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Voltammetric determination of glycopyrrolate in a pharmaceutical formulation

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Abstract: The electrochemical activity of glycopyrrolate was studied. Different voltammetric techniques were applied in this study, including cyclic voltammetry (CV), differential pulse voltammetry (DPV), and linear sweep voltammetry (LSV). Glassy carbon and platinum working electrodes were utilized. CV indicated that glycopyrrolate has a reversible redox reaction on the working electrode surface, with an anodic peak current at approximately 1.05 V and a cathodic peak at 0.80 V. Several parameters that affect the sensitivity of these methods were optimized for the quantitation of glycopyrrolate. LSV showed a better correlation coefficient than DPV did, with a value of ca. 0.9990 in the range of 0.1–0.5 mg/mL. The LSV and DPV recovery and relative standard deviation (RSD) results fell within the accepted range, with a better recovery (102.07%) for DPV and a better RSD (0.511%) for LSV. The limits of detections were ca. 16 and ca. 25 µg/mL for LSV and DPV, respectively.

Key words: Glycopyrrolate, linear sweep voltammetry, differential pulse voltammetry

1. Introduction

The most common instrumental analysis methods used for quantitation in pharmaceutical analysis are chromatography, spectrophotometry, and electrochemistry.[1] Voltammetric methods have become popular tools for studying electrochemical reactions in applications such as environmental monitoring, industrial quality control, and the determination of trace concentrations of biological and clinically important compounds.[2,3] The standard techniques that are currently used for the determination of drugs in biological fluids, bulk form, and pharmaceutical formulations are based on chromatographic or spectroscopic assays.[2] Such techniques for the determination of drug concentrations are necessary in a clinical environment to provide appropriate drug levels and avoid toxic concentrations of these drugs. Derivatization and time-consuming extraction are the major problems of these procedures.[2] The high costs of the instrumentation and operation of spectroscopic and chromatographic techniques make electrochemical techniques, which are simpler, faster, cheaper, and more sensitive, better alternatives.[2] Electroanalytical methods have many advantages that make them attractive choices for pharmaceutical analysis, such as simplicity, moderate instrumentation and running costs, and portability.[4–6]

The chemical name of glycopyrrolate is 3-[(phenylacetyl) 2-cyclopentyl-2-hydroxy-2- oxy]-1,1-dimethylpyrrolidin-1-ium, which is depicted in Figure 1. Glycopyrrolate was synthesized for the first time in 1960. Glycopyrrolate is a synthetic anticholinergic agent with a quaternary ammonium structure. It is a muscarinic

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competitive antagonist that is used as an antispasmodic in some disorders of the gastrointestinal tract and to reduce salivation with some anesthetics.[7,8]

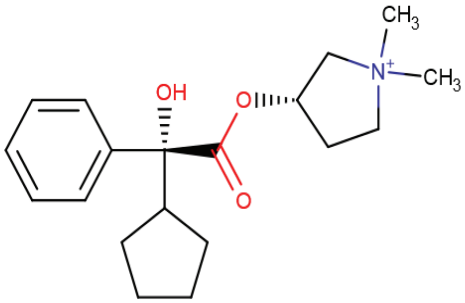

Figure 1. Chemical structure of glycopyrrolate.

All of the methods used for the determination of glycopyrrolate were chromatographic methods.[7,9,10] The linear dynamic range reaches 20–80 μg/mL by reverse phase high-performance liquid chromatography (RP-HPLC) for glycopyrrolate in its bulk and tablet dosage forms.[7] Stormeet et al. developed a quantitative tool for the determination of glycopyrrolate in human plasma samples using LC–MS/MS. This method shows a good dynamic range of 0.101 to 101 ng/mL.[9] Rumpler et al. used a UHPLC–MS/MS method for the quantitation of glycopyrrolate in horse urine. Their used method showed a linear dynamic range of 5–2500 pg/mL, a LOQ of 5 pg/mL, and a LOD of 1 pg/mL.[10] Zayed and Belal used the HPLC method for determination of a combination of indacaterol maleate and glycopyrronium bromide using tenoxicam as an internal standard.[11]

Hussein et al. used a potentiometric method for glycopyrrolate determination; they fabricated and studied three different kinds of ion-selective potentiometric sensors using multiwalled carbon nanotubes, polyaniline nanoparticles, and polyaniline microparticles.[12]

The aim of this work is the determination of glycopyrrolate in pharmaceutical preparations using different voltammetric techniques, namely linear sweep voltammetry (LSV), cyclic voltammetry (CV), and differential pulse voltammetry (DPV).

2. Results and discussion

2.1. Optimization of working electrodes and supporting electrolytes

The CV method was used to study the electroactivity of glycopyrrolate. Figure 2 shows cyclic voltammograms that indicate the presence of a reversible reaction at the electrode surface with anodic peak currents of approximately 1.05 V when GC and Pt electrodes were used as working electrodes and KNO_3 (1.0 M) was used as supporting electrolyte. A similar anodic peak potential appeared when H_2SO_4 (0.1 M) was used as the supporting electrolyte with the Pt working electrode, but it jumped to approximately 1.25 V with the GC working electrode. The cathodic peak potential for all of the experiments was located at approximately 0.8 V. For Na_2SO_4 (1 M) supporting electrolyte and GC working electrode, there was a quasi-revisable cycle with anodic peak at 1.35 V and cathodic peak at around 0.45 V. On other hand, the Pt working electrode did not show any response to 10 mM glycopyrrolate with Na_2SO_4 (1 M), as shown in Figure 2. A scan rate of 0.1 V/s was used for all cyclic voltammetry experiments because it showed the highest anodic potential compared to lower scan rates.

LSV and DPV methods were selected for the glycopyrrolate assays because they show sharper peak

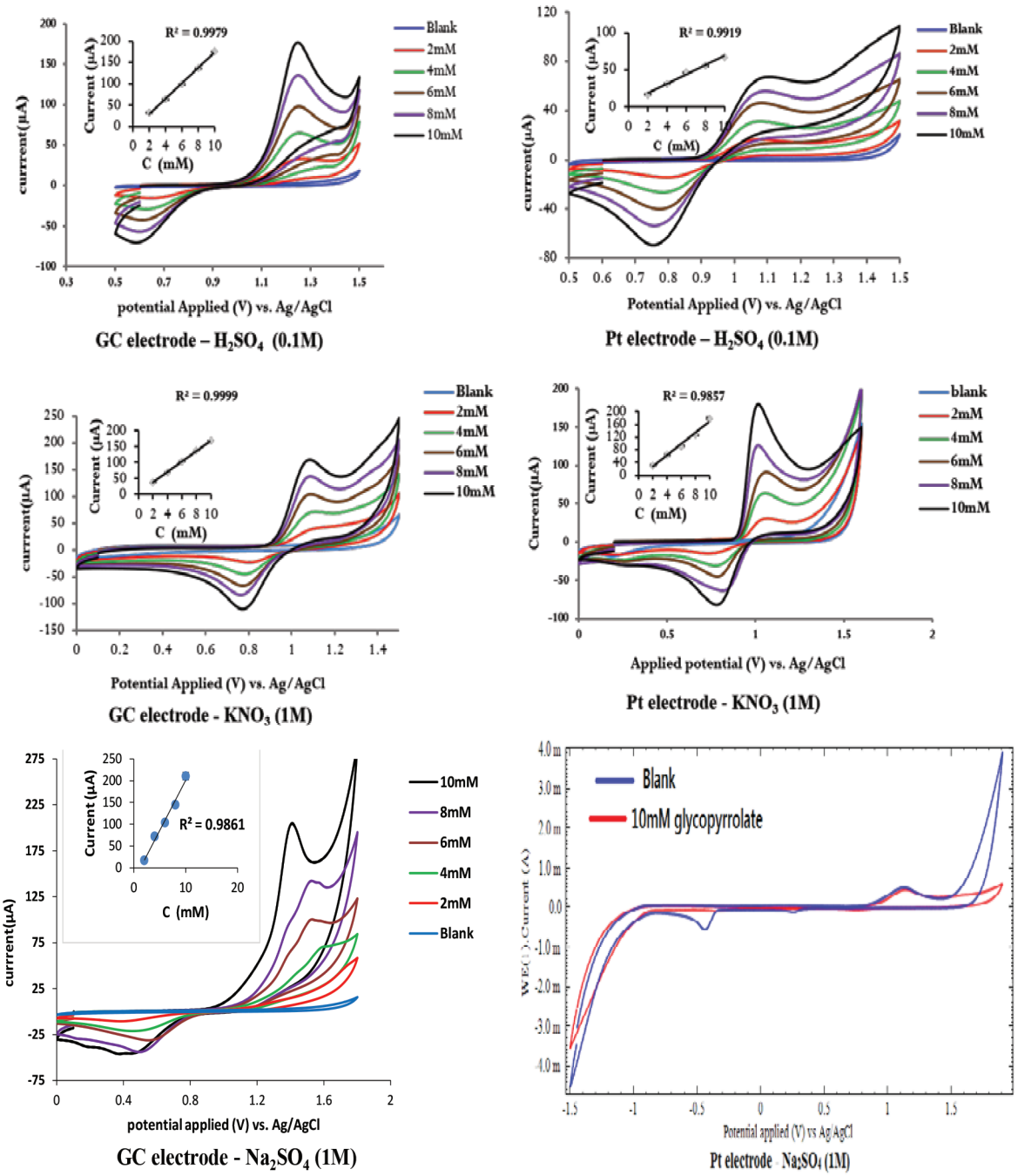

Figure 2. CV study of glycopyrrolate (2.0–10.0 mM) using Pt and GC electrodes, with 0.1 M H_2SO_4, 1 M KNO_3, and Na_2SO_4 (1 M).

currents with better correlation coefficients than other methods (not shown). The working electrode and supporting electrolyte were optimized for both the LSV and DPV methods as shown in Figures 3 and 4. The calibration curves were constructed by plotting the glycopyrrolate concentration (mM) versus the peak current (µA), and all glycopyrrolate concentration measurements were done in triplicate. LSV showed the highest correlation coefficient with the GC working electrode and the KNO_3 supporting electrolyte. For DPV,

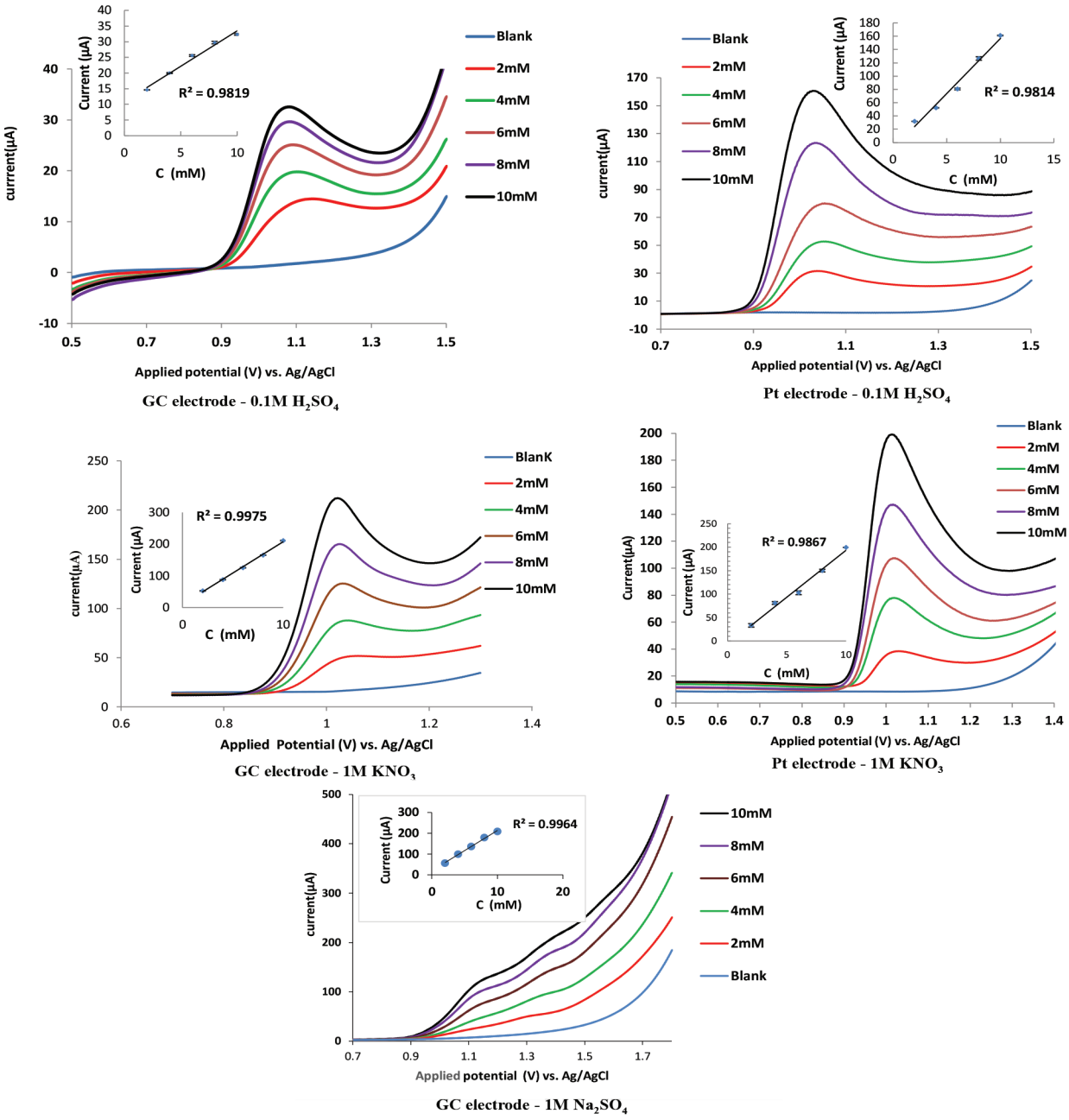

Figure 3. LSV study of glycopyrrolate (2.0–10.0 mM) using Pt and GC electrodes, with 0.1 M H_2SO_4, 1 M KNO_3, and Na_2SO_4 (1 M).

using the 1 M KNO_3 supporting electrolyte resulted in sharper peaks and higher correlation coefficients than did using 0.1 M H_2SO_4 and Na_2SO_4 (1 M) for both the GC and Pt electrodes. According to the results of the voltammograms and calibration curves shown in Figures 3 and 4, a GC working electrode and 1 M KNO_3 supporting electrolyte are recommended for the voltammetric analysis of glycopyrrolate.

Since commercially available glycopyrrolate is a solution for injection with a concentration of 0.2 mg/mL, calibration curves of concentration (mg/mL) versus peak current (µA) were constructed to cover this concentra-

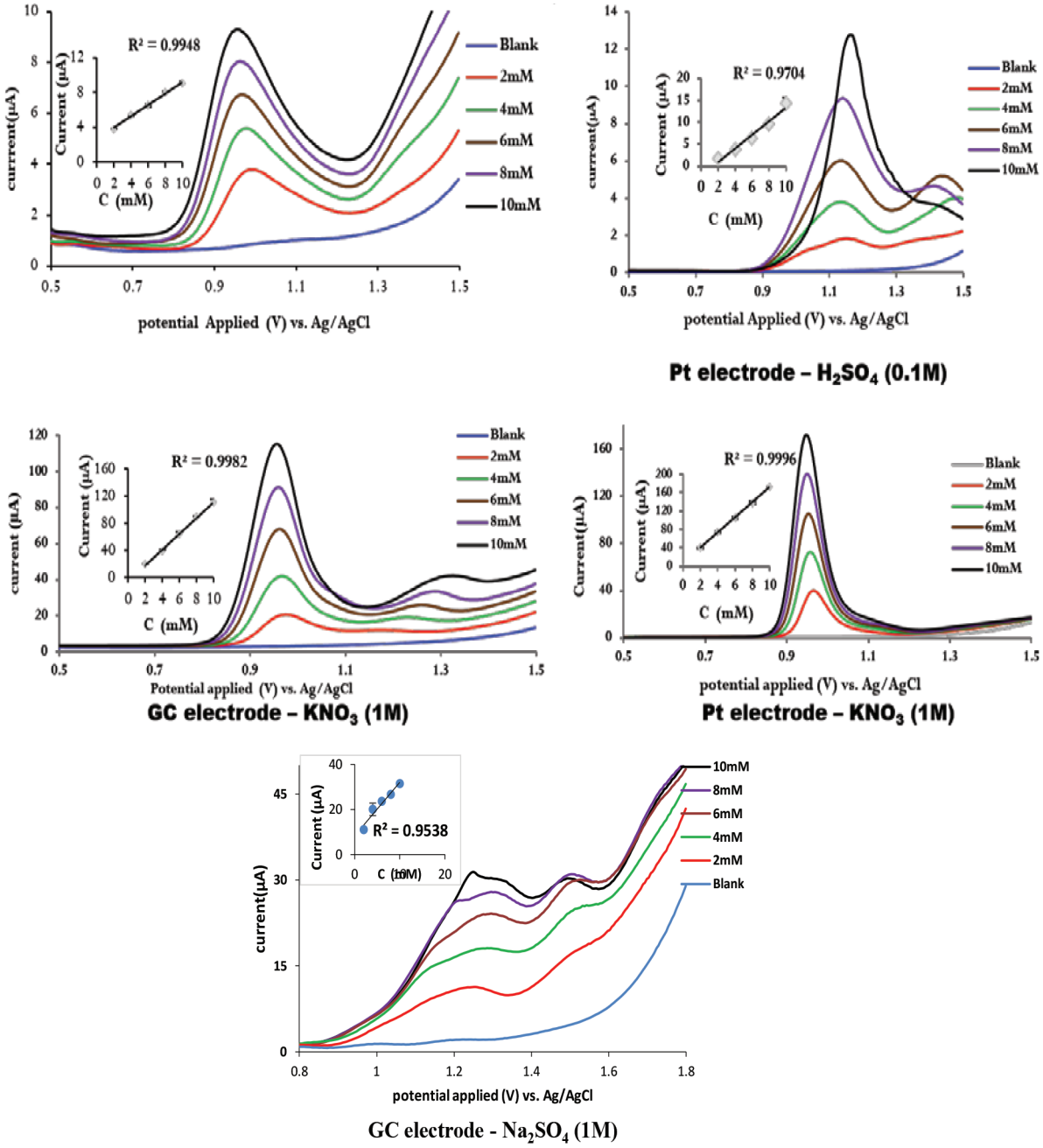

Figure 4. DPV study of glycopyrrolate (2.0–10.0 mM) using Pt and GC electrodes, with 0.1 M H_2SO_4, 1 M KNO_3, and Na_2SO_4 (1 M).

tion for both LSV and DPV using GC working electrodes and a 1 M KNO_3 supporting electrolyte, as shown in Figures 5 and 6. The LSV calibration curve showed a higher R^2 (0.9990) than DPV did (0.9860). Furthermore, LSV had a lower LOD and LOQ than DPV did, as shown in Table 1.

The effects of the additives in the commercially available glycopyrrolate on the assay were examined by studying the recovery and RSD. The accuracy and precision of the method are represented by the recovery and RSD, respectively. Both were considered, and the results are shown in Table 2. The LSV and DPV recovery

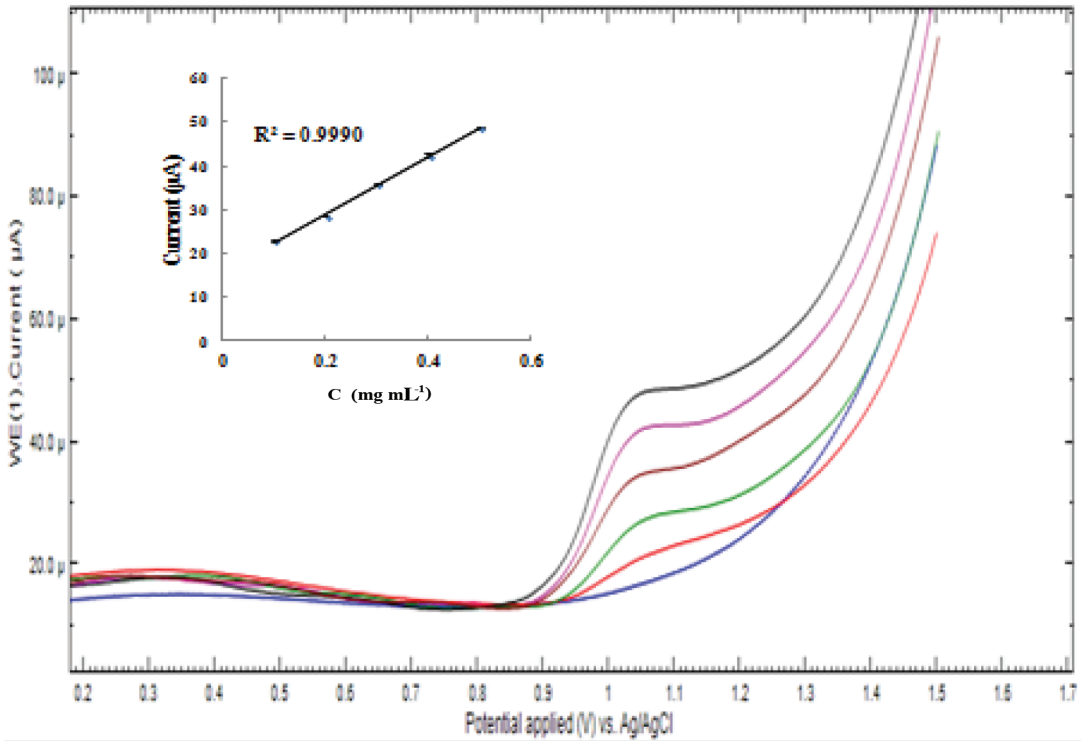

Figure 5. LSV study of glycopyrrolate (0.10–0.50 mg/mL) using GC as working electrode and 1 M KNO_3 as supporting electrolyte. Blue line: Supporting electrolyte; red line: 0.10 mg/mL; green line: 0.20 mg/mL; brown line: 0.30 mg/mL; pink line: 0.40 mg/mL; black line: 0.50 mg/mL.

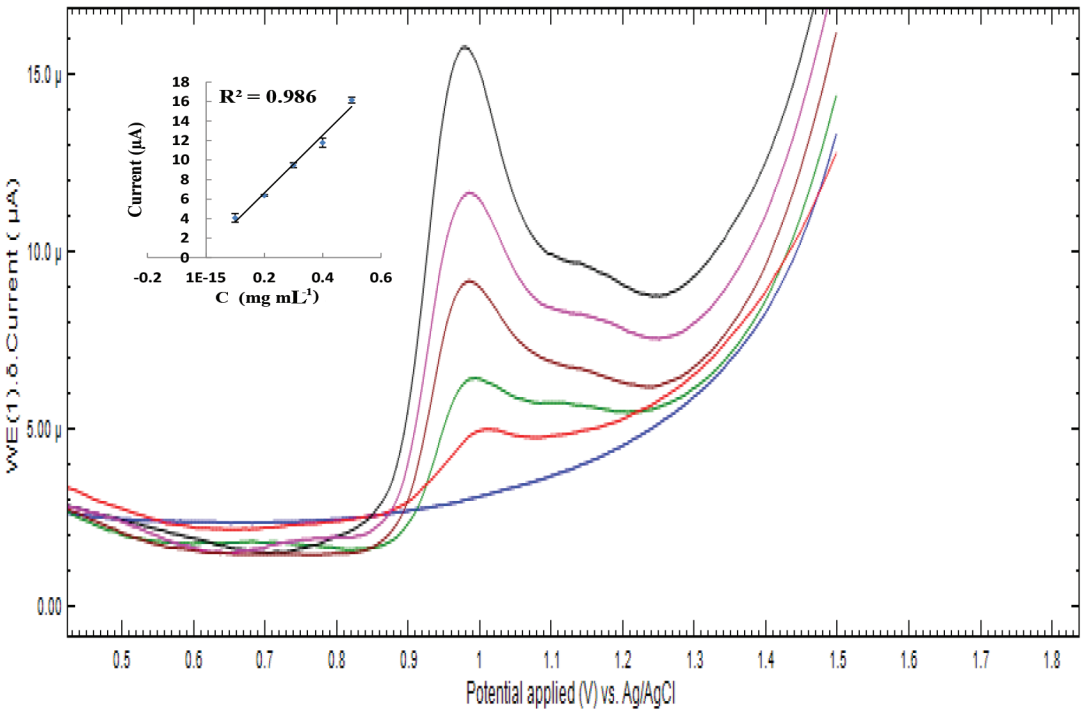

Figure 6. DPV study of glycopyrrolate (0.10–0.50 mg/mL) using GC as working electrode and 1 M KNO_3 as supporting electrolyte. Blue line: Supporting electrolyte; red line: 0.10 mg/mL; green line: 0.20 mg/mL; brown line: 0.30 mg/mL; pink line: 0.40 mg/mL; black line: 0.50 mg/mL.

and the RSD results fall within the acceptable range, with a better recovery (102.07%) for DPV and a better RSD (0.511%) for LSV.

Table 1. Linearity of glycopyrrolate (GC electrode, KNO_3 1 M).

Method	Range (mg/mL)	LR	R^2	LOD (mg/mL)	LOQ (mg/mL)
DPV	0.1–0.5	y = 29.523x + 0.71	0.9860	0.025	0.081
LSV	0.1–0.5	y = 65.114x + 16.181	0.9990	0.016	0.057

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

Table 2. Accuracy and precision of commercial glycopyrronium bromide 200 µg/mL solution for injection.

Method	Glycopyrrolate, mg/mL		
DPV	0.2	Found ±SD	0.204 ±0.011
		Recovery%	102.07
		RSD %	5.57
LSV	0.2	Found ±SD	0.216 ±0.001
		Recovery%	108
		RSD%	0.511

SD: Standard deviation of triplicate determinations, RSD: relative standard deviation, recovery: found/added ×100 %.

The electrochemical behaviors of glycopyrrolate were studied. CV indicated that glycopyrrolate is involved in a reversible redox reaction on the electrode surface, with an oxidation peak current of 1.05 V and reduction at approximately 0.80 V. A GC working electrode and 1 M KNO_3 supporting electrolyte are thus recommended for the voltammetric assay of glycopyrrolate. The recovery and RSD values of both LSV and DPV were within the accepted range for the assay of the commercially available glycopyrrolate.

3. Experimental

3.1. Materials and reagents

The standard pharmaceutical formulation of glycopyrrolate was obtained from Hikmah Pharmaceuticals (Jordan). A commercial glycopyrronium bromide 200 µg/mL solution for injection (Martindale Pharmaceuticals) was obtained from Al-Seif Company (Saudi Arabia). Potassium nitrate (KNO_3, ACS reagent, Fluka), sulfuric acid (H_2SO_4, reagent grade, Sigma Aldrich), and sodium sulfate anhydrous (Na_2SO_4, Janssen Chemica) were also obtained. Supporting electrolytes of 1 M KNO_3, 0.1 M H_2SO_4, and 1 M Na_2SO_4 were prepared using Milli-Q water.

3.2. Standard solutions

Stock solutions of 10 mM and 0.50 mg/mL glycopyrrolate were prepared. Supporting electrolytes were used to prepare stock solutions and dilute the stock solutions to prepare the working standard solutions.

3.3. Preparation of sample solutions

Ten ampoules of the commercial glycopyrronium bromide 200 mg/mL solution for injection were opened and poured into a beaker, and then a certain amount of solid KNO_3 was dissolved in the beaker in order to make the concentration of KNO_3 in the solution 1 M.

3.4. Apparatus

The potentiostat used for the electrochemical measurements was a PGSTAT 204 model from Metrohm Autolab. All measurements were done using a three-electrode system, i.e. a glassy carbon or Pt working electrode, Ag/AgCl reference electrode, and platinum (Pt) sheet auxiliary electrode.

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