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ARTICLES

Square-Wave Adsorptive Stripping Voltammetric Determination of Antihypertensive Agent Telmisartan in Tablets and Its Application to Human Plasma[1]

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Abstract—The adsorptive stripping voltammetry of telmisartan was investigated with a hanging mercury drop electrode. This compound produced a catalytic hydrogen wave at −1.5 V in Britton Robinson buffer of pH 10.38, and the peak current increased with adsorptive accumulation at the electrode. Adsorptive stripping voltammetry with the catalytic hydrogen wave could provide a sensitive novel method for the determination of telmisartan. Various chemical and instrumental parameters affecting the monitored electroanalytical response were investigated and optimized for telmisartan determination. Under these optimized conditions the square-wave adsorptive stripping voltammetric (**SW-AdSV**) peak current showed a linear dependence on drug concentration over the range 0.05–3.00 μg/mL (1×10^{-7}–6×10^{-6} M) ($r = 0.999$) with accumulation for 120 s at −1.0 V vs. Ag/AgCl. The proposed electrochemical procedure was successfully applied for the determination of telmisartan in pharmaceutical tablets and human plasma. The results of the developed SW-AdSV method were comparable with those obtained by reported analytical procedures.

Keywords: square-wave adsorptive stripping voltammetry, telmisartan, tablets, human plasma

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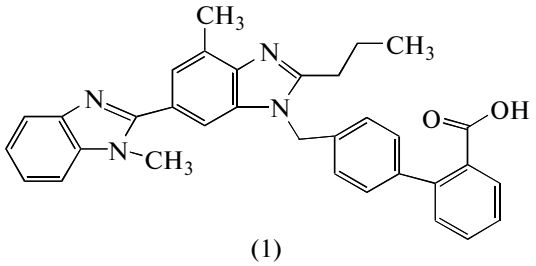
Over the last decade, adsorptive stripping voltammetry (**AdSV**) has been established as a very reliable analytical technique, widely recognized as one of the most sensitive methods in electrochemical chemistry. Hence, the interest in utilizing SW-AdSV technique in the determination and monitoring of a wide range of drugs raised considerably [1].

Telmisartan (1) is 4̄-[(1,4̄-dimethyl-2̄-propyl[2,6̄-bi-1H-benzimidazol]-1̄-yl)methyl-[1,1̄-biphenyl]-2-carboxylic acid. It is a potent, long-lasting, nonpeptide antagonist of the angiotensin II type-1 receptor that is indicated for the treatment of essential hypertension [2].



(1)

The reported methods for the determination of the drug include spectrophotometry [3–5], spectrofluorimetry [5]. electro-analysis [6–8], enzyme immunoassay [9], high performance liquid chromatrography [10], capillary zone electrophoresis [11–13], micellar electrophoresis [14] and liquid chromatography-tandem mass spectrometry [15, 16].

Telmisartan can produce a catalytic hydrogen wave owing to its nitrogen atoms. Surveying the literature revealed that the only polarographic methods reported for telmisartan determination were two methods using linear sweep polarography [6, 7]. In the first method [6], telmisartan was determined in a concentration range of 1×10^{-8}–2×10^{-6} M with a minimum detectability of 1×10^{-8} M and in the second method [7] in a range of 2×10^{-7}–3×10^{-6} M with a limit of detection of 1×10^{-7} M. Another electrochemical method [8] involves the use of sodium dodecyl benzene sulfonate to enhance the electrochemical determination of telmisartan in the concentration range 2.5×10^{-7}–2×10^{-5} M with a limit of detection of 7.5×10^{-8} M.

Till present, no square wave method was reported for determination of telmisartan in tablets or in human plasma. The scientific novelty of the present work is that the suggested polarographic method is simple, selective, less expensive and less time consuming compared with other published methods and could be used for routine analysis.

In this study, an investigation was made for the determination of telmisartan by means of the catalytic hydrogen wave produced by telmisartan accumulated

[1] The article is published in the original.

adsorptively on the hanging mercury drop electrode (**HMDE**) in Britton Robinson buffer of pH 10.38. It was expected that the sensitivity, already high for the catalytic hydrogen wave, would be further increased by the adsorptive preconcentration of the analyte on the HMDE.

EXPERIMENTAL

Apparatus. All SW-AdSV measurements were carried out with the Electrochemical 746VA Trace Analyzer, Metrohm, Herisau, Switzerland. A three-electrode system, composed of a HMDE as the working electrode, an Ag/AgCl reference electrode and a platinum wire as auxiliary electrode, was used. Stirring of the solution in the electrolysis cell was performed using complete stirrer comprising a part of the electrochemical analyzer to provide the convective transport during the preconcentration step. The whole measurements were semi-automated and controlled through the programming capacity of the apparatus. The data were treated through an external printer attached to the two RS 232 interfaces of the 746 VA Trace Analyzer.

A Hanna pH 211 (Romania) pH-meter with combined glass and saturated calomel electrodes was used for the pH measurements of the supporting electrolytes.

Materials and reagents. The de-ionized water used throughout the present study was supplied from Elgastat Micromeg, England.

Pure drug sample of telmisartan was provided by Dr. Reddy's Laboratories Limited Ltd., India. Pharmaceutical preparations containing the drug were obtained from commercial sources.

Britton–Robinson buffer [16] (0.08 M), pH range 2–11; Walpale acetate buffer [17], pH range 3.6–5.6; ammonium chloride/ammonia buffer pH range 8.0–11.0; sodium sulphate 0.1 M; sodium nitrate 0.1 M; and potassium chloride 0.1 M solution (all from Fluka, Switzerland) were prepared by dissolving the material (analytical grade) in specific volumes of de-ionized water and used as supporting electrolytes. Methanol (BDH Ltd., UK) was used to dissolve telmisartan.

Plasma samples were kindly supplied by King Khalid Hospital in Riyadh, KSA.

General analytical procedure. Stock solution (1×10^{-3} M) of telmisartan was prepared in methanol. This solution was further diluted with methanol to give the appropriate concentrations of working standard solutions. Aliquots of these solutions in the concentration range 0.05–3.0 μg/mL (1×10^{-7}–6×10^{-6} M) were transferred into a series of 25 mL volumetric flasks and diluted to the mark with Britton–Robinson buffer of pH 10.38. Each solution was transferred into the electrolysis cell and purged with pure nitrogen. The accumulation potential of −1.0 V vs. Ag/AgCl was applied to a new mercury drop while the solution was stirred at 400 rpm for 120 s. At the end of the accumulation period, the stirring was stopped and a 5 s rest period was allowed for the solution to become quiescent. Then the voltammogram was recorded by scanning the potential towards the negative direction over the range of −1.0 to −2.0 V using the SW mode. All measurements were made at room temperature.

Procedure for tablets. An accurately weighed quantity of the mixed contents of ten pulverized tablets equivalent to 10.0 mg of the drug was transferred into a 50 mL volumetric flask. Then methanol was added to the mark. The flask with its contents were sonicated for 15 min and filtered. The desired concentrations of the drug were obtained by further dilution with methanol. An aliquot volume of this solution was transferred into a 25 mL volumetric flask and diluted to the mark with Britton–Robinson buffer of pH 10.38. The above general analytical procedure was followed. The nominal content of the drug was determined either from a previously plotted calibration graph or from the regression equation.

Procedure for spiked human plasma. Suitable aliquots of telmisartan stock solution containing 0.2–2.0 μg/mL were transferred into centrifugation tubes, and 0.5 mL of human plasma was added to each tube. The solution was mixed with 600 μL of acetonitrile, vortexed at high speed for 1 min and centrifuged at 20000 rpm for 15 min. The supernatant was transferred into a 5 mL centrifuge tube, evaporated to dryness under a stream of nitrogen and proceeded as described above under general procedure.

Procedure for patient samples. A healthy volunteer (male, 25 years old) had been administered one 40 mg tablet after 8 h of fasting. Blood samples were collected after several time intervals: 30 min, 1.0, 1.5, 2, 2.5, 3, and 8 h after administration. The samples were drawn into test tubes containing sodium citrate as anticoagulant and centrifuged at 1500 rpm for 15 min. The supernatant plasma was used for the monitoring of the drug concentration in plasma.

RESULTS AND DISCUSSION

The SW-AdSV determination of telmisartan was based on the catalytic hydrogen wave produced by telmisartan accumulated adsorptively at −1.0 V on the HMDE in Britton–Robinson buffer of pH 10.38. Figure 1 shows the peak of catalytic hydrogen wave at −1.5 V obtained after adsorptive accumulation of telmisartan on HMDE together with the background current recorded in the same conditions.

Optimization of the analytical procedure. *Effect of type and pH of the supporting electrolyte.* The influence of pH on the peak of the catalytic hydrogen wave of 3.0 μg/mL (6×10^{-6} M) telmisartan was examined in Britton–Robinson buffers of different pH values and following pre-concentration for 2 min. The voltammograms exhibited a single well-defined one-electron

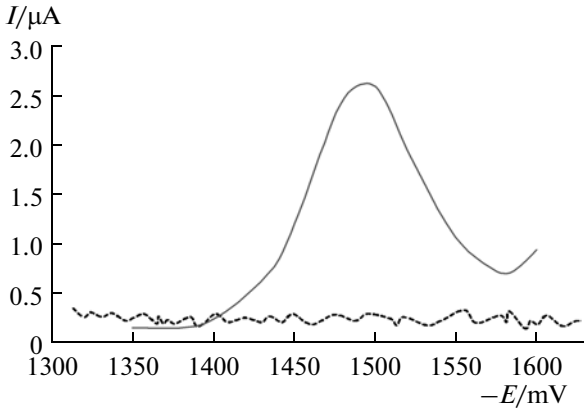


Fig. 1. (—) Peak of the catalytic hydrogen wave obtained after adsorptive accumulation of telmisartan (5×10^{-6} M) on HMDE in Britton–Robinson buffer of pH 10.38; $f = 120$ Hz, $\Delta E_s = 10$ mV; $E_{sw} = 60$ mV; $t_{ac} = 2$ min and $E_{ac} = -1.0$ V, (- - -) background current in the same conditions.

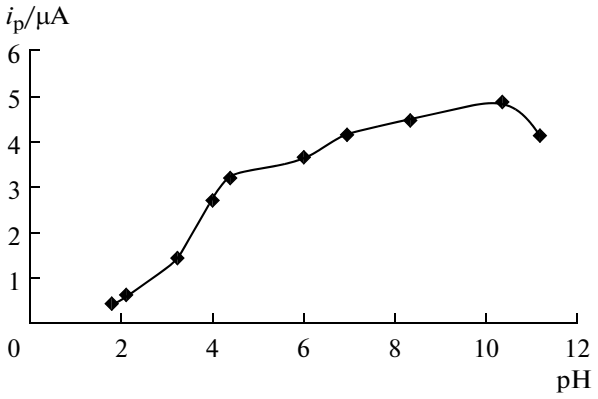


Fig. 2. Influence of pH (Britton–Robinson buffer) on the peak current of the catalytic hydrogen wave produced by telmisartan (4×10^{-5} M), $f = 120$ Hz; $\Delta E_s = 10$ mV; $E_{sw} = 60$ mV; $t_{ac} = 2$ min and $E_{ac} = -1.0$ V (each reading is the average of three replications).

irreversible cathodic peak over the pH range 2–11. As shown in Fig. 2, the peak current intensities (i_p) were recorded at different pH values following pre-concentration for 2 min. A much higher peak current intensity was achieved in Britton–Robinson buffer of pH 10.38. Other supporting electrolytes such as acetate buffer (pH 3.6–5.6), ammonium chloride/ammonia buffer (pH 8–11), sodium sulphate, sodium nitrate and potassium chloride were also tested. However, best performance was obtained in Britton–Robinson buffer of pH 10.38. Therefore, Britton–Robinson buffer of pH 10.38 was used as a supporting electrolyte in the rest of the present work.

Optimization of instrumental operational conditions. The SW-AdSV response of the catalytic hydrogen wave of telmisartan depends on the parameters of the excitement signal. In order to reach a maximum developed SW-AdSV peak current, the optimum instrumental conditions (frequency f, scan increment ΔE_s and pulse amplitude E_{sw}) were chosen for 6×10^{-6} M telmisartan in Britton–Robinson buffer of pH 10.38 following preconcentration for 2 min. At a scan increment of 10 mV and a pulse amplitude of 60 mV, the peak current intensity increased linearly over the frequency range 20–120 Hz following the relationship: i_p (μA) = 0.045f (Hz) – 0.113 ($r = 0.9919$ and $n = 8$). At a frequency of 120 Hz and a pulse amplitude of 60 mV, the peak current intensity increased linearly with the scan increment up to 12 mV following the relationship: i_p(μA) = 0.0415ΔE_s (mV) + 1.238 ($r = 0.9823$ and $n = 6$). Also, at $f = 60$ Hz and $\Delta E_s = 10$ mV, the peak current increased linearly with the increase of the pulse amplitude from 10 to 60 mV, however, the best peak shape and sharpness was obtained at 60 mV. Therefore, the optimal instrumental operational conditions of the proposed square-wave procedure can be concluded as: frequency $f = 120$ Hz, scan increment $\Delta E_s = 10$ mV and pulse amplitude $E_{sw} = 60$ mV.

On the other side, the effect of varying accumulation potential (E_{ac}) from –0.7 to –1.3 V on the peak current intensity of the SW-AdS voltammogram of 6×10^{-6} M telmisartan in Britton–Robinson buffer of pH 10.38 followed preconcentration for 2 min was also evaluated (Fig. 3). A maximum developed peak current was achieved at the potential of –1.0 V. The observed gradual decrease in peak current intensity may be attributed to the consequence of desorption of the drug at higher or lower potential values. Hence, a preconcentration potential of –1.0 V vs. Ag/AgCl was chosen throughout the present study.

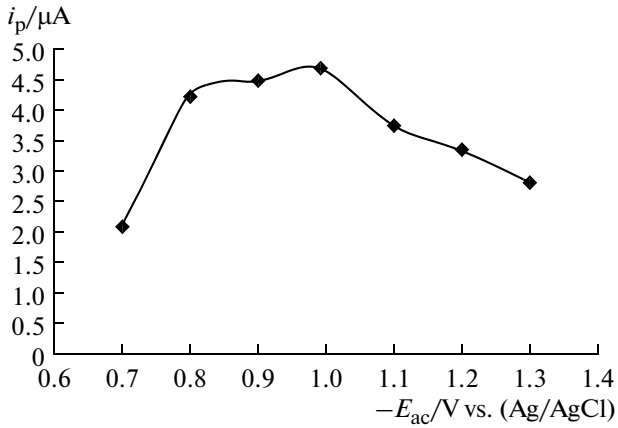


Fig. 3. Effect of accumulation potential on the peak current of the catalytic hydrogen wave produced by telmisartan (4×10^{-5} M) in Britton–Robinson buffer of pH 10.38; other conditions see in Fig. 2.

Table 1. SW-AdSV determination of telmisartan in pure and dosage forms

Drug form	Concentration taken, M	% Found[a]	
		Proposed method	Published method [5]
Telmisartan (pure form)	1×10^{-7}	99.1	
	3×10^{-7}	99.0	
	2×10^{-6}	99.8	
	4×10^{-6}	99.8	
	6×10^{-6}	99.7	
Mean ± SD		99.5 ± 0.4	99.8 ± 0.4[e]
Student's *t*-value		1.03 (2.31)[c]	
Variance ratio *F*-test		1.36 (6.39)[d]	
Micardis tablets[b] (40 mg/tablet)	1×10^{-7}	99.2	
	3×10^{-7}	99.0	
	2×10^{-6}	99.3	
	6×10^{-6}	99.7	
	9×10^{-5}	99.8	
Mean ± SD		99.4 ± 0.3	99.8 ± 0.4[f]
Student's *t*-value		1.73 (2.37)[c]	
Variance ratio *F*-test		1.06 (6.94)[d]	
Micardis tablets[b] (80 mg/tablet)	1×10^{-7}	99.1	
	2×10^{-7}	98.0	
	2×10^{-6}	99.1	
	4×10^{-6}	99.6	
	6×10^{-6}	99.7	
Mean ± SD		99.1 ± 0.64	98.6 ± 0.5[f]
Student's *t*-value		1.37 (2.31)[c]	
Variance ratio *F*-test		1.57 (6.39)[d]	

[a] Each determination is the average of three replications.
[b] Products of Boehringer Ingelheim, Pharma GmbH and Co. KG, Ingelhim am Rehin, Germany.
[c] Tabulated *t*-value at confidence level 95% [19].
[d] Tabulated *F*-value at confidence level 95% [19].
[e] For five different determinations.
[f] For three different determinations.

The effect of accumulation time parameter was studied for 6×10^{-6} M at $E_{ac} = -1.0$ V. It was found that peak height of the catalytic hydrogen wave at −1.5 V is increased by adsorptive accumulation of telmisartan at −1.0 V. The catalytic hydrogen wave obtained after the adsorptive accumulation is sharper than that without accumulation. It is considered that telmisartan adsorbed on the HMDE but not the diffusing from the bulk solution is concerned in the catalytic hydrogen evolution. Thus, for further SW-AdSV quantitative studies for telmisartan, an accumulation time of 2 min was selected as optimal value since it provided relatively high current with the best peak morphology and sharper peaks.

Analytical performance of the developed procedure. *Calibration graph and detection limit*. Under the optimum experimental conditions, the calibration graph for telmisartan was linear over the concentration range of 0.05–3.0 μg/mL (1×10^{-7}–6×10^{-6} M). The parameters of the concentration – current straight line were as follows: i_p (μA) = 1.843*c* + 0.025 ($r = 0.999$), standard deviation of the intercept ($s_a = 0.024$) and of the slope ($s_b = 0.037$). The small values given point to the low scattering of the points around the calibration curve.

The limit of detection (**LOD**) was calculated using the relation ($3.3\ s_a/b$) [18] and was found to be 0.043 μg/mL (8.36×10^{-8} M) where *b* is the slope of the calibration curve.

Accuracy, precision and selectivity. The accuracy of the proposed method was checked by calculating the recovery of known amounts of telmisartan added to Britton–Robinson buffer solution of pH 10.38 and analyzed by the proposed method. A mean recovery of 99.5 ± 0.4% was achieved, as shown in Table 1.

The analytical precision of the developed method was verified by calculating the relative standard deviation that was found to be 2.1%.

The selectivity of the optimized procedure was examined with some common excipients usually present in formulations, e.g. starch, lactose, talc and magnesium stearate. There is no significant effect on the SW-AdSV response of the catalytic hydrogen wave of telmisartan. Accordingly, the proposed procedure can be considered selective.

Analytical applications. *Analysis of dosage forms.* The proposed method was further applied to the determination of telmisartan in its tablets. As can be seen from Table 1, the analytical results achieved by the proposed SW-AdSV procedure were in good agreement with those obtained using the comparison method [5] which involves the measurement of the native fluorescence of telmisartan in NaOH medium.

Statistical analysis of the results obtained using the student's *t*-test and variance ratio *F*-test revealed no significant difference between the performance of the two methods regarding the accuracy and precision, respectively (Table 1). Moreover, the proposed method has some advantages over the reference method such as the wide concentration range and the higher correlation coefficients.

Analysis of spiked human plasma. Table 2 shows the results obtained from spiked plasma. Under the above described experimental conditions, a linear relationship was established by plotting telmisartan concentration against peak current intensity for telmisartan. The con-

Table 2. Assay of telmisartan in spiked human plasma using the proposed method

Conc. Taken, μg/mL	Conc. Found, μg/mL	Recovery, %*
0.2	0.209	104.5
0.4	0.411	102.1
0.5	0.510	102.0
0.7	0.670	97.4
0.9	0.864	96.0
1.0	0.940	95.3
2.0	2.101	105.0
Mean ± SD		101 ± 4

* Each determination is the average of three replications.

centration range was found to be 0.2–2.0 μg/mL. Linear regression analysis of the data gave the following equation: $i_p = 1.104c - 0.053$ ($r = 0.996$), where c is the concentration of telmisartan in μg/mL and i_p is the peak current intensity.

The high value of the correlation coefficient ($r = 0.996$) indicates the good linearity of the concentration graph. Statistical analysis of the data gave the standard deviation of intercept ($s_a = 0.091$) and standard deviation of slope ($s_b = 0.08$), % RSD = 0.041 and the relative error (% Er = 0.014%).

Analysis of patient sample. Telmisartan is readily absorbed after oral administration and the peak concentration is achieved within 0.5 to 1.0 h [19]. The plasma samples obtained from a volunteer were investigated using the previously obtained calibration graph or regression equation and the results obtained are shown in Fig. 4 showing the maximum plasma level reached after 1.0 h. Hence, the proposed method allows for the therapeutic drug monitoring of telmisartan level in plasma.

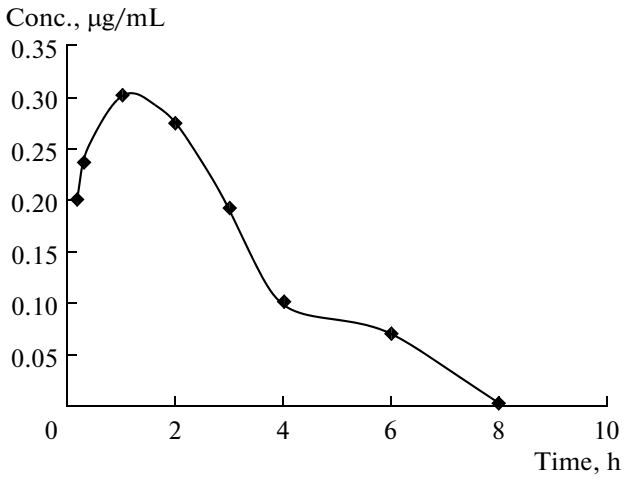


Fig. 4. Monitoring of the blood level of telmisartan in a patient plasma sample (each reading is the average of three replications).

* * *

Although telmisartan has been determined by a variety of techniques [3–16], the method described here is simple, rapid, convenient and does not require special working conditions unlike many other reported methods. The method is advantageous when compared to other reported electrochemical methods [6–8]. It is characterized by short reaction time, low standard deviations, and high correlation coefficients, although it has sensitivity similar to the most sensitive method [6].

The present work describes a validated SW-AdSV method for the determination of telmisartan without interference from common excipients. It could be applied for routine quality control for the studied drug either in bulk or in corresponding dosage forms. The proposed procedure is also suitable for the determination of telmisartan in human plasma, and it seems to be very promising for the therapeutic drug monitoring of patients undergoing chronic treatment with telmisartan.

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