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ORIGINAL ARTICLE / ÖZGÜN MAKALE

DETERMINATION OF ANTI-CANCER DRUG PALBOCICLIB FROM HUMAN BIOLOGICAL FLUIDS BY USING DIFFERENTIAL PULSE VOLTAMMETRIC METHOD AT BORON DOPED DIAMOND ELECTRODE

ANTİ-KANSER İLACI PALBOCICLIB'İN BOR KATKILI ELMAS ELEKTROTTA DİFERANSİYEL PULS VOLTAMETRİ YÖNTEMİ KULLANILARAK İNSAN BİYOLOJİK SIVILARINDAN TAYİNİ

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ABSTRACT

Objective: *A very efficient and sensitive electrochemical technique utilizing differential pulse voltammetry (DPV) at a boron-doped diamond electrode (BDDE) was devised to measure Palbociclib in this study.*
Material and Method: *All experiments employed typical three-electrode cell of 10 ml capacity in conjunction with boron-doped diamond electrode, a platinum wire counter electrode, and an Ag/AgCl reference electrode. During electrochemical measurements, DPV and cyclic voltammetry (CV) methods was utilized at BDDE.*
Result and Discussion: *Based on experimental findings from electrochemical characterization investigations, it was determined that oxidation behavior of Palbociclib in BDDE is irreversible and regulated by diffusion. Anodic peak current exhibited a linear relationship within concentration range of 0.01–1 µM, 0.02–0.8 µM, and 0.02–0.8 µM in pH 2.0 phosphate buffer solution (PBS) for reference substance solution, human serum, and urine samples, respectively. Limits of detection were found as 2.28 nM, 2.93 nM, and 1.31 nM for standard drug solution, human serum and urine samples, respectively. In order to validate the developed method, its repeatability, reproducibility, selectivity, precision and accuracy in all environments were investigated and calculated. This method was successfully applied for the analysis of Palbociclib in human serum and urine samples.*
Keywords: *Boron-doped diamond electrode, differential pulse voltammetry, human serum sample, palbociclib, urine sample*

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ÖZ

Amaç: *Bu çalışmada Palbociclib'i doğru bir şekilde ölçmek için bor katkılı elmas elektrotta (BDDE) diferansiyel puls voltametrisi (DPV) kullanan çok verimli ve hassas bir elektrokimyasal teknik geliştirilmiştir.*

Gereç ve Yöntem: *Tüm deneylerde bor katkılı elmas elektrot, platin tel karşı elektrot ve Ag/AgCl referans elektrot ile birlikte 10 ml kapasiteli tipik üç elektrotlu hücre kullanılmıştır. Elektrokimyasal ölçümler sırasında BDDE'de DPV ve döngüsel voltametri (CV) yöntemleri kullanılmıştır.*

Sonuç ve Tartışma: *Elektrokimyasal karakterizasyon incelemelerinden elde edilen deneysel bulgulara dayanarak, Palbociclib'in BDDE'deki oksidasyon davranışının geri dönüşümsüz olduğu ve difüzyonla düzenlendiği belirlenmiştir. Anodik pik akımı, referans madde çözeltisi, insan serumu ve idrar numuneleri için DPV yöntemiyle pH 2.0 fosfat tampon çözeltisinde (PBS) sırasıyla 0.01-1 µM, 0.02-0.8µM ve 0.02-0.8 µM konsantrasyon aralığında doğrusal bir ilişki görülmüştür Tespit limitleri standart ilaç çözeltisi, insan serumu ve idrar numuneleri için sırasıyla 2.28 nM, 2.93 nM ve 1.31 nM olarak bulunmuştur. Geliştirilen yöntemin validasyonu için tekrarlanabilirliği, tekrar üretilebilirliği, seçiciliği, kesinliği ve doğruluğu araştırılmış ve hesaplanmıştır. Bu yöntem insan serum ve idrar örneklerinde Palbociclib analizi için başarıyla uygulanmıştır.*

Anahtar Kelimeler: *Bor katkılı elmas elektrot, diferansiyel puls voltammetri, idrar örneği, insan serum örneği, palbociclib*

INTRODUCTION

Breast cancer (BC) is a major global health problem for women, with more than 2.1 million new cases diagnosed each year [1]. It affects individuals of all age groups, races and cultural backgrounds [1]. Unfortunately, there is currently no commercially available drug or treatment that can completely eradicate BC [2]. Rapid and accurate diagnosis of BC can significantly improve patients' chances of survival. Precise identification of the disease and subsequent adjustment of the drug dosage is crucial in this context [3].

Palbociclib is a pharmaceutical compound designed by Pfizer specifically to treat breast cancer that is positive for hormone receptors (HR-positive) and negative for human epidermal growth factor receptor 2 (HER2-negative) [4]. Structure of palbociclib contains cyclin-dependent kinases, enabling it to selectively inhibit CDK4 and CDK6 (Figure 1) [5]. Furthermore, palbociclib was the initial cyclin-dependent kinase 4/6 (CDK4/6) inhibitor to get approval for its application in cancer therapy [6]. Administering palbociclib to postmenopausal women alongside letrozole as their first endocrine therapy led to a notable rise in the rates of progression-free survival and clinical benefit [6,7]. Moreover, the administration of palbociclib to women alongside fulvestrant led to a significant increase in the duration of progression-free survival and overall survival rates. These data have been gathered from randomized clinical research [7].

There are only a few analytical methods used for determining pablociclib such as LC-MS/MS [8,9], SPE-LC-MS[10], UV-VIS spectroscopy [11], electropheroses [12], MIP-electrochemical [13], and spectrofluorimetry [14], from pharmaceutical preparations. The sample and electrode preparation procedure of the proposed new method is simpler, practical and inexpensive. Although the previously described method has been used for the analysis of pharmacological forms, this study demonstrated that it can also be realized with human serum samples [15]. Compared to conventional carbon electrodes and other metallic electrodes, BDDE differs in its chemical stability and its ability to be used in extreme chemical environments such as strongly acidic environments [16,17]. Therefore, this study aims to propose the development of electrochemical method for the quantification of pablociclib in human serum samples using differential pulse voltammetric method on BDDE. The electrochemical behavior of the drug was also studied in terms of buffer solution and pH in BBDE using DPV and CV techniques. Also, the variation of electrochemical behavior depending on the scan rate was studied. The proposed method can be an environmentally friendly alternative to chromatographic techniques in therapeutic drug monitoring by eliminating time-consuming steps such as evaporation, adsorption, extraction and separation prior to drug analysis.

MATERIAL AND METHOD

Instruments

The parameters of step potential: 10 mV; modulation amplitude: 50 mV; modulation time: 50 ms; interval time: 500 ms were chosen for the measurement of Palbociclib with DPV. A three-electrode system was employed for all electrochemical measurements. This system consisted of an Ag/AgCl (BAS, 3 M NaCl) reference electrode, a BDDE (Windsor Scientific Ltd., 3 mm diameter) working electrode, and an auxiliary electrode made of platinum wire. The measurements were conducted using an AUTOLAB 204 PGSTAT electrochemical analyzer (Eco Chemie, Utrecht, The Netherlands). Prior to every measurement, the electrode surface was prepared using alumina powder and a polishing cloth.

Reagents

Phosphate buffer solutions were prepared using K_2HPO_4 and KH_2PO_4 (PBS, 0.1 M, pH 2.0, 3.0, 5.0, 6.0, 7.0, 8.0). Sigma-Aldrich supplied synthetic human serum and sigmatrix urine diluent. Palbociclib was generously provided by Neutec Drug A.S., Istanbul. A stock solution of $1x10^{-3}$ M was prepared in double-distilled water. H_2SO_4 (0.1 M and 0.5 M), Britton-Robinson (BR) buffer solutions, phosphate buffer solutions, and acetate buffer solutions were prepared in distilled water.

Analysis of Human Serum Samples

The samples were stored frozen at -20°C until analysis [18]. A standard serum solution was prepared by adding 1.0 ml of a 1.0×10^{-3} M Palbociclib stock solution and 3.6 ml of the serum sample to 5.4 ml of acetonitrile to precipitate the proteins [19]. In order to eliminate any residual protein, the tubes were subjected to sonication for 15 minutes, followed by centrifugation at 5000 rpm for 20 minutes [20].The supernatant obtained was then used to perform the electrochemical experiments, where it was prepared in a selected buffer and added to the electrochemical cell.

Analysis of Spiked Urine Samples

An aliquot volume of urine sample was fortified with Palbociclib dissolved in bi-distilled water to achieve final concentration of 1×10^{-3} M and treated with 0.7 ml of acetonitrile as endogenous substance precipitating agent, and then the volume was completed to 2.0 ml with the same urine sample [21]. The tubes were vortexed for 10.0 min, and then centrifuged for 5 min at 5000 × g for getting rid of residues. The supernatant was taken carefully. These solutions were analyzed in the voltammetric cell containing PBS buffer at pH 2.0. The amount of Palbociclib in spiked human urine samples for the recovery studies was calculated from the related calibration equation [21].

RESULT AND DISCUSSION

Electrochemical Behavior of Palbociclib on the BDDE

To investigate the voltammetric behavior of Palbociclib using BDDE, repeated CV measurements were taken in different pH mediums. Figure 1 indicates repetitive cyclic voltammograms of 20 µM Palbociclib in 0.1 M H_2SO_4 solution (A), 0.5 M H_2SO_4 solution (B), pH 2.0 PBS (C), and pH 7.0 BRT (D) at a scan rate of 100 mV/s. Palbociclib showed one well-defined oxidation peak and a weak wave in pH 7.0 BRT solution while a well-defined oxidation peak and a wave in pH 2.0 PBS buffer (optimum pH value) and one well-defined oxidation peak in 0.5 M H_2SO_4 and 0.1 M H_2SO_4 buffer solutions. As can be seen from Figure 1, the intensity of the peaks was higher in the first scan compared to the second, third, fourth, and fifth scans for all different pH environments. The decrease in peak intensity can be explained by contamination on the electrode surface [22,23]. Also, for pH 7.0 BRT medium, in the cathodic direction, no peak was observed, which showed the irreversible electrode reaction (Figure 1D). Moreover, for acidic medium (0.1 M H_2SO_4, 0.5 M H_2SO_4, and pH 2.0 PBS), after the first CV scan, the oxidation product was formed, and the anodic peak of this product was obtained at 0.1 M H_2SO_4, 0.5 M H_2SO_4, and pH 2.0 PBS (Figure 1 A, B, and C).

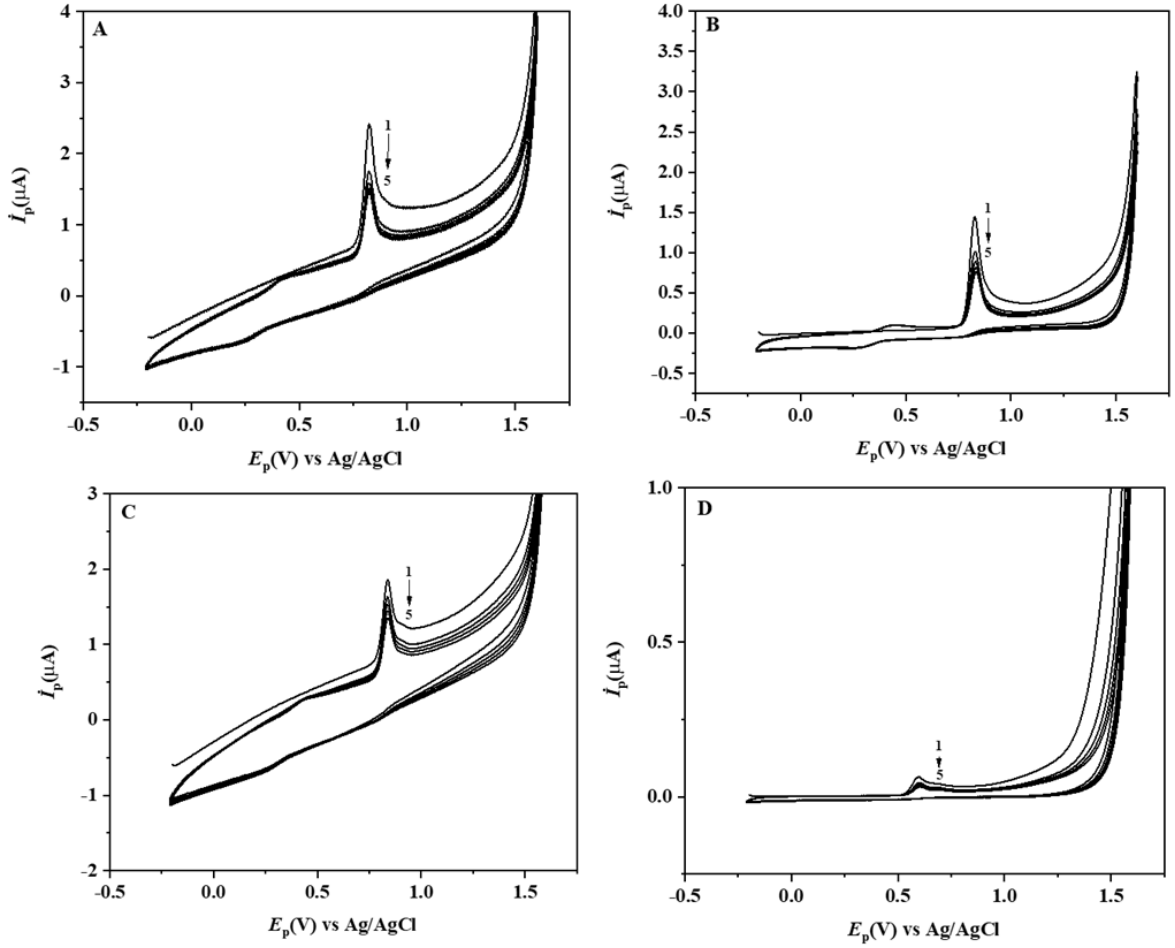

Figure 1. Repetitive cyclic voltammograms of 20 μM Palbociclib solutions in (a) 0.1 M H_2SO_4; (b) 0.5 M H_2SO_4 (c) pH 2.0 PBS (d) pH 7.0 BRT, as obtained at a scan rate of 100 mVs^{-1}

Due to the superior peak shape, maximum current, and most consistent measurement findings, the experiments including scan rate investigations and drug analysis quantification, were conducted using a pH 2.0 PBS solution. In order to determine whether the surface contact mechanism is influenced by diffusion, adsorption, or both, scan rate tests were conducted using CV. A solution of 20 μM palbociclib in pH 2.0 PBS was used, and the scan rate range was set between 0.005 and 1 Vs^{-1} (Figure 2).

When considering the change in scan rate values from 0.005 mV/s to 1 V/s, there is a shift of 63 mV towards positive potential values in relation to the irreversibility of the electrode reaction. For the proposed method, a linear response was found with the square root of the scan rate as follows:

$$I_p\,(\mu A) = 0.17\ v^{1/2}\,(mVs^{-1}) + 0.3009\ (r = 0.996) \quad (1)$$

The data analysis showed that when plotting the logarithm of the peak current against the logarithm of the scan rate, a straight line with a slope of 0.59 was obtained. The calculated slope closely approximates the theoretical value of 0.5, which is expected for a perfect reaction of solution species occurring as a diffusion-controlled process. The equation derived from the experimental data is as follows:

$$\log I_p\,(\mu A) = 0.59\ \log v\ (mV\ s^{-1}) - 1.05\ (r = 0.995) \quad (2)$$

Figures 3A and 3B show the potential values of the anodic oxidation peak and the graph of pH values versus observed current values, respectively, across the pH range of 2.0-9.0. The values obtained in pH 2.0 PBS, pH 2.0 BRT solutions were very close to each other. The peak obtained in pH 2.0 PBS was slightly higher but had more reproducible values. Thus, pH 2.0 PBS was utilized as working pH in further studies. Furthermore, the plot of the peak potential (E_p) vs. pH has one linear line (Figure 3B). The observed linear relationship between the values of Ep and pH ranging from 2.0 to 9.0 indicates that the electrochemical process involved an equal amount of protons and electrons, as indicated by the slope of the line.

$$E_p \text{ (mV)} = -47.2 \text{ pH} + 893;\ r = 0.9965 \text{ (pH 2.00 – 9.00 with DPV)} \qquad (3)$$

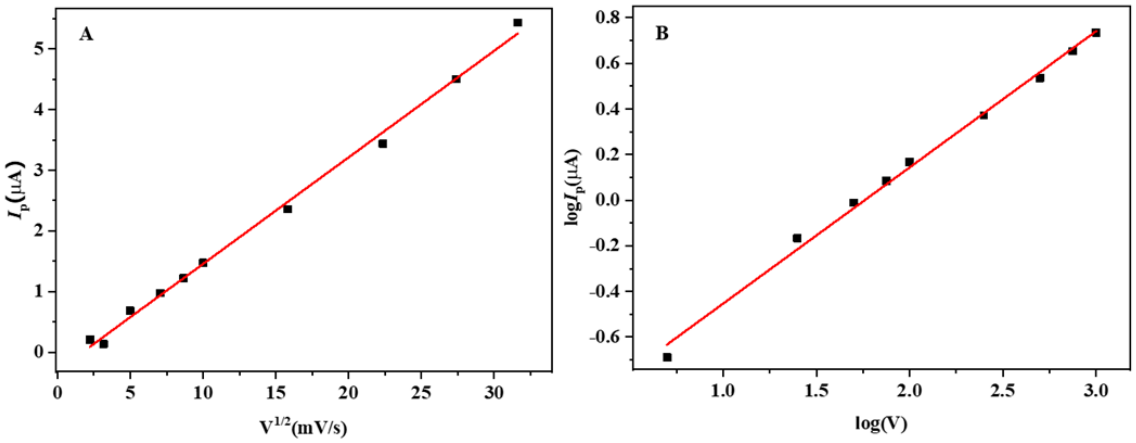

Figure 2. I_p vs $V^{1/2}$ (A) and log I_p vs log V (B) graphs of 1.0×10^{-5}M pablociclib in pH 2.0 PBS obtained in the range of 5-1000 mV/s

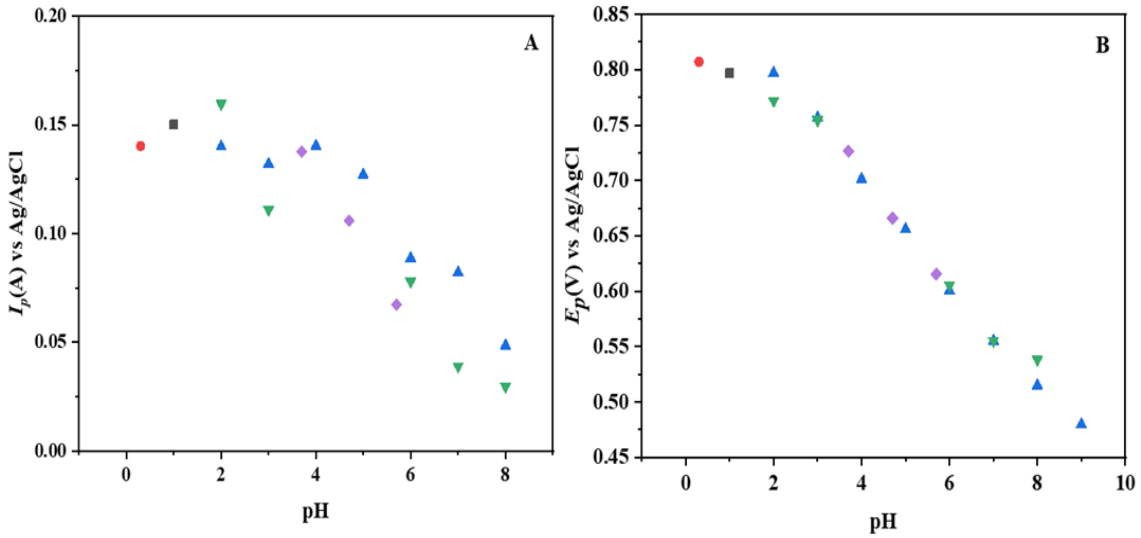

Figure 3. Effects of the pH on the pablocicilib peak potential (B) and peak current (A) in different supporting electrolytes, H_2SO_4 solutions (0.5M); (●)H_2SO_4 solutions (0.1 M); (■) Britton-Robinson buffer ; (▲) phospahate buffer; (▼) acetate buffer (♦) . These experiments were performed using DPV with the pablociclib concentration of 1×10^{-5}M

Electroanalytical Applications

An investigation was conducted to assess the analytical potential of pablociclib by examining the

correlation between pablociclib peak current and concentration. The experiments were carried out in pH 2.0 PBS, where the best peak symmetry and the highest peak current were obtained. The linearity was achieved in the concentration range of 10–1000 nM (Figure 4). The following was the related equation between peak current and concentration:

$$i_p\,(\mu A) = 0.311\ C\ (\mu M) - 0.0193 \text{ (n: 11, } r = 0.9907) \qquad (4)$$

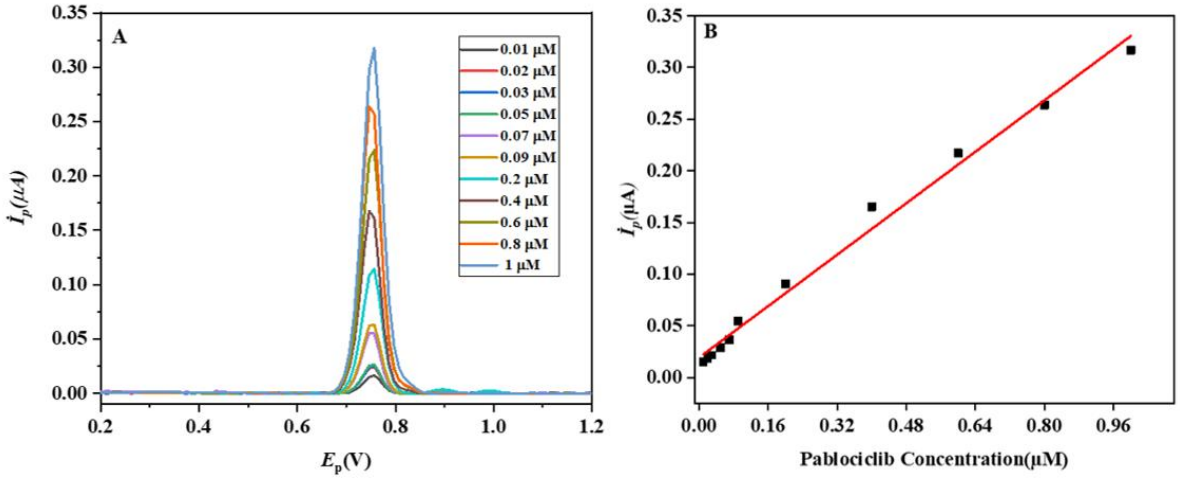

Figure 4. Calibration curve of DP voltammograms for standard solution of pablociclib in different concentration ranges from 0.01 µM to1 µM (A) and the calibration curve of standard pablocicilib (B) in pH 2 PBS

Determination of Pablocicilib in Spiked Biological Samples

The calibration equation was found for spiked biological samples to show that the proposed methods could be used on human serum samples (Figure 5) and urine (Figure 6).

$$I_p\,(\mu A) = 0.2408C\ (\mu M) - 0.0011 \text{ (n:9, } r = 0.9931) \qquad (5)$$

$$I_p\,(\mu A) = 0.3046C\ (\mu M) - 0.001 \text{ (n:9, } r = 0.9922) \qquad (6)$$

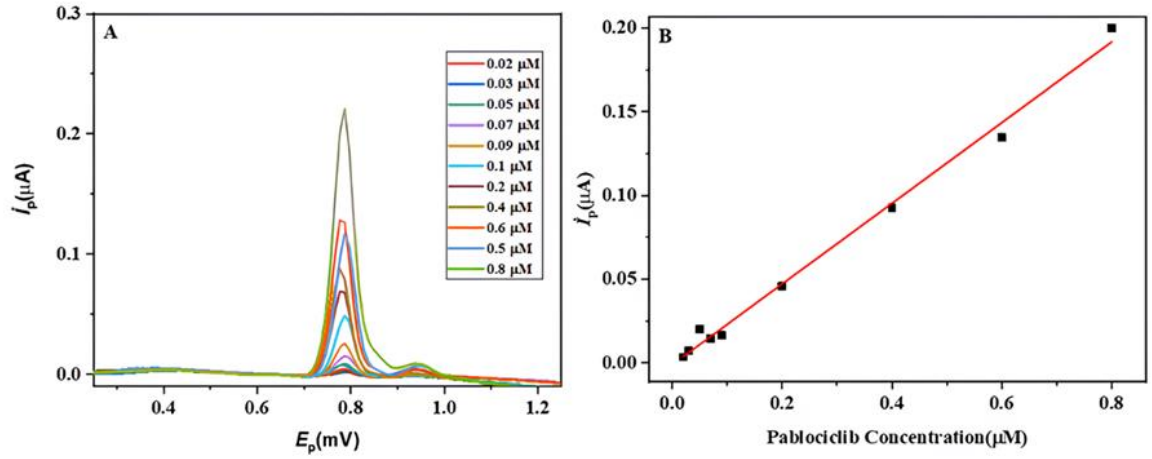

Figure 5. DP voltammograms of serum samples in the concentration range from 0.02 µM to 0.8 µM (A) and the calibration curve of serum samples (B) in pH 2 PBS

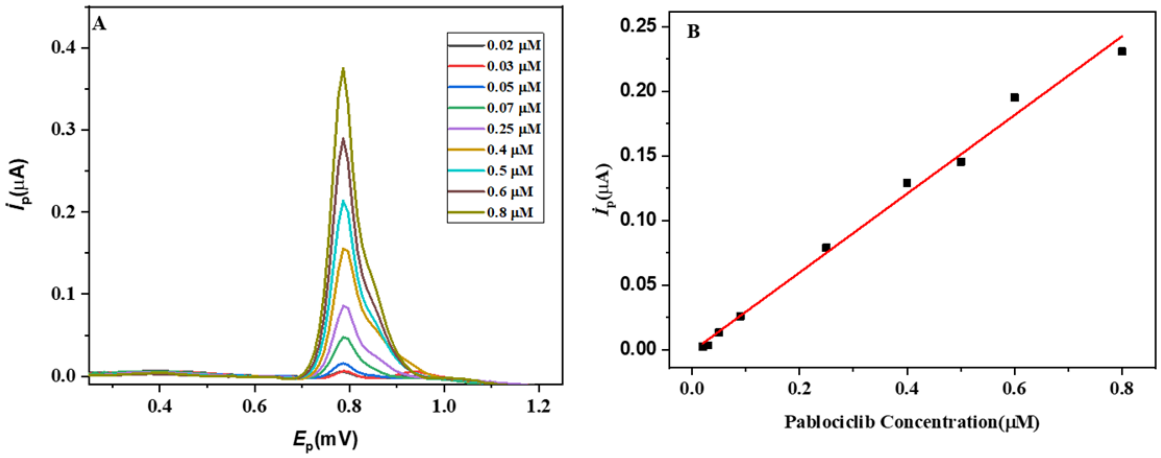

Figure 6. DP voltammograms of urine samples in different concentration ranges from 0.02 µM to 0.8 µM (A) and calibration curve of urine samples (B) in pH 2.0 PBS

Statistical data of the calibration are given in Table 1. Repeated measurements of pablocicilib peak potential and peak current within and between days demonstrate the precision of the developed method. The formulas 3 s/m and 10 s/m were used to determine the LOD and LOQ values, where "s" is the standard deviation of the response and "m" is the slope of the calibration curve. The LOD and LOQ values showed the sensitivity of the method (Table 1).

Table 1. Correlation data for pablociclib calibration generated using DPV in BDDE from standard solution, serum and urine samples

Parameters	**Standard**	**Serum**	**Urine**
Anodic potential (mV)	756	786	786
Linearity dynamic range (µM)	0.01-1	0.02-0.8	0.02-0.8
Slope (µA μM^{-1})	0.311	0.2408	0.3046
Intercept (µA)	0.02	-0.001	-0.001
Correlation coefficient (*r*)	0.9907	0.9931	0.9922
LOD (nM)	2.28	2.93	1.31
LOQ (nM)	7.60	9.77	4.89
Intra-day precision of peak current (RSD%)*	1.54	2.01	4.32
Inter-day precision of peak current (RSD%)*	1.87	1.48	1.14

*LOD and LOQ values were calculated based on the lowest value of the calibration range. For Serum and Urine, the intra-day precision of the peak current and the inter-day precision of the peak current values were calculated based on the midpoint of the calibration. Each value is the average of five experiments

The performance of the developed method was also compared with previous analytical methods (Table 2) and it was found that the developed method was the superior method in terms of sensitivity, while most of the other methods involved time-consuming preconcentration, high consumption of harmful and organic solvents and expensive equipment.

The proposed methods are simple to use and are based on human serum and urine obtained reproducible results that were sensitive enough to detect pablociclib in samples (Table 3).

Table 2. Comparison with other previously reported analytical methods to study the analytical performance of pablociclib determination

Analytical Method	Linearity range	LOD	Sample	Ref.
SPE-LC-MS	2-400 ng/ml	-	drug	[10]
Spectroflourimetry	1.0-20.0 µg/ml	0.021µg/ml	tablets	[14]
UV-Vis	2-10 mg/ml	0.0782	drug	[11]
LC-MS/MS	72.8-185.5 ng/ml	120 ng/ml	drug	[20]
LC-MS/MS	1-250 ng/ml	-	drug	[9]
LC-MS/MS	3.1-500 ng/ml	-	drug	[8]
Electrophoresis	10.0-100 µg/ml	0.11 µg/ml	tablet	[12]
MIP-voltammetry	2.5×10^{-11}-2.5×10^{-10}M	3.33×10-12M	Human serum	[13]
DPV	0.01–1 µM, 0.02–0.8 µM, 0.02–0.8 µM	2.28 nM 2.93 nM 1.31 nM	Standard serum urine	This Study

Table 3. Results of DPV recovery studies for BDDE from serum and urine samples

Parameters	Serum	Urine
Added concentration (µM)	0.2	0.2
Found concentration (µM)	0.195	0.1963
Average recorved %	98.75	99.75
Number of experiments	5	5
RSD % of recovery	2.012	4.32
Bias %	2.5	1.85

Conclusion

The voltammetric behavior of Palbociclib was examined by using a DPV approach to determine it from serum with a BDDE. The work stands out from the rest since no previous research has used voltammetry to measure Palbociclib with BDDE. Moreover, proposed electrochemical method was applied to human serum and urine samples.

AUTHOR CONTRIBUTIONS

Concept: C.K.D.; Design: C.K.D.; Control: N.A., B.U.; Sources: B.U.; Materials: C.K.D., B.U.; Data Collection and/or Processing: M.A., C.K.D.; Analysis and/or Interpretation: M.A., C.K.D.; Literature Review: M.A., C.K.D., N.A., B.U.; Manuscript Writing: M.A., C.K.D., N.A., B.U.; Critical Review: M.A., C.K.D., N.A., B.U.; Other: -

CONFLICT OF INTEREST

The authors declare that this article has no real, potential, or perceived conflict of interest.

ETHICS COMMITTEE APPROVAL

The authors declare that the ethics committee approval is not required for this study.

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