ELECTROCHEMICAL QUANTIFICATION OF IBUPROFEN IN COATED TABLETS USING BUCKYPAPER-BASED MULTI-WALLED CARBON NANOTUBE-MODIFIED ELECTRODES

R. MOSCOSO [a], A. CHARMELL [b,c] , AND J.A. SQUELLA [a]*

[a]*Universidad de Chile, Facultad de Ciencias Químicas y Farmacéuticas. Dpto. Química Orgánica y Fisicoquímica, Centro de investigación de Procesos Redox (CiPRex). Santiago, Chile.*

[b] *Universidad de Los Andes, Facultad de Ciencias, Dpto. de Química, Laboratorio de Electroquímica, Mérida, Venezuela.*

[c]*Escuela de Química y Farmacia, Facultad de Medicina, Universidad Andres Bello, Santiago, Chile*.

ABSTRACT

Illicit and unregulated pharmaceutical trade poses a growing public-health risk, particularly for widely self-medicated non-steroidal anti-inflammatory drugs such as ibuprofen (IBU). Here, we report a portable electroanalytical approach for the quantification of IBU in marketed coated tablets using buckypaper (BP)-based multi-walled carbon nanotube (MWCNT) electrodes. A BP-MWCNT sheet was transferred by a simple stamping procedure onto two transducers: a glassy carbon electrode (GC/BP) for differential pulse voltammetry (DPV) and a screen-printed electrode (SPE/BP) coupled to batch injection analysis (BIA) for amperometric, high-throughput screening. IBU exhibited an irreversible anodic response on BP-modified electrodes, with a pH-dependent peak potential enabling estimation of an operational interfacial pKa (~5.0) from Ep–pH trends. Quantification was linear from 0.3 to 1.0 mM. GC/BP–DPV delivered LOD/LOQ of 0.041/0.123 mM, while SPE/BP–BIA improved sensitivity (LOD/LOQ 0.022/0.066 mM) under hydrodynamic conditions using 10 µL injections. Accuracy was verified in commercial tablets, yielding recoveries near 100% (e.g., 103.2% for GC/BP and 100.2% for SPE/BP by external calibration) with low coefficients of variation. Application to unregulated street-market samples distinguished compliant tablets (~99%) from a substandard batch (~79%), below pharmacopeial limits (90–110%). Overall, the proposed BP-MWCNT workflow is positioned as a practical point-of-sale tool for shelf-level post-market monitoring in regulated retail, while also enabling rapid screening of tablets obtained from informal outlets.

Keywords: Amperometry, BIAS, Buckypaper, Carbon Nanotubes, Ibuprofen Screen Printed Electrodes.

1. INTRODUCTION

The illicit trade of pharmaceutical products represents a critical threat to public health. While these medications often mirror the packaging and aesthetic characteristics of authentic products, providing a deceptive sense of security to consumers seeking cost-effective alternatives, the lack of regulatory oversight leaves buyers unable to verify the chemical integrity of the active pharmaceutical ingredient (API). Beyond the risk of counterfeiting, substandard medications frequently arise from inadequate storage and handling conditions. In informal open-air markets, products are routinely exposed to uncontrolled environmental factors, such as extreme temperatures, humidity, and UV radiation, which may trigger chemical degradation or alter the medication's stability. In Latin American countries, the prevalence of self-medication has significantly intensified since the COVID-19 pandemic, with non-steroidal anti-inflammatory drugs (NSAIDs) like ibuprofen being among the most consumed [1]. This trend has been further exacerbated by the post-pandemic proliferation of unregulated points of sale. Consequently, there is an urgent need for robust, low-cost, and portable analytical tools—such as the electrochemical sensors developed in this work—capable of providing rapid on-site verification of ibuprofen content in samples obtained from these high-risk informal channels.

Ibuprofen (2RS)-1[4-(2-methylpropyl)phenyl]propanoic acid is a nonsteroidal anti-inflammatory drug (NSAID), based on its structure, it is classified in the family of aryl and heteroaryl acetic acid derivatives along with naproxen, fenoprofen and oxaprozin[2]. Ibuprofen is widely used to relieve pain, fever, and inflammation, including muscle aches, headaches, arthritis, menstrual cramps, toothaches, and other inflammatory conditions [3, 4]. Current literature extensively explores the determination of ibuprofen with low limits of detection and quantification in water samples [5-9], pharmaceutical preparations, and biological matrices such as tissues, plasma, and urine [10-15]. Most methods for detecting and quantifying ibuprofen are based on chromatographic techniques [16, 17]. However, despite their precision, these methods require bulky and expensive instrumentation, specialized laboratories, and significant reagent consumption, which renders them unsuitable for rapid, on-site monitoring in resource-limited settings. In response to the need for field-deployable analytical tools, electrochemical analysis has emerged as a superior alternative due to its high sensitivity, specificity, rapidity, low cost, and minimal reagent waste. Advances in nanotechnology and the development of modified electrodes have further catalyzed this field, enabling the miniaturization of sensors for in-situ applications. Among the available techniques, electrochemical analysis stands out due to its high sensitivity, specificity, rapidity, low cost, and minimal reagent consumption[9, 18]. One of the applications of the electrodes modified with this material is the electrochemical determination of drugs for their quality control [19]. From an electroanalytical standpoint, ibuprofen is most quantified through its anodic electrooxidation at carbon-based and diamond-based electrodes, which typically occurs at relatively positive potentials and is therefore highly sensitive to the electrode surface chemistry and the supporting electrolyte composition. Studies on boron-doped diamond have reported a well-defined oxidation response amenable to differential-pulse voltammetry, supporting the feasibility of direct voltammetric determination in aqueous media [20]. The electrooxidation of ibuprofen is frequently described as a largely irreversible process, and its voltammetric response exhibits a marked pH dependence, consistent with proton-coupled electron transfer contributions and changes in the interfacial speciation with pH. In practice, these features often motivate the use of surface-engineered electrodes and nanostructured carbons to improve signal definition, lower the effective overpotential, and enhance analytical performance in complex matrices [21, 22].

In this work, two methodologies were evaluated for the quantification of Ibuprofen (IBU) in marketed coated tablets, the first with the modification on a glassy carbon electrode (GCE) and the second on a screen-printed electrode (SPE).

Building upon our previous development and electrochemical characterization of the BP-MWCNT platform [23], a key remaining challenge is demonstrating analytical reliability under realistic, decentralized workflows and matrix-rich samples. In particular, translating buckypaper-type CNT networks from conventional laboratory electrodes to disposable formats—while preserving sensitivity, precision, and minimal sample preparation—remains underexplored for field verification of NSAID tablets circulating in unregulated supply chains.

In this study we address this gap by implementing a simple stamping transfer of BP-MWCNT onto both glassy carbon (GC/BP) and screen-printed electrodes (SPE/BP), enabling two complementary quantification modes: DPV for stationary measurements and BIA-amperometry for rapid, high-throughput screening with microliter injections. The method is validated in marketed 400 mg coated tablets and then applied to samples obtained from informal street markets, where degradation or falsification risks are elevated. By coupling a transferable CNT-buckypaper architecture with a practical on-site workflow, this work provides a robust, portable framework for rapid ibuprofen quality control and establishes a basis for extending the approach toward multi-drug field screening.

2. EXPERIMENTAL

2.1 Materials and Methods

Ibuprofen (IBU) coated tablets (400 mg) were obtained from two sources: authorized pharmacies and informal street markets and were used directly,

*Corresponding author email: asquella@ciq.uchile.cl

according to the packaging manufactured by the main and most common laboratories in Chile. Pharmaceutical grade ibuprofen ASC was obtained from Reutter S.A. Ibuprofen (CAS 15687-27-1, lot R13060 99.8% purity), type: USP reference standard, was acquired from store.usp.com. Boric acid, ortho-phosphoric acid, acetic acid, monobasic sodium phosphate, dibasic potassium phosphate, polystyrene and 1,3-dioxolane were of analytical grade obtained from Merck. All aqueous solutions were prepared with nano-pure water. Nylon membrane filters (0.20 µm, 47 mm diameter) were obtained from Whatman®. Multiwalled carbon nanotubes (MWCNT) were obtained from Metrohm Dropsens and were used without purification in the preparation of BP.

2.1.2 Electrochemical Measurements

The electrochemical measurements were carried out in a three-electrode system on an electrochemical workstation (CHI 660C). Glassy carbon electrodes as working electrode (GCE CHI104), Ag/AgCl (KCl 3.0 M) as reference electrode and Platinum wire as counter electrode. When screen-printed electrodes (SPEs) were employed, the working, reference, and counter electrodes corresponded to those included in the screen printed electrode SPECNT 110 model. The glassy carbon electrodes were polished with 0.3 µm and 0.05 µm of Al_2O_3 powder slurry before modification, and all the SP electrodes were used without previous pretreatment before modification with bucky paper electrodes (BPE). The supporting electrolytes consisted of a 0.1 M Britton-Robinson (BR) buffer for the DPV experiments, whereas a 0.1 M phosphate buffer at pH 7.4 was utilized for all amperometric measurements. The pH in all buffer solutions was adjusted before each experiment.

2.1.3 DPV measurements

Differential pulse voltammetry (DPV) measurements were performed using the GC/BP modified electrodes. For each analysis, a 10 µL aliquot of the analyte was deposited onto the buckypaper surface, followed by a 10 s quiet time at open-circuit potential (OCP) prior to the voltammetric scan. The potential was swept from 0.7 V to 1.3 V using a pulse amplitude of 50 mV and a pulse period of 0.5 s., with a 0.1 M Britton-Robinson buffer as the supporting electrolyte. The electrode preparation for scan rate studies involved a pre-concentration step where 10 µL of a 1.0 mM ibuprofen solution was cast onto the BP/GCE surface for 10 s, followed by the removal of excess solution. This protocol was designed to mirror the operational conditions of the SPE/BP BIAS system. For the standard addition method at the GC/BP electrode, ibuprofen was determined in commercial tablets (nominal dose of 400 mg) based on the average tablet weight. Increasing concentrations of ibuprofen standard (0.25, 0.30, 0.35, 0.40, and 0.45 mM) were added to the samples without prior filtration of the excipients. Each measurement was performed in triplicate (n = 3) using a different electrode to ensure reproducibility. All measurements were conducted at room temperature.

2.1.4 Amperometric analysis

Amperometric determination of ibuprofen in commercial coated tablets (400 mg nominal dose) was conducted using a Batch Injection Analysis System (BIAS). The measurements were performed by applying a constant potential of 1.0 V (vs Ag) to a non-pretreated SPE/BP working electrode, with a pH 7.4 phosphate buffer as the supporting electrolyte. Aliquots of 10 µL, containing ibuprofen at the required concentration depending on the specific analysis, were injected into the BIAS cell, enabling rapid and consecutive measurements. For the quantification studies, the calibration standards ranged from 0.3 to 1.0 mM.

Due to the pronounced adsorption of ibuprofen onto the buckypaper network, a specific stabilization protocol was implemented: the first signal in every series of consecutive injections was systematically discarded. This initial peak consistently exhibited a higher current intensity as it interacted with a pristine, unused BP surface. Subsequent injections provided the stabilized and reproducible current responses required for reliable analytical quantification.

2.1.5 BP electrode preparation

Buckypaper (BP) electrodes were fabricated according to the procedure previously reported[23]. Briefly, a dispersion of carbon nanotubes (CNTs) and polystyrene in 1,3-dioxolane was vacuum-filtered through a nylon membrane filter 45 mm diameter (0.2 µm) from Whatman®. The resulting macro-sheet was dried and patterned using a Silhouette Cameo 4 cutting system. To ensure optimal surface coverage, BPs were cut into different diameters depending on the substrate: 6.0 mm for glassy carbon (GC) electrodes and 4.5 mm for screen-printed (SP) electrodes.

2.1.6 BP Electrode modification

GCE and SP electrodes were modified with BP-MWCNT using a stamping technique. The BP, featuring a MWCNT layer on a nylon support, was treated with 5 µL of 1,3-dioxolane and immediately pressed onto the polished electrode surface [23, 24]. Following a 3-minute adhesion period, the nylon membrane was removed by applying 5 µL of ultrapure water; the inherent hydrophobicity of the MWCNTs facilitated a clean separation of the filter support. This straightforward transfer process yielded a GCE/BP assembly ready for electrochemical characterization.

2.1.7 Repetibility

The repeatability of the SPE/BP electrode (4.6 mm diameter) was evaluated through ten consecutive injections of 10 µL of a 1.0 mM ibuprofen standard in 0.1 M PBS (pH 7.4). For the GC/BP electrode (6.0 mm diameter), the reproducibility of the modification was examined by performing ten independent drop-casting procedures using 10 µL of a 1.0 mM ibuprofen solution. These studies were designed to assess the stability of the buckypaper network.

2.1.8 Sample preparation

A total of 20 representative ibuprofen coated tablets (400 mg) were randomly selected from original commercial packaging obtained from both authorized pharmacies and informal street markets. Regardless of the source, the sample preparation followed an identical protocol to ensure consistency: the tablets were weighed individually to determine the mean tablet mass and then pulverized in a porcelain mortar to obtain a fine, homogeneous powder. An amount of the powder equivalent to the calculated average weight of one tablet was accurately weighed and transferred to a 100 mL volumetric flask. The samples were diluted to volume using either Phosphate Buffered Saline (PBS) at pH 7.4 for amperometric measurements or Britton-Robinson (BR) buffer at pH 7.0 for DPV analysis. To ensure the complete dissolution of the active pharmaceutical ingredient (API), the solutions were sonicated for 15 minutes. Subsequently, a 1 mL aliquot of the resulting supernatant was quantitatively transferred to a 50 mL volumetric flask and diluted to the mark with a 50:50 (v/v) mixture of phosphate buffer and nanopure water for the amperometric assays, or with the corresponding BR buffer for the DPV measurements.

2.1.9 Ibuprofen USP reference standard.

The reference standard solution (1.1732 mM) and the pharmaceutical-grade ACS ibuprofen standard (1.1585 mM) were prepared in a 50:50 (v/v) mixture of ultrapure water and 0.1 M phosphate-buffered saline (PBS) at pH 7.4. Amperometric measurements were performed in triplicate for both solutions using the BP-SPE/BIAS system to determine the experimental purity of the ACS reagent against the primary pharmacopeia standard. For all subsequent experimental procedures, including the construction of linearity and standard addition calibration curves, a 1.0 mM stock solution of the secondary standard was prepared. All further working solutions and dilutions were derived from this secondary stock.

2.1.10 Recovery Studies

The analytical accuracy of the proposed methods was evaluated through recovery studies using commercial ibuprofen formulations (400 mg nominal dose). For each batch (from authorized pharmacies and informal markets), a representative sample of twenty coated tablets was weighed individually to determine the mean tablet mass and then pulverized into a fine, homogeneous powder. For the analysis, three independent replicates (n = 3) were prepared by taking an amount of powder equivalent to the calculated average tablet weight. These samples were dissolved in the supporting electrolyte and sonicated for 15 minutes to ensure complete API extraction. The resulting solutions were analyzed using two different quantification strategies: direct interpolation from an external calibration curve and the standard addition method. This dual approach was applied to both the GC/BP platform (via DPV) and the SPE/BP platform (coupled with the BIAS system) to evaluate the influence of the pharmaceutical matrix and the consistency of the electrochemical response across different transducer architectures

2.1.11 Statistical Analysis

All electrochemical measurements and analytical determinations were performed in triplicate (n = 3), and the data are expressed as the mean ± standard deviation (SD). Data processing and linear regression analysis were conducted using OriginPro software. To account for the experimental variance and ensure a robust analytical model, the calibration curve was adjusted using a weighted linear regression (instrumental weighting mode). The limits of detection (LOD) and quantification (LOQ) were calculated following IUPAC recommendations (LOD = 3.3 σ/S and LOQ = 10 σ/S) where S is the slope of the curve and were estimated based on the standard error (σ) of the intercept at a 95% confidence level. Significant differences between the analyzed batches were evaluated considering the coefficients of variation (CV%) and recovery percentages relative to the nominal dose.

3. RESULTS AND DISCUSSION

3.1 Electrochemical behavior

The electrochemical behavior of ibuprofen was investigated using cyclic voltammetry (CV) at a buckypaper-modified glassy carbon electrode (BP/GCE). Figure 1 displays the voltammetric response of a 1.0 mM ibuprofen solution (solid line) superimposed with the response of the blank electrolyte (dashed line) in 0.1 M PBS (pH 7.4) at a scan rate of 100 mV/s. The chemical structure of ibuprofen is also depicted in Figure 1 for clarity While the blank solution exhibited no activity, a well-defined, irreversible anodic peak (I) was observed at 1.20 V (vs. Ag/AgCl) for the ibuprofen electro-oxidation. The absence of a reduction peak in the reverse scan confirms the irreversible nature of the electron transfer. The high peak current of 1.4 mA can be attributed to the synergistic effect between the high conductivity and the large effective surface area provided by the carbon nanotube network within the buckypaper[25]. It has been proposed that the electro-oxidation mechanism of ibuprofen involves a single-electron transfer via radical cation formation followed by the decarboxylation of the ibuprofen molecule[21, 26], a process typically associated with high overpotentials, which in this case is efficiently mediated by the nanostructured surface of the working electrode.

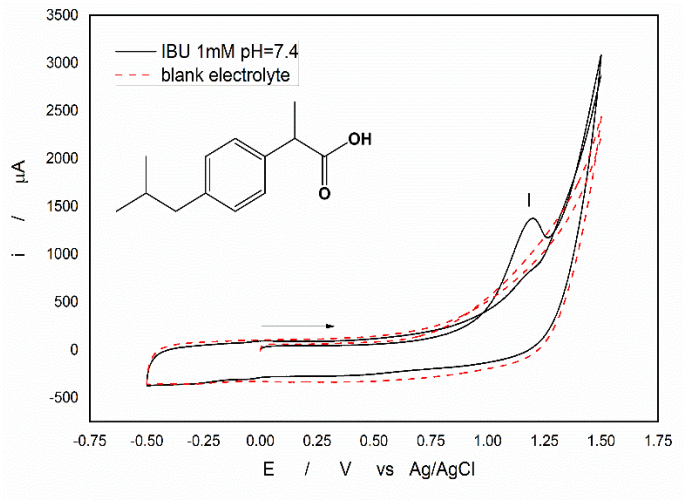

Figure 1. Cyclic voltammograms obtained at the BP/GCE for a 1.0 mM ibuprofen solution (solid line) and the blank electrolyte (dashed line) in 0.1 M PBS (pH 7.4). Scan rate: 100 mV/s. Potential range: -0.5 V to 1.4 V (vs. Ag/AgCl). The inset displays the chemical structure of ibuprofen.

3.2 Influence of pH

The influence of the pH solution on the oxidation peak potential (Ep) was further investigated using DPV over a range from pH 2.0 to pH 11.0. As shown in Figure 2, the Ep vs. pH plot reveals two distinct linear regimes. It was observed that at lower pH values, the oxidation of ibuprofen becomes increasingly difficult, as evidenced by the shift of Ep toward more positive potentials. Specifically, in the pH range between 4.0 and 5.0, the peak potential shifted towards less positive values as the pH increased. In contrast, from pH 5.0 to 9.0, the potential showed a weak dependence (-9.9 mV/pH), indicating a pH-independent mechanism in basic media which is consistent with findings reported in the literature [20].

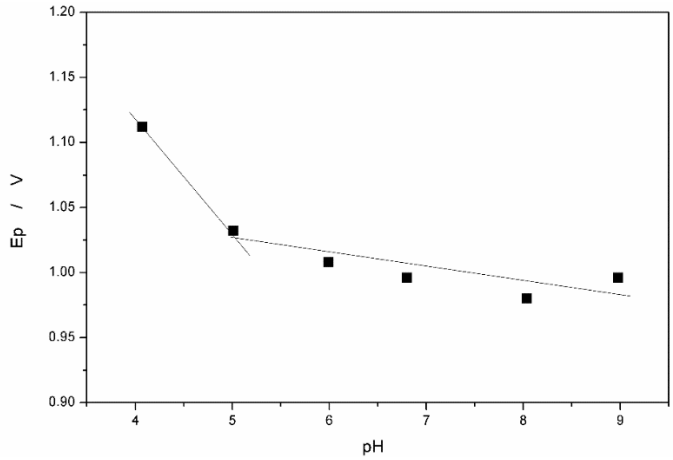

Figure 2: Ep vs pH plot for 1.00 mM ibuprofen solution in Britton Robinson buffer.

The intersection of the two linear trends at pH 5.0 provides an estimation of the operational or apparent pKa of ibuprofen at the electrode/electrolyte interface. At this point, the oxidation potential becomes essentially independent of the proton concentration in the medium. This experimental value is in good agreement with the thermodynamic pKa reported in the literature (4.6 – 4.9) determined by electrophoretic and spectrophotometric methods [27, 28]. Crucially, while photometric values are well-established, to the best of our knowledge, there is no evidence in the literature of a pKa value for ibuprofen determined via electrochemical methods. This finding represents a significant advantage of the buckypaper-modified electrode. The 3D nanostructure formed by the carbon nanotubes effectively traps insoluble or poorly soluble compounds, facilitating their study in aqueous media and enabling, for the first time, the electrochemical determination of the pKa[29]. Furthermore, the absence of oxidation signals at highly acidic (pH 2.0 and 3.0) and highly alkaline (pH 10.0 and 11.0) conditions defines a specific operational window for the sensor, providing a more comprehensive evaluation than the narrower ranges (pH 3.0 to 9.0) typically reported in the literature [8, 15, 21, 26, 30].

3.3 Influence of Scan Rate

Influence of scan rate was also investigated in order to determine whether there is diffusive or adsorptive control in the interaction of Ibuprofen with the BP sheet. Cyclic voltammetry (CV) was performed at various scan rates (ν) from 25 to 200 mV/s. As illustrated in the inset of Figure 3, the anodic peak current (Ip) increased progressively with the scan rate (ν). A double-logarithmic plot of peak current versus scan rate (log Ip vs. log ν) was constructed, Figure 3. The experimental data exhibited a strong linear correlation, described by the following regression equation:

$$\log Ip = 0.86 \log \nu + 1.20$$

The obtained slope of 0.86 indicates a significant deviation from a purely diffusion-controlled mechanism (theoretical slope of 0.5) toward a surface-confined process (theoretical slope of 1.0). This behavior is primarily attributed to the electrode preparation protocol, which involves a pre-concentration step where 10 µL of the ibuprofen solution is cast onto the BP/GCE surface for 10 s. Notably, this procedure was specifically designed to mirror the operational conditions and sampling methodology of the SPE/BP BIAS system, ensuring consistency between the fundamental characterization and the analytical application. The 3D nanostructured network of the buckypaper functions as a molecular reservoir, facilitating the adsorptive entrapment of ibuprofen molecules within its porous matrix. This effect ensures that the analyte is effectively 'trapped' near the transducer surface, preventing its rapid dissipation into the bulk solution and allowing adsorption-controlled kinetics to dominate during the measurement [31].

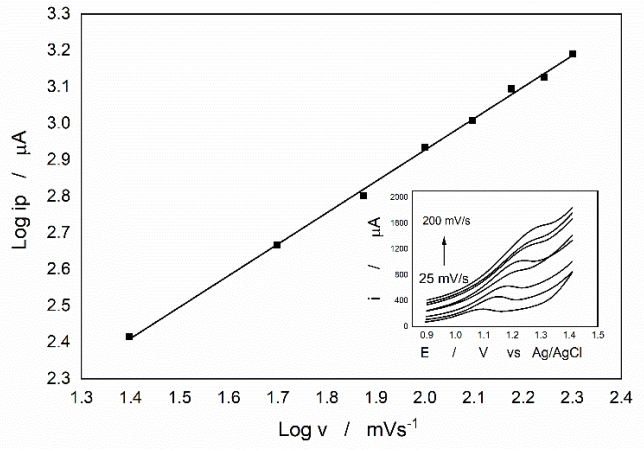

Figure 3: Log Ip vs Log ν for an electrode modified with 1.00 mM ibuprofen solution in phosphate buffer at pH=7.40. Inset: Cyclic voltammetric responses of 1.0 mM ibuprofen at different scan rates ranging from 25 to 200 mV/s. Potential range: 0.9 V to 1.4 V (vs. Ag/AgCl)

3.4 Analytical Performance

The determination of ibuprofen was performed using differential pulse voltammetry (DPV) exclusively with GC/BP electrodes. Conversely, screen-printed electrodes (SPE/BP) were utilized for analysis through the Batch Injection Analysis System (BIAS). A calibration curve was constructed by measuring the anodic peak current on DPV responses for ibuprofen standards across a concentration range from 0.3 to 1.0 mM. As illustrated in Figure 4-A, the modified electrode exhibited a robust linear relationship between the average peak current (Ip, n = 3) and the ibuprofen concentration ([IBU]). The resulting linear regression equation was:

$$Ip\ (\mu A) = 22.98\ (\mu A/mM)\ [IBU] - 1.41\ (\mu A)$$

with a correlation coefficient, $R^2 = 0.994$. Using the standard error of the intercept (0.28369), the LOD was determined to be 0.041 mM and the LOQ 0.123[32]. This statistical approach, incorporating experimental variance from triplicates (n = 3), ensures a robust estimation of the sensor's sensitivity.

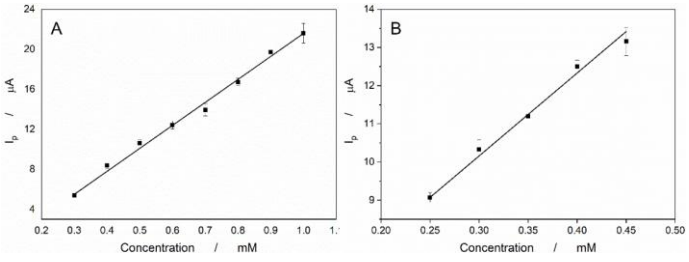

Figure 4: (A) Calibration curve of ibuprofen concentration ([IBU]) versus anodic peak current (Ip) obtained by DPV at the GC/BP electrode in 0.1 M PBS (pH 7.4). Each data point represents the mean value of three independent measurements (n = 3). $p < 0.05$). (B) Ibuprofen standard addition curve obtained from DPV measurements (n = 3). The linear fit demonstrates high statistical significance with a p-value<0.05.

3.5 Matrix Effect and Practical Applicability

The determination of ibuprofen in commercial tablets was conducted using the standard addition method at the GC/BP electrode to evaluate the potential matrix effects. As shown in Figure 4-B, the standard addition plot yielded a highly linear response, described by the following regression equation:

$$Ip(\mu A) = 21.72\ (\mu A/mM)\ [IBU] + 3.64\ (\mu A)$$

Based on this methodology, a recovery of 90.6% of the declared dose in the pharmaceutical formulation was achieved. No filtration of the excipients was performed. These results indicate that the GC/BP platform is highly effective for the quantification of ibuprofen in complex pharmaceutical matrices, with the matrix effect being successfully accounted for through the standard addition approach.

3.6 Analysis with SPE/BP and BIAS

To evaluate the versatility of the buckypaper modification across different platforms, screen-printed electrodes modified with BP (SPE/BP) were employed for ibuprofen determination. Quantification was performed using Batch Injection Analysis System (BIAS) coupled with amperometry, a technique that allows for high-throughput analysis by injecting micro-aliquots into a miniature cell. As illustrated in Figure 5-A, the system exhibited a highly linear response described by the equation:

$$Ip\ (\mu A) = 30.89\ (\mu A/mM)\ [IBU] - 5.54\ (\mu A)$$

with an adjusted $R^2 = 0.999$. The analytical sensitivity of the BIAS was superior to stationary methods, with a calculated LOD of 0.022 mM and an LOQ of 0.066 mM. These values were derived from the standard error of the intercept (0.20444). These results, obtained under hydrodynamic conditions in the BIAS, demonstrate that the SPE/BP platform provides superior sensitivity and faster analytical response compared to stationary methods.

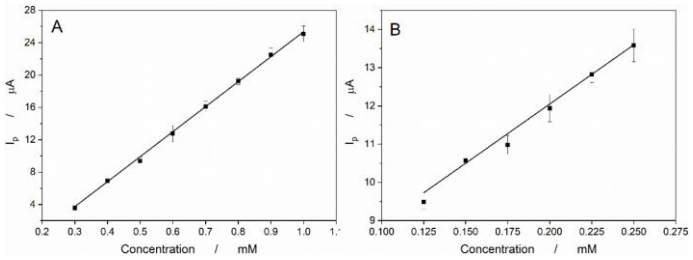

Figure 5: (A) Calibration curve of ibuprofen concentration ([IBU]) versus amperometric peak current (Ip) obtained by BIAS at 1.00 V using the external standard method (n = 3). $P < 0.05$). (B) Ibuprofen standard addition curve obtained via BIAS amperometry (n = 3) for pharmaceutical sample analysis.

3.7 Precision and Comparative Performance

The precision of the proposed methods was evaluated through repeatability studies for both SPE/BP and GC/BP platforms. For the SPE/BP electrode (4.6 mm diameter), the resulting amperometric signals, shown in Figure 6, exhibited a coefficient of variation (CV%) of less than 6%, demonstrating the high stability of the buckypaper-modified screen-printed surface under hydrodynamic conditions. In addition, the repeatability of the modification process for the GC/BP electrode (6 mm diameter) was examined. A comparison between both platforms reveals that while both electrodes provide excellent precision (CV% < 6%), the SPE/BP system coupled with BIA offers a faster analytical throughput. The SPE/BP system coupled with BIAS offers a significantly faster analytical throughput, making it suitable for routine monitoring. Conversely, the GC/BP electrode provides a larger active area due to its greater diameter, which is advantageous for applications requiring higher current signals. Overall, the consistent repeatability observed in both systems underscores the effectiveness of the buckypaper network in providing a stable and reproducible electrochemical environment for ibuprofen quantification.

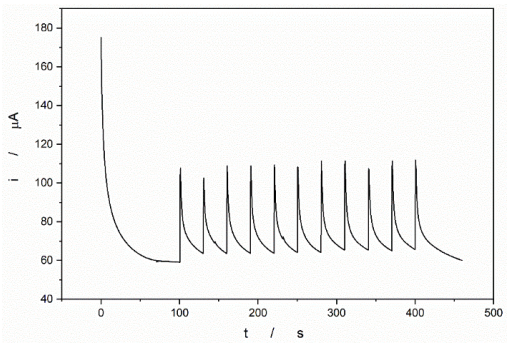

Figure 6: BIAS amperometric repeatability assay for 1.00 mM Ibuprofen in phosphate buffer at pH=7.40 at 1.00 V potential.

3.8 Comparison with Reference Standard

The purity of the ACS-grade ibuprofen standard was validated by comparing its amperometric response with a primary pharmacopeia reference standard. As summarized in Table 1, the primary standard exhibited an average current of 29.25 µA with a low coefficient of variation (CV% = 1.41%). In parallel, the ACS secondary standard produced a consistent average current of 28.92 µA (CV% = 4.19%), which corresponds to a calculated experimental concentration of 1.1576 mM. This comparison yielded an ibuprofen content of 99.92%, agreement within coefficient of variation, confirming the percentage of purity of the ACS reagent and its suitability for the subsequent analytical applications.

Table 1. Standardization results comparing the primary pharmacopeia standard and the secondary pharmaceutical-grade (ACS) standard using the BP-SPE/BIAS system (n=3).

Standard Type	$I_{average}$ (µA)	CV (%)	$C_{nominal}$ (mM)	C_{real} (mM)	Purity (%)
Primary (Pharmacopeia)	29.25	1.41	1.1732	1.1708	99.80
Secondary (ACS Grade)	28.92	4.19	1.1585	1.1576	99.92

3.9 Recovery Studies

The analytical validity of the proposed methods was evaluated through recovery studies using commercial ibuprofen formulations purchased from a local pharmacy. These commercial samples were utilized to demonstrate the sensor's performance in the presence of standard pharmaceutical excipients and to validate the accuracy of both the GC/BP and SPE/BP platforms. As summarized in Table 2, two different quantification strategies were compared for both GC/BP and SPE/BP platforms: direct interpolation from the external calibration curve and the standard addition method. the GC/BP electrode achieved a recovery of 103.19% with a remarkably low coefficient of variation (CV% = 1.1%) via external calibration, while the standard addition method yielded 90.4%. On the other hand, the SPE/BP platform coupled with the BIA system demonstrated excellent performance, with an average recovery of 100.2% (CV% = 3.2%, n = 3) via external calibration and 106.8% through the standard addition method (Figure 5B). The regression equation for the latter was:

$$Ip\ (\mu A) = 30.96(\mu A/mM)\ [IBU] + 5.85(\mu A) \qquad (R^2 = 0.9804)$$

where the standard error of the intercept (0.35169) allowed for the determination of an LOD of 0.037 mM and an LOQ of 0.114 mM.

Table 2. Percentage of recovery and concentration of IBU in coated tablet. Declared concentration of ibuprofen = 400 mg.

Electrode	n	Ibuprofen found (mg)	%, Recovery
GC/BP	1	416.0	104.0
	2	410.7	102.7
	3	419.9	105.0
		Mean, %	**103.19**
		SD	**1.15**
		CV, %	**1.1**
GC/BP Standard Addition	1	**361.6**	**90.4**
SPE/BP BIAS	1	403.3	100.8
	2	386.9	97.6
	3	412.3	103.1
		Mean, %	**100.2**
		SD	**3.21**
		CV, %	**3.2**
SPE/BP BIAS Standard Addition	1	**427.1**	**106.8**

The proximity of these recovery values to 100% across both electrochemical platforms indicates that the matrix effects from excipients in the pharmaceutical formulations are negligible or effectively managed. Furthermore, the high precision observed, particularly the CV% of 1.1% for the GC/BP, underscores the robustness of the buckypaper modification in providing stable and reproducible signals even when analyzing samples from non-ideal storage conditions. These results are in good agreement with previously reported literature, which shows similar recovery percentages for ibuprofen in pharmaceutical matrices [33].

3.10 Application to Unregulated Commercial Samples

The practical applicability of the developed electrochemical method was evaluated by analyzing two batches of ibuprofen tablets (400 mg nominal dose) acquired from informal markets or street markets. Amperometric analysis was conducted using the SPE/BP BIAS system as previously described. As summarized in Table 3, the first lot (OPKO batch) demonstrated high compliance with the declared dosage, yielding an average ibuprofen content of 99.2% with a coefficient of variation (CV%) of 2.7%. In contrast, the second lot (Laboratorios Chile batch) exhibited a significant deficiency in the pharmaceutical active ingredient (API), with an average recovery of only 78.9% (CV% = 5.7%) relative to the nominal dose. These findings highlight the effectiveness of the SPE/BP platform as a reliable screening tool for the rapid identification of substandard pharmaceutical products in unregulated supply chains. The ability of the SPE/BP BIAS system to distinguish these variations confirms its robustness as a reliable tool for the rapid screening and surveillance of pharmaceutical quality in resource-limited or decentralized settings.

Table 3. Percentage of recovery over declared doses and IBU found in coated tablet. Declared concentration of ibuprofen = 400 mg, obtained from informal markets.

Batch	Electrode	n	I average (µA)	Concentration found (mg)	% over declared doses
OPKO batch: 75324L02	SPE/BP	1	6.14	389.5	97.6
	BIAS	2	6.77	409.1	102.5
EXP: 11/27		3	6.19	391.7	98.1
				Mean, %	**99.2**
				SD	**2.68**
				CV, %	**2.7**
Laboratorios Chile batch:29897	SPE/BP	1	4.38	329.9	82.5
	BIAS	2	4.09	321.4	80.4
EXP: 01/27		3	3.27	295.6	73.9
				Mean, %	**78.9**
				SD	**4.47**
				CV, %	**5.7**

While the first lot (OPKO) showed high compliance with an average recovery of 99.2%, the second lot (Laboratorios Chile) exhibited a deficient recovery of only 78.9%, which falls substantially below the pharmacopeia limits of 90% to 110%. This non-compliance in the second batch suggests potential issues related to either the manufacturing source or the storage history of the tablets. Given that these samples were acquired from informal street markets; they are frequently subjected to adverse environmental conditions. Prolonged exposure to fluctuating temperatures, direct sunlight, and high humidity in outdoor stalls can trigger the chemical degradation of the active pharmaceutical ingredient (API) over time.

Alternatively, the significant deficiency in API content may characterize these samples as substandard or counterfeit. It is plausible that such batches were initially identified by internal quality control protocols and designated for destruction; however, their availability in informal markets suggests a potential breach in the final disposal chain. This observation highlights that safeguarding public health requires not only rigorous quality oversight during manufacturing but also the implementation of enhanced traceability mechanisms. Such systems are essential to ensure that non-compliant medications are effectively destroyed and not diverted into unregulated supply chains.

CONCLUSIONS

The proposed methodology eliminates the need for complex filtration processes of insoluble excipients present in commercial coated tablets, significantly simplifying the analytical workflow. The implementation of the BIA system coupled with SPE/BP electrodes significantly enhanced analytical sensitivity compared to stationary methods. Furthermore, this configuration drastically reduced analysis times, enabling high-throughput quantification without compromising the accuracy of the results. Also, the system demonstrates high potential for on-site (in-situ) applications. Its minimal requirement for sample preparation makes it an ideal candidate for the field-based monitoring of pharmaceuticals in unregulated or resource-limited environments. The BIA-amperometry approach is characterized by its efficiency and sustainability, requiring very low sample volumes (10 µL) per injection, which minimizes waste and reagent consumption. The GC/BP and SPE/BP sensors as robust, portable, and cost-effective tools for the quality control of ibuprofen, particularly in scenarios involving illicit trade or informal supply chains

ACKNOWLEDGMENT

The authors are grateful to the ANID / Fondecyt Regular Project No. 1250428 for the financial support and funding provided for this research.

ABBREVIATIONS

ACS:	American Chemical Society
API:	Active Pharmaceutical Ingredient
BIA:	Batch Injection Analisys
BP:	Buckypaper
BP/GCE:	Glassy Carbon Electrode modified with Buckypaper
BPE:	Bucky Paper Electrode
CV:	Cyclic Voltammetry
CV%:	Percentage Coefficient of Variation
DPV:	Differential Pulse Voltammetry
Ep:	Peak potential
GCE:	Glassy Carbon Electrodes
GCE/BP:	Glassy Carbon Electrodes Modified with Buckypaper
IBU:	Ibuprofen
Ip:	Peak current
LOD:	Limit of detection
LOQ:	Limit of quantification
MWCNT:	Multi-walled Carbon Nanotubes
NSAID:	Non-Steroidal Anti-Inflammatory Drugs
OCP:	Open-Circuit Potential
PBS:	Phosphate Buffered Saline
R^2:	Coefficient of determination
S:	Slope of the curve
σ:	Standard error of intercept
SPE:	Screen Printed Electrodes
SPE/BP:	Screen-printed Electrode modified with Buckypaper
v:	Sweep Rate

REFERENCES

1. Mejia, C.R., et al., Heliyon, 2024. **10**(1): p. e22299.https://doi.org/10.1016/j.heliyon.2023.e22299.
2. Bindu, S., S. Mazumder, and U. Bandyopadhyay, Biochemical Pharmacology, 2020. **180**: p. 114147.https://doi.org/10.1016/j.bcp.2020.114147.
3. Bushra, R. and N. Aslam, Oman Med J, 2010. **25**(3): p. 155-1661.10.5001/omj.2010.49.
4. Ainyanbhor, I.E., et al., Pharmacological Research - Reports, 2025. **4**: p. 100066.https://doi.org/10.1016/j.prerep.2025.100066.
5. Madikizela, L.M. and L. Chimuka, Journal of Pharmaceutical and Biomedical Analysis, 2016. **128**: p. 210-215.https://doi.org/10.1016/j.jpba.2016.05.037.
6. Márta, Z., et al., Journal of Pharmaceutical and Biomedical Analysis, 2018. **160**: p. 99-108.https://doi.org/10.1016/j.jpba.2018.07.016.
7. Al-Khateeb, L.A., W. Hakami, and M.A. Salam, Journal of Molecular Liquids, 2017. **241**: p. 733-741.https://doi.org/10.1016/j.molliq.2017.06.068
8. Amin, S., et al., Environmental Nanotechnology, Monitoring & Management, 2014. **1-2**: p. 8-13.https://doi.org/10.1016/j.enmm.2014.07.001.
9. Ndreka, X., et al., Electrochimica Acta, 2025. **539**: p. 147049.https://doi.org/10.1016/j.electacta.2025.147049.
10. Yu, J., et al., Sensors and Actuators B: Chemical, 2023. **385**: p. 133650.https://doi.org/10.1016/j.snb.2023.133650.
11. Puangpetch, A., et al., Clinical Mass Spectrometry, 2020. **15**: p. 6-12.https://doi.org/10.1016/j.clinms.2019.10.002.
12. Yuvali, D., et al., Journal of Pharmaceutical and Biomedical Analysis, 2020. **179**: p. 113001.https://doi.org/10.1016/j.jpba.2019.113001.
13. Hergert, L.A. and G.M. Escandar, Talanta, 2003. **60**(2): p. 235-246.https://doi.org/10.1016/S0039-9140(03)00095-X.
14. Palabiyik, İ.M., E. Dinç, and F. Onur, Journal of Pharmaceutical and Biomedical Analysis, 2004. **34**(3): p. 473-483.https://doi.org/10.1016/S0731-7085(03)00578-8.
15. Ouafy, H.E., et al., ChemistrySelect, 2019. **4**(38): p. 11282-11287.https://doi.org/10.1002/slct.201902508.
16. Vashistha, V.K., et al., Chirality, 2024. **36**(2): p. e23647.https://doi.org/10.1002/chir.23647.
17. Kumar, M., et al., Journal of the Indian Chemical Society, 2025. **102**(8): p. 101887.https://doi.org/10.1016/j.jics.2025.101887.
18. Meskher, H., et al., Critical Reviews in Analytical Chemistry, 2024. **54**(7): p. 2398-2421.10.1080/10408347.2023.2171277.
19. Cetinkaya, A., et al., Critical Reviews in Analytical Chemistry, 2024. **54**(5): p. 1227-1242.10.1080/10408347.2022.2109125.
20. Lima, A.B., et al., Electroanalysis, 2013. **25**(7): p. 1585-1588.https://doi.org/10.1002/elan.201300014.
21. Matijašević, I., et al., ChemistrySelect, 2023. **8**(24): p. e202300827.https://doi.org/10.1002/slct.202300827.
22. Lizzy Mokaba, P., et al., ChemistrySelect, 2024. **9**(38): p. e202400385.https://doi.org/10.1002/slct.202400385.
23. Moscoso, R., et al., Electrochimica Acta, 2023. **443**: p. 141984.https://doi.org/10.1016/j.electacta.2023.141984.
24. Lema, C., et al., Talanta, 2024. **269**.10.1016/j.talanta.2023.125494.
25. Cheng, Y., et al., Nano Letters, 2012. **12**(8): p. 4206-4211.10.1021/nl301804c.
26. Stoytcheva, M., et al., ChemistrySelect, 2022. **7**(48): p. e202203950.https://doi.org/10.1002/slct.202203950.
27. Vicenteno-Vera, A.G., et al., ECS Transactions, 2010. **29**(1): p. 443.10.1149/1.3532340.
28. Meloun, M., S. Bordovská, and L. Galla, Journal of Pharmaceutical and Biomedical Analysis, 2007. **45**(4): p. 552-564.https://doi.org/10.1016/j.jpba.2007.07.029.
29. Barrientos, C., et al., Journal of Solid State Electrochemistry, 2018. **22**(5): p. 1423-1429.10.1007/s10008-017-3750-9.
30. Lenik, J. and J. Nieszporek, Sensors and Actuators B: Chemical, 2018. **255**: p. 2282-2289.https://doi.org/10.1016/j.snb.2017.09.034.
31. Cho, H.-H., H. Huang, and K. Schwab, Langmuir, 2011. **27**(21): p. 12960-12967.10.1021/la202459g.
32. Currie, L.A., Pure and Applied Chemistry, 1995. **67**(10): p. 1699-1723.doi:10.1351/pac199567101699.
33. Švorc, Ľ., et al., Journal of Electroanalytical Chemistry, 2018. **822**: p. 144-152.https://doi.org/10.1016/j.jelechem.2018.05.026.