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Differential Pulse Polarographic Determination of Clopidogrel Bisulphate in Pure and Pharmaceutical Dosage Forms Using Dropping Mercury Electrode

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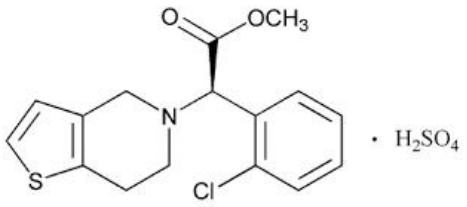
Abstract

Differential pulse polarographic analysis (DPPA) of Clopidogrel Bisulphate (CLPB) in pure and pharmaceutical dosage forms using drop mercury electrode (DME) has been studied. Various parameters (electrolyte, pH, pulse time, pulse amplitude, etc.) affecting on the CLPB determination were examined. The best definition of the analytical signals was found in sodium acetate 0.02 M buffer at pH 8.0. Under the optimum conditions, liner calibration graph, $I_p=f(C_{CLP})$, was obtained in the concentration ranges of $5x10^{-7}$ M to $3x10^{-5}$ M (0.1609 to 9.6546 µg.mL^{-1} of CLP), at -1275 to -1310 mV (versus Ag/AgCl) with percent relative standard deviations (RSD%) did not exceed 2.9% for the concentrations 0.1609 µg.mL^{-1} of CLP. Regression analysis showed a good correlation coefficient (R^2=0.9997) between I_p and concentration over the mentioned range. The limit of detection (LOD) and the limit of quantification (LOQ) were to be 0.0160 and 0.0485 µg.mL^{-1}, respectively. The proposed method was validated for linearity, precision and accuracy (LOD and LOQ), repeatability, sensitivity, robustness and specificity. The developed method is applicable for the determination of CLP in pure and different dosage forms in presence of aspirin with average recovery of 99.9 to 101.8% and the results are in good agreement with those obtained by the HPLC reference method.

Keywords: Differential pulse polarographic analysis; Clopidogrel.

Introduction

Clopidogrel bisulphate (CLPB), methyl(+)-(s)- α-(o-chlorophenyl)6,7-dihydrothieno (3, 2-c) pyridine-5(4H)-acetate bisulphate, is a new antiplatelet agent, and it is similar to ticlopidine in chemical structure (see scheme 1), its molecular weight of 419.8 g/mol of CLPB (draw CLP is 321.8 g/mol) [1,2].



Scheme 1 Chemical structure of clopidogrel bisulphate (CLPB)

Clopidogrel is as a potent anti-platelet aggregation agent, has become available in the market. The medical properties, pharmacodynamics, pharmacokinetics and various aspects of this compound have been published [3-5].

The literatures for the quantification of clopidogrel were including potentiometric method [6,7] and voltammetry [8-11], spectrophotometry [12,13], and high performance liquid chromatography [14,15].

The prepared electrode Bi_2O_3-poly *p*-aminophenol on glass carbon electrode (Bi_2O_3-P*p*-AP/GCE) was used for determination of clopidogrel in pharmaceutical productions by differential pulse voltammetry and there is a good linear relationship between concentrations of clopidogrel (CLP) in the range of 3×10^{-6} - 1×10^{-3} M and obtained areas of voltammograms [8].

The oxidation of CLP at multi-walled carbon nanotube/polyorthoaminophenol modified graphite electrode (MWCNT/POAP/GE) electrode has been performed in sulfuric acid (pH 3.7). Cyclic voltammetry (CV), chronoamperometry (CA) under different conditions of pH, scan rates and concentration of CLP were investigated for the determination of CLP using electrochemical techniques [9].

The determination of clopidogrel, an antiplatelet agent, was performed at a gold electrode in pH 3.7 acetate buffer using cyclic voltammetry (CV) and square wave voltammetry (SWV). Each voltammogram was characterized by the well defined peak at approximately 1.0 V. The current of anodic stripping peak exhibited a linear dependence on the clopidogrel concentration in the range from 317.89 to 935.16 $\mu g.mL^{-1}$ [10]. The voltammetric behavior of clopidogrel bisulfate (CLPB), an antiplatelet agent, was investigated for the first time in the literature on a cathodically pretreated boron-doped diamond electrode (CP-BDDE) using cyclic and square-wave voltammetry [11].

In the present work, electrochemical behavior and differential pulse polarographic analysis of clopidogrel in pure and pharmaceutical dosage forms using dropping mercury electrode was applied.

Experimental

Reagents

Working reference standard of clopidogrel bisulphate (98.5%) was supplied by D.K. Pharmachem Pvt. Ltd INDIA, (Mfg.11-2018, Exp. 11-2021). Lithium perchlorate trihydrate, di-sodium hydrogen phosphate dodecahydrate, sodium acetate trihydrate, sodium hydroxid, perchloric acid (70%), ortho-phosphoric acid (85%), acetic acid (100%), boric acid (100%) were of GR for analysis purchased from MERCK. Ultrapure mercury from Metrohm Company was used throughout the experiments.

Instruments and apparatus

A Metrohm 746 VA processor, a Metrohm 747 VA stand with a mercury drop electrode (DME) as a working electrode, an auxiliary platinum electrode and a reference electrode, double junction type, (Ag/AgCl) saturated with a 3.0 M KCl solution and the three-electrode cell were used. All measurements were done at room temperature 25 ± 5 ^{o}C. Highly pure nitrogen gas (99.999 %) was used for de-oxygenation. pH meter from Radiometer company model ion check was used. The diluter pipette model DIP-1 (Shimadzu), having 100 µL sample syringe and five continuously adjustable pipettes covering a volume range from 10 to 5000 µL (model PIPTMAN P, GILSON), were used for preparation of the experimental solutions. An ultrasonic processor model Powersonic 405 was used to sonicate the sample solutions. Electronic balance (Sartorius-2474; d=0.01 mg) was used.

Preparation of supporting electrolyte

Sodium acetate-acetic acid (HAc-NaAc), Britton Robinson, H_3PO_4-Na_2HPO_4, lithium perchlorate buffers at concentration 0.100 $mol.L^{-1}$ at pH (6.0 – 10.0) were used.

A stock standard solution of clopidogrel bisulphate

This solution was prepared by dissolving 42.63 mg from clopidogrel bisulphate (CLPB) in methanol 100 mL ($1x10^{-3}$ $mol.L^{-1}$), then dilute 10.000 mL from this solution to 100 mL ($1x10^{-4}$ $mol.L^{-1}$).

Working solutions

The stock solutions were further diluted to obtain working solutions daily just before use in the ranges of clopidogrel: 0.2100, 0.4200, 0.8400, 1.6796, 2.5194, 3.3592, 5.0388, 6.7184, 8.3980, 10.4975 and 12.5970 $\mu g.mL^{-1}$ of CLPB (equivalent 0.1609, 0.3218, 0.6436, 1.2873, 1.9309, 2.5746, 3.8618, 5.1491, 6.4360, 8.0460 and 9.6545 of CLP $\mu g.mL^{-1}$) or 0.500, 1.000, 2.000, 4.000, 6.000, 8.000, 12.00, 16.00, 20.00, 25.00 and 30.00 $\mu mol.L^{-1}$ by using of the volumes: 0.125, 0.250, 0.500, 1.000, 1.500, 2.000, 3.000, 4.000, 5.000, 6.250, and 7.500 mL from stock standard solutions ($1x10^{-4}$ $mol.L^{-1}$) were transferred into 25 mL volumetric flask. 5.0 mL of supporting electrolyte was added, and diluted with double distilled water to the mark.

Samples

A commercial formulations (as tablets) were used for the analysis of clopidogrel by using DPPA with DME electrode. The pharmaceutical formulations were subjected to the analytical procedures:

(1) **Pharma Grel,** F.C. Tablet, PHARMASYR, Damascus–SYRIA, each tablet contains: 75 mg of CLP (Exp. 08.2022).
(2) **Plaraz,** F.C. Tablet, AL–RAZI, Aleppo–SYRIA, each tablet contains: 75 mg of CLP and (Exp. 04.2022).
(3) **Norgrel Plus,** F.C. Tablet, UNIPHARMA, Damascus–SYRIA, each tablet contains: 75 mg of CLP and 75 mg ASPIRIN (Exp. 09.2020).
(4) **Glopid,** F.C. Tablet, EL–SAAD**,** Aleppo–SYRIA, each tablet contains: 75 mg of CLP (Exp. 09.2022).
(5) **Plofexine,** F.C. Tablet, ASIA**,** Aleppo–SYRIA, each tablet contains: 75 mg of CLP (Exp. 05.2020).
(6) **Clotless,** F.C. Tablet, APHAMEA**,** Hama–SYRIA, each tablet contains: 75 mg of CLP (Exp. 01.2021).

Stock solutions of pharmaceutical formulations

20 tablets of each studied pharmaceutical formulations were weighted accurately and mixed well. An amount of the powder equivalent to the weight of one tablet was solved in 25 mL methanol by using ultrasonic, filtered over a 100 mL flask and diluting to 100 mL with methanol; this solution contents 750 $\mu g.mL^{-1}$ of CLP for all studied pharmaceutical formulations.

Working solutions of pharmaceuticals

These solutions were prepared daily by diluting 100 µL (0.100 mL) from stock solutions of pharmaceutical formulations into 25 mL volumetric flask, diluted with sodium acetate buffer 0.02 M (pH 8) to the mark (each solution contents 3.000 $\mu g.mL^{-1}$ of CLP ($9.323x10^{-6}$ M).

Analytical procedure

25 mL of working standard of clopidogrel or working solutions of pharmaceuticals were transferred to the cell. The solution was deoxygenated with N_2 gas for 500 s. The potential range was from -1050 to -1500 mV (versus Ag/AgCl) with differential pulse polarographic analysis using drop mercury electrode in the optimum conditions were applied.

Results and Discussion

Differential pulse polarographic behavior

The polarograms for concentration 0.50 - 30.0 $\mu mol.L^{-1}$ (0.2100 - 12.5970 $\mu g.mL^{-1}$ of CLPB or 0.1609 – 9.6546 $\mu g.mL^{-1}$ of CLP) in the optimal conditions using DPPA at DME were studied. The best definition of the analytical signals was found in sodium acetate (0.02 M) buffer (pH 8.0) at -1050 to -1500 mV (versus Ag/AgCl).

The effect of supporting electrolytes (buffer)

The electrochemical behavior of clopidogrel was studied in various supporting electrolytes such as {Briton Robinson, di-sodium hydrogen phosphate dodecahydrate, sodium acetate-acetic acid (HAc-NaAc) and lithium perchlorate were studied} at pH (6.0 - 10.0). The best definition of the analytical signals was found in sodium acetate buffer (pH 8.0) at concentration 0.02 M. The effect of supporting electrolytes (buffer) on the I_p and E_p was studied. The values of E_p were -1242, -1267, -1285 and -1287 mV for the mentioned buffers, respectively, see Figure 1. The effect of the concentration of HAc-NaAc was tested over the 1, 2, 4, 8, 10, 20, 30, 40, 50, 60, 80, and 100 mM. The DPPA at DME of 12 µM of CLP with the varying concentrations of supporting electrolyte was studied. The values of I_p increase with increasing concentration of supporting electrolyte of 4 to 10 mM, then become semi-fixed until concentration of supporting electrolyte 100 mM, while E_p remains quasi-static.

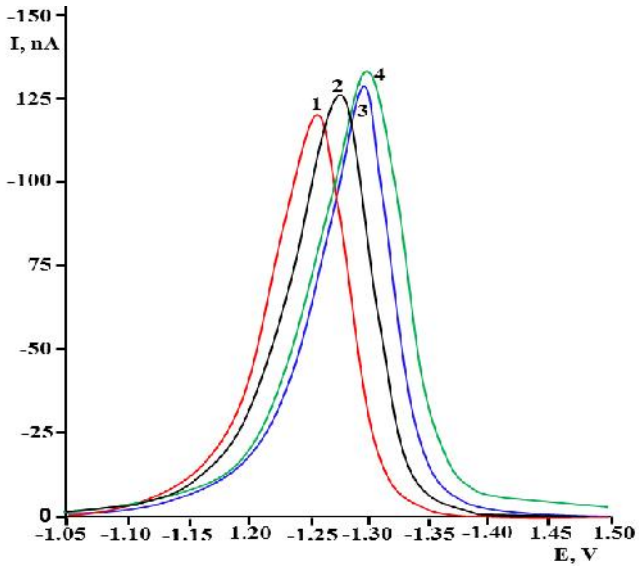


Fig.1:The effect of buffer solutions on polarograms 12 µM of CLP using DPPA at DME buffers (0.02 M) at pH 8.0: 1- Britton-Robinson, 2- $Na_2HPO_4.12H_2O$, 3- $CH_3COONa.3H_2O$, 4- $LiClO_4.3H_2O$ (Purge gas N_2, purge time 500 s, sweep rate 5 mV/s, U. amplitude -100 mV, t. meas 30 ms, t. pulse 35 ms, t. step 1.6 s, U. step 8 mV, temperature 25°± 5°C).

The effect of pH

The influence of pH from 6.0 to 10.0 using sodium acetate (0.02 M) buffer on I_p and E_p was studied. The values of I_p increase with increasing pH value of 6.0 to 8.0, then decrease until pH 9.0 and finally decreasing slowly until pH 10. While E_p values are growing a positive value from -1487 mV (when pH 6.0) to -1295 mV (when pH 7.0) then become semi-fixed until pH 10, see Figures 2,3.

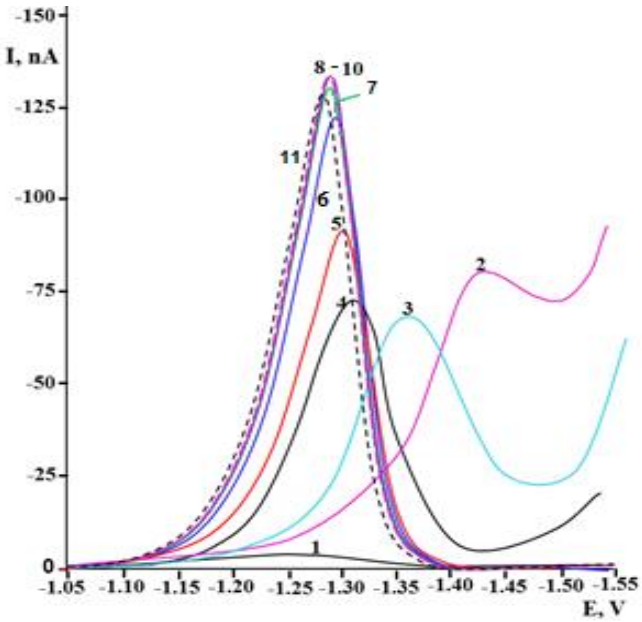


Fig.2: The effect of pH solution on polarograms of CLP (12 µM) using DPPA at DME buffers (0.02 M) HAc-NaAc at pH: 1- Electrolyte (pH 8.00) , 2- 6.00, 3- 6.50, 4- 6.75, 5- 7.00, 6 -7.50, 7 – 7.75, 8- 8.00, 9- 8.50, 10- 9.00 and 11- 10.0 (purge gas N_2, purge time 500 s, sweep rate 5 mV/s, U. amplitude -100 mV, t. meas 30 ms, t. pulse 35 ms, t. step 1.6 s, U. step 8 mV, temperature 25°± 5°C).

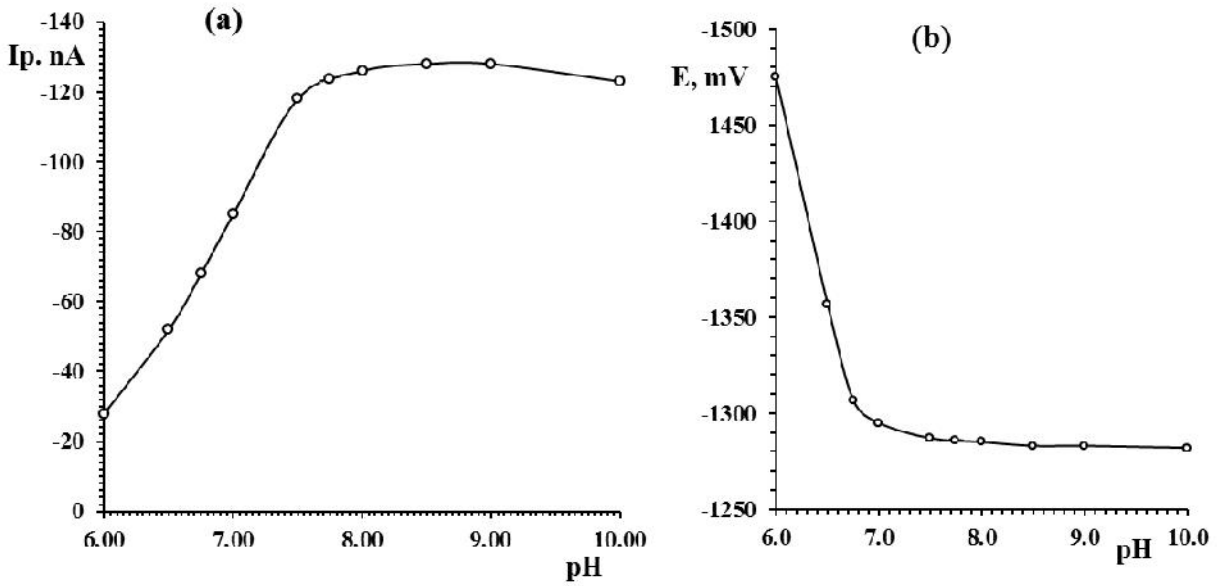


Fig.3: The effect of pH solution on I_p (a) & E_p (b) of CLP (12 µM) using DPPA at DME in buffer (0.02 M) HAc-NaAc (purge gas N_2, purge time 500 s, sweep rate 5 mV/s, U. amplitude -100 mV, t. meas 30 ms, t. pulse 35 ms, t. step 1.6 s, U. step 8 mV, temperature 25°± 5°C).

The effect of negative pulse amplitude (U.ampl)

The effect of negative pulse amplitude (U.ampl) between -10 to -100 mV on Ip and Ep was studied. Ip linearly increases with increasing amplitude value until -100 mV. While Ep stay semi-fixed. The value -100 mV was better than the others.

The effect of time pulse (t.pulse)

The effect of time pulse (35, 40, 50, 60, 70, 80, 90 and 100 ms) on polarograms was as the follows: Ip decreases with increasing time pulse and Ep has become increasingly negative value (-1275 to -1310 mV) with increasing t.pulse.

The peak was more symmetrical and Ip was the highest when the t.pulse value was 35 ms.

The effect of time interval for voltage step (t.step)

Ip linearly increases with increasing t.step (0.4, 0.8, 1.2, 1.6 and 1.8 s), while Ep has become increasingly positive value (-1310 to -1275 mV) with increasing t.step. The value of the preferred t.step was 1.6 s.

The effect of measurement time (t.meas)

Ip increases with increasing t.meas. (4, 8, 12, 16, 20, 24, 28, 30, and 32 ms), while Ep remains quasi-static. The value of the preferred t.meas. was 30 ms.

The effect of temperature and time

The effect of temperature and time on the electrochemical behavior of CLP was studied at different values (15-35^{o}C and 5-60 min) by continuous monitoring of the Ip. It was found that, the value of Ip was not affected by temperature between 20 to 30^{o}C (the temperature at 25±5°C was used). The effect of waiting time was determined at laboratory ambient temperature (25±5°C). It was found that, the value of Ip was not affected by time between 5 to 60 min.

The optimum parameters established for determination of CLP using DPPA on DME showed in Table 1.

Calibration curves

Calibration curves for the determination of clopidogrel using differential pulse polarographic analysis on drop mercury electrode with negative amplitude in sodium acetate (0.02 M) buffer at pH 8.0 were applied. One peak was observed in the range -1270 to -1310 mV (Ep). The peak current (Ip) was proportional to the concentration of CLP over the ranges 0.1609-9.6546 µg.mL^{-1} (0.500 - 30.00 µmol.L^{-1}). The polarograms in the optimum conditions using DPPA at DME of CLP at different concentrations are showed in figure 4. The regression equation and correlation coefficient (R^2) were as the follows: y=-31.9895x-1.5536, R^2=0.9997; while y: Ip, nA and x: C of CLP, µg.mL^{-1} .

Table 1: The optimum parameters established for determination of CLP using DPPA

Parameters	Operating modes
Working electrode	Dropping mercury electrode (DME)
Supporting electrolyte (buffer)	sodium acetate 0.02 M
pH	8.0
Solvent clopidogrel	double distilled water
Purge gas	Pure N_2
Purge time	500 s
Initial potential	-1050 mV
Final potential	-1500 mV
Scan rate	5 mV/s
U.step	8 mV
t. meas	30 ms
Value of pulse amplitude	-100 mV
t. pulse	35 ms
t. step	1.6 s
Temperature of solution	25°± 5°C

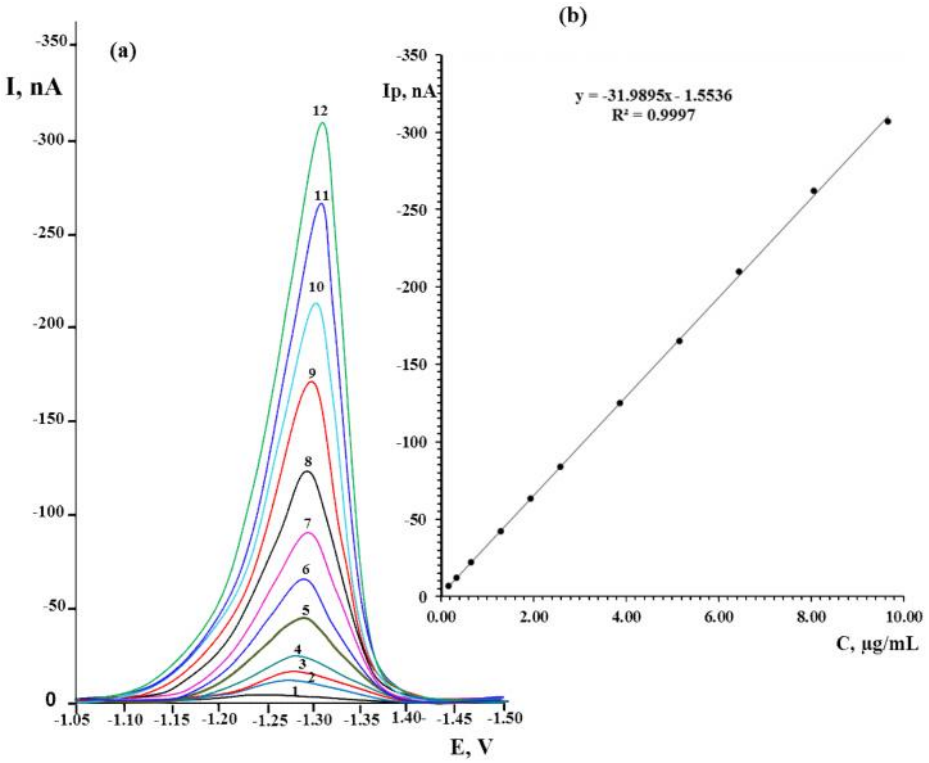


Fig.4: (a) The polarograms in the optimum conditions using DPPA on DME of CLP using DPPA at DME sodium acetate 0.02 M buffer at concentrations: 1- electrolyte, 2- 0.1609, 3- 0.3218, 4- 0.6436, 5- 1.2873, 6- 1.9309, 7- 2.5746, 8- 3.8618, 9- 5.1491, 10- 6.4360, 11- 8.0460, 12- 9.6545 µg.mL^{-1}, (b) Calibration curves for the determination of CLP (purge gas N_2, purge time 500 s, sweep rate 5 mV/s, U. amplitude -100 mV, t. meas 30 ms, t. pulse 35 ms, t. step 1.6 s, U. step 8 mV, temperature 25°± 5°C)

Analytical results

Determination of CLP using DPPA on DME in the optimum conditions using analytical curves, Ip=f(C_{CLP}), showed that the accuracy was ready over the ranges of CLP concentration between 0.500 - 30.00 µM (0.2100 - 12.5970 µg.mL^{-1} of CLB or 0.1609 - 9.6546 µg.mL^{-1} of CLP). The percent relative standard deviation (RSD%) not more than 2.9%, see Table 2. Limit of detection (LOD) and limit of quantitation (LOQ) for the determination of CLP by this method were as the follows: 0.0160 and 0.0485 µg.mL^{-1}, respectively.

Table 2: Determination of clopidogrel using differential pulse polarographic analysis on DME with negative amplitude in sodium acetate 0.02 M buffer pH 8.0.

Taken x_i		Found, $\bar{x}$	SD,	$\bar{x} \pm \frac{t.SD}{\sqrt{n}}$,	RSD%
μM	μg.mL^{-1} (CLp)	μg.mL^{-1}	μg.mL^{-1}	μg.mL^{-1}	
0.500	0.1609	0.1671	0.00485	0.1671 ± 0.00602	2.9
1.000	0.3218	0.3234	0.00906	0.3234 ± 0.01125	2.8
2.000	0.6436	0.6392	0.01662	0.6392 ± 0.02063	2.6
4.000	1.2873	1.2643	0.03161	1.2643 ± 0.03924	2.5
6.000	1.9309	1.9208	0.04610	1.9208 ± 0.05723	2.4
8.000	2.5746	2.5773	0.05928	2.5773 ± 0.07360	2.3
12.00	3.8618	3.8590	0.08876	3.8590 ± 0.11020	2.3
16.00	5.1491	5.1093	0.11240	5.1093 ± 0.13954	2.2
20.00	6.4360	6.5160	0.13684	6.5160 ± 0.16989	2.1
25.00	8.0460	8.1416	0.16283	8.1416 ± 0.20215	2.0
30.00	9.6546	9.5483	0.16232	9.5483 ±0.20152	1.7

***** n=5 t=2.776.

Applications

Many applications for the determination of clopidogrel in some Syrian pharmaceutical preparations using differential pulse polarographic analysis on drop mercury electrode with negative amplitude in sodium acetate 0.02 M buffer pH 8.0 according to the optimal conditions were proposed. The amount (m) of CLP in one tablet was calculated from the following relationship: m=h. m', where: m' is the amount of CLP in tablet calculated according to the regression equation of calibration curve, h conversion factors are equal to 25 for all pharmaceuticals content 75 mg/tab. The results of quantitative analysis for CLP in pharmaceutical preparations were summarized in Tables 3. The proposed method was simple, direct and successfully applied to the determination of CLP in pharmaceuticals without any interference from excipients. Average assay ranged between 99.3 to 102.0%. The results obtained by this method agree well with the contents stated on the labels and were validated by HPLC method [14]. Therefore, the presented method can be recommended for routine analysis of CLP in pharmaceutical formulations

Method validation

The developed method for simultaneous estimation of CLP has been validated in accordance with the International Conference on Harmonization guidelines (ICH) [12].

Selectivity

Several other components were examined under the conditions that had been optimized for clopidogrel determination. The results showed that aspirin did not interfere (The peak of aspirin did not appear within optimum conditions for clopidogrel determination).

Table 3: Determination of CLP in some Syrian pharmaceutical preparations using DPPA on DME with negative amplitude in sodium acetate 0.02 M buffer pH 8.0 according to the optimal condition.

Commercial name	Label Claim of CLP, mg/tab.	*Mean ±SD (as CLP), mg/tab.	RSD%	Assay %	* (Assay %), by HPLC [14]
Pharma Gre, F.C.Tablet **PHARMASYR**,	75.0	74.5	2.4	99.3	99.0
Plaraz, F.C. Tablet **AL–RAZI**	75.0	76.0	2.3	101.3	100.9
Norgrel Plus, F.C. Tablet, **UNIPHARMA**	75.0	75.5	2.5	100.7	101.0
Glopid, F.C. Tablet**, EL–SAAD**	75.0	74.3	2.3	99.1	99.5
Plofexine, F.C. Tablet, **ASIA,**	75.0	77.0	2.4	102.7	101.5
Clotless**,** F.C. Tablet, **APHAMEA**	75.0	76.5	2.4	102.0	101.8

***** n=5, Assay=(found mean/label claim)x100.

Linearity

Several aliquots of standard stock solution of CLP were taken in different 25 mL volumetric flasks such that their final concentrations were 0.1609 - 9.6546 $\mu g.mL^{-1}$ (0.500-30.00 $\mu mol.L^{-1}$) for CLP using DPPA at DME in sodium acetate 0.02 M buffer at pH 8.0. Linearity equation obtained for the mentioned range was y=-31.9895x-1.5536, (R^2=0.9997), see figure 4 and table 2.

Precision and Accuracy

The precision and accuracy of proposed method were checked by recovery study by addition of standard drug solution to pre-analyzed sample solution at three different concentration levels (80%,100% and 120%) within the range of linearity for CLP (one table 75.00 mg). The proposed method was validated statistically and through recovery studies. It was successfully applied for the determination of CLP in pure and dosage forms, table 4.

Table 4 : Results of recovery studies (n=5).

Level	Quantity present of CLP, mg	Quantity added of CLP, mg	The resulting quantity of CLP, mg	Quality determined of CLP,	Recovery%
80%	75.00	60.00	135.00	136.35	101.0
100%	75.00	75.00	150.00	149.85	99.9
120%	75.00	90.00	165.00	165.83	100.5

Repeatability

The repeatability was evaluated by performing 10 repeat measurements for 5.1491 $\mu g.mL^{-1}$ of CLP using the studied DPPA at DME sodium acetate 0.02 M buffer pH 8.0 under the optimum conditions. The found amount of CLP ($\bar{x}$ ± SD) was 5.1287 ± 0.110 $\mu g.mL^{-1}$ and the percentage recovery was found to be 99.6 ± 2.14 with RSD of 0.021. These values indicate that the proposed method has high repeatability for CLP analysis.

Sensitivity limit of detection [LOD] and limit of quantitation [LOQ]

The sensitivity of the presented method was evaluated by determining the LOD and LOQ. The values of LOD and LOQ for CLP are 0.0160 and 0.0485 $\mu g.mL^{-1}$, respectively.

Robustness

The robustness of the method adopted is demonstrated by the constancy of the current peak (I_p) with the deliberated minor change in the experimental parameters such as the change in the concentration of excipients, temperature (25 ±5°C), pH (8.0 ± 0.20), $\mathbf{C_{electrolyte}}$ and reaction time. Table 5 is indicates that the robustness of the proposed methods. It was found that the robustness is good.

Table 5: Robustness of the proposed DPPA method at DME for determination of CLP.

Experimental parameter variation	Average recovery (%)*	
	C_{CLP} =1.2873 µg.mL^{-1}	C_{CLP} =5.1491 µg.mL^{-1}
Temperature		
20^{o}C	99.6	99.8
25^{o}C	100.2	100.5
30^{o}C	101.1	100.7
pH		
7.8	99.5	99.7
8.2	100.2	99.9
$C_{electrolyte}$		
0.015 mol/L	100.5	99.5
0.025 mol/L	100.4	100.8
reaction time		
10 min	99.4	99.6
30 min	99.8	100.0
60 min	101.7	101.0

*** n=5.**

Specificity

The specificity of the method was ascertained by analyzing standard CLP in presence of excipients. These findings prove that the suggested method is specific for determination of the investigated drugs without interference from the coformulated adjuvants.

Conclusion

Electrochemical behavior and DPPA of CLP (as CLPB) in pure form and in pharmaceutical preparations using DME with sodium acetate 0.02 M buffer pH 8.0 according to the optimal conditions was applied. One reduction peak was observed. Ip is linear over the range 0.1609-9.6545 µg.mL^{-1} (0.500-30.00 µmol.L^{-1}) of CLP. The percent relative standard deviation did not exceed 2.9% for the concentration 0.1609 µg.mL^{-1} of CLP. Regression analysis showed a good correlation coefficient (R^2=0.9997) between Ip and concentration over the mentioned range. The proposed method was successfully applied to the direct analysis of CLP in pharmaceutical formulations without any interference from excipients and with adequate accuracy and sensitivity without any pre-separation such as extraction.

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