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Original Research Article

Voltammetric determination of vildagliptin in a pharmaceutical formulation

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Abstract

Purpose: *To determine vildagliptin concentration in a pharmaceutical formulation using voltammetric analysis techniques, and optimize the parameters affecting the techniques.*
Method: *Four types of voltammetry techniques, including cyclic voltammetry (CV), differential pulse voltammetry (DPV), square wave voltammetry (SWV), and linear sweep voltammetry (LSV), were employed to measure vildagliptin. Platinum (Pt) and glassy carbon (GC) were used as working electrodes, while KNO_3 (1 M) and phosphate buffer (NaH_2PO_4/H_3PO_4) pH 6.8 were used to study optimal voltammetric analysis conditions.*
Results: *CV results indicate that vildagliptin is electroactive and exhibits irreversible redox cycles while LSV results showed an oxidation peak current around 1.35 V that has high sensitivity and a linear standard regression line correlation coefficient of 0.9995. In addition, LSV results showed that vildagliptin has a lower limit of detection of ~ 0.241 mM and a limit of quantification of ~ 0.802 mM. Finally, the results show that vildagliptin has an acceptable level of recovery of 104.1 % and a relative standard deviation of 0.52 % for the commercially available vildagliptin tablets used in this study.*
Conclusion: *The accuracy and precision of all applied voltammetric techniques for vildagliptin analysis are within accepted limits stipulated in pharmaceutical analysis quality control guidelines. The recommended method for vildagliptin analysis is LSV with Pt as the working electrode and KNO3 (1 M) as the supporting electrolyte.*

Keywords: *Vildagliptin, Cyclic voltammetry, Square wave voltammetry, Differential pulse voltammetry, Linear sweep voltammetry*

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INTRODUCTION

Chromatography, spectrophotometry, and electrochemistry have traditionally been considered the most commonly used methods in pharmaceutical analyses [1]. Electroanalytical chemistry has been a fundamental branch of analytical chemistry since the beginning of the nineteenth century [2]. Recently, voltammetric analysis has become the most common electroanalytical method used in environmental research, chemical monitoring laboratories, and quality control units of several industries, biological and clinical laboratories [3]. Voltammetric analysis has many advantages such as simplicity, moderate instrumentation and

running costs, and instrument portability that make it a better alternative to chromatographic and spectroscopic techniques.

About two-thirds of the world population suffers from type 2 diabetes mellitus (T2DM), and this is expected to increase [4]. Vildagliptin is a relatively new oral antidiabetic agent and a member of a new class of orally active antidiabetic drugs called glyptins. [5,6]. These drugs also have positive cardiovascular and anti-inflammatory effects [5,7,8]. Vildagliptin is a good inhibitor of dipeptidyl peptidase-4 enzyme DPP-4 (IC_{50} = 3.5 – 34 nM; Figure 1) [9,10].

Previous chromatographic assessments of vildagliptin include reversed-phase high performance liquid chromatography (RP-HPLC) analysis of different matrices, such as bulk and tablet dosage forms [11-14]. Hydrophilic interaction liquid chromatography tandem mass spectrometry (HILIC–MS/MS) developed and validated for the determination of vildagliptin in human plasma [15]. Bratty *et al* developed a liquid chromatography (LC)-MS/MS method for the simultaneous determination of gliptins in human plasma. [16] Spectrophotometric methods to assess vildagliptin in bulk and pharmaceutical dosage forms have also been used [17-21].

In this study, we choose to use more accurate electrochemical voltammetric analysis technique for the determination of vildagliptin in a pharmaceutical formulation. The experimental parameters affecting the used technique, such as types of working electrodes and supporting electrolytes, were optimized.

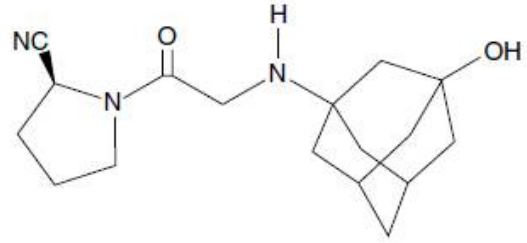

Figure 1: Chemical structure of vildagliptin

EXPERIMENTAL

Materials and reagents

The standard pharmaceutical formulation (pure powder) of vildagliptin was obtained from CAD Pharmaceuticals (Saudi Arabia). Commercially available tablets of vildagliptin Gulvus^{TM} (50 mg) were obtained from Novartis (Saudi Arabia). Standard Stock solutions of 10 mM were prepared from pure vildagliptin powder; Supporting electrolytes were used to prepare standard stock solutions and dilute the stock solutions to prepare the working standard solutions.

Gulvus^{TM} tablets were weighed and ground by mortar and pestle, and then a certain mass was dissolved in the supporting electrolyte solution. Next, the solution was filtered using simple filtration to remove undissolved substance. The filter used in the filtration was washed several times with supporting electrolytes, and the solution volume was completed to the mark with supporting electrolyte. The phosphate buffer supporting electrolyte solution was prepared by dissolving 24 g of $NaH_2PO_4{\cdot}H_2O$ in 800 ml of deionized water, adding 85 % H_3PO_4 until a pH of 6.8 was reached and making up the solution to 1 L with deionized water. Potassium nitrate (KNO_3, ACS reagent grade; Fluka) was used for the preparation of supporting electrolyte. Milli-Q water was used to prepare all samples and supporting electrolytes. Stock standard solutions were prepared by dissolving solid vildagliptin in supporting electrolyte solutions. Supporting electrolytes were also used to dilute the stock solution to prepare the working standard solutions.

Apparatus

All electrochemical measurements were made using a PGSTAT 204 potentiostat from Metrohm Autolab. All measurements were made using a three - electrodes system; a glassy carbon (GC) or platinum (Pt) working electrode, Ag/AgCl reference electrode, and a Pt sheet auxiliary electrode.

Statistical analysis methods

All voltammetric analysis data have been processed by Microsoft excel software. All experimental parameters were done in triplicates. Standard calibration curves of concentration versus anodic peak current and statistical analysis have been done by Microsoft excel software.

Limit of detection was taken as the analyte concentration giving a signal equal to the blank signal, Y_B, plus three standard deviations of the blank, S_B,

Limit of detection = $Y_B + 3S_B$ …… (1)

Limit of quantifiction was computed as in Eq 2.

Limit of quantitation = $Y_B + 10S_B$ ……. (2)

Relative standard deviation (RSD) was obtained as in Eq 3.

$RSD = 100 * S / \bar{X}$ …….. (3)

where S is standard deviation, and $\bar{X}$ is the mean.

RESULTS

Cyclic voltammetry

Cyclic voltammetry was used to study the electroactivity of pure vildagliptin. Glassy carbon and Pt electrodes were applied, and 1 M KNO_3 and phosphate buffer were used as supporting electrolytes (Figure 2). Voltammograms show that vildagliptin was electroactive with an irreversible redox cycle and anodic peak current in the range of 1.25 – 1.45 V when Pt was used as the working electrode and KNO_3 was used as the supporting electrolyte. When a GC electrode was used, anodic peaks of 1.15 and 1.25 V were evident for KNO_3 and phosphate buffer supporting electrolytes, respectively (Figure 2). When phosphate buffer was used with Pt as the working electrode, the voltammograms showed erratic results (not shown). According to the voltammograms in Figure 2, the Pt electrode showed sharper anodic peaks than the GC electrode. Furthermore, high correlation coefficients were exhibited for all calibration curves of vildagliptin (2 – 10 mM) determined by cyclic voltammetry (Figure 2 and Table 1).

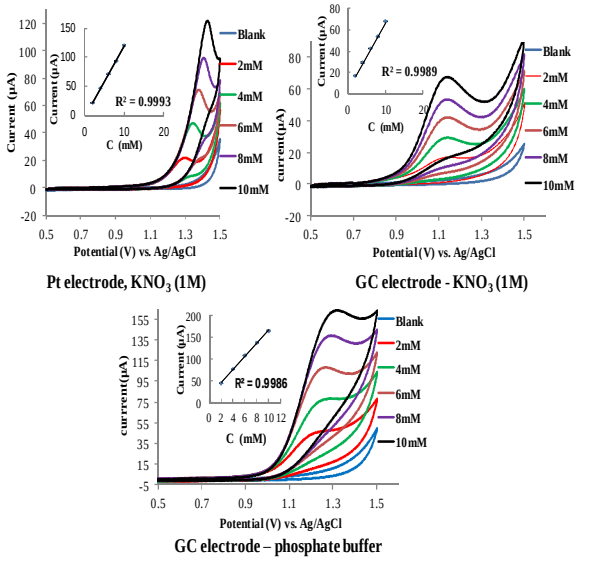

Figure 2: Cyclic Voltammetry of pure vildagliptin (2 – 10 mM) using Pt and GC electrodes, with phosphate buffer pH 6.8 and 1 M KNO_3 supporting electrolytes, scan rate of 0.1 V/s. Triplicate determinations of all concentrations

Differential pulse voltammetry (DPV) and square wave voltammetry (SWV)

Use of a Pt working electrode with KNO_3 supporting electrolyte showed a sharper peak than that of GC electrode for both DPV and SWV methods (Figure 3 and Figure 4, respectively). On the other hand, using KNO_3 as supporting electrolyte gave a better correlation coefficient than phosphate buffer (Figure 3 and Figure 4, respectively). The anodic peak potential shifts to higher values as pure vildagliptin concentration increases when Pt is used as working electrode in both DPV and SWV methods (Figure 3 and Figure 4, respectively).

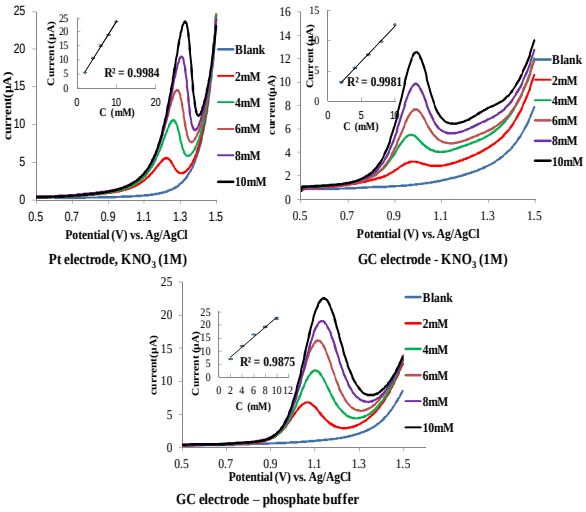

Figure 3: DPV of pure vildagliptin (2 – 10 mM) using Pt and GC electrodes, with phosphate buffer pH 6.8 and 1 M KNO_3 supporting electrolytes. Triplicate determination was made at all concentrations

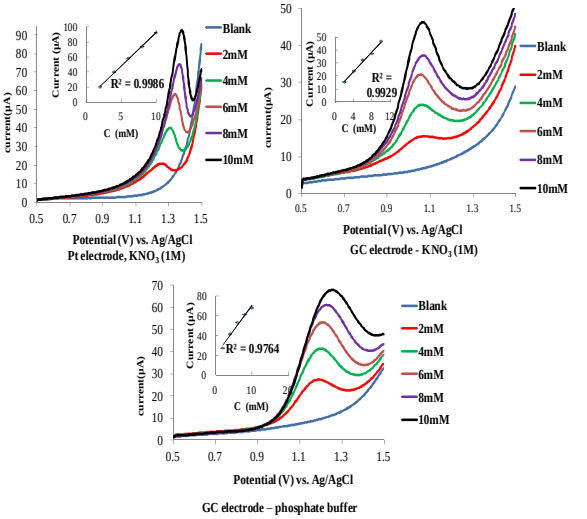

Figure 4: SWV of pure vildagliptin (2 – 10 mM) using Pt and GC electrodes, with phosphate buffer pH 6.8 and 1 M KNO_3 supporting electrolytes. Triplicate determinations of all concentrations.

Linear sweep voltammetry (LSV)

Linear sweep voltammetry showed the highest peak currents and correlation coefficients compared with results of all previously mentioned methods for pure vildagliptin analysis (Figure 5). In the optimization of electrode and supporting electrolyte, all voltammograms showed good results. The best conditions for determination of vildagliptin included a Pt working electrode with KNO_3 as supporting electrolyte (Figure 5).

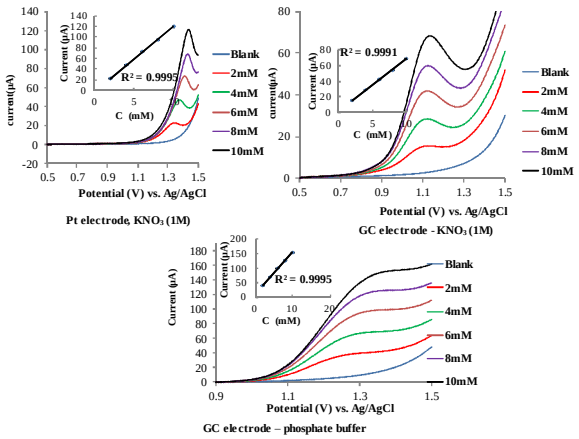

Figure 5: LSV of pure vildagliptin (2 – 10 mM) using Pt and GC electrodes, with phosphate buffer pH 6.8 and 1 M KNO_3 supporting electrolytes. Triplicate determinations of all concentrations

DISCUSSION

A comparison of correlation coefficient (R^2), limit of detection (LOD), and limit of quantitation (LOQ) between Pt and GC electrodes used in all applied voltammetric methods in this study is shown in Table 1. Only the KNO_3 supporting electrolyte results are shown in this table because they were better than the phosphate buffer results in all voltammetric methods (as discussed earlier). According to the results in Table 1, it can be concluded that the LSV method with Pt working electrode was the optimal combination for vildagliptin analysis because it has the lowest LOD and LOQ and the highest sensitivity.

The concentration, recovery, and relative standard deviation (RSD) results of four voltammetric methods (CV, DPV, SWV, and LSV) using a 4 mM solution of commercially available vildagliptin (Gulvus^{TM}) are shown in Table 2.

Table 1: Linearity of pure vildagliptin standard solution (range 2 – 10 mM, KNO_3 1 M)

Method	LR	R^2	LOD (mM)	LOQ (mM)
CV (GC Electrode)	y = 6.312x + 4.5012	0.9989	0.366	1.221
CV (Pt Electrode)	y = 12.209x - 2.060	0.9993	0.281	0.939
DPV (GC Electrode)	y = 1.167x + 0.7451	0.9981	0.473	1.576
DPV (Pt Electrode)	y = 2.2417x + 1.312	0.9984	0.431	1.439
SWV (GC Electrode)	y = 3.7915x + 8.305	0.9929	0.823	2.011
SWV (Pt Electrode)	y = 8.864x + 3.9411	0.9986	0.411	1.370
LSV (GC Electrode)	y = 6.527x + 2.5213	0.9991	0.320	1.069
LSV (Pt Electrode)	y = 12.16x - 1.4499	0.9995	0.241	0.802

LR: Linear regression, **R^2:** correlation coefficient, **LOD**: limit of detection, **LOQ**: limit of quantification

Table 2: Accuracy and precision of commercial preparation of Gulvus (vildagliptin 50 mg)

Method	Gulvus^{TM} commercial preparation	Statistical parameters	Pt electrode (KNO_3)	GC electrode (KNO_3)
CV	4mM	Found ± SD	4.17± 0.003	4.20 ± 0.025
		Recovery%	104.2	104.93
		RSD%	0.07	0.61
DPV	4mM	Found ± SD	3.67 ± 0.007	3.88 ± 0.036
		Recovery %	91.65	97.02
		RSD %	0.19	0.92
SWV	4mM	Found ± SD	4.28 ± 0.03	4.42 ± 0.007
		Recovery %	106.9	110.5
		RSD%	0.80	0.16
LSV	4mM	Found ± SD	4.16 ± 0.02	4.46 ± 0.018
		Recovery%	104.1	111.6
		RSD%	0.52	0.41

SD: standard deviation of triplicate determinations, RSD: relative standard deviation, Recovery = found/added *100

According to these results, LSV and CV showed better recovery than other methods when a Pt electrode was used. On other hand, CV and DPV showed better recovery than other methods when a GC electrode was used. The RSD results of all methods were good and within the accepted limits, which reflects the high precision of voltammetric determination of vildagliptin.

CONCLUSION

Voltammetric analysis indicates that vildagliptin is electroactive with an irreversible redox reaction. All voltammetric results show that vildagliptin is within the accepted limits. Thus, voltammetric analysis is suitable for the determination of vildagliptin in pharmaceutical formulation. However, LSV displayed the best accuracy, precision, recovery, LOD and LOQ of all the voltammetric methods.

DECLARATIONS

Conflict of Interest

No conflict of interest associated with this work.

Contribution of Authors

The authors declare that this work was done by the authors named in this manuscript and all liabilities regarding the content of this article will be borne by them. Muneer Fadr did experimental part supervised by Abdulaziz Nabil Amro and Sami Ben Aoun.

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