0.1 M KCl. A potential of −0.4 V was set against a Ag/AgCl

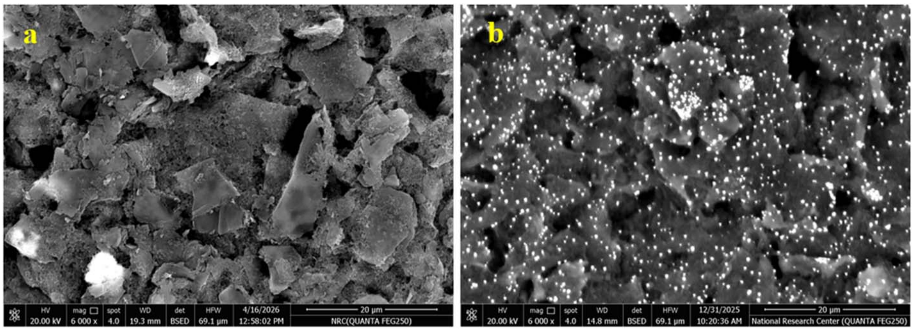


Fig. 2 Scanning electron microscope (SEM) images of (a) a bare screen-printed electrode (SPE) and (b) SPE after electrodeposition of Au-NPs.

reference electrode, with a Pt counter electrode, for 5 seconds. This process successfully deposited Au-NPs onto the CPE surface.

2.3.4. Electrochemical measurements. The DPV method was used for BZ determination in its pure, mouthwash and artificial saliva samples. The DPV measurements were carried out by scanning potential from 0.0 V to 1.6 V *versus* Ag/AgCl reference electrode utilizing the Au-NPs/CPE electrode. The scan rate was set at 200 mV s^{-1}, with a modulation amplitude of 50 mV, an interval time of 500 ms, a modulation time of 50 ms, and a quiet time of 5 s.

2.4. Construction of the calibration curve

The prepared working standard solutions of BZ (1.00–10.00 µM) were transferred to an electrolytic cell, and their DPV voltammograms were generated utilizing the Au-NPs/CPE electrode across a potential window of 0.0 to 1.6 V relative to the Ag/AgCl reference electrode. The electrode exhibited consistent results, which were obtained from the average of three measurements. A calibration curve was plotted relating the oxidation peak height (I_p) at 1.1 V to the molar concentration of BZ.

2.4.1. Determination of BZ in mouthwash. The mouthwash sample of BZ was used for real-sample application. An accurately measured 5.7 mL aliquot of Tantum Verde® mouthwash, labelled to contain 0.15% BZ, was transferred into a 25-mL measuring flask and diluted with 0.01 M H_2SO_4 to prepare a concentration of 1.00×10^{-3} M BZ. Then, 100.0 µL was transferred into another 25-mL measuring flask, and it was filled to the mark with 0.01 M H_2SO_4 to prepare a concentration of 4.00 µM BZ. The measurement was carried out as mentioned before and the BZ concentration was derived from the computed regression equation.

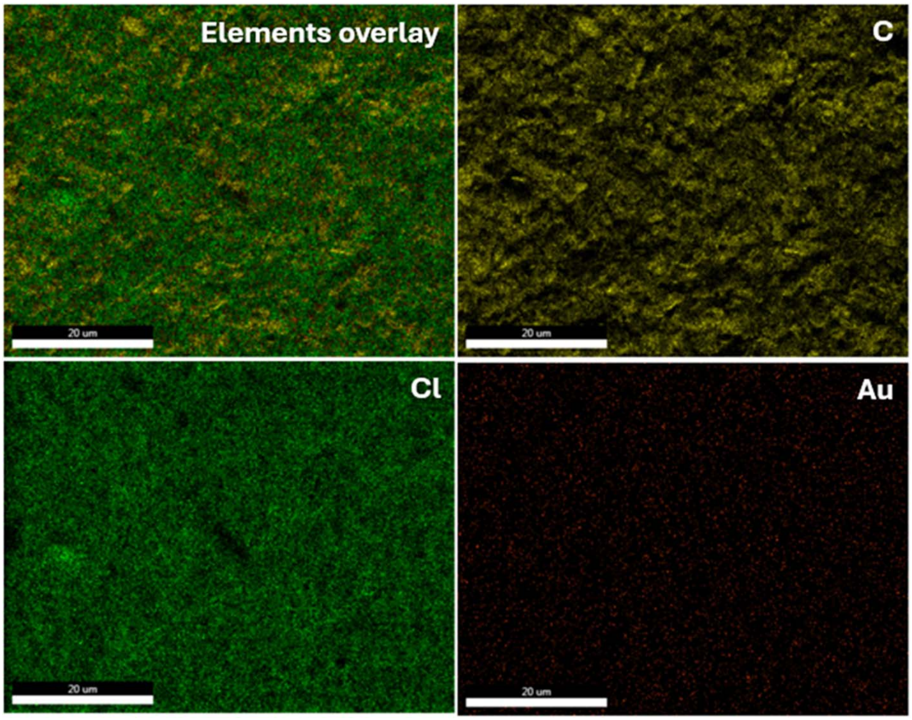


Fig. 3 Energy-dispersive X-ray (EDX) images of the substrate material (carbon), chloride (impurity), Au-NPs electrodeposited on the screen-printed electrode (SPE) surface, and their corresponding overlay.

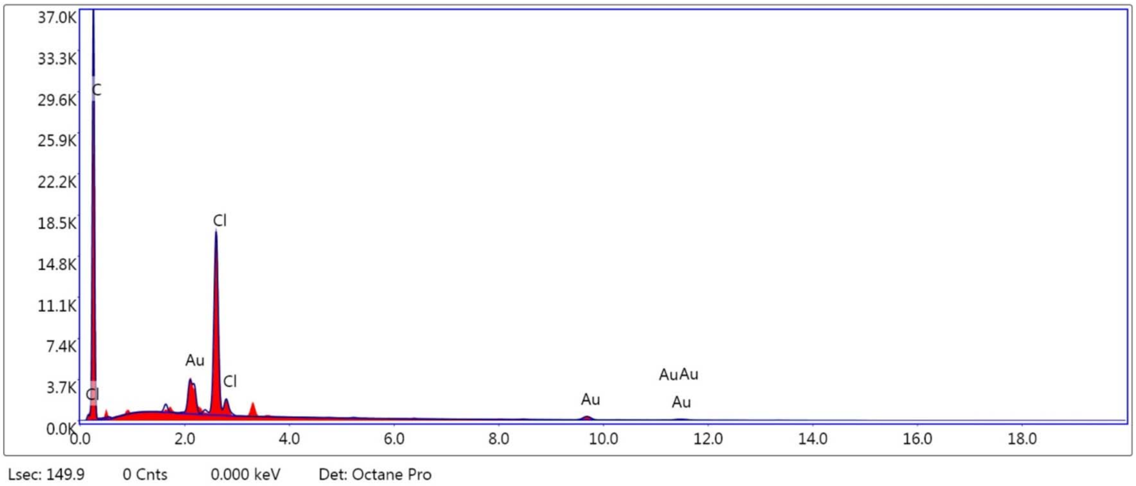


Fig. 4 Energy-dispersive X-ray (EDX) spectrum of Au-NPs electrodeposited on the screen-printed electrode (SPE).

2.4.2. **Determination of BZ in artificial saliva.** Four milliliter of 10.00 μM BZ and the same volume of artificial saliva were transferred into a 10-mL volumetric flask, and the volume was made up to the mark with a 0.01 M H_2SO_4 solution to reach a final concentration of 4.00 μM BZ.

3. Results and discussion

3.1. Au-NPs characterization

The pattern of Au-NPs electrodeposited on an SPE was examined by SEM and energy-dispersive X-ray (EDX) spectroscopy. The SEM and EDX images (Fig. 2 and 3) reveal the existence of homogenously disseminated Au-NPs on the SPE surface, with particles exhibiting a generally spherical morphology. These observations confirm the successful electrodeposition of Au-NPs on the electrode surface.

The elemental composition of the electrodeposited Au-NPs was further investigated using EDX analysis. Characteristic signals corresponding to Au-NPs were observed, along with signals arising from the substrate material and chloride (Cl) atom (impurity due to Au-NPs preparation in KCl). As shown in Fig. 4, the EDX spectrum exhibits three elemental peaks assigned to C, Cl, and Au. This elemental composition is summarized in Table S1 and shows the following atomic percentage: carbon shows 97.98%, Cl shows 1.90%, while Au-NPs show 0.12%.

3.2. Method optimization

3.2.1. **Effect of different electrodes.** Differential pulse voltammograms of 10.00 μM BZ in 0.01 M H_2SO_4 were recorded utilizing a CPE modified with a carbon nanotube and gold nanoparticles (Au-NPs/CNT/CPE), a gold nanoparticles-modified glassy carbon electrode (Au-NPs/GCE), and Au-NPs/CPE. As shown in Fig. 5, Au-NPs/CPE showed the highest oxidation peak current, owing to its large surface area, enhanced conductivity, and strong electrocatalytic activity.

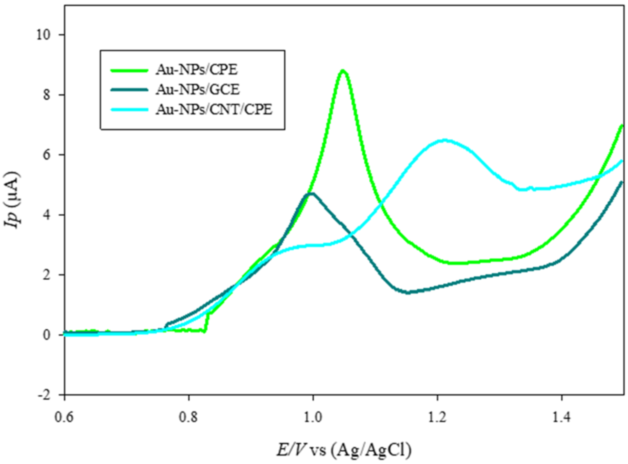


Fig. 5 Electrochemical behavior of different electrodes in the presence of 10.00 μM benzydamine hydrochloride in a 0.01 M sulphuric acid solution at a scan rate of 200 mV s^{-1}. *CPE is the carbon paste electrode, GCE is the glassy carbon electrode, and CNT is the carbon nanotube.

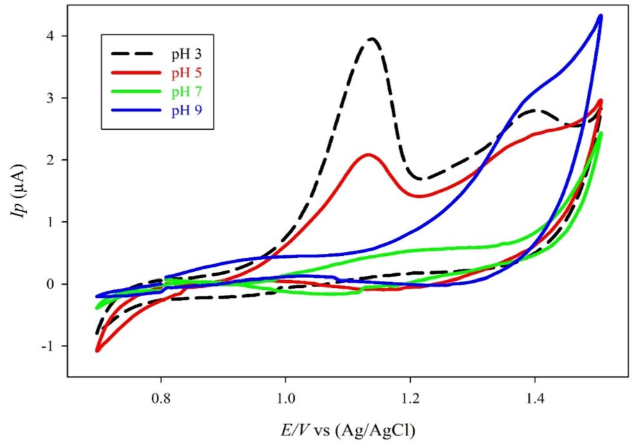


Fig. 6 Cyclic voltammograms of 8.00 μM benzydamine hydrochloride at different pH values (3.0, 5.0, 7.0, and 9.0); scan rate = 200 mV s^{-1}.

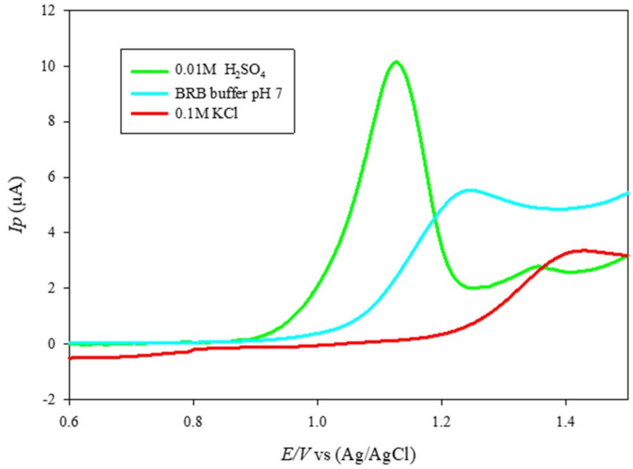


Fig. 7 DPV responses of 10.00 µM benzydamine hydrochloride in different supporting electrolytes (0.01 M H_2SO_4, Britton–Robinson buffer (BRB), and 0.1 M KCl).

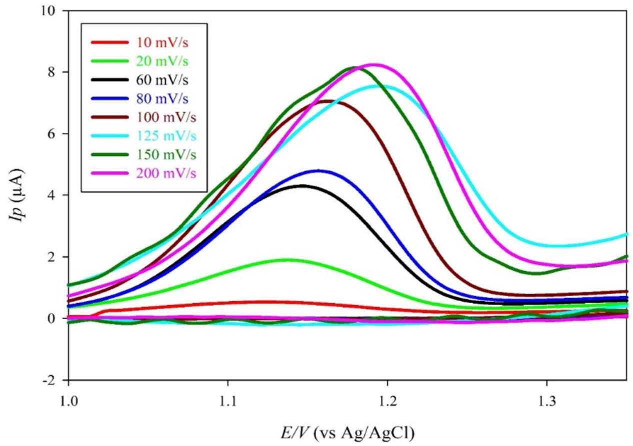


Fig. 8 Cyclic voltammograms of 8.00 µM benzydamine hydrochloride using Au-NPs/CPE at different scan rates (10, 20, 60, 80, 100, 125, 150, and 200 mV s^{-1}) in a 0.01 M sulphuric acid solution.

3.2.2. Influence of pH and different supporting electrolytes. Both the pH of the measurement medium and the supporting electrolyte composition significantly influenced the electrochemical response of BZ. Accordingly, these parameters were optimized through two steps. First, the pH influence in the range of 3.0–9.0 was investigated using cyclic voltammetry (CV) in the BRB buffer to measure the electroactivity of 8.00 µM BZ using Au-NPs/CPE. Fig. 6 illustrates that a decrease in pH led to an increase in the oxidation peak current, with the highest I_p detected under the most acidic conditions tested. Second, the influence of various supporting electrolytes including 0.1 M KCl, 0.01 M H_2SO_4, and BRB buffer (pH 7.0) was studied. Among these electrolytes, 0.01 M H_2SO_4 produced the highest oxidation peak current for BZ with well-defined peak morphology (Fig. 7). Consequently, 0.01 M H_2SO_4 was chosen as the supporting electrolyte for all the following experiments to ensure a recognizable peak with a reproducible current.

3.2.3. Effect of scan rate. Investigating the impact of scan rate on the electrochemical response of analytes is vital to detect if the mass transfer process is governed by diffusion, adsorption, or a combination of both.[44] Accordingly, the effect of scan rate (ν) in the span of 10–200 mV s^{-1} was examined through recording the peak currents of BZ using Au-NPs/CPE. The results demonstrated that a higher scan rate enhanced the electrochemical responses (Fig. 8).

Fig. 9A illustrates the graph of log peak current (I_p) against log scan rate, with the following regression equation: $\log I_p = 1.1044 \log \nu + 0.0733$ ($r = 0.9736$). As mentioned in the literature,[7,8] a slope of 1 for the plotting of log peak current (I_p) *versus* log scan rate (ν) indicates a purely adsorption-controlled electron-transferred mechanism. A slope between 0.5 and 1 denotes a mixed control involving both adsorption and diffusion, whereas a value less than 0.5 is an indication of a diffusion-controlled process. The slope value of the relationship obtained is approximately equal to 1, which indicated that the electron transfer mechanism at the surface of the electrode is adsorption controlled.

Additionally, a linear relationship between the peak current (I_p) and the square root of scan rate ($\nu^{1/2}$) was derived ($I_p =$

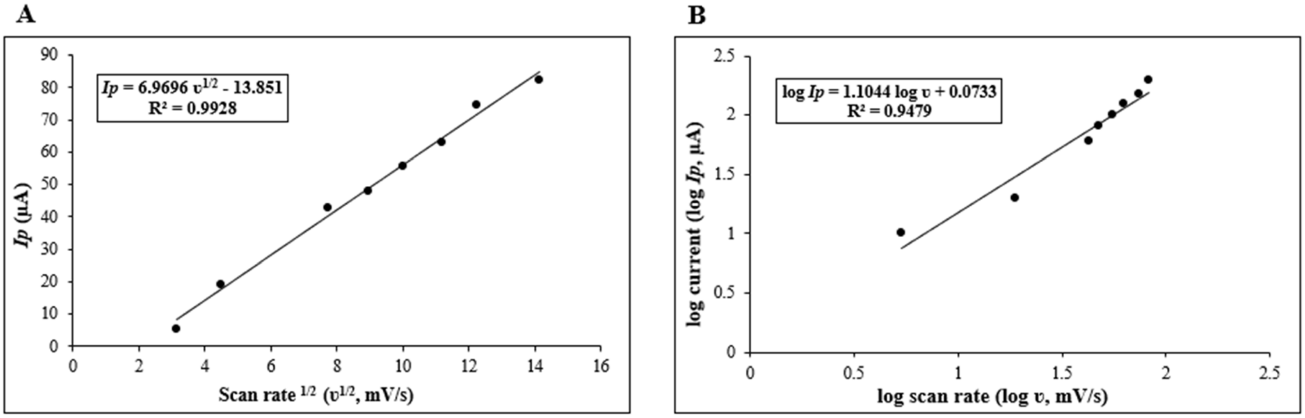


Fig. 9 (A) Plot of the oxidation peak current of benzydamine hydrochloride and the square root of scan rate ($\nu^{1/2}$). (B) Plot of the logarithm of peak current ($\log I_p$) and the logarithm of scan rate ($\log \nu$).

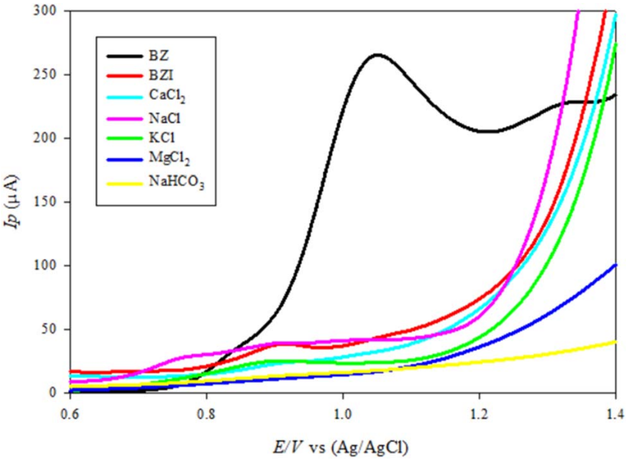


Fig. 10 Differential pulse voltammograms of 10^3 μM benzydamine hydrochloride along with its official impurity C and various salts present in the artificial saliva matrix.

$6.9696\nu^{1/2} - 13.851$, $r =$ of 0.9963, Fig. 9B), confirming that I_p increases across the studied scan rate of 10–200 mV s^{-1}.

3.2.4. Selectivity study. The selectivity of the proposed Au-NPs/CPE toward BZ was evaluated by measuring different interferents, such as the official impurity C (BZI) and various salts commonly found in the artificial saliva matrix, including $MgCl_2$, KCl, NaCl, $CaCl_2$, and $NaHCO_3$. The enhanced selectivity of the modified electrode for BZ determination is attributed to its distinct oxidation peak, detected at nearly 1.1 V *vs.* Ag/AgCl. Under these conditions, neither BZI nor the matrix salts exhibit redox activity within the same region as the target analyte, ensuring reliable detection (Fig. 10).

3.3. Method validation

The suggested method was validated according to the ICH guidelines,[45] regarding these parameters: linearity, LOD, LOQ, accuracy, and precision.

3.3.1. Linearity. Under the previously optimal conditions, the DPV oxidation peak current was recorded for six different concentrations of BZ (1.00–10.00 μM; Fig. 11a). A linear calibration plot of peak current *versus* BZ concentration was obtained (Fig. 11b), yielding the following regression equation:

$$I_p\ (\mu A) = 1.0958C\ (\mu M) - 0.6027\ (r = 0.9999) \quad (1)$$

where I_p is the peak current in μA, C is the concentration in μM, and r is the correlation coefficient. Data are presented in Table 1.

3.3.2. Limit of detection and quantification. The sensitivity of Au-NPs/CPE was gauged by calculating the limit of detection (LOD) and quantification (LOQ) values. Based on the formulae LOD $= 3.3\sigma/S$ and LOQ $= 10\sigma/S$ (where σ represents the standard deviation of the intercept and S is the slope), values of 0.1024 μM and 0.3103 μM were obtained for the LOD and LOQ, respectively (Table 1), confirming the high sensitivity of Au-NPs/CPE.

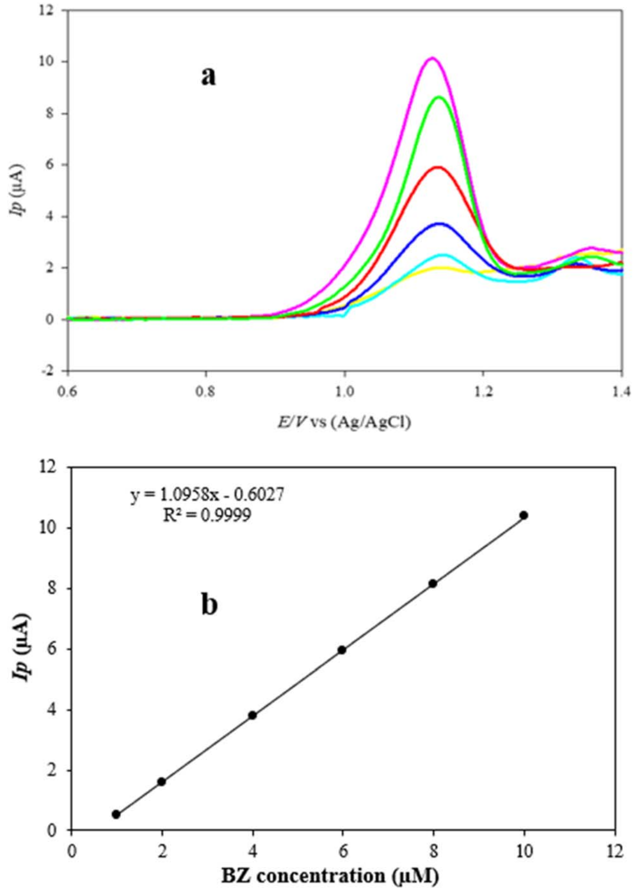


Fig. 11 (a) Differential pulse voltammograms of different concentrations of benzydamine hydrochloride. (b) Calibration curve of benzydamine hydrochloride in μM (1.00–10.00 μM) in 0.01 M sulphuric acid at Au-NPs/CPE.

3.3.3. Accuracy and precision. The accuracy of the suggested method was evaluated through triplicate analysis of five different concentrations of BZ, yielding satisfactory mean

Table 1 Validation parameters of the proposed voltammetric method for the determination of benzydamine hydrochloride using Au-NPs/CPE[a]

Parameters	Standard solution
Linearity	
Range (μM)	1.00–10.00
Slope	1.0958
Intercept	−0.6027
Correlation coefficient (r)	0.9999
LOD (μM)	0.1024
LOQ (μM)	0.3103
Accuracy (mean ± SD)	100.09 ± 1.40
Precision (% RSD)	
Repeatability[a]	1.043
Intermediate precision[b]	1.108

[a] (a) and (b) are the intra-day and inter-day precision, respectively (n = 9), with the relative standard deviation of 3 concentrations repeated three times on the same day and 3 successive days, calculated for (4.00, 6.00 and 8.00 μM) benzydamine hydrochloride.

recovery percentage and standard deviation (Table 1). For precision, intra-day (repeatability) and inter-day (intermediate precision) analyses were conducted on three BZ concentrations, with all relative standard deviation (RSD) values less than 2% (Table 1).

3.4. Determination of BZ in Tantum Verde® mouthwash and artificial saliva using the DPV method

To estimate the BZ concentration in the Tantum Verde® mouthwash product and artificial saliva, the developed DPV method was successfully employed (Table 2). The results derived from the determination of pure BZ were statistically compared with those collected from the reported potentiometric method.[35] The comparison (Table 3) showed no significant difference in accuracy between the developed and reported methods, as both the calculated *t*-test and *F* values fell below their tabulated critical values at 95% confidence interval.

A comparison of the suggested voltammetric method with formerly reported electrochemical methods for BZ reveals clear differences in sensor design and analytical performance. Most published studies are dominated by potentiometric techniques, which mainly utilize PVC-based ion selective electrodes,[31,33] coated-wire sensors,[31] advanced liquid contact ISE (LC-ISE)/solid contact ISE (SC-ISE) configuration,[35] modified carbon paste electrodes,[32,34] or all solid-state ISE (ASS-ISE) and LC-ISE systems.[36] These systems generally exhibit wide linearity ranges, extending from the sub-micromolar level up to 10^{-2} M, along with very low limits of detection (10^{-7}–10^{-8} M) and near-Nernstian sensitivities (between 58 and 60 mV per decade). Their high selectivity against common inorganic ions, excipients, sugars, amino acids, and degradation products has enabled successful application to pharmaceutical preparations and complex biological matrices, including urine, plasma, artificial saliva, and surface water samples.

In contrast, the amperometric[37] and the proposed voltammetric methods mainly employ carbon-based electrodes, including bare or modified CPEs. These methods typically operate within narrower linearity ranges at the micromolar level and provide limits of detection of 10^{-6}–10^{-7} M, respectively, which are nevertheless sufficient for routine quality control purposes. Notably, voltammetric techniques offer high sensitivity and enhanced selectivity, leading to effective discrimination of BZ from inorganic salts, pharmaceutical excipients, sugars, urea, and related impurities. Moreover, the applicability of the proposed approach to direct analysis of mouthwash formulation and artificial saliva with minimal sample preparation highlights its practical value. Consequently, despite the dominance of potentiometric techniques in the literature, the voltammetric determination of BZ represents a promising and complementary analytical approach, particularly when coupled with electrode surface modification to improve sensitivity and selectivity.

Table 3 Statistical comparison between the results of pure benzydamine hydrochloride by the proposed voltammetric method and previously reported potentiometric method

Parameters	Proposed voltammetric method	Reported potentiometric method[35]
Mean	100.09	100.91
SD	1.40	1.10
n	6	9
Variance	1.96	1.21
Student's *t*-test (2.179)[a]	1.217	—
F value (4.82)[a]	1.62	—

[a] The values in parenthesis are the corresponding theoretical values of *t* and *F* at $p = 0.05$.

3.5. Sustainability assessment

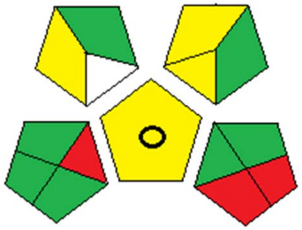
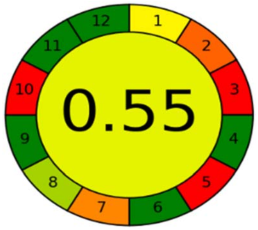
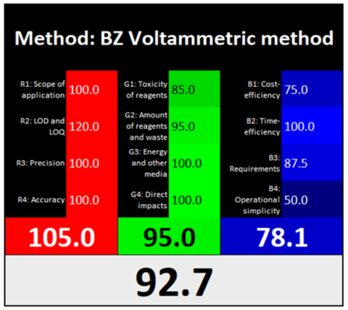
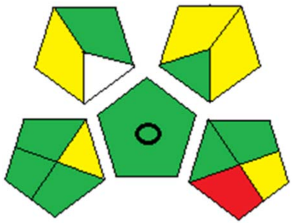
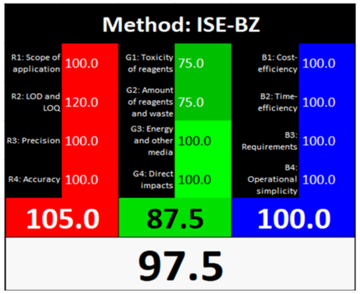
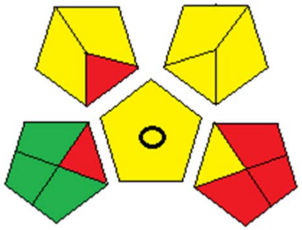
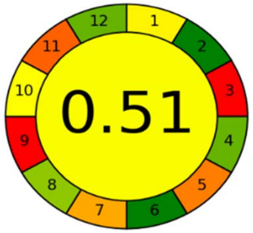
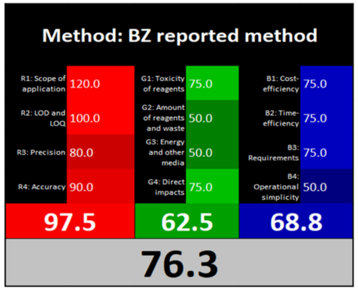
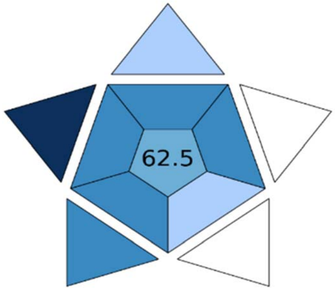
Growing awareness of the environmental and health consequences of conventional analytical approaches has accelerated the integration of Green Analytical Chemistry (GAC) principles[46] into modern practice. These principles emphasize minimizing hazardous materials, energy requirement, and waste production without compromising analytical performance,[7,19,47–49] thereby fostering the implementation of eco-friendly techniques such as electroanalytical methods, like voltammetry. To facilitate implementation, standardized metrics comprising the Analytical Eco-Scale (AES), the Green Analytical Procedure Index (GAPI), and the Analytical GREEnness (AGREE) metric have been established to quantify the ecological impact. This framework has evolved further with White Analytical Chemistry (WAC),[41] which introduces a holistic "whiteness" score through the incorporation of environmental sustainability, analytical performance, and practical/economic viability. Complementary tools such as the Blue Applicability Grade Index (BAGI) extend this approach, enabling comprehensive sustainability

Table 2 Determination of benzydamine hydrochloride in Tantum Verde® and artificial saliva by the developed voltammetric procedure

Voltammetric procedure	
Found % (mean ± SD)[a]	
Tantum Verde® mouthwash (0.15 g benzydamine hydrochloride/100 mL), batch no. 2209038[b]	99.61 ± 1.68
Recovery % (mean ± SD)[a]	
Spiked concentration (4.00 μM) of benzydamine hydrochloride in artificial saliva	98.95 ± 1.31

[a] Results of the analysis of 4.00 μM benzydamine hydrochloride conducted three times. [b] The acceptance limit for benzydamine hydrochloride is 92.5–107.5%.

Table 4 Sustainability assessment of the developed voltammetric method and the reported potentiometric and HPLC methods for the determination of benzydamine hydrochloride

	AES score	GAPI assessment	AGREE assessment	Whiteness assessment tool (RGB12 model)	Blueness assessment tool (BAGI)
Proposed voltammetric method	84			 Method: BZ Voltammetric method R1: Scope of application 100.0 R2: LOD and LOQ 120.0 R3: Precision 100.0 R4: Accuracy 100.0 105.0 G1: Toxicity of reagents 85.0 G2: Amount of reagents and waste 95.0 G3: Energy and other media 100.0 G4: Direct impacts 100.0 95.0 B1: Cost-efficiency 75.0 B2: Time-efficiency 100.0 B3: Requirements 87.5 B4: Operational simplicity 50.0 78.1 92.7	
Reported potentiometric method[35]	85			 Method: ISE-BZ R1: Scope of application 100.0 R2: LOD and LOQ 120.0 R3: Precision 100.0 R4: Accuracy 100.0 105.0 G1: Toxicity of reagents 75.0 G2: Amount of reagents and waste 75.0 G3: Energy and other media 100.0 G4: Direct impacts 100.0 87.5 B1: Cost-efficiency 100.0 B2: Time-efficiency 100.0 B3: Requirements 100.0 B4: Operational simplicity 100.0 100.0 97.5	
Reported HPLC method[24]	62			 Method: BZ reported method R1: Scope of application 120.0 R2: LOD and LOQ 100.0 R3: Precision 80.0 R4: Accuracy 90.0 97.5 G1: Toxicity of reagents 75.0 G2: Amount of reagents and waste 50.0 G3: Energy and other media 50.0 G4: Direct impacts 75.0 62.5 B1: Cost-efficiency 75.0 B2: Time-efficiency 75.0 B3: Requirements 75.0 B4: Operational simplicity 50.0 68.8 76.3	

assessments that balance ecological responsibility with laboratory applicability.

3.5.1. Analytical eco-scale (AES). The AES[38] was used to evaluate the ecological effect of the developed approach, following the GAC principles,[46] and to compare its eco-friendliness to that of the reported methods.[24,35] This semi-quantitative scoring method allocates penalty points (PPs) based on aspects like reagent amounts and hazards, energy usage, occupational hazard, and waste production and treatment. The developed method and the reported potentiometric method[35] achieved AES scores of 84 and 85, respectively (Table 4), labeling them as excellent green analysis (additional elaboration is available in Table S2), while the reported HPLC method[24] scored 62, indicating acceptable green analysis.

3.5.2. Green analytical procedure index (GAPI). The GAPI tool offers a holistic framework for assessing the environmental consequences of analytical methods according to the GAC principles.[46] By employing a color-coded pentagram scheme (green, yellow, and red), GAPI enables rapid visual comparison of procedures across all steps, from sample treatment to solvents, reagents, and instrumentation.[39]

The application of GAPI to the developed voltammetric method demonstrated strong environmental performance, with most zones (2, 3, 4, 6, 8, 11, 12, and 13) classified as green. This reflects the absence of chemical or physical preservation requirements, lack of special storage conditions, and elimination of further treatments like cleanup or derivatization. The method employed reagents with low hazard ratings (instability score of 0 and flammability score of 1), consumed minimal energy (<0.1 kWh per sample), and was found to be free of vapor emission.

Several zones were designated yellow, including zone 5 (simplified sample preparation without extraction), zones 7 and 9 (use of 0.01 M H_2SO_4 in small volumes), considering it as environmentally benign,[50] and zone 10 (health hazard ratings of paraffin oil and gold nanoparticles are 2 and 3, respectively). In contrast, zones 1, 14, and 15 were classified red due to the off-line process, the waste volume exceeding 10 mL, and the lack of waste treatment. These findings are detailed in Table S3 and illustrated as pictograms in comparison to the methods[24,35] reported in Table 4.

3.5.3. Analytical greenness metric (AGREE). The environmental performance of the suggested voltammetric approach was evaluated by exploiting the AGREE tool, which provides a pictogram of twelve colored sections[40] corresponding to the principles of GAC[46] and a cumulative score ranging from 0 to 1.[51]

This analytical procedure exhibits notable adherence to several principles of GAC, requiring minimal sample preparation, avoiding derivatization agents, enabling high-throughput single-analyte determination, and employing an energy-efficient technique. Although bio-based reagents were not employed, the utilization of non-toxic reagents enhanced safety and lessened occupational hazards. In contrast, the method is not fully consistent with GAC principles 1, 2, 3, 5, and 7 due to certain limitations including offline analysis, relatively large sample volumes, generation of considerable waste volume, and lack of automation and miniaturization. These limitations are outweighed by the significant advantages in safety, simplicity, and energy efficiency.

The AGREE pictograms of the proposed approach and the reported approaches[24,35] are illustrated in Table 4, showing that the suggested method achieved a total score of 0.55, indicating its environmental compatibility.

3.5.4. Red-green-blue (RGB12) model. White Analytical Chemistry (WAC) integrates the analytical performance, environmental considerations, and operational efficiency into a unified framework expressed through 12 complementary principles[41] to the 12 principles of GAC.[46] Using the RGB12 model, these principles are visualized as red (analytical performance), green (following GAC principles), and blue (practical and economic effectiveness).[52] Based on the WAC assessment (Table 4), the proposed voltammetric method attained a whiteness score of 92.7%, compared to 97.5% for the reported potentiometric method[35] and 76.3% for the reported HPLC method.[24] The reported electrochemical methods (voltammetry and potentiometry) showed high analytical sensitivity with very low detection limits, while the HPLC method provided a broader analytical scope through the determination of impurities. Additionally, with respect to environmental aspects, the electrochemical methods required lower solvent consumption and energy input and avoided hazardous reagents typically associated with HPLC analysis. In terms of practicality, the proposed and the reported electrochemical methods relied on simpler instrumentation and reduced operational demands, whereas the HPLC method involved higher costs and longer analysis time. Overall, the comparison highlights the differences among the evaluated approaches within the WAC framework.

3.5.5. Blue applicability grade index (BAGI). The practical assessment tool BAGI complements greenness metrics by addressing the operational and applicability dimensions of WAC. It evaluates ten criteria related to the type of analysis, the number of analytes, apparatus, sample preparation and throughput, reagent use, preconcentration, automation, and sample amount, offering both a score value and a pictorial representation.[42] The evaluation is facilitated through bagi-index.anvil.app, which also allows straightforward comparison of different analytical methods. Based on the BAGI assessment (Table 4), the suggested voltammetric approach attained a score of 72.5, compared to 75.0 for the reported potentiometric method[35] and 62.5 for the reported HPLC method.[24] The developed method demonstrated favorable attributes in terms of on-site sample preparation, higher sample throughput, use of readily available solvents, and avoidance of preconcentration steps, while its limitations were associated with single-analyte determination and manual operation. The reported potentiometric method showed comparable overall practicality, whereas the reported HPLC method exhibited lower BAGI performance, mainly due to more complex sample handling and lower throughput. Overall, the BAGI comparison highlights distinct practical advantages and constraints among the evaluated methods.

4. Conclusion

A sensitive and reliable DPV method employing Au-NPs/CPE was successfully developed and validated for the quantification of BZ in pure powder, mouthwash, and artificial saliva. In contrast to previously reported electrochemical approaches, this work presents the first application of DPV using Au-NPs/CPE for BZ determination offering satisfactory analytical performance and practical applicability. The proposed method demonstrated good compliance with ICH validation guidelines, where the incorporation of Au-NPs markedly enhanced the electrode's activity and improved analytical sensitivity. Owing to its simplicity, rapid analysis, and minimal sample preparation, the method exhibits a clear advantage over conventional chromatographic techniques and complementary alternatives to the reported electrochemical techniques. Furthermore, its reliance on environmentally benign materials and procedures affirms its compliance with GAC principles verified by different assessment tools. Therefore, this Au-NPs/CPE-based voltammetric approach represents a sustainable and practical substitute for routine quality control and therapeutic monitoring of BZ.

Author contributions

Maryam Ahmed Bakr: investigation, formal analysis, writing – original draft. Samah Said Abbas: conceptualization, supervision, writing – review and editing. Maha Abd El-Monem Hegazy: conceptualization, supervision, writing – review and editing. Amr Mohamed Badawey: conceptualization, supervision, writing – review and editing. Sally Saad El-Mosallamy: conceptualization, supervision, validation, writing – review and editing.

Conflicts of interest

The authors declare that they have no known competing financial interests or personal relationships that might have influenced the work presented in this study.

Data availability

The datasets generated or analyzed during this study are available from the corresponding author on reasonable request.

Supplementary information (SI) is available. See DOI: https://doi.org/10.1039/d6ra02390h.

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