Chemistry and Materials Research
ISSN 2224- 3224 (Print) ISSN 2225- 0956 (Online)
Vol.7 No.8, 2015
www.iiste.org

Determination of Fluvastatin Sodium In Pharmaceutical Preparations Utilizing A Modified Carbon Paste Electrode

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Abstract

A simple, rapid and sensitive method for the determination of fluvastatin sodium (FLS) in pharmaceutical preparations using two modified carbon paste electrodes were developed. One electrode (sensor A) is based on ion-associations of fluvastatin sodium (FLS) with 5,6 diamino-2-thiouracil hydrochloride (DTUH) and the other (sensor B) with a mixture of FLS -with sodium cobaltinitrite (FLS-CoN) and (FLS-DTUH). Among three different solvent mediators tested, dioctylphthalate (DOPH), exhibited a proper behavior including Nernstian slopes of the calibration curve at 57.78±0.4 and 57.18±0.8mV per decade for sensors A and B. The response times were 8 and 5 s; detection limits 4.9×10^{-7} and 2.2×10^{-7} M; the concentration range 9.0×10^{-7}- 2.5×10^{-1} M and 7.3×10^{-7} -2.5×10^{-1}M respectively. The present electrodes show good discrimination of fluvastatin sodium (FLS) from several inorganic, organic ions, sugars and some common drug excipients. The sensors were applied for the determination of fluvastatin sodium in pharmaceutical preparations using potentiometric determination, 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

Keywords: key words, Potentiometric, modified carbon paste electrodes, fluvastatin sodium

1. Introduction

Fluvastatin sodium (FLS) is (3R,5S,6E)-rel-7-[3-(4-fluorophenyl)-1-(1-methylethyl)-1H-indol-2-yl]-3,5-dihyroxy-6-heptenoic acid monosodium salt Fig.1, is a competitive inhibitor of HMG-CoA reductase, which is responsible for the conversion of 3-hydroxy-3- methylglutaryl-coenzyme A (HMG-CoA) to mevalonate, a precursor of sterols including cholesterol. It is used to reduce triglycerides, LDL-cholesterol, apoliporotein B and to increase HDL cholesterol, in the treatment of hyperlipidaemias including hypercholesterolemia's and combined hyperlipidaemia. FLS is metabolized in the liver, primarily via hydroxylation of the indole ring at the 5 and 6-positions. N-dealkylation and beta-oxidation of the side-chain also occurs. The hydroxyl metabolites have some pharmacological activity, but do not circulate in the blood. FLS has two optical enantiomers, an active 3R, 5S and an inactive 3S, 5R form. FLS is 98% bound to plasma proteins (Walsh 2005 & Sweetman 2005 & Merck Inde 2001).

Literature survey reveals that FLS is official in U.S.P. (United States Pharmacopoeia 2007). Several electroanalytical methods are available for the determination of the latter compound by differential plus voltammetry (Jin Long & Xiu-Ping 2006), square-wave adsorptive-stripping voltammetry (SWAdSV) (Nevesa *et al*. 2008) in pharmaceutical preparations, cyclic voltammetry (Dogan *et al*. 2007) and variety of voltammetric techniques (Ozkan & Uslu 2002) in pharmaceutical dosage forms and biological fluids. FLS has been determined by capillary electrophoresis (CE) (Dogrukol-Ak *et al.* 2001), first derivative spectrophotometry (Erk 2002), High performance liquid chromatography (HPLC) with fluorescence detector (Al-Rawithi *et al*. 2003, Lanchote *et al*. 2001, Toreson & Eriksson 1996, Kalafsky & Smith 1993, Toreson & Eriksson 1997) and ultraviolet detector (Liu Yu *et al*. 2011, Gomes *et al*. 2009), Liquid chromatography/negative ion electrospray tandem mass spectrometry (Nirogi *et al.* 2006), Liquid chromatography/ electrospray mass spectrometry (Di Pietro *et al*. 2006), LC–MS/MS (Taillon *et al*. 2011), and gas chromatography/ negative ion chemical ionization mass spectrometry (Leis & Windischhofer 2005) in pharmaceutical formulations and biological samples

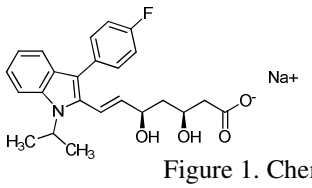

Figure 1. Chemical structure of Fluvastatin Sodium

The development and application of ion-selective electrodes for pharmaceutical analysis continue to be of interest because these sensors offer the advantage of simple design and operation, reasonable selectivity, fast response, applicability to colored and turbid solutions and possible interface with automated and computerized

systems (Cosofret 1991, Santini *et al*. 2008). For these advantages, ISEs found various applications: in clinical chemistry, environmental protection, water, soil, etc. and analytical chemistry in general (Zholt *et al*. 2008).

Over the past five decades, carbon paste, i.e., a mixture of carbon (graphite) powder and a binder (pasting liquid), has become one of the most popular electrode materials used for the laboratory preparation of various electrodes, sensors, and detectors. Chemically modified carbon paste electrodes, CMCPEs, possess important advantages such as ease of preparation, or regeneration, and very stable response in addition to very low Ohmic resistance (Svancara *et al*. 2009). Therefore, CMCPEs have found direct application in a variety of analytical situations, such as amperometry (Ozoemen, et al. 2004, Malongo *et al*. 2008), voltammetry (Mashhadizadeh & Akbarian 2009),]. These advantages drew the attention of researchers in recent years (Abu-Shawish *et al*. 2008, Gismera *et al*. 2006).

In the present work, a simple potentiometric chemically modified carbon paste electrode for the determination of fluvastatin sodium 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 single ion-association (FLS-DTUH) (sensor A) and the mixed ion-association (FLS-DTUH and FLS-CoN) (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 fluvastatin sodium in pharmaceuticals samples.

2. Experimental

2.1 Reagents

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) sodium cobaltinitrite (NaCoN) and phosphomolybdic acid (PMA) phosphotungstic acid (PTA) were supplied by BDH, and chloride or nitrates salts of all cations, investigated as interferences were used as received from Merck.

Fluvastatin sodium ($C_{24}H_{25}FNO_4Na$, 433.46g $mole^{-1}$) was supplied by ALPHARM Chemical Co (China)). Its purity was found to be 99.2% according to the compendial method.

5,6-diamino-2-thio ,Uracil hydrochloride (DTUH) (C4H7N4OSCl, 194.5 g mole-1) was synthesis Fig. 2 and identified in laboratory by IR and NMR..

IR - spectrum of compound Fig.3 shows absorption band at 2479 cm^{-1} due to S-H group and bands at

3460, 3328. 3390, 1666, 1536, and 1175 cm^{-1} which are characteristic of OH, NH2, C=C, C=N and C-N, respectively.

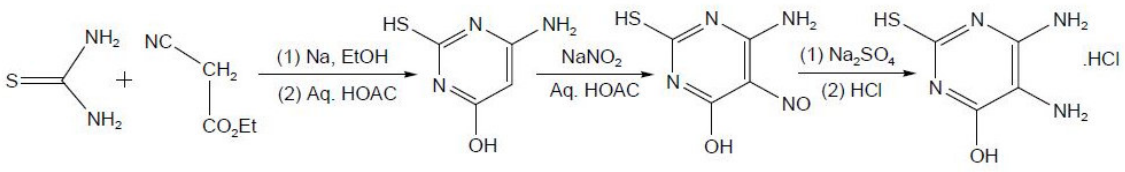

Figure 2**.** Synthesis of DTUH.

The 1H-NMR spectrum of this compound showed the presence one proton at δ 12.48 ppm for S-H, one at δ 11.55 ppm for O-H, δ 8.00 ppm for $NH3^{+}$.

2.2 Formulationst

Almastatin capsules supplied by Alma company (Homs, Syria), each capsule was labeled to contains fluvastatin sodium 20 or 40 mg and fluvastatin capsules supplied by Kimi (Aleppo, Syria), each capsule was labeled to contain fluvastatin sodium 20 or 40 mg.

2.3 Apparatus

Potentiometric measurements were carried out with a digital millivoltmeter (CD-771) Sanwl. and pH meter, were made with Consort C 830 (Belgium) with combined glass pH electrode. A water bath shaker (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 ,400MHz. FT/IR 4100(Fourier transform infrared spectrometer) Jasco. The electrochemical system of the FLS carbon paste electrodes would be represented as:

carbon paste electrode/test solution/saturated calomel electrode

2.4 Solutions

Stock solutions, 10^{-2} M DTUH, FLS, NaCoN, PTA and PMA were prepared by dissolving the accurately weighed amounts of the pure solid in doubly distilled water or methanol, Stock solutions of 1M for each of LiCl, NaCl, KCl, NH_4Cl, $CaCl_2$, $MgCl_2$, $BaCl_2$, $ZnCl_2$, $MnSO_4$, $Ni(NO_3)_2$, $Co(NO_3)_2$, $Cu(NO_3)_2$, $Pb(NO_3)_2$, $FeCl_3$, $AlCl_3$, CrCl , glucose, fructose, lactose, starch, microcrystalline cellulose, carboxy methylcellulose, poly ethylene glycol, titanium dioxide, and poly sorbate 80 were prepared by dissolving the appropriate amount of the compounds. More diluted solutions were prepared by subsequent dilutions of the stock solutions. potassium di hydrogen phosphate used for adjusting the pH of the medium, while 0.5M NaCl solution was used for adjusting the ionic strength, All solution stored in dark bottles and kept in the refrigerator:

2.5 Preparation of ion-associations

The ion- associations FLS -DTUH and FLS -CoN were prepared by adding 50 mL of 10^{-2} M DTUH and 50 mL of CoN to appropriate volume of 10^{-2} M of FLS. FLS-PMA, FLS-PTA ion – associations was prepared by mixing 150 ml of 10^{-2} M of the FLS with 50 ml of 10^{-2} M of PMA or PTA. The obtained precipitates under stirring The yellow, red, dark green and light brown precipitates resulted respectively. The obtained precipitates was filtered, washed thoroughly with distilled water to remove any non-complex material, and dried at room temperature and ground to a fine powder in a mortar and used as the active substances for preparing the chemically modified carbon paste electrodes of fluvastatin sodium.

The composition of the ion-associations was confirmed by elemental analysis and found to be 1:1 (FLS-DAUH) and (FLS-CoN) and 1:3 (FLS-PMA) and (FLS-PTA).

2. 6 Preparation of the electrode

Modified carbon paste electrode was prepared by thoroughly mixing weighed amounts of ion associations (FLS-DTUH), (FLS-CoN), (FLS-PT) or (FLS-PM) with high purity graphite and dioctylphthalate until obtaining a uniformly wetted paste. The mixture was packed in the end of a polypropylene syringe (1 mL). Electrical contact to the carbon paste was made by a copper wire. The carbon paste was smoothed onto paper until it had a shiny appearance. It was then used directly for potentiometric measurements without preconditioning.

2.7 Selectivity coefficient determination

The separate solution method (SSM) and the matched potential method (MPM) (Umezawa *et al*. 2000) are employed to determine the selectivity coefficients $K^{POT}_{Drug,j^{z+}}$ of the potentiometric sensors towards different species using this equation in SSM:

$$K^{POT}_{Drug,j^{z+}} = \frac{E_2 - E_1}{S} + \log[Drug] - \log[j^{z+}]^{\frac{1}{z}} \quad (1)$$

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 MPM:

$$K^{POT}_{Drug,j^{z+}} = \frac{a_{Drug}}{a_j} \quad (2)$$

where a_j is the activity. of interfering ions .

2.8 Construction of calibration graphs

The performance of the electrodes obtained was investigated by measuring e.m.f. values of 5.0×10^{-7}-1.0×10^{-1}

M. of FLS. The electrodes were calibrated by added Suitable volumes of 1.0×10^{-1} M working solution of FLS successively in 50 ml of water to generate a total concentration ranging from 5.0×10^{-7}-1.0×10^{-1} M FLS, 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, pC (-log [FLS]). The constructed calibration graphs were used for subsequent measurements of unknown FLS test solutions.

2.9 Standard addition method

FLS was determined using the prepared electrodes by the standard addition method [(Umezawa *et al*. 1995) Small increments of standard FLS solution (0.03 M) were added to 15ml 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:

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

Where C_x and V_x are the concentration and the volume of an unknown sample, Cs and Vs are the concentration and the volume of the standard, respectively. S is the slope of the calibration graph ($mVdecade^{-1}$), and ΔE is the change in the potential (mV).

2.10 Analysis of FLS 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 distilled water, 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

In this work chemically modified carbon paste electrodes were used in attempts to reduce the detection limit where 4.9×10^{-7} and 2.2×10^{-7}M were achieved.

3 1 Ion-associations selection

At the outset, an ion-associations of Fluvastatin (FLS) with 5,6-diamino-2-thio ,Uracil hydrochloride (DTUH), sodium cobaltinitrite (NaCoN), phosphotungstic acid (PTA), or phosphomolybdic acid (PMA). were prepared then electrodes containing some or no ion-associations were made and their emf measured at various concentrations of the drug. The paste with no ion-associations showed no response (composition # 1). The electrode that contain FLS-DTUH (composition # 6) and the mixture of FLS-DTUH and FLS-CoN (composition # 25) gave the best results with a response that improved with optimization of the composition of the paste according to Table 1. The results clearly indicate that the electrode containing 0.1–1.0 wt% FLS-DTUH and the one containing the mixed ion associations FLS-CoN and FLS-DTUH have a sub-Nernstian slope. In order to obtain Nernstian response, the electrodes must have sufficient amount of lipophilic ion-associations. That was observed for **sensor A** containing 2.0 wt% FLS-DTUH and for **sensor B** containing 1.5% FLS- DTUH and 0.5 % FLS- CoN which exhibited improved sensitivity and working range. However, increasing the wt% above 3.0–10.0 the response deteriorates due to in homogeneity in the paste and possible saturation of the paste (Arvand & Asadollahzadeh 2008).

Table 1. The optimization of the carbon paste ingredients

NO	Ion - associations	Graphite	Plasticizer	Slope (mV.decade)	Linear Range (M)	Response time (s)
1	——	50.00	50.00	16.18	9.2×10^{-4}-2.0×10^{-3}	35
2	0.1 (FLS – DTUH)	49.95	49.95	31.22	8.0×10^{-5}-4.3×10^{-2}	25
3	0.5 (FLS – DTUH)	49.75	49.75	40.92	4.5×10^{-6}-5.4×10^{-2}	15
4	1.0 (FLS – DTUH)	49.50	49.50	49.75	3.8×10^{-6}-7.1×10^{-2}	15
5	1.5 (FLS – DTUH)	49.25	49.25	53.92	1.4×10^{-6}-2.5×10^{-1}	10
6	**2.0 (FLS – DTUH)**	**49.00**	**49.00**	**57.78**	**9.0×10^{-7}-2.5×10^{-1}**	**8**
7	2.5 (FLS - DTUH)	48.75	48.75	51.04	8.5×10^{-6}-2.5×10^{-1}	10
8	3.0 (FLS – DTUH)	48.50	48.50	48.28	7.2×10^{-6}-1.2×10^{-1}	15
9	5.0 (FLS- DTUH)	47.50	47.50	46.42	6.7×10^{-5}-2.5×10^{-1}	20
10	10.0 (FLS - DTUH)	45.00	45.00	41.39	8.9×10^{-5}-4.2×10^{-1}	30
11	1.5 (FLS - CoN)	49.25	49.25	50.45	2.8×10^{-6}-2.0×10^{-1}	15
12	2.0 (FLS – CoN)	49.00	49.00	55.98	1.4×10^{-6}-2.0×10^{-1}	15
13	2.5 (FLS – CoN)	48.75	48.75	49.78	3.3×10^{-6}-2.0×10^{-1}	15
14	1.2 (FLS3 – PT)	49.25	49.25	47.54	4.3×10^{-6}-2.0×10^{-1}	20
15	2.0 (FLS3 – PT)	49.00	49.00	53.95	3.7×10^{-6}-2.0×10^{-1}	20
16	2.5 (FLS3 – PT)	48.75	48.75	48.77	4.3×10^{-6}-3.1×10^{-1}	20
17	2.0 (FLS3 – PM)	49.00	49.00	47.82	4.9×10^{-5}-7.5×10^{-2}	18
18	2.0 (FLS – DTUH)	53.00	45.00	55.04	1.1×10^{-6}-2.5×10^{-1}	10
19	2.0 (FLS – DTUH)	52.00	46.00	55.98	1.1×10^{-6}-2.5×10^{-1}	10
20	2.0 (FLS – DTUH)	51.00	47.00	56.27	9.8×10^{-7}-2.5×10^{-1}	10
21	2.0 (FLS – DTUH)	50.00	48.00	57.50	9.2×10^{-7}-2.5×10^{-1}	10
22	0.3%(FLS-DTUH)+1.7%(FLS-CoN)	49.00	49.00	38.76	5.9×10^{-5}-1.0×10^{-1}	15
23	0.5%(FLS-DTUH)+1.5%(FLS-CoN)	49.00	49.00	44.58	4.5×10^{-6}-1.0×10^{-1}	10
24	1%(FLS-DTUH)+1%(FLS-CoN)	49.00	49.00	55.41	8.5×10^{-7}-2.5×10^{-1}	5
25	**1.5%(FLS-DTUH)+0.5%(FLS-CoN**	**49.00**	**49.00**	**57.18**	**7.3×10^{-7}-2.5×10^{-1}**	**5**
26	1.7%(FLS-DTUH)+0.3%(FLS-CoN)	49.00	49.00	54.22	8.8×10^{-7}-2.5×10^{-1}	8
27	1.5%(FLS-DTUH)+0.5%(FLS-PM)	49.00	49.00	43.64	2.9×10^{-5}-2.0×10^{-1}	10
28	1.5%(FLS-DTUH)+0.5%(FLS-PT)	49.00	49.00	35.68	8.7×10^{-5}-2.0×10^{-1}	15

3. 2 The graphite/plasticizer (g/p) ratio study

Two parameters are of importance when manufacturing a carbon paste: (1) its mechanical stability and (2) its active surface area. Mechanical stability can be interpreted as the ability of the carbon paste to avoid erosion in solution. The use of plasticizers will give some permeable properties to the paste and will improve its mechanical stability by promoting binding between grains

It is well known that the sensitivity and selectivity of the electrode depend on (g/p) ratio used (Ensafi *et al*. 2008). The (g/p) ratios of 0.909–1.438 were examined as shown in Table 2. It was observed that the highest useful ratio of (g/p) considered was 1.239, that is likely due to the optimum physical properties that ensured high enough mobilities of their constituents [Shamsipur *et al*. 2002].

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. 3 Solvent mediators effect

The solvent mediator, in particular, has a dual function: it acts as a liquefying agent, enabling homogenous solubilization and modifying the distribution constant of the ionophore used The proportion of solvent mediator must be optimized in order to minimize the electrical asymmetry of the paste, to keep the sensor as clean as possible, and to stop leaching to the aqueous phase.

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

Compositions								
Ion –associations	G	P	G/P	sensor	S (mV/decade)	C.R(M)	LOD	R(S)
2.0	47.00	52.00	0.909	S_A	54.83	4.8×10^{-6}-7.9×10^{-2}	1.2×10^{-6}	12

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

Physical parameters						Response characteristi			
plasticizers	sensor	D.C	$logP_{TLC}$	V(ɳ)	M.wt	S , mv/deacde	L.R, M	R,s	LOD,M
DOPH	S_A	5.1	7.1	39.0	390	57.78	9.0×10^{-7}-2.5×10^{-1}	8	4.9×10^{-7}
	S_B					57.18	7.3×10^{-7}-2.5×10^{-1}	5	2.2×10^{-7}
DBPH	S_A	6.4	4.5	15.7	278	52.18	2.5×10^{-6}-1.9×10^{-1}	12	9.8×10^{-5}
	S_B					52.04	1.5×10^{-6}-1.9×10^{-1}	8	8.3×10^{-5}
TBP	S_A	8.0	4.0	3.4	266	49.29	8.7×10^{-5}-7.9×10^{-2}	25	3.5×10^{-5}
					S_B	51.71	9.7×10^{-6}-7.9×10^{-2}	1.3×10^{-5}	10
2.0	49.00	49.00	1.000	S_A	56.95	4.6×10^{-7}-1.9×10^{-1}	2.3×10^{-7}	10	
				S_B	56.31	3.4×10^{-7}-1.9×10^{-1}	1.5×10^{-7}	8	
2.0	54.00	44.00	1.239	S_A	57.78	9.0×10^{-7}-2.5×10^{-1}	4.9×10^{-7}	8	
				S_B	57.18	7.3×10^{-7}-2.5×10^{-1}	2.2x10-^{7}	5	
2.0	58.00	40.00	1.438	S_A	55.53	5.4×10^{-6}-2.5×10^{-1}	3.1×10^{-6}	15	
				S_B	55.48	2.1×10^{-6}-2.5×10^{1}	0.5×10^{-7}	15	

S: slope (mV/decade), C.R.: concentration range (M), LOD: limit of detection, R(s): response time(s), S_A: sensor A(FLS-DTUH), S_B: sensor B.(FLS- DTUH+ FLS – CoN)

For a plasticizer to be adequate for use in sensors, it should gather certain properties and characteristics such as having high lipophilicity, high molecular weight, low tendency for exudation from the paste matrix, low vapor pressure and high capacity to dissolve the substrate and other additives present in the paste.

In exploration for a suitable plasticizer for constructing this electrode, we used plasticizers, with the values of dielectric constants (ε), lipophilicity (log PTLC), molecular weight (M.wt) and viscosity (ɳ).

In this work three solvent mediators were used to explore this effect. Their properties (Perez *et al.* 2003), 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. DOPH has a low dielectric constant, and high lipophilicity to avoid exudation and to considerably affect dissolution of ion-associations within the paste. This effect is due to increasing its partition coefficient property to it compared with other plasticizers (Mostafa & Al-Majed 2008).

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

Out of the electrodes tested, compositions # 6 and # 25 have the shortest response time, Nernstian slope and maximum working concentration. Composition # 25 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.

3. 4 pH dependence

The influence of the pH of the solution on the response of the proposed electrodes was studied for 1.0×10^{-6} and 1.0×10^{-1}M FLS ion in the pH range of 1.0-12.0. The pH was adjusted with potassium dihydrogen phosphate buffer. It can be seen from Fig. 3 that the variation in potential is acceptable in the pH range 4.5–10.5. Nevertheless, at pH values less than 4.5 a decrease was observed that is probably caused by the $H3O^{+}$ effects on the electrodes and may also be due to leaching of the ion associations in acidic media. On the other hand the potentials decrease gradually in solutions as pH is raised above 10.5, a drop that can be attributed to the formation of free fluvastatin base in the test solution.

3. 5 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. However, at temperatures higher than 50 ˚C the slopes show a significant deviation. This deviation may be related to destruction of the electrode surface

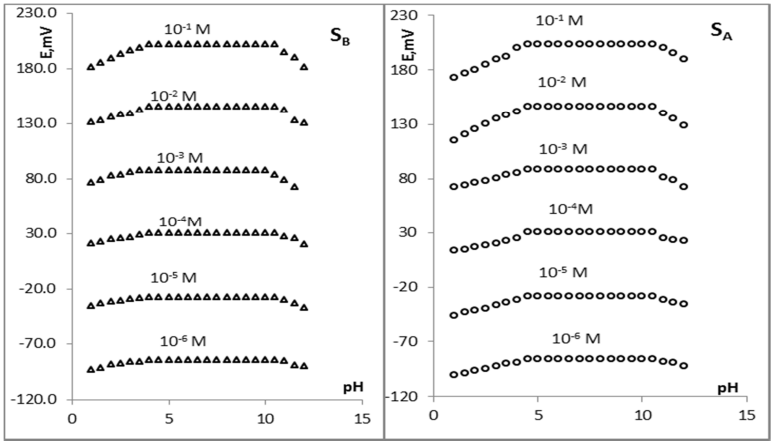

Figure 3. Effect of the pH on the response of the SA, SB

3. 6 Calibration graphs

Using the optimized electrodes composition and conditions described above, the potentiometric response of the electrode was studied based on the FLS concentration in the range of 5×10^{-7}- 5×10^{-1} M. The calibration curves for the electrodes A and B containing DOPH as plasticizer gave an excellent linear response from 7.3×10^{-7}–2.5×10^{-1} M, as shown in Fig. 4. 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×log([FLS,M]+intercept

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

Table 4. Response characteristics of electrodes

Electrode number	S_A	S_B
Plasticizer	DOP	DOP
Ion-pair	2%(FLS- DTUH)	1.5%(FLS-DTUH)+0.5%(FLS CoN)
Parameter		
Slope mV/decad^{-1}	57.78	57.18
Correlation cofficient	0.999	0.999
Linearity range (M)	9.0×10^{-7}-2.5×10^{-1}	7.3×10^{-7}-2.5×10^{-1}
Lower detection limit(M)	4.9×10^{-7}	2.2×10^{-7}
Response time(s)	≤8	≤5

Working pH range	4.5-10.5	4.0-10.5
Temperature ºC	25	25
Life time(day)	120	80

3. 7 Response time and reversibility of the electrode

The response time was recorded by increasing the FLS ion concentration in solution from 1.0×10^{-6} to 1.0×10^{-1} M, with subsequent measurement of the corresponding stable potentials. To evaluate the reversibility of the electrode, a similar procedure in the opposite direction was adopted with measurements

performed in the sequence of high-to-low sample concentrations.

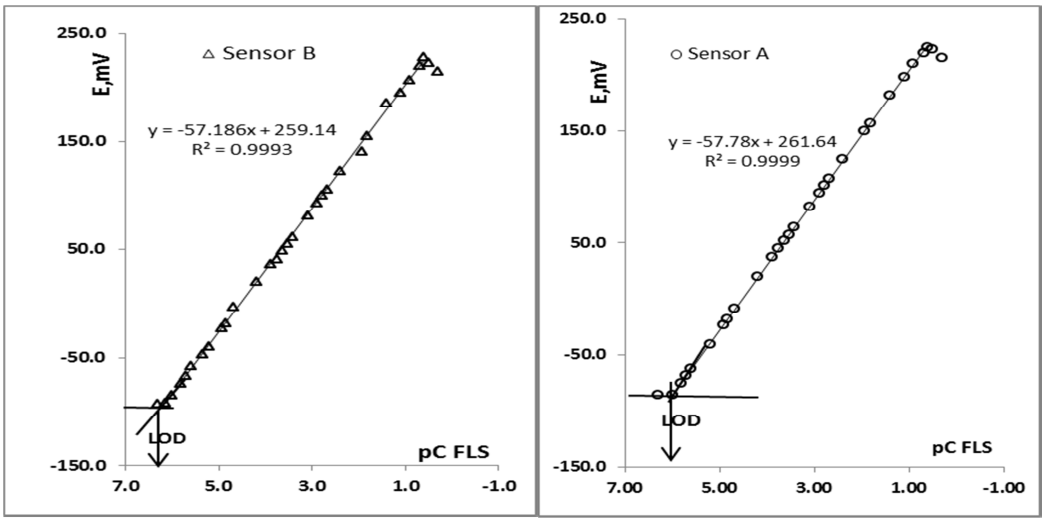

Figure 4. Calibration graph of FLS Sensors

The results, depicted in Fig. 5, for sensor A, which closely represents those for sensor B, clearly indicate that equilibrium is reached in a very short time (8s) where measurements were made either from low to high concentrations or vice versa

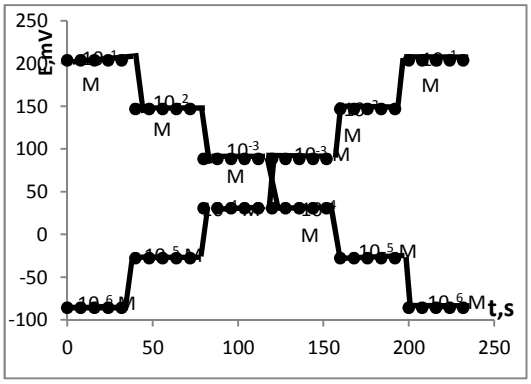

Figure 5. Dynamic response of sensor A

3. 8 Effect of soaking

Freshly prepared electrodes can be used without soaking in dilute solution of FLS. 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 FLS-DTUH electrode remained near Nernstian for about 120 days and was found to be 55.19 ± 1.0

mV/concentration decade, before decreasing gradually to reach about 52.87± 1.2 mV/concentration decade after 120 days. Meanwhile, in the case of the FLS-DTUH/FLS-CoN electrode, the slope reached 54.09 ± 1.0 mV/concentration decade after 80days, then decreased gradually to reach about 51.58± 1.0 mV/concentration decade after 85 days. The results indicated that the life span is 120 days for the FLS-DTUH electrode, and 80 days for the FLS-DTUH/FLS-CoN electrode. It is obvious that after cutting and polishing the electrode surface, the slopes of the electrodes increase again to reach about 57.0 mV/concentration decade.

3. 9 Effect of foreign ions

The influence of some inorganic cations, sugars on the FLS 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 as shown in Table 5. This reflects a very high selectivity of the investigated electrodes towards FLS ion. Inorganic cations do not interfere because of the differences in ionic size, mobility and permeability as compared with FLS. 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-associations (Abdel-Ghani *et al*. 2001). The electrodes exhibit good tolerance towards the common excipients of the tablets, i.e., glucose and lactose.

Table 5 .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	
7.10×10^{-7}	6.50×10^{-7}	9.10×10^{-7}	8.12×10^{-7}	Li^{+1}
2.14×10^{-7}	5.15×10^{-7}	9.07×10^{-7}	3.22×10^{-6}	K^{+1}
1.20×10^{-6}	7.13×10^{-7}	8.19×10^{-7}	9.56×10^{-6}	Na^{+1}
3.51×10^{-8}	5.98×10^{-7}	7.46×10^{-7}	5.34×10^{-7}	NH_4^+
1.01×10^{-7}	2.58×10^{-7}	1.67×10^{-6}	7.52×10^{-6}	Mg^{+2}
2.57×10^{-8}	4.57×10^{-7}	3.53×10^{-6}	6.94×10^{-6}	Mn^{+2}
2.18×10^{-6}	3.69×10^{-6}	9.1×10^{-7}	2.27×10^{-6}	Ca^{+2}
6.25×10^{-7}	4.53×10^{-7}	3.74×10^{-6}	6.97×10^{-6}	Ba^{+2}
1.96×10^{-7}	2.73×10^{-7}	3.89×10^{-6}	1.02×10^{-5}	Ni^{+2}
2.36×10^{-6}	9.12×10^{-6}	1.02×10^{-6}	9.41×10^{-6}	Cu^{+2}
1.06×10^{-6}	1.54×10^{-6}	9.36×10^{-6}	9.08×10^{-6}	Zn^{+2}
3.29×10^{-7}	8.03×10^{-7}	8.4×10^{-7}	3.54×10^{-7}	pb^{+2}
3.46×10^{-7}	8.74×10^{-7}	9.4×10^{-7}	8.29×10^{-7}	Cr^{+3}
2.19×10^{-7}	8.26×10^{-7}	6.45×10^{-6}	5.91×10^{-6}	Fe^{+3}
2.15×10^{-8}	4.25×10^{-8}	No response	No response	Glucose
2.41×10^{-8}	3.46×10^{-8}	No response	No response	Fructose
5.87×10^{-8}	9.58×10^{-8}	No response	No response	Lactose
7.13×10^{-8}	9.15×10^{-8}	No response	No response	starch
No response	No response	No response	No response	Microcrestaline cellulose
No response	No response	No response	No response	Carboxy metyle 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

3 10 Validity of the proposed method

The accuracy and precision of the proposed methods were carried out by five determination 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 (99.0 -101.2) and (100.0-102.6)%, Percentage relative standard deviation (RSD%) (2.47-0.37)and (2.09-0.58)% respectively for sensor-A and B and for two methods. Table 6 shows the values(RSD%) ,(R%) and five different concentrations of the FLS determined from the calibration curves and by using standard-addition methods.

Table 6. Accuracy and precision for the determination of FLS using the proposed electrodes.in pure solution

Electrode	Direct mdothe				standard-addition methode		
	Taken, M	**Found, M**	**RSD%**	**R%**	**Found, M**	**RSD%**	**R%**
S_A	5.0×10^{-6}	5.01×10^{-6}	1.87	100.2	4.96×10^{-6}	2.47	99.2
	5.0×10^{-4}	5.02×10^{-4}	1.23	100.4	5.06×10^{-4}	1.88	101.2
	5.0×10^{-3}	5.00×10^{-3}	1.20	100.0	4.99×10^{-3}	0.98	99.8
	5.0×10^{-2}	5.06×10^{-2}	0.61	101.2	5.03×10^{-2}	0.60	100.6
	1.0×10^{-1}	1.01×10^{-1}	0.46	101.0	0.99×10^{-1}	0.37	99.0
S_B	5.0×10^{-6}	5.07×10^{-6}	2.07	101.4	5.08×10^{-6}	2.09	101.6
	5.0×10^{-4}	5.05×10^{-4}	1.68	101.0	5.01×10^{-4}	1.99	100.2
	5.0×10^{-3}	5.01×10^{-3}	0.84	100.2	5.00×10^{-3}	1.82	100.0
	5.0×10^{-2}	5.03×10^{-2}	0.61	100.6	5.13×10^{-2}	0.98	102.6
	1.0×10^{-1}	1.00×10^{-1}	0.58	100.0	1.00×10^{-1}	0.73	100.0

Average of five determinations

4. **Analytical applications**

The investigated electrodes can be used in the determination of FLS ion in pure solution and pharmaceutical preparations by standard-addition and direct method. The direct method is the simplest for obtaining quantitative results. Direct determination of FLS in tablets were carried out using the developed electrodes. the results are summarized in Table 7. The content of drug in its formulation had good agreement with the declared amount. The standard-addition method was applied, and the equation (3) were used to calculate the concentration of FLS. 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 too.

The results were compared to those obtained using the Official non-aqueous titration method for FLS (British Pharmacopoeia, 2009). The determination of FLS in its pharmaceutical formulations Almastatin capsules (20, 40mg) and Fluvastatin capsules (20, 40mg) gave an average Recovery of (99.17-101.14) 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

Table 7. Analysis of FLS in various tablets using standard addition, and the calibration curve method

Sample	SD± Recovery[a] %				Official method
	Direct mothed		Standard-additionmethode		
	S_A	S_B	S_A	S_B	
Pure VLS	100.93±0.13	101.14 ±0.15	100.45±0.23	99.98±0.19	99.60±0.28
t-value [b]	1.59	2.08	1.48	1.97	
F-value [b]	4.64	3.48	1.48	2.17	
Almastatin capsules (20mg)					
X ± S.D[a]	101.01±0.22	100.44±0.12	99.95±0.15	99.72±0.25	100.64±0.11
t-value [b]	2.63	2.56	0.47	1.80	2.13
F-value [b]	5.58	1.19	5.16	2.38	
Almastatin capsules (40mg)					
X ± S.D[a]	100.14±0.10	99.99±0.14	100.63±0.41	99.89±0.38	99.84±0.17
t-value [b]	2.41	0.15	2.59	1.51	1.92
F-value [b]	2.98	1.47	5.81	4.99	
Fluvastatin capsules (20mg)					
X ± S.D[a]	99.17±0.49	99.63±0.30	100.12±0.10	100.23±0.15	100.28±0.23
t-value [b]	2.84	2.07	2.09	2.59	2.06
F-value [b]	4.53	1.70	5.29	2.35	
Fluvastatin capsules (40mg)					
X ± S.D[a]	100.23±0.16	100.08±0.14	100.14±0.18	100.06±0.16	101.05±0.09
t-value [b]	2.41	0.09	1.26	0.66	1.78
F-value [b]	3.16	2.41	4.00	3.16	

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).

5. Conclusions

The proposed CMCPEs electrodes based on the single ion- associations (FLS-DTUH) and mixed ion associations FLS-CoN and FLS-DTUH as the electroactive materials might be useful detectors and interesting alternative methods for the determination of FLS 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 fluvastatin with the prescribed electrodes are simple, sensitive, highly specific and advantageous over the previously described procedures for FLS determination.

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