



Short communication

# Gallamine–tetraphenylborate-modified carbon paste electrode for the potentiometric determination of gallamine triethiodide (Flaxedil)

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## Abstract

The construction and general performance of a novel modified carbon paste electrode for the determination of gallamine triethiodide have been developed. The electrode shows a stable, potentiometric response for gallamine in the concentration range  $1 \times 10^{-3}$ – $2 \times 10^{-6}$  M at 25 °C independent of pH in the range 5–8. The electrode passes a near-Nernstian cationic slope of  $17.0 \pm 0.7$  mV and lower detection limit of  $1 \times 10^{-6}$  M with a fast response time of 20–45 s. Selectivity coefficients for gallamine relative to a number of interfering substances were investigated. There is a negligible interference from the studied cations, anions, and pharmaceutical excipients. The determination of gallamine in aqueous solution shows an average recovery of 99.5% and a mean relative standard deviation (RSD) of 1.4% at 100 µg/ml. The direct determination of gallamine in injection solution gave results that compare favorably with those obtained by the British pharmacopoeia method. Potentiometric titration of gallamine with sodium tetraphenylborate and phosphotungstic acid as a titrant has been monitored with the modified carbon paste electrode as an end-point indicator electrode.

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## 1. Introduction

Gallamine triethiodide {2,2',2''-(benzene-1,2,3-triyltrioxy)tris(tetraethyl-ammonium)triiodide} [1] is a widely used muscle relaxant medication (Fig. 1). Most of the methods cited in literature for its

determinations involve high-performance liquid chromatography (HPLC) [2–5] and thin-layer chromatography [6]. Despite the sensitivity of chromatographic methods is quite reasonable, however, the analysis time usually needed to perform efficient separation is rather not a short time compared with the direct potentiometric measurements method. Recently, a cathodic adsorptive stripping voltammetric determination of gallamine triethiodide has been described using a hanging mercury drop electrode whereby mercur-

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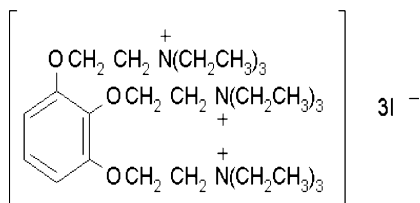


Fig. 1. Structural formula of gallamine triethiodide.

ous iodide salts are formed [7]. The method is sensitive and simple; however, the use of mercury and the formation of mercury salts are not appreciated. Potentiometric methods using ion-selective electrodes have been proved to be fast, simple, and selective that can easily be applied in different fields including pharmaceutical analysis [8–10]. PVC membrane electrodes selective to some muscle relaxants including gallamine using dipicrylamine and tetraphenylborate as counter ions have been described [8]. However, these membranes have not been examined for the determination of the corresponding relaxants in their pharmaceutical preparation. On the other hand, carbon pastes are well known as useful materials for the fabrication of various electro-metric sensors for analytical purposes [9–11]. The operation mechanism of such chemically modified carbon paste electrodes (CMCPEs) depends on the properties of the modifier materials used to impart selectivity towards the target species [12]. In comparison with ion-selective electrodes based on polymeric membranes, CMCPEs possess advantages of much lower ohmic resistance, very stable response, and easy renewal of its surface. Although considerable attention has been given to the preparation of CMCPEs so far, the application of these CMCPEs has been mainly focused on the voltammetric determination [13,14], and only very few of these types of the electrodes have been used for potentiometric measurements. This work describes the construction, potentiometric characterization, and analytical application of a novel gallamine-modified carbon paste electrode based on the use of gallamine–tetraphenylborate (GAL–TPB) as electroactive material and dioctylphthalate (DOP) as plasticizer.

## 2. Experimental

### 2.1. Apparatus

All potentiometric measurements were made at  $25 \pm 1$  °C unless otherwise stated using an Orion pH/mV meter (model 330), and a combined Ross glass pH electrode (Orion 81-02) was used for pH measurements. An Orion double-junction Ag–AgCl reference electrode (model 90-02) containing 10% (w/v) potassium nitrate in the outer compartment was used.

### 2.2. Reagents and materials

All chemicals used were of analytical reagent grade unless otherwise stated, and doubly distilled water was used throughout. DOP, paraffin oil, graphite powder, sodium tetraphenylborate, and tetrahydrofuran (THF) of purity >99% were obtained from Aldrich Chemical Company.  $1 \times 10^{-2}$  M aqueous solution of gallamine triethiodide was prepared by dissolving appropriate amount of gallamine (Alexandria Company, Egypt) in water. Gallamine ampoules (each 2 ml containing gallamine triethiodide 40 mg in pyrogenic water) were obtained from Alexandria Company. Phosphate buffer of pH 7.0 was prepared by mixing 61 ml of 0.066 M sodium hydrogen phosphate with 39 ml of 0.066 M of potassium dihydrogen phosphate.

### 2.3. Preparation of the gallamine-modified carbon paste electrode

GAL–TPB was formed upon the addition of 25 ml of  $1 \times 10^{-2}$  M of gallamine triethiodide solution to 75 ml of  $1 \times 10^{-2}$  M sodium tetraphenylborate solution as a white precipitate. The gallamine-modified carbon paste electrode (GALCPE) was prepared by mixing weighed amounts of GAL–TPB, high-purity graphite, DOP, and paraffin oil thoroughly until obtaining a uniformly wetted paste. Portions of the resulting composite material were then packed in the end of a disposable polyethylene syringe (3 mm i.d., 1 ml), the tip of which had been cut-off with a razor blade. Electrical contact to the carbon paste was made with a platinum wire. Fresh surface was

obtained by applying manual pressure to the carbon paste. The resulting fresh surface was polished on a filter paper until it had a shiny surface. The electrode surface was polished gently with smooth tissue of paper when the gallamine solution is changed from high concentration to a dilute solution. The newly prepared indicator electrode was conditioned by soaking in a  $1 \times 10^{-2}$  M aqueous gallamine solution for 1 h and stored in the same solution when not in use.

#### 2.4. Procedure

The gallamine-modified carbon electrode was calibrated by immersion in conjunction with the reference electrode in a 50 ml beaker containing 9 ml of phosphate buffer solution of pH 7. Then 1 ml aliquot of gallamine solution of concentration ranging from  $1 \times 10^{-2}$  to  $1 \times 10^{-5}$  M was added with continuous stirring and the potential was recorded after stabilization to  $\pm 0.2$  mV. A calibration graph was then constructed by plotting the recorded potentials as a function of  $-\log[\text{gallamine}]$ . The resulting graph was used for subsequent determination of unknown gallamine concentration.

#### 2.5. Determination of gallamine in gallamine ampoules

Gallamine triethiodide was determined in gallamine injection solution (40 mg/2 ml) by transferring the contents of one ampoule of gallamine into a 100 ml measuring flask, and making up to the mark with water. Fifty and hundred microliters aliquots of the solution were transferred to the measuring cell containing 9.0 ml of phosphate buffer, and the e.m.f. of the electrode systems was measured. The concentration of gallamine was calculated from the previous calibration graph as in the procedure. Alternatively, the standard addition technique was used for the determination of gallamine triethiodide by monitoring the potential of the drug solution before and after the addition of a known concentration of the gallamine solution. The determination of gallamine content in gallamine ampoule has been carried out using British pharmacopoeia and HPLC

methods [2] after appropriate dilution of the gallamine concentration.

### 3. Results and discussion

Tetraphenylborate was used as an ion-pairing agent for the preparation of an electroactive ion-association complex for gallamine. The elemental analysis of the sparingly soluble complex of GAL-TPB showed that the composition of the complex is 1:3 (gallamine:tetraphenylborate). The dry powder of the formed ion-pair was used for the preparation of the new GALCPE.

#### 3.1. Influence of the electrode composition

It is known that the sensitivity and linearity for a given electrode depend significantly on the amount of the ion-pair in the membrane composition. Thus, the influence of the percent of GAL-TPB in the carbon paste composition was investigated. Preliminary experiment showed that carbon paste electrode which does not contain the ion-pair modifier has no response towards the analyte. For this purpose, four electrodes were prepared that contain the ion-pair modifier in 1.2, 2.4, 4.0, and 7.5%, while the other components have been kept unchanged, and the results are summarized in Table 1. The resulting slopes and correlation coefficients are 13.6 (0.987), 17.0 (0.999), 15.0 (0.996), and 13.7 (0.98) mV per decade. Fig. 2 shows that the linear ranges of the electrodes are  $1 \times 10^{-3}$ – $2 \times 10^{-6}$ ,  $1 \times 10^{-3}$ – $6 \times 10^{-5}$ , and  $1 \times 10^{-3}$ – $8 \times 10^{-5}$  M in the same order. These results show that for the electrode that contains 2.40% of the modifier, a Nernstian slope has been obtained. A nonlinearity in the electrode response has been observed with electrodes that contain less or higher ratios of the modifier. Since the electrode with 2.4% of ion-pair has a good slope and wide range of linearity, this percentage was chosen as the optimum amount for the gallamine electrode.

#### 3.2. Sensor performance

The potentiometric performance characteristics of GALCPE based on the use of GAL-TPB ion-

Table 1  
General characteristic of some different composition of GALCPE

Composition of the modified chemical (%)	Slope	Range of determination (M)	Lower LOD (M)	Correlation coefficient, <i>r</i>
1.2	14.5±0.5	1 × 10 <sup>-3</sup> –1 × 10 <sup>-4</sup>	7 × 10 <sup>-5</sup>	0.877
2.4	17.0±0.7	1 × 10 <sup>-3</sup> –2 × 10 <sup>-6</sup>	1 × 10 <sup>-6</sup>	0.999
4.0	16.5±0.8	1 × 10 <sup>-3</sup> –4 × 10 <sup>-6</sup>	2 × 10 <sup>-6</sup>	0.998
7.5	16.5±0.7	1 × 10 <sup>-3</sup> –4 × 10 <sup>-6</sup>	2 × 10 <sup>-6</sup>	0.998

pair as an electroactive material and DOP as a plasticizer in a graphite carbon matrix were evaluated according to IUPAC recommendations [15], and the results are given in Table 2. The sensor displays a linear response for 4 × 10<sup>-6</sup>–1 × 10<sup>-3</sup> M gallamine with a Nernstian cationic slope of 17.0 ± 0.5 mV per decade concentration. The limit of quantitation (LOQ) and the limit of detection (LOD) are 4 × 10<sup>-6</sup> and 2 × 10<sup>-6</sup> M, respectively. The least-squares equation obtained

Table 2  
Response characteristics of gallamine-modified carbon paste electrode

Parameter	Value
Slope (mV per decade)	17.0 ± 0.7
Intercept (mV)	225 ± 0.6
Correlation coefficient, <i>r</i>	0.999
Lower detection limit (M)	1 × 10 <sup>-6</sup>
Response time for 1 × 10 <sup>-3</sup> M solution (s)	20 ± 0.5
Working pH range	5–8

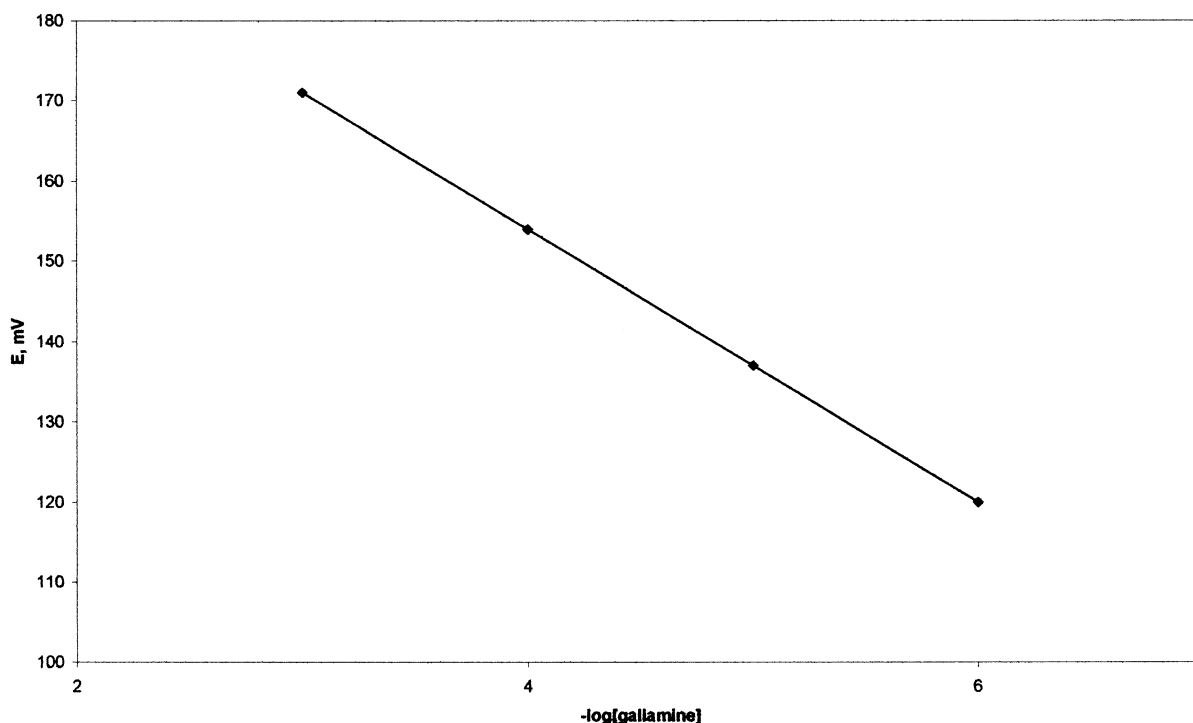


Fig. 2. Calibration graph.

from the calibration data is

$$E \text{ (mV)} = (17.0 \pm 0.5)\log[\text{gallamine}] + (225 \pm 0.6).$$

### 3.3. Repeatability/reproducibility

The repeatability of the method has been examined by measuring the potential response of different concentrations of gallamine over a wide time interval of 1 week. The repeatability of the measuring solution has been found to be within  $\pm 1$  mV over a week.

### 3.4. Robustness/ruggedness of the electrode

The carbon paste electrode is stable towards mechanical shocks with increasing the temperature up to 50 °C, and with the advantage of the renewal of its surface without changing its properties.

### 3.5. Effect of pH and the response time

The electrode response for different gallamine concentrations was tested at different pH values, the pH being adjusted using hydrochloric acid or sodium hydroxide. GALCPE was dipped into gallamine solution of  $1 \times 10^{-3}$ ,  $1 \times 10^{-4}$ , and  $1 \times 10^{-6}$  M concentration and the potential of the electrode was plotted against the pH of solution (Fig. 3). This figure shows that the slope per decade concentration is constant  $\sim 17 \pm 0.5$  mV in the pH range 4–7. The average response time is defined [15] as the time required for the electrode to reach a stable potential within  $\pm 1$  mV of the final equilibrium value, after successive immersion of the electrode in different gallamine solutions each having a 10-fold difference in concentration or after rapid 10-fold increase in concentration by the addition of gallamine. This time was found to be 20 s for the concentration of  $1 \times 10^{-3}$  M, and 45 s for the concentration  $1 \times 10^{-4}$  M. Day-to-day reproducibility of the sensor is about  $\pm 0.5$  mV for the same solution and the useful lifetime of the sensor is 4 weeks, during which the potential slope is reproducible within  $\pm 1$  mV per decade concentration. Squeezing out a

small amount of paste, and polishing the electrode on a smooth filter paper obtained a fresh electrode surface.

### 3.6. Effect of diverse ions

The influence of 20 different organic and inorganic ions on the response of gallamine sensor was investigated. The selectivity coefficients were determined by the separate solution method [15,16] in a phosphate buffer solution of pH 7 using  $1 \times 10^{-2}$  M concentration of both gallamine and interfering species. The selectivity coefficient was calculated from the following equation:

$$\frac{E_2 - E_1}{S} = \log[a_{\text{gallamine}} + K_{\text{gallamine}, j}^{\text{pot}}(a_j)^{z/y}],$$

where  $E_1$  and  $E_2$  are the potential readings observed after 1 min of exposing the sensor to the same concentrations of gallamine ion and interfering ions alternatively.  $a_{\text{gallamine}}$  and  $a_j$  are the activities or concentrations of the gallamine ion and interfering ions of  $z$  and  $y$  charges, respectively, and  $S$  is the slope of calibration graph (mV per decade concentration). Table 3 reveals that there is no interference from all the studied ions, indicating high selectivity of GALCPE.

### 3.7. Determination of gallamine

For verifying the feasibility of the developed method, the determination of gallamine in water was carried out using the developed, modified carbon paste electrode. The analysis of 50–250  $\mu\text{g}/\text{ml}$  gallamine solutions (in five replicates) by direct potentiometry gave an average recovery of 99.45% and relative standard deviation (RSD) of 1.2%, and results are shown in Table 4.

### 3.8. Determination of gallamine in injection solution

The versatility of the method has been investigated by measuring the gallamine concentration in injection ampoules and comparing the results with those obtained with the pharmacopoeia and

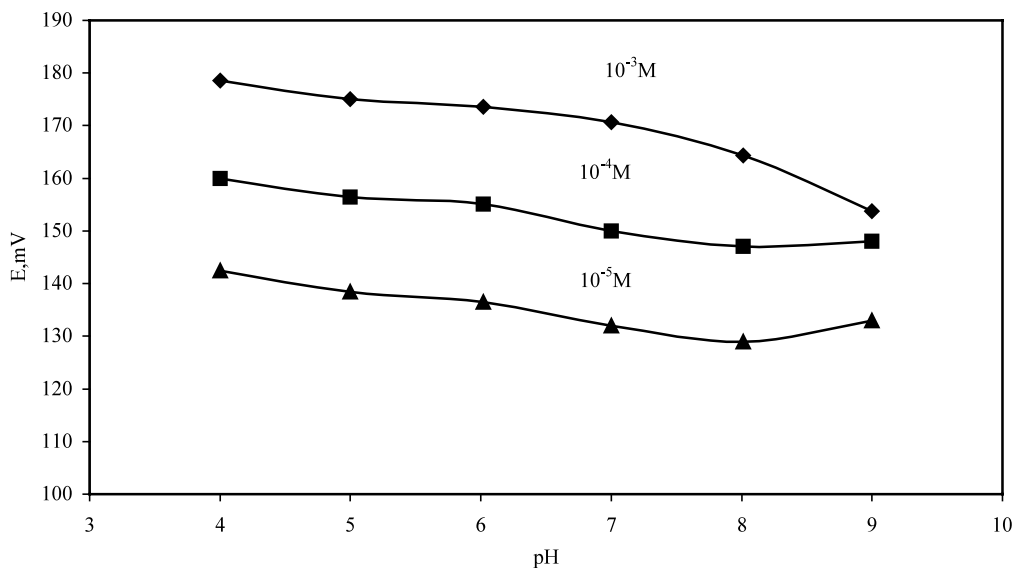


Fig. 3. Effect of pH on the response of gallamine-modified carbon paste electrode using three series of gallamine solutions,  $1 \times 10^{-3}$ ,  $1 \times 10^{-4}$ , and  $1 \times 10^{-5}$  M.

Table 3

Potentiometric selectivity coefficients of some interfering ions using Flaxedil-modified carbon paste electrode

Interferent, J	$K_{\text{gallamine, J}}^{\text{pot}}$
Na <sup>+</sup>	$1.3 \times 10^{-3}$
K <sup>+</sup>	$1.3 \times 10^{-3}$
Ca <sup>2+</sup>	$1.5 \times 10^{-3}$
Mg <sup>2+</sup>	$1.3 \times 10^{-3}$
Cu <sup>2+</sup>	$1.3 \times 10^{-3}$
Zn <sup>2+</sup>	$1.3 \times 10^{-3}$
Al <sup>3+</sup>	$1.3 \times 10^{-3}$
CO <sub>3</sub> <sup>2-</sup>	$1.3 \times 10^{-3}$
Cl <sup>-</sup>	$1.3 \times 10^{-3}$
PO <sub>4</sub> <sup>3-</sup>	$1.3 \times 10^{-3}$
CH <sub>3</sub> COO <sup>-</sup>	$1.3 \times 10^{-3}$
NO <sub>3</sub> <sup>-</sup>	$1.3 \times 10^{-3}$
Citrate	$8.7 \times 10^{-3}$
Urea	$8.7 \times 10^{-3}$
Hydrazine	$8.1 \times 10^{-3}$
L-Tryptophane	$2.6 \times 10^{-3}$
D,L-Alanine	$1.4 \times 10^{-3}$
Formate	$2.9 \times 10^{-3}$
Glycine	$3.3 \times 10^{-3}$
Glucose	$2.8 \times 10^{-3}$
Fructose	$1.8 \times 10^{-3}$

Table 4

Recovery of gallamine from water by direct potentiometry using GALCPE

Added ( $\mu\text{g/ml}$ )	Found <sup>a</sup> ( $\mu\text{g/ml}$ )	%Recovery	%RSD
50	49.5	99.0	1.6
100	99.5	99.5	1.4
200	198.0	99.0	1.1
250	250	100	0.9

<sup>a</sup> Each result is a mean of five determinations.

HPLC methods. The average recovery for injection solution (40 mg/2 ml) was 98.5% with an RSD of 1.7% for injection. The results (Table 5) are in agreement with those obtained from the British pharmacopoeia [17] and HPLC method [2], with a relative recovery of 98.6% and an RSD of 1.6%.

The proposed method has proved to be simple and accurate, and higher throughput compared with three determinations of the HPLC method. On the other hand is by far not simple and safe compared with pharmacopoeia method that uses mercuric acetate and perchloric acid.

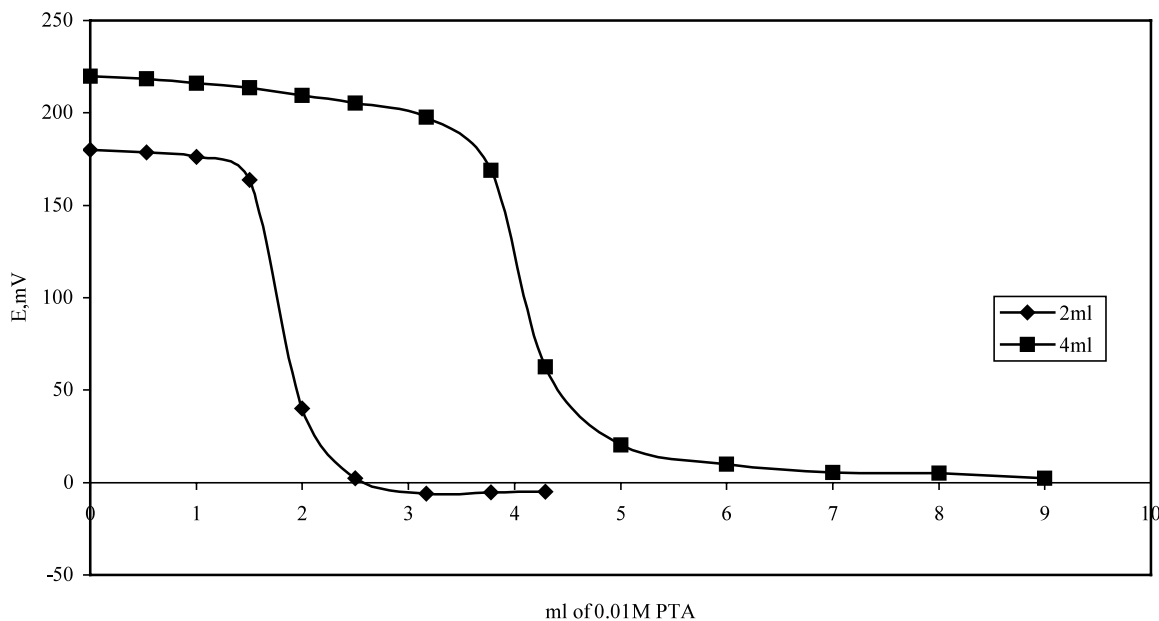


Fig. 4. Typical potentiometric titration curves of 0.01 M gallamine solution with standard 0.01 M phosphotungstic acid solution using GALCPE.

Table 5  
Determination of gallamine in injection solution using the proposed modified carbon paste electrode

Volume of gallamine taken ( $\mu$ l)	Nominal value of gallamine (mg)	Proposed method <sup>a</sup>		British pharmacopoeia		HPLC	
		%Recovery	%RSD	%Recovery	%RSD	%Recovery	%RSD
50	0.02	99.0	1.7	98.7	1.6	99.2	1.3
100	0.04	100.0	1.5	99.2	1.1	99.3	1.2

<sup>a</sup> Average of five determinations.

Table 6  
Analysis of gallamine triethiodide in the injection solution containing 100  $\mu$ g/ml for studying the stability of gallamine

Time (days)	Added ( $\mu$ g/ml)	Found <sup>a</sup> ( $\mu$ g/ml)	%Recovery	%RSD
0	100	99.5	99.5	1.4
1	100	99.0	99.0	1.5
2	100	98.5	98.5	1.4
5	100	98.5	98.5	1.4
7	100	99.0	99.0	1.5

<sup>a</sup> Each result is a mean of five determinations.

### 3.9. Stability of the analyte

The proposed electrode offered an accurate and fast method for evaluating the stability of the analyte. The stability of the analyte was tested over 1 week by measuring the concentration of gallamine using the proposed GALCPE; the recovery data is shown in Table 6. The high recoveries were obtained in the results indicating that the drug was stable over 1 week. In addition, the recovery of gallamine from injection ampoules that have about 3-month difference in the manufacturing date was found to be less only by 0.5%.

### 3.10. Potentiometric titration of gallamine

In addition, the developed electrode in conjunction with an Ag–AgCl reference electrode has been examined as an end-point indicator electrode for some potentiometric reactions. Titration of gallamine with phosphotungstic acid has been performed and it is clear that gallamine reacts with phosphotungstic acid in 1:1 molar ratio. The titration curve was symmetrical with a very well-defined potential jump of about 150 mV indicating the high sensitivity of the electrode (Fig. 4).

## 4. Conclusion

In conclusion, the developed gallamine-modified carbon paste electrode described in this work offers a simple, accurate, selective, and specific tool for quantitative determination of gallamine content in its pharmaceutical preparation, gallamine ampoule. The developed method is considered to be fast compared with chromatographic methods and does not use any hazardous mercury

or mercuric salts, like the case in adsorptive voltammetric methods using HMDE or the pharmacopoeia method used for gallamine determination. In the same time, the electrode was used as an indicator electrode for the potentiometric titration of gallamine using phosphotungstic acid standard solutions.

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