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Full Paper

Simultaneous Determination of Ramipril and Felodipine using Carbon Paste Electrode in Micellar Medium

Elham A. Taha,[1] Ali K. Attia,[1,*] Manal M. Fouad[2] and Zainab M. Yousef[1]

[1]*National Organization for Drug Control and Research (NODCAR), Giza, Egypt*
[2]*Analytical Chemistry Department, Faculty of Pharmacy, Al-Azhar University, Cairo Egypt and October University for Modern Sciences and Arts, 6 October City, Egypt*

*Corresponding Author, Tel.: +20 1069716429 (mobile); Fax: +20 235855582
E-Mail: zeze.badawy@gmail.com

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Abstract- Simple, precise, inexpensive and sensitive voltammetric method was developed for simultaneous determination of Ramipril (RAM) and felodipine (FLD) mixture in drug substance, drug product and human urine using carbon paste electrode (CPE). Effect of different surfactants on peak current was studied in acetate buffer solution of pH 4.8. Sodium dodecyl sulphate (SDS) is the optimum surfactant based on the enhancement of the peak current. The peak current varied linearly over the concentration ranges from 5×10^{-5} mol L^{-1} to 8×10^{-4} mol L^{-1} for both drugs. The quantification limits were 1.78×10^{-5} and 1.94×10^{-5} mol L^{-1} and detections limits were 4.5×10^{-6} and 2.7×10^{-6} mol L^{-1} for RAM and FLD, respectively. The proposed voltammetric method was successfully applied to determine RAM and FLD mixture in drug product and human urine. The results of the proposed method were statistically compared with those of the reported method and showed no significant difference. Thus, it can be applied for quality control of both drugs.

Keywords- Voltammetry, ramipril, felodipine, Micellar medium, Urine

1. INTRODUCTION

Ramipril (RAM) Fig. 1, (2S,3aS,6aS)-1-[(2S)-2[[(1S)-1-(Ethoxycarbonyl)-3 phenylpropyl]amino]propanoyl]octahydrocyclopenta[b]pyrrole-2-carboxylic acid, used as

angiotensin converting enzyme inhibitor (ACE inhibitor) [1]. ACE inhibitor are recommended as first-line treatment of hypertension in patients with a variety of compelling indications, including high coronary disease risk or history of diabetes, stroke, heart failure, myocardial infarction, or chronic kidney disease. The ACE inhibitors lower blood pressure by reducing peripheral vascular resistance without reflexively increasing cardiac output, heart rate, or contractility. These drugs block the enzyme ACE which cleaves angiotensin I to form the potent vasoconstrictor angiotensin II. ACE is also responsible for the breakdown of bradykinin, a peptide that increases the production of nitric oxide and prostacyclin by the blood vessels. Both nitric oxide and prostacyclin are potent vasodilators[2]. RAM is officially listed in British Pharmacopoeia, which describes a potentiometric titration with 0.1 M sodium hydroxide for its assay in bulk [1].

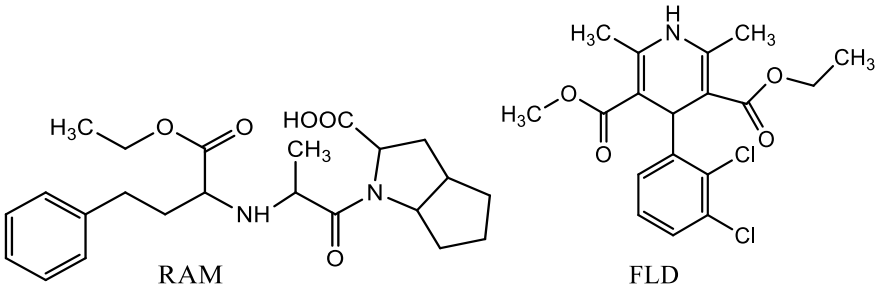

Fig. 1. Chemical structures of RAM and FLD

Felodipine (FLD), Fig. 1, ethylmethyl(4RS)-4-(2,3-dichlorophenyl)-2,6-dimethyl-1,4dihydropyridine-3,dicarboxylate, used as calcium channel blocker [1]. Calcium channel blockers are a recommended treatment option in hypertensive patients with diabetes or angina. FLD was classified as dihydropyridines, this class of calcium channel blockers have a much greater affinity for vascular calcium channels than for calcium channels in the heart. They are, therefore, particularly beneficial in treating hypertension. The dihydropyridines have the advantage that they show little interaction with other cardiovascular drugs, such as *digoxin* or *warfarin*, which are often used concomitantly with calcium channel blockers [2]. The drug is officially listed in British Pharmacopoeia, which describes a titration with 0.1M cerium sulfate for its assay in bulk [1].

RAM in combination with FLD is used in several antihypertension preparations. The antihypertensive efficacy of the combination was additive and the coadministration of RAM did not attenuate the incidence of headache attributable to FLD [3].

RAM was determined individually by spectrophotometric methods [4-6], HPLC [7-9], HPTLC [10,11] and electrochemical methods [12-15]. On the other hand, FLD was determined individually using UV spectrophotometry [16-20], HPLC [16,17,21,22], spectrofluorimetric [23], gas chromatography [24] and electrochemical methods [25,26]. Meanwhile, some

spectrophotometric [27,28], HPLC [27-30] and HPTLC [31] methods were reported for the simultaneous determination of both drugs.

Up to our knowledge no electrochemical method was suggested for their simultaneous determination. In the present work, rapid, economical, simple and precise voltammetric method was developed for determination of RAM and FLD simultaneously at carbon paste electrode (CPE) in presence of sodium dodecyl sulphate (SDS) as a surfactant.

2. EXPERIMENTAL

2.1. Materials and Reagents

RAM purity 99.96% [1] was obtained from Kahira Pharmaceuticals & Chemical Industries Company, and FLD purity 98.9% [3] was kindly supplied from Egyptian Group for Pharmaceutical Industries (EGPI) Company, Egypt. Triacor® tablet, (Aventis Pharma Deutschland GmbH, Germany) labelled to contain 5 mg RAM and 5 mg FLD. It was purchased from local market. All chemicals and reagents used throughout the work were of analytical reagent grade and solutions were made with doubly distilled water. Ascorbic acid (AA), uric acid (UA), dextrose, sodium dodecyl sulphate (SDS), Triton, and cetyltrimethyl ammonium bromide (CTAB) were provided from Sigma-Aldrich, Germany. Acetate buffer solutions were used as supporting electrolytes. Acetate buffer was prepared by mixing x mL and (50-x) mL of 0.2 mol L^{-1} acetic acid and sodium acetate solutions, respectively, diluted to 100 mL to obtain solutions of different pH values (from 3.6 to 5.6). Britton-Robinson (BR) buffers were made by mixing a solution of 0.04 mol L^{-1} phosphoric acid, 0.04 mol L^{-1} acetic acid and 0.04 mol L^{-1} boric acid. Buffer solutions were adjusted by 2.0 mol L^{-1} NaOH solutions. Phosphate buffer was prepared by adding 34.7 mL of 0.2 mol L^{-1} NaOH to 50 mL of 0.2 mol L^{-1} potassium dihydrogen phosphate and completed to 200 mL with water. Graphite powder and mineral oil were supplied from Sigma-Aldrich, Taufkirchen, Germany. Stock solutions of RAM and FLD (1.0×10^{-2} mol L^{-1}) were prepared in methanol. Mixture stock solution was freshly prepared by mixing 12.5 mL of each of stock solutions of RAM and FLD in 25 mL flask which completed with methanol. The stock solutions were stored in dark bottle and kept in the refrigerator for seven days.

2.2. Electrochemical measurements

All voltammetric measurements were performed using SP-150 electrochemistry work station and data were analyzed with EC-Lab electrochemistry software, manufactured by Bio-logic Science Instruments Pvt.ltd. (France). Platinum wire was employed as auxiliary electrode. All the cell potentials were measured with respect to Ag/AgCl (3 mol L^{-1} NaCl) reference electrode. All electrodes and the C3 stand were obtained from BASi (Indiana, USA). A

JENWAY 3510 pH meter (Staffordshire, England) was used for pH measurements. All the electrochemical experiments were performed at an ambient temperature of 25±2 ºC.

2.3. Procedures

2.3.1. Preparation of working electrode

The paste was prepared by mixing 0.5 g of graphite powder with 0.3 mL of paraffin oil in a mortar with a pestle. The carbon paste was packed into the hole of the electrode and smoothed on a filter paper until it had a shiny appearance [32].

2.3.2. Effect of buffer type and pH

To study the effect of buffer type on the peak current (I_p) of the used drugs, the working CPE electrode was immersed in different types of buffer solutions with different pH [acetate (3.6-5.6), BR (2-11) and phosphate (5.8-8) buffers] containing an appropriate amounts of 1.0×10^{-2} mol L^{-1} drugs solutions, the electrolytic cell containing (3.5 mL of acetate buffer and 1.5 mL methanol) and the cyclic voltammogram was recorded.

2.3.3. Effect of surfactant

Different successive additions of different surfactants SDS, CTAB and Triton (10-90 µL) of the same concentration (1.0×10^{-2} mol L^{-1}) were added to the voltammetric cell containing 1.0×10^{-3} mol L^{-1} of RAM and FLD mixture in acetate buffer of pH 4.8 and the cyclic voltammograms were recorded at CPE.

2.3.4. Effect of scan rate

The influence of scan rate (ν) on the peak current (I_p) of RAM and FLD was carried out by immersing the working electrode in the acetate buffer solution (pH 4.8), 60 µL SDS and 1.0×10^{-3} mol L^{-1} of mixture drug solution, then the cyclic voltammograms were recorded at different scan rates over the scan range 25-300 mV s^{-1}. Plot log I_p versus log ν.

2.4. Determination of RAM and FLD

2.4.1. Determination of RAM and FLD in mixture

Voltammetric analysis was performed in 3.5 mL Acetate buffer pH 4.8, 1.5 mL methanol and 1.2×10^{-4} mol L^{-1} SDS. Aliquots of the mixture stock solution (1.0×10^{-2} mol L^{-1}) were introduced into the electrolytic cell and the procedure was repeated. The voltammograms were recorded. The peak current was evaluated as the difference between each voltammogram and the background electrolyte voltammogram.

2.4.2. Determination of RAM and FLD in Triacor® tablets

Ten tablets of Triacor® were weighed and finely powdered, an accurately weight amount needed to obtain 1.0×10^{-2} mol L^{-1} drug solution was accurately weighed and transferred into a 50 mL volumetric flask which contains 30 mL of methanol. The content of the flask was sonicated for about 10 min, made up to the volume with methanol and the solution was filtered. Aliquots of the drug solution (50, 75, 100, 150, 200, 250 µL) were introduced into the electrolytic cell and the general procedure was carried out.

2.4.3. Determination of RAM and FLD in urine

Urine (1 mL) was mixed with 9 mL of acetate buffer of pH 4.8. Aliquots of mixture stock solution equivalent to (1.5×10^{-4}-7×10^{-4} mol L^{-1}) were added to the voltammetric cell containing 5 mL of the prepared drugs mixture. The differential pulse voltammetric procedure was carried out as for both drugs.

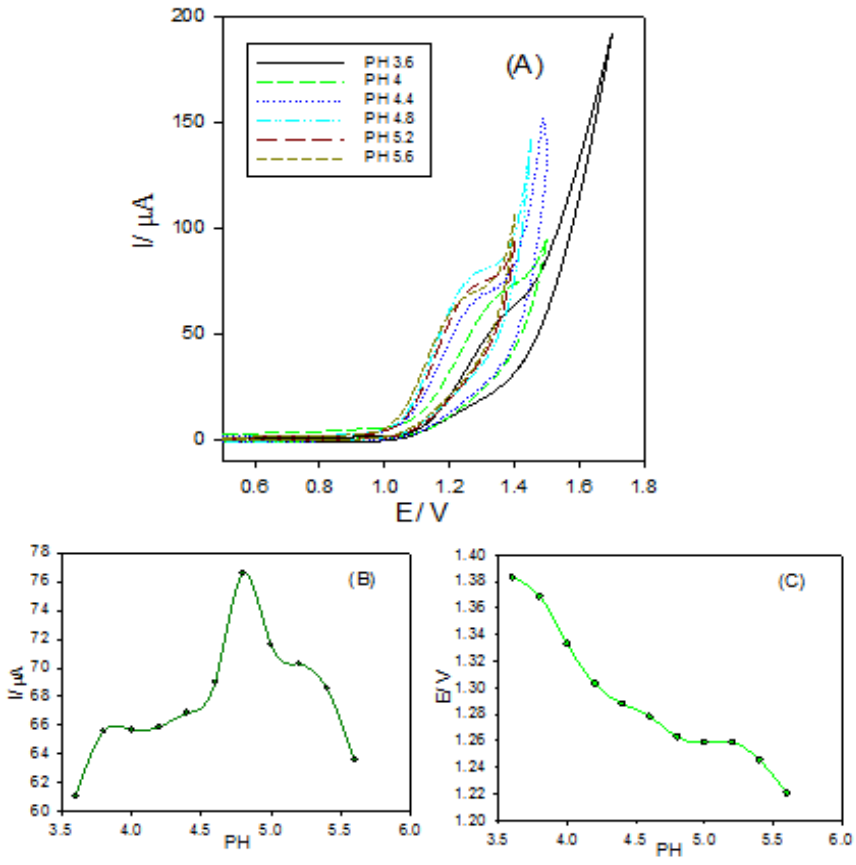

Fig. 2. Cyclic voltammograms of 1.0×10^{-3} mol L^{-1} RAM at CPE in acetate buffers of pH values ranging from 3.6 to 5.6 at scan rate of 100 mV s^{-1} (A); the relations of peak current (B) and potential (C) as a function of pH

3. RESULTS AND DISCUSSION

3.1. Electrochemical behaviour of RAM and FLD

Fig. 2A and Fig. 3A show the cyclic voltammograms of RAM and FLD solutions (1.0×10^{-3} mol L^{-1}) in acetate buffer of different pH values ranging from 3.6 to 5.6 at CPE, exhibit anodic peaks with no peaks on the reverse scan, suggesting the irreversible nature of the electrode reaction. Fig. 2B and Fig. 3B show that the anodic peak current of RAM and FLD increased as the pH increases up to 4.8 then decreased. Fig. 2C and Fig. 3C show that the anodic peak potential was shifted negatively with the increase of the solution pH indicating that the oxidation of RAM and FLD was pH dependent reaction and that protons have taken part in their electrode reaction processes. The results showed that acetate buffer of pH 4.8 was chosen as the optimum pH used in subsequent experiments.

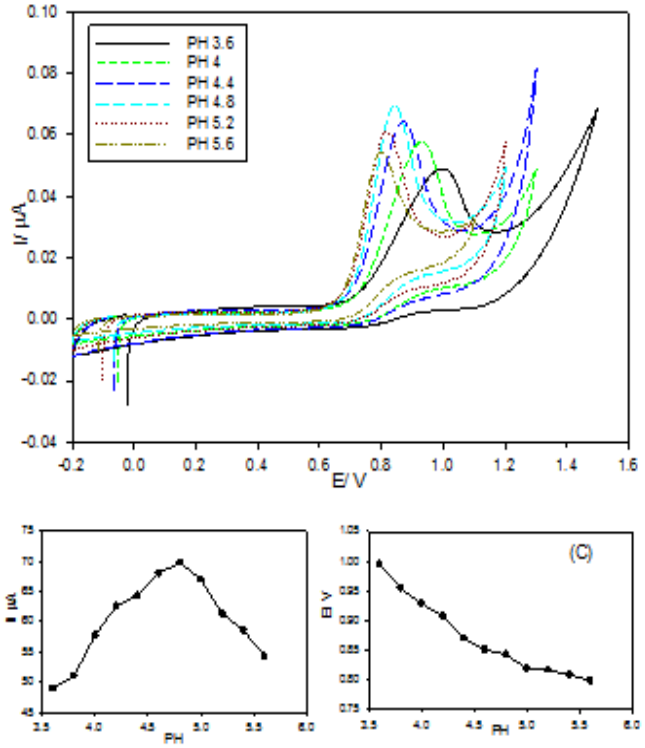

Fig. 3. Cyclic voltammograms of 1.0×10^{-3} mol L^{-1} FLD at CPE in acetate buffers of pH values ranging from 3.6 to 5.6 at scan rate of 100 mV s^{-1} (A); the relations of peak current (B) and potential (C) as a function of pH

3.2. Effect of buffer type

Fig. 4 shows the cyclic voltammograms of 1.0×10^{-3} mol L^{-1} RAM and FLD mixture solution in BR and acetate buffers. Different BR buffers (acidic, neutral, basic) was used to obtain good well defined separate peaks, and then compared by Acetate buffer pH 4.8. At BR

buffer pH 10, the cyclic voltammograms showed only the anodic peak of FLD while the anodic peak of RAM disappeared. At BR buffer pH 4.0, the very broad anodic peaks of the two drugs were appeared. At BR buffer pH 7.0, the anodic peaks of the two drugs were appeared but a broad peak in case of RAM.

At acetate buffer of pH 4.8, well-defined anodic peaks of the two drugs appeared, with maximum current values 79.35 µA and 65.48 µA for RAM and FLD, respectively. It is obvious from the figure that acetate buffer was chosen for electrochemical determination of RAM and FLD.

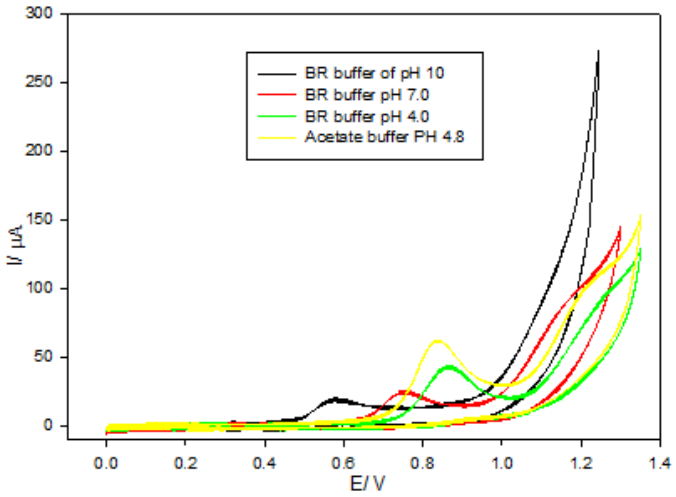

Fig. 4. The cyclic voltammograms of 1.0×10^{-3} mol L^{-1} RAM and FLD mixture solution in BR and acetate buffers

3.3. Effect of different surfactants

Fig. 5 shows the relations of peak current of 1.0×10^{-3} mol L^{-1} RAM and FLD mixture at CPE in acetate buffers of pH 4.8 at scan rate of 100 mV s^{-1} using different surfactants. The maximum current values (107.76 µA, 88.93 µA and 90.105 µA) of RAM was found in the presence of 1.2×10^{-4}, 8.0×10^{-5} and 8.0×10^{-5} mol L^{-1} of SDS, CTAB and Triton, respectively, while the maximum current values (215.73 µA, 123.80 µA and 123.70 µA) in case of FLD was found at 1.2×10^{-4}, 8.0 10^{-5} and 8.0×10^{-5} mol L^{-1} of SDS, CTAB and Triton, respectively.

Fig. 6 exhibits the cyclic voltammograms of 1.0×10^{-3} mol L^{-1} RAM and FLD at CPE in acetate buffer of pH 4.8 at scan rate of 100 mV s^{-1}, exhibiting the maximum current values of RAM and FLD in presence of 1.2×10^{-4}, 8.0×10^{-5} and 8.0×10^{-5} mol L^{-1} of SDS, CTAB and Triton, respectively. Therefore, 1.2×10^{-4} mol L^{-1} of SDS was chosen as the optimum surfactant in this study, the maximum current values 82.86 µA and 78.65 µA for RAM and FLD, respectively.

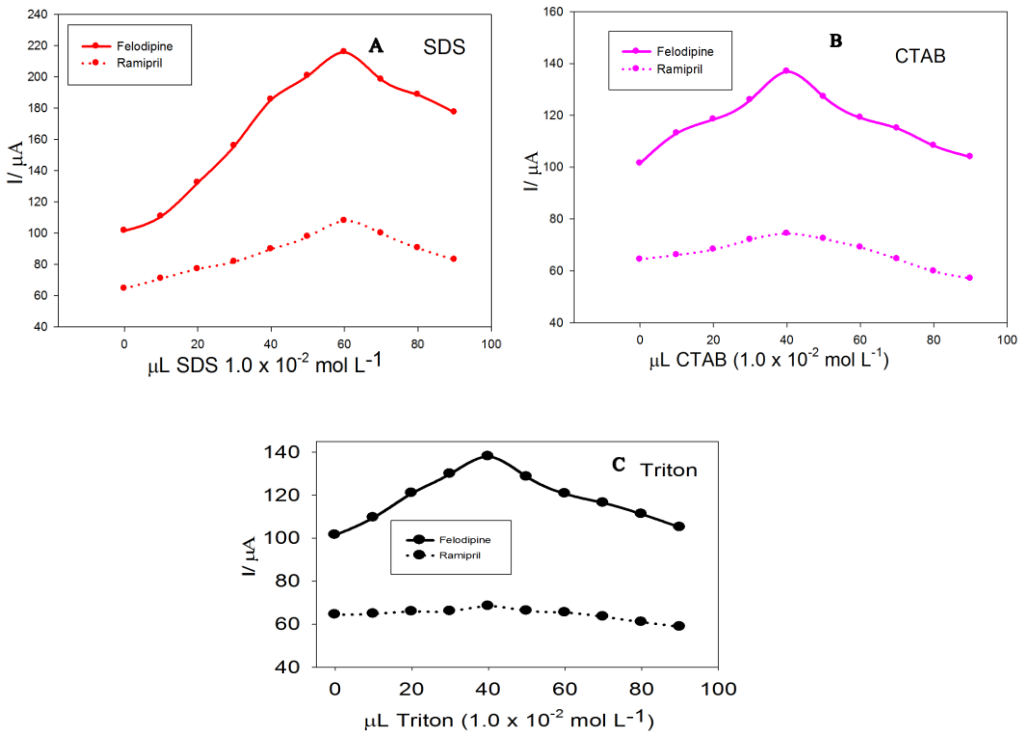

Fig. 5. Effect of different surfactants on peak current of 1×10^{-3} mol L^{-1} RAM and FLD mixture at CPE in acetate buffers of pH 4.8 at scan rate of 100 mV s^{-1} as a function of surfactants types (A) SDS; (B) CTAB and (C) Triton

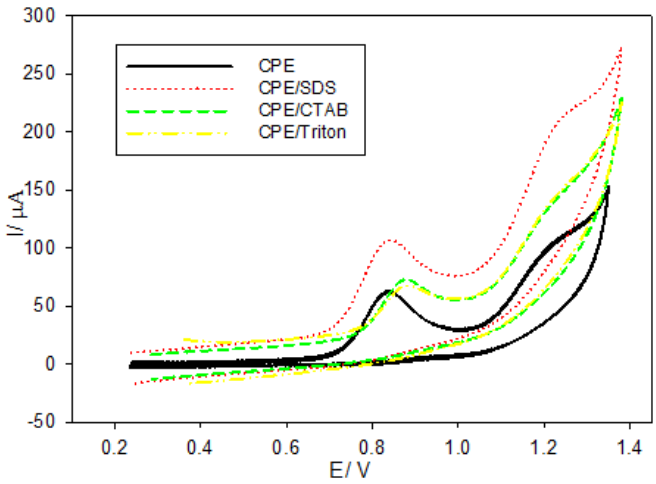

Fig. 6. Cyclic voltammograms of 1.0×10^{-3} mol L^{-1} RAM and FLD in acetate buffer of pH 4.8 at scan rate of 100 mV s^{-1} recorded using CPE and three different surfactant: SDS, CTAB and Triton

3.4. Effect of the scan rate

The linear relationship was found for the logarithm of the oxidation peak currents and the logarithm of the scan rates (Fig. 7). For RAM, the oxidation peak current increased linearly

with the increased scan rate which represented by linear regression equation as I_p=1.24+ 0.5381 log ν, r^2 (correlation coefficient=0.9978). For FLD, the linear regression equations was I_p=0.49+1.03 log ν, r^2=0.9989. The slopes 0.53 for RAM and 0.49 for FLD suggested that the oxidation reactions at the electrode surface take place under diffusion controlled process [33].

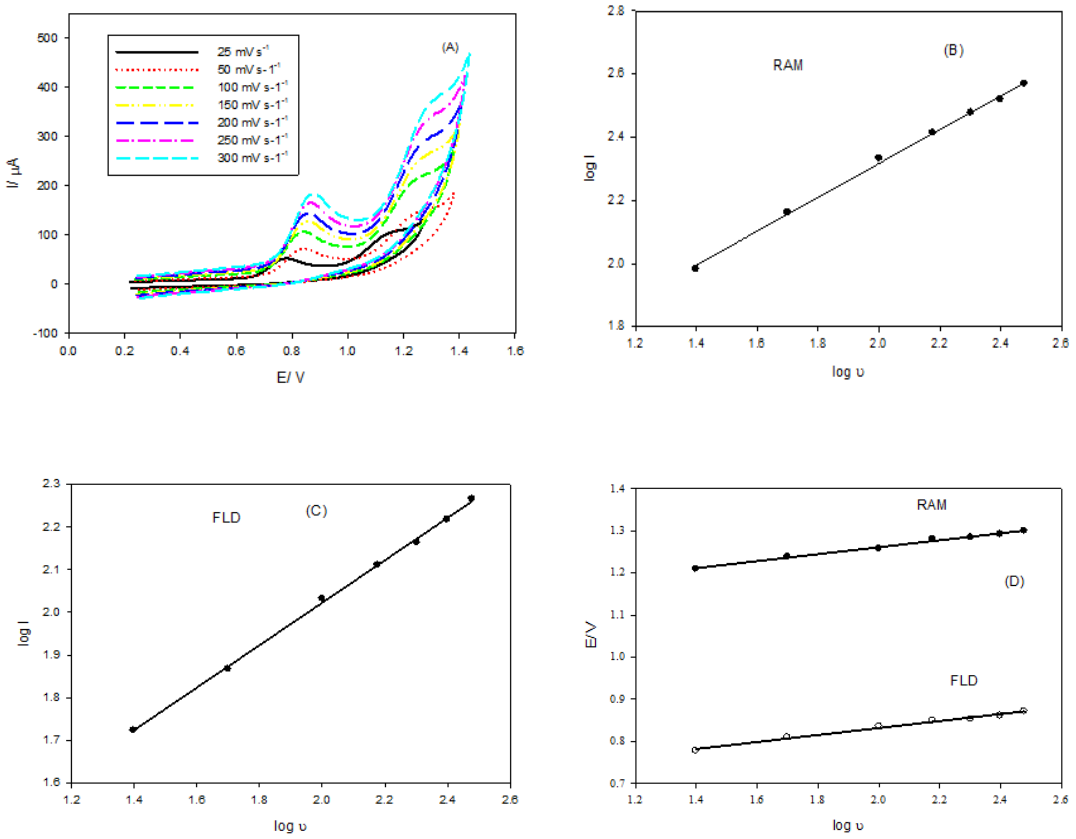

Fig. 7. Cyclic voltammograms of 1×10^{-3} mol L^{-1} RAM and FLD mixture in acetate buffer (pH 4.8) as a function of scan rate (A); Plot of log (I) versus log (υ) (B); (C) and Laviron plot (D)

In case of irreversible electrode process, the peak potential (E_p) and scan rate (ν) are defined by the following Laviron equation [34] $E_p=E^o+2.303RT/\alpha nF[\log RTK^o/\alpha nF+\log \nu]$ where α is the electron transfer coefficient, n is the number of electrons, T is the temperature (298 K), R is the gas constant (8.314 J K mol^{-1}) and F the Faraday constant (96,485 C mol^{-1}), respectively. Thus we can calculate αn from the slope of the relation between E_p versus log ν. In this case, the slope values were 0.082 and 0.083, for RAM and FLD, respectively; αn values were calculated to be 0.721 and 0.712. Generally, a (electron transfer coefficient) was assumed to be 0.5. Thus, the value of electrons number n=1.44 (≈1) and 1.42 (≈1) obtained confirming the proposed electro-oxidation mechanisms of RAM and FLD as shown in Fig. 8. The possible mechanism for the electrochemical oxidation of RAM and FLD can be assigned to oxidation of the secondary amine group in the molecule.

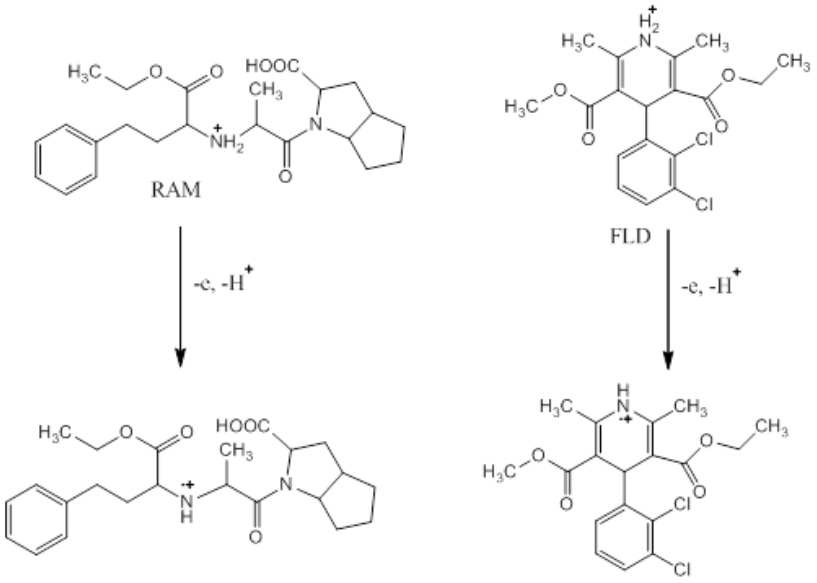

Fig. 8. Possible electro-oxidation reaction proposed for the RAM and FLD

3.5. Method validation

As shown in Table 1, the method was validated according to ICH guidelines for linearity and range, limit of detection, limit of quantification, accuracy, precision and specificity.[35]

3.5.1. Interference study

The ability of sensor to discriminate between the interfering species commonly present in similar physiological environment and the target analyte is very important.

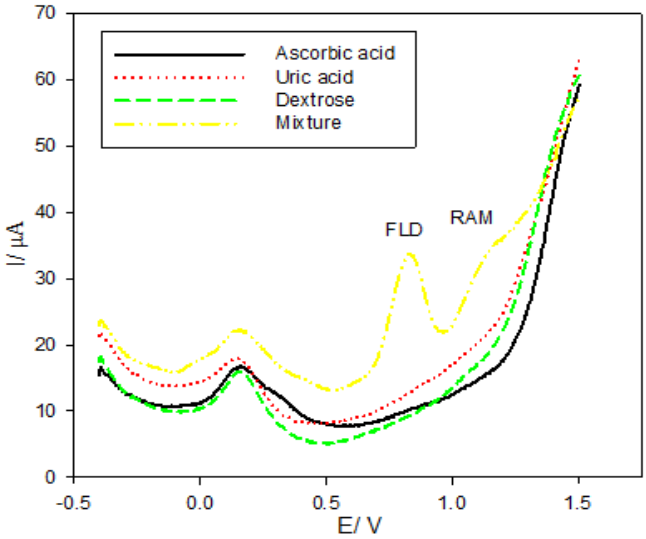

Fig. 9. The differential pulse voltammograms of (1.0×10^{-3} mol L^{-1}) RAM and FLD in presence of (1×10^{-4} mol L^{-1}) AA, dextrose and UA mixture in acetate buffer of pH 4.8 at CPE-SDS at scan rate of 100 mV s^{-1}

Ascorbic acid (AA) is a naturally occurring organic compound with antioxidant properties. Humans require it as part of their nutrition [36]. Uric acid (UA) is the primary end product of purine metabolism in the human body [37]. Therefore, determination of RAM and FLD in the presence of AA, dextrose and UA is very important for the clinical point of view.

Differential pulse voltammetry (DPV) was used to determine RAM and FLD (1.0×10^{-3} mol L^{-1}) in presence of equimolar solutions of AA, dextrose and UA (1.0×10^{-4} mol L^{-1}), the applied scan rate was 100 mV s^{-1}. Fig. 9 shows the differential pulse voltammograms at CPE-SDS in acetate buffer (pH 4.8)., the presence of solutions of AA, dextrose, UA or mixture of them, did not significantly affect the peak current response for the RAM or FLD, indicating that the CPE/SDS can be employed for the determination of RAM and FLD mixture in the presence of AA, dextrose and UA.

3.5.2. Determination of RAM and FLD in the drug substances

Fig. 10A shows the calibration plots of RAM and FLD at CPE/SDS over the concentration ranges from 5.0×10^{-5} mol L^{-1} to 8×10^{-4} mol L^{-1}. Validation of the proposed methods was assessed as per the International Conference on Harmonization (ICH)[35] was followed to validate the method.

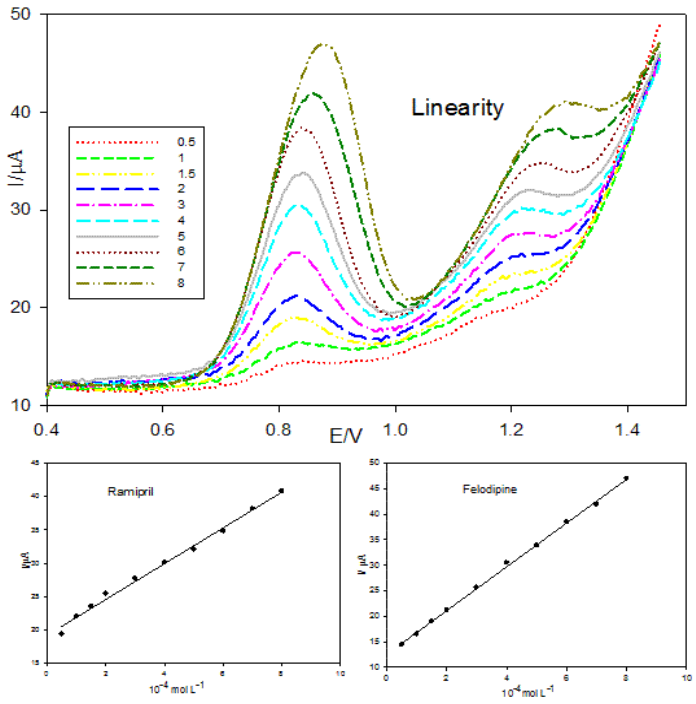

Fig. 10. The calibration plots of RAM and FLD at CPE-SDS over the concentration ranges from 5×10^{-5} mol L^{-1} to 8×10^{-4} mol L^{-1} for RAM and FLD (A); Linear calibration curve of the anodic peak current to the corresponding concentration (B) and (C)

For RAM, LOD and LOQ were found to be 4.5×10^{-6} mol L^{-1} and 1.78×10^{-5} mol L^{-1}, respectively. While for FLD, LOD and LOQ were found to be 2.7×10^{-6} mol L^{-1} and 1.94×10^{-5} mol L^{-1}, respectively. Both LOD and LOQ values confirm the sensitivity of CPE/SDS.

The mean of recoveries were found 100.56% for RAM and 101.62%, for FLD. The results are shown in Table 1. The precision of the proposed DPV procedure was investigated on three measurements of 3.0×10^{-4}, 6.0×10^{-4} and 8.0×10^{-4} mol L^{-1} of RAM and FLD solution, indicating good results.

Table 1. Regression data of linear range for quantitative determination of ramipiril and felodipine in bulk and urine sample

Parameters	**RAM in bulk**	**RAM in urine**	**FLD in bulk**	**FLD in urine**
Linearity range (mol L^{-1})	5×10^{-5} to 8×10^{-4}	1.5×10^{-4} to 7×10^{-4}	5×10^{-5} to $8\ 10^{-4}$	1.5×10^{-4} to 7×10^{-4}
Slope	2.6884	2.604	4.2887	4.0826
Intercept	19.18	19.234	12.533	13.485
Correlation coefficient (r^2)	0.9932	0.9938	0.9988	0.9964
LOD (mol L^{-1})	$4.^{o}\times10^{-6}$	3.6×10^{-5}	2.7×10^{-6}	4.0×10^{-5}
LOQ (mol L^{-1})	1.78×10^{-5}	1.20×10^{-4}	1.94×10^{-5}	1.34×10^{-4}
Accuracy (Mean ± SD)	100.56±1.16		101.62 ± 1.97	
Precision (RSD %)				
Intraday	0.78-1.11		0.50-1.27	
Interday	0.72-1.42		0.91-1.63	

Table 2 shows the comparison of the proposed method with some of mentioned reported methods for the determination of RAM and FLD.

Table 2. Comparison of the proposed method with the reported methods for RAM and FLD

Method	**RAM linear range**	**LOD**	**Ref.**	**FLD linear range**	**LOD**	**Ref.**
Proposed voltammetry (mol L^{-1})	5×10^{-5}-8×10^{-4}	4.5×10^{-6}	This work	5×10^{-5}–8×10^{-4}	2.7×10^{-6}	This work
(μg mL^{-1})	20.83–333.21	1.87		19.22–307.40	1.04	
Voltammetry (mol L^{-1})				2×10^{-4} –2×10^{-3}	not calculated	[25]
Spectrophotometry (μg mL^{-1})	56-112	1.412	[5]	10-60	9.72	[17]
	60-132	2.735	[5]			
Chromatography (μgmL^{-1})	50-150	0.062	[28]	50-150	0.029	[28]

3.5.3. Assay of RAM and FLD in dosage form

The proposed method was successfully applied for the determination of RAM and FLD in drug product in the presence of excipients and additives in the same concentration range as in the drug substance without interference, with good recovery percentage of 100.51±0.97 for RAM and 99.62±1.36 for FLD. The validation of the method was accessed using standard addition technique without the necessity of the sample pre-treatment or time consuming extraction steps prior to the analysis. Based on the average of five replicate measurements, the values of mean recovery and mean RSD were 99.55% ±1.09 and 100.42% ±0.81, for RAM and FLD respectively.

Statistical analysis of the results obtained by the proposed method compared with those obtained by the official method[1] revealed that there is no significant difference between the proposed and official method confirming accuracy and precision at 95% confidence limit [38] as shown in Table 3.

Table 3. Statistical analysis of results obtained by the proposed and official method for the determination of ramipril/felodipine in their pharmaceutical formulation

Parameters	**Proposed method**		**Official method[1]**	
	RAM	**FLD**	**RAM**	**FLD**
Mean%	100.4	100.74	99.68	100.13
N	5	5	5	5
SD	1.04	1.11	1.04	1.22
Variance	1.09	1.24	1.08	1.50
t- test	1.19	0.81		
F- test	0.99	1.21		

The theoretical t- and F- values at P= 0.05 (1.860) and (5.19) respectively.

3.5.4. Assay of RAM and FLD in urine

The proposed voltammetric method was applied for determination of RAM and FLD in urine sample. The results gave linear range from 1.5×10^{-4} to 7.0×10^{-4} mol L^{-1} for both drugs. The LOD and LOQ were 3.6×10^{-5} mol L^{-1} and 1.20×10^{-4} mol L^{-1} for RAM. While 4.0×10^{-5} mol L^{-1} and 1.34×10^{-4} mol L^{-1} for FLD. Five different concentrations on the calibration curve were chosen to be repeated three times to evaluate the accuracy and precision of the proposed method as represented in Table 1.

4. CONCLUSION

The described voltammetric method is simple, sensitive and eco-friendly for simultaneous determination of RAM and FLD mixture in drug product and urine with good precision,

accuracy and selectivity with low detection limit. The high percentage of recoveries in drug product without any treatment confirms the suitability of the proposed method. The method can be successfully used in routine analysis of both drugs in quality control labs.

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