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Chemically modified carbon paste ion-selective electrodes for determination of atorvastatin calcium in pharmaceutical preparations

Salwa Fares Rassi

Department of Chemistry, Faculty of Sciences, University of Al-Baath, Homs, Syria

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ABSTRACT

A simple, rapid and sensitive method for the determination of atorvastatin calcium in pharmaceutical preparations using two modified carbon paste electrodes was developed. One electrode (sensor A) is based on ion-pair of atorvastatin with 5,6-diaminouracil hydrochloride (ATS-DAUH) and the other (sensor B) is based on atorvastatin with picric acid (ATS-PC). Among three different solvent mediators tested, dioctylphthalate (DOPH) exhibited a proper behavior including Nernstian slopes of the calibration curve at 58.76 ± 0.8 and 57.48±1 mV per decade for sensors A and B. The response times were 10 and 12 s, detection limits 1.3×10^{-6} and 2.2×10^{-6} M; the concentration range 2.5×10^{-6}-7.9×10^{-2} M and 3.0×10^{-6} to 7.9×10^{-2} M respectively. The present electrodes show good discrimination of atorvastatin calcium from several inorganic, organic ions, sugars and some common excipients. The sensors were applied for the determination of atorvastatin calcium in pharmaceutical preparations using standard addition and the calibration curve methods. The results obtained were satisfactory with excellent percentage recovery comparable and sometimes better than those obtained by other routine methods for the assay. The proposed potentiometric methods offer the advantages of simplicity, accuracy, automation feasibility and applicability to turbid and colored sample solutions.

1. Introduction

Atorvastatin calcium (ATS) is chemically 1H-pyrrole-1-heptanoic acid, [R-(R*,R*)]-2-(4-flurophenyl)-β,δ-dihydroxy-5-(1-methylethyl)-3-phenyl-4-[(phenylamino)carbonyl], calcium salt tri hydrate (2:1). Atorvastatin calcium is an inhibitor of 3-hydroxy-3-methyl glutaryl coenzyme A (HMG-Co A) reductase. This enzyme catalysis the conversion of HMG-Co A to mevalonate, an early and rate limiting step in cholesterol biosynthesis [1,2]. Literature survey revealed that extractive spectrophotometry [3,4], liquid chromatographic (LC) [5–9], GC-MS [10], LC-MS [11,12], LC- electrospray tandem mass spectrometry [13–15] and HPTLC [16], RP-HPLC/UV [17–19], Voltammetry [20,21], British Pharmacopoeia [22], pharmaceutical preparations [23], along with impurities in pharmaceutical preparations [24,25], in combination with amlodipine [26], nicotinic acid [27] and ezetimibe [28] in dosage forms. An UPLC method [29] for simultaneous determination of atorvastatin, fenfibrate and their degradation products in tablets has also been reported.

Atorvastatin has been determined along with its metabolites using LC/MS in biological matrices [30–34], HPLC-UV methods have also been reported for the determination of atorvastatin alone in biological matrices [35,36].

In the present paper a simple potentiometric chemically modified carbon paste electrode for the determination of atorvastatin calcium is presented. Attempts have been made to lower detection limit and widen the concentration range by using three plasticizers and different ion-associations. The sensors based on the ion-association (ATS-DAUH) (sensor A) and the ion-association (ATS-PC) (sensor B) plasticized with dioctylphthalate (DOPH)) show a sensitive response with good performance characteristics. These electrodes were found to give accurate results for the determination of atorvastatin in pharmaceuticals.

2. Experimental

2.1. Apparatus

Potentiometric and pH measurements were carried out using a digital Shott Gerate pH meter, were made with Consort C 830 (Belgium) with combined glass pH electrode. A water bath shaker

E-mail address: rassi.salwa@gmail.com.

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(Grant instruments, Cambridge Ltd, England) was used to control the temperature of the test solutions. A saturated calomel electrode (SEC) was used as the external reference Mettler from Switzerland, NMR Spectrometry Bruker,400 MHz. FT/IR 4100(Fourier transform infrared spectrometer) Jasco. The electrochemical system of the ATS carbon paste electrodes would be represented as carbon paste electrode |test solution ||saturated calomel electrode.

2.2. Reagents and materials

All chemicals and reagents used throughout this work were of analytical-reagent grade and solutions were made with doubly distilled water. Graphite powder, dioctylphthalate (DOPH), dibutylphthalate (DBPH), tri−n-butyl phosphate (TBP) were supplied by BDH and picric acid was obtained from Fluka Chemical Co. and chloride or nitrates salts of all cations, investigated as interferences were used as received from Merck.

Atorvastatin calcium, $(C_{33}H_{34}FN_2O_5)_2Ca\cdot 3H_2O$, 1209.42 g mol^{-1}, was supplied by CADILA Healthcare (Gujarat, India). Its purity was found to be 98.3% according to the compendial method. (Fig. 1). 5,6 diaminouracil Hydrochloride DAUH ($C_4H_8N_4O_2Cl_2$, 215 g mol^{-1}) was **synthesized** and identified in laboratory by IR and NMR [37]. Chemical structures of DAUH, is shown in (Fig. 2).

2.3. Formulations

The following commercial formulations were subjected to the analytical procedures:

- Atoraz tablets (Razi Labs, Syria) labeled to contain 40 mg ATS/tablet.
- Lowlip tablets (Al Fares-Industries Co., Syria) labeled to contain 20 mg ATS/tablet

2.4. Solutions

Stock solutions, 10^{-2} M DAUH, ATS, PC were prepared by dissolving the accurately weighed amounts of the pure solid in doubly distilled water or methanol, Stock solutions of 1 M for each of LiCl, NaCl, KCl, NH_4Cl, $CaCl_2$, $MgCl_2$, $BaCl_2$, $ZnCl_2$, $MnSO_4$, $Ni(NO3)_2$, $Co(NO3)_2$, $Cu(NO3)_2$, $Pb(NO3)_2$, $FeCl_3$, $AlCl_3$, $CrCl_3$, glucose, fructose, lactose, starch, microcrystalline cellulose, carboxymethylcellulose, polyethyleneglycol, titaniumdioxide, and polysorbate 80 were prepared by dissolving the appropriate amount of the compounds. More diluted solutions were prepared by subsequent dilutions of the stock solutions. Solutions of sodium hydroxide and hydrochloric acid of concentrations within the range 0.1–1.0 M were used for adjusting the pH of the medium, while 0.5 M NaCl solution was used for adjusting the ionic strength, All solution stored in dark bottles and kept in the refrigerator.

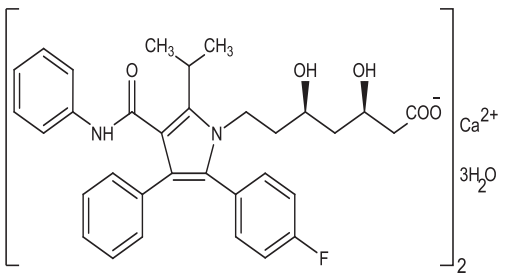

Fig. 1. Chemical structure of Atorvastatin Calcium.

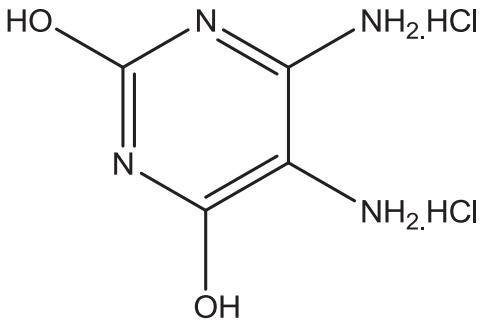

Fig. 2. Chemical structure of 5,6-Diaminouracil Hydrochloride.

2.5. Preparation of ion-pair

The ion-pair ATS-DAUH and ATS-PC were prepared by adding 50 mL of 0.01 M DAUH hot solution and 50 mL of PC to appropriate volume of 0.01 M of ATS. The formed precipitates were filtered off, washed thoroughly with distilled water, dried at room temperature and ground to a fine powder.

The composition of the ion-pair was confirmed by elemental analysis and found to be 1:1 (ATS-DAUH) and (ATS-PC).

2.6. Preparation of the electrode

Modified carbon paste electrode was prepared by thoroughly mixing weighed amounts of ion pair (ATS-DAUH), (ATS-PC) with high purity graphite and dioctylphthalate until obtaining a uniformly wetted paste. The mixture was packed in the end of a polypropylene syringe (3 mmi d., 1 mL). Electrical contact to the carbon paste was made by a copper wire. The carbon paste was smoothened onto paper until it had a shiny appearance and was used directly for potentiometric measurements without preconditioning requirements.

2.7. Selectivity coefficient determination

The selectivity coefficients of the electrode towards different cationic species, sugars and amino acids were determined by The separate solution method (SSM) and the matched potential method (MPM) [38] are employed to determine the selectivity coefficients $K^{Pot}_{Durg,J^{z+}}$ of the potentiometric sensors towards different species using this equation in SSM

$$K^{Pot}_{Drug,J^{z+}} = \frac{E_2 - E_1}{S} + \log[\text{Drug}] - \log\left[J^{z+}\right]^{1/z} \quad (1)$$

where E_1 is the potential for the drug ion, E_2 for the interfering ion J with charge z and S the slope of the calibration graph and this equation for matched potential method (MPM).

$$K^{Pot}_{Drug,J^{z+}} = \frac{a_{Drug}}{a_J} \quad (2)$$

where a_J is the activity of the added interfering.

2.8. Construction of calibration graphs

The performance of the electrodes obtained was investigated by measuring e.m.f. values of 1.0×10^{-6}-5.0×10^{-2} M of ATS. The electrodes were calibrated by added suitable volumes of 1.0×10^{-1} M working solution of ATS successively in 50 ml of water to generate a total concentration ranging from 1.0×10^{-6}-

1.0×10^{-1} M ATS, and subjected to potentiometric measurements using the carbon paste and saturated calomel electrodes. The potential readings of the stirred solutions were measured at (25 ± 1 °C), after each addition. The values were plotted versus the negative logarithmic value of the drug concentration, pATS (-log [ATS]). The constructed calibration graphs were used for subsequent measurements of unknown ATS test solutions.

2.9. Standard addition method

ATS was determined using the prepared electrodes by the standard addition method [39]. Small increments of standard ATS solution were added to 50-ml aliquot of samples of various concentrations. The change in potential (at 25 ± 1 °C) was recorded for each increment. We could determine the concentration of the testing sample using the equation:

$$C_X = C_s V_s \Big/ \left[(V_x + V_s) \times 10^{\Delta E/S} - V_x \right] \quad (3)$$

where C_x and V_x are the concentration and the volume of an unknown sample, C_s and V_s are the concentration and the volume of the standard, respectively S is the slope of the calibration graph (mV decade^{-1}), and ΔE is the change in the potential (mV).

2.10. Analysis of ATS in pharmaceutical formulations

Pharmaceutical formulation solutions: For tablets, twenty tablets were accurately weighed and finely powdered. The required amount of powder was weighed, dissolved in about 15 ml methanol, filtered in a 50 ml-volumetric flask, volume was completed with distilled water. The standard addition and direct methods were then applied.

3. Results and discussion

3.1. Influence of membrane composition

3.1.1. Ion-pair selection

At the outset, an ion-exchanger of atorvastatin (ATS) with 5,6-diaminouracil hydrochloride DAUH, picric acid PC-H. was prepared then electrodes containing some or no ion-pair were made and their emf measured at various concentrations of the drug. The paste with no ion-pair showed no response (composition # 1). The electrode that contain ATS-DAUH (composition # 5) and the ATS-PC (composition # 13) gave the best results with a response according to (Table 1). The results clearly indicate that the electrode containing 0.1–0.5 wt% ATS-DAUH and the one containing the ion pairs ATS-PC have a sub-Nernstian slope. In order to obtain Nernstian response, the electrodes must have sufficient amount of lipophilic ion-pair. That was observed for sensor A containing 1.5 wt% ATS-DAUH and for sensor B containing ATS-PC which exhibited improved sensitivity and working range. However, increasing the wt% above 3.0–10.0 turns the membrane turbid and the response deteriorates due to in homogeneity in the membrane and possible saturation of the paste [40].

3.1.2. The graphite/plasticizer (g/p) ratio study

It is well known that the sensitivity and selectivity of the electrode depend on (g/p) ratio used [41]. The (g/p) ratios of 0.909–1.4385 were examined as shown in (Table 2). It was observed that the highest useful ratio of (g/p) considered was 1.0, that is likely due to the optimum physical properties that ensured high enough mobilities of their constituents [42]. Pastes with (g/p) more than 1.438 produced “crumbly” pastes and those with ratio smaller than 0.90 had a consistency resembling that of “peanut butter”, i.e., not workable.

3.1.3. Solvent mediators effect

The plasticizer influences the mobility of the ion-pair through extraction of both ions into the organic phase. Therefore, it is necessary to use other plasticizers with different physical parameters such as dielectric constant (ε), lipophilicity (log P_{TLC}), viscosity (η) and molecular weight (M.wt).

In this work three solvent mediators were used to explore this effect. Their properties, with the corresponding response characteristic of the tested electrodes are listed in (Table 3). It was found that DOPH improved the selectivity of the electrode. The best performance, in terms of slopes, linear range, detection limit and response time obtained have the following order: DOPH > DBPH > TBP. From (Fig. 3). DOPH has a polarity, and high lipophilicity to avoid exudation and to considerably affect dissolution of ion-exchanger within the paste. This effect is due to increasing its partition coefficient property to it compared with other plasticizers (see Fig. 4).

Out of the electrodes tested, compositions # 5 and # 13 have the shortest response time, Nernstian slope and maximum working

Table 1
Characteristics of the ATS-CMCPEs evaluated from the calibration curves. The optimization of the carbon paste ingredients.

NO	Ion -exchanger	Composition (%)			Slope		Detection
		Graphite	Ion -exchanger	Plasticizer	(mV/decade)	Linear Range (M)	Limit (M)
1	–	50.00	0.0	50.00	16.18	9.2×10^{-4}-2.0×10^{-3}	6.3×10^{-4}
2	ATS-DAUH	49.95	0.1	49.95	35.72	8.0×10^{-5}-2.0×10^{-3}	6.1×10^{-5}
3	ATS-DAUH	49.74	0.5	49.75	44.68	4.5×10^{-6}-6.3×10^{-2}	3.1×10^{-5}
4	ATS-DAUH	49.50	1.0	49.50	56.35	3.8×10^{-6}-6.4×10^{-2}	2.1×10^{-6}
5	ATS-DAUH	49.25	1.5	49.25	58.76	2.5×10^{-6}-7.9×10^{-2}	1.3×10^{-6}
6	ATS-DAUH	49.00	2.0	49.00	54.67	4.2×10^{-6}-5.3×10^{-2}	3.3×10^{-6}
7	ATS-DAUH	48.75	2.5	48.75	51.59	6.8×10^{-5}-5.9×10^{-2}	4.3×10^{-5}
8	ATS-DAUH	48.50	3.0	48.50	49.31	7.4×10^{-5}-3.7×10^{-2}	5.9×10^{-5}
9	ATS-DAUH	47.50	5.0	47.50	45.69	8.8×10^{-5}-2.1×10^{-2}	6.5×10^{-5}
10	ATS-DAUH	45.00	10.0	45.00	41.95	9.5×10^{-5}-1.7×10^{-2}	7.3×10^{-5}
11	ATS-PC	49.75	0.5	49.75	41.75	9.9×10^{-6}-6.8×10^{-2}	6.1×10^{-5}
12	ATS-PC	49.50	1.0	49.50	55.98	5.8×10^{-6}-7.2×10^{-2}	4.1×10^{-6}
13	ATS-Pc	49.25	1.5	49.25	57.78	3.0×10^{-6}-7.2×10^{-2}	2.2×10^{-6}
14	ATS-PM	49.50	1.5	49.50	49.54	4.3×10^{-5}-6.8×10^{-2}	2.3×10^{-5}
15	ATS-DAUH	53.25	1.5	45.25	55.13	3.1×10^{-6}-3.2×10^{-2}	1.9×10^{-6}
16	ATS-DAUH	52.50	1.5	46.00	55.98	3.2×10^{-6}-4.3×10^{-2}	2.3×10^{-6}
17	ATS-DAUH	51.25	1.5	47.25	56.02	3.2×10^{-6}-6.8×10^{-2}	1.8×10^{-6}
18	ATS-DAUH	50.00	1.5	49.50	55.13	2.9×10^{-6}-6.7×10^{-2}	1.5×10^{-6}

Table 2
Effect of g/p on the characteristics of sensor A and sensor B.

Compositions			G/P	Sensor	S (mV/decade)	C.R(M)	LOD	R(S)
Ion -exchanger	G	P						
1.5	46.90	51.60	0.909	S_A	54.83	3.8×10^{-5}-7.9×10^{-2}	1.4×10^{-5}	15
				S_B	51.71	2.7×10^{-5}-7.9×10^{-2}	9.3×10^{-5}	15
1.5	49.25	49.25	1.000	S_A	58.76	2.5×10^{-6}-7.9×10^{-2}	1.3×10^{-6}	10
				S_B	57.48	3.0×10^{-6}-7.9×10^{-2}	2.2×10^{-6}	12
1.5	54.50	44.00	1.239	S_A	52.95	4.6×10^{-5}-7.9×10^{-2}	2.6×10^{-5}	15
				S_B	53.31	3.4×10^{-5}-7.9×10^{-2}	1.0×10^{-5}	15
1.5	58.10	40.40	1.438	S_A	50.91	6.1×10^{-5}-7.9×10^{-2}	4.1×10^{-5}	20
				S_B	49.86	5.1×10^{-5}-7.9×10^{-2}	2.9×10^{-5}	20

S: slope (mV/decade), C.R.: concentration range (M), LOD: limit of detection, R(s): response time(s), S_A: sensor A(ATS-DAUH), S_B: sensor B (ATS-Pc).

Table 3
Effect of physical parameters of different plasticizers on characteristics of electrodes.

Physical parameters					S (mv/deacde)	Response characteristics			
	DC	$logP_{TLC}$	V(η)	M.wt		D.R(M)	$R_{(S}$	LOD(M)	RSD%
DOPH	5.1	7.1	39.0	390	58.76	2.5×10^{-6}-7.9×10^{-2}	10	1.3×10^{-6}	0.66
DBPH	6.4	4.5	15.7	278	57.78	1.5×10^{-5}-8.1×10^{-2}	12	5.4×10^{-5}	0.98
TBP	8.0	4.0	3.4	266	50.92	2.7×10^{-4}-8.12×10^{-3}	25	1.5×10^{-4}	1.32

D.C, Dielectric constant; $logP_{TLC}$ lipophilicity; V,Viscosity; M.wt, molecular weight; S, slope; D.R(M), dynamic range; R(S), response time; LOD(M), limit of detection; RSD, relative standard deviation.

Table 4
Response characteristics of electrodes.

Electrode number	A	B
Plasticizer	DOP	DOP
Ion-pair	ATS-DAUH	ATS-Pc
Parameter		
Slope mV/decade^{-1}	58.76	57.48
Correlation coefficient	0.999	0.999
Linearity range (M)	2.5×10^{-6}-7.9×10^{-2}	3.0×10^{-6}-7.2×10^{-2}
Lower detection limit(M)	1.3×10^{-6}	2.2×10^{-6}
Response time(s)	≤10	≤12
Working pH range	2.0–8.0	3.2–8.5
Temperature °C	25	25
Life time (day)	93	50

concentration. Composition # 5 provided a lower detection limit. Based on these findings, sensor A and B were selected for further study and their electrochemical performance characteristics were systematically evaluated according to IUPAC recommendations, and the results are compiled in (Table 1). LOD was calculated from (Fig. 6).

3.2. Effect of temperature

To investigate the thermal stability of the electrode, calibration curves were constructed at different temperatures covering the range 25–60 °C. The electrode exhibited good Nernstian behavior in the range of 25–50 °C. The results are shown in However, at temperatures higher than 50 °C the slopes show a significant deviation. This deviation may be related to destruction of the electrode surface.

3.3. pH dependence

The influence of pH of the test solution on the response of the proposed electrodes the for (1.0×10^{-2}., 1.0×10^{-3},1.0×10^{-4},1.0×10^{-5} M) ATS solution was tested by following the potential variation in the pH range 1–12. The electrode response for different ATS concentration was tested at various pH values, each time being adjusted by using hydrochloride acid or sodium hydroxide solution. Potential -pH plots the results are given in (Fig. 5). As is obvious, the proposed electrodes could be suitably within the pH rang 2.0–8.0, the potentials remain constant did not vary by more than, ±0.5mv. At higher pH (pH > 8) values the potential decrease may be due to the formation of free atorvastatin base in the test solution.

3.4. Calibration graphs

Using the optimized electrodes composition and conditions described above, the potentiometric response of the electrode was

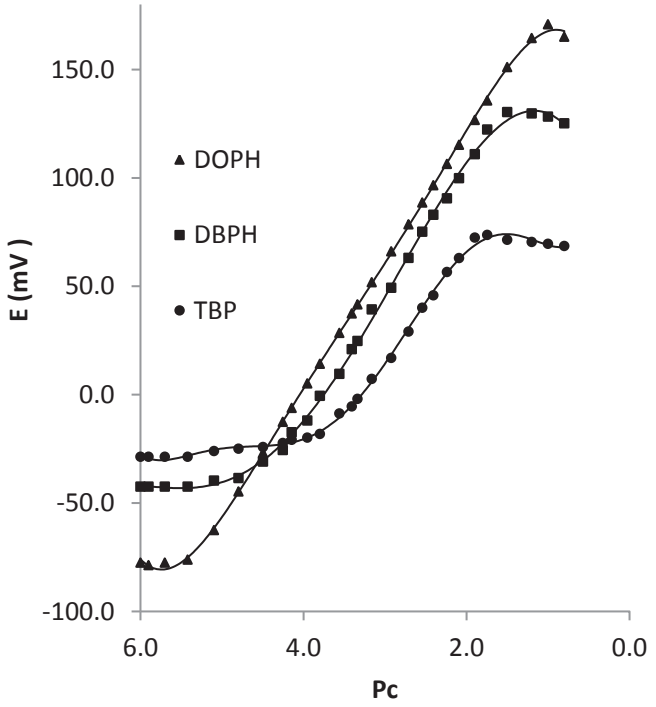

Fig. 3. Effect of the nature of plasticizers on the response of electrode A.

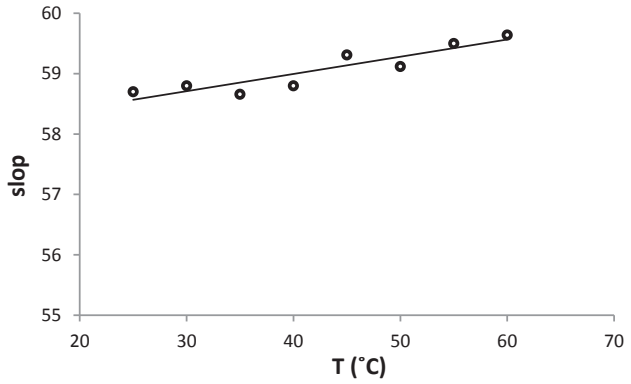

Fig. 4. Effect of the temperature of the test solution on the potential response of the electrode.

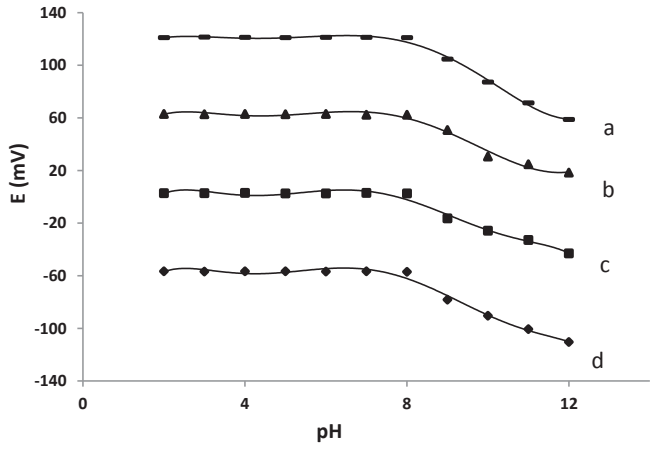

Fig. 5. Effect of the pH on the response of the electrode A (a = 1 × 10^{-2} M, b = 1 × 10^{-3} M, c = 1 × 10^{-4} M, d = 1 × 10^{-5} M).

studied based on the ATS concentration in the range of 1 × 10^{-6}- 1 × 10^{-1} M. The calibration curves for the electrodes A and B containing DOP as plasticizer gave an excellent linear response from 2 × 10^{-6}– 7.9 × 10^{-2} M, as shown in (Fig. 6). Higher than 7.9 × 10^{-2} M electrodes didn't response to changes in the concentration of the ATS. The results given in (Table 4) show the characteristics Performance of the electrodes.

The least squares equation obtained from the calibration data is as follows:

$$E(mV) = S \times \log([ATS, M] + intercept)$$

where E is the potential and S the slope of the electrodes.

3.5. Response time

The response time [43] of each electrode was tested by measuring the time required to achieve a steady state potential (within ±1 mV)

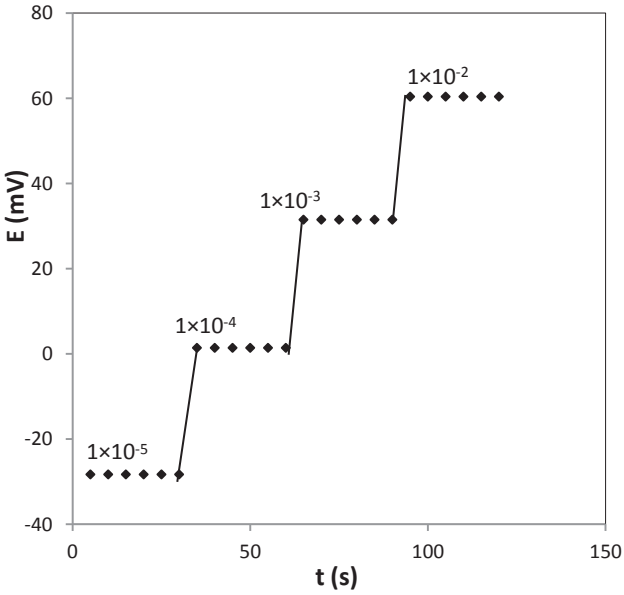

Fig. 7. Potential–time plot for the response of ATS-DAUH.

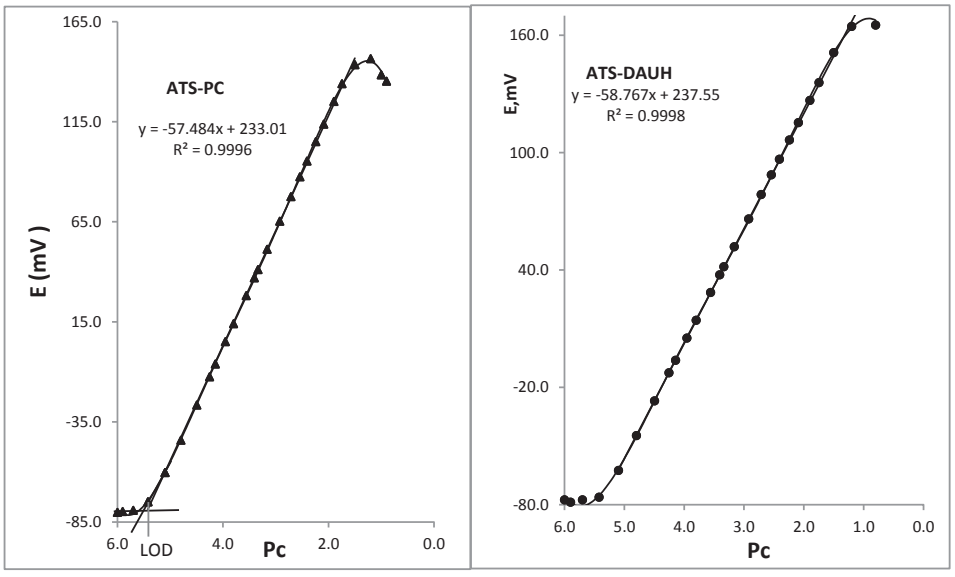

Fig. 6. Calibration graph of ATS electrodes.

Table 5
Effect of soaking time on ATS-CMCPEs.

Soaking time	Slope (mV/decade)	Linear range (M)	Response time (tresp) (s)
ATS-DAUH			
1 h	58.78 ± 0.8	2.5×10^{-6}-7.9×10^{-2}	≤10
24	58.82 ± 0.7	2.5×10^{-6}-7.9×10^{-2}	≤10
3days	58.73 ± 0.5	2.5×10^{-6}-7.9×10^{-2}	≤10
5	58.56 ± 0.7	3.1×10^{-6}-7.9×10^{-2}	≤10
10	58.61 ± 0.8	4.5×10^{-6}-7.9×10^{-2}	≤10
15	58.76 ± 0.7	2.5×10^{-6}-7.9×10^{-2}	≤10
20	57.91 ± 0.9	2.5×10^{-6}-7.9×10^{-2}	≤10
25	58.56 ± 0.7	5.3×10^{-6}-7.9×10^{-2}	≤8
30	59.02 ± 0.5	5.9×10^{-6}-7.9×10^{-2}	≤8
40	59.86 ± 0.4	6.2×10^{-6}-7.9×10^{-2}	≤8
50	59.49 ± 0.6	2.5×10^{-6}-7.9×10^{-2}	≤8
60	60.12 ± 0.7	2.5×10^{-6}-7.9×10^{-2}	≤8
65	58.42 ± 0.6	2.5×10^{-6}-7.9×10^{-2}	≤8
70	57.68 ± 0.7	3.3×10^{-6}-7.9×10^{-2}	≤8
80	57.34 ± 0.8	4.9×10^{-6}-7.9×10^{-2}	≤8
85	56.23 ± 0.9	5.5×10^{-6}-7.9×10^{-2}	≤8
90	55.64 ± 1.0	3.5×10^{-6}-7.9×10^{-2}	≤8
93	54.83 ± 0.9	2.5×10^{-6}-7.9×10^{-2}	≤8
95	51.98 ± 1.2	2.5×10^{-6}-7.9×10^{-2}	≤8
ATS-Pc			
1days	57.48 ± 1.0	3.0×10^{-6}-7.9×10^{-2}	≤12
10	57.18 ± 1.0	3.0×10^{-6}-7.9×10^{-2}	≤12
20	56.98 ± 0.9	3.0×10^{-6}-7.9×10^{-2}	≤12
25	57.05 ± 0.8	3.2×10^{-6}-7.9×10^{-2}	≤12
30	56.98 ± 0.9	4.1×10^{-6}-7.9×10^{-2}	≤12
40	57.28 ± 0.8	3.7×10^{-6}-7.9×10^{-2}	≤9
45	54.13 ± 0.4	3.2×10^{-6}-7.9×10^{-2}	≤9
50	51.25 ± 0.8	3.0×10^{-6}-7.9×10^{-2}	≤9
55	49.38 ± 1.0	3.0×10^{-6}-7.9×10^{-2}	≤9

Table 6
Selectivity coefficients of various interfering ions for sensor A (S_A) and sensor B (S_B).

MPM		SMS		Foreign
S_B	S_A	S_B	S_A	
1.90×10^{-4}	1.90×10^{-4}	2.30×10^{-4}	1.05×10^{-4}	Li^{+1}
2.14×10^{-4}	2.11×10^{-4}	3.22×10^{-4}	1.22×10^{-4}	K^{+1}
1.22×10^{-4}	6.42×10^{-4}	1.61×10^{-5}	9.09×10^{-5}	Na^{+1}
4.16×10^{-5}	3.69×10^{-5}	4.26×10^{-5}	5.56×10^{-5}	NH_4^+
4.63×10^{-5}	2.58×10^{-5}	2.25×10^{-5}	6.25×10^{-5}	Mg^{+2}
3.25×10^{-5}	4.37×10^{-5}	4.75×10^{-5}	6.45×10^{-5}	Mn^{+2}
2.58×10^{-5}	1.31×10^{-4}	3.81×10^{-4}	1.06×10^{-4}	Ca^{+2}
6.25×10^{-4}	5.48×10^{-5}	5.14×10^{-5}	7.14×10^{-5}	Ba^{+2}
1.96×10^{-5}	4.21×10^{-4}	2.13×10^{-5}	5.13×10^{-5}	Ni^{+2}
2.36×10^{-5}	3.95×10^{-4}	3.21×10^{-4}	5.81×10^{-4}	Cu^{+2}
4.68×10^{-4}	5.06×10^{-4}	5.39×10^{-4}	7.69×10^{-4}	Zn^{+2}
3.89×10^{-4}	6.21×10^{-5}	3.52×10^{-5}	9.52×10^{-5}	pb^{+2}
4.92×10^{-5}	3.23×10^{-5}	5.34×10^{-5}	7.81×10^{-5}	Cr^{+3}
2.89×10^{-5}	4.35×10^{-4}	4.17×10^{-4}	6.76×10^{-4}	Fe^{+3}
9.17×10^{-6}	9.05×10^{-6}	No response	No response	Glucose
4.54×10^{-6}	4.15×10^{-5}	No response	No response	Fructose
5.91×10^{-6}	6.70×10^{-6}	No response	No response	Lactose
9.11×10^{-6}	8.31×10^{-6}	No response	No response	starch
No response	No response	No response	No response	Microcrystalline cellulose
No response	No response	No response	No response	Carboxy methyl cellulose
No response	No response	No response	No response	polyethylene glycol
No response	No response	No response	No response	titanium dioxide
No response	No response	No response	No response	polysorbate 80

after successive immersion of the electrode in a series of its respective ion solution, each g having a 10-fold increase in concentration from 1×10^{-5}, 1×10^{-4}, 1×10^{-3}, 1×10^{-2} M. The electrodes gave steady potentials within 10,12 s using ATS-DAUH and ATS-PC electrodes. The potential readings remained constant, to within ±1 mV, for at least 5 min. Typical potential–time plots for the response characteristics of ATS-DAUH electrode are shown in (Fig. 7).

3.6. Effect of soaking

Freshly prepared electrodes can be used without soaking in dilute solution of ATS. The effect of soaking time on the performance of the carbon paste electrode surfaces was studied by measuring the slope of the calibration graphs for variable intervals of time starting from 1 h reaching to 4 months. The slope of the calibration graph for the ATS-DAUH electrode remained near

Table 7
Accuracy and precision for the determination of ATS using the proposed electrodes.in pure solution.

Electrode	Direct method				Standard-addition method		
	Taken M	Found M	RSD%	R%	Found M	RSD%	R%
A	5.0×10^{-5}	5.03×10^{-5}	2.35	100.6	4.9 × 10-5	2.40	98.0
	5.0×10^{-4}	5.05×10^{-4}	1.77	100.8	5.01 × 0-4	1.85	100.2
	2.5×10^{-3}	2.52×10^{-3}	1.58	100.4	2.51 × 10-3	0.97	100.4
	1.0×10^{-2}	1.00×10^{-2}	0.82	100.0	1.0 × 10-2	0.66	100.0
	5.0×10^{-2}	5.02×10^{-2}	0.49	100.4	4.99 × 10-2	0.55	99.8
B	5.0×10^{-5}	5.01×10^{-5}	2.03	100.2	5.04 × 10-5	2.61	100.8
	5.0×10^{-4}	4.98×10^{-4}	1.75	99.6	4.99 × 10-4	1.11	99.8
	2.5×10^{-3}	2.48×10^{-3}	1.23	99.2	2.49 × 10-3	1.03	99.6
	1.0×10^{-2}	0.99×10^{-2}	0.84	99.0	0.98 × 10-2	0.65	98.0
	5.0×10^{-2}	5.01×10^{-2}	0.61	100.2	5.01 × 10-2	0.30	100.2

Average of five determinations.

Table 8
Analysis of ATS in various tablets using standard addition, and the calibration curve method.

Sample		Nominal value mgATS/Tab	Potentiometry Direct	Official method	*t*-Value[b]	*F*-Value[b]
			R% ± SD[a]			
Atoraz	S_A	20mgATS/Tab	100.19 ± 0.45	100.56 ± 0.60	1.49	0.56
	S_B		100.38 ± 0.62		2.19	1.06
Atoraz	S_A	40mgATS/Tab	99.98 ± 1.49	100.38 ± 0.73	0.60	4.16
	S_B		100.19 ± 0.84		1.31	1.32
Lowlip	S_A	20mgATS/Tab	99.92 ± 0.78	99.86 ± 0.50	0.95	2.43
	S_B		100.04 ± 0.85		1.62	2.89
			Standard addition			
			R% ± SD[a]			
Atoraz	S_A	20mgATS/Tab	100.01 ± 0.94	100.56 ± 0.60	1.89	2.45
	S_B		100.23 ± 0.62		1.21	1.06
Atoraz	S_A	40mgATS/Tab	100.10 ± 0.96	100.38 ± 0.73	1.39	1.72
	S_B		100.13 ± 0.71		2.55	0.94
Lowlip	S_A	20mgATS/Tab	100.34 ± 0.64	99.86 ± 0.50	0.71	1.63
	S_B		99.93 ± 0.86		1.32	2.95

[a] Five independent analyses.
[b] Theoretical values for t- and F-values at four degree of freedom and 95% confidence limit are (t = 2.776) and (F = 6.26).

Nernstian for about 93 days and was found to be 54.83 ± 0.8 mV/concentration decade, before decreasing gradually to reach about 51.98 ± 1.2 mV/concentration decade after 95 days. Meanwhile, in the case of the ATS-PC electrode, the slope reached 51.25 ± 0.8 mV/concentration decade after 50days, then decreased gradually to reach about 49.38 ± 1.0 mV/concentration decade after 55 days. The results listed in (Table 5) indicate that the life span (t) is 93 days for the ATS-DAUH electrode, and 50 days for the ATS-PC- electrode. It is obvious that after cutting and polishing the electrode surface, the slopes of the electrodes increase again to reach about 58.0 mV/concentration decade.

3.7. Effect of foreign ions

The influence of some inorganic cations, sugars on the ATS electrodes and different excipients which may have been present in the pharmaceutical preparations were investigated. The selectivity coefficients were determined by the separate solution method (SSM) and matched potential method (MPM). None of the investigated species interfered, as shown by the very small values of $K^{Pot}_{Durg,J^{Z+}}$ as shown in (Table 6). This reflects a very high selectivity of the investigated electrodes towards ATS ion. Inorganic cations do not interfere because of the differences in ionic size, mobility and permeability as compared with ATS. The mechanism of selectivity is mainly based on the stereo specificity and electrostatic environment, and is dependent on how much fitting is present between the locations of the lipophilicity sites in two competing species in the bathing solution side and those present in the receptor of the ion-exchanger [44]. The electrodes exhibit good tolerance towards the common excipients of the tablets, i.e., glucose and lactose.

3.8. Validity of the proposed method

The accuracy and precision of the proposed methods were carried out by four determinations at five different concentrations using both direct and standard-addition methods. The precision and accuracy of the method expressed as percentage relative standard deviation as precision and % of deviation of the measured concentration (recovery %) as accuracy. The results obtained are within the acceptance range. Average recovery of (98.2–100.8)% and (98.0–100.8)%, percentage relative standard deviation (RSD%) (2.40–0.49) and (2.61–0.30)% respectively for sensor-A and B and for two methods. (Table 7) shows the values (RSD%), (R%) and for different concentrations of the ATS determined from the calibration curves and by using standard-addition methods.

3.9. Analytical applications

The investigated electrodes were used for the determination of ATS in pharmaceutical preparations using both direct and standard-addition methods. The direct method is the simplest for obtaining quantitative results. Direct determination of ATS in tablets were carried out using the developed electrodes. The results are summarized in (Table 8). The content of drug in its formulation had good agreement with the declared amount. The standard-addition method was applied, and equation (3) were used to calculate the concentration of ATS. the determination of the

concentration depends mainly on ΔE; hence, to obtain a noticeable ΔE, are needs to prepare a higher concentration of the standard. Results of the standard-addition method are given in (Table 8). The results were compared to those obtained using the official method [45]. The determination of ATS in its pharmaceutical formulations Atoraz and Lowlip gave an average recovery of (99.92–100.34%). Mean values were obtained with a Student's t- and F-tests at 95% confidence limits for four degrees of freedom. As shown in Table 8. The data reveal that results compare favorably with those obtained by Official methods. The results showed comparable accuracy (*t*-test) and precision (*F*-test), since the calculated values of *t*-tests and *F*-tests were less than the theoretical data. Value indicating no significant difference was found between the two methods.

4. Conclusions

The proposed CMCPEs electrodes based on the single ion-exchanger (ATS-DAUH) and ion-exchanger (ATS-PC) as the electroactive materials might be useful detectors and interesting alternative methods for the determination of [ATS] in different real samples. The present electrodes show high sensitivity, reasonable selectivity, fast static response, long-term stability and applicability over a wide pH range with minimal sample pretreatment. The presented methods for the determination of atorvastatin calcium with the prescribed electrodes are simple, sensitive, highly specific and advantageous over the previously described procedures for ATS determinations.

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