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Determination of Dipyrone in Pure Form and Pharmaceutical Formulations by Differential Pulse Polarographic Analysis

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Differential pulse polarographic analysis of dipyrone in phosphate buffer (0.002 M $Na_2HPO_4 \cdot 12H_2O + H_3PO_4$) at pH 3.5 was performed by using dropping mercury electrode, static mercury drop electrode and hanging mercury drop electrode. One oxidation peak was observed in the range -540 to -560 mV (Ep) and the peak current Ip is linear over the ranges 1.00-50.00 µM using dropping mercury electrode and 3.80-50.00 µM using static mercury drop electrode and hanging mercury drop electrode. differential pulse polarographic analysis has been used successfully for the determination of dipyrone in pure and pharmaceutical formulations. The relative standard deviation did not exceed 4.9, 4.2 and 4.5 % for the following concentrations of dipyrone: 1.00 µM using dropping mercury electrode and 3.80 µM using static mercury drop electrode and hanging mercury drop electrode, respectively.

Key Words: Differential Pulse Polarographic Analysis, Dipyrone.

INTRODUCTION

Dipyrone ($C_{13}H_{16}N_3O_4SNa$; metamizole sodium; sodium [(2,3-dihydro-1,5-dimethyl-3-oxo-2-phenyl-1*H*-pyrazol-4-yl)methylamino]methanesulfonate); sodium salt of 1-phenyl-2,3-dimethyl-4-methylaminomethanesulfonate -5-pyrazolone, molecular weight 333.34 g (Fig. 1), is an antipyretic and analgesic extensively used in diverse countries. Its analgesic efficiency is approximately twice that of acetylsalicylic acid (aspirin)[1] and some uses include post-surgical pain, renal and biliary colic, cancer pain and osteoarthritic pain. The analgesic effect of dipyrone (metamizole) is attributed to inhibition of prostaglandin synthesis, which takes place both peripherally and centrally[2]. However, since dipyrone is associated with some toxic side effects, its commercialization is not allowed in many Northern European markets and in the USA[3]. This is due to the fact that antipyretics are a continuous target of illegal laboratories, justifying us to continue the search for new analytical procedures for simple, sensitive and reliable determination of dipyrone. The polarographic analysis has been used successfully to determine some of pharmaceutical formulations, which characterized by high accuracy and selective[4-6].

Various analytical techniques have been applied for the determination of the direct amperometric detection of the analyte in pharmaceutical formulations such as, flow injection analysis (FIA)[7]. Other current methods described in literature for dipyrone determination are based on titrimetry in aqueous and nonaqueous media[8,9], spectrophotometry[10-12] and electrochemical methods, such as coulometry[13], polarography[14,15] and voltammetry[16,17].

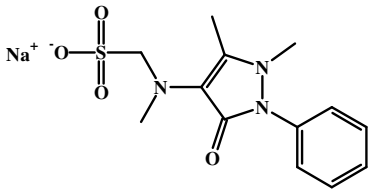

Fig. 1. Chemical structure of dipyrone (R-SO_3Na)

In the present study, differential pulse polarographic (DPP) analysis of dipyrone in phosphate buffer at pH = 3.5 using dropping mercury electrode (DME), static mercury drop electrode (SMDE) and hanging mercury drop electrode (HMDE) were applied.

EXPERIMENTAL

Dipyrone was provided by Hebei Jiheng group pharmacy Co. Ltd. Concentrated phosphoric acids, $Na_2HPO_4 \cdot 12H_2O$. (Analytical grade) were purchased from Merck. Supporting electrolytes were prepared by taking 100 mL from $Na_2HPO_4 \cdot 12H_2O$ (0.01 M) then adding 2 mL from H_3PO_4 (1.0 M) and completing to 500 mL volumetric flask by adding double distilled deionized water until reaching to the desired pH = 3.5 and we adjusted pH values by adding different volumes of H_3PO_4

(1.0 M). A stock standard solution of 0.01 M was prepared by dissolving dipyrone in supporting electrolyte:methanol (9:1, v/v) and stored in dark bottles at 4 ºC. Then prepared dilute solution of 200 µM daily just before use.

Working standards: 0.80, 1.00, 1.40, 3.80, 4.00, 5.20, 7.40, 8.00, 10.40, 12.80, 14.20, 16.00, 24.00, 27.00, 39.00, 42.00, 50.00, 55.00 and 60.00 µM were prepared daily by dilution of different volumes of stock solution (200 µM): 0.100, 0.125, 0.175, 0.475, 0.500, 0.650, 0.925, 1.000, 1.300, 1.600 , 1.775, 2.000, 3.000, 3.375, 4.875, 5.250, 6.250, 6.875 and 7.500 mL to 25 mL with supporting electrolyte:methanol (9:1, v/v). All solutions and reagents were prepared with double-distilled deionized water and analytical grade chemicals. Ultrapure mercury from Metrohm Company was used throughout the experiments.

A Metrohm 746 VA processor, A Metrohm 747 VA stand with a multi-mode electrode (MME) comprising a dropping mercury electrode (DME), static mercury drop electrode (SMDE) and hanging mercury drop electrode (HMDE) as a working electrode, an auxiliary platinum electrode and a reference electrode, double junction type, (Ag/AgCl) saturated with a 3.0 M KCl solution and the three-electrode cell were used. All measurements were done at room temperature 25 ± 2 ºC. Pure nitrogen gas (99.999 %) was used for de-oxygenation. pH meter from Radio meter company model ion check was used for the studying and monitoring the pH effects.

Sample preparation: A suitable volume from a pharmaceutical formulation: (Vitalgin oral liquid from Al-Faihaa for veterinary industries) was used. A quantity equivalent to 0.75 mL from this sample transferred to a 1000 mL volumetric flask and diluted to the mark with double-distilled deionized water. The solution was slightly turbid but no further treatment was done. Known volumes (1 mL) of the sample solution were diluted to 25 mL aliquots of the electrolyte with methanol (9:1, v/v) .

Procedure: 25 mL of working standards solution were added to the measurement cell. The solution was mixed well by automatic mixer and deoxygenated with pure nitrogen gas for 10 min. The polarograms of dipyrone was recorded by using differential pulse polarography (DPP) in the potential range from -300 to -800 mV, scan rate 20 mV/s, step time 0.2 s. The number of experiments (n = 5) according to this value the statistical calculations were done.

RESULTS AND DISCUSSION

Proposed mechanism for dipyrone oxidation at the DME: Oxidation of dipyrone using differential pulse polarographic analysis at the DME (Fig. 2) based on the observed transfer of two electrons and two protons and the similarity of the peak with that sodium sulphite[14], according to the following equations:

$$R\text{-}SO_3Na \rightleftharpoons R\text{-}SO_3^- + Na^+$$

$$R\text{-}SO_3^- + H_2O \longrightarrow R\text{-}SO_4^- + 2H^+ + 2e^-$$

Effect of pH: The influence of the solution phosphate buffer (pH 2.00 - 4.50) was analyzed with the response of the peak current. The dependence of peak current (I_p) and peak potential (E_p) with pH solution was studied. Fig. 3 shows that, the differential pulse polarographic (DPP) analysis for 27.0 µM dipyrone has been studied in buffer phosphate at different pH values using dropping mercury electrode (DME). The potential peak in the range -540 to -550 mV was observed at pH 3.25-4.00 (Fig. 4). The best results with respect to enhancement, shape and reproducibility of the peak current were obtained in 0.002 M phosphate buffer solution pH 3.5 by using differential pulse polarographic method.

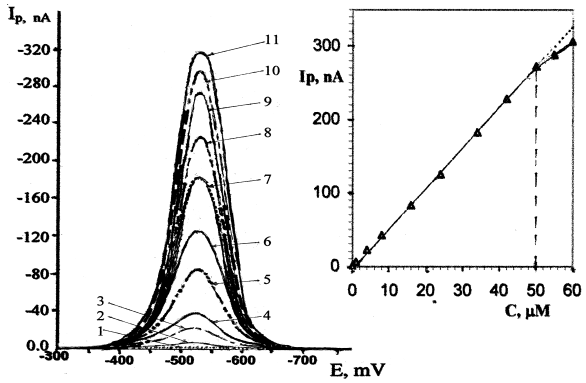

Fig. 2. Differential pulse polarographic analysis of dipyrone in phosphate buffer at pH 3.5 using dropping mercury electrode (DME) for concentrations: 1-0, 2.0-1.0, 3.0-4.0, 4.0-8.0, 5.0-16.0, 6.0-24.0, 7.0-34.0, 8.0-42.0, 9.0-50.0, 10.0-55.0 and 11.0-60.0 µM (deoxygenated with nitrogen gas for 10 min, amplitude pulse 100 mV)

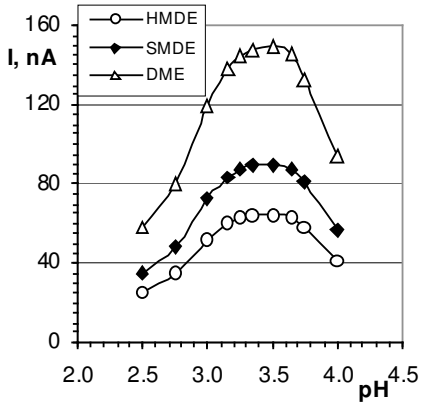

Fig 3. Effect of pH values on DPP analysis of dipyrone 27.0 µM (pulse amplitude 100 mV, deoxygenated with nitrogen gas for 10 min using DME, SMDE and HMDE in phosphate buffer 0.002 M)

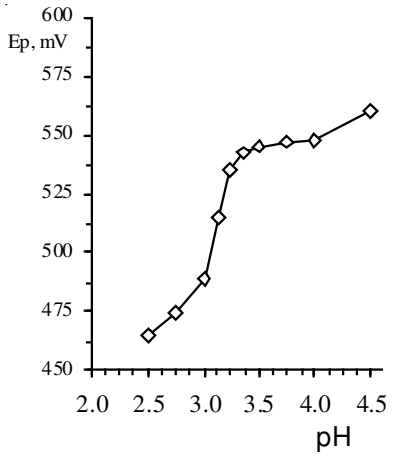

Fig. 4. Effect of pH values on DPP analysis of dipyrone 27.0 µM (pulse amplitude 100 mV, deoxygenated with nitrogen gas for 10 min using DME, SMDE and HMDE in phosphate buffer 0.002 M)

Effect of pulse amplitude: The effect of pulse amplitude on polarograms of differential pulse polarographic using HMDE for the determination of dipyrone in phosphate buffer pH 3.5 was studied. The peak current I_p increases proportionally as a function to the increasing of pulse amplitude (DPP) up to the value 70 mV for pulse positive polarity and 100 mV for pulse negative polarity. Therefore the value of pulse amplitude negative polarity 100 mV was chosen as optimum value (Fig. 5).

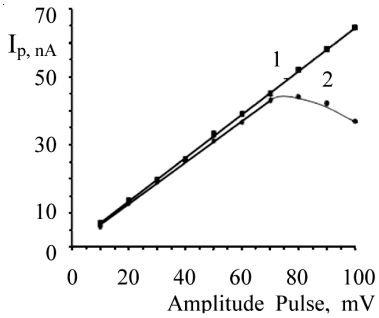

Fig. 5. Effect of pulse amplitude on DPP analysis of dipyrone 27.0 μM using HMDE,deoxygenated with nitrogen gas for 10 min using HMDE in phosphate buffer 0.002M at pH 3.5: 1-Pulse negative polarity , 2-Pulse positive polarity

Effect of electrodes of DME, SMDE and HMDE: Polarograms of differential pulse polarographic analysis for standard solutions of 27.0 μM dipyrone at the potential range from -300 to -800 mV in phosphate buffer pH 3.5 using DME, SMDE and HMDE electrodes were studied. Well-defined electrochemical oxidation peak for dipyrone was noticed at E_p range between -540 to -550 mV. It was found that, the diffusion factor (K; I_p = KC) DME was more than their values using HMDE and SMDE (Fig. 6) as in the following: K_{DME} = 2.296 K_{HMDE} = 1.6497 K_{SMDE}.

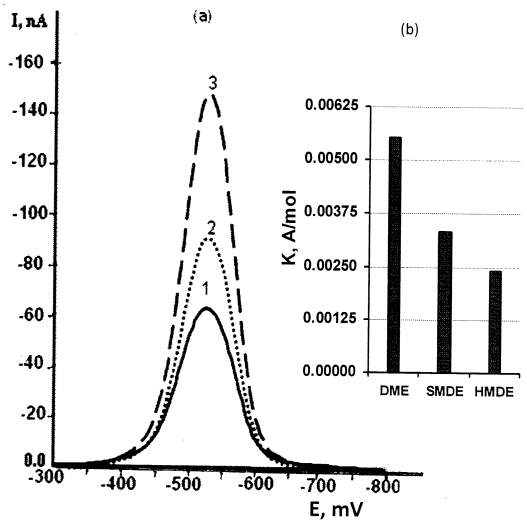

Fig. 6. (a) Polarograms for the determination of dipyrone 27.0 μM using HMDE (1), SMDE (2), DME (3), deoxygenated with nitrogen gas for 10 min in phosphate buffer 0.002 M at pH 3.5, amplitude pulse 100 mV. (b) K = f (electrode type)

Calibration curves: Calibration curves for the determination of dipyrone by differential pulse polarographic using DME, SMDE and HMDE electrodes at pH = 3.5 were studied. One peak was observed, the peak current (I_p) is linear over the concentration range of dipyrone 1.00-50.00 μM using DME (y = 5.510X - 0.167, R^2 = 0.9995) and 3.80-50.00 μM using SMDE (y = 3.344X - 0.076, R^2 = 0.9988) and HMDE (y = 2.402X - 0.476, R^2 = 0.9993); y: I_p, nA and X: $C_{dipyrone}$ (C_{Dip}), μM (Table-1). The limits of dipyrone concentration were 1.00 μM using DME with relative standard deviation (RSD) of 4.9 and 3.80 μM using SMDE and HMDE with RSD of 4.2 and 4.5 %, respectively.

TABLE-1
EVALUATION OF ACCURACY AND PRECISION OF THE PROPOSED METHOD FOR DETERMINATION OF DIPYRONE ON DME, HMDE AND SMDE BY DPPNP

Electrodes type	C_{Dip} taken (μM)	C_{Dip} found $\bar{x}^*$ (μM)	SD (μM)	Analytical standard error, $\frac{SD}{\sqrt{n}}$ (μM)	Confidence limits ($\bar{x} \pm \frac{t.SD}{\sqrt{n}}$) (μM)	RSD (%)
DME	0.80	0.76	0.052	0.023	0.76 ± 0.064	6.8
	1.00	0.98	0.048	0.021	0.98 ± 0.058	4.9
	1.40	1.38	0.066	0.030	1.38 ± 0.082	4.8
	3.80	3.80	0.152	0.068	3.80 ± 0.189	4.0
	6.20	6.22	0.200	0.089	6.22 ± 0.247	3.2
	7.40	7.38	0.214	0.096	7.38 ± 0.266	2.9
	10.40	10.40	0.250	0.112	10.40 ± 0.310	2.4
	12.80	12.80	0.256	0.115	12.80 ± 0.318	2.0
	14.20	14.25	0.257	0.115	14.25 ± 0.320	1.8
	27.00	27.00	0.432	0.193	27.00 ± 0.536	1.6
	39.00	39.10	0.704	0.315	39.10 ± 0.875	1.8
	50.00	49.82	1.744	0.780	49.82 ± 2.166	3.5
	55.00	53.36	2.775	1.241	53.36 ± 3.447	5.2
	60.00	56.80	3.465	1.550	56.80 ± 4.302	6.1
SMDE	1.40	1.25	0.094	0.042	1.25 ± 0.116	7.5
	3.80	3.78	0.159	0.071	3.78 ± 0.197	4.2
	6.20	6.18	0.222	0.100	6.18 ± 0.276	3.6
	7.40	7.45	0.246	0.110	7.45 ± 0.305	3.3
	10.40	10.46	0.313	0.140	10.46 ± 0.390	3.0
	12.80	12.80	0.320	0.143	12.80 ± 0.397	2.5
	14.20	14.30	0.329	0.147	14.30 ± 0.408	2.3
	27.00	27.10	0.569	0.255	27.10 ± 0.707	2.1
	39.00	38.90	0.934	0.418	38.90 ± 1.159	2.4
	50.00	49.75	1.891	0.845	49.75 ± 2.347	3.8
	55.00	53.30	2.932	1.311	53.30 ± 3.641	5.5
	60.00	56.50	4.068	1.819	56.50 ± 5.050	7.2
HMDE	1.40	1.20	0.098	0.044	1.20 ± 0.122	8.2
	3.80	3.74	0.168	0.075	3.74 ± 0.209	4.5
	6.20	6.15	0.264	0.118	6.15 ± 0.328	4.3
	7.40	7.35	0.265	0.117	7.35 ± 0329	3.6
	10.40	10.50	0.320	0.143	10.50 ± 0.397	3.2
	12.80	12.90	0.380	0.179	12.90 ± 0.471	2.9
	14.20	14.30	0.400	0.179	14.30 ± 0.497	2.7
	27.00	27.20	0.762	0.341	27.20 ± 0.946	2.8
	39.00	39.10	1.408	0.630	39.10 ± 1.748	3.6
	50.00	49.50	2.228	0.996	49.50 ± 2.765	4.5
	55.00	53.13	3.135	1.402	53.13 ± 3.892	5.9
	60.00	56.01	4.369	1.954	56.01 ± 5.424	7.8

*Average of five measurements.

Applications: Determination of dipyrone in pharmaceutical preparations (vitalgin, oral liquid contains 30 g/100 mL of dipyrone) using differential pulse polarography in phosphate buffer (pH 3.5) and dropping mercury electrode DME were proceeded. The obtained sample solutions were applied to the differential pulse polarography determination of dipyrone. The results of quantitative analysis for dipyrone were calculated by calibration curves and the standard addition methods (Table-2).

TABLE-2
DETERMINATION OF DIPYRONE IN SOME PHARMACEUTICAL FORMULATIONS USING DPPNP METHODS ON DME AT pH = 3.5 USING STANDARD ADDITION METHOD

Vitalgin, oral liquid Alfaihaa-veterinary S.A.R. (Damascus-Syria)	Contents of dipyrone (g/100 mL)	$\bar{x}$ (g/100 mL)	RSD (%)	Recovery (%)
1	30	31.20	2.2	104.0
2	30	30.40	2.4	101.3
3	30	29.60	2.6	98.7
4	30	29.80	2.1	99.3
5	30	29.90	2.3	99.7
6	30	30.60	2.2	102.0
$\bar{x}$	30	30.25	2.3	100.8

Conclusion

In this method, differential pulse polarographic analysis of dipyrone in both pure and pharmaceutical formulations at pH 3.5 over the ranges 1.00-50.00 μM using DME and in the range 3.80-50.00 μM applying SMDE and HMDE methods were successfully studied. The relative standard deviation (RSD) was not exceed of 4.9, 4.2 and 4.5 % for the concentration: 1.00 μM using DME and 3.80 μM using SMDE and HMDE, respectively. The proposed methods can be used for routine determination of dipyrone in pharmaceutical formulations with high sensitivity.

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