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VOLTAMMETRIC BEHAVIOR AND DETERMINATION OF VINCAMINE IN PURE FORM, PHARMACEUTICAL FORM AND BIOLOGICAL FLUIDS

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ABSTRACT

Voltammetric oxidation of Vincamine was studied in Britton - Robinson buffer by cyclic voltammetry (CV), differential pulse voltammetry (DPV) and square-wave voltammetry (SWV) at glassy carbon electrode (GCE). These sensitive validation and consistent reproducible voltammetric technique were investigated for the trace quantification of the drug in pure, human urine and in pharmaceutical formulations. The optimum experiential parameters were by way of follow: Britton - Robinson (BR) (pH 6.0). The peak current exhibited a linear correlation with the drug concentration in the range limit of 0.658 - 8.36µg/ml,1.65-24.75 µg/ml, with the limit of detection 0.502, 1.67µg/ml and limit of quantitation were 0.066, 0.382µg/ml Differential pulse and Square Wave Voltammetry respectively. The proposed voltammetric procedures successfully applied for determination of VIN in its pure form and pharmaceutical formulation using GCE. The method allows a simple, rapid and reproducible determination of this compound without any interference from other ingredients present and furthermore applicability was tested in urine samples.

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INTRODUCTION

Vincamineis (VINC) (3α, 14β, 16α) -14, 15 – dihydro - 14 – hydroxyeburnamenine – 14 - carboxylic acid methyl ester {(C_{21} H_{26} N_2O_3) as in Fig(1).It is a peripheral vasodilator that rises blood flow to the brain (sold under the trade mark Oxybral SR). Vincamine[1] is often used as a nootropic agent to combat the effects of aging [2-4], or in conjunction with other nootropics (such as piracetam) for a variety of purposes.[3, 5-8]

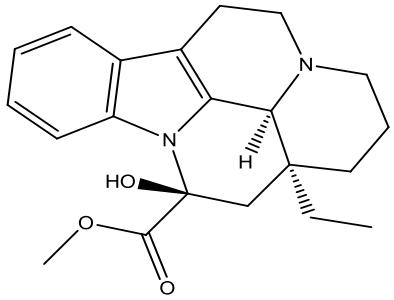

Fig.1. Chemical structure of Vincamine.

Many analytical methods for the quantitative determination of Vincamin in pharmaceutical formulations and biological fluids have been described as can be successfully Spectrophotometric [9-13], gas chromatography (GC) [14-16], selected ion monitoring[17], high-performance liquid chromatography through voltammetric detection (HPLC)[11, 18-24], TLC[25]and micro dialysis [26]. No report describing the utility of voltammetric methods in the determination of Vincamine, either in pharmaceutical forms or in human plasma, is available in the literature. voltammetric methods, such as cyclic voltammetry (CV),differential pulls (DPV) and square wave have been widely applied for the determination of compounds of pharmaceutical interest In general, these methods are faster, easier, cheaper, and more sensitive than spectrometric and HPLC methods. In addition, the experimental methodology is less tedious. Moreover, they employed for the analysis of materials in complicated systems (e.g., tablets and biological fluids). Currently, furthermore, an official method for the determination of this drug in pharmaceutical forms has not been described yet in any national pharmacopoeia. Although the chromatographic methods are sensitive enough for the determination of Vincamine in pharmaceutical dosage forms and in human plasma, they require sample pretreatment and time-consuming extraction steps prior to assay of the drug. Therefore, the goal of the present study optimizes the experimental and instrumental conditions of a more simple, low coast and sensitive voltammetry (SWV) and differential pulse voltammetry (DPV) to determination of Vincamine in pure, pharmaceutical formulations and biological fluids.

Experimental

Apparatus

Voltammetric measurements were performed using Metrohm797 VA Processor and a Metrohm797 VA stand.The three-electrode system consisted of a glassy carbon electrode as working electrode (diameter2mm±0.1), Ag/AgCl/saturated KCl reference electrode and a platinum wire auxiliary electrode

All measurements were achieved at room temperature. A digital pH/mV meter (JEANWAY 3510) with a glass combination electrode was used for the preparation of the buffer solution calibrated with standard buffers at room temperature. A micropipette (Eppendorf-multipette plus) was used throughout the present experimental work.

Reagents

- All chemical reagents used were of analytical grade.
- Vincamine (99.80%) was kindly supplied by the National Organization for Drug Control and Research (NODCAR) (Cairo, Egypt),
- Pharmaceutical dosage forms; Oxybral. GSK Pharmaceuticals Corporation, Egypt) containing 30mg capsule, were purchased from the local market.
- Stock solutions of 10^{-3} M was preparing by dissolving an adequate weighed of Vincamine in 25ml 0.1M HCl then complete the suitable volume (100ml) with the same solvent. The stock solution was stocked in a refrigerator.
- Britton - Robinson (BR) buffer solutions (2.0-12)[27] were applied as supporting electrolyte.
- Double distilled water was applied throughout all experiments.

Working electrodes

To increase the sensitivity and enhancement of the voltammetric peaks, the glassy carbon electrode (GCE) was polished surface manually with aqueous slurry of 0.3m alumina powder on a smooth fine polishing cloth prior to each electrochemical exponent. Then, it was carefully washed with methanol and bidistilled water, and softly dried by a tissue paper.

The optimizations

The optimization of pH, an suitable amount of Vincamine standard solution 10^{-3} M was placed in the electrolytic cell, which containing 25 ml of B-R buffer electrolyte solution then voltammograms was recorded. The experiment was repeated by using buffer solutions of different pH values (3.0-10) and the optimal pH was obtained.

The investigation the scan rate effect (υ) with the peak current (Ip) of Vincamine, the working electrode was put in the optimum buffer electrolyte solution containing an suitable amount of Vincamine standard solution 7.5µgm/m, and the voltammograms were registered at different series scan rates in the range 10 - 250 mV s^{-1} .

To study the influence of accumulation time, the working electrode was immersed in the optimal buffer electrolyte solution containing a suitable amount of Vincamine standard solution 2.5 x 10^{-5} M to select times with stirring at 1200 rpm at open circuit condition. After accumulation, the cyclic voltammograms were registered then plot the peak current (I_p) versus with time to get the optimal accumulation time.

The optimal instrumental parameters for the quantitative determination of Vincamine by using DPV technique were selected from investigation of the variation of the peak current height with pulse amplitude (pulse width and scan rate). Throughout the study, each factor was varied while the remained others were kept constant: pulse amplitude over the range of 30-100 mV, pulse width 30-80 ms, and scan rate 20-250 mV s^{-1}.

General procedure

Voltammetric determination were achieved in 25 ml of B-R electrolyte buffer holding a fitting concentration of drug moved into a voltammetric cell. The solution was continuously stirred at 1200 rpm once accumulation potential (usually open circuit conditions) was functional for a convinced time to the working electrode. Once the end of accumulation time, the stirring was stopped, and subsequently 5.0 sec rest period was allowable for the electrolyte solution to become quiescent. The investigated drug was quantitative determined by using DPV and SWV technique. Aliquots of the drug solution of 10^{-3} M were introduced into the electrolytic cell and the procedure was repeated. The voltammograms were registered. The peak current was estimated as the difference between each voltammograms and the background electrolyte voltammograms. All measurements were carried out at room temperature.

Analysis of VINC in dosage form

An amount of ten capsule of Vincamine from local market was mixed well until become a homogeneous fine powder. Portion equivalent to a stock solution of a concentration about 1x10^{-3}M was accurately weighed and then dissolved in 25 ml 0.1M HCl. It was sonicated for 5 minutes. The solution content was allowed to settle after magnetically stirring for 5.0 min. The solution of sample was filtered through a whatman no.42 filter paper. Suitable solutions were ready by taking a suitable aliquots of the clear supernatant liquid and diluted it with the same solvent to achieve a final concentration solution of 10^{-3} M Vincamine. Each solution was moved to a voltammetric cell and the voltammograms were subsequently recorded according to the optimized conditions. The content of the drug in dosage form was carried out by the standard addition method.

Preparation of urine sample

Quantitative determination of Vincamine in samples of spiked urine, 1.0 ml of urine sample mixed with 24 ml of electrolyte buffer of the optimal pH, without pretreatment then moved to the voltammetric cell, and carried out the differential pulse voltammetric procedure as illustrated above for the pure drug.

RESULTS AND DISCUSSION

Electrochemical oxidation of Vincamine at GCE

In preliminary experiments we applied several voltammetric techniques to study the electrochemical oxidation of EA at the glassy carbon electrode: cyclic voltammetry (CV), differential pulse voltammetry (DPV) and square-wave voltammetry (SWV). The corresponding voltammograms waves are shown in Fig. 2. Which illustrated there is one anodic beak.

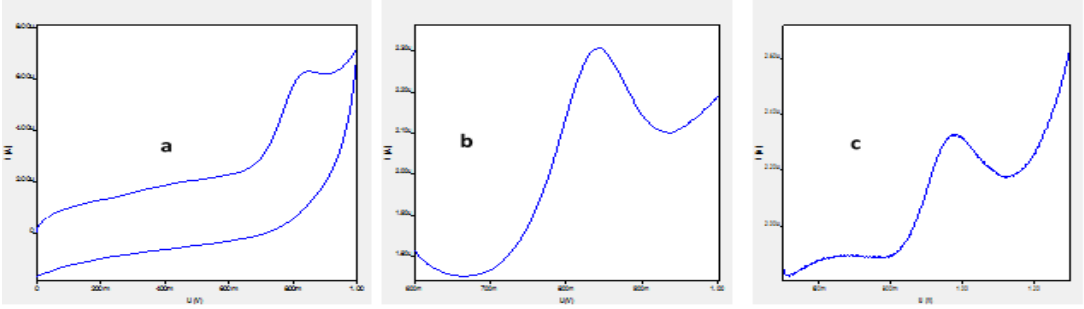

Fig. 2.(a) Cyclic voltammetry CV (scan rate 100 mVs-1), (b) DPV (sweep rate 5mVs-1, voltage step time 0.4s, pulls amplitude 50mv) and (c) SWV (sweep rate 10 mVs-1, frequency 50 Hz, amplitude 20 mV) recordings of 1.5µg/ml VAN in 0.04 M B-R buffer of pH 6.

Cyclic voltammetric study

The effect of the scan rate on the electrooxidation of Vincamine was studied by recording the voltammograms of a 1.5µg/ml of VNH solution in 0.04MB-R buffer of pH 6 at 20–240 mV s^{-1}, typical CV curves of VAN at different scan rates are shown in Fig. 3. In case of irreversible electrode process, a plot of peak current (ip) versus the square root of the scan rate ($\upsilon^{1/2}$) gave a straight line relationship linear relationships were obtained for the peak currents and square root of scan rate.
The regression equations were

$$\mathbf{Ip = 2.11\upsilon^{1/2} - 0.20\ (Vs^{-1})\ (r2 = 0.9942).}$$

This indicates that the anodic reactions of VAN drug was controlled by diffusion at GCE electrode surface According to the Randles–Sevcik equation, for a linear diffusion controlled process[28, 29]. The peak-to-peak separation also increased with increasing the scan rate. A good linear relationship was found for the oxidation peak currents, with different scan rates (Fig. 3 inset).

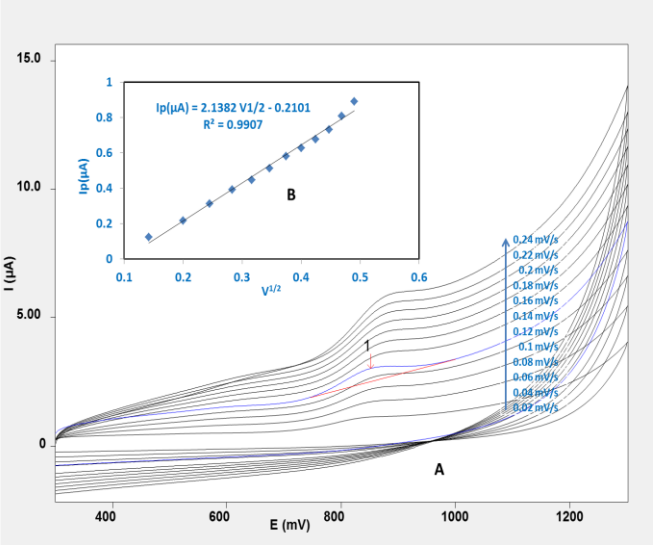

Fig 3.(A) Cyclic voltammograms of 1.5µg/mlVAN at scan rate 20–240 mV s-1 in 0.04 M B-R buffer of pH 6 (B)shows variations of Ip vs. the square root of scan rate.

The peak potential was also reliant on scan rate. The peak potential was shifted towards positive value by increasing scan rate, which approves the irreversible nature of the oxidation process. The relation between Ep and log v can be stated by the equation for 0.04M B-R electrolyte .

$$\mathbf{Ep\ (mV) = 0.0679\ log\upsilon + 0.9271r = 0.9978}$$

The plot of Ep against logv give a linear relation with a correlation coefficient 0.9978, this performance is reliable with the EC nature of the reaction in which indicate that the electrode reaction is Accompanied with an irreversible follow-up chemical step[30]. As for an irreversible electrode process, according to Laviron [29], Ep is defined by the following equation:

$$Ep = E^0 + \frac{2.303RT}{\alpha nF} log \frac{RTK^{\upsilon}}{\alpha nF} + \frac{2.303RT}{\alpha nF} log\upsilon$$

where α is the transfer coefficient, K^0 the standard heterogeneous rate constant of the reaction, n the number of electron transferred, v the scan rate, and E^0 is the formal redox potential. Othersymbols take their usual implications. Thus value of αn can be easily calculated from the slope of Ep vs. log υ. In this method, the slope is 0.0679, taking T = 298, R = 8.314, and F= 96480, αn was calculated to be 0.8704.The value of α can be easily studied from equation

$$\mathbf{\alpha = 47.7/(E_p - E_{p/2})}$$

Where $E_{p/2}$ is the potential corresponding to $I_{p/2}$. The values forα were found to be 0.743 at the surface of GCE. Further, the number of electron n transferred in the electro oxidation of VINC was calculated to be 1.17 ~1.

Effect of pH on the supporting electrolyte

pH of the electrolytes medium is important variable that often severely affects the shape of the voltammograms. The effect of pH on Peak potential and peak current are investigated in detail. The voltammetric behavior of VAN was examined in the pH range 3 –10, as can be seen in Fig.4. The maximum current response was obtained at pH 6. Therefore, this pH was selected as the optimal pH.

Also, it was found that the pH value of the solution has a significant influence on the peak potential of the oxidation of VAN, representative that the electro oxidation at the GCE is a pH dependent reaction and that protons had booked part in their electrode reaction processes. The peak potential value moved to lower values by the way of pH was increased and the consistent linear relationship between Ep and pH was linear

$$\mathbf{Ep\ (V) = -0.0534pH + 1.2808 \qquad (r = 0.9927).}$$

The slope value found (0.0534mV/pH) fairly close to the Nersntian [31] slope shows that an equal number of electrons and protons was involved.

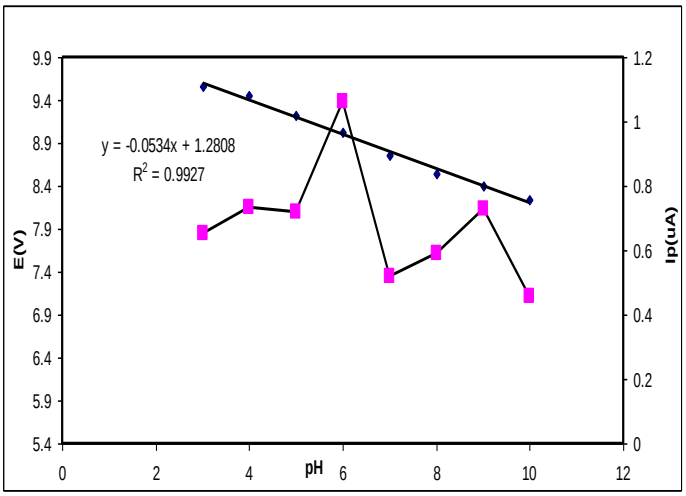

Fig.4.Influence of pH on the anodic peak current and potential response for 1.5µg/ml VINC in 0.04M BR various pH (3–10).

Mechanism

In the proposed method the VAN undergoes electro oxidation with one electron and the possible mechanisms are as shown in Fig.5. for one peak was proposed in 0.04 M B-R buffer of pH 6.

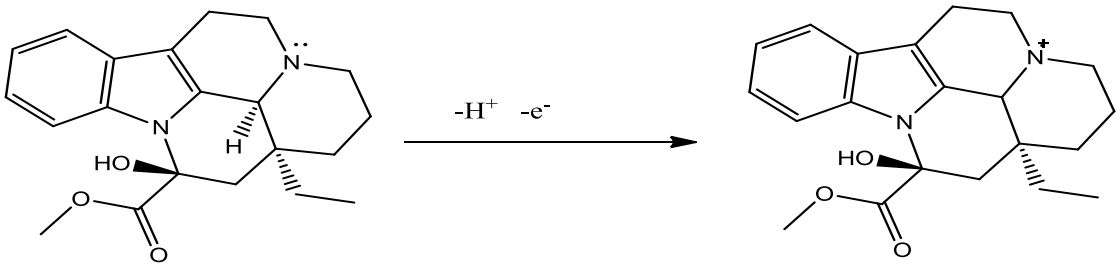

Fig.5. Proposal mechanisms of electro oxidation of VAN.

Method validation

The validation of the studied method was evaluated by investigate the following factors: linearity range, LOD, LOQ, accuracy, specificity, precision, robustness and system suitability according to ICH guidelines [32-34]

Linearity

The applicability of the proposed DPV and SWV procedures as an analytical technique for the determination of VAN was examined by evaluating the peak current as a function of concentration of the bulk drug at least three times underthe optimized chemical conditions and instrumental parameters for the DPV and SWV determination of VAN were established, When we applied the waveform allowed sensitive and rapid determination. Both the peak height and the peak shape were taken in consideration during choosing the optimum instrumental conditions, The calibration curve was studied with the VAN using the optimized experimental conditions by adding aliquots of VAN standard solution to the supporting electrolyte and, consequently, increasing the VAN concentration in the electrochemical cell. The linear relation between concentration and peak height for DPV and SWV are depicted in fig. (6,7) respectively, Under the optimized conditions, a linear correlation between DPV and SWV peak height and the drug concentrations was obtained over the range of0.66 – 8.36 µg/ml(r^2=0.9959) and 1.65 – 24.75 µg/ml(r^2=0.9947)For DPV and SWV respectively. Lower detection limit of 0.502 and 1.67µg/ml for DPV and SWV respectively and remain statistical parameters illustrated in table 1.

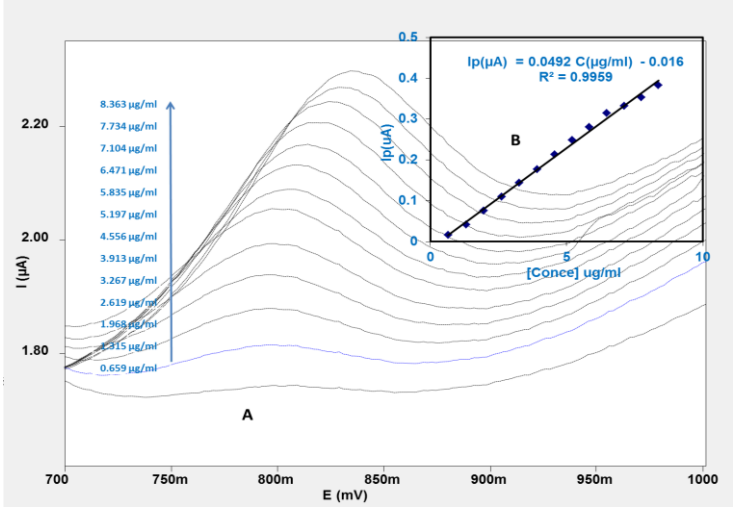

Fig.6. Differential pulse voltammograms (DPVs) for increasing concentration of VANB-R buffer pH =6.9 (0.04 M):Pulse amplitude, 50mV; pulse width, 30 s; sample width, 0.02 s. Inset is the calibration plot.

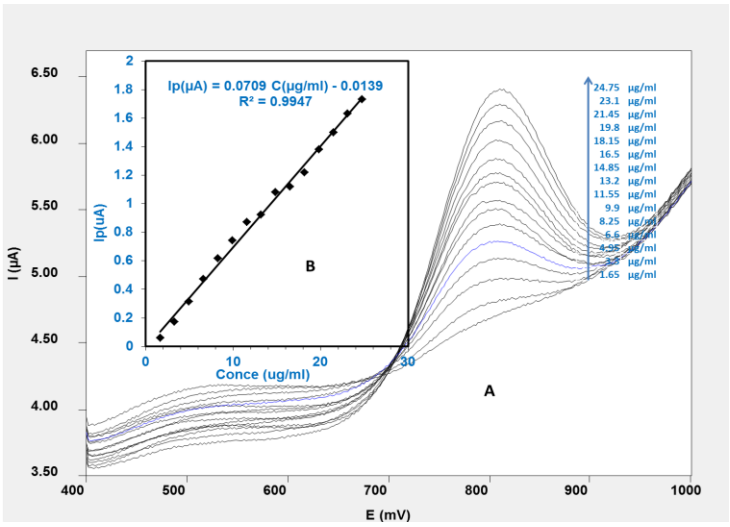

Fig. 7.Square-wave voltammograms for VAN in 0.04M B-R at pH 6.0 on the GCE, with f=50 s−1, a =30 mV, ΔEs =2 mV, and concentrations in the interval from1.65 – 24.75 µg/ml of VAN. Insert corresponds to the analytical curves obtained from voltammograms.

Table. 1. Analytical regression parameters obtained from DPV and SWV calibration curves of VAN at GCE.

Parameter	DPV	SWV
Concentration range (µgml^{-1})	0.658 - 8.36	1.65 - 24.75
Correlation coefficient (r2)	0.9959	0.9947
Slope (lp(A)/ (µgml-1)	0.0492	0.0709
Intercept Ip (A)	- 0.016	- 0.0139
SD of the residuals (Sy/x)	0.0082	0.0395
SD of intercept of regression line S_a	0.0049	0.0214
SD of the slope of regression line S_b	0.0009	0.0014
LOD	0.502	1.67
LOQ	1.675	5.576

SE is the standard Error.

Accuracy

Accuracy is the measure of exactness of an analytical method[35], or the confidence of agreement between the measured value and the value that is accepted either as a conventional, true value. To confirm the accuracy of the proposed method, the results of the assay of VIN in pure form assessed by the suggested voltammetric method was compared with those obtained using the reported non aqueous titration method. Statistical comparison of the results obtained from both methods shows non-significant difference between the two methods which summarized in table 2.

Table. 2. Accuracy of the proposed DP and SWV voltammetric method for determination of VAN at GCE in its pure form.

Parameter	Proposed method			Ref. method
	Amount taken (µg/mL)	Amount found (µg/mL)	% found*	% found*
DPV	2.5	2.52	100.8	100.12
	4.5	4.51	100.22	99.97
	6.5	6.498	99.97	99.992
Mean ± SD			100.33± 0.18	100.03± 0.43
t-Test			0.146	
F-test			0.035	
SWV	2.5	2.508	100.32	100.23
	4.5	4.502	100.04	99.98
	6.5	6.497	99.95	99.99
Mean ± SD			100.11± 0.02	100.07± 0.14
t-Test			0.287	
F-test			1.815	
t-Tabulated at p= 0.05	2.77			
F-tabulated at p= 0.05	19			

*Each result is the average of three separate determinations.

Pharmaceutical assay and urine application

The optimized procedure was successfully applied for determination of VINC in capsule, Just dilution of an aliquot from the supernatant layer with the supporting electrolyte (BR buffer, pH 6) is required before measurement. Voltammograms of VINC in BR buffer (pH 6) exhibit very well-defined anodic peak. The precision was estimated by using standard addition method; the recovery parameter for pharmaceutical and urine application are summarized in table 3.

Table. 3 Application of the investigated analytical voltammetric methods for the analysis of dosage form and spiked human urine.

Parameter	Dosage form		Urine	
	DPV	SWV	DPV	SWV
Labeled amount (mg)	100	100	-	-
Amount found (mg)	100.1	99.98	-	-
Added (µgml-1)	0.1	0.3	3	4.5
Found(µgml-1)	0.1003	0.301	0.311	4.505
Standard error	0.0157	0.0164	0.017	0.0123
Recovery (%)	100.3	100.33	10.04	100.11
Standard Deviation	0.0352	0.0367	0.0378	0.0301

Precision

Precision is the measure of the degree of repeatability[36] of an analytical method under normal operation. The intra- and inter-day precision was evaluated by the determination freshly prepared solutions in triplicate on the same day and on three different days. Repeatability (intra-day) and reproducibility (inter-day) of the results obtained by means of DP and SW voltammetric procedures were examined.

Robustness

Robustness is the capacity of a studied method to remain unaffected by small deliberate variations in method parameters[37]. The robustness of a method is evaluated by varying method parameters such as percent organic solvent, pH, ionic strength, or temperature, and determining the effect (if any) on the results of the method. The robustness of the proposed method was shown by constancy of the peak current with deliberate small changes in the analytical parameters. The studied variables included; change in pH (±0.5), preconcentration time (±5 s). These minor changes that may take place during normal experimental work didn't affect the peak current intensity of the cited drug, thus confirming that the method is robust.

Specificity/selectivity

The specificity[38]is the ability of the method to measure analyte response in the presence of all of the potential impurities. The specificity of the optimized procedure for estimation of VINC was examined in the presence of excipients such as colloidal silicon dioxide, and steric acid; alternatively, starch, precipitated silica and talc were added to dosage form. Samples containing 1,5 μgml^{-1}bulk VINC and different concentrations of the excipient under evaluation were analyzed by means of the proposed procedure. The obtained mean percentage recoveries and %RSD values based on an average of five replicate measurements, 99.89 ± 0.40 to 100.05 ± 1.05 for DPV and 99.88 ± 0.87 to 100.02 ± 0.650 for SWV, showed no significant interference from excipients. Thus, the proposed procedure can be considered to be specific.

CONCLUSION

The proposed voltammetric procedures can be successfully applied for determination of VIN in its pure form and pharmaceutical formulation using GCE . The method allows a simple, rapid and reproducible determination of this compound without any interference from other ingredients present. The present method is found to be practically precise, accurate, inexpensive and highly sensitive. According to LOD and LOQ electrochemical data. This method could possibly be adopted for the quality control laboratories.

Recommend future Research determination of studied drug simultaneously with piracetam at Nano modified electrode with melty wall carbon nanotube and surfactant.

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