Int. J. Electrochem. Sci., 11 **(2016)** 2317 - 2325

International Journal of
ELECTROCHEMICAL
SCIENCE
www.electrochemsci.org

Anodic Adsorptive Stripping Voltammetric Determination of Alverine Citrate in its Pharmaceutical Formulation

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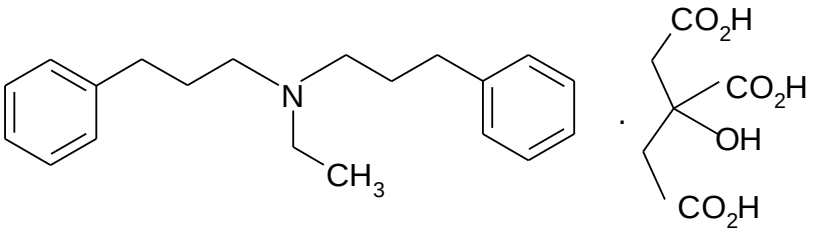
Received: 27 November 2015 / *Accepted:* 12 December 2015 / *Published:* 1 February 2016

The electrochemical behavior of alverine at carbon paste electrodes has been investigated in 0.04 M Britton-Robinson buffer pH 6.25 using cyclic and differential pulse voltammetric methods. Cyclic voltammetric studies indicated that the oxidation of alverine was irreversible adsorption controlled process. Experimental and instrumental parameters were optimized, and a sensitive differential pulse adsorptive anodic stripping procedure has been investigated for determination of the drug over the concentration range, 0.47 – 6.15 µg/ml alverine citrate, with detection and quantification limits of 0.14 and 0.47 µg/ml alverine citrate, respectively. The proposed method was successfully applied to the determination of alverine citrate in its pharmaceutical formulation.

Keywords: Alverine citrate, Carbon paste electrodes, Differential pulse adsorptive anodic stripping voltammetry, Pharmaceutical formulation

1. INTRODUCTION

Alverine citrate, N-Ethyl-3,3'-diphenyldipropylamine citrate, [5560-59-8] (Scheme 1), It is an antispasmodic that acts directly on intestinal and uterine smooth muscle. It is used for the relieve of smooth muscle spasm in the treatment of gastrointestinal disorders such as irritable bowel syndrome, it is also used in the treatment of dysmenorrhoea [1]. Literature survey to this drug indicated that very limited methods have been used for its determination, including liquid chromatography tandem mass spectrometry [2-4], spectrophotometry [5], non aqueous titration [6] and potentiometry [7,8]



Scheme 1. Structural formula of alverine citrate

Voltammetric methods have been found to be convenient and effective techniques for the analysis of pharmaceutical compounds due to their sensitivity, low cost of its instrumentations and short analysis time as compared to the other analytical techniques. To date no voltammetric methods is available in literature for the determination of alverine citrate. The aim of the present investigation is to investigate the adsorptive voltammetric behavior of alverine citrate at carbon paste electrode, and the development of a new, sensitive, simple and robust differential pulse adsorptive anodic stripping procedure for the determination of this drug in its pharmaceutical formulation.

2. EXPERIMENTAL

2.1. Reagents and materials

All chemicals were of analytical grade. Double distilled water was used throughout all experiments. Pure grade alverine citrate, and the pharmaceutical formulation Meteospasmyl Capsules **(**60 mg alverine citrate/capsule**)** were obtained from Pharco Pharmaceuticals company, graphite powder (1-2 micron) from Aldrich and paraffin oil from BDH. As a supporting electrolyte, a series of 0.04 M Britton-Robinson (BR) buffer pH 2.0-11.5 (a mixture of each of acetic, orthophosphoric and boric acids), adjusted to the required pH with 0.2 M sodium hydroxide was prepared.

2.2. Apparatus

All voltammetric measurements were performed using Metrohm 797 VA Computrace (Herisau, Switzerland) equipped with a Metrohm VA 694 stand. The three electrodes assembly cell consisted of carbon paste electrode (CPE) as working electrode, an Ag/AgCl in 3 mol/L KCl as a reference electrode, and platinium wire as an auxiliary electrode. The pH measurements were carried out using Hanna pH 211 microprocessor pH meter.

2.3. Preparation of carbon paste electrodes

The carbon paste was prepared by hand mixing of 5 g of graphite powder with 1.8 ml of paraffin oil in a mortar with pestle. The resulting carbon paste was tightly packed into the hole of the

electrode body and smoothed on a clean paper until it had a shiny appearance. The electrode body was constructed by pressing a small rod of stainless steel (diameter 2 mm) inside a micropipette tip (1 ml volume capacity), leaving a depression at the tip surface of approximately 1 mm for housing the carbon paste, and a thin wire was inserted through the opposite end for electrical contact [9]. The prepared carbon paste electrode was immersed in the supporting electrolyte in the cell, and applying sweeps to obtain a low and stable background current.

2.4. General procedure

A volume of 10 ml 0.04 M BR buffer pH 6.25 and a known concentration of the drug were added to the voltammetric cell. After preconcentration at 0 V for 30 s, with stirring, the stirring is stopped and allowed to equilibrium for 10 s. The differential pulse voltammogram is obtained by scanning from 0 to 1.4 V, with scan rate of 50 mVs^{-1} and pulse amplitude of 50 mV.

2.5. Determination of alverine citrate in Meteospasmyl Capsules

Twenty capsules (Meteospasmyl, 60 mg alverine citrate/capsule) were accurately weighed separately, each capsule was weighed filled with the gel and empty after removing the gel from it. Then the average weight of the gel in the capsule was calculated. The required amount from the capsules gel was dissolved in 30 ml bidistilled water, and filtered in 100 ml measuring flask, the residue of the gel was washed three times with bidistilled water, and the volume was completed to the mark by the same solvent. Then, the analysis was done as described in general procedure. The nominal content of the capsule is calculated using standard addition technique.

3. RESULTS AND DISCUSSION

3.1. Cyclic voltammetric studies

The repeatative cyclic voltammograms for 1.96 $x10^{-5}$ M alverine citrate solution in 0.04 M Britton-Robinson buffer pH 6.25, scan rate 50 mV/s, and accumulation time 30 s, were illustrated in Fig. 1. An oxidation peak appears at 0.83 V; this may be due to the oxidation of the tertiary amine group of the drug molecule. No reduction peak is observed in the reverse scan, which suggests that the process is irreversible. The repeatative cyclic voltammograms show that the peak current decreases sharply in the second and third cycles, and this behavior gives an indication of an adsorption character. The effects of the rate of the scan on the peak current and peak potential were examined from 10 to 100 mV/s. A plot of logarithm of the oxidation current versus logarithm of the scan rate gave a straight line relation with a slope of 0.80, which is close to the theoretically expected 1.0 for an ideal reaction of surface species [10], this also confirm the adsorptive character of the drug.

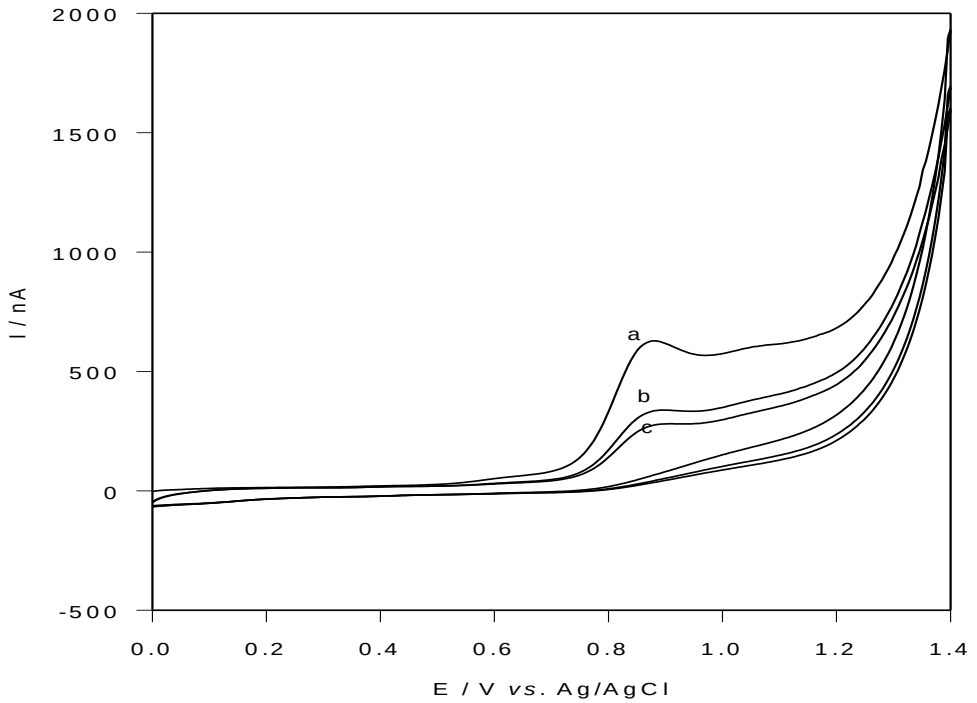


Figure 1. Successive cyclic voltammograms of 1.96×10^{-5} M alverine citrate solution in 0.04 M BR buffer pH 6.25, scan rate, 50 mV, and accumulation time, 30 s. curve a, first cycle; curve b, second cycle and curve c, third cycle.

3.2. DP voltammetric studies

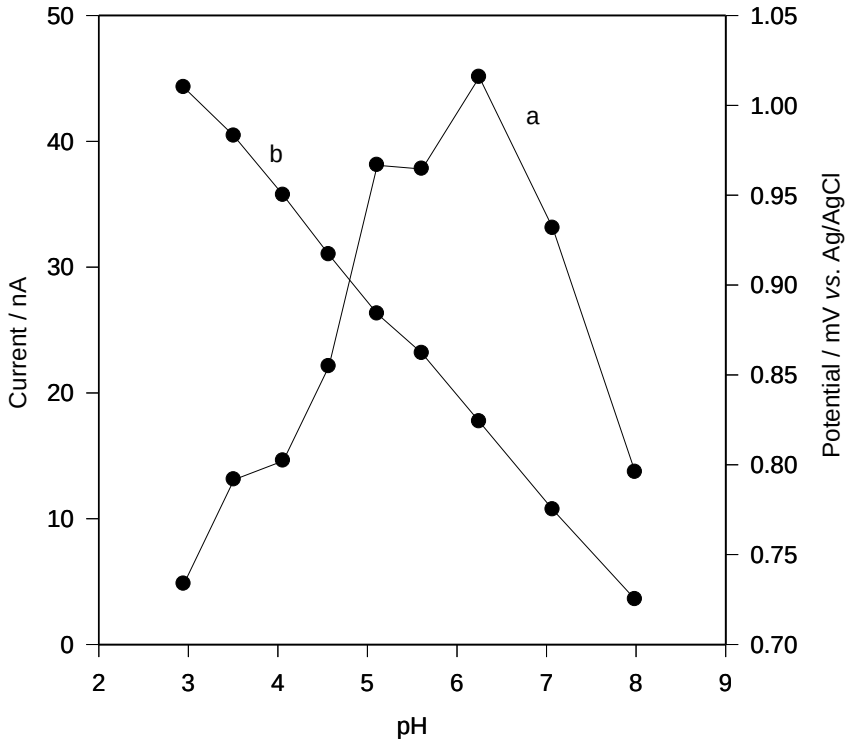


Figure 2. Effect of pH on the DP adsorptive anodic stripping peak current (a), and peak potential (b), of 3.98×10^{-6} M alverine citrate in 0.04 M BR buffer, t_a, 30 s, E_a, 0 V, scan rate 50 mVs^{-1}, and pulse amplitude 50 mV

The factors affecting the enhancement of the peak associated with the preconcentration step was studied. Various electrolytes such as phosphate buffer, citrate buffer, Britton-Robinson buffer, and potassium chloride, were examined. Britton-Robinson buffer gave the highest peak current and the best peak shape than in case of other electrolytes, so Britton-Robinson buffer was selected for further work. The effect of pH on the peak current and oxidation potential were studied over the pH range 2.0 – 10.0. Plots of pH vs. peak current and peak potential are given in Fig. 2. The peak potential is shifted to more negative values with increasing pH, indicating the involvement of protons in the electrode reaction process. The anodic peak potential shows a linear relation with pH with a slope of 57 mV per pH unit, with correlation coefficient of 0.9993. The anodic current increased by increasing pH, and the peak current reached its maximum value at pH 6.25, which was selected as optimal value for subsequent studies.

The effect of accumulation potential on the adsorptive anodic current was studied for 3.98 x 10^{-6} M alverine citrate, at 30 s accumulation time, 50 mV pulse amplitude, and 50 mV/s scan rate. The anodic current was nearly constant by changing the accumulation potential (E_a) from 0 to 0.6 V, and decreased by changing the accumulation potential more than 0.6 V.

The influence of time of accumulation t_a on the adsorptive stripping anodic current was studied at three concentration ranges, 2 x 10^{-6}, 3.98 x 10^{-6}, and 5.96 x 10^{-6} M alverine citrate, Fig. 3. The anodic current increases linearly with increasing the accumulation time t_a, indicating that the longer the accumulation time, the increase the drug concentration at the electrode surface, and the larger the anodic peak current, then as the accumulation time increases the anodic current tends to level off. 30 s accumulation time was selected for subsequent studies.

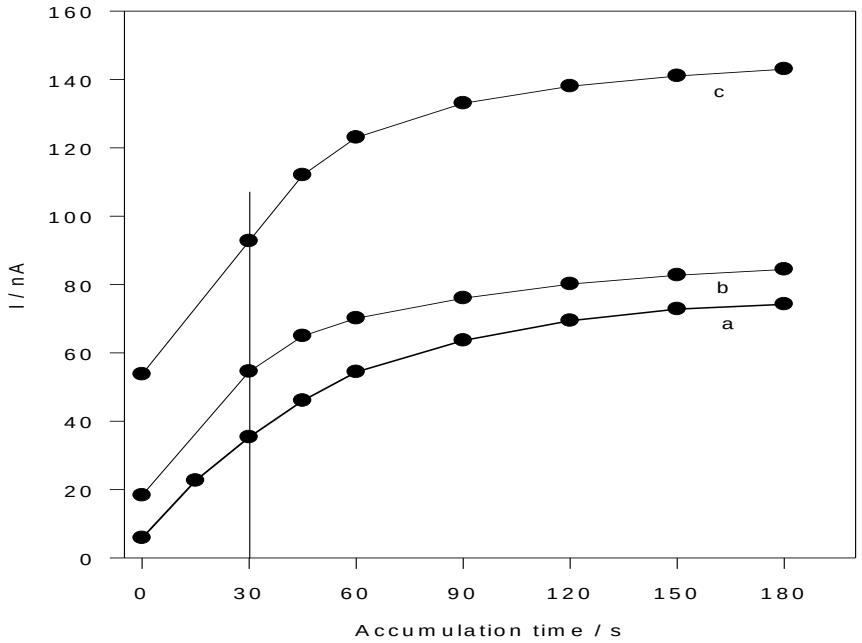


Figure 3. Effect of accumulation time on the peak current, for a, 2x10^{-6}; b, 3.98x10^{-6} and c, 5.96x10^{-6} M alverine citrate, in 0.04 M BR buffer pH 6.25, accumulation potential, 0 V, scan rate 50 mV/s, and pulse amplitude 50 mV.

Instrumental parameters such as pulse amplitude and scan rate were also optimized. Variations of pulse amplitude (10-100 mV), and scan rate (10-100 mV/s) at 3.98×10^{-6} M alverine citrate, were examined. The anodic current increases linearly with increasing the pulse amplitude up to 50 mV then tends to level off, and the anodic oxidation peak is displaced towards less positive potential. The anodic current is also increased by increasing scan rate over the range 10-50 mV/s, then remains nearly constant, so 50 mV pulse amplitude and scan rate of 50 mV/s were used for further measurements.

3.3. Calibration graph, limit of detection and limit of quantification

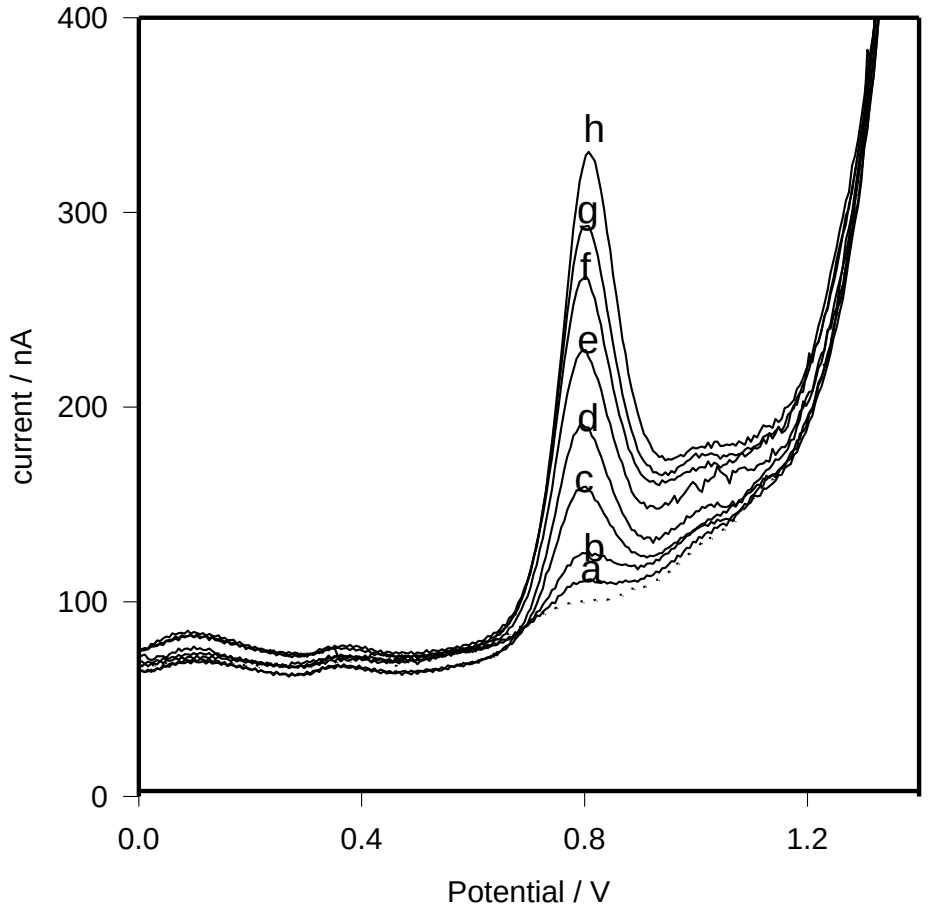


Figure 4. Differential pulse adsorptive anodic stripping voltammograms for different concentrations of alverine citrate in 0.04 M BR buffer pH 6.25, E_a = 0 V, t_a = 30 s, scan rate 50 mVs^{-1}, and pulse amplitude 50 mV: a, 0.473; b, 0.946; c, 1.892; d, 2.838; e, 3.784; f, 4.73; g, 5.676; h, 7.095 µg/ml alverine citrate. The dotted line represents the blank solution

On the basis of the electrochemical oxidation of alverine citrate at carbon paste electrode, and under the optimized conditions of preconcentration potential of 0 V, preconcentration time 30 s, scan rate 50 mV/s, and pulse amplitude of 50 mV, the peak current of the differential pulse adsorptive anodic stripping voltammograms was found to be linearly related to the alverine citrate concentration in the linear range 0.47 – 6.15 µg/ml alverine citrate. Fig. 4 represents the differential pulse adsorptive anodic stripping voltammograms using the standard addition method. The linear regression

equation was, I (nA) = -2.30 + 31.88 C (µg/ml). Limit of detection (LOD), and limit of quantification (LOQ) were calculated [11] using the relation (k(SD)/s) where k = 3 for LOD and 10 for LOQ, SD is the standard deviation of the intercept, and s is the slope of the calibration curve, LOD and LOQ were found to be 0.14 and o.47 µg/ml, respectively. The analytical parameters for the calibration graph are summarized in Table 1.

3.4. Repeatability and robustness

Table 1. The analytical parameters of the calibration graph for the determination of alverine citrate by differential pulse adsorptive anodic stripping voltammetric method

Parameter	
Linear range, µg/ml	0.47 - 6.15
Slope	31.88
Intercept	-2.298
Correlation coefficient (r)	0.9992
LOD, µg/ml	0.14
LOQ, µg/ml	0.47

Table 2. Robustness results of the proposed method

Variable	Recovery/%	RSD/%
pH = 6.00	98.13	1.37
6.25	97.93	0.75
6.50	97.39	2.13
Pulse amplitude / mV		
= 47	98.86	1.10
50	97.93	0.75
53	96.60	1.01
Accumulation time /s		
= 27	100.27	0.58
30	97.93	0.75
33	96.56	1.39

(Average of four determinations)

The intra day and inter day (day-to-day) precision expressed as relative standard deviations for 2 x 10^{-6} M alverine citrate (n = 8), were 1.62% and 2.75%, respectively. The robustness [11] of the proposed method was also examined, by evaluating the effect of small changes in some of procedure parameters, including pH of the Britton-Robinson buffer (6.0 – 6.5), pulse amplitude (47 – 53 mV) and accumulation time (27 – 33 s). None of the changes significantly affect the drug recovery (Table 2), this provides an indication of the reliability of the proposed method.

3.5. Interferences

The effect of interferences from excipients usually present in pharmaceutical formulations was examined under the optimum conditions. No interferences (< 3.0% change in the adsorptive anodic stripping current), was observed in the presence of 100 fold excess of magnesium stearate, maize starch, talc, lactose, and titanium oxide, suggesting a high selectivity of the proposed method towards the determination of alverine citrate.

3.6. Assay of alverine citrate in Meteospasmyl Capsules

The proposed voltammetric method was successfully applied to the determination of alverine citrate in its dosage form Meteospasmyl capsules (60 mg alverine citrate/capsule), using standard addition technique. The percentage mean recoveries obtained for four determinations, and the relative standard deviation are summarized in Table 3. The data obtained were compared statistically with those from official British Pharmacopoeia HPLC method,[12] by using Student's t-test, and the variance ratio F-test at 95% confidence level [13]. The results in Table 3 show that the calculated t- and F- values were less than the critical values, indicating that, there is no significant difference in accuracy or precision between the two methods.

Table 3. Statistical comparison between the results of Meteospasmyl capsules using the proposed DP adsorptive anodic stripping voltammetric method and the official HPLC pharmacopeial method

Parameters	Proposed DP voltammetric method	Reference method[12]
Mean recovery/%	98.89	97.89
SD/%	1.219	1.372
RSD/%	1.233	1.402
F-ratio (9.12)	1.267	
t-test (2.365)	1.782	

4. CONCLUSIONS

The anodic voltammetric behavior of alverine citrate on carbon paste electrode was investigated, using cyclic and differential pulse voltammetry. On the basis of these voltammetric studies, a novel differential pulse adsorptive anodic stripping voltammetric method have been developed for the quantification of this drug in its pharmaceutical formulation. The proposed voltammetric method is more sensitive (LOD = 0.14 µg/ml), than the published spectrophotometric method [5] (LOD = 24.42 µg/ml), potentiometric methods [7,8] (LOD = 1.88 µg/ml) and also less expensive than the published liquid chromatography tandem mass spectrometry,[2-4].

ACKNOWLEDGEMENTS
This work was financially supported by Taif University, KSA, project No: 1-436-4069.

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