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# Voltammetric Determination of Thioridazine Hydrochloride

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This study describes the optimal conditions for the determination of Thioridazine HCl (Tz-HCl) in 0.2 M sulphuric acid by voltammetry using ruthenium (Ru), platinum (Pt) and glassy carbon (GC) electrodes.

A new and sensitive method is described for electrochemical determination of Tz-HCl in the concentration range $5.10^{-5} - 10^{-3}$ M (20.35-407 $\mu gml^{-1}$); $6.10^{-4} - 10^{-2}$ M (244.2 - 4070 $\mu gml^{-1}$); $10^{-4} - 10^{-3}$ M (40,7 - 407 $\mu gml^{-1}$), with Ru, Pt and glassy carbon electrodes, respectively. The method was applied successfully to the determination of Tz-HCl in pure form or incorporated in their representative pharmaceutical preparations. The precision of the assay was comparable with that of the official assays.

**Keywords:** Thioridazine hydrochloride; voltammetry; ruthenium, platinum, glassy carbon electrodes.

## Introduction

Thioridazine hydrochloride, a member of the phenothiazine group, is one of the most widely used drugs in the treatment of psychiatric patients. It has a tranquilizing effect, but no therapeutically significant anti-emetic or hypothermic effect, which other phenothiazine drugs have, and does not potentiate the action of anestetics. Thioridazine is used mainly in the treatment of schizophrenia and the control of mania and agitation. It may be used in the management of anxiety states, children who have behavior problems. In thioridazine hydrochloride [(Tz-HCl)-[10-2-(1-methyl-2-piperidyl)ethyl]-2-(methylthio)phenothiazine monohydrochloride] the piperidyl group has important tranquilizing effects (Figure 1). Thioridazine hydrochloride can be determined by various techniques, including chromatography[1−13], spectroscopy[14,15], titrimetry[1,15,16] and electrochemical[18−23] methods. Thioridazine has two S atoms in the structure which can be easily oxidized, one in the ring and the other in the side chain. Since Ring-S-oxidation is an important step in the metabolism of phenothiazine drugs in man, extensive studies have been done on the oxidation mechanism of this group. In recent studies, $RuO_2$ has been of considerable interest as an effective electrocatalyst for certain electro-oxidation reactions. In our previous studies, electro-oxidation of phenothiazines were investigated with Ru and Pt electrodes[22−25]. The surface of a solid electrode changes with time due to adsorption of species

from solutions or chemical changes to the surface itself. Nevertheless, in recent years solid electrodes have gained popularity in electroanalytical chemistry because of their applicability to anodic oxidations and to liquid chromatography with electrochemical detection, which is a very useful method for the measurement of trace quantities of organic compounds, and because of the possibility of in vivo determinations with solid electrodes. In order to obtain reproducible results, the electrodes should be pretreated before each experiment, and the pretreatment procedure varies from one electrode material to the other.

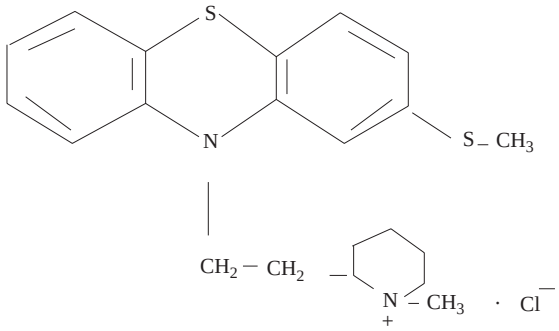


**Figure 1.** Structure of thioridazine hydrochloride.

In this study, the electro-oxidation of Tz-HCl was investigated with Ru, Pt, GC electrodes and the experimental results obtained under optimum conditions were discussed. A further aim of this study was to compare the results obtained by applying the proposed technique to the analysis of the dosage forms of tablets containing Tz-HCl, available in Turkey, with those of the pharmacopoeial technique[14].

# Experimental

### Apparatus

A Tacussel PRG 3 polarographic potentiostat with an EPL 2 recorder was used to record the voltammograms. A ruthenium wire (Engelhard, 1 mm in diammeter and 38.1 mm in length) and a platinum wire (Tacussel, 1 mm in diammeter and 14.8 mm in length) and a glassy carbon electrode (Tacussel, Type XM 540, area: 1.013 $cm^2$) were used as working electrodes.

A Wenking model HP 10 potentiostat and an exact-type 250 function generator were employed for square-wave and high-frequency, multiscan triangular sweep. The ruthenium electrode was constructed in our laboratory by welding onto a pyrex glass by means of a platinum joint. A platinum wire (Johnson Matthey)® was used as a counter electrode. The potential was measured with reference to a Tacussel, type C-10 saturated calomel electrode, but the potentials in the figures were given relative to the standard hydrogen electrode. All electrochemical experiments and electrode pre-treatment were performed in a three-compartment experimental cell made of Pyrex® glass.

### Chemicals

The thioridazine hydrochloride used as the standard was obtained from Sandoz Pharmaceuticals (Turkey), and the Melleril® tablets and Mellerettes® drops, containing Tz-HCl (100mg dosage) and (30 mg dosage), respectively, were obtained from local drugstores. All chemicals and standard substances were of analytical grade. Pure nitrogen gas was bubbled through the electrolytic solution to remove dissolved oxygen before each experiment. In order to prepare a $10^{-3}$ M stock solution of the standard, Tz-HCl was weighted and dissolved in 0.2 M $H_2SO_4$ (as supporting electrolyte). Solutions of different concentrations, in which

voltammograms were recorded, were prepared by diluting this stock solution. Doubly distilled water was used in preparation of all solutions, and spectroscopic determinations were performed using a Pye-Unicam SP 8-100 spectrophotometer.

**Electrode Pre-treatment**

In order to obtain reproducible results, the solid electrodes were cleaned and activated by the proper procedures. The ruthenium electrode was electrolytically reduced at -0.1 V for 5 min and then oxidized at 0.4 V for 15 min, in 0.5 M $H_2SO_4$, before each experiment. The platinum electrode was oxidized at 1350 mV for 5 min, and then a potential of 300 mV was applied until the current became zero.

A new GC electrode was pretreated in five steps: (I) It was polished with emery (No:600), followed by 0.3 $\mu$m alumina slurry and rinsed with water; (II) The electrode was subjected to an electrochemical pretreatment by applying a potential of 1.75 V for 5 min followed by the application of -0.75 V for 2 sec in 0.1 M $KNO_3$; (III) A square wave potential with a frequency of 350 Hz between $\pm 6$ V for 30 min in 0.1 M $KNO_3$ was cycled; (IV) A triangular potential sweep was applied between $\pm 6$ V with a frequency of 3500 Hz in 0.1 M $KNO_3$; (V) All previous steps were repeated in the order I, III, IV and II. Step V was repeated until the voltammograms become reproducible. Thus the surface of the electrode was stable for about 40 measurements, and the electrochemical pretreatment alone (Step II) was sufficient for the purpose. According to previous experiments, when Step V is repeated in the order given above, the best results are obtained[29].

## Results and Discussion

In this study, the tests were performed in 0.2 M $H_2SO_4$ solution using Pt, Ru, and GC electrodes. The best results were obtained with a scan rate of 10 $mVs^{-1}$ with Pt and Ru and 100 $mVs^{-1}$ with GC electrode (Figures 2, 3, 4, respectively). With a Pt electrode, the voltammograms have three oxidation steps. The first two are peak-shaped, the peak potentials of which are 850 mV and 1150 mV, and as Tz-HCl concentration increases, the peaks become sharper. The third one beginning from about 1300 mV shows a limiting current region. Another step, not well-defined, is seen at more positive potentials overlapped with the oxygene evolution step. On the reverse sweep, the only well-defined peak, which is observed at about 700 mV, corresponds to the reduction of the surface oxides of Pt[17]. The peak current of this peak decreases with the increase in Tz-HCl concentration. The reason may be that the oxide layers was not completely formed at the anodic step because of the coverage of the surface with the oxidation products.

The peak current-concentration relationships for the peaks at approximately 800 and 1150 mV are linear in the concentration range of $6.10^{-4} - 10^{-2}$ M. The linear regression analysis of Figure 2 is given in Table 1.

**Table 1.** Concentration-Limiting current density relationship* with Pt electrode in Figure 2.

| Concentration (M) | $6.10^{-4}$ | $8.10^{-4}$ | $1.10^{-3}$ | $2.10^{-3}$ | $4.10^{-3}$ | $6.10^{-3}$ | $8.10^{-3}$ | $10^{-2}$ |
|---|---|---|---|---|---|---|---|---|
| (Limiting current density $\mu Acm^{-2}$ at 800mV) | 10.85 | 15.20 | 18.95 | 27.12 | 43.4 | 62.35 | 80.12 | 97.65 |

* Regression line: $Y = 8,99.10^3 x + 8{,}03$; r = 0.999 (n=8)

Standard error of slope = $1,29 \times 10^2$

Standard error of intercept = 0,68

The electro-oxidation of phenothiazines has been the subject of a number of studies because the data give some information about their clinical activities, and the explanation of the electrode reaction may shed some light on the drug-receptor interaction[27,28]. Although the electro-oxidation mechanism of phenothiazines is still under investigation, according to a possible mechanism proposed by Takamura et.al.[26], the three peaks in strongly acidic media correspond to the formation of Chlorpromazine cation ($CPZ^{+}$.), and CPZ sulfoxide (CPZO), and, in the case of Tz-HCl, oxidation of this substance.

The additional peak on the oxidation branch of the voltammograms of Figure 2 may be attributed to the side chain S oxidation.

In Figure 3, the voltammograms, obtained in 0.2 M $H_2SO_4$ solution having $5.10^{-5} - 10^{-3}$ M Tz-HCl with a Ru electrode, are shown.

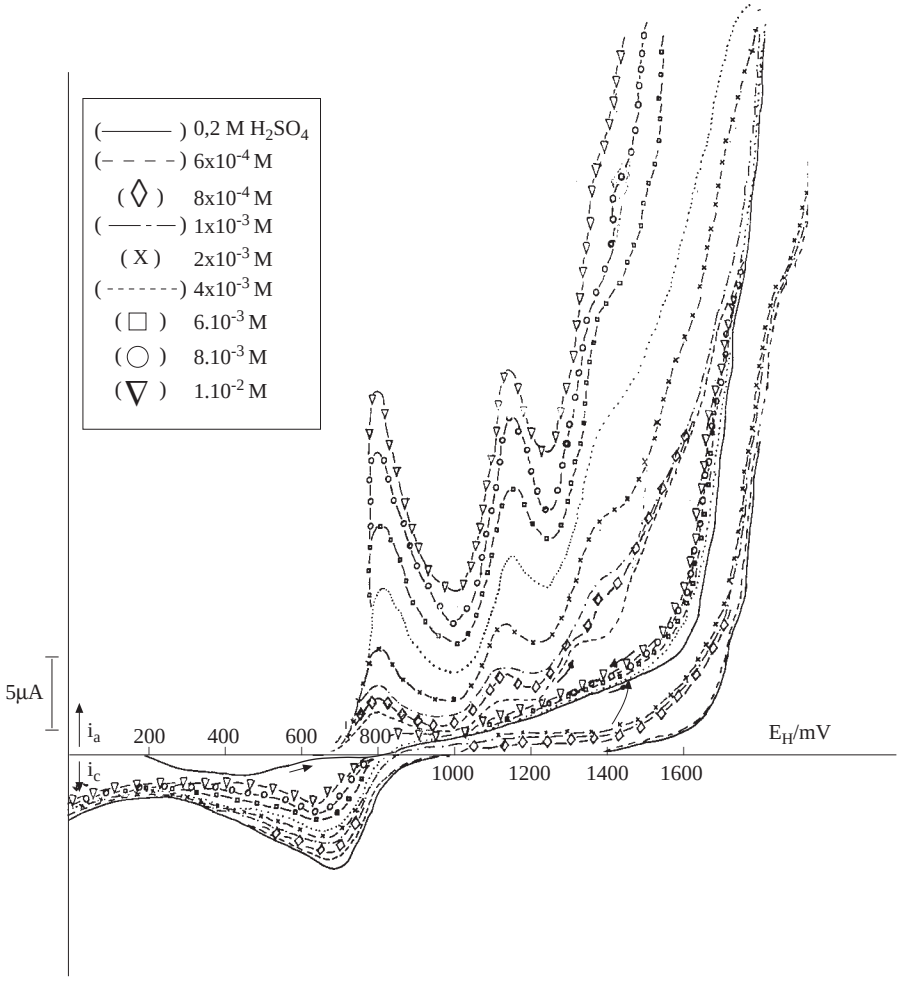


**Figure 2.** Voltammograms obtained for solutions 0.2 M $H_2SO_4$ of various concentration of Thioridazine HCl using Pt electrode. Scan rate, 10 $mVs^{-1}$.

On these curves, only one oxidation peak can be seen, at about 800 mV, because $RuO_4$ formation begins with oxygene evolution at the potential range corresponding to the second and third peaks in Figure 2. Oxygen evolves at less positive potentials on Ru than on Pt. On the reduction branch, a broad reduction peak can be seen at about 700 mV, the peak current of which decreases with the increase in concentration. A linear relationship between the anodic peak current and Tz-HCl concentration was obtained in the concentration

range of $5.10^{-5} - 10^{-3}$ M, the linear regression analysis of which is given in Table 2. With activated G.C.E. (Figure 4), three oxidation peaks were obtained at about 650, 800, and 1100 mV.

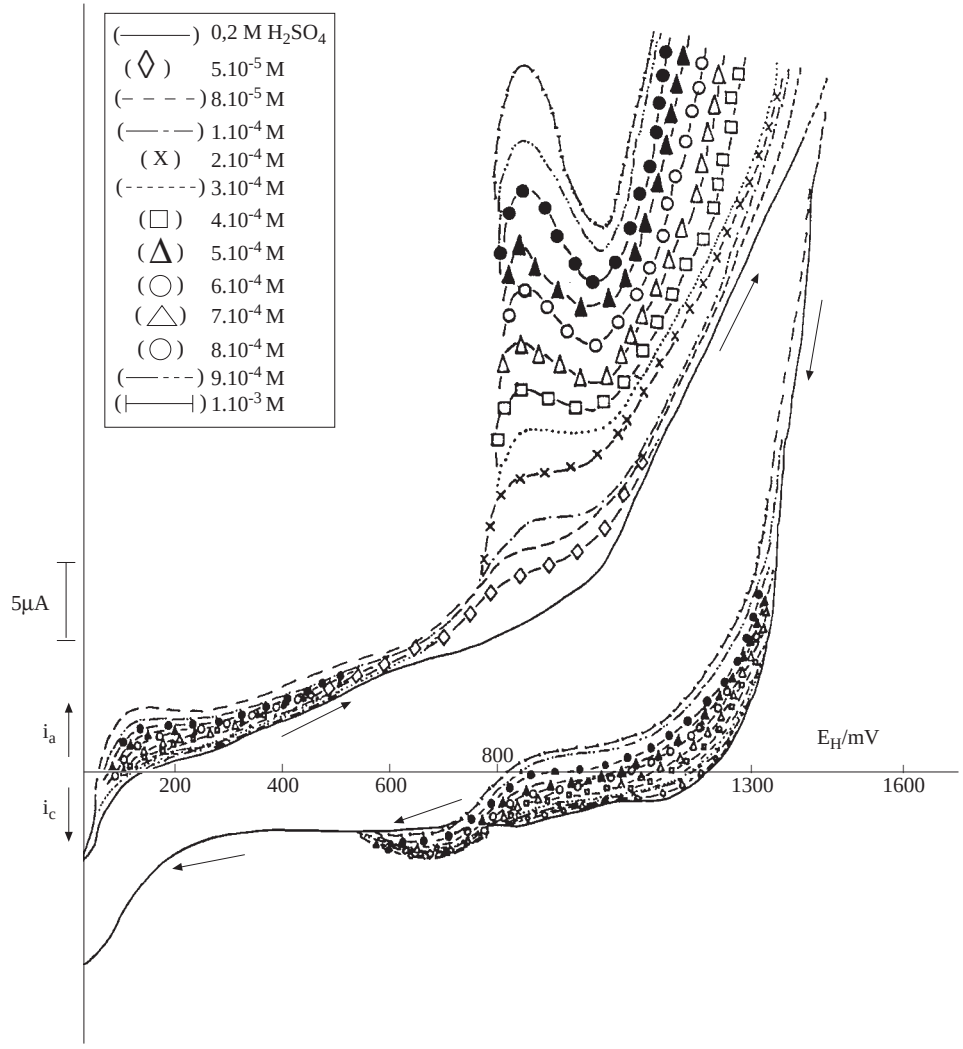


**Figure 3.** Voltammograms obtained for 0.2 M $H_2SO_4$ containing various concentration of Thioridazine HCl. Ru electrode was used in stirred solutions. Scan rate, 10 $mVs^{-1}$.

**Table 2.** Concentration-Limiting current density relationship* with Ru electrode in Figure 3.

| Concentration (M) | $5.10^{-5}$ | $8.10^{-5}$ | $1.10^{-4}$ | $2.10^{-4}$ | $3.10^{-4}$ | $4.10^{-4}$ | $5.10^{-4}$ | $6.10^{-4}$ | $7.10^{-4}$ | $8.10^{-4}$ | $9.10^{-4}$ | $1.10^{-3}$ |
|---|---|---|---|---|---|---|---|---|---|---|---|---|
| (Limiting current density $\mu Acm^{-2}$ at 800mV | 3.92 | 5.79 | 7.83 | 11.75 | 15.66 | 19.58 | 23.49 | 27.41 | 31.33 | 35.24 | 39.16 | 43.07 |

*Regression line: $y = 4{,}02.10^4 x + 3{,}14$; r = 0.999 (n=12)

Standard error of slope = $4{,}63 \times 10^2$

Standard error of intercept = 0,26

The peak potential of the second peak shifts towards more positive potentials as the concentration increases. On the reverse scan, the reduction of the substance begins at about 600 mV. The current of this reduction step is higher than in supporting electrolyte, but no regular increase with the Tz-HCl concentration was observed. A linear dependence of peak current on the Tz-HCl concentration was obtained for the second

peak at about 800 mV, in the concentration range of $10^{-4} - 10^{-3}$ M, the linear regression analysis of which is shown in Table 3.

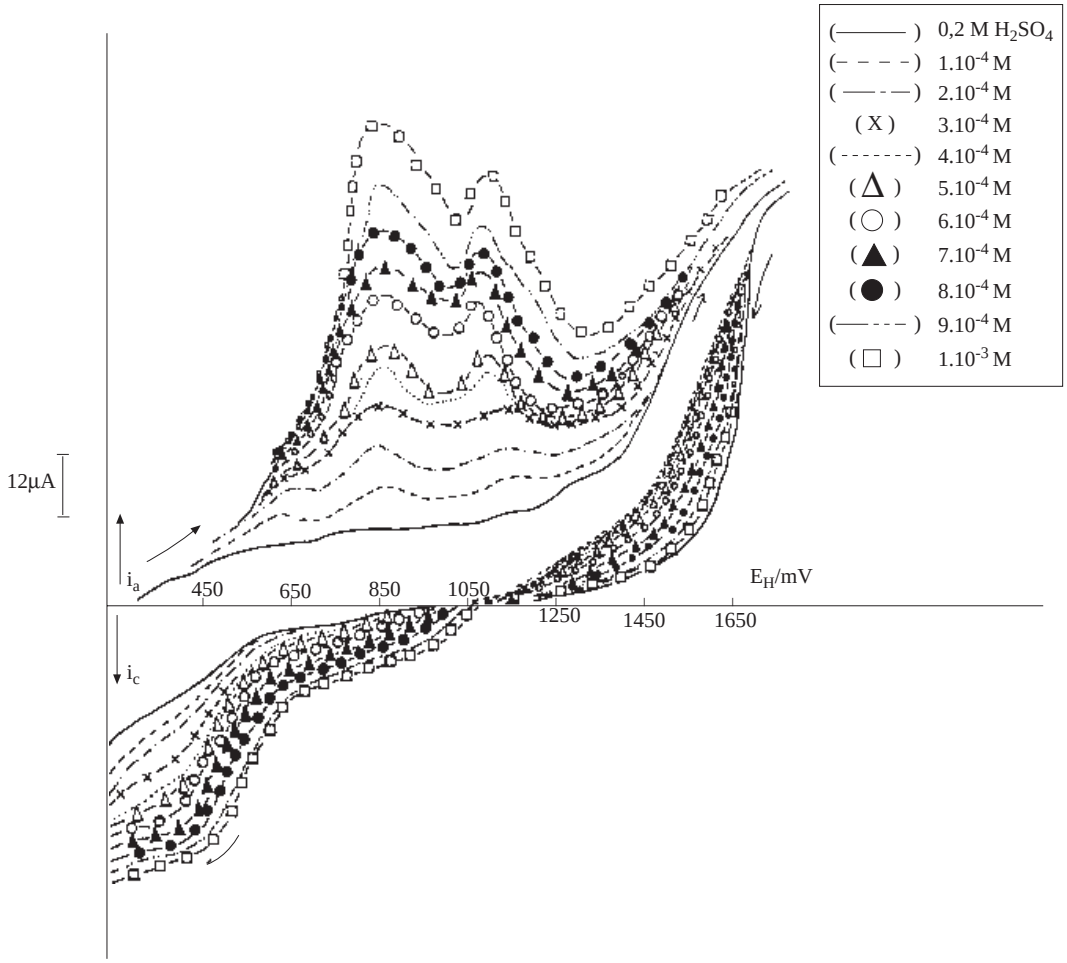


**Figure 4.** Voltammograms obtained for 0.2 M $H_2SO_4$ containing various concentrations of Thioridazine HCl with glassy carbon electrode. Scan rate, 100 $mVs^{-1}$.

**Table 3.** Concentration-Limiting current density relationship* with GC electrode in Figure 4.

| Concentration (M) | $1.10^{-4}$ | $2.10^{-4}$ | $3.10^{-4}$ | $4.10^{-4}$ | $5.10^{-4}$ | $6.10^{-4}$ | $7.10^{-4}$ | $8.10^{-4}$ | $9.10^{-4}$ | $10^{-3}$ |
|---|---|---|---|---|---|---|---|---|---|---|
| (Limiting current density $\mu Acm^{-2}$ at 850mV | 9.67 | 19.7 | 29.6 | 41.10 | 49.2 | 59.95 | 71.0 | 79.85 | 92.5 | 100 |

*Regression line: y = $1{,}02.10^5$ x - 0,57; r = 0.999 (n=10)
Standard error of slope = $9{,}08 \times 10^2$
Standard error of intercept = 0,56

The results revealed that voltammetric determination of thioridazine HCl is possible with Pt, Ru, and GC electrodes. In Tables 1, 2 and 3, the linear regression analysis of peak current concentration relationship obtained with these electrodes is given. It is seen that lowest determination limit can be obtained with a Ru electrode.

## Analysis of Pharmaceutical Dosage Forms

The applicability of the voltammetric method for the assay of a simple dosage-form was examined by analysing Thioridazine hydrochloride tablets and oral solutions. The results confirm the suitability of the proposed method for the accurate and sensitive analysis of Thioridazine hydrochloride, both in the bulk drug and in dosage-form.

Melleril® and Mellerettes® commercial drugs, which contain Thioridazine hydrochloride, were analysed under the electro-oxidation conditions used for the determination of standard Thioridazine hydrochloride. Comparison of the voltammograms obtained for the same concentration of Tz-HCl in both the standard and drug solutions showed that the additives present in the drug did not affect the procedure.

For the drug analysis, 20 tablets were weighed accurately and ground to a fine powder. Melleril® tablets containing the equivalent of 100 mg Tz-HCl weighed 0.651 gr, accurately dissolved in 0.2 M $H_2SO_4$, and made up to 100 ml in a calibrated flask with the same solution. A 50.0 ml aliquot of the solution was stirred with a magnetic stirrer for about 30 min and transferred to a tube and centrifuged and diluted to 100 ml with 0.2 M $H_2SO_4$. 75.00 ml was taken from this solution and a drug solution of $6 \times 10^{-4}$ M was prepared by the addition of 0.2 M $H_2SO_4$ solution. Voltammograms of this solution were recorded under standard working conditions.

For oral solution analysis, the same procedure was followed by taking 1.0 ml of drug solution instead of tablet and dilutions. The British Pharmacopeial method[15] was also applied to the same tablet and oral forms of the drug.

The voltammetric results obtained for tablet and oral solution forms were compared to those of spectrophotometric methods given in the British Pharmacopeia[15]. For the statistical analysis of these parameters, one-tailed student's t-test was used. On applying the t-test at the 95% confidence level, no significant difference was found between the mean recoveries obtained with the voltammetric and spectrophotometric method given in BP[15]. The results are given in Table 4.

The United States Pharmocopeia states that Tz-HCl should be in the range between 90% and 110% of the given amount for one tablet or one dose. The voltammetric and spectroscopic analysis data obtained in this study fall within this range, and furthermore there is no important difference between the two techniques for all the electrodes used in this study.

Thus the voltammetric method is directly applicable to drugs and is more rapid than the United States Pharmacopeia method, as it has no extraction step.

**Table 4.** Results of the analysis of Melleril® tablet and Mellerettes ® oral-drops for Thioridazine HCl

| | Found by Voltammetric method (Ru electrode) | | Found by Voltammetric method (Pt electrode) | | Found by Voltammetric method (GC electrode) | | F Offi (Spectroph |
|---|---|---|---|---|---|---|---|
| Sample No | Melleril® mg per tablet | Mellerettes® mg per drop | Melleril® mg per tablet | Mellerettes® mg per drop | Melleril® mg per tablet | Mellerettes® mg per drop | Melleril® mg per tab |
| 1 | 101.70 | 29.91 | 100.01 | 28.95 | 98.47 | 29.25 | 103. |
| 2 | 99.70 | 29.50 | 98.96 | 29.90 | 99.78 | 28.90 | 98. |
| 3 | 99.30 | 29.31 | 99.01 | 29.96 | 100.10 | 31.40 | 98. |
| 4 | 96.90 | 30.50 | 97.92 | 30.30 | 101.80 | 29.31 | 102. |
| 5 | 100.10 | 30.40 | 98.02 | 30.46 | 101.10 | 28.40 | 101. |
| 6 | 98.90 | 31.08 | 98.33 | 31.00 | 101.80 | 30.00 | 101. |
| 7 | 99.70 | 31.40 | 100.01 | 31.10 | 96.80 | 29.40 | 98. |
| 8 | 98.50 | 31.20 | 101.40 | 30.40 | 97.80 | 31.08 | 101. |
| 9 | 101.10 | 29.00 | 99.86 | 31.08 | 97.92 | 30.50 | 101. |
| 10 | 97.00 | 29.75 | 96.86 | 28.75 | 97.00 | 30.80 | 99. |
| Mean value | $99.61 \pm 1.21$ | $30.20 \pm 0.6$ | $99.52 \pm 1.42$ | $30.19 \pm 0.61$ | $99.25 \pm 1.37$ | $29.9 \pm 0.72$ | $100.68 \pm 1$ |
| Standard deviation | 1.69 | 0.84 | 1.98 | 0.83 | 1.91 | 1 | 1. |
| Standard error | 0.54 | 0.26 | 0.63 | 0.26 | 0.61 | 0.32 | 0. |
| Theoretical value | 100 | 30 | 100 | 30 | 100 | 30 | 1 |
| Calculated t values | 1.35 | 1.66 | 1.36 | 1.73 | 1.70 | 1.92 | |
| Tabulated t-value ($\Phi = 9$; P'=0.05) | 2.26 | 2.26 | 2.26 | 2.26 | 2.26 | 2.26 | |

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