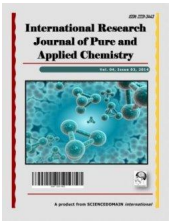

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Simultaneous Determination of Camylofin Dihydrochloride and Paracetamol Using Differential Pulse Voltammetry in Micellar Media

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Authors' contributions

This work was carried out in collaboration between all authors. All authors read and approved the final manuscript.

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ABSTRACT

Simple and sensitive differential pulse voltammetric (DPV) method has been developed for simultaneous determination of camylofin-2HCl and paracetamol. The electrochemical oxidation of camylofin was studied at carbon paste electrode using cyclic and differential pulse voltammetry. A reproducible and reliable oxidation current peak was obtained at pH 7. The oxidation current was enhanced in presence of sodium dodecylsulphate as an erosion reagent. Under optimal conditions the oxidation current was proportional to camylofin concentration in the range from 5.0 to 100.0 µM. Besides, the method was linear for paracetamol which is an active ingredient in the concentration range from 5.0 to 1000.0 µM. The proposed DPV method was selective for simultaneous determination of the two drugs with mean recovery of 99.58±2.13% and 99.44±0.57% for camylofin-2HCl and paracetamol, respectively. The method was validated according to ICH guidelines and successfully applied for the determination of the two drugs in combined pharmaceutical formulations.

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Keywords: Camylofin; electro-oxidation; carbon paste electrode; differential pulse voltammetry; micellar media.

1. INTRODUCTION

Camylofin-2HCl is isopentyl 2-(2-diethylaminoethylamino)2-phenylacetate dihydrochloride (Fig. 1) [1]. Camylofin is used usually in combination preparations with analgin, paracetamol, diclofenac and nimsulide as an antispasmodic [1]. Therefore, development of a sensitive, selective and rapid analytical method for the drug combination preparations is challenging.

Several analytical methods have been reported for determination of camylofin -2HCl either alone or in combination with other drugs including HPLC [2-7], GC [8-10] and TLC densitometry [3,6]. Although good results including separation and quantification of camylofin were obtained, the reported methods remained time consuming and solvent consuming as well as low sensitivity. In contrast to separation-based methods, electrochemical methods are fast, simple and more sensitivity for drug analysis with a number of excellent review articles [11-14].

Carbon paste electrodes have some benefits including the very low background current, individual polarizability, different alternatives for pretreating and easy to apply modifications, A variety of pasting liquids used for preparing carbon paste electrode are available however, careful choice of pasting liquid is necessary. They are usually chosen for inertness, low volatility, low solubility in the studied media and purity as paraffin oil [15]. The amount of the pasting liquid has a big impact on the response, where a high amount of pasting liquid decreases electron transfer rates, as well as the background current contributions [16,17]. Electrodes themselves are not selective, except for the direction of the applied potential. However, by modifying the electrode in a different styles, the degree of selectivity may be improved [15].

One of the most common and simple modification are the using of different types of surfactants. Electrode surfaces with hydrophobic characters such as carbon paste electrodes interact with surfactants through surface adsorption. Thus, carbon paste electrode modified with surfactants proved to be useful for the determination of both inorganic species and biological compounds [18].

Paracetamol is a para-aminophenol derivative (N-acetyl-para-amino- phenol) with antipyretic and analgesic characters and weak anti-inflammatory effect, (Fig. 1). Various techniques have been used for quantification of paracetamol include HPLC [19,20], GC [21,22], spectrophotometric [23-24], TLC [25-27], electrochemical [28-31], fluorometric methods [23-33].

To the best of our knowledge, the electrochemical oxidation of camylofin-2HCl has not been reported. Therefore, the present work aims at determination of camylofin -2HCl at carbon paste electrode using differential pulse voltammetry (DPV). The effect of the surfactant and different types of nano particles were investigated. Moreover, the method wass useful for simultaneous determination of camylofin-2HCl in a binary mixture with paracetamol.

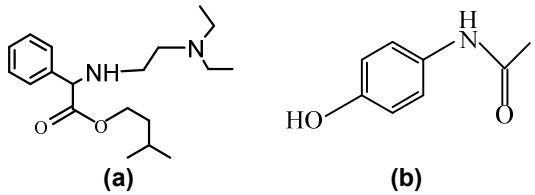

Fig. 1. Molecular structure of camylofin (a) and paracetamol (b)

2. EXPERIMENTAL

2.1 Chemicals and Reagents

Camylofin-2HCl and paracetamol drug substances were kindely supplied by El Kahira Pharmaceutical and Chemical Industries Co., Cairo, Egypt with purity of 99.64% and 99.85% for both drugs, respectively. Anafortan^{R} Tablets labeled to contain 25 mg of camylofin-2HCl ,300 mg paracetamol , Excipient ;q.s. and colors; Lake Tartrazine, Lake Brilliant Blue FCF, black oxide of iron , titanium dioxide I.P. ,(Abbot, India) was obtained from a local pharmacy.

Boric acid was purchased from Elnasr Pharmaceutical Chemicals Co. (Abou Zaabal, Egypt). Phosphoric acid was from Fisher Scientific. Acetic acid was purchased from Loba Chemie PVT Ltd (Mumbai, India). Paraffin oil and graphite powder were purchased from Sigma-Aldrich and were used as received. Britton-Robinson buffer (B-R buffer) 0.04 M was

prepared by mixing phosphoric, acetic and boric acids and the pH was adjusted by NaOH to the desired pH value. Solutions of reacting materials were prepared in bidistilled water. Sodium dodecylsulphate (SDS) and Triton were obtained from Sigma-Aldrich, Germany and Cetyl trimethyl ammonium bromide (CTAB) was obtained from SD Fine-Chem Limited, India.

2.2 Apparatus

Voltammetric measurements were performed using SP-150 potentiostat (BioLogic Science Instrument, France) provided with EC-Lab for windows v11.02 software. A platinum wire used as the auxiliary electrode. The cell potentials were measured with respect to Ag/AgCl (3.0 M KCl) reference electrode. A Cyberscan 500 digital (Eutech Instruments, USA) pH meter with a glass combination electrode was used for the pH adjustment. All the electrochemical experiments were performed at ambient temperature.

2.3 Stock Standard Solutions

Stock standard solution of the two drugs, ($1x10^{-2}$ M each) were prepared separately by transferring about 393.0 and 151.0 mg of camylofin and paracetamol each in 100-mL volumetric flask, dissolved in suitable amount of water, then the flask was completed to mark with bidistilled water. Working standard solutions were prepared by suitable dilution with bidistilled water.

2.4 Electrode Preparation and Pre-treatment

Carbon paste was prepared by hand mixing 1.0 g of graphite powder with 0.5 mL paraffin oil in a glass mortar using a pestle for 20 min. The electrode body was packed with a portion of the paste and the electrode surface was polished on a filter paper until the electrode showed a shiny appearance.

2.5 Recommended Procedure

The electrode was cycled in the potential range from 0 to 1.5 V with a scan rate of 100 mVs^{-1} in B-R buffer of pH 7.0 containing 50 µL of SDS ($1x10^{-3}$ M) for several times (i.e., approx. 15 cycles) until a stable response was achieved. Subsequently, a proper amount of camylofin-2HCl was added and the cyclic voltammograms were recorded from 0 to 1.5 V at a scan rate of 100 mVs^{-1}. For DPV procedure, aliquots from camylofin-2HCl standard solution was transferred using a micropipette into a series of 10-mL volumetric flasks to cover the concentration range from 5.0 to100.0 µM. Then 50 µL) of 1.0×10^{-2} M SDS solution was added and the volume was completed to the mark with B-R buffer (pH 7.0) and the DPV were recorded for each concentration. The same procedure was followed for paracetamol in the concentration range from 5.0 to 1000.0 µM

2.6 Construction of Calibration Curves (linearity)

Aliquots of camylofin-2HCl (1.0×10^{-3} M) and paracetamol (1.0×10^{-3}, 1.0×10^{-2} M) working standard solutions equivalent to 50.0 to1000.0 µM and 0.05 to 10.0 mM were transferred separately into two series of 10-mL volumetric for camylofin and paracetamol , respectively. Fifty µL of 1.0×10^{-2} M SDS solution was added followed by dilution to the mark with B-R buffer (pH 7.0) .The solution was stirred for 30 seconds followed by measuring peak current by DPV method. The peak current was plotted versus the drug concentration and the regression parameters were deduced.

2.7 Accuracy and Precision

Three different concentrations (10.0, 50.0 and 100.0 µM for camylofin and 50.0, 500.0, and 1000.0 µM for paracetamol were analyzed by the above recommended procedure three times on a single day and on three consecutive days.

2.8 Application to Laboratory Prepared Mixture

Aliquots of camylofin-2HCl (1.0×10^{-3} M) equivalent to 50.0 to1000.0 µM were transferred and mixed with aliquots of paracetamol (1.0×10^{-3}, 1.0×10^{-2} M) equivalent to 50 to 10000 µM into 10-mL measuring flask to prepare 5 mixtures containing different ratios of camylofin-2HCl and paracetamol the volume of each flask was completed to mark with B-R buffer. The DPV procedure was recorded for each mixture.

2.9 Application to Pharmaceutical Formulation

Ten tablets of Anafortan® were finely powdered in a mortar and an accurately weighed amounts of the powder equivalent to 98.35 mg of

camylofin-2HCl and 151.16 mg paracetamol were transferred into 25-mL and 100-mL measuring flask, respectively. The powder was dissolved in 50 mL bidistilled water and sonicated for 15 minutes. Each flask was completed to mark with bidistilled water and filtered to give a 0.01 M solution of camylofin-2HCl and paracetamol. Diluted solutions of 40 µM camylofin-2HCl and 100 µM paracetamol were obtained by dilution with buffer. These solutions were used for determination of camylofin-2HCl and paracetamol by the standard addition method all as described under "2.6 .Construction of calibration curves".

3. RESULTS AND DISCUSSION

3.1 Electrochemical Behavior at Carbon Paste Electrode

Fig. 2 shows the cyclic voltammogram of camylofin-2HCl at a carbon paste electrode in B-R buffer pH 7. The Cyclic voltammogram was recorded in the range from 0 to 1.4 v at scan rate of 100 mV/s. An oxidation peak current was observed at about 1 V and no peak was observed in the reverse scan, indicating that the electrochemical oxidation process is irreversible. The electrochemical oxidation mechanism is shown in Fig. 3.

3.2 Effect of Different Types of Surfactants on the Electrochemical Oxidation of Camylofin-2HCl

Carbon paste electrodes are characterized by their easy preparation, new active surface regeneration and low ohmic resistance [11]. Besides, they allow easy surface modification [14]. The use of surfactants in electroanalytical chemistry is well known either for electrode modification or in the aqueous electrolytic solution [34,35]. Surfactants cause modification of the double layer structure at the electrode/solution interface and, hence, affect the charge transfer rate constant [34]. Additionally, due to their amphiphilic properties, they help dissolve hydrophobic substances and stabilize radicals or intermediate reaction products in solution.

Fig. 4 shows the cyclic voltammetry of camylofin-2HCl at carbon paste electrode in B–R buffer (pH 7.0) in presence of different types of surfactants including SDS (anionic), CTAB (cationic), and Triton (nonionic surfactant). The peak current of camylofin-2HCl almost disappeared in presence of CTAB, whereas, a broad peak current was observed when triton was used as a surfactant. In contrast, the peak current was enhanced with a concomitant peak potential shift towards negative direction in presence of SDS. The peak current is dependent on SDS concentration and its maximum was obtained when 50 µL of SDS ($1.0x10^{-2}$M) was added to the measuring cell. Further increase of SDS to 70 and 100 µl did not affect the peak current (Fig. 5). Besides the erosion effect [36], SDS worked as a counter ion and helped accumulation of camylofin at the electrode surface. Therefore, all subsequent measurements were performed in presence of 50 µL of $1.0x10^{-2}$M SDS.

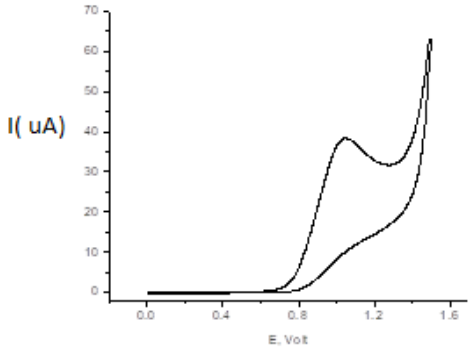

Fig. 2. Cyclic voltammograms of camylofin-2HCl (1x10-3M) at pH 7.0 in B-R buffer at a carbon paste electrode, the scan rate 100 mV/s

3.3 Effect of PH

The effect of pH was studied in the pH range from 3-9 (Fig. 6). At low pH values the oxidation peak is deteriorated with a broad peak potential and small peak current. The peak current is increased with a peak potential shift towards negative direction as the pH is raised from pH 3 to pH 7. Increasing the pH from 7 to 9 resulted in an increase in the peak current and a negligible shift in the peak potential. Unfortunately, the peaks current at pH 8 and 9 were not reproducible, probably due to working close to the pKa value (8.79) of camylofin-2HCl [37] and drug precipitation was observed at pH10. Thus, the pH of the working solutions was adjusted to pH 7 for all subsequent measurements. The peak potential is shifted about 58 mV in the negative direction when the pH was changed from 5 to 6.(Ep=1506 - 58 pH) indicating an electron transfer and proton during the oxidation process.

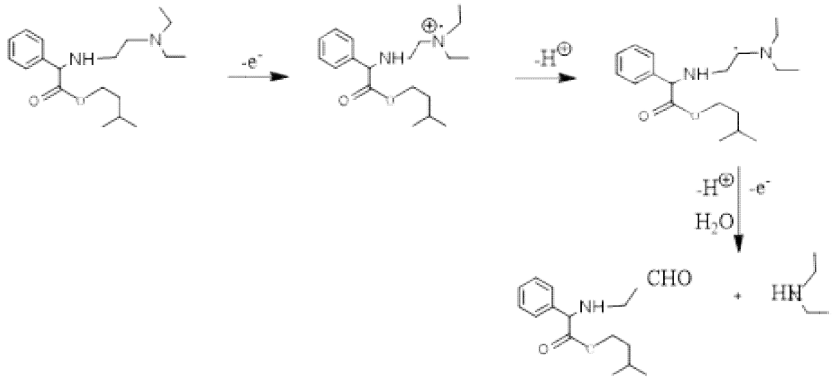

Fig. 3. Proposed electrochemical oxidation mechanism of camylofin

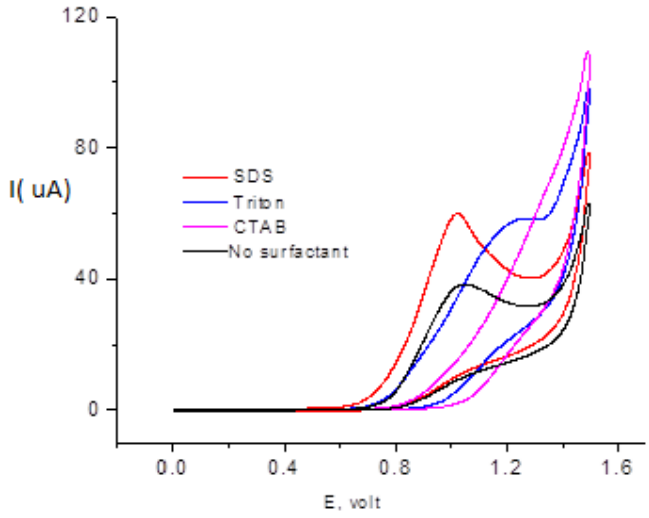

Fig. 4. Cyclic voltammograms of camylofin-2HCl (1x10-3 M) at pH 7.0 in B-R buffer at a carbon paste electrode using 50 µL of 1.0x10-2M of three different surfactants: CTAB, Triton and SDS, the scan rate is 100 mV/s

3.4 Effect of Scan Rate

Useful information about the electrochemical mechanism can be obtained from the relationship between the scan rate and peak current. Therefore, the effect of scan rate (10 to 250 mV s^{-1}) on the peak current was studied in BR buffer pH 7 (Fig. 7A). A good linear relationship between the peak current and the scan rate was obtained in the range from 50 to 300 mV/s (Fig. 7B). The regression equation representing this relationship is ip = 473.77 v + 20.086, r^2 = 0.9972. This indicates that the electrode process is controlled by adsorption. A good relationship between the peak current and the square root of the scan rate was obtained as well (Fig. 7C); I = 351.64 v1/2- 29.369 (r^2 = 0.9955), indicating a diffusion controlled electrode process. Furthermore, the relationship between log ip vs. log v was linear (Fig. 7D) and controlled by the following equation: Log ip = 0.71 log v + 2.548, r^2 = 0.9981. The slope 0.71 is between the values 0.5 for diffusion controlled and 1.0 for adsorption controlled electrochemical process, suggesting a mixed diffusion-adsorption peak current [38,39]. The peak potential is scan rate dependent (155 mV by unit log v at low scan rate and 64 mV by unit log v at high scan rate), indicating a mixed kinetic controlled electrode process. Such behavior suggests an electron transfer followed by a chemical reaction process [40].

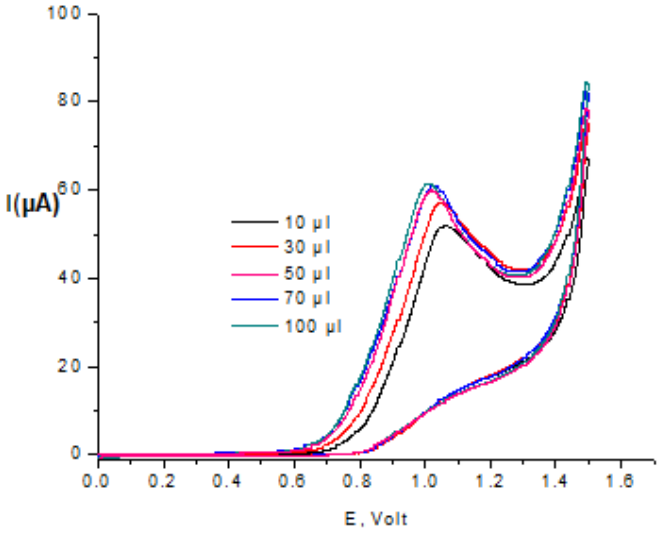

Fig. 5. Cyclic voltammograms of camylofin-2HCl (1x10^{-3} M) at pH 7.0 in B-R buffer at a carbon paste electrode in presence of different concentrations of SDS at scan rate 100 mV/s

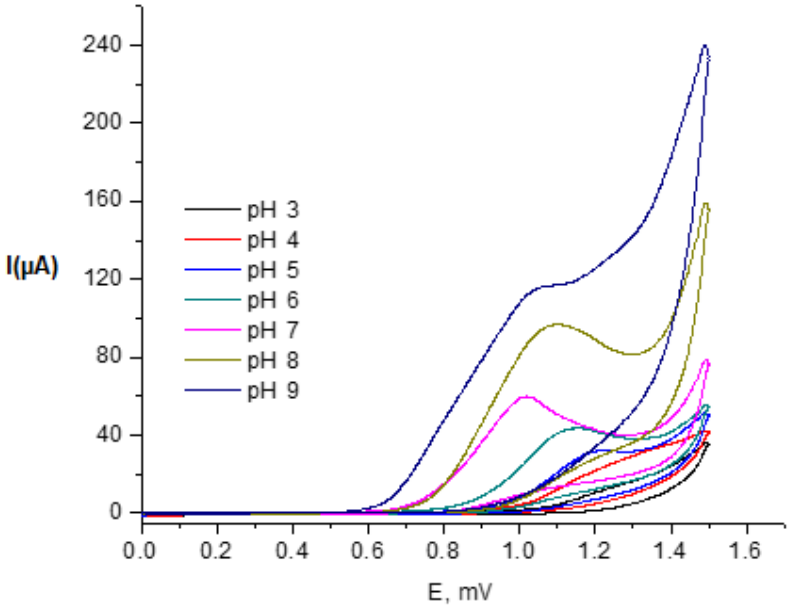

Fig. 6. Cyclic voltammograms of camylofin-2HCl (1x10^{-3} M) at a carbon paste electrode in B-R buffer at different pH

3.5 Electrochemical Behavior of Paracetamol

Literature survey revealed a huge variety of modifications concerning voltammetric determination of paracetamol. Since the response of camylofin achieved after many failed modifications and was on edge so we tried to apply the camylofin conditions on paracetamol as both have optimum response at pH 7. By studying the effect of stirring and different types of surfactant on its electrochemical response, it was found that stirring has enhanced effect on response, also no effect of anionic and non ionic surfactant, so we added anionic surfactant (SDS) just for making universal conditions for both drugs.

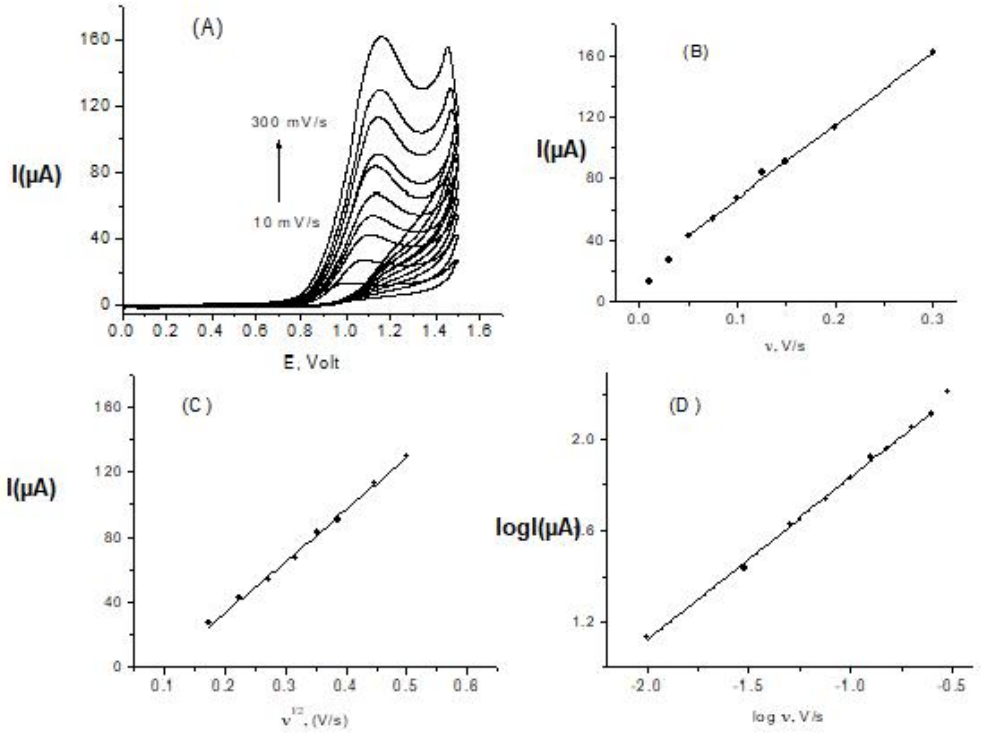

Fig. 7. Cyclic voltammograms of 1×10−3 M camylofin-2HCl in Briton Robinson buffer solution at pH 7.0 at scan rates of: (A) 10, 30, 50, 75, 100, 125, 150, 200, 250 and 300 mV/s (B) Dependence of peak current on the scan rate. (C) Dependence of peak current on square root of scan rate and (D) Dependence of logarithm peak current on logarithm scan rate

3.6 Quantitative Determination of Camylofin and Paracetamol and Its Validation

Cyclic voltammetry, square wave voltammetry and DPV were studied for the quantitative determination of camylofin-2HCl but only DPV gives reliable results and suitable sensitivity.

DPV was used as a sensitive method for quantitative determination of camylofin-2HCl and paracetamol. The optimum DPV parameters were step height 5 mV, step time 250 ms, pulse width 100 ms and pulse height 25 mV.

3.6.1 Linearity

The linearity was examined in the concentration range from 5.0 to 100.0 μM (Figs. 8a) for camylofin -2HCl and in the range of 5.0-1000.0 μM for paracetamol (Fig. 8 b). The linear regression equations were computed to be:

y = 0.0199x + 0.0375 (r2 >0.999) ……. for camylofin-2HCl

y = 0.0075x + 0.1466 (r2 >0.999) …… for paracetamol

Regression parameters for both drugs were summarized in Table 1.

3.6.2 Accuracy and precision

The intra-day precision and accuracy of the proposed method were studied by analysis of three different concentrations three times on a single day (repeatability) and the mean recoveries obtained for camylofin-2HCl and paracetamol were 99.58% ±2.13 and 99.44% ±0.57, respectively (Table 1). The same concentrations were analyzed on three consecutive days (intermediate precision). The inetra-day %RSD for camylofin-2HCl and paracetamol were ≤1.4% and ≤0.84%, while inter-day %RSD were ≤1.73% and ≤1.61%, respectively.

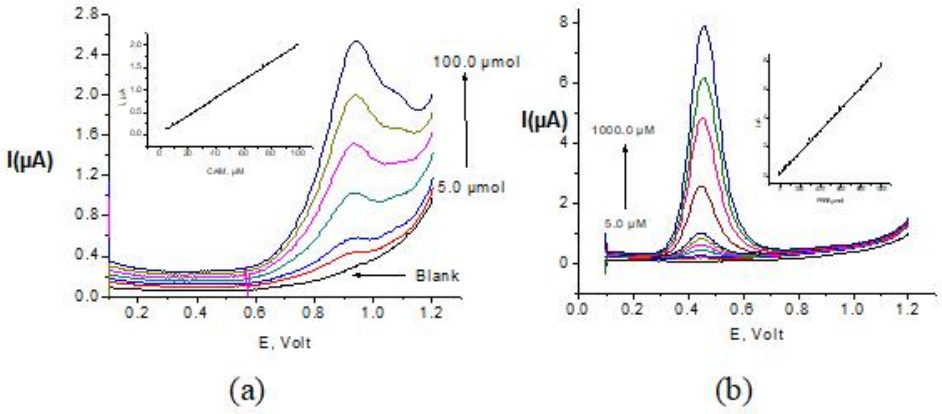

Fig. 8. DPV voltammograms of a) 5.0, 10.0, 30.0, 50.0, 70.0 and 100.0 µM of camylofin-2HCl; the inset is corresponding linear calibration curve and b) 5,0, 10,0, 30.0, 50.0, 70.0,100.0, 300.0, 600.0, 800.0 and 1000.0 µM of paracetamol; the inset is corresponding linear calibration curve

Table 1. Regression and validation parameters for camylofin-2HCl and paracetmol by proposed voltammetric method

	Camylofin	Paracetamol
Linearity range, µM	5.0-100.0	5.0-1000.0
Slope	0.0199	0.0075
Intercept	0.0375	0.1466
Correlation coefficient (r2)	0.9995	0.9994
SE of slope	2.19x10-4	6.37x10-5
SE of intercept	1.24x10-2	2.93x10-2
Accuracy (Mean%±SD)*	99.58±2.13	99.44±0.57
Precision (RSD%)*		
Interaday	1.40	0.84
Interday	1.73	1.61

**Average of 9 determination*

3.6.4 Selectivity

The selectivity of the proposed method was studied by analyzing different laboratory prepared mixtures of camylofin-2HCl and paracetamol at different ratios (the ratio of camylofin-2HCl to paracetamol in the pharmaceutical formulation is 1:12). Good recovery percentages were obtained at all studied ratios from 1:1 to 1:20 of camylofin-2HCl: Paracetamol, respectively, (Table 2 and Fig. 9). It is noteworthy to mention that the ratio of the two drugs in commercial tablets is 1: 12.

Table 2. Determination of camylofin-2HCl and paracetamol in laboratory prepared mixtures by the proposed DPV method

Camylofin	Paracetamol	Ratio (Camylofin: Paracetamol)	Recovery%	
(µM)	(µM)		Camylofin	Paracetamol
50	50	1:1	99.25	102.14
100	50	2:1	97.86	*120.68
50	100	1:2	98.9	100.23
50	500	1:10	98.44	98.64
50	1000	1:20	98.48	98.04
30	500	1:16.67	97.64	102.58
Mean% ±SD			98.43±0.61	100.33±2.03

**rejected*

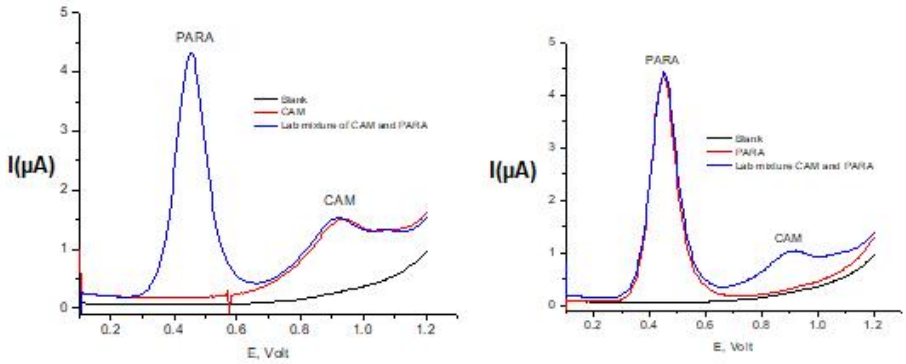

Fig. 9. a) DPV voltammogram of a laboratory prepared mixture (50.0 µM camylofin-2HCl and 500.0 µM paracetamol) and 50.0 µM camylofin-2HCl; and b) DPV voltammogram of a laboratory prepared mixture (30.0 µM camylofin-2HCl and 500.0 µM paracetamol

Table 3. Determination of camylofin-2HCl and paracetamol in pharmaceutical formulations by the proposed DPV method and reported method [2]

	Camylofin-2hcl		Paracetamol	
	DPV	**Reported** [2]**	**DPV**	**Reported** [2]**
Mean ±SD	101.42±1.49	99.55±1.28	101.17±1.32	99.52±1.13
Variance	2.21	1.65	1.74	1.28
Number	5	5	5	5
t-test*	2.13	-	2.12	-
f-test*	1.34	-	1.36	-

**Theoretical t- and F- values at P=0.05 were 2.31 and 6.39; respectively.*

***HPLC method for simultaneous determination of camylofin and paracetamol solution using water C18 column with UV detection at 220 nm and a mobile phase consisting of 0.05% trifluoroacetic acid in water and 0.05% trifluoroacetic acid in acetonitrile (50:50 v/v), at a flow rate of 1.0 mL/ min*

Table 4. Determination of CAM and PARA in pharmaceutical formulations by standard addition Technique

	Camylofin-2HCL				Paracetamol			
	Taken	**Added**	**Found**	**Recovery**	**Taken**	**Added**	**Found**	**Recovery**
	(µM)	**(µM)**	**(µM)**	**(%)**	**(µM)**	**(µM)**	**(µM)**	**(%)**
	40	20	19.68	98.4	100	20	19.69	98.45
Anafortan	40	40	40.46	101.16	100	100	101.91	101.91
	40	50	49.04	98.08	100	500	514.15	102.83
	40	60	60.73	101.22	100	900	882.72	98.08
Mean ±SD				99.71±1.71				100.31±2.41

3.6.5 Application to pharmaceutical formulation

The proposed method was applied for the determination of camylofin-2HCl and paracetamol in their pharmaceutical formulations (Anafortan^{R}). The average recovery for camylofin-2HCl and paracetamol were 101.42±1.49 and 101.17±1.32, respectively. Further, the results were statistically compared with those obtained by another published method [2]. No significant difference was observed between the two methods as indicated by lower values of t- and F- tests than theoretical ones (Table 3). However, the proposed DPV method was proven to be more sensitive, more economic and less organic solvent consuming than the reported one [2]. Again, the proposed DPV method was more sensitive and more economic than GC, HPLC and UV spectrophotometric methods [10,41,42] reported to determine the two drugs in combination.

For further assessment of proposed method validity, standard addition technique was applied. The results of analysis of dosage form and standard addition, (Table 4) showed suitability of this method for application on pharmaceutical formulation without interference from excipients.

4. CONCLUSION

The proposed DPV method is simple and selective for the selective assay of camylofin-2HCl and paracetamol. The method is linear for camylofin-2HCl over the concentration range from 5.0-100.0 µM. The method was applied for simultaneous determination of camylofin-2HCl and paracetamol in combined pharmaceutical formulations with high accuracy and precision (%RSD ≤2).

COMPETING INTERESTS

Authors have declared that no competing interests exist.

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