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Differential Pulse Polarographic Determination of Atorvastatin in Pharmaceutical Dosage Forms Using Dropping Mercury Electrode

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New, simple and rapid differential pulse polarographic analysis by using dropping mercury electrode with negative amplitude pulse was developed for determination of atorvastatin in pure and pharmaceutical dosage forms in borax buffer at pH 7.5. One reduction peak was observed in the range -1310 to -1340 mV (E_p). The peak current I_p is linear over the ranges 2-60 μmol L^{-1}. The differential pulse polarographic analysis has been used successfully for the determination of atorvastatin in pure form and in pharmaceutical formulations. The relative standard deviation did not exceed 3.8 % for the concentrations of atorvastatin 2.00 μmol L^{-1} (1.117 μg mL^{-1}). Regression analysis showed a good correlation coefficient ($R^2 = 0.9994$) between I_p and concentration over the range of 1.117 to 33.52 μg mL^{-1}. The limit of detection and the limit of quantification were 0.129 μg mL^{-1} and 0.390 μg mL^{-1}, respectively. The proposed method was successfully applied to the analysis of atorvastatin in pure and pharmaceutical dosage forms with average recovery of 97.2 to 104.2 %. The results obtained agree well with the contents stated on the labels.

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

INTRODUCTION

Atorvastatin calcium[1,2] is a calcium (bR, dR)-2-(r-fluorophenyl)-b,d-dihydroxy-5-isopropyl-3-phenyl-4-(phenylcarbamoyl)pyrrole-1-hepatanoicacid (1:2) trihydrate. The empirical formula of atorvastatin calcium trihydrate is $C_{66}H_{68}N_4O_{10}CaF_2{\cdot}3H_2O$ or $(C_{33}H_{34}N_2O_5F)_2Ca{\cdot}3H_2O$, mol.mass 1209.4 g; where the empirical formula of atorvastatin is $C_{33}H_{35}FN_2O_5$, mol. mass 558.64 g (Fig. 1). Atorvastatin calcium is a white to off-white crystalline powder that is insoluble in aqueous solutions of pH 4 and below. Atorvastatin calcium is very slightly soluble in distilled water, pH 7.4 phosphate buffer and acetonitrile; slightly soluble in ethanol and freely soluble in methanol. Atorvastatin is a member of the drug class known as statins, used for lowering blood cholesterol. It also stabilizes plaque and prevents strokes through antiinflammatory and other mechanisms. It is alipid regulating drug with actions on plasma lipids similar to those of simvastatin[2-4]. Several studies have been reported for the determination of atorvastatin in pure form, in pharmaceutical formations and in biological fluids including spectrophotometric methods[2,5-8], electrophoresis[9,10], chromatographic methods with different detectors[11-16] and electrochemical, polarographic and voltammetric methods[17-21].

The electrochemical behaviour of atorvastatin calcium at glassy carbon and boron-doped diamond electrodes has been studied using voltammetric techniques. The possible mechanism of oxidation was discussed with model compounds. The dependence of the peak current and potentials on pH, concentration, scan rate and nature of the buffer were investigated for both electrodes. The oxidation of atorvastatin was irreversible and exhibited a diffusion controlled fashion on the diamond electrode. A linear response was obtained within the range of $9.65 \times 10^{-7} - 3.86 \times 10^{-5}$ M in 0.1 M H_2SO_4 solution for both electrodes. The detection limits of a standard solution are estimated to be 2.11×10^{-7} M with differential pulse voltammetry (DPV) and 2.05×10^{-7} M with square wave voltammetry (SWV) for glassy carbon electrode and 2.27×10^{-7} M with differential pulse voltammetry and 1.31×10^{-7} M with square wave voltammetry for diamond electrodes in 0.1 M H_2SO_4 solution. The repeatability of the methods was found good for both electrodes. The methods were fully validated and successfully applied to the high-throughput determination of the drug in tablets, human serum and human urine with good recoveries[19].

The electrochemical behaviour of atorvastatin and amlodipine at a glassy carbon electrode has been studied using different voltammetric techniques. First derivative of the ratio voltammetric methods for determination of amlodipine and atorvastatin in tablets in the presence of the other compound has been described. This technique depends on the measuring

of first derivative of the ratio voltammograms of each concentration as a function of the increased concentrations. Differential pulse and square wave voltammetric methods depend on first derivative of the ratio voltammetry by measurements of the selected potentials for amlodipine and atorvastatin. The linear response was within the range of 4×10^{-6} - 1×10^{-4} M for amlodipine and 2×10^{-6} -1×10^{-4} M for atorvastatin. The proposed methods have been extensively validated[20].

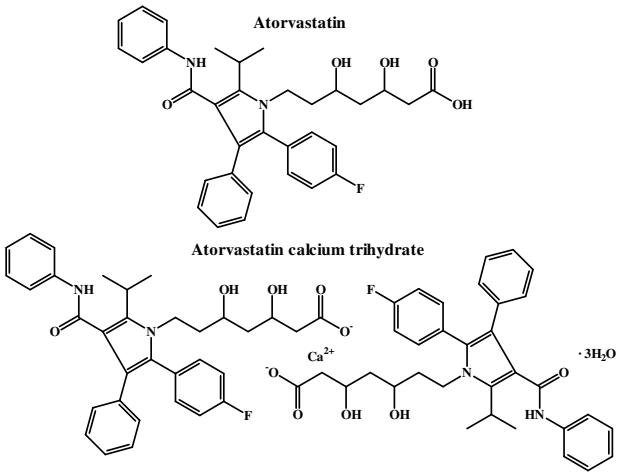

Fig. 1. Chemical structure of atorvastatin and atorvastatin calcium trihydrate

Electrochemical behaviour of atorvastatin and optimum conditions to its quantitative determination were investigated using voltammetric methods. Some electrochemical parameters such as diffusion coefficient, surface coverage of adsorbed molecules, electron transfer coefficient, standard rate constant and number of electrons were calculated using the results of cyclic voltammetry. A tentative mechanism for the oxidation for atorvastatin has been suggested. The oxidation signal of atorvastatin molecule was used to develop fully validated, new, rapid, selective and simple square-wave anodic adsorptive stripping voltammetric (AdsSWV) and differential pulse anodic stripping voltammetric (AdsDPV) methods to direct determination of atorvastatin in pharmaceutical dosage forms and biological samples. For the AdsDPV and AdsSWV techniques, linear working ranges were found to be $1.0 \times 10^{-7} - 5.0 \times 10^{-6}$ and 3.0×10^{-7}-5.0×10^{-6} molL^{-1}, respectively. The detection limits obtained from AdsDPV and AdsSWV were calculated to be 6.55×10^{-8} and 1.53×10^{-7} mol L^{-1}, respectively. The methods were successfully applied to assay the drug in tablets, human blood serum and human urine[21].

In the present work, novel differential pulse polarographic method on dropping mercury electrode with negative amplitude was applied for determination of atorvastatin in pure and in pharmaceutical dosage forms using borax buffer at pH 7.5.

EXPERIMENTAL

A Metrohm 746 VA processor, A Metrohm 747 VA stand with a multi-mode electrode (MME) comprising a dropping mercury electrode, static mercury drop electrode 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 and the three-electrode cell were used. All measurements were done at room temperature 25 ± 5 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. The diluter pipette model DIP-1 (Shimadzu), having 100 mL sample syringe and five continuously adjustable pipettes covering a volume range from 20 to 5000 µL (model PIPTMAN P, GILSON), were used for preparation of the experimental solutions. A ultrasonic processor model POWERSONIC 405 was used to sonicate the sample solutions. Electronic balance (Sartorius-2474; 0.01 mg) was used for weighing the samples.

Working reference standard of atorvastatin calcium trihydrate was supplied by ind-swift (India), its purity as atorvastatin was 92.0 %. Concentrated phosphoric acids, di-sodium tetraborate decahydrate (borax) $Na_2B_4O_7.10H_2O$, mol mass 381.37 g, were of extra pure purchased from Merck. Ultrapure mercury from Metrohm company was used. Supporting electrolytes (buffer) were prepared by dissolving 7.15 g borax in 240 mL then adding 6.5 mL from H_3PO_4 (1.0 M) and completing to 250 mL volumetric flask by adding double distilled deionized water until reaching to the desired pH = 7.5. A stock standard solutions of atorvastatin calcium trihydrate (a) 1×10^{-3} mol L^{-1} and (b) 1×10^{-5} mol L^{-1} of atorvastatin was prepared from atorvastatin calcium trihydrate in 50 mL mixture methanol: water (9:1, v/v). These stock solutions were further diluted to obtain working solutions daily just before use in the ranges of atorvastatin: 2, 4, 8, 16, 24, 32, 40, 50, 60 and 70 µmol L^{-1} (1.117, 2.234, 4.468, 8.936, 13.404, 17.872, 22.340, 27.925, 33.52 and 39.10 µg mL^{-1}) by dilution of the volumes: 0.5, 1 from stock standard solutions (b), 0.2, 0.4, 0.6, 0.8, 1, 1.25, 1.5 and 1.75 mL from stock standard solutions(a) to 25 mL with supporting electrolyte. All solutions and reagents were prepared with double-distilled deionized water and analytical grade chemicals.

Sample preparation: A commercial formulations (as tablet) were used for the analysis of atorvastatin by using differential pulse polarographic analysis. The pharmaceutical formulations were subjected to the analytical procedures:

(1) Atorvex tablets, Asia pharmaceutical industries, Aleppo-Syria, each tablet contains: 10, 20 and 40 mg of atorvastatin.

(2) Atorvatin tablets, Alpha, Aleppo pharmaceutical industries, Aleppo-Syria, each tablet contains: 10, 20 and 40 mg of atorvastatin.

(3) Lipito-med tablets, Medico labs., Homs-Syria, each tablet contains: 10, 20 and 40 mg of atorvastatin.

(4) Lipostatin tablets, Ibn Al-Haytham Pharma Industries Co., Aleppo-Syria, each tablet contains: 10, 20 and 40 mg of atorvastatin.

(5) Atoraz tablets, Razi pharmaceutical industries, Aleppo-Syria, each tablet contains: 10, 20 and 40 mg of atorvastatin. Stock solutions of pharmaceutical formulations: Three tablets of each studied pharmaceutical formulations were weighted accurately, crushed to a fine powder and mixed well. Equivalent tenth the weight of one tablet, was solved in 40 mL methanol : water (9:1) by using ultrasonic, filtered over a 50 mL flask and diluting to 50 mL with methanol : water, which

content as the follows : 20, 40 and 80 mg mL^{-1} for all studied pharmaceutical formulations content 10, 20 and 40 mg/tab, respectively.

Working solutions of pharmaceuticals: These solutions were prepared daily by diluting 5, 2.5 and 1.25 mL from stock solutions of pharmaceutical formulations, respectively, then diluting to 25 mL with supporting electrolyte (each solution contents 4 μg mL^{-1} of atorvastatin).

Working standard addition solutions of pharmaceuticals: These solutions were prepared as the follows: same mentioned volumes of stock solutions of pharmaceuticals with 0.2, 0.4, 0.6 and 0.8 mL from stock solution (a) of atorvastatin and diluting to 25 mL with supporting electrolytes; these solutions content 4.000 μg mL^{-1} of atorvastatin (from different pharmaceuticals) plus 4.469, 8.938, 13.407 and 17.876 μg mL^{-1} of atorvastatin, respectively.

Procedure: A 25 mL volume of a solution containing an appropriate concentration of atorvastatin with supporting electrolytes (buffer), or working solutions of pharmaceuticals at pH 7.5 and temperature at 25 ± 5 ºC was transferred into the three-electrode cell. The potential was scanned from -600 to -1500 mV with the auto-scan facility.

RESULTS AND DISCUSSION

Polarographic behaviour: The polarograms in the optimal conditions (supporting electrolytes, pH, scan rate, initial potential and final potential, *etc*.) using differential pulse polarographic analysis at dropping mercury electrode were studied. The peak potential was measured at -1310 to -1340 mV.

Effect of pH: First, the influence of pH on I_p was studied. The maximum peak (I_p) occurs at approximately pH 7.5 (Fig. 2). The effect of pH on peak potential (E_p) shows the following: when pH value decreasing between 9 to 6.5, E_p remains almost constant, but decreases pH value after that E_p increases sharply to negative value (Fig. 3).

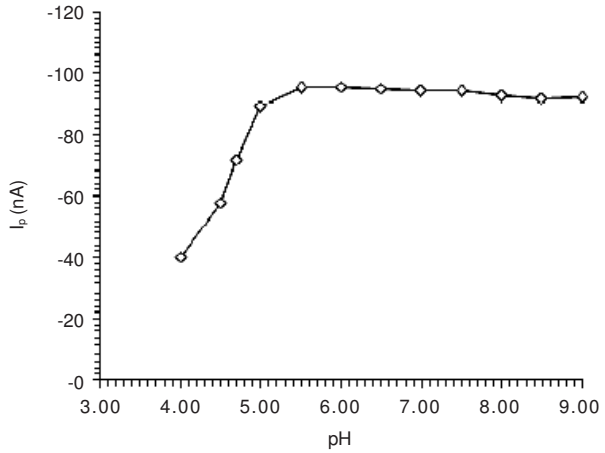

Fig. 2. Effect of pH solution on I_p of AT using DPPA at DME, (C_{AT} = 20.5 μg mL^{-1})

Effect of supporting electrolytes (buffer): The effect of supporting electrolytes (buffer) on the I_p was studied. It was found that, the borax was the better buffer at concentration 0.075 mol L^{-1} (Fig. 4).

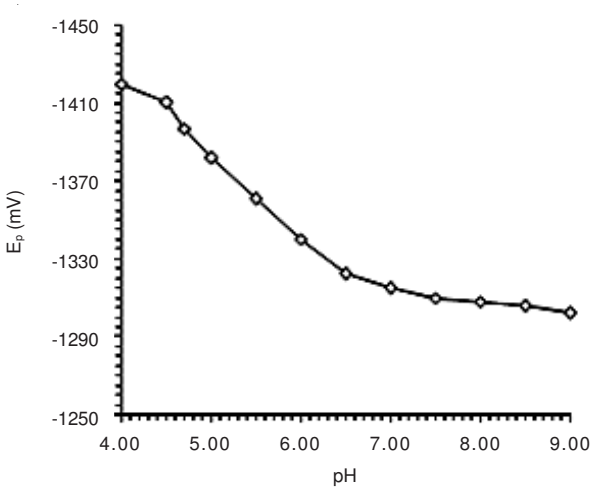

Fig. 3. Effect of pH solution on E_p of atorvastatin using DPPA at DME, (C_{AT} = 20.5 μg mL^{-1})

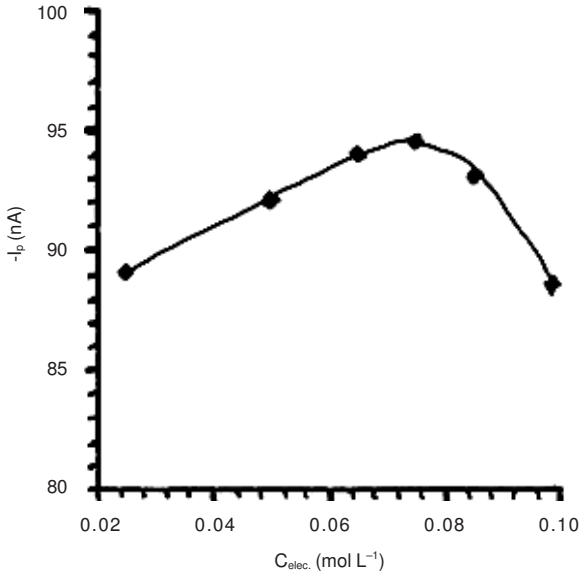

Fig. 4. Effect of electrolyte concentration on I_p, of atorvastatin using DPPA at DME, (C_{AT} = 20.5 μg mL^{-1}, pH = 7.5)

Effect of negative pulse amplitude: The effect of negative pulse amplitude between 0 to 100 mV on I_p showed that, the value 90 mV was better than another's.

Effect of scan rate: The different values of scan rate (3.3, 6.6, 10, 13.3, 16.6 and 20 mV/s) were studied. It was found that, the value scan rate 10 mV/s was the better.

Effect of initial and final potential: The effect of initial and final potential on the I_p was studied. It was found that better initial potential was -600 mV and better final potential was -1500 mV.

Effect of temperature and time: The effect of temperature and time on the electrochemical reaction of atorvastatin was studied at different values (15-35 ºC, 5-60 min) by continuous monitoring of the I_p. It was found that, the value of I_p was not affected by temperature between 20 to 30 (the temperature at 25 ± 5 ºC was used). The effect of waiting time was determined at laboratory ambient temperature (25 ± 5 ºC). It was found that, the value of I_p was not affected by time between 5 to 60 min.

The optimum parameters established for determination of atorvastatin using differential pulse polarographic analysis on dropping mercury electrode showed in Table-1.

TABLE-1
THE OPTIMUM PARAMETERS ESTABLISHED FOR DETERMINATION OF ATORVASTATIN USING DIFFERENTIAL PULSE POLAROGRAPHIC ANALYSIS ON DROPPING MERCURY ELECTRODE WITH NEGATIVE AMPLITUDE IN BORAX BUFFER AT pH 7.5

Parameters	Operating modes
Indicator electrode	Dropping mercury electrode
Supporting electrolytes (buffer)	Borax, 0.075 mol L^{-1}
pH	7.5
Solvent for atorvastatin	Methanol : water (9 : 1, v/v)
Value of pulse amplitude	-90 mV
Purge gas	Pure N_2
Purge time	200 sec.
Initial potential	-600 mV
Final potential	-1500 mV
Pulse duration	20 ms
Scan rate	10 mV/s
Age drop of mercury	0.6 sec
Temperature of solution	25º ± 5 ºC
Peak Potential, mV	-1310 to -1340 mV
LOD(3.3SD)	0.129 µg mL^{-1}
LOQ (10SD)	0.390 µg mL^{-1}
Linearity range of concentration	1.117 µg mL^{-1} (2.00 µM) to 33.52 µg mL^{-1} (60.00 µM)
Regression equation:	*y = 4.576x + 0.283
Slope	4.576
Intercept	0.283
Correlation coefficient (R^2)	0.9994
RSD	3.8 %

*y = nA, x = concentration of atorvastatin (µg mL^{-1})

Calibration curves: Calibration curves for the determination of atorvastatin using differential pulse polarographic analysis on dropping mercury electrode with negative amplitude in borax buffer at pH 7.5 were applied. The peak current (I_p) was proportional to the concentration of atorvastatin over the ranges 2-60 µM (1.117-33.52 µg mL^{-1}), the regression equation and correlation coefficient (R^2) were as the follows: y = 4.576x + 0.283, R^2 = 0.9994; y: I_p, nA and x: C_{AT}, µg mL^{-1} (Fig. 5).

Analytical results: Determination of atorvastatin using differential pulse polarographic analysis on dropping mercury electrode with negative amplitude in borax buffer at pH 7.5 using analytical curves, $I_p = f(CAT)$, showed that the accuracy was ready over the ranges of atorvastatin concentration between 1.117-33.52 mg mL^{-1} and relative standard deviation (RSD) not more than 3.8 %, see Table-2. Limit of detection (LOD) and limit of quantitation (LOQ) for the determination of atorvastatin by this method were as the follows : 0.136 and 0.413 mg mL^{-1}, respectively.

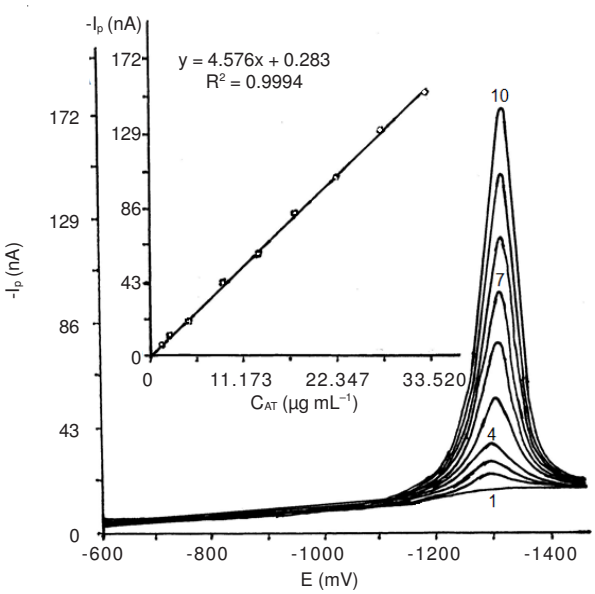

Fig. 5. Polarogramsin the optimum conditions using DPPA at DME of atorvastatin at concentrations: 1) 0; 2) 1.117; 3) 2.234; 4) 4.468; 5) 8.936; 6) 13.404; 7) 17.872; 8) 22.340; 9) 27.925; 10) 33.52 mg mL^{-1} and calibration curve (pH7.5)

Applications: Many applications for the determination of atorvastatin in some Syrian pharmaceutical preparations using differential pulse polarographic analysis on dropping mercury electrode with negative amplitude in borax buffer at pH 7.5 were proposed. Standard addition curves for determination of atorvastatin in different Syrian pharmaceutical preparations (atorvex, atorvatin, lipito-med, lipostatin and atoraz) were used. The standard addition curve of atorvex (10 mg/tab.) was showed in Fig. 6. Regression equations and correlation coefficients were included in Table-3. Standard addition curves for determination of atorvastatin in different Syrian pharmaceutical preparations were used. The amount

TABLE-2
DETERMINATION OF ATORVASTATIN USING DIFFERENTIAL PULSE POLAROGRAPHIC ANALYSIS ON DROPPING MERCURY ELECTRODE WITH NEGATIVE AMPLITUDE IN BORAX BUFFER AT pH 7.5

x_i, µg mL^{-1} (Taken)	$\bar{x}$ *, µg mL^{-1} (Found)	SD, µg mL^{-1}	$\frac{SD}{\sqrt{n}}$, µg mL^{-1}	$\bar{x} \pm \frac{t.SD}{\sqrt{n}}$, µg mL^{-1}	RSD (%)
1.028	1.02	0.039	0.017	1.02 ± 0.048	3.8
2.055	2.06	0.076	0.034	2.06 ± 0.094	3.7
4.110	4.12	0.14	0.062	4.12 ± 0.174	3.5
8.221	8.25	0.27	0.121	8.25 ± 0.335	3.3
12.332	12.32	0.38	0.170	12.32 ± 0.472	3.1
16.442	16.46	0.50	0.224	15.71 ± 0.621	3.0
20.553	20.55	0.62	0.277	23.67 ± 0.770	3.0
25.69	25.70	0.80	0.358	25.70 ± 0.993	3.1
30.83	30.78	0.98	0.438	30.78 ± 1.217	3.2

*n = 5, t = 2.776

TABLE-3
REGRESSION EQUATIONS AND CORRELATION COEFFICIENTS FOR DETERMINATION OF ATORVASTATIN IN SYRIAN PHARMACEUTICAL PREPARATIONS USING DIFFERENTIAL PULSE POLAROGRAPHIC ANALYSIS ON DROPPING MERCURY ELECTRODE WITH NEGATIVE AMPLITUDE IN BORAX BUFFER AT pH 7.5

Pharmaceutical preparations	Atorvastatin in tab (mg)	Operating modes		
		Regression equations*	Correlation coefficients	Amount of atorvastatin (m) (mg/tab)
Atorvex, ctd. tab. Asia	10	y = 4.575x + 18.70	R^2 = 0.9988	$m_{AT/tab.}$ = 2.5 m' = 10.22
pharmaceutical industries	20	y = 4.576x + 19.07	R^2 = 0.9989	$m_{AT/tab.}$ = 5 m' = 20.84
Aleppo–SYRIA	40	y = 4.575x + 18.67	R^2 = 0.9991	$m_{AT/tab.}$ = 10 m' = 40.80
Atorvatin, Ctd. tab. Alpha	10	y = 4.578x + 18.10	R^2 = 0.9981	$m_{AT/tab.}$ = 2.5 m' = 9.88
Aleppo Pharmaceutical	20	y = 4.572x + 18.42	R^2 = 0.9987	$m_{AT/tab.}$ = 5 m' = 20.14
Industries - SYRIA	40	y = 4.579x + 18.30	R^2 = 0.9989	$m_{AT/tab.}$ = 10 m' = 40.0
Lipito-med, Ctd.tab.	10	y = 4.574x + 18.22	R^2 = 0.9985	$m_{AT/tab.}$ = 2.5 m' = 9.96
Medico Labs.	20	y = 4.577x +18.86	R^2 = 0.9987	$m_{AT/tab.}$ = 5 m' = 20.60
Homs–SYRIA	40	y = 4.573x + 18.38	R^2 = 0.9990	$m_{AT/tab.}$ = 1 0 m' = 40.20
Liostatin, ctd. tab. Ibn Ai	10	y = 4.576x + 18.87	R^2 = 0.9984	$m_{AT/tab.}$ = 2.5 m' = 10.31
Haytham, Pharma Industries	20	y = 4.574x + 18.61	R^2 = 0.9986	$m_{AT/tab.}$ = 5 m' = 20.34
Co., Aleppo–SYRIA	40	y = 4.577x + 18.51	R^2 = 0.9991	$m_{AT/tab.}$ = 10 m' = 40.44
Atoraz, Ctd.tab. Razi	10	y = 4.575x + 17.79	R^2 = 0.9980	$m_{AT/tab.}$ = 2.5 m' = 9.72
pharmaceutical industries	20	y = 4.577x + 18.23	R^2 = 0.9983	$m_{AT/tab.}$ = 5 m' = 19.92
Aleppo–SYRIA	40	y = 4.576x + 18.39	R^2 = 0.9987	$m_{AT/tab.}$ = 10 m' = 40.20

*y = n A, x = concentration of atorvastatin (μg mL^{-1}) = m' = intercept/slope

TABLE-4
DETERMINATION OF ATORVASTATIN IN SYRIAN PHARMACEUTICAL PREPARATIONS USING DIFFERENTIAL PULSE POLAROGRAPHIC ANALYSISON DROPPING MERCURY ELECTRODE WITH NEGATIVE AMPLITUDE IN BORAX BUFFER AT pH 7.5

Commercial name	Contents (mg/tab)	*$\overline{x}$, (mg/tab)	RSD (%)	Recovery (%)
Atorvex, ctd. tab., Asia	10	10.22	3.6	102.2
Pharmaceutical Industries	20	20.84	3.5	104.2
Aleppo–SYRIA	40	40.80	3.4	102.0
Atorvatin, ctd. tab., Alpha	10	9.88	3.7	98.8
Aleppo Pharmaceutical Industries,	20	20.14	3.6	100.7
Aleppo–SYRIA	40	40.00	3.4	100.0
Lipito-med, Ctd. tab.	10	9.96	3.7	99.6
Medico Labs.	20	20.60	3.5	103.0
Homs–SYRIA	40	40.20	3.4	100.5
Liostatin, ctd. tab. Ibn Al	10	10.31	3.6	103.1
Haytham, Pharma Industries Co.	20	20.34	3.5	101.7
Aleppo–SYRIA	40	40.44	3.4	101.1
Atoraz, Ctd. tab. Razi	10	9.72	3.8	97.2
pharmaceutical industries	20	19.92	3.6	99.6
Aleppo–SYRIA	40	40.20	3.5	100.5

*n = 5

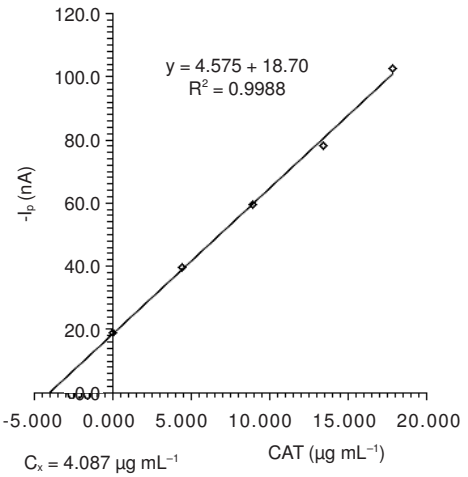

Fig. 6. Standard addition curve for determination of atorvastatin in atorvex (10 mg/tab.) using differential pulse polarographic analysis on dropping mercury electrode with negative amplitude in borax buffer at pH 7.5

(m) of atorvastatin in one tablet by mg/tab (m_{AT}/tab.) calculated from the following relationship: m = h.m', where: m' is the amount of atorvastatin in tablet, which calculated from the standard additions curve according to the following regression equation: y = a.x + b; when y = 0; m' = x = b/a = intercept/slope (μg mL^{-1}) and h conversion factor is equal to 2.5, 5.0 and 10 for all pharmaceuticals content 10, 20 and 40 mg/tab, respectively.The results of quantitative analysis for atorvastatin in the pharmaceutical preparations using this method were included in Table-4. The proposed method was simple, economic, accurate and successfully applied to the determination of atorvastatin in pharmaceuticals. The results obtained agree well with the contents stated on the labels.

Conclusion

New, simple and rapid differential pulse polarographic analysis on dropping mercury electrode with negative amplitude in borax buffer at pH 7.5 was developed for determination of atorvastatin in pure form and in pharmaceutical formulations.

One reduction peak was observed in the range -1310 to -1340 mV (E_p). The peak current I_p is linear over the ranges 2.00-60.00 µM. The relative standard deviation did not exceed 3.8 % for the concentrations of atorvastatin 1.117 µg mL^{-1}. Regression analysis showed a good correlation coefficient ($R^2 = 0.9994$) between I_p and concentration over the range of 1.117-33.52 µg mL^{-1}. The LOD and the LOQ were to be 0.129 µg mL^{-1} and 0.390 µg mL^{-1}, respectively. The proposed method was successfully applied to the analysis of atorvastatin in pure and pharmaceutical dosage forms with average recovery of 97.2 to 104.2 %. The results obtained agree well with the contents stated on the labels.

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