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Research Article

Determination of Nifedipine in Pharmaceutical Preparations by Square Wave Voltammetry Method

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Abstract

In the present study, the electroanalytical behaviour of nifedipine was investigated by cyclic voltammetry method. The method was based on nifedipine being electrochemically oxidized at a platinum electrode in nonaqueous solutions. At 1.16 V, the oxidation peak was noted. It was determined that nifedipine's oxidation was diffusion-controlled. Additionally, a quick and easy square wave voltammetry method was developed and validated in this work to determine nifedipine in pharmaceutical preparations. At concentrations between 5 and 50 μg/mL, the calibration curve is linear. The precision was given by relative standard deviation and was less than 3.96%. Accuracy was given with relative error and did not exceed 2.00%. In pharmaceutical preparations, nifedipine had an average recovery of 100.6%. Under the chosen experimental conditions no interference was found. The suggested method is extremely accurate and precise. Therefore, the method is applicable to the measurement of nifedipine in Adalat Crono tablets as pharmaceutical formulation.

Keywords: Nifedipine, voltammetry, validation, tablet

Farmasötik Preparatlarda Nifedipinin Kare Dalga Voltammetri Yöntemi ile Tayini

Öz

Bu çalışmada, nifedipinin elektroanalitik davranışı döngüsel voltametri yöntemiyle incelenmiştir. Yöntem, susuz çözeltilerde bir platin elektrotta elektrokimyasal olarak oksitlenen nifedipine dayanıyordu. 1.16 V'ta oksidasyon piki kaydedildi. Nifedipinin oksidasyonunun difüzyon kontrollü olduğu belirlendi. Ek olarak, farmasötik preparasyonlarda nifedipini belirlemek için bu çalışmada hızlı ve kolay bir kare dalga voltametri yöntemi geliştirildi ve valide edildi. 5 ve 50 μg/mL arasındaki konsantrasyonlarda kalibrasyon eğrisi doğrusaldır. Kesinlik bağıl standart sapma ile verildi ve %3.96'dan azdı. Doğruluk bağıl hata ile verildi ve %2.00'yi geçmedi. Farmasötik preparasyonlarda, nifedipinin ortalama geri kazanımı %100.6'dır. Seçilen deneysel koşullar altında hiçbir girişim bulunmadı. Önerilen yöntem son derece doğru ve kesindir. Bu nedenle yöntem, farmasötik formülasyon olarak Adalat Crono tabletlerdeki nifedipin ölçümüne uygulanabilir.

Anahtar Kelimeler: Nifedipin, voltametri, validasyon, tablet

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1. Introduction

Nifedipine (Figure 1) is a calcium channel antagonist of the dihydropyridine class that is frequently used to treat vascular diseases such Raynaud's phenomenon, hypertension, and angina pectoris. When taken orally, the lipid-soluble medication nifedipine is quickly and thoroughly absorbed from the digestive tract. Due to extensive first-pass metabolism, nifedipine has a systematic bioavailability of 50-70%, which may cause significant intersubject pharmacokinetic variability. Nifedipine has a 2 to 5 hour elimination half-life [1].

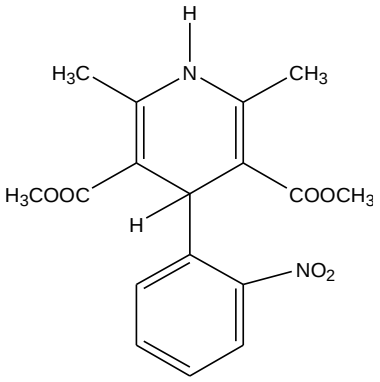

Figure 1. Structure of nifedipine

Several nifedipine determination methods have been published in reports. These include mass spectrophotometric detection, multivariate image analysis, UV or electrochemical detection in conjunction with HPLC [2-5], gas chromatography with electron capture [6-8] and LC-MS/MS [9-10] methods.

According to reports, nifedipine's spectrophotometric detection involves interactions with oxidation of the medication with iron(III) [11,12], subcritical water extraction of the medication [13], reaction of the medication's nitro group with potassium hydroxide in dimethyl sulfoxide medium [14] and reduction of the medication with zinc/naphthalene chloride followed by coupling with N-methyl-1,4-benzoquinon [15]. A thorough review of the literature revealed that there are several chromatographic techniques for determining the presence of nifedipine in human plasma, while the quantitative determination of nifedipine in pharmaceutical formulation samples has only been covered in a small number of other publications [7, 9, 12].

An extensive literature analysis revealed a variety of chromatographic techniques for assessing the presence of nifedipine in human plasma. Endogenous interference, probable drug loss during re-extraction, arduous and time-consuming procedures for preparing and extracting plasma samples, and the requirement for high-end, pricey equipment all had an impact on the revealed procedures.

It's critical to develop a new formula for figuring out how much medication is in pharmaceutical dose forms. Numerous therapeutic substances have been identified using electroanalytical techniques, which have the advantages of frequently not requiring derivatization and being less susceptible to matrix effects than other analytical techniques. Identifying electrode mechanisms is another use of electrochemistry [16-19]. Drugs' redox characteristics may provide

information on their pharmacological effectiveness, in vivo redox activities, or metabolic destiny.

Although the electrochemical behavior and oxidation mechanism of nifedipine have analytical significance, no research on the voltammetric oxidation of nifedipine in nonaqueous media has been published. It is widely known that the electrochemical process and voltammetric response of pharmaceuticals are directly influenced by the experimental and operational parameters. So, it would be interesting to look at how nifedipine oxidizes in aprotic environments. However, the voltammetry method has not yet been used to quantitatively assess nifedipine using a platinum electrode.

This study describes Square Wave Voltammetry (SWV) method using a platinum disc electrode to determine nifedipine using simple, quick, and selective processes that have been completely verified. Also, the method was effectively used to evaluate the consistency of the formulation content and to quantitate a commercially available nifedipine medication for QC.

2. Materials and Methods

2.1. Chemicals and reagents

Nifedipine standard (98≥ purity), lithium perchlorate ($LiClO_4$) and acetonitrile were purchased from Sigma (Germany). The nifedipine-containing Adalat Crono tablets were bought at a pharmacy in Erzurum, Turkey.

2.2. Electrochemical instrumentation

Electrochemical experiments were carried out on a Gamry Potentiostat Interface 1000. The single-compartment electrochemical cell used for all tests has a conventional three-electrode setup. Platinum wire served as the counter electrode and a platinum disk served as the working electrode. On microcloth pads, 1.0, 0.3, and 0.05 μm alumina slurries were used to incrementally polish the working electrode. The reference electrode for each potential was made of Ag/AgCl/KCl (3.0 M). The SWV was operated at pulse amplitudes of 25 mV, 10 Hz, 4 mV potential step and 0.1 V s^{-1} scan rate.

2.3. Preparation of standard and quality control samples

In 0.1 M $LiClO_4$/acetonitrile, the stock standard solution of nifedipine (100 μg/mL) was prepared. This stock solution was used to prepare working standard solutions. The concentrations of the standard solutions were 5, 7.5, 10, 15, 20, 25, 30, 40 and 50 μg/mL. The QC solutions were made at 7.5, 25 and 45 μg/mL concentrations.

2.4. Statistical analysis

With the use of a computer program, SPSS V.15.0 was used for the statistical analyses. The nifedipine standard line and calculations were made using regression analyses. The mean and standard deviation of the results were provided.

3. Results and Discussion

3.1. Method development and optimization

At the Pt disc electrode, the electrochemical behavior of nifedipine was studied. The supporting electrolyte in cyclic voltammetry was an acetonitrile solution with 0.1 M $LiClO_4$. Figure 2 depicts a typical cyclic voltammogram for 100 µg/mL nifedipine at 0.1 V s^{-1} scan rate. The oxidation peak was seen in the anodic sweep at 1.16 V.

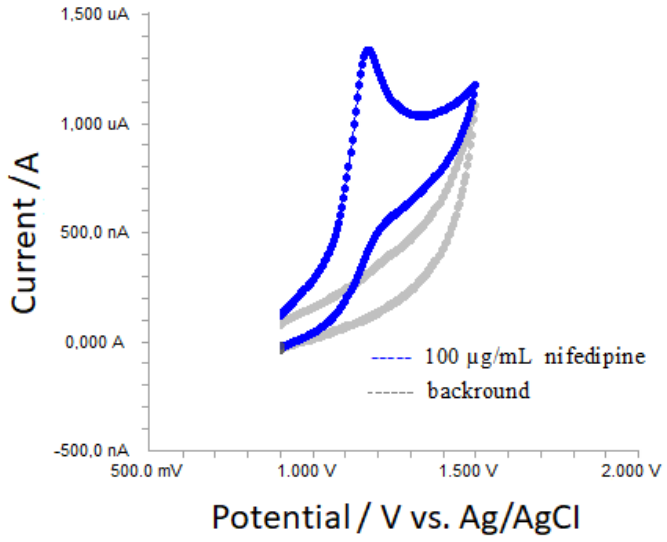

Figure 2. Cyclic voltammogram of nifedipine (100 µg/mL)

The influence of scan rate on the anodic peak currents and peak potentials was investigated in the range of 0.01-1 V s^{-1} of the potential scan rates in order to better understand the voltammetric waves (Figure 3).

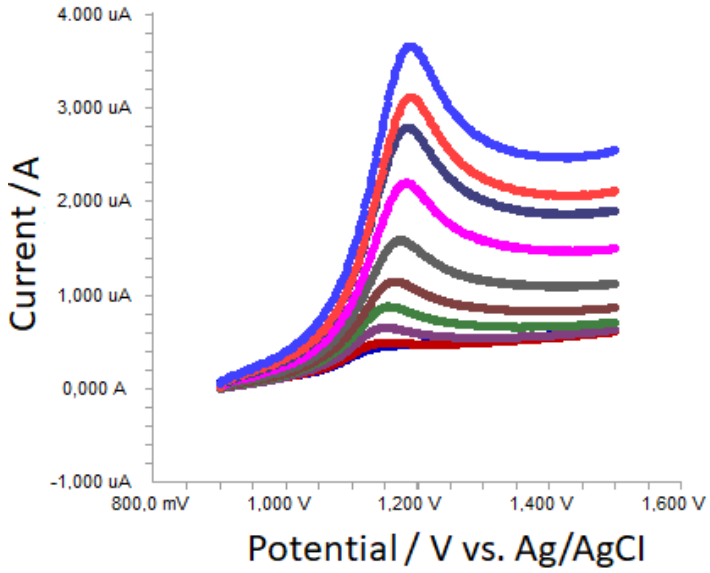

Figure 3. Linear sweep voltammograms of 20 µg/mL nifedipine as a function of scan rate

Figures 4a,b display the linear sweep voltammograms for nifedipine as a function of scan rate. However, the logarithm of peak currents against logarithm of scan rates graphs at nifedipine concentrations of 20 µg/mL show straight lines with a slope of 0.42, which is close to the predicted value of 0.5 anticipated for an ideal diffusion-controlled electrode process [20].

This should be done using the *log I-log v* curve, therefore a diffusional process for the peak should be taken into consideration. The redox species quickly diffuse from the solution rather than precipitate onto the electrode surface, according to these data. This phenomenon may be caused by the solubility of the intermediate species in acetonitrile.

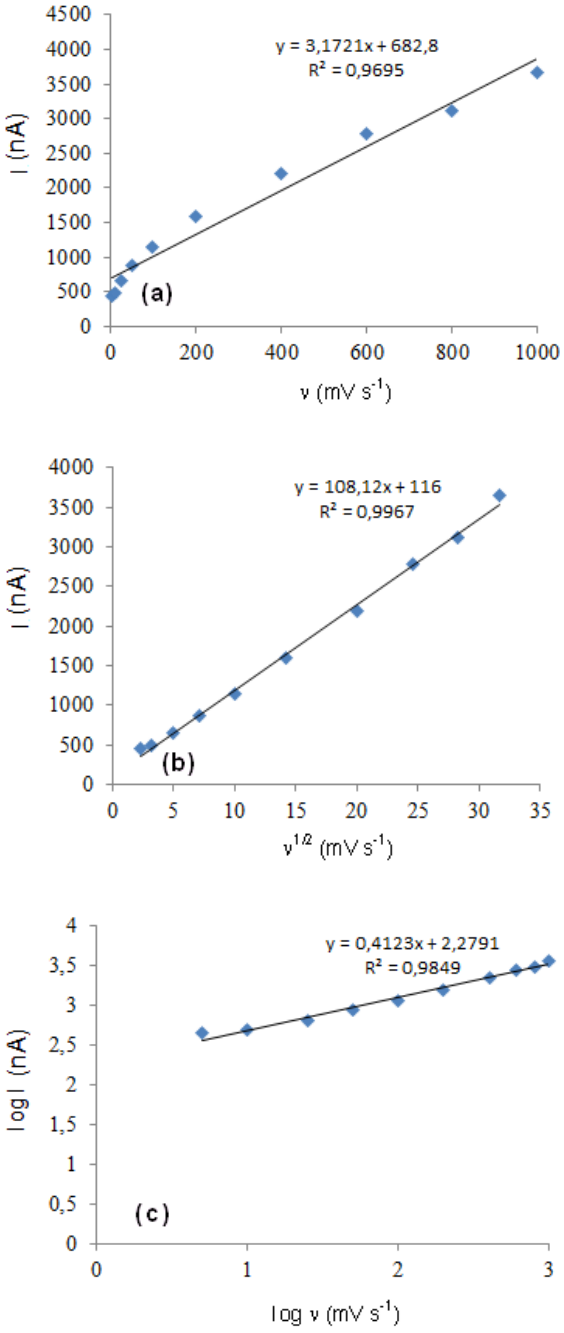

Figure 4(a-c). Scan rate dependence on the peak current (20 µg/mL)

As the scan rate is raised, Figure 3 depicts how the oxidation peak potential *(E_{pa})* for peaks moves toward more positive values. The equation below describes the relationship between the peak potential and scan rate [21].

$$E_{pa} = E^{0'} + RT/[(1-\alpha)n_aF][0.78 + \ln(D^{1/2}k_s^{-1}) - 0.5\ln RT/[(1-\alpha)n_aF]] + RT/[(1-\alpha)n_aF]/2\ln\nu$$

The plots of the oxidation peak potentials against *ln v* demonstrate a linear connection in accordance with this equation (Figure 5).

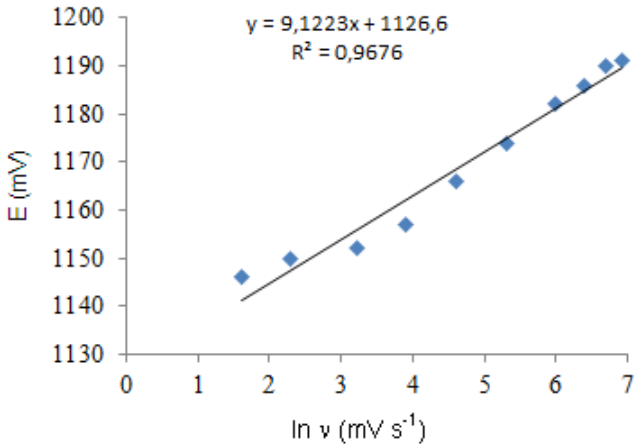

Figure 5. Dependency of the nifedipine anodic peak potentials on the scan rate

The slope indicates that the highest value of αn is 0.75. Additionally, this value shows that the processes of electron transfer are completely irreversible. This outcome demonstrates that the chemical step is a charge transfer and a quick following reaction.

3.2. Validation of the method

ICH Q2B guidelines were followed while determining the validation parameters [22]. These criteria include specificity, linearity, precision, accuracy, recovery, limit of detection (LOD), limit of quantification (LOQ), robustness and stability.

3.2.1. Selectivity

In this study, it was investigated the potential interferences of common excipients and additives. The QC samples were prepared and examined. At the concentrations present in dosage forms, there is no evidence of any interference from these chemicals. The excipient employed in this formulation was one that the pharmaceutical industry employs most frequently. The method's specificity was examined by keeping an eye out for any interference from common tablet ingredients like talc, lactose, sodium chloride, titanium dioxide and magnesium stearate. These exceptions had no negative effects on the suggested method. The procedure might be selective in accordance with the findings of the analysis.

3.2.2. Linearity

Standard solutions at concentration of 5, 7.5, 10, 15, 20, 25, 30, 40 and 50 µg/mL were prepared for SWV (Figure 6). Plotting the nifedipine concentration versus peak current responses allowed for the construction of the calibration curve for the nifedipine (Figure 7).

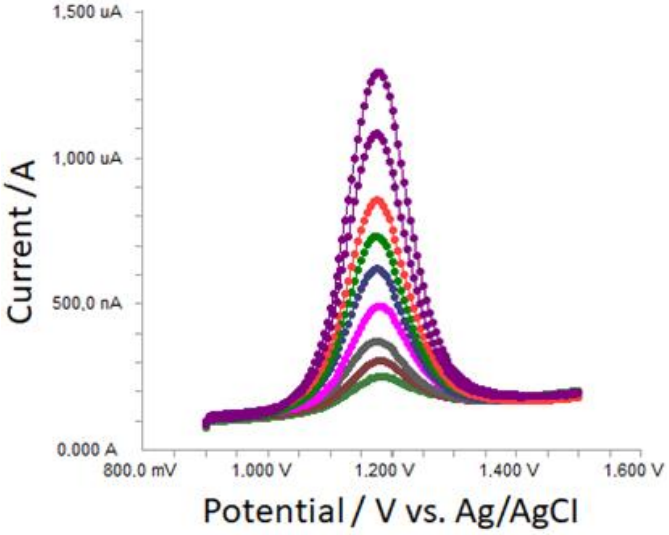

Figure 6. SWV voltammograms of nifedipine (5-50 µg/mL)

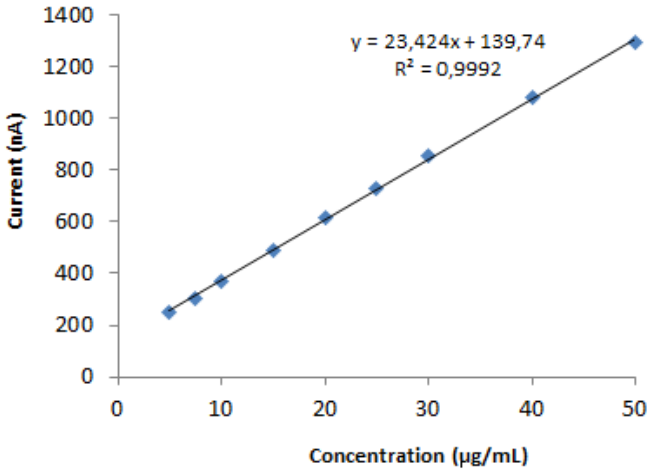

Figure 7. Calibration curve of nifedipine (5, 10, 15, 20, 25, 30, 40 and 50 µg/mL)

All of the calibration curves' correlation coefficients (r) were consistently higher than 0.99. Using the least squares method and the Microsoft Excel® application, the linear regression equations were derived and described in Table 1.

Table 1. Linearity of nifedipine

Parameter	Nifedipine
Linearity range (µg/mL)	5-50
Slope	23.524
Intercept	139.74
Correlation coefficient	0.9992
LOD (µg/mL)	0.90
LOQ (µg/mL)	2.70

3.2.3. Precision and accuracy

Using the QC samples, the SWV method's precision and accuracy were assessed for intra-day and inter-day. The same-day analysis of the QC samples served to assess intra-day precision and accuracy. It was able to assess the precision and accuracy between days by contrasting the assays performed on two distinct days. The intra-day accuracy ranged from 0.04% to 1.55%, while the precision ranged from 1.58% to 3.56% (Table 2). It is evident from the results that this process has good accuracy and precision.

Table 2. Precision and accuracy of nifedipine

	Intra-day			Inter-day		
Added (µg/mL)	**Found ± SD[a]**	**Precision % RSD[b]**	**Accuracy[c]**	**Found ± SD[a]**	**Precision % RSD[b]**	**Accuracy[c]**
7.5	7.38±0.12	1.58	-1.55	7.47±0.10	1.38	-0.44
25	25.01±0.89	3.56	0.04	24.83±0.98	3.96	-0.67
45	45.33±1.03	2.28	0.74	45.67±1.03	2.26	1.48

3.2.4. Recovery

To evaluate the effects of formulation interference, the recovery was investigated at three different concentrations. The recoveries were done by combining nifedipine tablet samples that had already undergone analysis with a known quantity of pure medications. The recoveries were calculated by comparing the amounts recovered from the spiked samples with the actual added concentrations. The results are listed in Table 3.

Table 3. Recovery of nifedipine in tablets (n=6)

Tablet	Found ± SD	%Recovery	%RSD[a]	Confidence Interval
Adalat Crono (30 mg/tablet)	30.2±0.51	100.7	1.69	29.2- 31.3
	29.3±0.44	98.7	1.49	28.6- 30.2
	30.8±0.67	102.3	2.18	29.3- 31.4
Adalat Crono (60 mg/tablet)	59.2±1.29	98.8	2.18	58.6-61.2
	61.1±1.33	101.8	2.21	60.3-62.1
	58.9±1.22	98.2	2.07	57.9-61.6

3.2.5. LOD and LOQ

The LOD and LOQ values of the proposed method were determined using calibration standards. The computed values for LOD and LOQ were 3.3 and 10/S, respectively [22]. The results are summarized in Table 1.

3.2.6. Ruggedness

The same instrument and standard standard solution were used in this study by a separate analyst to assess the concentration of nifedipine (Table 4). No statistically significant discrepancies between the operators were found in the results, indicating the ruggedness of the developed method.

Table 4. Results of another analyst's studies of nifedipine (n=6)

Added (µg/mL)	Found (µg/mL) (Mean±SD)	% Recovery	% RSD[a]
5	5.1 ± 0.18	102.0	3.53
15	14.8 ± 0.25	98.7	1.69
35	35.2 ± 1.67	100.6	4.74

3.2.7. Stability

The stability of the medication was established since it is known that nifedipine deteriorates in light. Standards of 10, 25 and 50 µg/mL nifedipine were examined for a week under various circumstances in the dark at 4 °C and in the light at room temperature (25 °C) to assess stability. The solutions were reanalyzed against recently generated standard solutions after 2, 4, 8, 12, 24, and 48 h (light, 25°C), and 2, 4, 8, 12, 24, and 48 h (dark, 4°C) respectively (Table 5). The findings demonstrate the stability of nifedipine standards, with recoveries >93% for up to 2 hours when stored in light at 25°C and for up to 2 days when stored in darkness at 4°C.

Table 5. Stability of the nifedipine (n=3)

	Time	Recovery (%)	% RSD[a]
Light (25°C)	Initial	100.1	2.92
	2 h	93.5	1.97
	4 h	87.9	3.67
	8 h	83.6	2.03
	12 h	73.8	3.78
	24 h	68.9	2.47
Dark (4°C)	Initial	99.8	3.28
	2 h	98.6	1.99
	4 h	97.4	4.04
	8 h	96.2	3.01
	12 h	95.3	1.67
	24 h	95.8	3.16
	48 h	94.9	2.93

3.3. Procedure for pharmaceutical preparations

Each Adalat Crono tablets, which contains 30 or 60 milligrams of nifedipine, was precisely weighed and finely powdered. A suitable amount of powder was dissolved in 50 mL of 0.1 M $LiClO_4$/acetonitrile. Then, the final volume was made up to 100 mL in a balloon flask. Whatman filter (paper no 42) was used to filter the tablet solutions after they had been properly diluted in order to provide a final concentration that was within the linearity constraints of the SWV method (Figure 8). The calibration curve was used to determine the drug concentration for nifedipine.

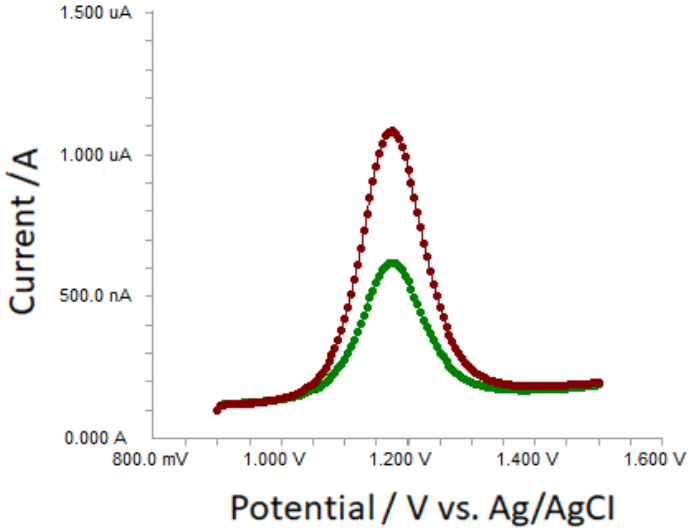

Figure 8. The voltammograms of Adalat Crono tablet containing nifedipine (25 and 40 µg/mL)

Additionally, the presented SWV voltammetric method was statistically evaluated with the reported methods [14-16] using the F-test. The estimated F-values do not surpass the theoretical values at a 95% confidence level (Table 6). Consequently, the differences between the methods are negligible.

Table 6. Comparison of the proposed and reported methods for determination of nifedipine

Parameter	Proposed SWV	Reported Method [14]	Reported Method [15]	Reported Method [16]	Reported Method [24]
Mean (Recovery %)	100.6	99.9-100.1	98.7-100.5	99.5-101.3	99.9-100.1
SD	2.49				
%RSD	2.45	0.52	0.60	1.50	0.72
Variance	5.95				
F-test	3.78				

The analytical findings in this investigation showed that the level of active ingredient in the medicine is within the reported method's recommended range. The developed method was demonstrated to be practical, accurate, and adaptable to drug dose forms. Therefore, developed SWV method can be advised for the routine QC analyses of nifedipine in pharmaceutical preparations.

3.4. Comparison of the methods

Nifedipine is covered in a monograph in the State Pharmacopoeia of Ukraine [25]. The SPhU offers melting point analysis, infrared absorption spectrophotometry, qualitative TLC analysis of the development of azo dye following the earlier restoration of the nitro group to amino group, and quantitative analysis of the content of nifedipine. The definition of nifedipine in pharmaceuticals and tablet form is governed by the United States Pharmacopoeia. Identification is recommended using the definitions of UV-spectrophotometry and infrared absorption spectrophotometry. Nifedipine in pills should be precisely measured using the HPLC method.

An extensive literature analysis revealed a variety of spectrophotometric methods for the determination of nifedipine in pharmaceutical preparations. In these studies, the amount of nifedipine in single and mixed dose forms was estimated using first order [26] and second order [27] derivative spectra, respectively. The amount of the drug was calculated based on its reactions with the folin-Ciocalteau reagent [26] and chloranil [28].

Also, two spectrophotometric methods have been developed based on the drug's interactions with potassium hydroxide in dimethyl sulfoxide and ammonium molybdate in acidic buffer

solution to yield colorful products with absorbance peaks at 430 nm and 830 nm, respectively [14]. A kinetic spectrophotometric method has also been reported [29] based on the drug's oxidation with $KMnO_4$ at neutral pH. The other spectrophotometric method was based on Rahman et al.'s [15]. Zn/NH_4Cl reduction of the nitro group of nifedipine to hydoxylamino derivatives. Extractive spectrophotometric methods have also been published for the measurement of the drug concentration in pharmaceutical formulations [24]. These methods rely on the colorful drug complex made with dyes such eriochrome black-T, bromocresol green, bromophenol blue and bromothymol blue.

The recommended SWV approach was compared to other methods from the literature. Furthermore, statistical comparisons between the results obtained by the specified method and those produced by the suggested methodology were done [14, 19, 24]. A statistical analysis of the data using the variance ratio F test revealed no appreciable differences between the performance of the suggested and reference procedures (Table 6). We found that the calculated F-values did not significantly surpass the theoretical values, which led us to the conclusion that the suggested method does not significantly deviate from spectrophotometric procedures.

4. Conclusion

The cyclic voltammetry method has been used in the current study to examine the electrochemical behavior of nifedipine in nonaqueous media. Additionally, a fast, accurate, simple and precise SWV method for nifedipine detection in pharmaceutical formulations was developed and validated in the study. The method makes it possible to quickly analyze a number of samples. Therefore, the method can be used to regularly monitor nifedipine, both in its formulations and pure form.

Author Contributions

The author contributed to laboratory examinations and writing manuscripts.

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