Electroreduction of the Muscle Relaxant Drug Dantrolene Sodium at the Mercury Electrode and Its Determination in Bulk Form and Pharmaceutical Formulation

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The electroreduction of the muscle relaxant drug dantrolene sodium at the mercury electrode has been studied in the Britton–Robinson universal buffer of pH 2.5—11.5 containing 20% (v/v) methanol by means of dc-polarography, cyclic voltammetry and controlled-potential coulometry. Its reduction took place *via* three irreversible cathodic steps in solutions of pH ≤6, two steps in solutions of 6<pH<10 and a single step at pH values ≥10 through the consumption of 10, 8 or 4 electrons, respectively. This behavior was attributed to the reduction of NO_2 group (1st and 2nd steps at pH ≤6 or the single step at pH ≥10) and the –CH=N– double bond (3rd step at pH <10). Two polarographic procedures (direct current and differential-pulse modes) and three adsorptive cathodic stripping voltammetric procedures (linear-sweep, differential-pulse and square-wave modes) were described and successfully applied for quantification of dantrolene sodium in its bulk form and in pharmaceutical formulation (Dantrolex tablets).

Key words dantrolene sodium; dantrolex tablets; quantification; polarography; cyclic voltammetry; stripping voltammetry

Dantrolene sodium (Chart 1) is the hemihepta hydrate of sodium salt of 1-[5-(4-nitrophenyl)furfulidene amino]imidazolidene-2,4-dione. It is a muscle relaxant reported to act by blocking muscle concentration beyond the neuromuscular junction.[1] It is described for the symptomatic relief of muscular spasm due to condition such as stroke, multiple sclerosis, spinal cord injury and cerebral palsy. Dantrolene sodium is used also intravenously in the treatment of malignant hyperthermia.[1]

Only few liquid chromatographic methods[2—8] were described for assay of dantrolene sodium in dosage form and biological fluids. The chromatographic methods usually necessitate sample pretreatment and time-consuming extraction steps prior to analysis of the drug. Moreover, these methods required expensive equipment and considerable skills are necessary to operate them successfully. Although no official analytical method for determination of dantrolene sodium is reported in British or the United States pharmacopoeia an official electrometric titration method for determination of the drug is available in the Japanese pharmacopoeia. Besides, no any information is available in the literature to date concerning the electroreduction of dantrolene sodium or its electroanalytical determination. Therefore, the present work aimed to study the electroreduction pathway of dantrolene sodium at the mercury electrode and to describe simple and precise electroanalytical procedures for its determination in bulk form and pharmaceutical formulation.

Experimental

Instrumentation A Sargent-Welech Polarograph Model 4001 (Fisher, U.S.A.) was used for the present polarographic measurements. The electrolysis cell was as that previously described by Meites.[9] Characteristics of the capillary of the dropping mercury electrode (DME) were: $m=1.13$ mg/s and $t=3.36$ s in a solution of 0.1 M KCl at open circuit conditions for a mercury height of 60 cm. A saturated calomel electrode was used as a reference electrode.

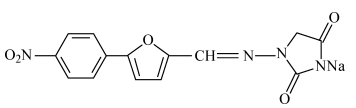

Chart 1. Structure of Dantrolene Sodium Molecule

Computer-controlled Electrochemical Analyzers Models 273A and 363A-PAR (Princeton Applied Research, Oak Ridge, TN, U.S.A.) controlled *via* 270/250-PAR software were used for the voltammetric measurements. An electrode assembly (303A-PAR) incorporated with a three-electrode configuration system comprising of a hanging mercury drop electrode (HMDE) or a dropping mercury electrode (DME) as a working electrode (surface area=0.026 cm^2), an Ag/AgCl/KCl_s reference electrode and a platinum wire auxiliary electrode, was used. A magnetic stirrer (305-PAR) and a stirring bar were used to provide the convective transport during the accumulation step.

A potentiostat/galvanostat (Model 173-PAR) incorporated with a digital coulometer Model 179-PAR was used for controlled-potential electrolysis of dantrolene sodium solutions. The coulometric cell used was designed by Princeton Applied Research (PAR) Corporation to have a large electrode surface area to solution volume ratio as possible. A mercury pool as a working electrode, a saturated calomel electrode as a reference and a platinum gauze as a counter electrode were used. The potential selected was adjusted to a value equal to the $E_{1/2}$ of the more negative polarographic wave of dantrolene sodium plus −0.1 V or at a potential lies at the beginning of the limiting current of each wave. The electrolyzed solutions were deoxygenated before measurements by bubbling pure nitrogen while a stream of nitrogen gas was kept over surface of the electrolysis solution during the measurements. The number of electrons (n) transferred per dantrolene sodium molecule was determined using Faraday's relation: $N=Q/nF$ (where N is the number of moles of substance being electrolyzed) and was found to equal 10, 8 or 4 per dantrolene sodium molecule in the B–R universal buffers of pH values 3, 7 or 11.5, respectively. The number of electrons consumed *via* each of the 1st (pH ≤11.5), 2nd (pH ≤6) and 3rd (pH <10) reduction steps, respectively, were 4, 2 and 4.

Solutions and Reagents (i) A 1×10^{-3} M stock standard solution of bulk dantrolene sodium (Chemipharm Pharmaceutical Industries, Egypt) in methanol (Merck) was prepared and stored at 4 °C. Working solutions of bulk dantrolene sodium (10^{-6} to 10^{-4} M) were prepared by appropriate dilution of the standard solution with methanol. The solutions were analyzed according to the general analytical procedure.

(ii) Ten tablets of dantrolex (Chemipharm Pharmaceutical Industries, Egypt) of a declared content of 25 mg of dantrolene sodium per tablet were quantitatively weighed and the average mass per tablet was determined. Then, they were grounded to a homogeneous fine powder. An amount of the homogeneous powder equivalent to mass of one tablet was accurately transferred to 70 ml methanol (Merck) in a 100-ml volume calibrated flask. The mixture was then sonicated for about 10 min and then the volume was made up to the mark with methanol. Afterwards, the solution was filtered through

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a 0.45 μm Milli-pore filter (Gelman, Germany). Desired concentrations of dantrolene sodium were obtained by accurate dilution of the obtained solution with methanol. The solutions were analyzed according to the described general analytical procedure.

A series of the Britton–Robinson (B–R) universal buffer of pH 2—11.5 as a supporting electrolyte was prepared in deionized water.[10] All the chemicals used were of Analytical-grade. A pH-meter (Crison, Barcelona, Spain) was used for the pH measurements.

General Analytical Procedure A known volume of the previously prepared standard solution of bulk dantrolene sodium or dantrolex tablets was pipetted into a 10-ml volume calibrated flask and the volume was completed to the mark with the B–R universal buffer containing 20% (v/v) methanol of a selected pH value. Then the solution was placed in the electrochemical cell and deoxygenated with pure nitrogen for about 5 min before measurement, while the nitrogen gas was kept over the solution during the measurements. In stripping voltammetric analysis, preconcentration of dantrolene sodium onto the HMDE was performed by its adsorptive accumulation at a selected potential for a selected time period (both are depending on the used potential-waveform), while stirring of the solution at 400 rpm with a magnetic stirrer. Then, the solution was left quiescent for 5 s to equilibrate. Afterwards the voltammograms were recorded by scanning the potential towards negative direction using a selected potential-waveform.

Results and Discussion

Electrochemical Behavior DC-polarograms of 1×10^{-4} M dantrolene sodium in the B–R universal buffer of pH 2.5—6 containing 20% (v/v) methanol exhibited three irreversible cathodic waves (Fig. 1). The half-wave potentials ($E_{1/2}$) of the three waves were shifted to more negative values with the increase of pH indicating the participation of protons in the electrode reaction and that the proton transfer reaction precedes the rate limiting electron transfer.[11] In solutions of pH values >6 the 2nd wave disappeared completely while the limiting current of the 3rd wave decreased with the increase of pH until disappeared completely at pH ≥10 where the polarograms exhibited a single irreversible cathodic wave (which is the 1st wave observed over the whole pH range).

Logarithmic analysis of the obtained two mean polarographic waves (1st and 3rd waves) at various pH values using the fundamental equation for the irreversible polarographic waves[9] exhibited linear $E_{d.e.}$ *versus* $\log(i/i_d-i)$ plots with the slope values S_1 ($S_1=59/\alpha n_a$) reported in Table 1. The estimated values of αn_a and those of the symmetry transfer coefficient α at various pH values (Table 1) confirmed the irreversible nature of the electrode process. The $E_{1/2}$–pH plots for the 1st and 3rd waves are straight lines with the slope values S_2 {$S_2=(59/\alpha n_a)Z_H^+$) reported in Table 1. Values of the symmetry transfer coefficient (α) were estimated at different ratios of (Z_H^+/n_a) using the relation[9,12]: $\alpha=(59/S_2)$. (Z_H^+/n_a). The ratio (Z_H^+/n_a) may have the values 2, 1 or 0.5, depending on whether one or two electrons and one or two protons are involved in the rate-determining step. From the results shown in Table 1, the most probable values of α-parameter denoted that the ratio (Z_H^+/n_a) equals 0.5 which suggests that the number of electrons n_a involved in the rate-determining step should be double that of the involved protons (Z_H^+).

Cyclic voltammograms of 1×10^{-4} M dantrolene sodium at the HMDE displayed three, two and a single irreversible cathodic peaks over the pH ranges ≤6, 7—9.5 and ≥10, respectively (Figs. 2a—c) which is a behavior similar to that observed by dc-polarography. The peak potentials (E_p) shifted to more negative values upon rising of either the pH (2.5—11) or the scan rate v (25—500 mV/s) confirming the involvement of protons in the electrode reaction[11] or the irreversible nature of the reduction process,[13] respectively. The main cathodic peaks (1st, 3rd peaks) obtained at various pH values (Figs. 2a—c) are very sharp which may be attributed to the adsorption of dantrolene sodium onto the mercury

Table 1. DC-Polarographic Data for 1×10^{-4} M Dantrolene Sodium in the B–R Universal Buffer of Various pH Values Containing 20% (v/v) Methanol; 25 °C

pH	S_1 (mV)	αn_a	α (n_a=2)	S_2 (mV)	α (Z_H^+/n_a) 2	1	0.5
1st wave							
2.5	73	0.81	0.40	67	1.76	0.88	0.44
4.6	76	0.78	0.39				
5.8	70	0.84	0.42				
7.0	66	0.89	0.45				
10.5	68	0.87	0.43				
3rd wave							
2.5	86	0.68	0.34	90	1.32	0.66	0.33
4.6	76	0.90	0.45				
5.8	80	0.74	0.37				

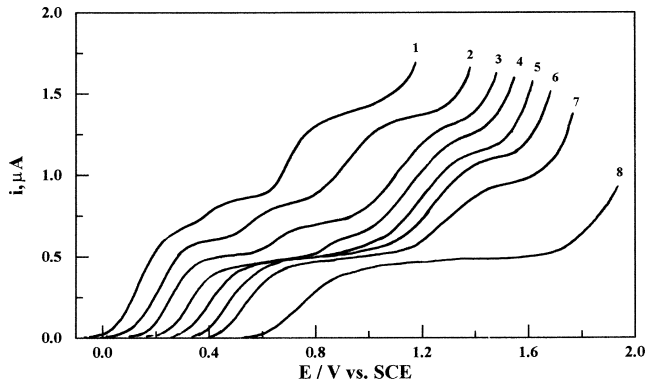


Fig. 1. DC-Polarograms of 1×10^{-4} M Dantrolene Sodium in the B–R Universal Buffer of Various pH Values Containing 20% (v/v) Methanol

(1) pH 2.5, (2) 3.6, (3) 4.6, (4) 5.8, (5) 7, (6) 8, (7) 9.4 and (8) pH 11.4.

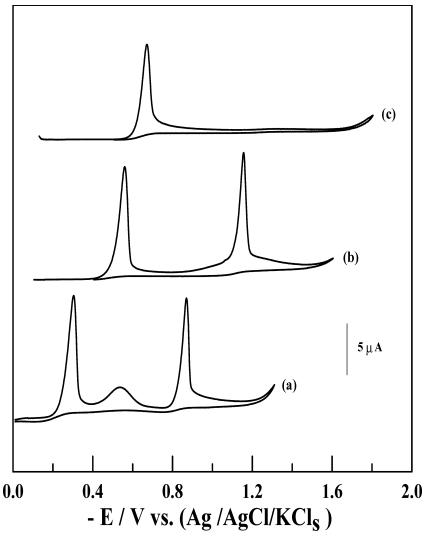


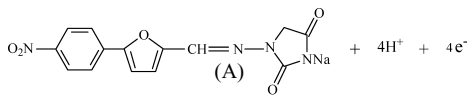
Fig. 2. Cyclic Voltammograms of 1×10^{-4} M Dantrolene Sodium at the HMDE in the B–R Universal Buffer of Various pH Values

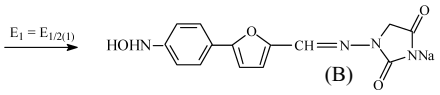
(a) pH 2.5, (b) pH 6.7 and (c) pH 10.5, at scan rate of 300 mV s^{-1}.

electrode surface. Adsorption of dantrolene sodium onto the mercury surface was identified by recording its cyclic voltammograms for 1×10^{-5} M at various scan rates (v) 50—300 mV s^{-1}. A linear $\log(i_p)$ *versus* $\log(v)$ plot following the relation: $\log(i_p)=0.89\log(v)+0.37$ ($r=0.999$ and $n=8$) was obtained. The slope value of 0.89 may be considered as closed to the expected theoretical value of 1.0 for an ideal case of the surface-adsorbed species[14] with some contribution from diffusion.

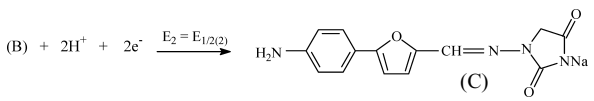
Results of controlled-potential electrolysis of various concentrations of dantrolene sodium in the B–R universal buffers of pH 3, 7 or 11.5 indicated the consumption of 10, 8 or 4 electrons per dantrolene sodium molecule, respectively. The number of electrons consumed *via* each of the 1st (pH ≤11.5), 2nd (pH ≤6) or 3rd (pH <10) reduction steps, respectively, was 4, 2 or 4. The first two reduction steps (pH ≤6) may be attributed to reduction of the $-NO_2$ group to the hydroxylamine stage, *via* the consumption of four electrons (1st step) then to the amine stage *via* the consumption of two electrons (2nd step, pH ≤6), while the 3rd step (pH ≤6) or the 2nd step (6<pH<10) may be attributed to reduction of the –CH=N– double bond of the aliphatic chain *via* the consumption of four electrons. The single wave obtained at pH ≥10 may be attributed to reduction of the NO_2 group to the hydroxylamine stage only *via* the consumption of four electrons. Accordingly, the electroreduction reaction pathway of dantrolene sodium at the mercury electrode can be expressed as follows:

(i) In solutions of pH ≤6, reduction of dantrolene sodium takes place in three steps *via* the total consumption of 10 electrons (Fig. 2, curve a):

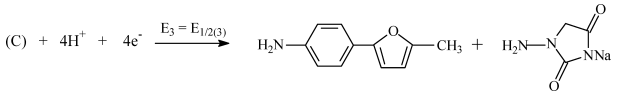




(Step 1)

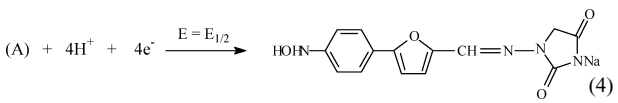


(Step 2)



(Step 3)

(ii) In solutions of pH ≥10: reduction of dantrolene sodium takes place in a single one step *via* the consumption of 4 electrons (Fig. 2, curve c)



(Single step)

(iii) In solutions of the intermediate pH values (6<pH<10), reduction of dantrolene sodium takes place in two steps (Steps 1 and 3) *via* the consumption of 4 electrons in each step with the disappearance of the 2nd step (Fig. 2, curve b).

Analytical Studies. Polarographic Procedures Polarograms of various concentrations of bulk dantrolene sodium were recorded by means of DC-polarography (DCP) and differential-pulse polarography (DPP) in a B–R universal buffer of pH 5. Linear variations of the DC-polarographic total limiting current (i_l) and the DPP 1st peak current (i_p) with concentration (C) of bulk dantrolene sodium were obtained within the ranges 1×10^{-5} to 1×10^{-4} M and 1×10^{-6} to 1×10^{-5} M bulk dantrolene sodium following the regression equations: $i_l(\mu A)=0.008C(\mu M)+0.114$ ($r=0.998$, $n=9$) and $i_p(\mu A)=0.108C(\mu M)-0.025$ ($r=0.995$, $n=11$), respectively.

From analysis of 5×10^{-5} M and 5×10^{-6} M bulk dantrolene sodium by means of DCP and DPP, respectively, mean percentage recoveries of 101.3±0.16 ($n=4$) and 98.54±0.25 ($n=4$) were achieved. Limits of detection (LOD) of 3×10^{-6} M and 3×10^{-7} M and limits of quantification (LOQ) of 1×10^{-5} M and 1×10^{-6} M dantrolene sodium were achieved by means of DCP and DPP procedures applying the following expressions, respectively[15]: LOD=3 S.D./b and LOQ=10 S.D./b, where S.D. is the standard deviation of the intercept (or the blank) and b is the slope of the calibration curve. The obtained results indicated the reliability of the described polarographic procedures for assay of dantrolene sodium within their limits of quantitation.

Stripping Voltammetric Procedures Based on the adsorption behavior of dantrolene sodium onto the mercury electrode surface, stripping voltammetric procedures were optimized for its trace determination using different potential-waveforms such as linear-sweep, differential-pulse- and square-wave.

Linear-Sweep Voltammetry Procedure The optimum procedural conditions for determination of bulk dantrolene sodium using linear-sweep adsorptive cathodic stripping voltammetry (LS-AdCSV) at the HMDE were identified by studying the effect of change of pH of the medium (2—11), preconcentration potential E_{acc} (−0.1 to −0.5 V) and time t_{acc} (0—80 s) on the peak current intensity of 5×10^{-7} M bulk dantrolene sodium at 100 mV s^{-1}. A sharper peak and a much developed peak current intensity were achieved in a B–R universal buffer of pH 11 following preconcentration of dantrolene sodium onto the HMDE by adsorptive accumulation at a potential E_{acc} of −0.2 V (*vs.* Ag/AgCl/KCl_s) for 50 s. A linear calibration graph was obtained over the concentration range 6×10^{-9} to 3×10^{-7} M bulk dantrolene sodium which follows the regression equation $i_p(\mu A)=20.65C(\mu M)+0.32$ ($r=0.996$, $n=8$). Limits of detection (LOD) and quantitation (LOQ) of 1.8×10^{-9} M and 6×10^{-9} M dantrolene sodium, respectively, were achieved[15] by means of the described LS-AdCSV procedure.

Differential-Pulse Voltammetry Procedure The optimum procedural conditions (pH of the supporting electrolyte, preconcentration potential E_{acc} and preconcentration time t_{acc}, scan rate v and pulse-height a) for the quantitative determination of dantrolene sodium at the HMDE using differential-pulse adsorptive cathodic stripping voltammetry (DP-AdCSV) were studied. A much developed peak current in-

tensity and a sharper peak shape were obtained under the following procedural conditions: $E_{acc}=-0.2$ V, $t_{acc}=80$ s, $a=10$ mV, $v=5$ mV s^{-1} and a B–R universal buffer of pH 11 as a supporting electrolyte. A linear calibration curve was obtained over the concentration range 1×10^{-8} to 2×10^{-7} M bulk dantrolene sodium which follows the regression equation $i_p(\mu A)=10.0C(\mu M)+0.15$ ($r=0.995$, $n=9$). Limits of detection (LOD) and quantitation (LOQ) of 3×10^{-9} and 1×10^{-8} dantrolene sodium, respectively, were achieved[15] by means of the described DP-AdCSV procedure.

Square-Wave Voltammetry Procedure For optimizing a square-wave adsorptive cathodic stripping voltammetric (SW-AdCSV) procedure to assay of bulk dantrolene sodium, effects of pH of the electrolysis solution (2—11), and the instrumental conditions namely: frequency f (10—100 Hz), scan increment Δs (2—10 mV) and pulse-amplitude a (10—50 mV) on the peak current intensity of 5×10^{-7} M dantrolene sodium following its preconcentration onto the HMDE by adsorptive accumulation at -0.30 V for 60 s were studied. A much developed peak current intensity and a sharper peak shape were achieved at $f=100$ Hz, $\Delta s=10$ mV, $a=50$ mV in a B–R universal buffer of pH 11 as a supporting electrolyte. Effect of preconcentration potential (E_{acc}) on the SW-AdCSV peak current intensity of 5×10^{-7} M dantrolene sodium in a B–R universal buffer of pH 11 was examined over the range -0.1 to -0.45 V (*vs.* Ag/AgCl/KCl$_s$) following preconcentration of the analyte onto the HMDE by adsorptive accumulation for 60 s. A much developed peak current was achieved over the potential range -0.1 to -0.4 V. Hence, an accumulation potential of -0.35 V was chosen throughout the rest of study. Also, effect of preconcentration time (t_{acc}) at -0.35 V on the SW-AdCSV peak current intensity for various concentrations of bulk dantrolene sodium (5×10^{-7}, 5×10^{-8} and 5×10^{-9} M) in a B–R universal buffer of pH 11 was evaluated. As shown in Fig. 3, for 5×10^{-7} and 5×10^{-8} M dantrolene sodium the response was linear up to 80 s then leveled off (curves 1 and 2); this behavior may be attributed to the complete coverage of the mercury electrode surface with the analyte species. While for 5×10^{-9} M dantrolene sodium solution, as accumulation duration increases, linearity is prevailed over all the tested accumulation durations (curve 3). This means that the lower the concentration of the analyte, the longer of the accumulation duration is. Thus, the accumulation duration of choice will be dictated by the sensitivity needed. On the other hand, the square-wave signal was found to increase as the mercury electrode area was increased (0.01 to 0.026 cm^2). Therefore, the present study was carried out at a large HMDE area (0.026 cm^2). The influence of the rest time was also considered and a time period of 5 s was chosen. Accordingly, a much developed peak current intensity and a sharper peak shape were obtained under the following procedural conditions: $E_{acc}=-0.35$ V, $t_{acc}=80$—120 s, $f=100$ Hz, $a=50$ mV, $\Delta Es=10$ mV and a B–R universal buffer of pH 11 as a supporting electrolyte. Using the described SW-AdCSV procedure for assay of standard solutions of various concentrations of dantrolene sodium, a linear calibration curve was obtained over the concentration range 7×10^{-10} to 5×10^{-7} M bulk dantrolene sodium which follows the regression equation $i_p(\mu A)=157.0C(\mu M)+2.97$ ($r=0.998$, $n=9$). Limits of detection (LOD) and quantitation (LOQ) of 2.1×10^{-10} and 7×10^{-10} M dantrolene sodium, respectively, were achieved[15] by means of the described SW-AdCSV procedure.

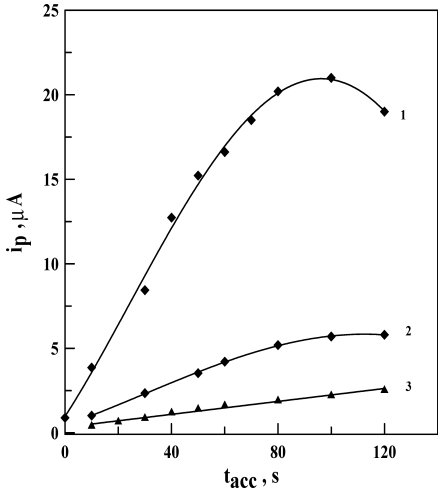


Fig. 3. Effect of Preconcentration Time (t_{acc}) on the SW-AdCS Voltammetric Peak Current (i_p) of (1) 5×10^{-7} (2) 5×10^{-8} and (3) 5×10^{-9} M Dantrolene Sodium in a B–R Universal Buffer of pH 11; Preconcentration Potential (E_p) $=-0.35$ V onto the HMDE, Frequency $f=100$ Hz, Pulse-Height $=50$ mV and Scan Increment $=10$ mV

Table 2. Results of Validation Study of the Determination of 1×10^{-7} M Bulk Dantrolene Sodium by Means of the Described SW-AdCS Voltammetry Procedure

Variables	Procedural conditions	R%±S.D. ($n=4$)
pH of the medium		
10.5	$E_{acc}=-0.35$ V	97.6±0.15
11.0	$t_{acc}=80$ s	98.7±0.05
11.5		98.1±0.63
Preconcentration potential (E_{acc}):		
−0.30	pH=11,	98.1±0.12
−0.35	$t_{acc}=80$ s	98.7±0.05
−0.40		97.4±0.24
Inter-laboratory precision:		
Lab (1)	pH=11,	98.7±0.05
Lab (2)	$E_{acc}=-0.35$ V,	98.1±0.22
	$t_{acc}=80$ s	
Intra & inter-day precisions:		
Day: 1	pH=11,	98.7±0.05
2	$E_{acc}=-0.35$ V,	98.5±0.18
3	$t_{acc}=80$ s	98.0±0.25
4		97.8±0.33

Methods Validation Validation of the proposed electro-analytical procedures for assay of bulk dantrolene sodium was examined *via* accuracy, precision, selectivity, robustness and inter-laboratory precision.[16] Accuracy of the results of DCP, DPP, LS-AdCSV, DP-AdCSV and SW-AdCSV procedures were examined by performing four replicate analysis of standard solutions of bulk dantrolene sodium then calculating the mean percentage recovery (%R) for the found concentrations as a percent of the nominal concentrations in the standard solutions. Precision was assessed from the relative standard deviation (RSD) in % of the mean recovery. The obtained results (*e.g.*, as shown in Table 2) confirmed the reliability of the proposed procedures for assay of bulk dantrolene sodium.

The selectivity[16] of the described electro-analytical proce-

dures was tested by analysis of 5×10^{-5} and 5×10^{-6} M bulk dantrolene sodium solutions using the described DCP and DPP procedures, respectively, or 1×10^{-7} M bulk dantrolene sodium solutions (Excipients are absent) using the described adsorptive stripping voltammetry procedures ($E_{acc}=-0.2$ to -0.35 V and $t_{acc}=80$ s). On the other hand, analysis of standard solutions of 5×10^{-5} and 5×10^{-6} M of dantrolex tablets solution (using the described DCP and DPP procedures) and 1×10^{-7} M of dantrolex tablets solution (Excipients are present) were paralleled analyzed using the described adsorptive stripping voltammetry procedures. No significant differences in the recoveries or the relative standard deviations were obtained in the absence (98.7±0.30 to 101.3±0.16) and presence of excipients (98.1±0.37 to 99.7±0.68). Thus, the proposed procedures can be considered selective.

Since the robustness[16] of results of an analytical procedure is the ability to remain unaffected with some changes of the operational conditions, effects of variation of some of the neck procedural conditions such as pH (10.5—11.5) and preconcentration potential (-0.30 to -0.40 V) on the peak current intensity of dantrolene sodium were studied. The mean percentage recoveries (%R) based on four replicate measurements were not significantly affected (*e.g.*, Table 2) and consequently the optimized electro-analytical procedures were reliable for assay of dantrolene sodium and could be considered robust.

The inter-laboratory precision[16] of measurements by means of the proposed SW-AdCSV procedure was examined by assay of dantrolene sodium using PAR-Potentistat of two different Models: 273A (Lab. 1) and 263A (Lab. 2). The obtained results (*e.g.*, Table 2) were found reproducible, since there was no significant difference in the mean percentage recoveries or the standard deviation values.

Assay of Dantrelax Tablets The described electro-analytical procedures (DCP, DPP, LS-AdCSV, DP-AdCSV and SW-AdCSV) were successfully applied for the analysis of various concentrations of dantrolene sodium in the previously prepared dantrelax tablet's solutions (see Experimental) without prior extraction of the drug using the calibration curve method (*e.g.*, Fig. 4) or the standard addition method.[17] The obtained satisfactory results (Table 3) were statistically compared with those obtained by a reported liquid chromatographic method.[3] The calculated *F*-values did not exceed the theoretical ones (Table 3), which means that there is no significant difference between the described methods and the reported one with respect to reproducibility.[16] As shown in Table 3, no significant difference was noticed between the described and the reported methods regarding the accuracy and precision as revealed by *t*-test.[18] The simple, fast, inexpensive and successful assay of dantrelax tablets by means of the described electroanalytical procedures without prior extraction of the drug are great advantages over the reported liquid chromatographic methods[2—8] which usually require complex and time-consuming pretreatment and extraction steps for removal of interferences prior to analysis of the drug. Moreover, the chromatographic methods usually require expensive reagents and equipment which are not economically feasible for routine analysis; in addition considerable skills are necessary to operate them successfully.

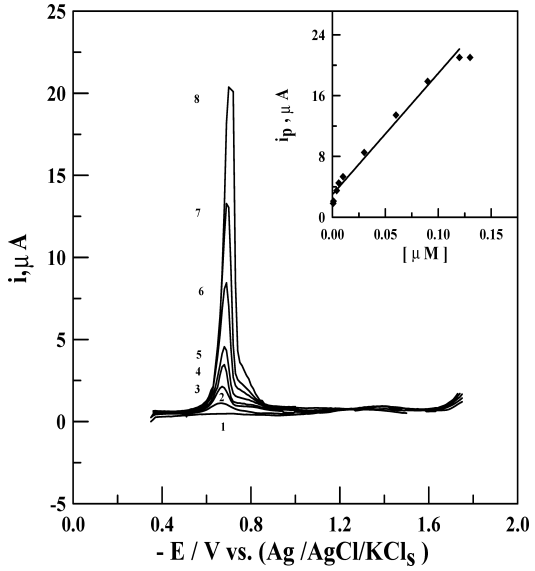


Fig. 4. SW-AdCS Voltammograms of Various Concentrations of Dantrolene Sodium in Solutions of Dantrelax Tablets

(1) Background, (2) 7×10^{-10}, (3) 1×10^{-9}, (4) 4×10^{-9}, (5) 6×10^{-9}, (6) 3×10^{-7}, (7) 6×10^{-7}, and (8) 1.2×10^{-6} M dantrolene following preconcentration onto the HMDE by adsorptive accumulation at $E_{acc}=-0.35$ V for 80 s in a B–R universal buffer of pH 11; frequency=100 Hz; pulse height=50 mV and scan increment=10 mV.

Table 3. Assay of Standard Solutions of Dantrelax Tablets by Means of the Described Electroanalytical Procedures and a Reported Chromatographic Method[3]; (n=4)

Procedure/ [Drug]	(% R±S.D.)		(Calculated)	
	Calibration curve method	Standard addition method	*F*-value	*t*-test
5×10^{-5} M				
DCP	98.5±0.55	98.8±0.74	1.49	2.53
5×10^{-6} M				
DPP	98.8±0.42	99.1±0.28	1.15	1.95
1×10^{-7} M				
DP-AdCSV	99.0±0.52	98.7±0.88	1.34	1.16
LS-AdCSV	99.2±0.33	99.7±0.65	1.86	0.72
SW-AdCSV	99.7±0.68	100.3±0.55	2.28	0.38
Reported[3]	99.4±0.45	—	—	—

The theoretical values of *F* and *t*-test at 95% confidence limit (for n_1=4 and n_2=4) are 9.28 and 2.78, respectively.

Conclusion

The electroreduction of dantrolene sodium at the mercury electrode was studied and the electrode reaction pathway was suggested. Polarographic (direct current and differential-pulse modes) and adsorptive cathodic stripping voltammetric (linear-sweep, differential-pulse and square-wave modes) procedures were described and successfully applied for quantification of dantrolene sodium in bulk form and in pharmaceutical formulation. The described electro-analytical procedures could be recommended for use in quality control laboratories.

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