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Polarographic Determination of Topiramate in Some Pharmaceuticals

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A differential pulse polarographic analysis has been used for the determination of topiramate in aqueous medium, which contains a phosphate buffer 0.01 M at pH = 9.50 using dropping mercury electrode (DME), static mercury drop electrode (SMDE) and hanging mercury drop electrode (HMDE). Reduction peak for topiramate was occurred in potential (E_p) range from 74 to 77 mV. The peak current (I_p) is proportional to the concentration of topiramate over the ranges 1.36-19.04 μg mL^{-1} using DME and 4.08-27.2 μg mL^{-1} using SMDE and HMDE. The limit of quantitation was 1.36 μg mL^{-1} with a relative standard deviation (RSD) of 3.8 % using DME and 4.08 μg mL^{-1} with a relative standard deviation of 2.8 % and 4.5 % using HMDE and SMDE, respectively. Therefore, this polarographic method can be applied successfully for the determination of topiramate. The proposed method is applied to the direct determination of topiramate in some pharmaceutical formulations (tablets), by differential pulse polarography (DPP). The results obtained can be observed that, the difference between the expected and the results found values by this method are less than 1.36 μg mL^{-1} with the RSD is less than ± 3.8 %.

Key Words: Topiramate, Differential pulse polarographic analysis, Pharmaceuticals.

INTRODUCTION

Chemically topiramate is [2,3:4,5-*bis*-O-(1-methylethylidene)-β-D-fructopyranose-sulfamate] (Fig. 1), which is a novel compound has been shown to be an effective anticonvulsant with a good safety profile after oral administration in humans and animals[1]. It was developed by the R.W. Johnson Pharmaceutical Research Institute, Spring House, PA. Topiramate has been approved for the use as adjunctive therapy in patients with partial onset seizures with or without secondarily generalized seizures and a reliable method of analysis was needed to support clinical studies[2-4].

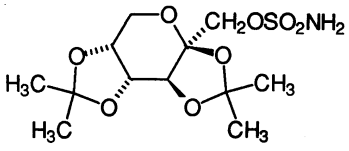

Fig. 1. Chemical structure of topiramate

Both ion chromatography method[5] and capillary electrophoresis technique[6] have been used for determination of the inorganic degradation product sulfate and sulfamate in the antiepileptic drug topiramate. Gas chromatography with FID detection was also used for analysis of topiramate in biological fluids which gave non-specific detection and more endogenous peaks in the chromatograms[7]. A capillary gas chromatographic assay with nitrogen phosphorus detection was developed and validated for the quantitative determination of topiramate, in human plasma, urine and whole blood[8]. A high-performance liquid chromatography coupled with either turbo ion spray mass spectrometry[9], or UV detector[10] has been used for the determination of topiramate in human plasma or serum. In another study, this method (HPLC) using a chemiluminescent nitrogen detector along with reversed-phase HPLC has been developed for determination of topiramate and its degradation product in liquid oral solutions[11].

The present work aims to offer simple, sensitive and selective polarographic methods for the determination of topiramate in drug substance and finished product. So that the investigated method can be applied to the analysis of topiramate in pharmaceutical industry and they are characterized by simplicity and less running costs with high accuracy and precision in comparison with above-mentioned techniques.

EXPERIMENTAL

A Metrohm 797 VA processor stand with a multi-mode electrode (MME) comprising a dropping mercury electrode (DME), static mercury drop electrode (SMDE) and hanging mercury drop electrode 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) completed the three-electrode cell is used. All measurements were done at room temperature 25 ± 2 °C, nitrogen gas was used for deoxygenation. pH-meter from radio meter company model ion check was used for the studying the pH effects.

Topiramate standard was supplied from Cadila Health Care Ltd. India, standard solutions were prepared daily by weighing 17 mg of topiramate and dissolution in 50 mL volumetric flask by double-distilled deionized water to give a concentration of 340 mg/L. Supporting electrolyte phosphate buffer (pH 9.5) was prepared by dissolution 3.5814 g of $Na_2HPO_4.12H_2O$ in 1000 mL volumetric flask by double-distilled deionized water, appropriate volume of H_3PO_4 or NaOH (0.01 M) was added to give the desired pH. 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.

Procedure: 20 mL of supporting electrolyte (phosphate buffer pH 9.50), different volumes of topiramate standard solution 340 mg/L, diluting to 25 mL with supporting electrolyte and transferred to the cell. The solution was well mixed by automatic mixer and deoxygenated with pure nitrogen gas for 5 min. The polarograms of topiramate was recorded by using direct current polarography (DCP), cyclic voltammetry (CV), square wave (SqW) and differential pulse polarography (DPP)

in the potential range from 20 mV to 200 mV, scan rate 2 mV/s with step time 1 s. The number of experiments (n = 6) according to this value and the statistical calculations were done.

RESULTS AND DISCUSSION

Effect of polarographic method: Direct current polarography (DCP), cyclic voltammetry(CV), square wave (SqW), differential pulse polarography positive polarity (DPPPP) and differential pulse polarography negative polarity (DPPNP) of topiramate in presence of 0.01 M $Na_2HPO_4.12H_2O$ at pH 9.50 as electrolyte by using hanging mercury drop electrode (HMDE) were studied. Differential pulse polarography negative polarity (DPPNP) was found to give the greatest sensitivity. A cathodic peak was obtained at potential varying between 66 to 75 mV due to the reduction of topiramate (Fig. 2).

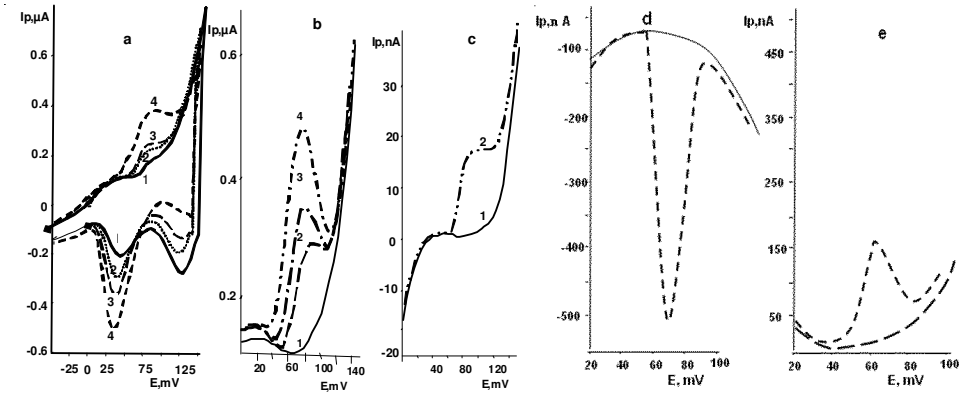

Fig. 2. The voltammetric curves for the determination of topiramate in presence of 0.01 M $Na_2HPO_4.12H_2O$ at pH 9.50 on HMDE by: **a**: CV (1-5.44, 2- 8.16, 3-10.88, 4-13.60 µg/mL), **b**: SqW (1-0.0, 2- 8.16, 3-10.88, 4-13.60 µg/mL), **c**: DCP (1-0.0 , 2-35.36 µg/mL µg/mL), **d**: DPPPP (19.04 µg/mL), e: DPPNP (19.04 µg/mL)

Effect of pH: The influence of the solution phosphate buffer (pH 7.0-11.0) was analyzed in the response of the peak current. The dependence of peak current (I_p) and peak potential (E_p) on pH is shown in Fig. 3a. The best results with respect to enhancement, shape and reproducibility of the peak current were obtained in 0.01 mol L^{-1} phosphate buffer solution pH 9.5 by using DPP method.

Effect of pulse amplitude: The effect of pulse amplitude on DPP polarograms using DME to determine the topiramate in phosphate buffer pH 9.5 was studied. The peak current I_p increases proportional as a function to the increasing of pulse amplitude negative polarity (DPPNP) up to the value 50 mV. Therefore the value of pulse amplitude E = 40 mV was chosen as optimum value and the peak current I_p increases proportional as a function to the increasing of pulse amplitude positive polarity (DPPPP) up to the value 30 mV. Therefore the value of pulse amplitude E = 20 mV was chosen as optimum value (Fig. 4).

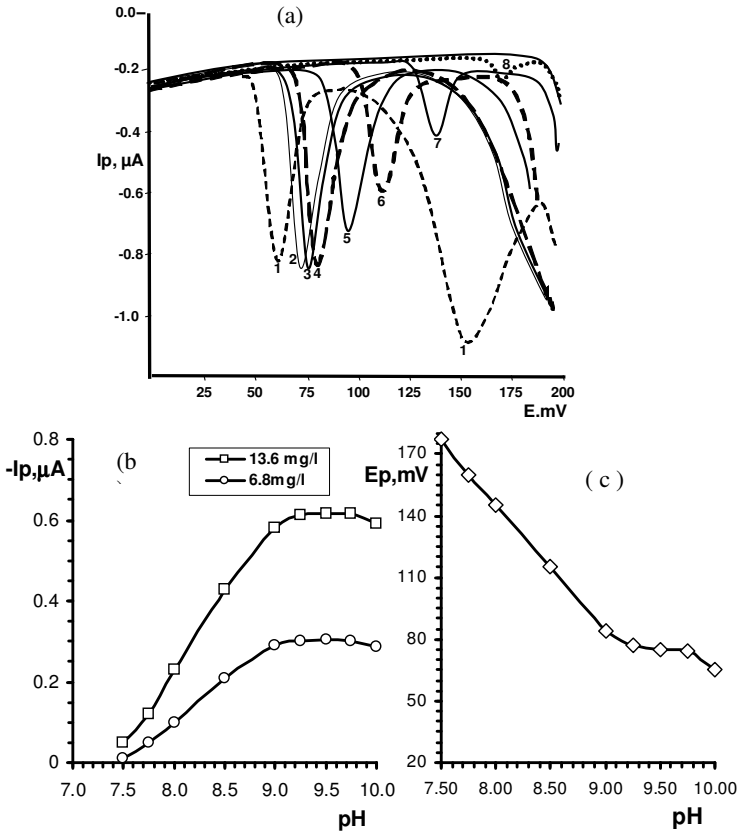

Fig. 3. Effect of pH values (for DPP-using DME-of topiramate 13.6 g/mL in phosphate buffer on: **a**: polarograms (1-8) represent pH = 10.0, 9.75, 9.50, 9.25,9.00, 8.50, 8.00 and 7.50; **b**: I_p; **c**: E_p

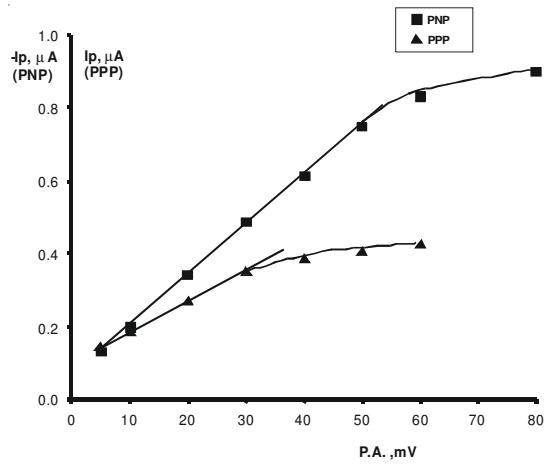

Fig. 4. Effect of pulse amplitude for DPP of topiramate 13.6 µg/mL for DPPNP and 19.04 µg/mL DPPPP using DME

Effect of electrodes sorts DME, SMDE and HMDE: Differential pulse polarograms was studied for standard solutions of topiramate on the potential range from 0.0 mV to 200 mV in phosphate buffer pH = 9.5 by using DME, SMDE, HMDE electrodes. Well-defined electrochemical reduction wave for topiramate was noticed at E_p range between 60 mV to 75 mV. It was found that, the diffusion factor using DME was greater than their values using HMDE and using SMDE:

$$K_{DME} = 1.95\ K_{HMDE} = 2.197\ K_{SMDE}$$

Calibration curves: Calibration curves for the determination of topiramate by DPP using DME, SMDE and HMDE electrodes were studied. The heights of current peaks I_p was proportional to the concentration of topiramate over the range 2.27-43.42 and 1.36-19.04 μg mL^{-1} using DME by DPPPP and DPPNP methods, respectively, 16.32-51.68 and 4.08-27.20 μg mL^{-1} using SMDE and HMDE electrodes by DPPPP and DPPNP methods, respectively, with a relative standard deviations over the ranges 3.8-4.5 % for the concentrations from 1.36 μg mL^{-1} to 4.08 μg mL^{-1} using DME, SMDE and HMDE, respectively (Tables 1 and 2).

TABLE-1
EVALUATION OF ACCURACY AND PRECISION OF THE PROPOSED METHODS FOR DETERMINATION OF TOPIRAMATE ON DME, HMDE AND SMDE BY DPPPP

Electrodes sorts	Concentration taken (μg/mL)	Concentration found $\bar{X}$ (μg/mL)	SD (μg/mL)	Analytical standard error $\frac{SD}{\sqrt{n}}$ (μg/mL)	Confidence limits $\frac{SD}{\sqrt{n}} t \pm \bar{X}$ (μg/mL)	RSD (%)
DME	2.27	2.68	0.118	0.0480	2.68±0.1234	4.4
	5.44	5.33	0.203	0.0828	5.33±0.2128	3.8
	8.16	8.24	0.297	0.1212	8.24±0.3116	3.6
	10.88	10.78	0.302	0.1233	10.78±0.317	2.8
	16.32	16.25	0.325	0.1326	16.25±0.341	2.0
	19.04	18.95	0.341	0.1392	18.95±0.3578	1.8
	27.20	27.13	0.407	0.1661	27.13±0.4270	1.5
	32.64	32.58	0.456	0.1862	32.58±0.5193	1.4
	38.08	38.04	0.495	0.2020	38.04±0.5193	1.3
	43.42	43.49	0.522	0.2131	43.49±0.5478	1.2
HMDE	16.32	16.48	0.593	0.2421	16.48±0.6455	3.6
	19.04	19.22	0.615	0.2511	19.22±0.6455	3.2
	27.20	27.05	0.703	0.2869	27.05±0.7376	2.6
	32.64	32.55	0.846	0.3453	32.55±0.8877	2.6
	35.36	35.10	0.842	0.3437	35.10±0.8836	2.4
	43.42	43.40	0.868	0.3543	43.40±0.9109	2.0
	51.68	51.80	1.191	0.4862	51.80±1.250	2.3
SMDE	16.32	16.40	0.593	0.2421	16.40±0.6224	3.3
	19.04	19.11	0.535	0.2184	19.10±0.5615	2.8
	27.20	27.13	0.597	0.2437	27.05±0.6265	2.2
	32.64	32.70	0.654	0.2669	32.55±0.6862	2.0
	35.36	35.42	0.638	0.2605	35.10±0.6697	1.8
	43.42	43.42	0.695	0.2837	43.40±0.7294	1.6
	51.68	51.80	0.777	0.3172	51.80±0.8155	1.5

TABLE-2
EVALUATION OF ACCURACY AND PRECISION OF THE PROPOSED METHODS FOR DETERMINATION OF TOPIRAMATE USING DME, HMDE AND SMDE BY DPPNP

Electrodes sorts	Concentration taken (μg/mL)	Concentration found $\overline{X}$ (μg/mL)	SD (μg/mL)	Analytical standard error $\frac{SD}{\sqrt{n}}$ (μg/mL)	Confidence limits $\frac{SD}{\sqrt{n}} t \pm \overline{X}$ (μg/mL)	RSD (%)
DME	1.36	1.28	0.049	0.020	1.28±0.051	3.8
	2.72	2.72	0.068	0.028	2.72±0.071	2.5
	4.08	4.14	0.095	0.039	4.14±0.100	2.3
	5.44	5.45	0.125	0.051	5.45±0.131	2.3
	6.80	6.76	0.155	0.063	6.76±0.163	2.3
	8.16	8.24	0.181	0.074	8.24±0.190	2.2
	10.88	10.89	0.218	0.089	10.89±0.229	2.0
	13.60	13.52	0.257	0.105	13.52±0.269	1.9
	16.32	16.26	0.276	0.113	16.26±0.289	1.7
	19.04	19.15	0.306	0.125	19.15±0.321	1.6
HMDE	4.08	4.01	0.180	0.0735	4.01±0.189	4.5
	5.44	5.47	0.230	0.094	5.47±0.241	4.2
	8.16	8.00	0.320	0.131	8.00±0.336	4.0
	10.88	10.79	0.410	0.167	10.79±0.429	3.8
	13.60	13.65	0.464	0.189	13.65±0.487	3.4
	19.04	19.13	0.536	0.240	19.13±0.615	2.8
	27.20	27.35	0.711	0.219	27.35±0.563	2.6
SMDE	4.08	4.15	0.116	0.047	4.15±0.122	2.8
	5.44	5.46	0.142	0.058	5.46±0.149	2.6
	8.16	8.22	0.206	0.084	8.22±0.216	2.5
	10.88	10.85	0.250	0.102	10.85±0.262	2.3
	13.60	13.52	0.297	0.121	13.52±0.312	2.2
	19.04	19.10	0.383	0.156	19.10±0.402	2.0
	27.20	27.26	0.491	0.200	27.26±0.515	1.8

Applications: Many applications for the determination of topiramate in pharmaceutical preparations (maxaram tablets and topimate tablets) were proceeded by differential pulse polarography in pH = 9.5 phosphate buffer and dropping mercury electrode.

The sample solutions obtained above were applied to the differential pulse polarography determination of topiramate. The results of quantitative analysis for topiramate were calculated by calibration curves and the standard addition methods (Table-3).

Conclusion

The proposed methods are simple, accurate and highly sensitive with good precision and accuracy. They also have the advantage of doing the analysis at low cost high accuracy. The proposed methods can be used, depending upon the availability of chemicals and equipment, for routine determination of topiramate in pharmaceutical formulations.

TABLE-3
DETERMINATION OF TOPIRAMATE IN SOME PHARMACEUTICAL FORMULATIONS USING DPPNP METHODS ON DME

Commercial name	Contents	$\bar{x}$	RSD (%)	Recovery (%)
Maxaram tablet (Shifa-Aleppo-Syria)	25 mg	25.17	2.6	100.68
	100 mg	100.85	2.1	100.85
	200 mg	201.5	1.5	100.75
Topimate tablet (Mediotec-Homs-Syria)	25 mg	25.10	2.8	100.25
	100 mg	101.08	1.9	101.80
	200 mg	202.15	1.4	101.08

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