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Differential pulse and square wave voltammetric determination of cisapride in tablet dosage form

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Cisapride (CIS) is a substituted benzamide which stimulates gastro-intestinal motility probably by increasing the release of acetylcholine in the gut wall at the level of the myenteric plexus. CIS is effective in a wide variety of gastroparetic conditions [1–3]. Reviewing the literature revealed that all the reported methods rely on the use of chromatographic techniques, such as HPTLC [4], HPLC [5–10], spectrophotometry [11–14], fluorimetry [15].

During the past few years only one paper on the polarographic behaviour of CIS and the similar compound cinitapride appeared in the literature, including polarographic investigation of the electroreduction mechanism and the determination of CIS and cinitapride on mercury electrode [16]. However, the electroanalytical method for this drug with a non-mercury electrode and oxidation mechanism has not yet been reported up to now. This work is concerned with a study of the voltammetric behaviour using the particularly rapid, simple, selective and sensitive techniques of differential pulse and square wave voltammetry on a glassy carbon electrode. Two proposed electrochemical methods were applied for the determination of CIS in commercial tablet dosage forms. Specifically, the drug is capable to be both oxidizable and reducible. Reduction behaviour of CIS on mercury electrode has already been reported [16]. But the oxidative behaviour and redox mechanism and differential pulse (DPV) and square wave (SWV) voltammetric determination of CIS have not yet been reported.

As a first step, CIS was subjected to a voltammetric assay in the DPV modes and SWV modes and to a cyclic and linear sweep studies with the aim of characterizing its electrochemical oxidation behaviour. The electrochemical oxidation of CIS appears to be a complex process and different reaction pathways are possible. From the cyclic and linear sweep voltammograms and bearing in mind the main voltammetric behaviour of aromatic amin derivatives which is structurally related to CIS the main mechanism of oxidation of CIS may be postulated by oxidation of the amin group of purine moiety of the molecule. The electrochemical behaviour of CIS at this electrode over the pH range 1.8–11.01 in all instances yields one main irreversible oxidation peak and in less acidic media additional one ill defined wave, which are shifted towards more negative potentials as the pH increases. Various electrolytes, such as sulphuric acid, Britton-Robinson, phosphate and acetate buffers were examined. The best results with respect to signal enhancement accompanied by sharper response were obtained with acetate buffer at pH 3.5, thus this pH value and this supporting electrolyte was chosen to carry out the electroanalytical study (Fig.). Scan rate studies were then carried out to assess whether the processes on glassy carbon electrode were under diffusion or adsorption control. A 116 mV positive shift in the peak potential was observed upon increasing the scan rate from 5 to 750 mVs^{-1}, as well as the increase of peak current when the scan rate was increased. This data confirms the irreversibility of the process. The linear relationship existing between peak current and the square root of the scan rate (correlation coefficient 0.995) with a slope of 0.80 showed that the oxidation process is predominantly diffusion-controlled in the whole scan rate range studied. On glassy carbon electrode, a plot of logarithm of peak current versus logarithm of scan rate gave a straight line (correlation coefficient 0.998) with a slope of 0.61 (close to 0.5), which is the expected value for an ideal reaction of solution species. The quantitative evaluation is based on the dependence of the peak current on CIS concentration using by DPV and SWV techniques. The calibration graph of the peak current versus concentration was found to be linear over the range of 1×10^{-6}–1×10^{-4} M for CIS in the DPV and SWV methods. The characteristics of the calibration plots are listed in the Table. For the sensitivity of the procedures, LOD and LOQ values were calculated

Table: Parameters of calibration curves of CIS obtained from both developed methods and the determination of CIS in tablets by proposed and literature methods and mean recoveries obtained for CIS in spiked Desapride® tablets

	Derivative UV-spectrophotometry ($\Delta\lambda = 320$ nm) [12]	DPV	SWV
Working electrode potential (V vs Ag/AgCl)		1.02	1.05
Linearity range (M)		1×10^{-6}–1×10^{-4}	1×10^{-6}–1×10^{-4}
Slope of the calibration graph (μAM^{-1})		2.03×10^4	1.90×10^4
Intercept (μA)		0.12	0.29
Correl. coeff.		0.999	0.999
RSD of slope		1.47	1.28
RSD of intercept		0.62	0.69
Number of data points		11	11
LOD		1.86×10^{-7}	2.41×10^{-7}
LOQ		6.21×10^{-7}	8.05×10^{-7}
Labelled claim (mg)	10	10.0	10.0
Amount found (mg)[a]	10.01	9.97	10.02
RSD%	1.21	0.79	0.84
t values	$t_{theoretical} = 2.31$	0.65	1.43
F values	$F_{theoretical} = 2.61$	0.44	0.50
Added (mg)		2.0	2.0
Found (mg)		2.00	1.98
Recovered %[b]		100.2	99.05
RSD % of recovery		0.95	0.52

[a] Each value is the mean of five experiments
[b] Recovery value is the mean of five experiments

and showed as well. The within-day reproducibility of peak potential and peak current was tested by repeating four experiments on 1×10^{-4} M CIS for both methods. The relative standard deviations were calculated to be 0.23 and 0.38% for peak potential and 0.92 and 0.56% for peak current using DPV and SWV techniques, respectively.The between-day reproducibility of peak potential and peak current was also tested by repeating four experiments on four different days with 1×10^{-4} M CIS for both techniques. The relative standard deviations were calculated to be 0.70 and 0.48% for peak potential and 0.64 and 0.98% for peak current using DPV and SWV techniques, respectively. Sample solutions recorded after one week did not show any appreciable change in assay values.

At the moment the Turkish Pharmaceutical industry has one commercial product that contains CIS as principal component in Desapride® (10 mg). The declared composition of this pharmaceutical product is: CIS, colloidal silicon dioxide, lactose monohydrate, magnesium stearate, microcrystalline cellulose, polysorbate 20, povidone, and starch (corn). Ten tablets were analyzed following the procedure described in the Experimental section. Well-defined DPV and SWV peaks were obtained and no interferences were observed. There is no need for any extraction procedure before voltammetric analysis. Moreover, in order to know whether the excipients in the tablets show any interference with the analysis and the accuracy of the proposed methods were evaluated by recovery tests after addition of known amounts of pure drug to various pre-analyzed formulations of CIS. The results demonstrate the specificity and selectivity of the proposed methods for the determination of CIS in tablets. The results obtained for the determination of CIS in commercial dosage forms and recovery data were given in the Table.

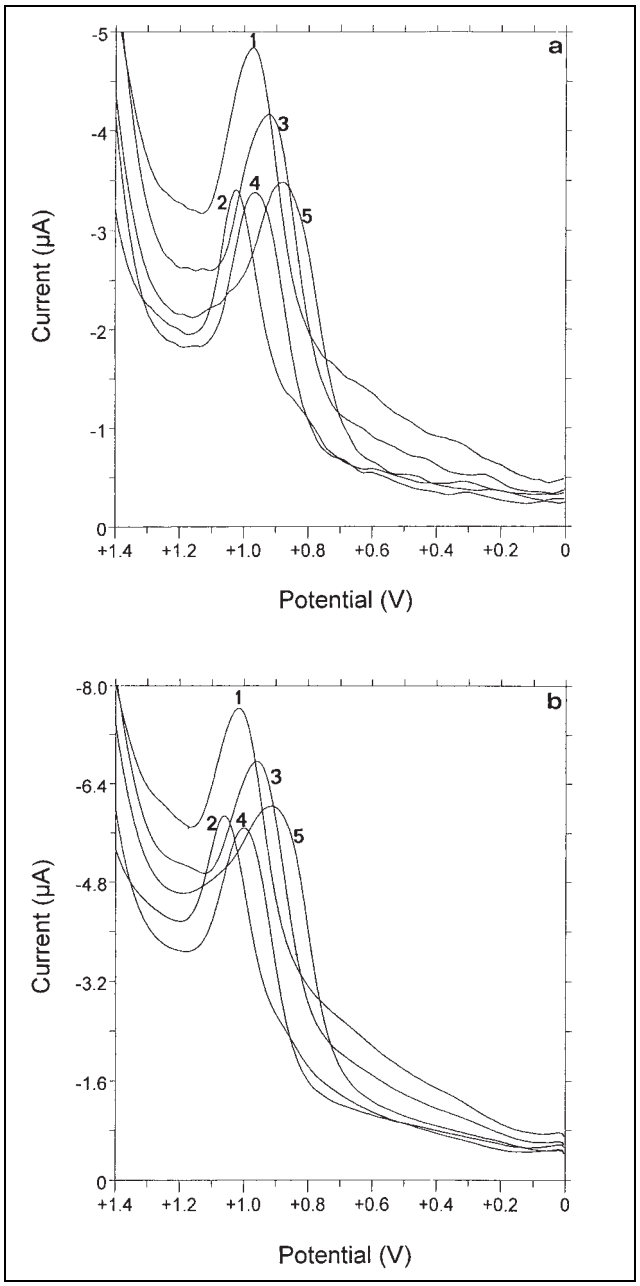

Fig.: Differential pulse (a) and square wave (b) voltammograms of 10^{-4} M CIS in different buffer systems. For operating conditions see Experimental part. (1) Acetate buffer pH 3.04; (2) Britton-Robinson buffer pH 3.04; (3) Acetate buffer pH 4.15; (4) Phosphate buffer pH 4.18; (5) Britton-Robinson buffer pH 6.01

As far as we know, there is no official method in any pharmacopoeias related to pharmaceutical preparations of CIS except bulk analysis of CIS in British Pharmacopoeia. For this reason the derivative spectrophotometric method [12] was used for comparison and for the reliability of the developed procedures. The results obtained for the formulation are listed in the Table and compared with the derivative spectrophotometric method which has been described in the literature [12]. The results of the proposed methods were compared with results of the literature method by common statistical tests at the 95% probability level. The results of the statistical evaluations are given in the Table. According to the results of student's t-test and F-test, insignificant difference was observed between the spectrophotometric and voltammetric methods.

The LOD and LOQ values obtained from proposed DPV and SWV methods were low and the linearity range was wider than published spectrophotometric [12] and polarographic [16] methods. The preparation of the sample was easy and since the excipients did not interfere in the electrochemical determination separation was not necessary, as in the spectrophotometric method. Furthermore the analysis time was not long and the procedure had adequate precision and accuracy and consequently is strongly recommended for CIS analysis in quality control laboratories.

Experimental

1. Apparatus and reagents

Voltammetric measurements were carried out with a BAS 100 W (Bioanalytical System) Electrochemical Analyser. Voltammetric measurements were utilized a glassy carbon ($\phi = 3$ mm, BAS) working electrode, a platinum wire auxiliary electrode and Ag/AgCl (NaCl 3M, BAS) reference electrode. Before each experiments the glassy carbon electrode was polished manually with alumina ($\phi = 0.01$ μm) in the presence of double distilled water on a smooth polishing cloth. DPV conditions were: pulse amplitude, 50 mV; pulse width 50 ms; scan rate 20 mVs^{-1} and SWV conditions were: pulse amplitude, 25 mV; frequency, 15 Hz; potential step 4 mV. For comparison study, spectrophotometric measurements were carried out by using a Shimadzu UV 1601 spectrophotometer with 1 cm quartz cell.

All investigations were carried out with CIS produced by Deva Pharm. Ind. (Istanbul, Turkey) and the corresponding commercial tablets, Desapride® 10 mg. The following buffer solutions were used: sulphuric acid (0.1 M), Britton-Robinson (0.04 M, pH 2.01–11.01), phosphate (0.2 M, pH 2.5–10.83), acetate (0.2 M, pH 3.5–5.71).

2. Procedure for tablets

Ten tablets were weighed and pulverized. An adequate amount of this powder corresponding to a stock solution of ca 1×10^{-3} M was accurately weighed and transferred into a 25 ml calibrated flask and complated to the volume with methanol. The content of the flask were sonicated for 10 min to effect complete dissolution. Appropriate solutions were prepared by tak-

ing suitable aliquots of the clear supernatant liquor and diluting with the selected supporting electrolyte. DPV and SWV curves were recorded. In order to know whether the excipients show any interference with the analysis, known amounts of the pure drug were added to the different pre-analysed formulations of CIS and the mixtures were analysed by the proposed methods.

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Determination of the antihypertensive drug lacidipine in pharmaceuticals by differential pulse and square wave voltammetry

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Lacidipine (LCD) is, like other dihydropyridine calcium channel blockers [1, 2], widely used in the treatment of hypertension, Angina pectoris and in the therapy of cerebrovascular spasm of various origins.

Several articles describe HPLC methods for the determination of LCD in plasma [3–5]. Also micellar electrokinetic chromatography has been used for the determination of plasma levels of LCD [6]. However, to our knowledge at present no information about the electrochemical redox properties of LCD and its analytical applications have appeared in the literature. The only work that involves electrochemical aspects has been published recently [7]. It deals with the voltammetric behaviour of LCD and its determination by differential pulse voltammetry.

Electrochemistry has a distinct advantage compared to most analytical techniques. Many studies have demonstrated that the electroanalytical techniques – voltammetry and various pulse methods – are useful for making concentration measurements as well as for studying reaction mechanisms of electroactive compounds in pharmaceuticals [8–12].

The purpose of the present study was to carry out a detailed investigation on the electrochemical behaviour of LCD at a glassy carbon electrode using cyclic, differential pulse (DPV) and square wave voltammetry (SWV) and performed a study concerning the determination of LCD in pharmaceutical dosage forms using DPV and SWV.

The oxidation of LCD was studied by cyclic, DPV and SWV using methanol as solvent and sulphuric acid, phosphate and Britton-Robinson buffers as supporting electrolytes. LCD was oxidized at the glassy carbon electrode, producing only one anodic peak. The electrochemical oxidation can be represented by the following equation [7, 13, 14]:

$$\text{Dihydropyridine} \rightarrow \text{pyridine} + 2e^- + 2H^+$$

LCD is oxidized in an alcoholic medium (30% methanol; v/v) in the pH range 1.5–11.04 at a glassy carbon electrode in sulphuric acid, Britton-Robinson and phosphate buffers as supporting electrolytes giving rise to voltammetric peaks whose potentials and currents are pH dependent. Cyclic voltammetric measurements performed on 1×10^{-4} M LCD solutions show the irreversible nature of the oxidation peak at the glassy carbon electrode in the range of scan rates comprised of between 15 and 750 mVs^{-1} and in the entire pH range investigated. A 152 mV positive shift in the peak potential was observed, which confirms the irreversibility of the process, with the simultaneous increase in peak current when the scan rate was increased. Scan rate studies were then carried out to assess whether the processes on the glassy carbon electrode were under diffusion or adsorption control. When scan rate is varied from 5 to 750 mVs^{-1} in a 1×10^{-4} M LCD, a linear dependence of the peak intensity upon the square root of the scan rate is found, demonstrating a diffusional behaviour (correlation coefficient 0.997). Plotting log i vs log v, a straight line was obtained