



# Differential pulse anodic voltammetric determination of lithium ions in pharmaceutical formulations using a carbon paste electrode modified with spinel-type manganese oxide

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## Abstract

The use of the differential pulse voltammetry for the determination of lithium ions in pharmaceutical samples using a carbon paste electrode modified with spinel-type manganese oxide has been examined. The best voltammetric response was reached for a modified electrode in borate buffer solution of pH 9.0 and submitted to a scan rate of 5 mV s<sup>-1</sup> and a pulse amplitude of 50 mV. This electroanalytical procedure was able to determine lithium ions in the concentration range of 8.0 × 10<sup>-5</sup>–1.0 × 10<sup>-2</sup> mol l<sup>-1</sup> even in the presence of several alkali metals (1.0 × 10<sup>-3</sup> mol l<sup>-1</sup>) with a detection limit of 7.1 × 10<sup>-7</sup> mol l<sup>-1</sup>. Rapidity, precise and good selectivity were also found for the determination of lithium ions in pharmaceutical formulations.

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**Keywords:** Modified electrode; Spinel-type manganese oxide; Differential pulse voltammetry; Lithium ions

## 1. Introduction

The monitoring of lithium ions is of great importance in medical and clinical fields. Lithium ions are used in the treatment of manic depression psychosis. The level of lithium ions in blood must

be maintained between 0.5 and 1 mmol l<sup>-1</sup>. While levels of lithium ions higher than this last value are toxic, levels higher than 5 mmol l<sup>-1</sup> can be lethal [1]. Hence, the level of lithium ions in the patients' blood must be frequently monitored [1,2]. The determination of lithium ion is performed by the use of flame photometry or atomic absorption spectrophotometry [3,4]. The major challenge for the lithium ions analysis is the required selectivity against Na<sup>+</sup> and K<sup>+</sup>, which typically coexist with Li<sup>+</sup> at relatively high concentrations.

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Several ion selective electrodes with polymeric membranes containing ionophores (such as diamides, crown ethers, derivatives of natural polyether antibiotics, heteroaromatic compounds and polypropoxylates) were previously reported for the determination of lithium ions [5,6]. However, the determination of lithium ions using voltammetric techniques has only been rarely investigated. A voltammetric ion-selective electrode based on the facilitated transfer of lithium ions by dibenzyl-14-crown-4 at the *o*-nitrophenyl phenyl ether–water interface was applied by Sawada et al. [7,8] to the amperometric detector in a FIA system with a cation-exchange column. In the last work, the authors determined lithium ions in the concentration range of 0.2–2.0 mM in the presence of sodium ions (120–160 mM) with a detection limit of 0.15 mM.

In our laboratories, we are also interested in developing highly sensitive and selective methods for the determination of lithium ions using modified electrodes. Firstly, a  $\lambda$ -MnO<sub>2</sub>-based graphite-epoxy electrode was examined for the determination of lithium ions [9]. The potentiometric response of this electrode to lithium ions was linear in the concentration range  $10^{-6}$ – $3.3 \times 10^{-2}$  mol l<sup>-1</sup> with a slope of 58.2 mV per decade (at 25 °C) over a wide pH range (4–10). More recently, a carbon paste electrode modified with that same spinel-type manganese oxide ( $\lambda$ -MnO<sub>2</sub>) was developed for the voltammetric determination of lithium ions in pharmaceutical samples [10]. The voltammetric response of the proposed electrode presented good sensitivity and selectivity. It is noteworthy that even the newest review on carbon paste-based electrodes [11], has not included any reference on the determination of lithium ions. In this paper, an electroanalytical procedure (differential pulse voltammetry) for the determination of lithium ions in pharmaceutical formulations is proposed, using the same carbon paste electrode modified with spinel-type manganese oxide. The differential pulse voltammetry was selected by presenting better sensitivity than the cyclic voltammetry [12,13] already employed in the previous work. The influence of various experimental parameters (potential scan rate, potential pulse, pH

and interference) on the electrode response were investigated.

## 2. Experimental

### 2.1. Apparatus

All the voltammetric measurements were carried out in a 30 ml thermostated glass cell at 25 °C, containing the following three electrodes: carbon paste electrode modified with a spinel-type manganese oxide as working electrode, saturated calomel (SCE) and platinum as reference and auxiliary electrodes, respectively. During the measurements, the aerated borate buffer solution (pH 9.0) in the cell was not stirred. The cyclic and differential pulse voltammetric measurements were performed with a potentiostat Eco Chemie Autolab/PGSTAT30 under computer control. For the cyclic voltammetry, the potential range was from 0.40 to 1.05 V versus SCE with a scan rate was of 5 mV s<sup>-1</sup>. The parameters for differential pulse anodic voltammetric measurements were: potential range from 0.40 to 1.0 V versus SCE, scan rate from 1 to 50 mV s<sup>-1</sup> and pulse amplitude from 10 to 200 mV for a pulse width of 0.2 s.

### 2.2. Reagents and solutions

All the solutions were prepared using a Millipore Milli-Q water. All the chemicals were analytical reagent grade without further purification. The supporting electrolyte used for all the experiments was a 0.025 mol l<sup>-1</sup> borate buffer solution (pH 9.0). A 0.01 mol l<sup>-1</sup> lithium ions were prepared daily by dissolving lithium chloride (Merck) in 100 ml of the borate buffer solution.

### 2.3. Preparation of the carbon paste electrode

The synthesis of the spinel-type manganese oxide ( $\lambda$ -MnO<sub>2</sub>) was made as previously described by Bocchi et al. [14]. The modified carbon paste was prepared by carefully mixing 50% (m/m) of graphite powder (1–2  $\mu$ m particle size, Aldrich), 25% (m/m) of  $\lambda$ -MnO<sub>2</sub> and 25% (m/m) of mineral oil (Aldrich) in a mortar for at least 20 min. This

paste was then packed into an electrode body, consisting of a 1 ml plastic tube (insulin plastic syringe) arranged with a copper wire serving as an external electric contact.

#### 2.4. Preparation and analysis of pharmaceutical samples

For the analysis of pharmaceutical samples (Carbolitium® of 300 mg, Carbolitium® CR of 450 mg both from Eurofarma and Carbolim® of 300 mg from Dansk-Flama) an accurate amount of powder from tablets was transferred to a 100 ml volumetric flask and this volume completed with borate buffer solution (pH 9.0). Aliquots varying from 1 to 5 ml of these samples were added into a 30 ml thermostated glass cell at 25 °C, containing 20 ml of borate buffer. The final solution was finally homogenized with a magnetic stirrer. With the rest solution, the differential pulse anodic voltammograms were recorded, using the experimental parameters mentioned above. A blank solution without addition of lithium ions was used to obtain the base current. The lithium ions content was determined by the standard addition method and compared with that obtained by atomic absorption spectrophotometry at a wavelength of 678.8 nm.

### 3. Results and discussion

#### 3.1. Voltammetric measurements

Fig. 1 shows cyclic voltammograms obtained at a scan rate of 5 mV s<sup>-1</sup> for the carbon paste electrode modified with spinel-type manganese oxide in borate buffer solution (pH 9.0) containing 1.0 × 10<sup>-2</sup> mol l<sup>-1</sup> lithium ions. Two redox couples were observed, being the first at 0.63 V (peak I) and 0.55 V versus SCE (peaks III) and the second at 0.81 V (peak II) and 0.67 V versus SCE (peaks IV). As proposed by Kanoh and co-workers [15], these two redox couples correspond to the following electrochemical insertion/extraction processes of lithium ions into the manganese oxide matrix:

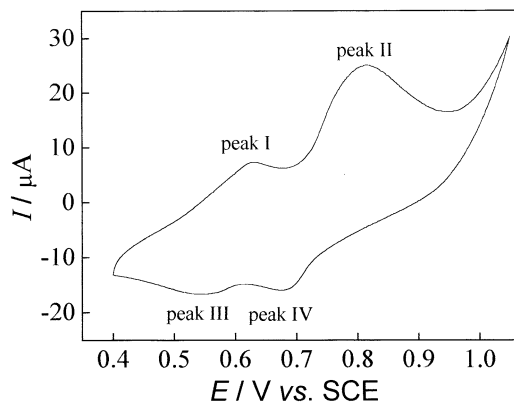


Fig. 1. Cyclic voltammogram obtained at a scan rate of 5 mV s<sup>-1</sup> for the carbon paste electrode modified with spinel-type manganese oxide in borate buffer solution (pH 9.0) containing 1.0 × 10<sup>-2</sup> mol l<sup>-1</sup> of lithium ions.

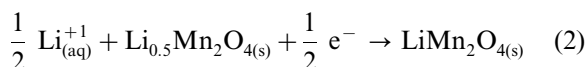
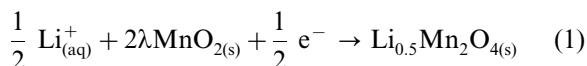


Fig. 2 shows a representative differential pulse anodic voltammogram recorded for the carbon paste electrode modified with spinel-type manganese oxide in borate buffer solution (pH = 9.0) containing 1.0 × 10<sup>-3</sup> mol l<sup>-1</sup> lithium ions. It displays well-defined differential anodic peaks

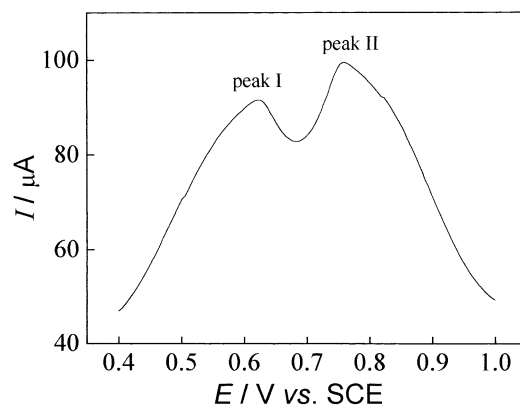


Fig. 2. Differential pulse anodic voltammogram recorded at a scan rate of 5 mV s<sup>-1</sup> and a pulse amplitude of 75 mV for the carbon paste electrode modified with spinel-type manganese oxide in borate buffer solution (pH 9.0) containing 1.0 × 10<sup>-3</sup> mol l<sup>-1</sup> of lithium ions.

located at 0.62 and 0.76 V versus SCE (peaks I and II, respectively), corresponding to the oxidation processes of manganese ions in the oxide as given by Eqs. (1) and (2).

As the current values of both anodic peaks in the differential pulse anodic voltammograms are dependent on the instrumental parameters, such as scan rate and pulse amplitude, they were investigated and optimized in the present study.

### 3.2. Effect of the scan rate and potential amplitude

The effect of the scan rate on the differential pulse voltammetric response of the carbon paste electrode modified with spinel-type manganese oxide in a borate buffer solution containing  $1.0 \times 10^{-3}$  mol  $l^{-1}$  of lithium ions is shown in Fig. 3A. The current values increase with the scan rate from 1 to  $50 \text{ mV s}^{-1}$ , mainly for the second anodic peak as observed in this figure. The increase of the values of peak current was accompanied by broadening and distortion of the peaks. Due to this a scan rate of  $5 \text{ mV s}^{-1}$  was chosen and subsequently used throughout the present study.

The current values of both anodic peaks were also found to vary with pulse amplitude (10–200 mV) applied in the differential pulse voltammograms recorded at a scan rate of  $5 \text{ mV s}^{-1}$  for a carbon paste electrode modified with spinel-type

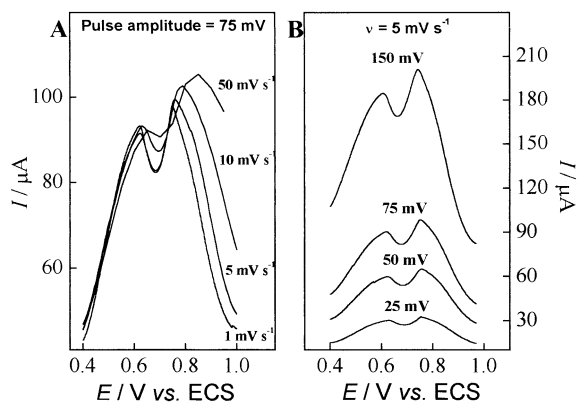
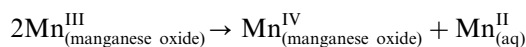


Fig. 3. The effect of the scan rate (A) and potential amplitude (B) on the voltammetric responses of a carbon paste electrode modified with spinel-type manganese oxide in a solution containing  $1.0 \times 10^{-3}$  mol  $l^{-1}$  lithium.

manganese oxide in a borate buffer solution containing  $1.0 \times 10^{-3}$  mol  $l^{-1}$  of lithium ions (see Fig. 3B). However, the use of pulse amplitudes larger than 50 mV led to an increase in the values of capacitive current. The better voltammetric profiles (with high sensibility) were obtained for a potential pulse of 50 mV and, therefore, this pulse value was chosen for further studies.

### 3.3. Effect of the pH

The effect of the pH on differential pulse anodic voltammograms of the carbon paste electrode modified with spinel-type manganese oxide in a borate buffer solution containing  $10 \times 10^{-3}$  mol  $l^{-1}$  lithium ions was investigated in the pH range of 3–11. The obtained results indicated that the current values of both the anodic peaks are strongly influenced by the pH except for pH 3 and 4 where the voltammetric profiles were not well defined. The current values for the second anodic peak increase in the pH range of 5–8 reach a maximum value at pH 9 as shown in Fig. 4. The surface disproportionation reaction proposed by Hunter [16] and Sato et al. [17], i.e.



could possibly explain such pH dependence of the values of peak current. So, as the pH increases, the

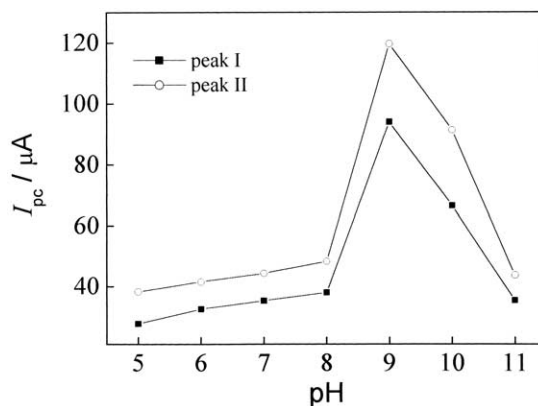


Fig. 4. pH dependence of the differential pulse voltammetric response of the carbon paste electrode modified with spinel-type manganese oxide in a borate buffer solution (pH 9.0) containing  $1.0 \times 10^{-3}$  mol  $l^{-1}$  of lithium ions. Scan rate of  $5 \text{ mV s}^{-1}$  and pulse amplitude of 50 mV.

surface amount of the  $(\text{Li})[\text{Mn}^{\text{III}}\text{Mn}^{\text{IV}}]\text{O}_4$  spinel also increases, leading to higher peak current values. For pH 10 and 11, the values of peak current decrease again probably due to another surface disproportionation proposed by Ammundsen et al. [18], i.e.



On the other hand, potential peak values were independent of the solution pH. Therefore, only a borate buffer solution of pH 9.0 was used in the further studies.

#### 3.4. Effect of the interference

In order to investigate the analytical application of this differential pulse voltammetric technique, the effect of the excipients present in pharmaceutical formulations was investigated by carrying out the determination of lithium ions in the presence of each one of those excipients at the same concentration of those formulations. These studies showed that none of those excipients caused positive or negative effects on the electrode response, indicating the absence of serious interferences.

The interference of cations usually present in blood ( $\text{Na}^+$ ,  $\text{K}^+$ ,  $\text{Mg}^{2+}$  and  $\text{Ca}^{2+}$ ) and also other cations such as  $\text{Cs}^+$  and  $\text{Ba}^{2+}$  at fixed concentration of  $1.0 \times 10^{-3} \text{ mol l}^{-1}$  on the differential pulse voltammetric response of a carbon paste electrode modified with spinel-type manganese oxide in a borate buffer solution (pH 9.0) with and without lithium ions ( $1.0 \times 10^{-3} \text{ mol l}^{-1}$ ) was also investigated. Modifications in the electrochemical extraction processes of lithium ions into the manganese oxide matrix were practically not found for all those cations. This occurred because the spinel-type manganese oxide shows more adsorptive capacity for  $\text{Li}^+$  than for the remaining alkali metals, since its small ionic radius (0.74 Å) makes easier its entrance in the three-dimensional tunnels ( $\sim 0.7$  Å) of the spinel structure [19]. Although,  $\text{Mg}^{2+}$  has small ionic radius (0.72 Å), it does not enter in the tunnels of the spinel structure, owing to its high dehydration energy [20].

#### 3.5. Calibration curve and reproducibility

After optimizing the best operating conditions for the carbon paste electrode modified with spinel-type manganese oxide (Table 1), differential pulse anodic voltammetries were carried out in the borate buffer solution (pH 9.0) containing different lithium ions concentrations in order to obtain the analytical curve for such electrode. The obtained values for the peak current (peak II in Fig. 2) gave a linear relationship with the lithium ions concentrations from  $8.0 \times 10^{-5}$  to  $1.0 \times 10^{-2} \text{ mol l}^{-1}$ . This plot could be represented by the equation  $I_p (\mu\text{A}) = 0.002 + 8.49 [\text{Li}^+] (\text{mmol l}^{-1})$  with a correlation coefficient of 0.9998. The detection and quantification limits calculated according to the recommendations of IUPAC [21] were  $7.1 \times 10^{-7}$  and  $2.4 \times 10^{-6} \text{ mol l}^{-1}$  of lithium ions, respectively. It is important to note that the detection limit obtained using the differential pulse voltammetry was two orders of magnitude smaller than that previously obtained with the cyclic voltammetry ( $2.2 \times 10^{-5} \text{ mol l}^{-1}$  [10]). The best sensitivity of the differential pulse voltammetry can be attributed to a decrease in the nonfaradaic charging current and consequently a decrease in the average standard deviation in the voltammetric responses in the absence of lithium ions. The precision of the method was also tested by analyzing five replicates containing  $1.0 \times 10^{-3} \text{ mol l}^{-1}$  of lithium ions. For each voltammogram, the surface of the electrode was renewed. The variation coefficient was 1.7%.

Table 1  
Experimental variables examined in the optimization of the differential pulse anodic voltammetric method

Variable	Range studied	Optimum
Scan rate ( $\text{mV s}^{-1}$ )	1–50	5
Pulse amplitude (mV)	10–200	50
pH	3–11	9

Table 2

Comparative results for the determination of lithium ions in pharmaceutical samples with differential pulse anodic voltammetry and atomic absorption spectrophotometry

Samples	Lithium ions (mg per tablet) <sup>a</sup>			$E_{r1}$ <sup>b</sup>	$E_{r2}$ <sup>c</sup>
	Label value	Spectrophotometry	Voltammetry		
Carbolitium®	56.4	59.6±0.4	59.8±1.0	6.0	0.3
Carbolitium® CR	84.5	85.1±0.6	85.3±1.1	0.9	0.2
Carbolim®	56.4	56.0±0.3	55.8±0.5	-1.1	-0.4

<sup>a</sup> Average of five determinations+S.D.

<sup>b</sup>  $E_{r1}$  = relative percent error for the voltammetric method vs. label value.

<sup>c</sup>  $E_{r2}$  = relative percent error for the voltammetric method vs. spectrophotometric method.

### 3.6. Analysis of lithium ions in pharmaceutical samples

The carbon paste electrode modified with spinel-type manganese oxide was applied for the voltammetric determination of lithium ions in pharmaceutical formulations. The data shown in Table 2 reveals that the obtained results with the differential pulse anodic voltammetry procedure are in good agreement with those atomic absorption spectrophotometry method. The statistical calculations for the assay results show good precision of the voltammetric method. The obtained results in the Table 2 were also compared by applying the *F*-test and *t*-test at 95% confidence level. None of these tests, the calculated *F* and *t* values exceed the theoretical values ( $F_{4,4} = 6.39$ ,  $t_8 = 2.306$ ), confirming that there are no significant differences between the calculated and comparative values with respect to precision and accuracy in the determination of lithium ions in pharmaceutical samples.

## 4. Conclusions

Well-defined and stable responses were obtained applying the differential pulse anodic voltammetry for a carbon paste electrode modified with spinel-type manganese oxide in aqueous solutions containing lithium ions. The best voltammetric response was reached for a modified electrode in borate buffer solution of pH 9.0 and submitted to a scan rate of 5 mV s<sup>-1</sup> and a pulse amplitude of

50 mV. This electroanalytical procedure was able to determine lithium ions in the concentration range of  $8.0 \times 10^{-5}$ – $1.0 \times 10^{-2}$  mol l<sup>-1</sup> even in the presence of several alkali metals ( $1.0 \times 10^{-3}$  mol l<sup>-1</sup>) with a detection limit of  $7.1 \times 10^{-7}$  mol l<sup>-1</sup>. This last analytical parameter resulted quite smaller than that previously obtained with the cyclic voltammetry ( $2.2 \times 10^{-5}$  mol l<sup>-1</sup> [10]). Rapidity, precise and good selectivity were also found among other interesting features for the determination of lithium ions in pharmaceutical formulations using the proposed procedure which make it applicable to lithium analysis and quality control of pharmaceutical samples.

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