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Determination of Ibuprofen in Pharmaceutical Formulations Using Differential Pulse Polarography

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Abstract

A reliable differential pulse polarographic (DPP) method has been developed and applied for the determination of ibuprofen IBU in dosage form with dropping mercury electrode (DME) versus Ag/AgCl. The best peak was found at cathodic peak of -1.18 V in phosphate buffer at pH=4 and 0.025M of KNO_3 as supporting electrolyte. In order to obtaine the highest sensitivity, instrumental and experimental parameters were examined including the type and concentration of supporting electrolyte, pH of buffer solution, pulse amplitude and voltage step time. Diffusion current showed a direct linear relationship to ibuprofen concentration in the range of (5 – 30) μg. mL^{-1} (2.43×10^{-5} – 1.45×10^{-4} mol·L^{-1}) with correlation coefficient r= 0.9999, detection limit (S/N = 3) =3.40 μg. mL^{-1} (1.65×10^{-5} mol·L^{-1}) and the value of precision in terms of relative standard deviation RSD%, ranged between 0.374-0.5176 %. The established DPP method offers an excellent analytical figure of merits as well as its successful applicability to examine two commercial drug forms (tablet and suspension) for the determination of ibuprofen.

Keywords: Differential Pulse Polarography (DPP); Ibuprofen.

1. Introduction

Ibuprofen, 2-(4-isobutylphenyl) propionic acid **Figure 1.** is one of the most common non-steroidal anti-inflammatory drugs (NSAIDs) which is widely used as an analgesic and antipyretic as well as it is used in the treatment of acute and chronic pain and many rheumatic and musculoskeletal disorders [1]. Ibuprofen was discovered in 1961[2]. and it belongs to the most commonly used over-the-counter drugs

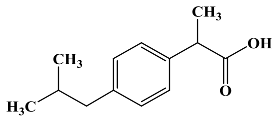

Figure 1: The structural formula of Ibuprofen.

Different techniques have been used for determination of IBU such as HPLC [3–5]. GC/MS [6,7]. spectrophotometric methods [8-11]. capillary electrophoresis [12]. as well as in recently years the determination of IBU by electroanalytical methods have more attention since of simplicity ,selectivity, economically and good precision of these methods. A survey of literature indicates some reports on the electrochemical determinations of ibuprofen including oxidation by cyclic voltammetry and differential pulse voltammetry using a screen-printed carbon electrode modified with carbon nanofibers [13]. square wave voltammetry on glassy carbon electrode [14]. and ion selective potentiometry [15]. and potentiometric indications are the official technique for the determination of ibuprofen [1]. The direct determination of IBP with differential pulse polarographic mode by using of DME had not been reported so far. So this work aims to introduce and development of a new simple, rapid,sensitive and direct polarographic method for the analysis of ibuprofen in pure forms and commercial pharmaceutical formulations.

2.Experimental

2.1 Apparatus

Electrochemical measurements were done using a 797VA Computrace Metrohm, Herisau, Switzerland polarographic analyzer. It was used with DME mode as an indicating electrode and Ag/AgCl as a reference electrode with Pt wire as an auxiliary electrode. All experiments were achieved at 25°C.Hanna model pH 211 pH-meter (Romania) was used for pH measurements.

2.2 Materials and Reagents

All experiments were achieved using analytical grade reagent, chemicals and solvents. Deionized water was used for preparing the standard and samples. Pure form ibuprofen standard material was obtained from the state company for drug industries and medical appliances Samara-Iraq (SDI). The APIFEN tablet was obtained from local pharmacies. 0.1g of the IBU was used to prepare a standard solution (1000 µg.mL^{-1}) by dissolving in 100mL volumetric flask with ethanol. Working solutions were prepared by serial dilution with distilled water. One liter (1M) solutions of potassium chloride, lithium chloride, and potassium nitrate were prepared by dissolving 7.450g, 4.239g and 10.100g of the salts respectively in 100 ml of deionized water. Phosphate buffer was prepared by dissolving 12 g of NaH_2PO_4 (0.1 mole) and 6.78 mL of H_3PO_4 (0.1 mole) in distilled water [10]. On the other hand, to obtain pH ≈ 2 of Britton-Robinson buffer, 2.47 g of H_3BO_3, 2.3 mL of glacial CH_3COOH and 2.7 ml of orthophosphoric acid were mixed and diluted to 1 liter with distilled water (0.04 M in each constituent).also the acetate buffer was prepared by mixing 1.68 g of $C_2H_3NaO_2$ with 1.12 ml of CH_3COOH in 500 mL of distilled water, the mixture was then diluted to one liter with same solvent [16].

2.3 General DPP Procedure

An aliquot volume of IBU samples was transferred to 20ml volumetric flasks, then 2 ml of 0.1M phosphate buffer at pH 4 was added with 0.5ml of KNO_3 (1M) as supporting electrolyte and diluted to the mark with deionized water. Each sample was transferred to a polarographic cell and de-aired with high purity nitrogen for 300sec to remove oxygen then the differential pulse mode was used and the cathodic scans were carried out at following optimum conditions , scan rate 3 mV. s^{-1},voltage step time 2sec, voltage step 6mV, pulse time 0.04sec, pulse amplitude 100mV and equilibrium time 10 sec.

2.4 Preparation of The Calibration Curve of Ibuprofen

A series of six standard solutions ranged between 5 -30 µg.mL^{-1} and were prepared by transfer volumes 1-6 ml of 100µg.mL^{-1} IBU the standard solution to 20 ml volumetric flask with 2 ml of 0.1M phosphate buffer at pH 4 and 2ml of 1M KNO_3 as supporting electrolyte, then diluted to the mark with deionized water. Each standard solution was analyzed using the general dpp procedure, under the optimal conditions. A standard calibration graph was prepared between the measured i_d against the IBU concentration.

2.5 Analysis of Pharmaceutical Preparations Samples

The content of 10 tablets was accurately weighed individually and ground into a fine powder then mixed well and the average weight was calculated. An amount of the powder equivalent 0.147 g, for IBU (APIFEN- 400mg) was accurately weighed and dissolved in a minimum volume of ethanol and stirred for 10 min to complete dissolution of the drug, then, solution transferred into 100 mL volumetric flask and diluted to the mark with distilled water to get 1000 µg. mL^{-1} for IBU. The solutions were filtered using filter paper Whatman No.41 to avoid any suspended or un-dissolved material before use. Working solutions were freshly prepared and analyzed by the previously mentioned procedure.

3.Results and Discussion

Preliminary Investigations

Typical differential pulse polarogram of 25µg.mL^{-1} IBU in phosphate buffer at pH = 4.0 is shown in **Figure 2**. The polarograms shows a well-defined peak appeared at -1.17 V versus Ag/AgCl/sat KCl electrode.

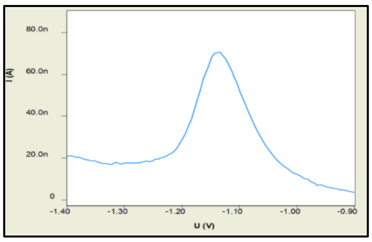

Figure 2: IBU polarogram in phosphate buffer at pH=4.

3.1 Optimization of the DPP method

In this work DPP technique was applied for the analysis of IBU. The effect of experimental paramenters (via; the type and pH of buffer, type and concentration of supporting electrolyte, the effect of the solvent system, in addition to, insetrumental parameters such as pulse amplitude and the voltage step time) were studied. This study was accomplished via one variable at a time optimization in which one parameter is changed keeping the others unchenged. The optimum conditions represent both the highest peak current and the best peak shape.

3.2 Effect of Buffers and pH

The differential-pulse polarogram of 25µg.mL^{-1} of IBU was investigated at different pH values ranged between 3 to 6. Three buffer solutions including Britton-Robinson, phosphate, and acetate buffer were used.

The polarographic response of IBU has been appeared as a one distinguished reduction peak at −1.17V applied potential versus Ag/AgCl in 0.025M phosphate buffer at pH=4 as a best buffer solution. This peak shifted to more positive potential with increasing the value of pH, **Figure 3.**

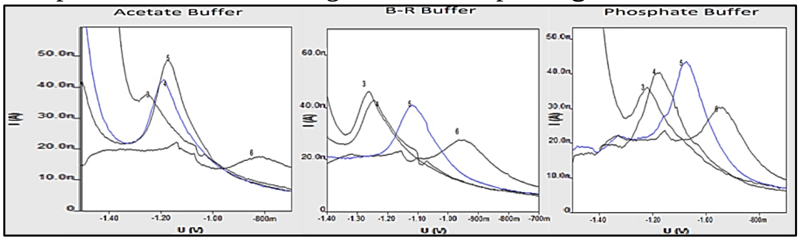

Figure 3: Polarograms of IBU at different pH and different buffer solutions.

3.3 Effect of Supporting Electrolytes

The differential pulse polarograms of 25µg.mL^{-1} IBU were measured in three different supporting electrolytes (KCl, KNO_3, LiCl) with four different concentration of each one (0.025,0.05,0.1,0.15M). The maximum peak current (Ip) was found in 0.025 M of KNO_3 as Figure 4 shows that.

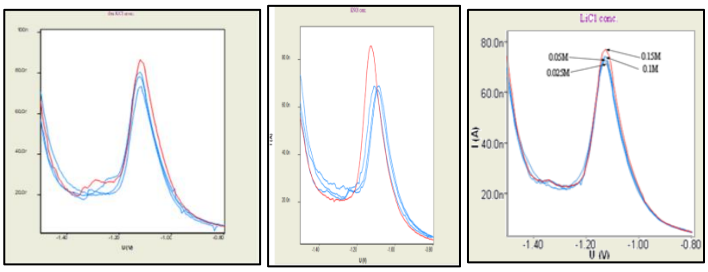

Figure 4: Polarograms of 25µg.mL^{-1} IBU at different supporting electrolytes solutions.

3.4 Effect of Solvent

The polarograms were recorded in three different solvents including water, ethanol, and methanol. It is clear that the behavior of polarograms was prominent in water medium.
Since it has a high current peak and best shape of peak compare with ethanol and methanol.

3.5Effect of Instrumental Parameters

3.5.1 Effect of Pulse Amplitude

The effect of different values of pulse amplitude (viz.; 50, 60,80,100, 120,140, 160,180, and 200 mV) on the peak current was investigated. The results showed that the value of peak current was in direct proportion to the applied amplitude up to 100mV, then after the peak starts to broaden. Therefore, an amplitude of 100mV was applied in the subsequent studies since it gave the best peak **Figure 5**.

3.5.2 Effect of Drop time (voltage step time)

Peak current increased by increasing voltage step time at values (0.6, 0.8, 1.0, 1.2, 1.4 and 2.0 s), while Ep remains quasi-static. The value of the preferred was 2 s, **Figure 6.**

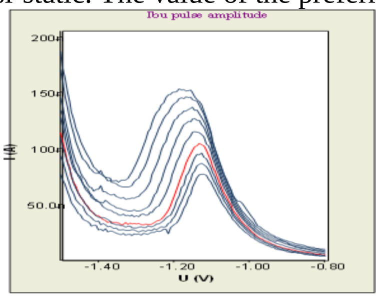

Figure 5: Effect of pulse amplitude on the on the peak current of 25µg.mL^{-1} IBU in pH 4 phosphate buffer.

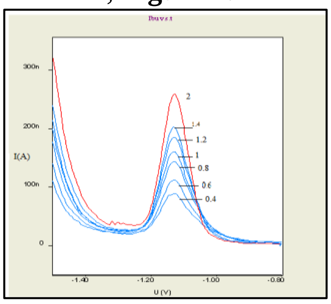

Figure 6: Effect of voltage step time on the peak current of 25µg.mL^{-1} IBU in pH 4 phosphate buffer, pulse amplitude (100) mV.

3.6 Number of Transferred Electrons and Actual $E_{½}$

The real electrons number involved in a reversible/irreversible electrode procedure and the value of half-wave potential ($E_{½}$) was calculated depending on the equation of Heyrovsky–Ilkovic, which shows that the produced wave due to the cathodic reduction of the drug is a reversible process at 25°C [17].

$$E_{applied} = E_{1/2} - \frac{0.0591}{n} \log\left(\frac{i}{i_d - 1}\right)$$

The given equation ascribes the obvious relation between the value of i_d and applied potential for a reversible/irrevrsible reaction. Therefore , the real number of electrons involved in the process could be obtained by plotting the values of $\log(\frac{i}{i_d-1})$ aganest the applied voltage (E) for a set group of drug concentrations. The processe assumed to be reversible when an exact number of electrons (n) is obtained, while incomplete number of n indicats irreversible process[18]. The actual peaks voltage Ep calculated were -1.17V and two electrons were required for the reduction, **Figure 7**.

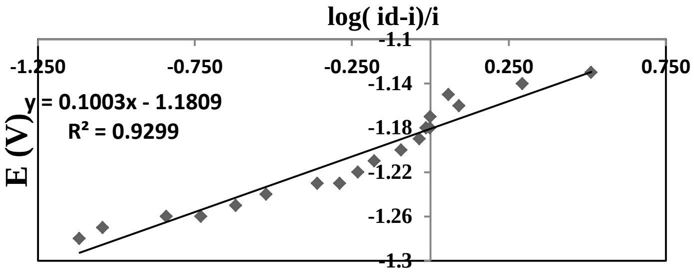

Figure 7: The plot of the applied potential versus $\log(i/(id-1))$ according to Heyrovsky-Ilkovic equation at 30µg.mL^{-1} of IBU.

3.7 Analytical Consideration and Calibration Graph

Under the optimum experimental conditions given in Table 1, the planograms of different concentrations of the studied drug were recorded using a serial of diluted standard solutions of IBU in an aqueous phosphate buffer at pH = 4.0, Figure 8. The constructed regression calibration curve for the relation of the measured polarographic peak current (nA) against IBU concentration in the range (5-30) µg.mL^{-1}shows an excellent linear relationship (R= 0.9999), **Figure 9**.

Table 1: The optimum parameters established for determination of IBU.

Condition	Value
Initial potential	-1.5V
Final potential	-0.8V
Pulse time	0.04sec
Buffer	Phosphate Buffer
pH	4
Supporting electrolytes	KNO_3 (0.025M)
Solvent	Water
Voltage step time	2sec
Pulse Amplitude	100 mV
Voltage step	0.006v
Scan rate	0.003 V/s
Equilibrium time	10 sec
Initial purge time	300sec

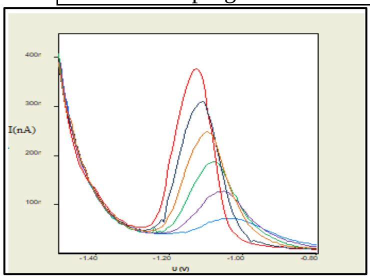

Figure 8: DPP polarograms of Ibuprofen at (5,10,15,20,25,30) µg.mL^{-1}.

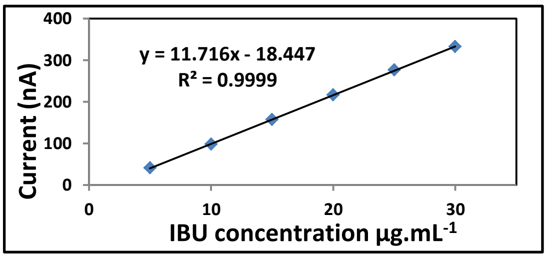

Figure 9: The relation between peak current and concentration.

Table 2: Analytical numbers of merit of the IBU estimation using DPP methods.

Parameter	Value
Peak potential, E_p (V)	-1.18
range of Concentrations (µg.mL^{-1})	5- 30
Regression equation (y = bx - a)	y=11.716x-18.447
Correlation coefficient (r)	0.9999
Linearity (R^2)	0.9999
Slope (b)	11.716

Intercept (a)	18.447
Standard deviation of regression line ($S_{y/x}$)	1.05
Standard deviation of intercept (S_a)	0.98
Standard deviation of slope (S_b)	0.05
C.L. for the intercept ($a \pm ts_a$) at 95%	18.447±0.98
C.L. for the slope ($b \pm ts_b$) at 95%	11.716±0.05
Limit of Detection- LOD, ($\mu g.mL^{-1}$)	3.40
Limit of Quantitation - LOQ, ($\mu g.mL^{-1}$)	10.25

The numerical estimate for the calibration graph exposed that the linear regression equations for the analyte are statistically suitable. The prediction based on the regression line is acceptable as listed in **Tables 2.** This regression line is used to estimate the IBU concentrations in the selected sample which appear justified on a statistical basis. The values of detection limit (LOD) and limit of quantification (LOQ) were determined by the standard deviation of the response, residual of standard deviation $S_{y/x}$ and the slope b of the calibration curve using the equations ($a + 3S_{y/x}$) and ($a + 10S_{y/x}$), respectively[19] . the results showed that the LOD and LOQ found was 3.4 and 10.25 $\mu g.mL^{-1}$ respectively.

The precision and accuracy of the proposed method were established. Triplicate measurements were carried out for each drug at two different concentrations within the linearity range for each drug. The obtained results indicated good and satisfied values of accuracy and precision of the recommended procedure at the studied concentration levels **Table 3.**

Table 3: The precision and accuracy of the proposed method.

Drug	Initial Conc. $\mu g.ml^{-1}$	Found Conc. $\mu g.ml^{-1}$*	Absolute Error	%RE	%RSD
IBU	10	9.9562	-0.0438	-0.4378	0.3740
	25	25.1889	0.1889	0.7557	0.5176

*Average of three measurements, n=3.

The proposed DPP procedure was applied for the determination of IBU in commercial APIFEN tablet 400 mg and Profinal oral suspension 100 mg/5mL. The pharmaceutical samples were treated and examined according to the recommended DPP procedure.
The results showed that the actual amounts of the cited drug in commercial 400 mg APIFEN tablet, ranged between 406 to 412 mg, while its mount in the 100mg/5mL Profinal oral suspension, ranged between 98.5 to 99 mg. These values are in good agreement with those values fixed on the original products. The results are presented in **Table 4.**

Table 4: Application of the suggested procedure for the determination of Ibuprofen in pharmaceutical formulations.

Sample	Conc. ($\mu g. mL^{-1}$)		Weight found (mg)	Recovery %	RSD%
	Taken	Found			
APIFEN-India Tablet 400mg	20	20.6	412	103	0.75
		20.3	406	101.5	
		20.4	408	102	
Profinal-Julphar - UAE oral suspension (100 mg /5 mL)	20	19.8	99	99	0.29
		19.8	99	99	
		19.7	98.5	98.5	

4.Conclusion

Base on the results, it is concluded that proposed method can be used successfully to determine the Ibuprofen concentration in pure forms and pharmaceuticals preparations.
The results show that the experimental and instrumental conditions have important role to obtain a well-defined polarographic wave of IBU inasmuch it affected by the pH of solution, nature of buffer, the type and concentration of supporting electrolyte, pulse amplitude and voltage step time .In addition to that, the relationship of peak potential and pH was roughly linear with peak potential shifting toward negative values with decreasing in pH. The proposed method with the optimized parameters demonstrated a good linear relationship between the peak current and the IBU concentration with a perfect value of correlation coefficient (R), this obeys Ilkovic equation that means the wave diffusion is controlled. The applicability of the proposed procedure was tested using a commercial pharmaceutical formulation of IBU and the results are in good agreement with the labeled values. Moreover, the advantages of the proposed

procedure are direct, simple, sensitive, and fast in comparison with other analytical methods used for the determination of drugs, needs no extra time-consuming steps or sample pretreatment prior to analysis.

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