

DETERMINATION OF PIOGLITAZONE HYDROCHLORIDE IN BOTH PURE FORM AND PHARMACEUTICAL FORMULATIONS

Manar Alkhoury^{1*}, Deeb Bakir², Yumen Hilal³

¹Doctor 's Student. in Electrical Chemistry- Faculty of Science at Al-Baath University, Homs, Syria.

²Prof. Dr. in Electrical Chemistry- Faculty of Science at Al-Baath University, Homs, Syria.

³Dr. in Pharmaceutical Analytical and Food Chemistry, – Faculty of Pharmacy at Al-Baath University, Homs, Syria.

Article Received date: 12 July 2025

Article Revised date: 01 August 2025

Article Accepted date: 20 August 2025



*Corresponding Author: Manar Alkhoury

Doctor 's Student. in Electrical Chemistry- Faculty of Science at Al-Baath University, Homs, Syria.

ABSTRACT

A novel, high throughput and sensitive method is described for the determination of pioglitazone hydrochloride (PGZ-HCl) as anti-diabetic in its pure form and pharmaceutical formulations. The proposed method depends on the polarographic activity of in HCl (0.5 M) using by cyclic voltammetry (CV), and it showed well-defined one cathodic peak with high selectivity. Polarograms of the PGZ-HCl at (CV) in HCl (0.5 M) exhibited 4-electron irreversible cathodic peak, versus Ag/AgCl. The peak may be attributed to the reduction of carbonyl group (-CO-). The diffusion current-concentration relationship was found to be rectilinear over the range (117 - 392) mg/L for Ep using by cyclic voltammetry (CV). The peaks were defined as being irreversible, diffusion-controlled although adsorption phenomenon played a limited role in the electrode process. The suggested method was novel, simple, accurate and successfully applied to the detection PGZ-HCl in pharmaceuticals and the average percentage recovery was in agreement with that obtained by the official USP method.

KEYWORDS: Cyclic voltammetry method, Reduction, Gold electrode, Diabetes mellitus, Pharmaceutical Formulations, Polarogram.

INTRODUCTION

Voltammetric methods used today in analytical laboratories comprise a suite of techniques, the creation of which was made possible by rapid advances in instrumentation, by the computerized processing of analytical data, and particularly by innovative electrochemists.^[1] Polarography is still the best known classical measuring method in electroanalytical chemistry. However, in recent years its position has been challenged by cyclic voltammetry (CV). Cyclic voltammetry has the further attraction of providing information not only on the thermodynamics of redox processes but also on the kinetics of heterogeneous electron-transfer reactions and coupled chemical reactions.^[2] Cyclic voltammetry is a popular member of a family of dynamic electrochemical methods in which the potential applied to an electrochemical cell is scanned.^[3] The resulting cell current is output vs. potential. A typical three-electrode cell suitable for studies of materials includes a reference electrode, a counter electrode, and a working electrode.^[4]

Type-2 diabetes mellitus (T2DM) is a complex metabolic disorder characterized by the pancreatic impairment to secrete the insulin or the resistance of peripheral tissues to the insulin or both.^[5]

The drugs used for the management of diabetes treat diabetes mellitus by lowering glucose levels in the blood. With the exceptions of insulin, exenatide, liraglutide and pramlintide; all are administered through oral route and are also called oral hypoglycemic agents/ oral anti-hyperglycemic agents. There are different classes of anti-diabetic drugs, and their selection depends on the nature of the diabetes, age and situation of the person, as well as other factors.^[6]

Recently, electrochemical analysis has gained great importance in the field of bioanalysis. There are many reasons why it occupies the first place, as it combines great sensitivity and excellent detection limit and wide dynamic range; The methods of electrochemical analysis are modular, easy, simple to apply and high selectivity,

and the possibility of biodegradation has become widely used. We developed methods to identify some of the following antidiabetics

Pioglitazone HCl

It is a drug from the group of thiazolidinedione (TZD) that lowers blood sugar, use to develop glucose control in adults with type 2 diabetes.^[7] Pioglitazone is a polar,

slightly soluble in aqueous solutions, therefore, it was used in its various forms to improve its solubility, including the salt form^[8] and the crystal form^[9] auxiliary solvents^[10] surface active agents,^[11] and ionic liquid^[12] Pioglitazone [(+)-5-[[4-[2-(5-ethyl-2-pyridinyl)ethoxy]phenyl]methyl]-2,4-]^[13] The structural formula is as shown:

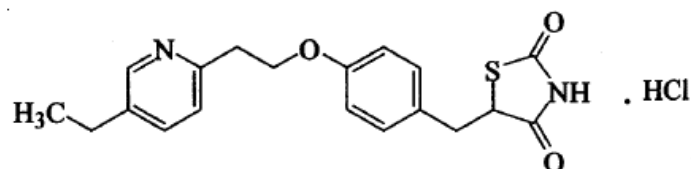


Figure 1: The structure of Pioglitazone Hydrochloride.

Pioglitazone hydrochloride is an odorless white crystalline powder that has a molecular formula of $C_{19}H_{20}N_2O_3S \cdot HCl$.^[14]

The importance of research

Some scientific methods have been described for the determination of pioglitazone HCl in pure form, pharmaceuticals and biological fluids. Most of the reported methods are chromatographic, and no official methods have been expressed for the determination of pioglitazone HCl. The reported methods consist of : spectrophotometry,^[15-17] high -performance liquid chromatography (HPLC).^[18,19] LC-MS/MS,^[20] AP-MALDI mass spectrometry imaging.^[21]

Electrochemical techniques are more attractive and fascinating due to their low cost and less time consumption compared to other methods to determine Pioglitazone hydrochloride.

MATERIALS AND METHODS

Instruments and apparatus

Electrochemical Analyzer (Model 433-AMEL Instruments) was used for cyclic voltammetry, a three electrode system comprising of a gold electrode as a working electrode, a saturated Ag/AgCl/KCl as a reference electrode and Pt wire as a counter electrode obtained from local scientific labs. All the solutions examined were carried out at room temperature $25 \pm 2^\circ C$, Nitrogen gas was used for deoxygenation. pH -meter from Radio meter company model Ion Check was used for the studying the pH effects. The measurements were semi-automated and controlled through the programming capacity of the apparatus.

MATERIALS

- Pioglitazone HCl 98% produced by Telangana.India
- Methanol 99% produced by Merck.
- Electrolyte: hydrochloride acid, HCl 99.5%, produced by Merck.
- Solutions were prepared in double distilled water.

Sample preparation

Twenty tablets of Pioglitazone (30 mg PGZ-HCl), were weighed and ground to a fine powder. Then the weight of one tablet was taken and dissolved in methanol, transferred to a 100 mL volumetric flask and diluted to the mark with HCl (0.5 M). The content of the flask was sonicated for about 15 min then solution was filtered to separate the insoluble excipients. Aliquots of the drug solution were introduced into the electrolytic cell and the general procedure was carried out.

RESULTS AND DISCUSSION

Effect of pH

The electrochemical behavior of PGZ-HCl has been investigated in HCl (0.5M), on the peak current (I_p) and peak potential (E_p) were examined. The polarograms of the CV for PGZ-HCl (117 - 392) mg/L in HCl (0.5 M) using CV shown in (Fig.2). One reduction peak were observed.

Indicating the presence of chemical reaction with participation of protons. Reduction of PGZ-HCl at the (CV) was found to be pH dependent as the E_p values indicating the irreversible nature of the reduction process.

Study of (CV)Method

The CV-polarograms of PGZ-HCl in HCl (0.5 M), exhibited one irreversible reduction wave (Fig.2).

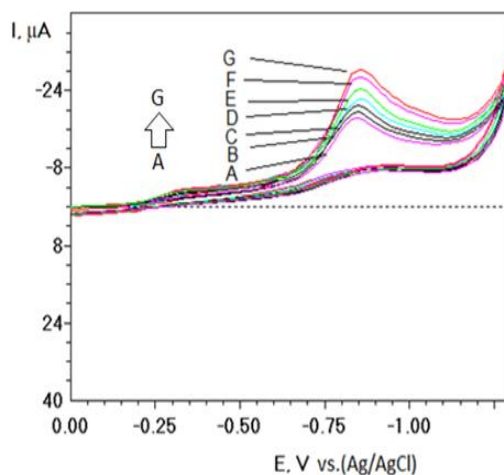


Figure 2: Cyclic voltammetry curves for different concentrations of Pioglitazone Hydrochloride.

(A: 117 - B: 161 - C: 208 - D: 255 - E: 298 - F: 345 - G: 392 mg/L in HCl at gold electrode

The total number of electrons transferred during the reduction reaction is determined by Determine the value of the transfer coefficient (α):

Study of the change in the potential value η of $(\log i)^{[22]}$ according to the Tafel relation for different concentrations of pioglitazone hydrochloride as in the following (Fig.3):

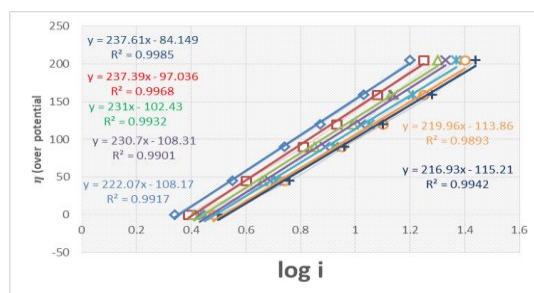


Figure 3: Graph of η of $\log(i)$ for different concentrations of Pioglitazone Hydrochloride.

-Then determine the value of the transfer coefficient (α) depending on the exchange current relationship (Fig.4).

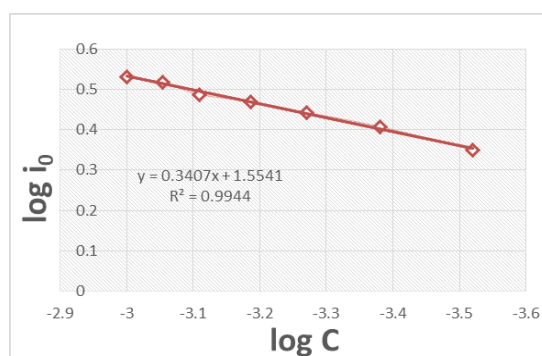


Figure 4: Graph of $\log(i_0)$ of $\log(C)$ in HCl.

According to the exchange current relationship,^[23,24] the value of the transfer coefficient was found

$\alpha = (0.6593)$ in the acid medium. After deducing the value of the transfer coefficient, we drew the values of $\log(\frac{i_d - i}{i})$ for potential (E) (Fig.5).

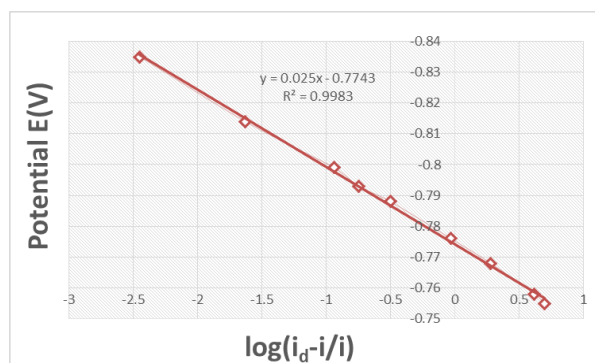


Figure 5: Graph of E(V) of $\log(i_d-i/i)$ in HCl.

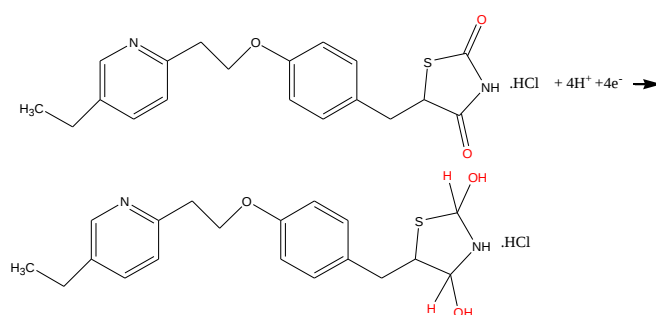
We notice that the slope of this linear relationship is (0.025) in the acid medium, and by applying the relationship.^[24] we find that ($n=4$) thus, the total number of electrons exchanged is ($4e^-$).

The electrochemical behavior of PGZ- HCl

The chemical structure of PGZ-HCl is characterized by the presence of C=O groups which are susceptible for the reduction into another groups at CV as shown in (Fig.1).

The electrochemical behavior was investigated for PGZ-HCl in HCl (0.5 M) using CV were given one defined

reduction peak, as shown in (Fig.2). The peak may be attributed to the reduction of carbonyl group ($-CO-$). A proposed mechanism, for the electrochemical reduction of this electro-active group, it was calculated and confirmed that the number of electron of this reduction operating were 4 electron. This mechanism suggests that the electrochemical reaction is an irreversible process. Such quantitation depends not only on the corresponding peak potentials but also on the width of the peak. The width of the peak (at half-height) is related to the electron stoichiometry. The electrode reaction is suggested to proceed as follows:



.....eq(1)

-Effect of scan rate on the electrochemical reduction of pioglitazone hydrochloride

The electrochemical reduction of pioglitazone hydrochloride was studied at different scan rates in hydrochloride acid (HCl) as electrolyte to determine the mechanism of transfer of pioglitazone hydrochloride

molecules from the depth of the solution to the surface the gold electrode using the (CV) method, to determine whether the electrochemical reaction on the gold electrode is subject to diffusion or chemical kinetics, based on the study of changes in the peak current with changing scan rates as shown in (Fig.6).

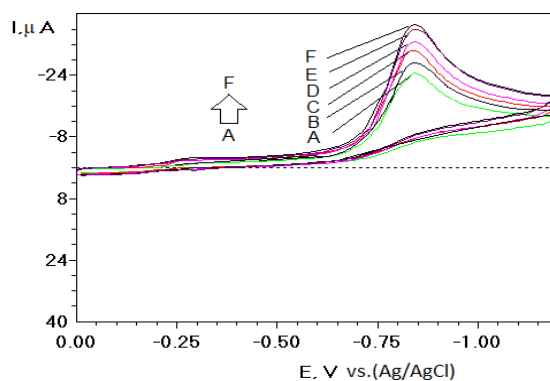


Figure 6: Cyclic voltammograms of Pioglitazone Hydrochloride at different scan rate (40 to 90 mV/s) in HCl.

We draw the curve that represents the changes of the values of current I_p (μA) with square root of scan rate $\sqrt{V}$ as shown in (Fig.7).

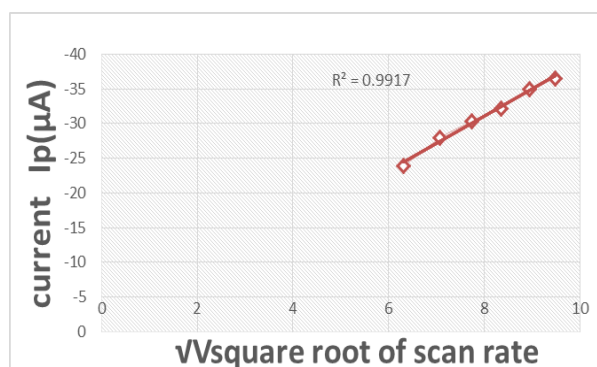


Figure 7: Graph of current versus square root of scan rate in the acid medium HCl.

The cathodic peak potential increased with increase in scan rate (40 to 90 mV/s). In (Fig.7) the graph of cathodic peak current (I_p) versus square root of scan rate gave a straight line with correlation coefficient values of 0.9917, it indicates that the electron transfer reaction was under diffusion controlled.

-Effect of concentration of pioglitazone hydrochloride at the electrochemical reduction

The (Fig.2) show the cyclic voltammograms for different concentration of pioglitazone hydrochloride from (117 - 392) mg/L in HCl (0.5 M), with a scan rate of 50 mV/s at the electrochemical reduction. The redox peak current was steadily increased with increasing the concentration of pioglitazone hydrochloride.

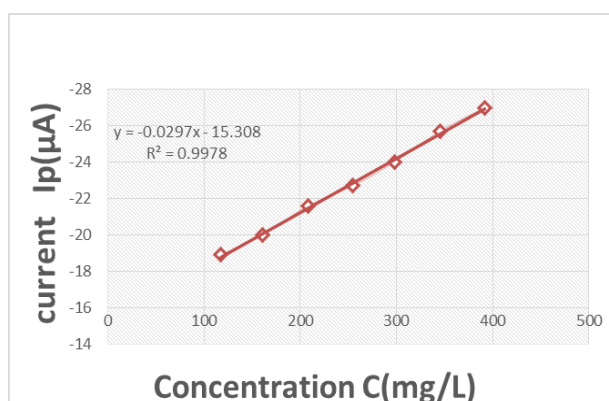


Figure 8: Graph of the limit of the current with different concentrations of Pioglitazone Hydrochloride in the acid medium.

The (Fig.8) show the graph of I_p versus concentration of Pioglitazone Hydrochloride and it results that the cathodic peak current was directly proportional to the concentration of Pioglitazone Hydrochloride. The linear regression equation as given by: $y = -0.0297x - 15.308$ with a correlation coefficient of $R^2 = 0.9978$.

Application to pharmaceutical preparations

The proposed method has been successfully applied for the analysis of PGZ-HCl in its commercial tablets. Pharmaceutical preparation determined using cyclic voltammetry in HCl (0.5 M). There were no interferences within containing of met form in HCl in some tablets.

The percentage of the active substance in the sample (30mg) was determined of (98.3%) in the acid medium it

is within the typical range allowed by the United States Pharmacopeia (USP)^[25]

CONCLUSIONS

In the proposed method, polarographic analysis of PGZ-HCl in pure and pharmaceutical formulations in HCl (0.5 M), have been investigated using cyclic voltammetry (CV) method. One reduction peak was observed. The peak (E_p) may be attributed to the reduction of the carbonyl group ($-\text{CO}-$). The I_p were proportional to the concentration over the ranges (117 - 392) mg/L in HCl (0.5 M) using CV.

Applying CV over mentioned methods in this context were successfully carried out for the first time. The proposed method was successfully applied to the analysis of PGZ-HCl in pure and pharmaceutical formulations

with average recovery of (98.3%).The results obtained agree well with the contents stated on the labels.

REFERENCES

1. Ibrahim, M. S. (2001) Voltammetric studies of the interaction of nogalamycin antitumor drug with DNA. *Analytica Chimica Acta*, 443(n/a), 63–72.
2. Heinze, J.(1984). Cyclic Voltammetry-"Electrochemical Spectroscopy. *Angew Chem. Int. Ed. Engl*, 23(n/a), 831-847.
3. Rusling, J. F. and Suib, S. (1994) L. Characterizing Materials with Cyclic Voltammetry. *ADVANCED MATERIALS*, 6,(12),n/a.
4. Wei Wang, H., Bringans, C. and Hickey, J. R.A. (2021).Cyclic Voltammetry in Biological Samples: A Systematic Review of Methods and Techniques Applicable to Clinical Settings *Signals*, 2(n/a), 138–158.
5. Elgawish, M. S., Nasser,S., Salama, I., Abbas, A. M. and Mostafa, S. M. (2019).Liquid chromatography tandem mass spectrometry for the simultaneous determination of metformin and pioglitazone in rat plasma: Application to pharmacokinetic and drug-drug interaction studies. *Journal of Chromatography. B*,1124 (n/a), 47-57.
6. Kelani, K. M., Rezk, M. R. and Badran, O. M. (2019).Determination of pioglitazone, its metabolite and alogliptin in human plasma by a novel LC-MS/MS method; application to a pharmacokinetic study. *Journal of Chromatography B*, S1570-0232(19),n/a.
7. Waugh, J., Keating, G.M., Plosker, G. L., Easthope. S. and Robinson, D.M. (2006).Pioglitazone: a review of its use in type 2 diabetes mellitus. *Drugs*, 66,(1): 85-109.
8. Chilcott,J., Tappenden, P., Jones, M. L. and Wight, J.P.A.(2001).systematic review of the clinical effectiveness of pioglitazone in the treatment of type 2 diabetes mellitus. *Clin. Ther*, 23(n/a),1792–1823.
9. Serajuddin, ATM. (2007).Salt formation to improve drug solubility, *Adv Drug Del Rev*,59(n/a), 603-616.
10. Babu, N. J. and Nangia, A. (2011). Solubility advantage of amorphous drugs and pharmaceutical cocrystals. *Crys Grow Des*, 11(n/a), 2662-2679.
11. Li, A. and Yalkowsky, S. H. (1998).Predicting cosolvency. 1. Solubility ratio and solute logKow. *Ind Eng Chem Res*,37(n/a), 4470-4475.
12. Anton, N. and Vandamme, T. F. (2011). Nano-emulsions and micro-emulsions: Clarification of the critical differences. *Pharm Res*,28(n/a), 978-985.
13. Sohda, T., Mizuno, K., Momose, Y., Ikeda, H., Fujita, T. and Meguro, K. (1992). Novel thiazolidinedione derivatives as potent hypoglycemic and hypolipidemic agents. *J. Med. Chem*, 35(n/a), 2617-2626.
14. Kobayashi, M., Iwanishi, M., Egawa, K. and Shigeta, Y. Pioglitazone increases insulin sensitivity by activating insulin receptor kinase. *Diabetes*, 1992; 41(4): 476-483.
15. Ravikanth, C. H., Anil Kumar, A., Uday Kiran, V., Prashanth, S., Madhu Seema, M. D., Pramod, B. K. and Nikhil, D.A. UV Spectrophotometric Absorption Correction Method for the Simultaneous Estimation of Pioglitazone HCl, Metformin HCl and Glibenclamide in Multicomponent Formulation. *International Journal of Analytical and Bioanalytical Chemistry*, 2013; 3(1): 18-22.
16. Shah, D., Gajjar, U. and Patel, V. Al. Estimation of Pioglitazone Hydrochloride and Alogliptin benzoate in combination by Second Order Derivative Spectrophotometry method. *International Research Journal of Pharmaceutical Sciences*, 2017; 8(1): 8001-8010.
17. Arabzadeh, V. and Sohrabi, M. R. (2022).Artificial neural network and multivariate calibration methods assisted UV spectrophotometric technique for the simultaneous determination of metformin and Pioqlitazone in anti-diabetic tablet dosage form. *Chemometrics and Intelligent Laboratory Systems*, 221(n/a),104475.
18. Kumar, A., Srivastava, S. K., Srivastava, M. and Prakash, R.(2021).Electrochemical sensing of pioglitazone hydrochloride on N-doped r-GO modified commercial electrodes. *The Royal Society of Chemistry*.n/a.
19. Stamou, P. and Parla, A. (2023). Hydrophilic interaction liquid chromatography- electrospray ionization mass spectrometry combined with fabric phase sorptive extraction for therapeutic drug monitoring of pioglitazone, repaglinide, and nateglinide in human plasma. *Journal of Chromatography B*, 1217(123628),(n/a).
20. Zhang, F., Jin, C.,Wang, X., Yan, H., Tan, H. and Gao, C. (2021). Dietary supplementation with pioglitazone hydrochloride and L-carnosine improves the growth performance, muscle fatty acid profiles and shelf life of yellow-feathered broiler chickens. *Animal Nutrition*,7(n/a), 168-175.
21. Morosi, L., Matteo, C. and Meroni, M,. (2022). Quantitative measurement of pioglitazone in neoplastic and normal tissues by AP-MALDI mass spectrometry imaging. *Talanta*, 237,(122918),n/a.
22. Bakir, D.,Sheikh,M.and Mualla,H. (2004).Physical Chemistry 3. *Al-Baath University*, first edition. Syria, 420. [in Arabic]
23. Stradins, J. Studies on the electrochemical mechanism of reduction of carbonyl compounds. *Electrochimica Acta*, 1964; 9(6): 711-720.
24. Bakir, D. and Naqar S. (2010). The kinetics of chemical reactions. -Al Baath University, first edition. Syria, 460.[in Arabic]
25. The United States Pharmacopeia and the National Formulary, USP 41-NF 36, 2018.