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CYCLIC VOLTAMMETRIC DETERMINATION OF ZOPICLONE IN PHARMACEUTICALS AND BLOOD SAMPLES USING GLASSY CARBON ELECTRODE

Dr. D. Srividya* and Dr. Vyshnavi Yelchuri

Department of Chemistry, PVKN Government Degree and P.G.College (Autonomous), Chittoor.

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***Corresponding Author**
Dr. D. Srividya
Department of Chemistry, PVKN Government Degree and P.G.College (Autonomous), Chittoor.

ABSTRACT

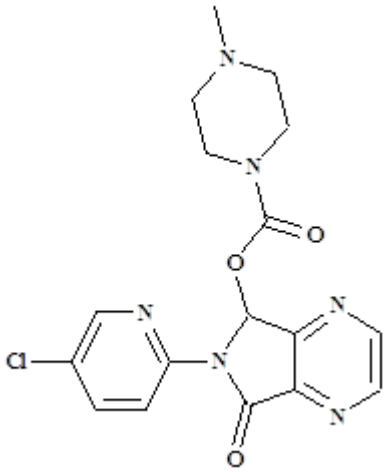
Cyclic voltammetric, and differential pulse voltammetric techniques are used todetermination of zopiclone in pharmaceuticals and blood samples using glassy carbon electrode. It was selected to get reduction mechanism of >C=O< group. Zoplicone was examined in phosphate buffer over a pH range from pH 2.0 to pH 8.0 by differential pulse voltammetry and cyclic voltammetric methods. GCE showed one reduction peak at -0.6V with a peak reduction current of -4.5 µA using phosphate buffer solution at pH 6.0. No oxidation peak wasobserved at this potential in the reverse scan, suggesting that the electrochemical reaction is a totally irreversible process. The procedure was applied to the analysis of human blood samples.

KEYWORDS: Zopiclone (ZPLN), acetonitrile, phosphate buffer, glassy carbon electrode, cyclic voltammetry, differential pulse voltammetry.

INTRODUCTION

Zopiclone is a central nervous system depressant and belongs to nonbenzodiazepine sedative and hypnotic. Structure of zopiclone was shown in Fig. It is used to treat insomnia where sleep initiation or sleep maintenance are prominent symptoms. Long term use is not recommended as tolerance, dependence, addiction can occur with prolonged use.[1-2] Zopiclone is a cyclopyrrone compound that has been reported to possess hypnotic, muscle relaxant, and anticonvulsant properties analogous to benzodiazepine compounds such as diazepam. Chemically,[3] it is 4-methyl-1piperazine-carboxylic acid- 6-(5-chloro-2-pyridinyl)-6,7dihydro-7-oxo-5*H*-pyrrolo[3,4-*b*]pyrazin-5-yl ester. Zopiclone belongs to the

group of medicines called central nervous system (CNS) depressants. The therapeutic pharmacological properties of zopiclone include hypnotic, anxiolytic, anticonvulsant, and myorelaxant properties.[4] Zopiclone is known colloquially as a "Z-drug". Zopiclone, as traditionally sold worldwide, is a racemic mixture of two stereoisomers, only one of which is active.[5-6] It is recommended that zopiclone be taken on an "as needed" basis. Daily or continuous use of the drug is not usually advised.[7] Zopiclone is a tranquillizer drug. It works by causing a depression or tranquillisation of the central nervous system.



Structure of zopiclone

Several analytical methods have been reported for the determination of ZPLN in pure drug, pharmaceutical dosage forms and in biological samples using spectrophotometry, liquid chromatography, electro kinetic chromatography high performance thin layer chromatography either in single or in combined formsa rapid, simple and accurate chromatographic (HPLC) and spectrophotometric methods for the determination of ZPLN in tablets were elaborated.[8]

A simple, selective and sensitive isocratic HPLC method with triple quadrapole mass spectrometry detection has been developed and validated for simultaneous quantification of ZPLN and its metabolites in human plasma.[9] A new HPLC method for ZPLN in postmortem specimens by GC-MS and HPLC with diode-array detection.[10] The preparative separation of ZPLNusing malic acid as the resolving agent.[11] A simple, rapid, sensitive and precise HPLC method has been developed for the estimation of zopiclone in pure and tablet dosage form.[12] No work was done regarding the voltammetric analysis of zopiclone.

This method was used for determination of zopiclone in pharmaceuticals and blood samples using glassy carbon electrode. It was selected to get reduction mechanism of >C=O< group by employing advanced electrochemical techniques such as cyclic voltammetry, differential pulse voltammetry. This method is simple, fast, accurate, precise and reproducible hence can be applied for the routine quality control analysis of zopiclone.

EXPERIMENTAL

MATERIALS AND METHOD

Ranbaxy pharmaceuticals gifted zopiclone (99% pure). Tablet containing ZPLN were obtained from commercial sources. KCl solution was prepared in distilled water and used as supporting electrolyte. Stock solutions of zopiclone were prepared in acetonitrile. Solutions of recording voltamogrammes were prepared by mixing appropriate volume of stock solution and phosphate buffer. All reagents were used are analytical grade and solutions were protected from light throughout this study.

Instrumentation

Cyclic and DPVwere measured using Autolab PG STAT101 supplied by Metrohm Autolab B.V., The Netherlands. A three electrode system composed of a glassy carbon electrode (GCE-3mm)as a working electrode saturated Ag/AgCl/KCl as a reference electrode and Pt wire as a counter electrode. pH metric studies were carried out using an Elico LI-120 pH meter supplied by Elico Ltd, Hyderabad, India.

Analytical procedure

After 10 mL of phosphate buffer (PBS) of pH 6.0 was placed in the electrochemical cell, to this certain volume of standard solution (2.25×10^{-7}M) of **ZPLN** was added and de-aerated with pure nitrogen for 10min. Then the voltammograms were recorded using cyclic voltammetry and differential pulse voltammetric studies over the potential range --0.05V to -1.25V Vs Ag/AgCl/KCl. All measurements were carried out at room temperature.

Assay of tablets

The determination of **zopiclone (ZPLN)** was made from commercial tablets available from local commercial sources. Thus, ten tablets were powdered and a suitable quantity of the sample was accurately weighed. The solubility was increased by using an ultrasonic bath. A portion of the powder equivalent to 1 mM **ZPLN** was transferred to a 100 mL volumetric flask and completed to volume with distilled water and sonicated for 15 min to affect

complete dissolution. The sample from the clear supernatant liquor was withdrawn and quantitatively diluted with the selected supporting electrolyte. The content of the drug in tablet was determined referring to the calibration graph using differential pulse voltammetry.

RESULTS AND DISCUSSIONS

Cyclic voltammetric study

Cyclic voltammetric technique was utilized to investigate the electrochemical behavior of **zopiclone**on GCE was shown in Fig. GCEshowed one reduction peak at -0.6V with a peak reduction current of -4.5 µA using phosphate buffer solution at pH 6.0. No oxidation peak wasobserved at this potential in the reverse scan, suggesting that the electrochemical reaction is a totally irreversible process. This drug shows significant electrochemical reduction takes place on GCE at pH 6.0. The number of electronstransferred involved in the reduction of **zopiclone**are two.

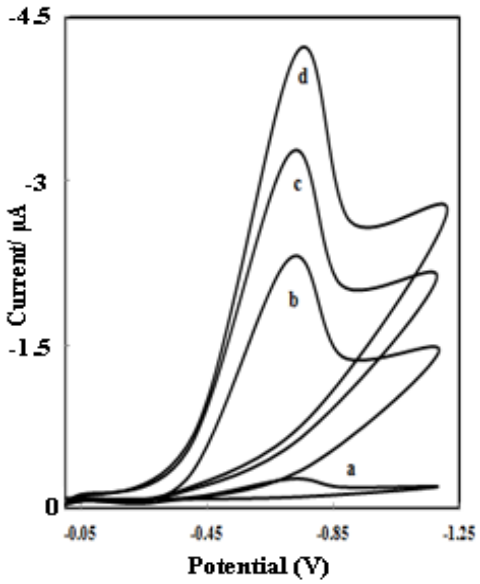


Fig. Cyclicvoltammograms of 2.25x10^{-7}Mzopiclone, at pH 6.0 of phosphate buffer at glassy carbon electrode at different scan rates (50 mV/s-200 mV/s).

Effect of pH

The effect of buffer pH on the electrochemical behaviour of **zopiclone** was investigated over the range of pH 2.0 to 8.0 and the results are depicted in Fig. shows that plot of resulting cathodic peak currents increases linearly as a function of pH until it reaches a maximum value at pH 6.0 and then declined. Therefore, pH 6.0 was chosen as the optimum pH for working phosphate buffer solution for subsequent measurements.

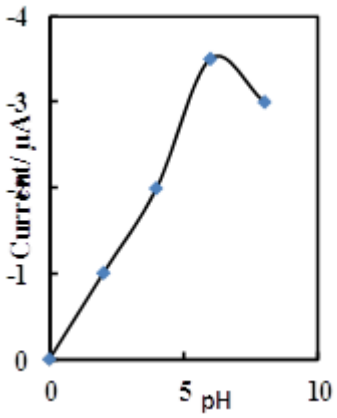


Fig. The plot of the current Vs pH of zopiclone in PB solution, Concentration: 2.55x10^{-7} M at glassy carbon electrode at different pH values (pH 2.0-8.0).

Differential pulse voltammetric studies

DPV was effective and rapid electroanalytical technique with well-established advantages, includinggood discrimination against background currents and low detection limits. The peak current-potential curve is the most useful analytical signal for this technique. Its peak height is usually proportional to concentration. Quantitative evaluation is based on the linear correlation between the peak current and concentration. Differential pulse experiments wereperformed on the GCE in phosphate buffer solution at pH6.0 withexperimental conditions were: scan rate 50mV/s; pulseamplitude 50 mV; sample width of 40 ms; pulse width of 50ms; and pulse period 40 ms.

The potential was scanned cathodically from an initial to a final potential of --0.6V to -1.25V. The DPV data for the determination of the drug under investigation in Fig. shows a linear relation between thepeak current (Ip) and ZPLN concentration (C) were found inthe following range: 2.25x10^{-7}M to 6.42×10^{-4}M. The calibration plotswere described by the following equations:Ip = 0.129C (μM) + 0.0655. Good correlations were obtained in DPV of ZPLN in a supporting electrolyte consisting of phosphate buffer at pH 6.0**.**

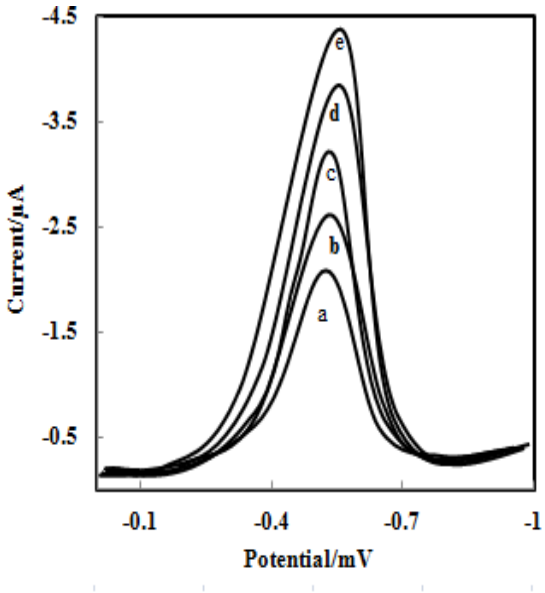


Fig. Typical DPV of zopiclone in phosphate buffer solution at pH 6.0, Concentration: 2.25x10^{-7}M to 6.42×10^{-4}Mat GCE.

Effect of scan rate

The relationship between the measured peak current and scan rate was studied over range 50 mV/s to 200 mV/s. It was found to be linearrelationship of peak current with different scan rates of ZPLN were evaluated in. Fig. shows a plot of peak current Vs scan rate gave a straight line with a slope of 0.8906 (correlation coefficient 0.9952), close to the theoretical value of 1.0, which is expected.

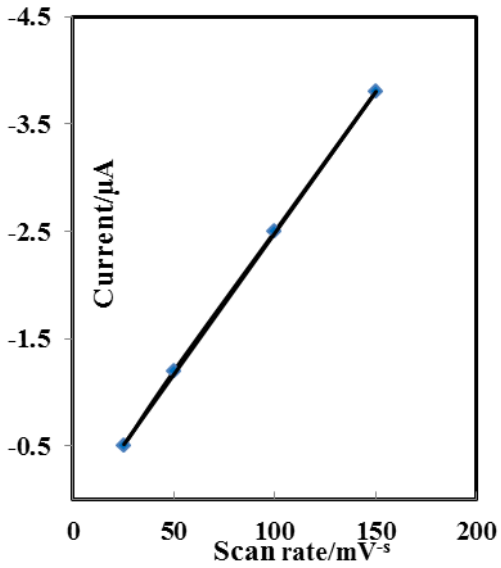


Fig. Effect of scan rate on ZPLN at pH 6.0 in phosphate buffer solution at Concentration: 2.25×10^{-7}M at different scan rates: 50mV/s to 200mV/s.

Validation of the analytical procedure

The linearity of the calibration curve was obtained for DPV technique as in above, the concentration range stands the linearity was probably due to the adsorption of ZPLN on the electrode surface. The precision of the method was investigated by repeatedly (n =5) measuring peak potential and peak current of ZPLN within a day and over three consecutive days for both techniques. The linear relationship of current with respective to the concentration was shown in Fig. LOD and LOQ were calculated as (3 sd/m) and (10 sd/m) respectively where's' is standard deviation of response (five runs) and 'm' is the slope of the calibration curve. LOD and LOQ values are 2.78 x 10^{-8}M and5.28 x 10^{-9}Mrespectively.

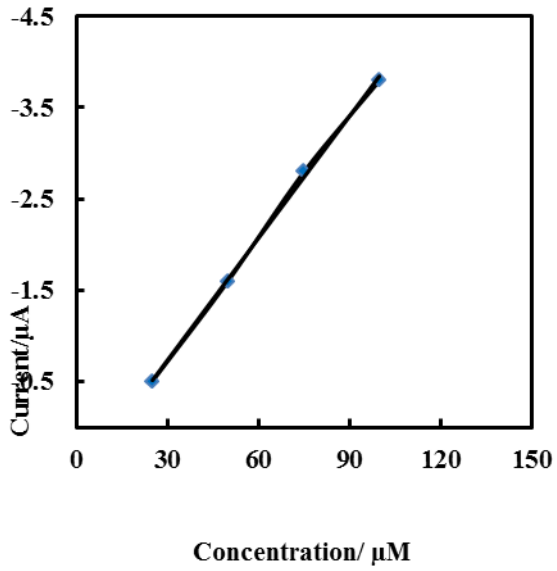


Fig. Calibration plot of the zopiclone in phosphate buffer solution at pH 6.0, at different Concentrations: 2.25x10^{-7} Mto 6.42×10^{-4}M at GCE.

Recovery study of zopiclone in human blood samples (serum)

Table. Recovery of zopiclone in blood sample (serum).

Sample	Amout added (µg/Ml)	Amont found* (µg/mL)	% Recory	%RSD
Rhovane (Serum sample)	20	19.72	98.60	0.89
	30	29.19	97.03	0.78
	50	49.53	99.06	0.90

Three human blood samples were prepared as described in the experimental part. The three human blood samples were spiked with appropriate amounts of standard samples until the final concentrations are 2.25 x 10^{-7}M for rhovane whichis commercial available form of

ZPLN. The recovery study was investigated by comparing the current response for the three human blood samples against the spiked concentrations in PB solution at pH 6.0. Recoveries are obtained from 97.03% to 99.06% for Rhovanein human blood samples, shown in Table It indicates the applicability of the method for determination of zopiclone in spiked blood samples.

CONCLUSION

The electrochemical behaviour of zopiclone at glassy carbon electrode was examined in phosphate buffer over a pH range from pH 2.0 to pH 8.0 by differential pulse voltammetry and cyclic voltammetric methods. Fully validated, simple, sensitive, selective, fast and low-cost differential pulse voltammetry method was developed for the determination of zopiclone in human blood samples. The described method could be recommended for use in trace analysis, quality control, and clinical laboratories.

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