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AC-POLAROGRAPHIC QUANTITATION OF TOLMETIN SODIUM

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ABSTRACT

Fundamental harmonic alternating current polarography has been described for the determination of tolmetin sodium and its capsules, (Tolectin$^{(R)}$-200 mg). The AC procedure was applied by superimposing 10 mV, rms, AC voltage on a DC ramp in the range -1200 to -1450 mV at a frequency of 50 Hz in acetate buffer of pH 5.0 containing 0.001% gelatin as a maxima suppressor. A three electrode assembly consisting of dropping mercury electrode (dme) and two Ag/AgCl/KCl (sat.) electrodes was employed. Mercury flow rate was 3 mg sec^{-1} under a corrected head pressure of 80 cm. The electrode reaction was investigated by Kalousek K_1 and K_2 techniques which indicated the non-reversibility of the electrode process on the AC time scale. The percent result obtained by standard addition procedure was 101:4±2.0 for tolmetin sodium capsules.

Introduction

AC polarography is not commonly used in *elecroanalytical* work as the DC mode (Smith and McCord, 1968). The former involves a direct current component as in the latter, but in addition a small AC pulse voltage is superimposed on the DC voltage ramp. The readout form in AC polarography is a peak-shaped polarogram which gives more reproducible results than the DC-sigmoid counterpart. The sensitivity of AC polarography, like DC, is *restricted* by the intrinsic charging current, ic. However, in the AC procedure minimization of ic is feasible by adopting phase-sensitive detection (Smith, 1966) which accrues from the fact that ic and the faradic component, if, lead the applied AC pulse voltage by 90° and 45° respectively.

Tolmetin, 1-methyl-5-(4-methylbenzoyl)-1H-pyrrole-2-acetic acid, sodium salt is clinically used as a non-steroidal anti-rhuematic drug for adult and juvenile rheumatic arthritis and in osteoarthritis (Muller *et al*, 1977 ; Kaplan and Salzman, 1979). A number of methods including thin layer chromatography (Shelley *et al.*, 1974; Cressman *et al.*, 1975; Giachetti and Canali, 1983), high performance liquid chromatography (Desiraju *et al*, 1982), colorimetry (Ozyadin, 1982), first-derivative spectrophotometry (Al-Rashood *et al.*, 1988) and DC-polarography (Proctova and Kakac, 1982) were published for the detection and quantitation of tolmetin in capsule dosage form and tolmetin and its mtabolites in biological fluids.

In this work the fundamental harmonic mode of AC polarography has been adopted for the analysis of tolmetin in bulk and in capsule dosage forms (Tolectin®). Furthermore, Kalousek polarography (Heyrovsky and Kuta, 1966; Kinard *et al*, 1967), which is a square-wave pulse technique in which the recorded current results in part from the reoxidation of the reduced species produced at dme, has been used for the investigation of the reversibility or otherwise of tolmetin reduction process at the electrode surface. Comparison between conventional and AC polarography, when applied to the quantitation of tolmetin, indicated that the latter is more sensitive, precise and advantageous as its peak-shaped readout format yields reproducible results.

Materials and Methods

Standard tolmetin sodium di-hydrate (Lot No. 87P2427) of purity 100.1% w/w and tolmetin sodium capsules were gratefully supplied by Cillag AG, 8201 Schaffhausen, Switzerland and Cilag Scientific Officer, Riyadh, Saudi Arabia, respectively. Standard solutions (1.25 mg ml^{-1}) and sample solutions of tolmetin sodium were freshly prepared daily in acetate buffer (B.P.) of pH 5 containing 0.001% w/v gelatin as maxima suppressor.

Apparatus

A Metrohm polarecord assembly (E506) with a polarography stand (E505) and three electrodes, namely, dme and two silver-silver chloride electrodes were used. The dme was a fine cappillary supplying a steady stream of mercury droplets at the frequency of 1 sec^{-1} and a flow rate of 3 mg sec^{t} under the influence of a drop controller.

Procedure

Twenty capsules were accurately weighed and carefully emptied. From the weights of the empty shells and the collected material the net fill mass per capsule was calculated. An amount of powder equivalent to about 125 mg of active ingredient was accurately weighed, transferred into 100 ml calibrated flask and 60 ml distilled water was added. The mixture was shaken for 10 min, its volume was adjusted with water and finally filtered. From the filtrate 10 ml was transferred into 100 ml calibrated flask and the volume was adjusted using the acetate buffer-gelatin solution. Twenty five millilitres from the final diluted solution were transferred into the polarographic vessel and the solution was degassed for 5 min with a stream of oxygen-free nitrogen. The AC polarogram for the sample solution was recorded according to the set experimental conditions compiled in Table-1. For standard addition, 0.1 ml portions of standard tolmetin solutions (i.e. 125 mg ml^{-1}) were added successively to the sample solution and the AC polarograms were again recorded. From the measured currents, the concentration of tolmetin in the sample solution was computed from the expression:

$$Cx = \frac{Cs\ itv}{I_{1v} + (i_2 - i_1)\ V} \quad \text{..... (A)}$$

where C_x (ppm) = conc. of tolmetin sodium in the sample solution
C_s (ppm) = conc. of tolmetin sodium in the stock standard solution
v(ml) = aliquot portion of added standard solution
V(ml) = initial volume of sample solution
i_1 = measured current of the polarographic wave recorded for sample solution
i_2 = measured current of the polarographic wave recorded after addition of v ml portion

Table-1

AC polarographic parameters for assay of tolmetin sodium

Mode:	AC_{1T}
Modulatin AC	
Amplitude (ΔE):	10 mV
Frequency:	50 Hz
Initial voltage:	-1200 mV
Final voltage:	-1450 mV
Phase angle (ϕ):	0
$t_{drop/s}$:	0.4
Sensitivity:	1.0×10^{-9} A/mm
Sweep rate:	1 mV S^{-1}
Damp:	5

Results and Discussion

Preliminary investigations revealed that a well-defined AC wave and an ill-defined DC wave were obtainable in acetate buffer of pH 5.0, Figure 1. The peak-shaped AC polarogram, compared to its DC counterpart, offers a more convenient and reliable estimate of polarographic current that can be used for quantitative analytical purposes The graphical analysis of the AC wave (Bond, 1972) as Ede vs log $((Ip/I)^{1/2} \pm ((Ip - I)/f)^{12})$ was worked out; $E_{dc,}$ I and Ip stand for the applied DC potential, AC polarographic and peak currents respectively. The observed non-linearity suggested that the AC electrode process was irreversible (Smith, 1966).

Variation of the AC amplitude voltage, AE, indicated that a linear relationship was held between the AC peak current, Ip, and AE in the range 5 to 15 mV. Above 15 mV the AC wave was considerably broad. The effect of frequency, f, on the peak current, Ip, was investigated. The non-linear dependence of Ip on the square root of frequency, f^{12}, agreed with theoretical predictions (Booman and Holbrook, 1963). The measured current, Ip, is composed of faradic current component, $_{iF,}$ which increases linearly with $f^{1/2}$ and ic that increases linearly with f. Subsequently the dependence of Ip on f deviates from linearity. For a reversible AC electrode process (Schaap and Mckinney, 1964; Bond, 1971), the charging current, ic, is about 90° out of phase with the input AC-voltage, ΔE, whereas the faradaic component, i_F, is about 45° out of phase provided resistance effects are absent. Consequently, measurement with a phase-sensitive detector at certain phase angles will minimize the charging current.

It was found experimentally that measurement, performed at phase angle (Φ) of zero gave optimum results Apparently the charging current was well discriminated against under such conditions (Bond, 1972). To improve the readout form, Tact fundamental AC polarography, ACtn (Bond, 1980), in which the current is measured toward the end of the mercury drop life-time was adopted. As a result convenient smooth AC polarograms (free from oscillations) were obtained using the polarographic parameters compiled in Table I.

Two different techniques, namely, K_1 and K_2 of Kalousek polarography, which enables reversibility investigations to be carried out (Heyrovsky and Kuta, 1966), were tried. For the designations K1 and K2, the pulse base voltage and the pulse amplitude are adjustable. As a rule, measurement of current is taken at the base of the pulses in Kt whereas measurement in 142 is taken at the peaks. The number of measurements per drop in all cases depends on life-time, tamp, of mercury drop and Kalousek pulse frequency, f_k.

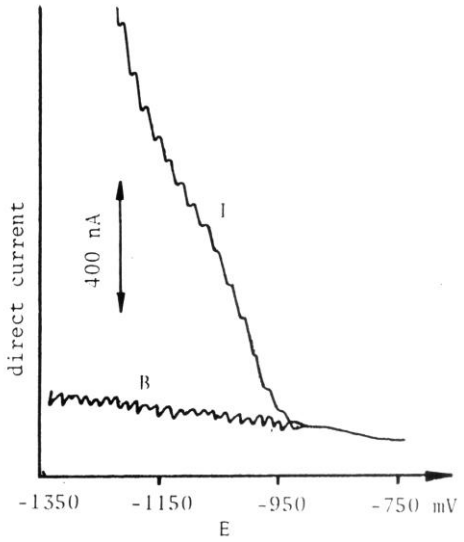

Figure la. DC-polarogram (I) in acetate buffer pH 5.0, 80pg ml^{-1} tolmelin sodium, acetate buffer (B). Electrode assembly: dme, Ag/AgCl (KCl (sat.)) and Pt-auxiliary.

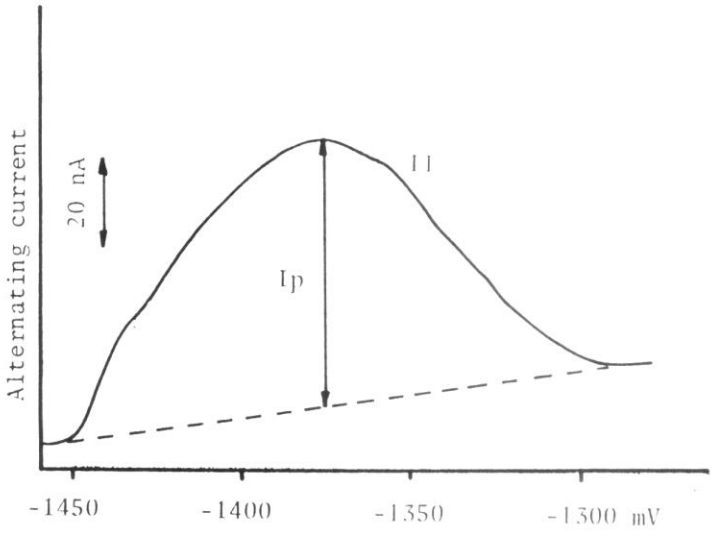

Figure lb. AC-polarogram (II) in acetate buffer pH 5.0, 12 µg ml^{-1} tolmetin sodium, acetate buffer (-------). electrode assembly: dme and two Ag/AgCl (KCl (sat)) electrodes.

The polarograms for K_1 and K_2 techniques were recorded by superimposing an amplitude square-wave of 15 mV on to the DC ramp in the range-400 and -1500 mV and setting the pulse base at -540 mV while the potential was cycled at fit of 75 Hz between these limits. Since the electrolysis current was monitored partly during positive half cycles, the oxidation of the reduced species produced on the negative half-cycles would result in an anodic current. For reversible depolarizers, e.g. Cd^{++} the anodic current decreases as the ramp voltage approaches the limiting current region and consequently the observed current rises to the diffusion controlled limited cathodic current.

Kalousek polarograms shown in Figure 2 were obtained with tolmetin sodium. When compared to those obtained for a reversible depolarizer, such as Cd^{++} (Figure 2), it is evident that tolmetin sodium behaves in an irreversible manner under the applied experimental conditions.

AC polarograhy is sensitive to variations in the working solution matrix (Bauer et at, 1978). Subsequently, standard addition technique was adopted to minimize errors. The results were evaluated by expression (A) and the mean percentage obtained for tolmetin sodium capsules (Table-2) was 101.4 ± 2.0. Alternatively a graphical plot can be used for evaluation.

Table-2

Results of the proposed AC_{1T} polarographic method for quantitation of tolmetin sodium capsules (Tolectin$^{(R)}$ -200 mg)

Aliquot portion added, v ml	Peak current (height, mm)	Conc. of unknown (C_x, ppm)	% Found
Zero	31	-	-
0.1	43	12.897	104.5
0.3	69	12.13	98.4
0.4	80	12.49	101.3
0.5	93	12.30	99.8
0.6	103	12.65	102.6
0.7	115	12.60	102.2
0.8	128	12.42	100.7
			Mean ± st. dev. = 101.4 ± 2.0

N.B.: C_s = 1266 ppm, (Tolmetin sod. dihydrate) Iitial volume, V, = 25.0 ml

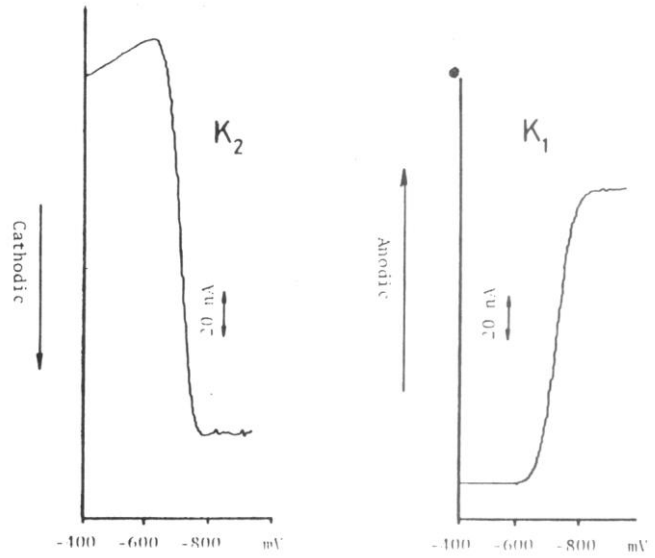

Figure 2a Kalousek polarograms K_1 and K_2 for Cd^{++} (1.0×10^{-3}M) in the voltage range -400to1000 mV. Pulse base - 540 mV, t_{drop} 0.6 sec. ΔE 15 mV, f_k 50 Hz.

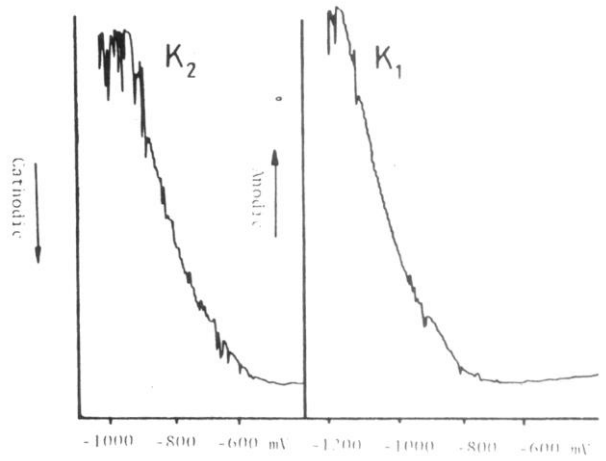

Figure 2b Kalousek polarograms K_1 and K_2 for tolmetin sodium (20 μg ml^{-1}) in the voltage range - 400 to -1000 mV. Pose bast-540 mV, temp 0.6 sec, ΔE 15 mV, f_K 50 Hz.

In conclusion it can be stated that AC polarographic procedure for determination of tolmetin sodium gives encouraging results and suggests that the use of AC polarography warrants careful study when applied to quantitation of electroactive pharmaceuticals.

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