Differential Pulse Anodic Voltammetric Determination of Tiapride Hydrochloride in Pharmaceutical Preparation and Human Urine Using Carbon Paste Electrodes

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The anodic voltammetric behavior of tiapride hydrochloride (TiapCl) was studied at carbon paste electrodes in 0.04 M Britton–Robinson buffer pH 7.0 using cyclic and differential pulse voltammetric techniques. The oxidation of TiapCl is an irreversible diffusion-controlled process. A differential pulse anodic voltammetric procedure has been developed for determination of the drug over the concentration range 0.36 – 19.35 μg/ml with detection and quantification limits of 0.12 and 0.40 μg/ml, respectively. The proposed method was successfully applied for the determination of the drug in commercial tablets and in spiked human urine samples.

Introduction

Tiapride hydrochloride (TiapCl), *N*-[2-(diethylamino)ethyl]-2-methoxy-5-(methylsulfonyl)benzamide hydrochloride [51012-33-0] (Scheme 1), is a substituted benzamide with general properties similar to those of sulpiride, and it is usually given in the management of behavioral disorders and to treat dyskinesias. Doses of 200 to 400 mg daily by mouth are usually given, although higher daily doses have been used, particularly in the management of dyskinesias. The drug has also been given by intramuscular or intravenous injection.[1] A review of the literature revealed that several methods have been used for the determination of tiapride hydrochloride. These include high performance liquid chromatography (HPLC),[2-5] gas chromatography,[6-8] spectrophotometry,[9,10] spectrofluorometry,[11] flow injection chemiluminometry,[12] ion selective electrodes,[13,14] capillary electrophoresis,[15] and capillary zone electrophoresis.[16] No voltammetric methods for the determination of this drug in pharmaceutical formulations or biological fluids have been reported in the literature to date. The present work aimed to study of the voltammetric behavior and assay of TiapCl at carbon paste electrodes using cyclic and differential pulse voltammetry.

Experimental

Reagents and materials

All chemicals were of analytical grade. Double distilled water was used throughout all experiments. Pure grade TiapCl and the pharmaceutical preparation tiapridal tablets (100 mg tiapride/tablet) were kindly supplied by Memphis Co. for Pharm. and Chem. Ind. Cairo, Egypt; graphite powder (1 – 2 μm) was from Aldrich, and paraffin oil was from Merck. As a supporting electrolyte, a series of 0.04 M Britton–Robinson (BR) buffers pH 2.0 – 11.5 (a mixture of each of acetic, orthophosphoric and boric acids), adjusted to the required pH with 0.2 M sodium hydroxide, was prepared.

Apparatus

All voltammetric measurements were performed using a Metrohm 757 VA Computrace (Herisau, Switzerland) equipped with a Metrohm VA 694 stand. The three electrode assembly cell consisted of a carbon paste electrode (CPE) as working electrode, an Ag/AgCl in 3 mol/L KCl (Metrohm 6.0728.000) as a reference electrode and a piece of platinum wire (Metrohm 6.0343.000) as an auxiliary electrode. The pH measurements were carried out with a Jenway Model 3305 pH meter.

Preparation of carbon paste electrode

The carbon paste was prepared by thoroughly mixing 5 g of graphite powder with 1.8 ml of paraffin oil in a mortar with a pestle. The carbon paste was packed into the hole of the electrode body and smoothed on a piece of clean paper until it had a shiny appearance. The electrode body was constructed by pressing a small rod of stainless-steel (diameter 2 mm) inside a micropipette tip (1 ml volume capacity), leaving a depression at the surface tip approximately 1 mm for housing the carbon paste; a thin wire was inserted through the opposite end to establish electrical contact.[17] The carbon paste electrode was

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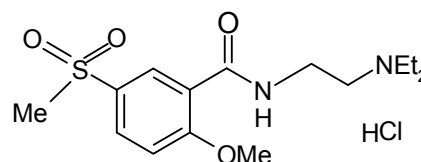
Scheme 1   Structural formula of tiapride hydrochloride.

immersed in the supporting electrolyte placed in the cell and several sweeps were applied to obtain a low background current.

Procedure

A 10-ml 0.04 M Britton–Robinson buffer pH 7.0 solution was introduced into the voltammetric cell then a known amount of the drug solution was pipetted into the cell. The differential pulse technique was applied by scanning from 0 to 1.2 V with a scan rate of 50 mV s^{-1}, and a pulse amplitude of 100 mV.

Determination of TiapCl in tiapridal tablets (100 mg tiapride/tablet)

Twenty tablets (each tablet contains 100 mg tiapride) were accurately weighed and powdered in a mortar. The required amount from the crushed tablet powder was dissolved in about 30 ml of bidistilled water and the mixture was filtered in a 100-ml measuring flask. The residue was washed three times with bidistilled water and the volume was completed to the mark by the same solvent. A 10-ml volume of 0.04 M Britton–Robinson buffer pH 7.0 was introduced into the voltammetric cell and a suitable volume of the above tablet solution was pipetted into the buffer in the voltammetric cell; the procedure is repeated as described above. The nominal content of the tablets is calculated using a standard addition technique.

Determination of TiapCl in spiked human urine

Here, 0.0365 g of TiapCl was dissolved in bidistilled water and transferred to a 100-ml measuring flask; 5 ml of urine of a healthy person was added and the mixture was completed to the mark by bidistilled water to prepare 10^{-3} M TiapCl in spiked urine sample. A 10-ml volume of 0.04 M Britton–Robinson buffer pH 7.0 was introduced into the voltammetric cell; different volumes of the above spiked urine sample were added. The procedure is repeated as described above. The amount of TiapCl is calculated using a standard addition technique.

Results and Discussion

Cyclic voltammetric studies

Figure 1 shows the cyclic voltammogram for 1.96 × 10^{-5} M TiapCl in 0.04 M Britton–Robinson buffer pH 7.0 at a scan rate of 50 mV s^{-1}. An oxidation peak appears at 0.821 V; this may be due to the oxidation of the amide group of the drug molecule. No reduction peak is observed in the cathodic branch, which suggests that the process is irreversible. The effects of scan rate on the peak current and peak potential were examined from 10 to 100 mV s^{-1}. A linear relation (plot of current against square root of scan rate) was obtained, indicating that diffusion is the means of mass transport.[18] This is confirmed by plotting the logarithm of peak current *vs.* the logarithm of the scan rate. This graph gives straight line relation with slope of 0.585, which is close to the theoretically expected 0.5 value for a diffusion-controlled process. The peak potential shifted to more positive values with increasing the scan rate. The suggested mechanism for the anodic oxidation of the amide group is that described by Radi *et al.*[19] It starts by one electron oxidation to form the cation radical at the nitrogen atom; this is followed by a rapid loss of a second electron and proton to give the iminium ion, to which the water is subsequently added. Therefore, the oxidation of TiapCl at carbon paste electrodes is an irreversible diffusion-controlled process with some kinetic control.
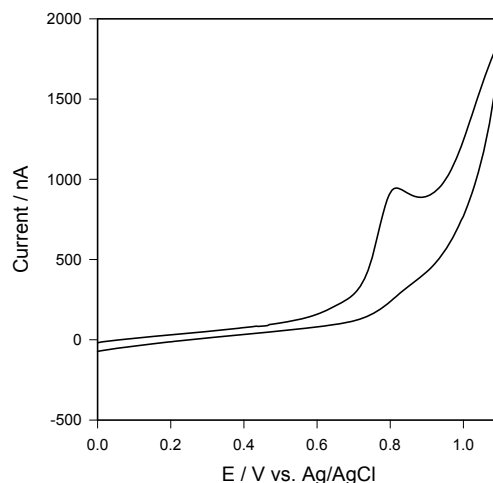

Fig. 1   Cyclic voltammogram for 1.96 × 10^{-5} M TiapCl in 0.04 M Britton–Robinson buffer pH 7.0 and scan rate of 50 mV s^{-1} on carbon paste electrode.
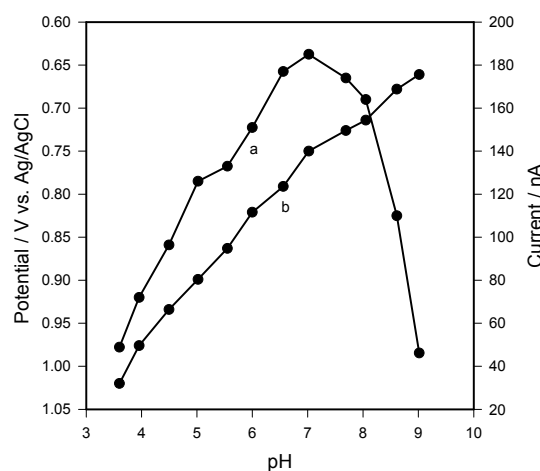

Fig. 2   Effect of pH on the DP anodic peak current (a) and peak potential (b) of 9.9 × 10^{-6} M TiapCl in 0.04 M BR buffer, pulse amplitude 50 mV.

DP voltammetric studies

Various supporting electrolytes such as phosphate buffer, Britton–Robinson buffer, potassium chloride and sodium perchlorate were examined. The best results with respect to sensitivity accompanied with sharper response were obtained in the case of Britton–Robinson buffer, so this electrolyte was selected for further work. The effects of pH on the peak current and oxidation potential were studied over the pH range 2.0 – 11.0. Plots of pH *vs.* peak current and peak potential are given in Fig. 2. The peak current shows its maximum value at pH 7.0; this was therefore used for the drug determination. The peak potential is shifted to less positive values with increasing pH, indicating that the protons are involved in the electrode reaction process. The plot of peak potential *vs.* pH exhibits two linear intervals in the pH ranges of 2.0 – 7.0 and 7.0 – 9.0 with slopes of –76.0 and –46.0 mV per pH unit. The break at pH 7.0 may be correlated to the pK_a of the drug. The effect of the supporting electrolyte (BR buffer) concentrations (0.02, 0.04 and 0.1 M) indicated that the highest peak current was obtained at 0.04 M BR buffer.
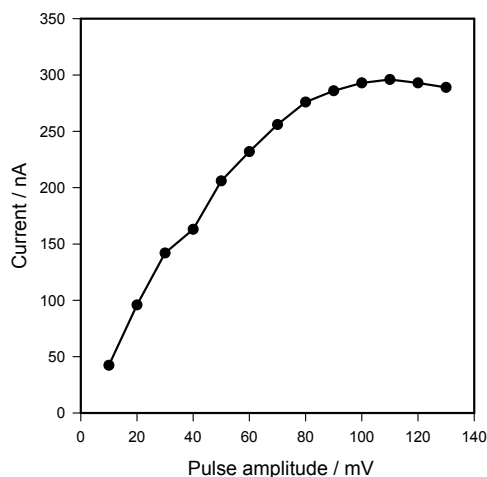
Fig. 3   Effect of pulse amplitude on the peak current for 9.9×10^{-6} M TiapCl in 0.04 M Britton–Robinson buffer pH 7.0 and a scan rate of 50 mV.
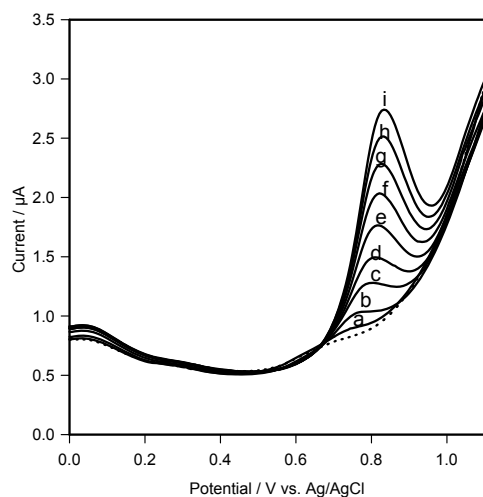

Fig. 4   Differential pulse voltammograms for different concentrations of TiapCl in 0.04 M Britton–Robinson buffer pH 7.0, scan rate of 50 mV s^{-1} and pulse amplitude 100 mV: a, 0.36; b, 1.45; c, 2.90; d, 5.75; e, 8.55; f, 11.31; g, 14.03; h, 16.71; i, 19.35 μg/ml TiapCl. The dotted line represents the blank solution.

Table 1   The analytical parameter of the calibration graph for the determination of TiapCl by differential pulse anodic voltammetric method

Parameter	
Linear range/μg ml^{-1}	0.36 – 19.35
Slope	69.98
Intercept	10.27
Correlation coefficient (r)	0.9998
LOD/μg ml^{-1}	0.12
LOQ/μg ml^{-1}	0.40

Table 2   Robustness results of the proposed method

Variable		Recovery, %	RSD
pH 6.9		98.50	1.19
7.0		99.12	1.52
7.1		100.90	0.96
Pulse ampltude	98	98.31	1.05
	100	99.12	1.52
	102	99.74	1.14

Average of four determinations.

of the calibration graph. LOD and LOQ were found to be 0.12 and 0.40 μg/ml, respectively. The analytical parameters for the calibration graph are summarized in Table 1.

Reproducibility and robustness

The intra-day and inter-day (day-to-day) precision expressed as relative standard deviations were 1.77 and 2.24%, respectively.

The robustness[19] of the proposed method was examined by evaluating the effect of small changes in some of the most important procedure parameters, including the pH of the Britton–Robinson (BR) buffer (6.9 – 7.1) and the pulse amplitude (98 – 102 mV). None of the changes significantly affect the drug recovery (Table 2); consequently, the optimized procedure was reliable for the assay of TiapCl and it could be considered robust.

Interference

The effect of interference from excipients usually present in pharmaceutical formulations was examined. No interference (<2.7% change in oxidation current) was observed in the presence of 100 fold excess of lactose, talc, starch or magnesium stearate.

Determination of tiapride in tiapridal tablets

The proposed DP volltammetric method was successfully applied for the assay of tiapride in tiapridal tablets (100 mg tiapride/tablet).   Figure 5 represents the differential pulse voltammograms recorded after the standard addition for the determination of the drug in pharmaceutical preparation tiapridal tablets. The percentage mean recovery based on the average of four replicate determinations and the relative standard deviation values are summarized in Table 3. The data indicate that there is no interference from the excipients used in the formulations of the tablets. The results of the proposed voltammetric method were compared with the results of the manufacturers spectrophotometric method supplied by Memphis (personal communication) by means of Student's t- and F-ratio tests at 95% confidence level;[21] there is no significant difference in accuracy or precision between the two methods.

The influence of the peak current of 9.9×10^{-6} M TiapCl with change in pulse amplitude over the range 10 – 100 mV was studied; the peak current increased from 10 to 100 mV pulse amplitude, then remained nearly constant as in Fig. 3, so a pulse amplitude of 100 mV was selected for further work.

Calibration graph, limit of detection and limit of quantitation

On the basis of the electrochemical oxidation of TiapCl at carbon paste electrodes under the optimum conditions, the differential pulse voltammetric method was developed for the determination of the drug over the concentration range 0.36 – 19.35 μg/ml TiapCl. Figure 4 represents the differential pulse anodic voltammograms recorded using the standard addition method.   The linear regression equation was I (nA) = 10.27 + 69.98C (μg/ml) with a correlation coefficient of 0.9998. The limit of detection (LOD = 3(SDa)/b) and limit of quantitation (LOQ = 10(SDa)/b) were calculated,[20] where SDa is the standard deviation of the intercept and b is the slope
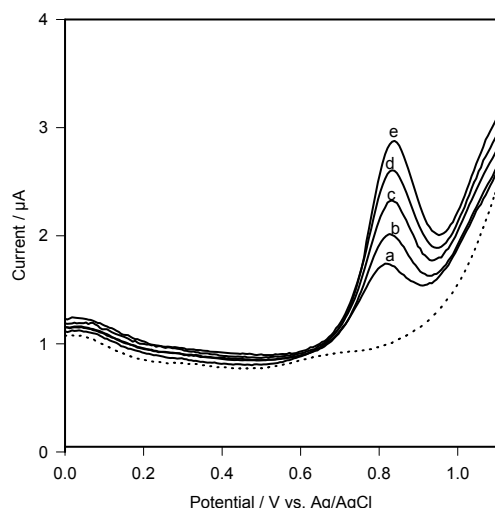
Fig. 5 Differential pulse voltammograms obtained for the determination of TiapCl in the pharmaceutical preparation tiapridal tablets in 0.04 M Britton–Robinson buffer pH 7.0 at a scan rate of 50 mV s^{-1} and pulse amplitude 100 mV: a, 1.96×10^{-5} M TiapCl in tablets; b, 9.71×10^{-6}; c, 1.92×10^{-5}; d, 2.86×10^{-5}; e, 3.77×10^{-5} M TiapCl. The dotted line represents the blank solution.
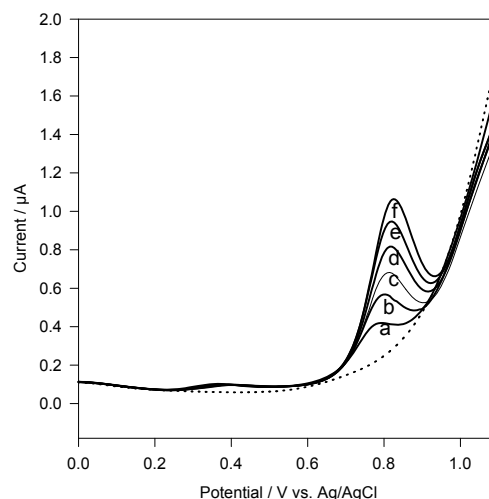

Fig. 6 Differential pulse voltammograms obtained for the determination of TiapCl spiked into human urine in 0.04 M Britton–Robinson buffer pH 7.0 at scan rate of 50 mV s^{-1} and pulse amplitude 100 mV: a, spiked urine sample containing 7.94×10^{-6} M TiapCl; b, 7.87×10^{-6}; c, 1.56×10^{-5}; d, 2.33×10^{-5}; e, 3.08×10^{-5}; f, 3.82×10^{-5} M TiapCl. The dotted line represents the blank solution.

Table 3 Statistical comparison between the results of tiapridal tablets using the proposed DP voltammetric method and those using the reference method

Parameter	Proposed method	Reference method
Mean recovery, %	99.32	99.44
SD	0.489	0.594
RSD, %	0.492	0.597
F-ratio (6.59)	1.476	
t-test (2.36)	0.325	

Table 4 Determination of TiapCl in spiked urine samples using the proposed method

Taken/M	Found/M	Recovery, %	RSD
7.94×10^{-6}	7.91×10^{-6}	99.62	0.59
9.90×10^{-6}	9.94×10^{-6}	100.40	1.31

Average of four determinations.

Determination of TiapCl in human urine

Tiapride is rapidly absorbed after oral doses and peak plasma concentrations occur after 1 to 2 h. It is excreted largely unchanged in the urine.[1] The high selectivity of the method allowed the determination of TiapCl in spiked human urine using the standard addition method at two different levels of concentrations: 7.94×10^{-6} and 9.90×10^{-6} M TiapCl. The mean recoveries for the two concentrations were 99.62 and 100.40% with relative standard deviations of 0.59 and 1.31% (Table 4). Typical differential pulse voltammograms for the determination of TiapCl in spiked human urine are shown in Fig. 6.

Conclusions

The electrochemical behavior of tiapride hydrochloride (TiapCl)

on carbon paste electrodes was established. Novel DP voltammetric procedures have been developed for the determination of this drug in pharmaceutical formulation and in spiked human urine samples. The simplicity, sensitivity, selectivity, low cost and short time of analysis of the developed method suggest its applications in quality control analysis.

References

1. S. C. Sweetman, "Martindale", The Complete Drug Reference, 35th ed., **2007**, Pharmaceutical Press, London, 928.
2. R. Chiba, A. Ogasawara, T. Kubo, H. Yamazaki, M. Umino, and Y. Ishizuka, *Anal. Sci.*, **2003**, *19*, 785.
3. T. R. Norman, R. H. James, and M. S. Gregory, *J. Chromatogr. Biomed. Appl.*, **1986**, *48*, 197.
4. G. Duan, M. Lu, and B. Wu, *Yaoxue Xuebao*, **1986**, *21*, 917.
5. N. Verbies-Genard, M. Hanocq, C. Alvoet, and L. Molle, *Anal. Lett.*, **1982**, *15*, 1317.
6. F. Plossl, M. Giera, and F. Bracher, *J. Chromatogr., A*, **2006**, *1135*, 19.
7. A. Valli, A. Polettini, P. Papa, and M. Montagna, *Therapeutic Drug Monitoring*, **2001**, *23*, 287.
8. A. Kamizono, N. Inotsume, K. Miyamoto, K. Ueda, T. Miyakawa, H. Arimoto, and M. Nakano, *J. Chromatogr. Biomed. Appl.*, **1991**, *105*, 113.
9. B. Wu, M. Lu, Y. Wang, and X. Fang, *Yaowu Fenxi Zazhi*, **1985**, *5*, 20.
10. B. Wu, M. Lu, Y. Wang, and X. Fang, *Yaoxue Tongbao*, **1984**, *19*, 58.
11. M. Buna, J.-J. Aaron, P. Prognon, and G. Mahuzier, *Analyst*, **1996**, *121*, 1551.
12. F. A. Aly, N. A. Alarfaj, and A. A. Alwarthan, *Talanta*, **2001**, *54*, 715.
13. F. H. Metwally, *Yakugaku Zasshi*, **2007**, *127*, 1267.
14. J. A. Ortuno, V. Rodenas, M. S. Garcia, M. I. Albero, and C. Sanchez-Pedreno, *Sensors*, **2007**, *7*, 400.

15. J. G. Li, F. J. Zhao, and H. X. Ju, *J. Chromatogr., B: Anal. Technol. Biomed. Life Sci*., **2006**, *835*, 84

16. Y. Wang, L. Zhou, Y. Hui, and X. Chen, *Chromatographia*, **2009**, *70*, 293.

17. A. Elyacoubi, S. I. M. Zayed, B. Blankert, and J.-M. Kauffmann, *Electroanalysis*, **2006**, *18*, 345.

18. P. Monk, "*Fundamentals of Electroanalytical Chemistry*," **2001**, Wiley, 162 – 166.

19. A. Radi, M. A. El Ries, F. El Anwar, and Z. El Sherif, *Anal. Lett*., **2001**, *34*, 739.

20. M. Swartz and I. S. Krull, "*Analytical Method Development and Validation*", **1997**, Marcel Dekker, Inc., 61.

21. J. C. Miller and J. N. Miller, "*Statistics for Analytical Chemistry*", 3rd ed., **1993**, Ellis Horwood, Chichester, 53.