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Research Article

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Electroanalytical Studies and Simultaneous Validated Assay of Antihypertensive Compounds in Their Binary Mixtures Using Fast Electrochemical Technique

Hızlı Elektrokimyasal Teknik Kullanılarak Antihipertansif Bileşiklerin İkili Karışımlarda Elektroanalitik Çalışmalar ve Eşzamanlı Doğrulanmış Testi

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ABSTRACT

The electrochemical behavior of amlodipine (AML) and telmisartan (TLM) on a glassy carbon electrode were investigated in different aqueous solutions by using cyclic, differential pulse, and square wave voltammetric techniques. AML and TLM exhibited one peak (both of them) to the anodic direction. The oxidation process was found to be irreversible and adsorption controlled. To obtain good sensitivity, the instrumental and accumulation variables were studied using square wave voltammetry (SWV) techniques in 0.5 M H_2SO_4 solution, which was obtained as the most repeatabile and sensitive media. In this study; sensitive, fast and reliable method development was aimed for simultaneous detection of AML and TLM. This voltammetric method exhibited linear dynamic responses in the concentration range between 1.0×10^{-7} M and 1.0×10^{-4} M for AML and 1.0×10^{-7} M and 1.0×10^{-5} M for TLM, with detection limits of 0.654 nM and 22.6 nM, respectively. The proposed method is validated and successfully applied for the analysis of AML and TLM tablets.

Keywords

Amlodipine, telmisartan, square-wave voltammetry, glassy carbon electrode.

ÖZ

Amlodipine (AML) ve telmisartan (TLM)'ın elektrokimyasal davranışı; farklı sulu çözeltilerde, camsı karbon elektrotta, dönüşümlü, diferansiyel puls ve kare dalga voltametri (KDV) teknikleri kullanılarak araştırılmıştır. AML ve TLM anodik yönde bir pik (her ikisi de) vermiştir. Oksidasyon prosesi geri dönüşümsüz ve adsorpsiyon kontrollü olarak bulunmuştur. En tekrar edilebilir ve duyarlı ortam olarak 0.5 M H_2SO_4 çözeltisi bulunmuş ve bu ortamda iyi bir hassasiyet elde edebilmek için enstrümantal ve biriktirme değişkenleri KDV tekniği ile çalışılmııştır. Bu çalışmada, AML ve TLM'ın eş zamanlı tayini için duyarlı, hızlı ve güvenilir yöntemin geliştirilmesi amaçlanmıştır. Bu voltametrik yöntem, 1.0×10^{-7} M ve 1.0×10^{-4} M aralığında AML için ve 1.0×10^{-7} M ve 1.0×10^{-5} M aralığında TLM için doğrusal dinamik cevaplar vermiş olup gözlenebilme sınırları AML ve TLM için sırasıyla 0.654 nM, 22.6 nM olarak bulunmuştur. Önerilen yöntem, AML ve TLM tabletlerinden analiz çalışmalarına başarıyla uygulanmış olup tamamen doğrulanmıştır.

Anahtar Kelimeler

Amlodipin, telmisartan, kare dalga voltametri, camsı karbon elektrot.

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INTRODUCTION

Amlodipine (AML), ({R, S-2-[(2-aminoethoxy) methyl]-4-(2-chlorophenyl)-3-ethoxy-carbonyl-5-methoxycarbonyl-6-methyl-1,4-dihydro pyridine}) (Scheme 1), is a relatively new potent long-acting dihydropyridine calcium channel blocker [1]. AML is clinically used as an antihypertensive and antianginal agent [2].

Telmisartan (TLM), 4-((2-n-propyl-4-methyl-6-(1-methylbenzimidazolol-2-yl)-benzimidazol-1-yl)-methyl)-biphenyl-2 carboxylic acid (Scheme 1), is an angiotensin II receptor antagonist (ARA II) essentially used in the treatment of hypertension [3]. TLM works by blocking the action of certain chemicals that tighten the blood. Therefore blood flows more smoothly [4].

Use of the tablets with AML and TLM combination may provide lower high blood pressure (hypertension). Lowering blood pressure may lower your risk of a stroke or heart attack.

This work is concerned with a study of the voltammetric behavior using the particularly rapid, selective, full validated, reliable and sensitive technique of square wave voltammetry on a glassy carbon electrode.

Up to date, AML and TLM compounds have been studied simultaneously with spectrophotometry [5], liquid chromatography [6–8]. However, there is no information about the simultaneous determination of these two compounds with sensitive and selective electrochemical methods from their dosage form. According to published study results, they obtained a narrow linearity range. LOD and LOQ values of our method were more sensitive. In our study, we did not apply any pretreatments or extractions steps. Our developed method also very fast, it can give response in seconds.

This work aims to carry out a detailed investigation on the electrochemical behavior and sensitive detection of AML and TLM disodium by square wave voltammetry.

MATERIALS and METHODS

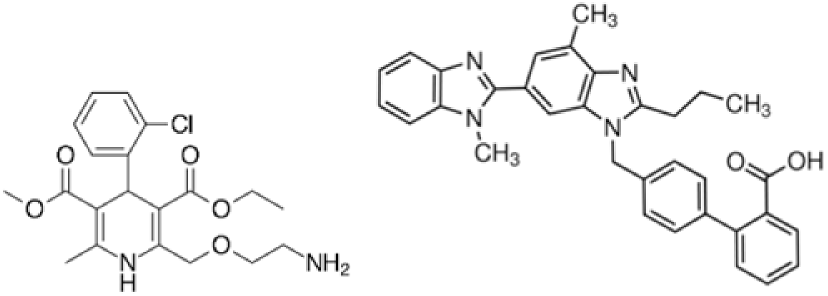
Instrumentation

All voltammetric measurements such as cyclic, differential pulse, square-wave, adsorptive stripping square-wave voltammetry were carried out in a BAS® 100 W electrochemical analyzer (Bioanalytical system, USA) with a suitable software program of BAS for totally automated control of the experiments and data acquisition. AUTOLAB-PGSTAT 302 (Eco Chemie, Utrecht, The Netherlands) was also used in some part of experiments. A 10 ml capacity BAS cell equipped with a three-electrode system was used. The working electrode was a glassy carbon electrode, BAS® model (ϕ=3 mm). An Ag/AgCl (KCl 3 M, BAS) reference electrode and platinum wire auxiliary electrode (BAS) was used. Before each measurement, the glassy carbon electrode was polished manually with alumina (ϕ=0.01 mm) in the presence of bi-distilled water on a damp smooth polishing cloth (BAS velvet polishing pad). All measurements were done at room temperature.

The pH measurements were carried out with a pH meter Model 538 (WTW, Weilheim, Germany) using a combined electrode (glass electrode-reference electrode) with an accuracy of ±0.05 pH.

Reagents

AML, TLM, and their dosage form were kindly provided by Boehringer Ingelheim. Film-coated tablet (Twynsta®)



Scheme 1. Chemical structure of AML and TLM, respectively.

contained 10 mg and 80 mg of AML and TLM, respectively.

$1x10^{-3}$ M standard stock solutions of AML and TLM were prepared in methanol and they put in refrigerator to keep fresh. In electrochemical measurement solutions, standard stock solutions of AML and TLM were diluted by supporting electrolyte solutions. The methanol percentage was fixed to %10 in all measurement solutions. The used supporting electrolytes were ordered as; sulphuric acid solutions with 0.1 M and 0.5 M concentrations, phosphate buffer solutions at pH 2.0-8.0 range, 1.0 M acetate buffer solutions at pH 3.5-5.5 range and 0.04 M Britton-Robinson buffer solutions at pH 2.00-10.0.

The determination studies were applied with the addition of aliquots of AML and TLM standard stock solutions into the measurement cell containing 10.0 mL of the 0.5 M H_2SO_4. SW voltammograms were obtained after each aliquot addition.

Procedure

Cycliv voltammetry (CV), differential pulse voltammetry (DPV), SWV methods were applied to investigate electrochemical behavior ALM and TLM in aqueous solutions. Cyclic voltammetry was applied under -0.25 and +1.8 V potential ranges with 0.1 V scan rate. DPV conditions were used as following conditions; modulation amplitude: 0.0505 V; interval time: 0.500 s; step potential: 0.00795 V; modulation time: 0.050 s. SWV method was performed with pulse amplitude, 20 mV; frequency, 70 Hz; potential step, 5 mV.

According to the three electrochemical methods results, the most sensitive responses were obtained by SWV for simultaneous detection of AML and TLM. Hence, further experiments were made with SWV.

Analytical application study was applied on Twnysta pharmaceutical dosage form. To obtain homogenous powder, ten tablets of Twnysta were weighed and homogenated in a mortar. A known amount of powder of Twnysta was weighed and put into the 10 mL flask and then diluted and filled with methanol. In the next step, the ultrasonic bath procedure was applied to dissolve of AML and TLM in tablet solution. To preparation of the electrochemical measurement solution, a known volume was put into 10 mL flask and completed with 0.5 M H_2SO_4. The calibration equations obtained from standard solutions were used to obtain AML and TLM concentrations from studied tablet solution. The results showed that the simultaneous detection of AML and TLM compounds form pharmaceutical form was successfully performed without any pretreatment procedures.

Recovery study was applied via taken of proper volumes of standard solutions of AML and TLM and added to the solutions of commercial form. The percentage of recoveries of AML and TLM were obtained using a comparison of the concentration obtained from spiked samples with the labeled concentration. Recovery results showed that our proposed method was precise and accurate for the simultaneous detection of both compounds.

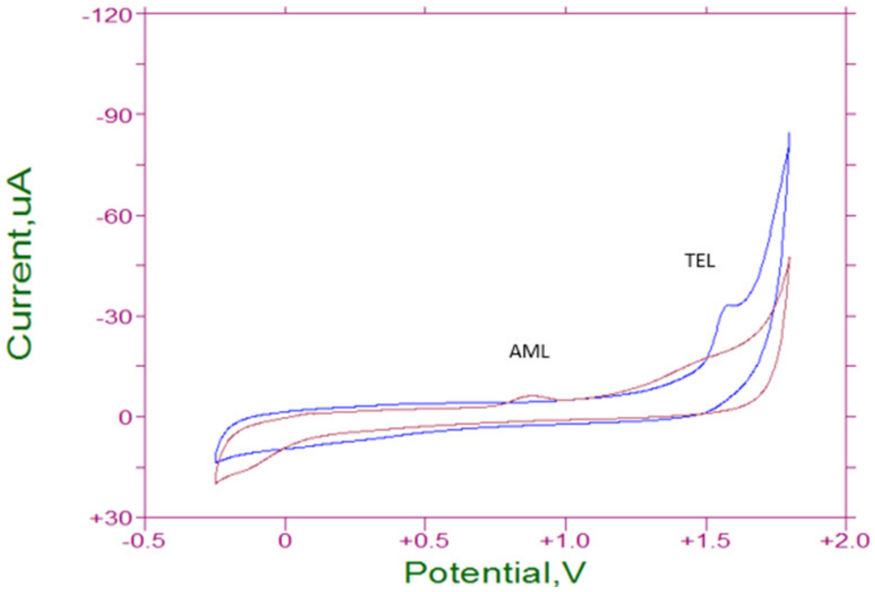


Figure 1. Cyclic voltammograms (100 mVs^{-1}) obtained with GCE for: red line, 1.0×10^{-4} M AML; blue line 1.0×10^{-4} M TLM in 0.5 M H_2SO_4 solution.

RESULTS and DISCUSSION

Electrochemical Behavior of AML and TLM

CV was used to investigation of electrochemical behavior of ALM and TLM in different aqueous solutions. 1.0×10^{-4} M AML and TLM redox behaviors were seen in Figure1 by CV. It was obvious that irreversible behaviors of both compounds were observed in 0.5 M H_2SO_4 solution at the glassy carbon electrode (GCE). Anodic responses were obtained at 0.87 V and 1.4 V for AML and 1.55 V for TLM, respectively. Cathodic response was not observed for both compounds on the reverse scan (Figure1).

The effects of pH on the anodic peak potential and current of AML and TLM was examined using GCE with CV method. The linear relationships between the peak potential (E_p) and pH at GCE can be expressed by the equations below. The effects of pH on peak potentials were investigated by CV.

For AML;

E_p (mV) = 977.88 – 33.643 pH (r = 0.995)

GCE (pH: 2.0 – 8.0) for AML with CV

For TLM;

E_p (mV) = 1593.6 – 47.94 pH (r = 0.977)

GCE (pH: 0.3-6.0) for TLM with CV

It is observed that with increase in pH, the AML peak potential shifts towards less positive values, which indicates the participation of protons in the electrode process. The E_p–pH equations of AML and TLM were linear and the obtained slopes were 33.64 and 47.9 by CV, respectively. The equal number of protons and electrons are involved in the electrode reaction at GCE [9]. The obtained slope values are in good agreement with each other with all working techniques for both compounds. TLM peak potential was slowly decreased during the buffer solution pH was increasing. The oxidation reaction

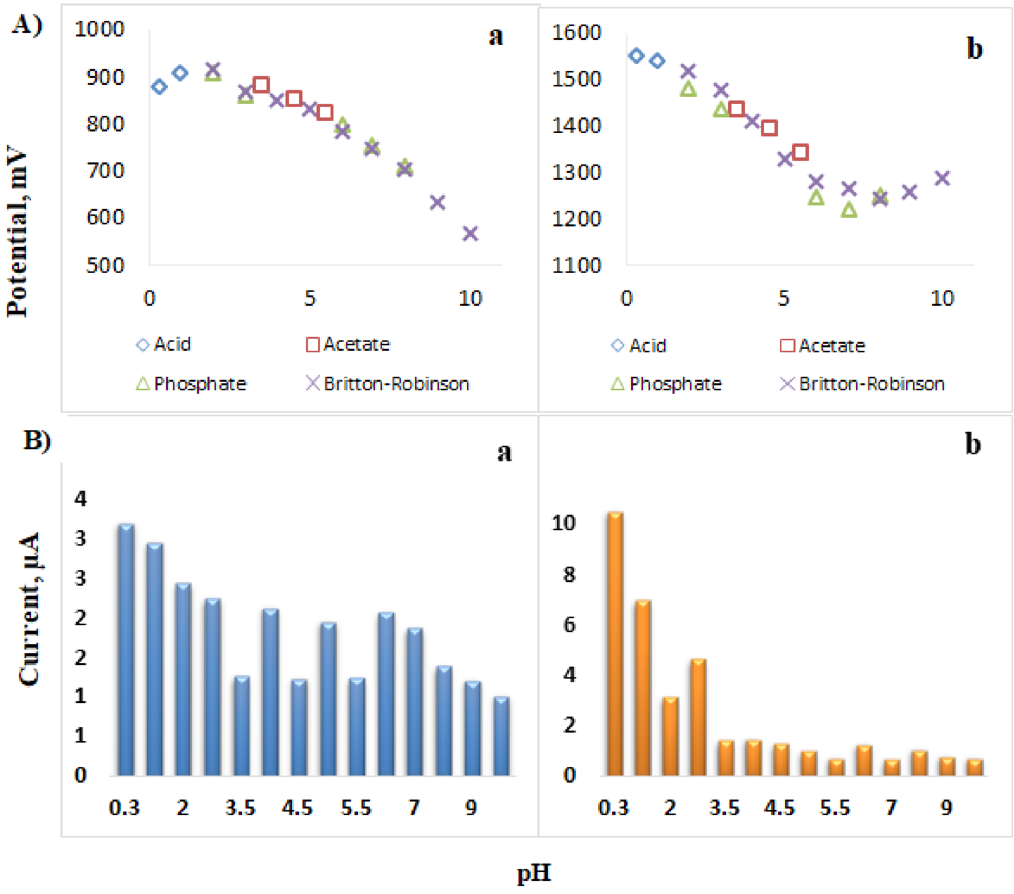


Figure 2. Influence of pH values on A) peak potential and B) current values of a) 1.0×10^{-4} M AML and b) 1.0×10^{-4} M TLM with CV at 0.1 mV/s.

mechanisms of AML and TLM were investigated in literature [4,10]. According to the published papers, AML oxidation might be occurred from 1,4-dihydropyridine ring, involving a two-electron two-proton mechanism [11]. TLM oxidation may be occurred from benzimidazole part [4].

According to the E_p-pH equations, CV, DPV, and SWV are approximately in agreement about electrochemical behavior of AML and TLM in aqueous solutions. The most sensitive responses were obtained in 0.1 M H_2SO_4 for AML and TLM (Figure 2). But, the best separation of two peaks and better repeatability of current-potential values were observed in 0.5 M H_2SO_4. The anodic peak currents values were decreased in other buffer solutions. The solubility of compounds in solutions are very important to obtain good responses. In acidic media, the solubility of both compounds can be increased and/or electron transfer rate may be faster than other solutions. So that, 0.5 M H_2SO_4 was used in further studies.

Scan rate study was performed between 5 and 750 mVs^{-1} to identify redox mechanism of 1.0×10^{-4} M AML and 1.0×10^{-4} M TLM on the GCE by CV. The results showed that the irreversible reactions of AML and TLM were occurred in acidic media. The increasing peak currents and shifting peak potentials were observed with increasing scan rates.

In scan rate study, the anodic peak was shifted at 43 and 26 mV per ten-fold change in scan rate for AML and TLM, respectively. In many situations, α can be between 0.3 and 0.7, and it can usually assumed as 0.5 in organic electrode reactions. So that, the transferred number of electrons are calculated as 1.4 and 2.3 for the AML and TLM, respectively. The linear responses for AML and TLM were observed with the square root of the scan rate in 0.5 M H_2SO_4 solution as follows:

I_{pa} (µA) = 0.254 $v^{1/2}$ (mV/s) – 0.311(r = 0.999) for AML
I_{pa} (µA) = 1.544 $v^{1/2}$ (mV/s) – 4.941(r = 0.985) for TLM

The straight lines with slopes 0.585 for AML and 0.699 for TLM were obtained from the plots of logarithm of the peak currents versus the logarithm of the scan rates. According to the slope values, the redox reaction types such as diffusion or adsorption processes could be predicted. If this value is near to 0.5, it means that the diffusion controlled process can be occurred. If this value approximately 1, it means that the adsorption controlled process can be expected. The intermediate value shows that the mixed diffusion-adsorption controlled process can occur.

$\log I_p = 0.585\log v - 0.844$ (r = 0.999) for AML
$\log I_p = 0.699\log v - 0.249$ (r = 0.995) for TLM

The diffusion-controlled process can be occurred for AML from the relation of logarithm peak current and logarithm scan rate [10,15–21]. The mixed diffusion-adsorption controlled process can be expected from TLM due to the slope value of 0.699. The anodic stripping voltammetry method was applied on TLM, but there was no significant increase in anodic current value. Because of these results, the diffusion-controlled reactions were assumed for both compound redox reactions on GCE.

Optimization of SWV Parameters

DPV and SWV methods were compared for sensitive simultaneous detection of AML and TLM. SWV responses were found higher current values than DPV responses. Hence, SWV without stripping parameters was used under its optimized conditions.

Before recording the analytical curves for the simultaneous determination of AML and TLM using the GCE, the effects of experimental parameters of the SWV on the peak potential and peak current were studied in the following ranges: square-wave frequency (10–100 Hz), pulse amplitude (10–45 mV), and step potential (3–10 mV) (Figure 3). The values of the optimized SWV parameters used for the subsequent simultaneous determination of these analytes were: frequency (f), 70 Hz; pulse amplitude, 20 mV; and step potential: 5 mV. According to the optimized conditions of SWV, the responses of AML and TLM increased with optimized conditions (Figure 4).

Simultaneous Determination of AML and TLM

When using electroanalytical techniques; SWV and DPV established a good separation, which clearly allows the simultaneous determination of AML and TLM. However, SWV gave more sensitive responses than DPV for these compounds. Hence, SWV conditions were optimized and determination procedure was carried out with this method. After this optimization, AML and TLM were determined by simultaneously changing their equal concentrations (Figure 5).

Table 1 also presents the analytical characteristics and calibration data obtained for simultaneous determination of AML and TLM by SWV.

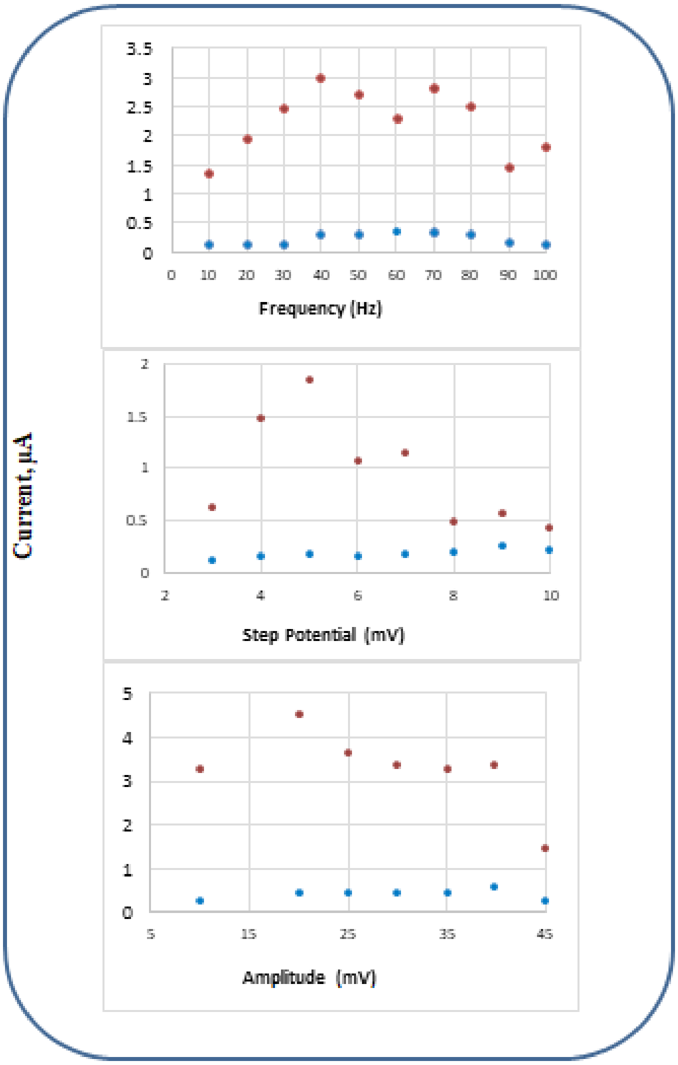


Figure 3. Optimization of SWV parameters (frequency, step potential and amplitude).

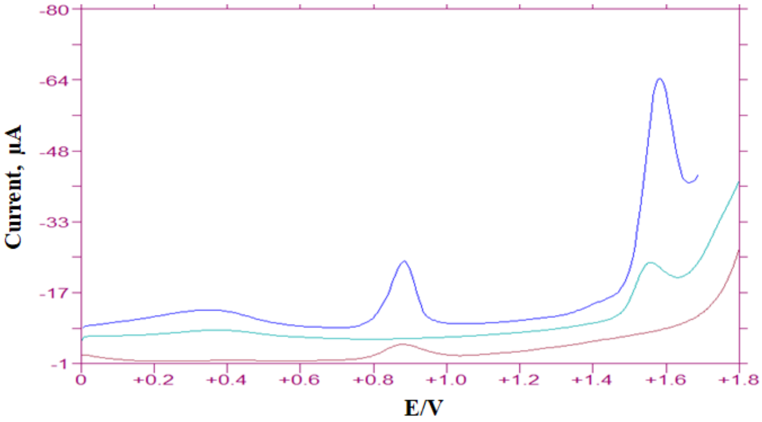


Figure 4. SW voltammograms with red line, 1.0×10^{-4} M AML and green line 1.0×10^{-4} M TLM under unoptimized conditions; blue line, 1.0×10^{-4} M AML and 1.0×10^{-4} M TLM under optimized conditions as f= 70 Hz, amplitude= 20 mV, step potential= 5 mV.

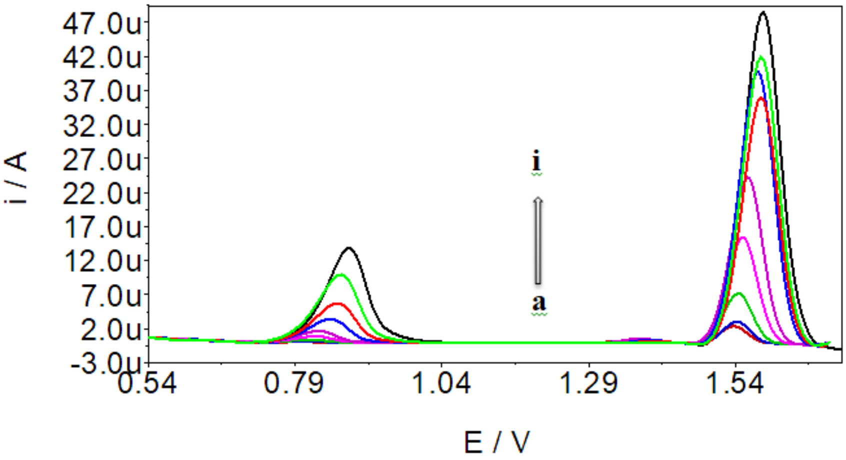


Figure 5. SW voltammograms obtained for the oxidation of AML and TLM in 0.5 M H_2SO_4 solution, using GCE. The concentrations of AML and TLM were changed simultaneously as, a.) 0.1 µM, b.) 0.5 µM, c.) 1.0 µM, d.) 2.5 µM, e.) 5 µM, f.) 10 µM, g.) 25 µM, h.) 50 µM, i- 100 µM .

Table 1. Regression data of the calibration line for quantitative determination of AML and TLM by SWV method.

SWV		
	AML	TLM
Measured Potential (V)	0.879	1.553
Linearity Range (M)	$1.0\times10^{-7} – 1\times10^{-4}$	$1.0\times10^{-7} – 1.0\times10^{-5}$
Slope ($\times10^3$)	198.47	3830.64
Intercept	0.345	2.207
Correlation coefficient	0.999	0.999
SE. of slope ($\times10^3$)	3.036	29.89
SE. of intercept	0.1165	0.1502
LOD (M)	6.54×10^{-10}	2.26×10^{-8}
LOQ (M)	2.18×10^{-9}	7.54×10^{-8}
Within-day measurement of peak current (RSD %)	0.94	1.84
Within-day measurement of peak potential (RSD %)	0.33	0.18
Between-day of peak current (RSD %)	1.90	1.95
Between-day of peak potential (RSD %)	0.54	0.39

The interference of each analyte for the simultaneous determination of its pairs was applied by increasing the concentration of one compound linearly in the presence of unchanging concentrations of the other compound. Electroanalytical interference effects of these two compounds on each other were investigated in the 0.5 M H_2SO_4 by SWV (Figure 6).

The determination of AML in the concentration range between 5.0×10^{-7} M and 1.0×10^{-5} M was accomplished in solutions containing TLM at the fixed concentration of 2.5×10^{-6} M. On the other hand, the determination of TLM in the concentration range of 5.0×10^{-7} to 1.0×10^{-5} M was accomplished in solutions containing AML at the fixed concentration of 2.5×10^{-6} M. The tolerance limits of compounds were evaluated as the maximum concentration of the other compound, which caused a relative error of lower than 2% in the determination of AML or TLM. Within-day and between-day measurements of peak currents and potentials were checked by successive measurements (n= 5) of both compounds from their fresh solutions.

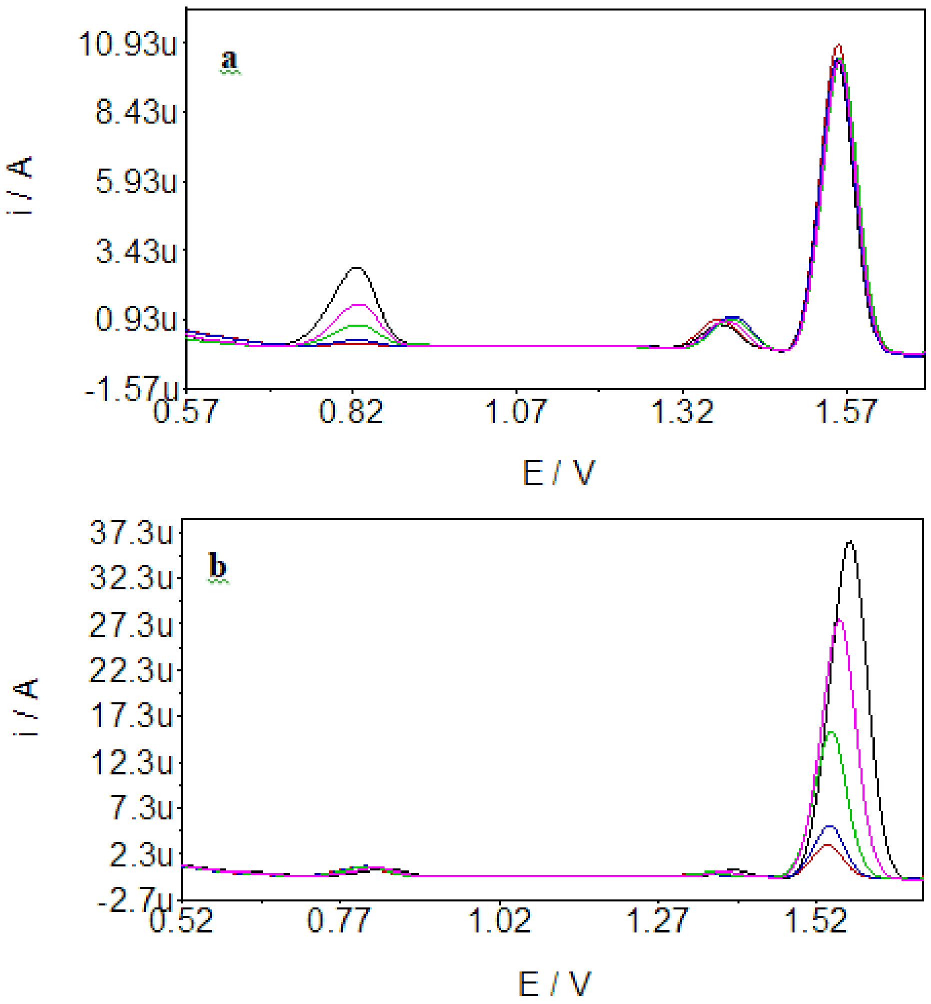


Figure 6. SWV curves obtained with binary mixtures of a) 5×10^{-7} M, 1×10^{-6} M, 2.5×10^{-6} M, 5×10^{-6} M, 1×10^{-5} M AML and constant 2.5×10^{-6} M TLM, b) 5×10^{-7} M, 1×10^{-6} M, 2.5×10^{-6} M, 5×10^{-6} M, 1×10^{-5} M TLM and constant 2.5×10^{-6} M AML, in 0.5 M H_2SO_4 solutions.

Analysis of Pharmaceutical Dosage Form

Twynsta ® tablet was analyzed to determine AML and TLM in order to evaluate the validity of the developed methods. Each Twynsta® tablet contains 10 mg of AML and 80 mg of TLM with ingredients such as sorbitol, colloidal anhydrous silica brilliant blue FCF, ferric oxide black, ferric oxide yellow, magnesium stearate, maize starch, meglumine, microcrystalline, povidone K25, pregelatinised starch, sodium hydroxide. A known amount of Twynsta® was evaluated by determining AML and TLM in commercial preparete. The utility of all of the proposed methods was verified by means of replicate estimations of commercial preparetes and the results obtained were evaluated statistically. Table 2 shows the results for commercial preparates.

The recovery of the procedure was applied by spiking the already analyzed samples of tablet with the known amounts of standard solutions of AML and TLM. The results of the recovery study for the developed method are given in Table 2. It is showing that the developed method is sufficiently accurate and precise in order to be applied to commercial form of AML and TLM. High percentage recovery data also shows that the developed method is not affected from the ingredients used in the formulations. To check accuracy of developed method, possible interferents such as ascorbic acid, dopamine, glucose, and sodium chloride were individually added into the standard solution containing 2.5×10^{-6} M AML and 2.5×10^{-6} M TLM. K^+, Mg^{2+}, Cl^- ions had no effect on signals at a concentration of about 100-fold of AML and TLM.

CONCLUSION

In this work, electrochemical simultaneous detection of amlodipine and telmisartan which are antihypertensive drugs were successfully applied by square wave voltammetry. Electrochemical behaviors of both drugs in aqueous solutions were investigated. The irreversible

Table 2. The results for the determination of AML and TLM from tablet dosage form and recovery experiments.

Parameters	SWV	
	AML	TLM
Labeled claim (mg)	10.00	80.00
Amount found (mg)	10.11	80.58
RSD %	1.64	0.37
Bias %	-1.07	-0.72
Added (mg)	10.00	80.00
Found (mg)	10.002	79.386
Average recovered (%)	100.02	99.23
RSD % of recovery	0.71	0.73
Bias %	-0.02	0.77

redox reactions were seemed for both of them. A rapid, reliable, repeatable, precise electrochemical method was developed for simultaneous fast quantification of amlodipine and telmisartan. Under optimized and validated square wave voltammetry, current answers of both drug significantly increased. Recovery experiments also presented that the proposed method was not influence from the species in tablet dosage forms. Till present, no electrochemical method was reported for simultaneous determination of amlodipine and telmisartan in tablets. The scientific novelty of the present work is that the suggested voltammetric method is fast, simple, selective, less expensive and less time consuming compared with other published methods and could be used for clinical routine analysis.

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