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Stripping voltammetric determination of valsartan in bulk and pharmaceutical products

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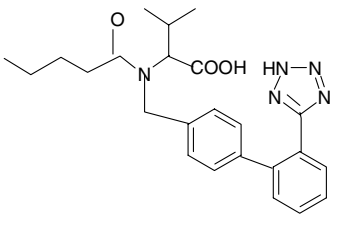
Stripping voltammetric determination of valsartan using a hanging mercury drop electrode (HMDE) was described. The method was based on adsorptive accumulation of the species at HMDE, followed by first harmonic alternating current AC stripping sweep at pH 6. The behavior of adsorptive stripping response was thoroughly studied under various experimental conditions, e.g. type of supporting electrolyte, pH, accumulation time, scan rate and mode of sweep. In Britton-Robinson buffer solution, a quasi-reversible reduction process involving transfer two electrons and two protons was took place. The response was linear over the concentration range of 0.08–0.64 μg/ml with regression coefficient 0.999 and limit of detection 0.02 μg/ml. The average of determinations of the cited compound in oral dosages with its standard deviation was 101.11 ± 4.38%. The result obtained by the proposed method was compared with that obtained by the UV-spectrophotometric technique. Furthermore, the proposed method was successfully applied as stability-indicating method for determining valsartan in the presence of its acid induced degradation products.

1. Introduction

Valsartan (3-methyl-2-[pentanoyl-[[4-[2-(2H-tetrazol-5-yl) phenyl] phenyl] methyl] amino]-butanoic acid) is a new orally active, potent and specific antihypertensive drug belonging to the family of angiotensin II receptor antagonists, either alone, or in conjunction with hydrochlorothiazide (HCZ), a thiazide diuretic. This combination is more effective in patients who are not responding to monotherapy with either agent (Wellington and Faulds 2002).

Limited methods for analysis of cited compound have been reported. These include spectrophotometry (Dinc et al. 2004; Tatar and Saglik 2002; Erk 2002; Cagigal et al. 2001; Satana et al. 2001; Cagigal et al. 2001), high performance liquid chromatography HPLC (Li et al. 2007; Tatar and Saglik 2002; Satana et al. 2001; Koseki et al. 2007; Kristoffersen et al. 2007; Macek et al. 2006; Nie et al. 2005; Chen et al. 2005; Gonzalez et al. 2002; Daneshtalab et al. 2002; Gonzalez et al. 2000; Li et al. 2000; Carlucci et al. 2000; Francotte et al. 1996) and capillary electrophoresis (Hillaert and Van den Bossche 2003, 2002).



Valsartan

Electrochemical methods have proved to be very sensitive for the determination of organic molecules, including drugs and related molecules in pharmaceutical dosage forms and biological fluids. The advance in experimental electrochemical techniques in the field of analysis of drugs is due to their simplicity, low cost and relatively short analysis time when compared to other techniques. Surveying the literature revealed that no electroanalytical methods for determination of valsartan were reported. In the present work, the electrochemical behavior of valsartan on a hanging mercury drop electrode (HMDE) was thoroughly investigated and the optimum conditions for the quantification analysis and for applying as stability-indicating method were studied.

2. Investigations, results and discussion

The electrochemical behavior of valsartan on HMDE was carefully studied in various types of supporting electrolytes and the modified Britton-Robinson (BR) buffer solution was selected because it not only gave the highest peak current but also gave the most symmetric peak shape. Valsartan exhibited one distinct and well-defined cathodic peak at a potential around −1.1 V as depicted by

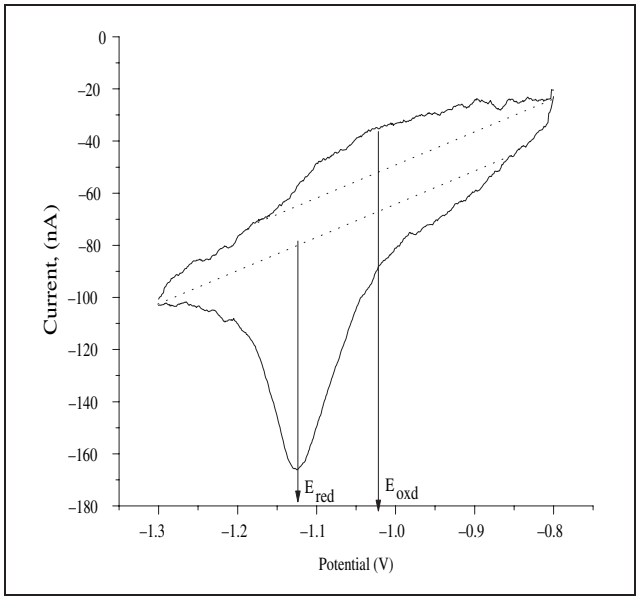


Fig. 1: Cyclic voltammogram showing quasi-reversible reaction of valsartan with reduction peak height greater than oxidation at −1.12 and −1.02 V, respectively

the cyclic voltammogram shown in Fig. 1. A broad and weak peak could also be observed in the anodic scan. The ratio of cathodic and anodic peak heights is greater than one and the distance between both peaks is in the range 60–100 mV suggesting the quasi-reversible nature of the electrode process.

At pH values lower than 5, no reduction peak was noticeable. The cathodic peak current was increased gradually from pH 5 to 6 and then pH becomes independent up to 11 as shown in Fig. 2. Parallel to this behavior the peak potential shifted toward less negative values up to pH 7. This voltammetric behavior may indicate that the electrode process could involve a strong desorption of reduced valsartan on HMDE (Laviron 1974). The pH effect study revealed that protons participate directly in the rate-determining step of reduction process (Zuman 1969). A good linear relation was got in the pH range 5–7 with a slope

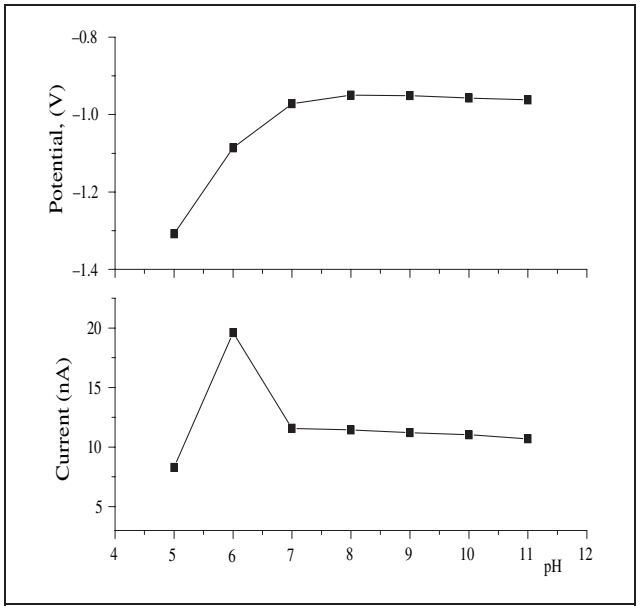


Fig. 2: Variation of pH with peak current and potential using 0.08 μg/ml valsartan at ν = 60 mV/s, ta = 30 s and ΔE = 50 mV

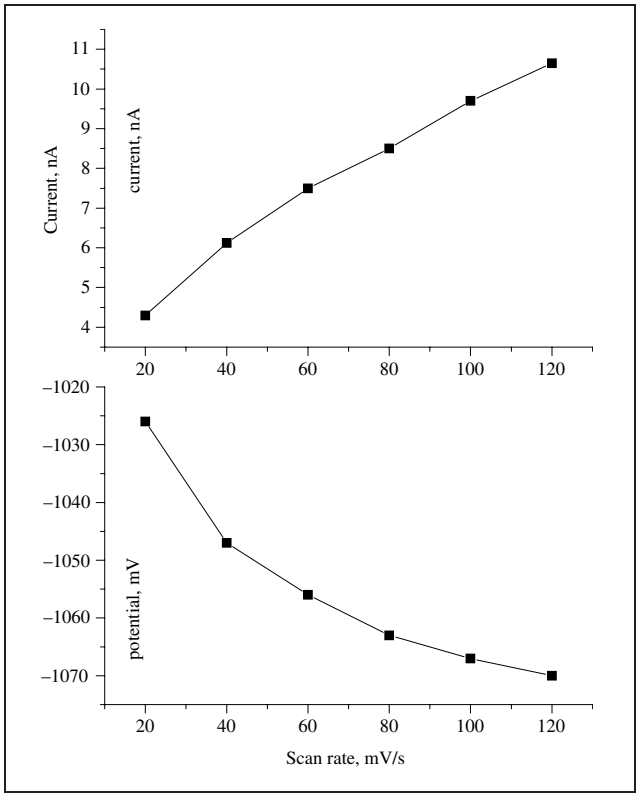


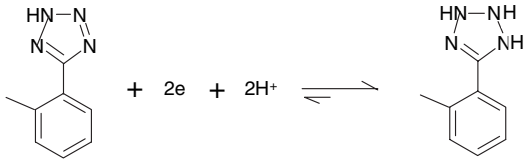
Fig. 3: Effect scan rate ν, on the peak current and potential, using BR pH 6, 0.08 μg/ml valsartan and DP-mode, at ν = 60 mV/s, ta = 30 s and ΔE = 50 mV

0.168 and correlation coefficient r = 0.983. It can be concluded from the expression $\Delta Ep/\Delta pH = 0.059\ p/\alpha n$ that the ratio between protons p and fractional electrons transferred αn is 2.85. For quasi-reversible electrode reaction, the value of αn is found to be 0.77 obtained as an average from the relation $(E_p - E_{p/2}) = 0.048/\alpha n$ at different pH, where $E_{p/2}$ is the potential at half peak current (Zuman 1969).

It can be concluded, from these results, that the number of protons participated p is 2, while that electrons transferred n is 2 (electron transfer coefficient α is selected arbitrary between 0.35–0.5).

The valsartan molecule possesses a carbonyl group, a carboxylic group and a tetrazolyl group. The carboxylic group can be reduced drastically at ca. −2.0 V in organic media (Kanoute et al. 1984). On the other hand, the carbonyl group in most organic compounds can also be reduced at ca. −1.7 V (Ghoneim et al. 2004), which is far away from the true potential of valsartan (at −1.1 V). The azomethine group C=N cannot polarographically reduce in aqueous solution (Elving et al. 1973), but it can be reduced drastically at ca. −1.77 V in organic media (Pekmez et al. 2007). Accordingly, and based on similar behaviors proposed by other authors (Chuang et al. 1965; Holleck et al. 1970; Thomas and Boto 1975), the mechan-

Scheme



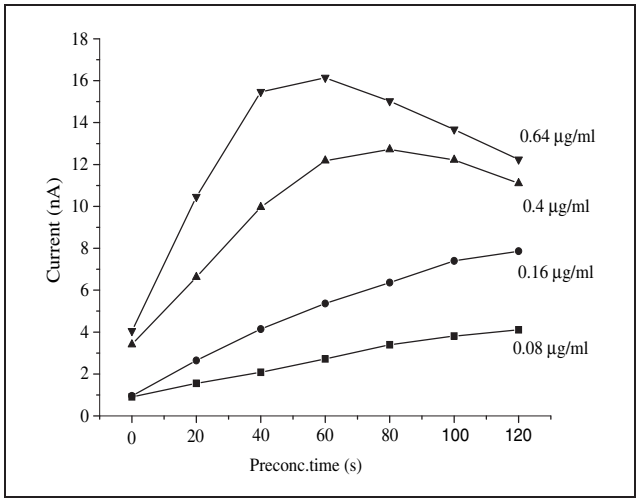


Fig. 4: Effect of accumulation time (ta) at different concentration of valsartan, using DP mode at $\nu = 60$ mV/s, $\Delta E = 50$ mV and pH 6 (0.04 M)

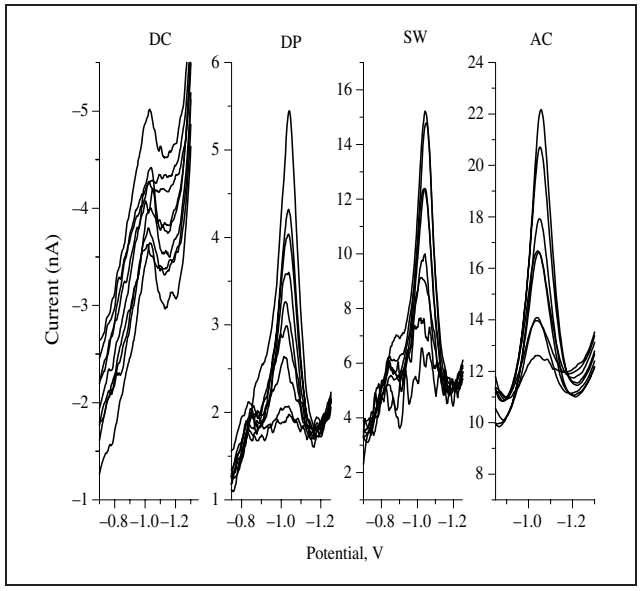


Fig. 5: Effect of different modes of scan over the concentration range of 0.08–0.64 µg/ml with ta = 30 s at $\nu = 20$ mV/s, $\Delta E = 30$ mV and pH 6 (0.04 M)

ism of electrode reaction can be assigned to the reduction of azo group N=N by consuming 2 electrons and 2 protons to form hydrazo group as shown in the Scheme.

Variation of ionic strength at 0.04, 0.1 and 1.0 M supporting electrolyte BR at pH 6, has no distinct effect on the peak current and potential indicating the reduction is predominantly diffusion controlled. Addition of 0.1 ml 0.1 M Na EDTA was necessary to eliminate the interfering effect of zinc on the measurement of valsartan.

The variation of scan rate from 20 to 120 mV/s revealed that the peak current is increased while the potential is shifted to more negative values when the scan rate is increased as shown in Fig. 3, confirming the quasi-reversible nature of the reduction process where the rate of electron transfer is slower than the scan rate. Plotting log I versus log ν gave up a straight line with a slope = 0.5 ($r = 0.999$) which is expected for an ideal reaction of diffused species (Laviron 1980).

The interfacial adsorptive character of the drug on the HMDE was, however, identified from the peak current dependence, upon preconcentration of the drug in BR buffer at pH 6. The peak current increased linearly, as shown in Fig. 4, with increasing the accumulation time for all concentrations studied (0.08–0.64 µg/ml). The deviation from the linearity is observed above accumulation time $t_a = 40$s at high concentration, 0.64 µg/ml valsartan because of the formation of multilayer on the surface of the electrode.

Based on the optimized parameter mentioned above, the curves are constructed using different modes of sweep, viz. direct current DC, differential pulse DP, square wave SW and first harmonic alternating current AC, for the comparison purpose, over the concentration range 0.08–0.64 µg/ml valsartan. As shown in Figs. 5 and 6, the AC mode gave highest proportionality compared with other modes and lowest detection limit at 0.02 µg/ml as explicit in Table 1. It is worth to mention that hydrochlorothiazide (HCZ) could be determined polarographically at pH 9 only (Martin et al. 1999). In the present medium, pH 6, no peak due to HCZ has been detected.

The intra- and interday precision was evaluated by assaying freshly prepared solutions in triplicate on the same day and on three successive days. The repeatability of the

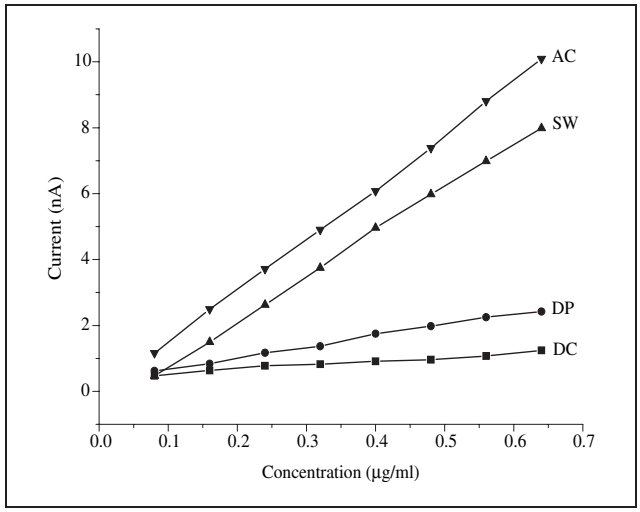


Fig. 6: Effect of calibration curves using different modes of scan over the concentration range of 0.08–0.64 µg/ml with ta = 30 s at $\nu = 20$ mV/s, $\Delta E = 30$ mV and pH 6 (0.04 M)

Table 1: Regression parameters for the determination of valsartan using different modes of sweeps

	DC	DP	SW	AC
Slope	1.14 ± 0.096	3.34 ± 0.094	13.59 ±0.155	15.81 ± 0.17
Intercept	0.46 ± 0.04	0.35 ± 0.038	−0.61 ± 0.063	−0.116 ± 0.07
Regression coef.	0.983 ± 0.04	0.998 ± 0.049	0.9996 ± 0.08	0.9996 ± 0.09
L.O.D. (µg/ml)	0.11	0.04	0.02	0.02
Concentation range (µg/ml)	0.16–0.64	0.08–0.64	0.08–0.64	0.08–0.64

Table 2: Determination of valsartan in pharmaceutical tablets using the alternating current method

Trade name (mg valsartan/tablet)	Found*, mean ± sd%	
	Proposed	Reference
Tareg, 40 mg	100.53 ± 4.54	100.82 ± 3.79
Co-Tareg, 80 mg	99.23 ± 4.9	100.03 ± 4.12
Mean ± SD	100.11 ± 4.38	100.21 ± 4.32
t-test ($t_{theor} = 2.26$ at n = 10)	0.76	
F-test ($F_{theor} = 3.18$ at n = 10)	1.03	

*Average of five determinations

results obtained by means of the proposed AC voltammetric procedure was examined by performing five replicate measurements for 0.48 μg/ml VAL following pre-concentration for 30 s. Mean recoveries of 99.75 ± 0.8 and 98.53 ± 1.24% (n = 5) on the same day and on three success days were achieved, respectively, that indicated high precision of the proposed procedure and is suitable for quality control of valsartan.

The optimized parameters were also applied for determining valsartan in Egyptian pharmaceutical products, viz. Tareg and Co-Tareg containing 40 and 80 mg/tablet valsartan alone or in combination with 12.5 mg hydrochlorothiazide (HCZ), respectively, using the standard addition technique as given in Table 2. Hydrochlorothiazide and additives did not interfere with the measurement. The average value measured by the alternating current adsorptive stripping voltammetry with its relative standard deviation was 100.53 ± 4.54% for valsartan alone and 99.23 ± 4.9 in the presence of HCZ showing that they were in good agreement with those obtained using UV first derivative spectrophotometry as a reference method (Satana et al. 2001). The results show that the calculated t- and F-values did not exceed the theoretical values at 95% confidence level (Miller and Miller 1993).

Stability testing of valsartan was performed under various stress conditions in order to assure the selectivity and provide an indication of the stability-indicating properties of the proposed voltammetric method. Thus, the acid effect on the stability of valsartan is depicted in Fig. 7 where 83 and 90% degradation of valsartan proceed rapidly within the first hour in 1.5 and 5 M HCl, respectively and a plot of log concentration versus degradation time exhibits a linear relationship with a slope −0.28 (R = 0.990) representing the rate of first order degradation. The sample preparations did not exhibit any degradation peaks that could interfere with the reduction peak of valsartan. No degradation was seen in hydrogen peroxide oxidation and alkaline degradation (Fatahalla 2002).

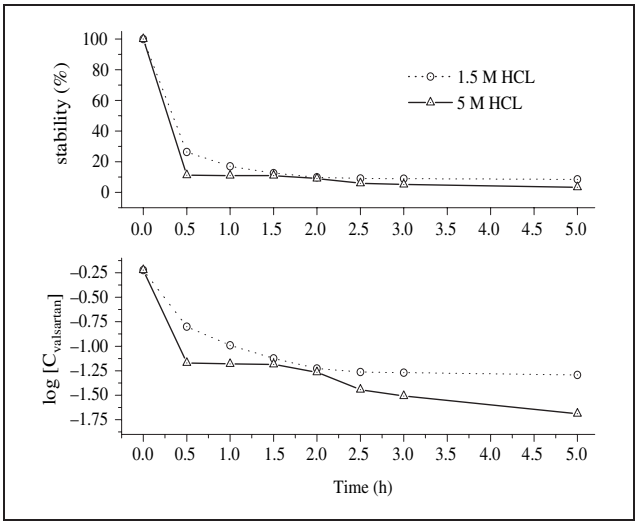


Fig. 7: Rate of degradation of valsartan under effect of 1.5 and 5 M HCl at 85 °C (above) and good first order kinetic correlation with the concentration (below)

The TLC chromatogram of the acid-degraded spots for valsartan showed two degraded spots at R_f 0.54 and 0.89 using chloroform-methanol-ammonia solution (60 : 30 : 5) as a mobile phase which is in accordance with the results given in the thesis (Fatahalla 2002).

3. Experimental

3.1. Apparatus

All different modes of adsorptive stripping voltammograms (direct current DC, differential pulse DP, square wave SW, and alternating current AC) were recorded using Metrohm 693 VA processor (Switzerland) and VA 694 stand equipped with three electrodes Ag/AgCl-3M KCl, a platinum electrode and hanging mercury drop electrode (HMDE). The pH measurements were carried out using a digital pH-meter Metrohm.

3.2. Reagents

All chemicals used were of analytical grade. Twice distilled water was used throughout all experiments. Two pharmaceutical products, either in single form, namely Tareg (Novartis Pharm.), containing 40 mg valsartan per tablet or in mixture, namely Co-Tareg (Novartis Pharm.) containing 80 mg valsartan in combination with 12.5 mg hydrochlorothiazide per tablet, were used.

A stock solution of valsartan (0.4 mg/ml) was prepared by dissolving the drug in absolute methanol. Three different buffer solutions, viz. acetate, phosphate and modified Britton-Robinson (BR) buffer solutions were also prepared. The solution of 0.1 M sodium ethylene diamine tetracetate was freshly prepared.

3.3. Procedure

An aliquot of valsartan solution (0.8–6.4 μg/ml) was placed in a 10 ml-measuring flask containing 5 ml modified Britton-Robinson (BR) buffer pH 6 (0.04 M) and 0.1 ml 0.1 M Na EDTA. The flask was then completed with distilled water to the mark. The solution was transferred into the electrode cell and de-aerated by pure nitrogen gas at 1 atmosphere for 2 min. Adsorption was carried out with a new HMDE (∼0.15 mm^2 drop area) at −700 mV and the solution was stirred at 2000 rpm speed for 30 s. The stirrer was stopped and the solution was allowed to rest for 10 s, then the voltammogram was recorded by AC scanning over a reduction potential range from −700 to −1400 mV with 20 mV/s scan rate "v", 30 mV pulse amplitude "ΔE" and frequency 25 Hz. The mean of triplicate measurements of content in the sample was calculated using standard addition method at room temperature (ca. 27 °C).

To assay valsartan in pharmaceutical products, a known weight of a tablet was ultrasonated in 50 ml methanol for 30 min. The beaker was transferred to a 100 ml measuring flask and completed to the mark with washing methanol without any filtration. Aliquot of the solution containing 0.8–6.4 μg/ml valsartan was transferred to a 10 ml measuring flask and the procedure was repeated as described above. UV first derivative spectrophotometry was performed as reference method (Satana et al. 2001) for the determination of valsartan in the tablets either alone or in mixture with hydrochlorothiazide.

To study the stability of valsartan under stressed acidic conditions, an appropriate amount of valsartan at a final concentration of 200 μg/ml in alcoholic 1.5 M HCl was heated at 85 °C under reflux. The same experiment was repeated but in 5 M HCl. Portion of the stressed solution was transferred into 10 ml measuring flask containing BR buffer solution adjusted at pH 6 and valsartan was assayed in triplicate at zero time and every 30 min intervals as described above.

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