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Development of Carbon Paste Electrodes for the Selective Determination of Venlafaxine and Its Metabolite Desvenlafaxine in their Pure and Pharmaceutical Formulations

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DESVENLAFAXINE succinate anhydrous is a cyclohexanol and phenol derivative and metabolite of venlafaxine that functions as a Serotonin and Norepinephrine Reuptake Inhibitor (SNRI) class and is used as an anti-depressive agent. This research introduces design and construction of four ion-selective carbon paste electrodes for fast and simple determination of Venlafaxine and its metabolite Desvenlafaxine in pure and in their pharmaceutical formulations. The best electrodes performance were obtained with a paste composition of 55.8% graphite, 37.2% dibutylphethalate (DBP), and 7% ion-pair for Desvenlafaxine-borate electrode DV-TPB and 46.5% graphite, 46.5% o-NPOE, and 5% ion-associate for Venlafaxine-borate electrode V-TPB, and paste composition of 46.5% graphite, 46.5% DBP, and 7% ion-associate for Desvenlafaxine–phosphotungistate electrode DV-PT and 47.5% graphite, 47.5% o-NPOE, and 5% ion-associate for venlafaxine–phosphotungistate V-PT electrode. These four electrodes illustrated fast, stable and Nernstian response over concentration range of 5.96×10^{-5}-1.00×10^{-2} mol L^{-1} for both V-TPB and V-PT sensors and 5.66×10^{-4} -1×10^{-2} mol L^{-1} for both DV-TPB and DV-PT sensors. Validation of methods shows suitability of the sensors for application in quality control analysis of drug in pharmaceutical formulation. The obtained results were compared with official method using F- and t-tests.

Keywords: Venlafaxine, Desvenlafaxine succinate, Ion-selective electrodes, Metabolite, and ion-associate.

Introduction

The development and application of ion-selective electrodes (ISEs) 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 [1,2]. The ISEs found various applications: in clinical chemistry, environmental protection, water, soil, etc. and analytical chemistry in general [3].

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. Potentiometric carbon

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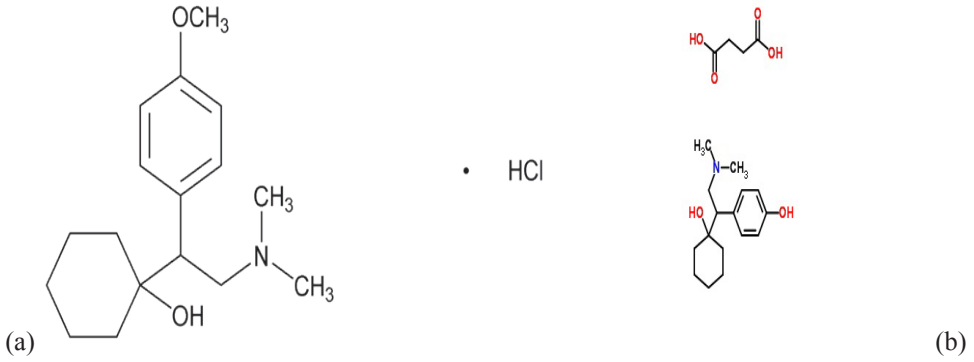
paste electrodes offer very attractive properties for the electrochemical investigation of inorganic and organic species over polymeric membrane electrodes. The ISEs are ease of preparation and use, renewal of surface, chemical inertness, robustness, stability of response, no need of internal solution and suitability for a variety of sensing and detection application [4-6]. A distinct advantage of carbon paste-based electrodes is due to their very low ohmic resistance (less than 10Ω instead of up to MΩ values for electrodes equipped with polymeric membranes). Thus, experimental work with carbon paste ion selective electrodes (CPISEs) is more convenient and simpler allowing voltage measurements of potentiometric cells with lower inner resistance. This fact accompanied with a very quick response time is especially appreciated in automatic titration procedures [7]. Due to the above mentioned properties; carbon paste electrode seems to be especially promising.

Venlafaxine hydrochloride (V.HCl), has an IUPAC name of 1-[2-(dimethylamino)-1-(4-methoxyphenyl) ethyl]cyclohexan-1-ol; hydrochloride, molar mass 313.86 g mol-1, and Desvenlafaxine Succinate (DVS), has an IUPAC name of 4-[2-(dimethylamino)-1-(1-hydroxycyclohexyl) ethyl] phenol, butanedioic acid with molar mass 381.4632 g mol^{-1}, belong to the class of Serotonin- and Norepinephrine-Reuptake Inhibitors (SNRIs) [8]. They have the following structural formula (scheme. 1). They are used to treat major depressive disorder.



(a) (b)

Scheme 1: Chemical structures of Venlafaxine hydrochloride (a) and Desvenlafaxine succinate (b).

A large number of analytical methodologies for V.HCl determination have been published; liquid chromatography-mass spectrometry [9], high-performance liquid chromatography [10-13], reversed phase high performance liquid [14], liquid chromatography–tandem mass spectrometry [15], capillary electrophoresis [16], spectrophotometric [17-19], and chemiluminescence [20].

A large number of analytical methodologies for DVS determination have been published; high-performance liquid chromatography [21, 22] reversed phase high performance liquid chromatography [23, 24], high performance thin layer chromatography [25, 26], spectrophotometric [27, 28].

Most of these methods require the use of relatively cost sophisticated apparatus and complicated pre-treatment procedures like extraction of the active component. These requirements make it difficult for such methods to be used in routine analysis of large number of samples. As a result, suggesting of electrochemical methods of analysis using ion-selective sensors is an attractive and alternative method for organic and inorganic detection, due to its advantages of being simple, rapid, reliable, low cost and non-destructive.

Revealing the literature review, potentiometric methods were found for determination of V.HCl [29-32] and DVS [33]. Hence, the present work aims to develop chemically modified carbon paste sensors and to study their performance characteristics and their appliciability in potentiometric determination of V.HCl and DVS in pure solution, and in their pharmaceutical formulations.

Experimental

Materials

Chemicals used are of analytical reagent

grade. They included sodium tetraphenyl borate (NaTPB) from CCI (Lab Chemical Company-USA), Phosphotungstic acid (PTA) from Fluka, ortho nitrophenyloctylether (o-NPOE) from Alfa Aeasar; diocyl phthalate (DOP), dibutylphethalate (DBP) , spectroscopy pure Graphite powder with a <50 μm particle size (were used for the preparation of the carbon pastes), L-Threonine, L-Ornithine L-Aspartate, L-Carnitine, and L-Arginine monohydrochloride were obtained from Sigma Aldrich, England.

Venelafaxine.HCl (99%) was obtained from EVA-Pharma company its purity was assessed by official method [34]. and Desvenlafaxine succinate (98.8%) was obtained from EVA-Pharma company its purity was assessed by in house method using potentiometric titration method. Their pharmaceutical formulations were obtained from local stores.

Reagent Solutions

Aqueous solution of NaTPB (10^{-2} mol L^{-1}) was prepared, and the exact concentration of this solution was determined by the appropriate recommended method [35]. Na, K, Cu, Ca, Fe and Mg solutions (1000 μg mL^{-1}) were obtained from Merck, Germany.

Stock solutions 10^{-2} mol L^{-1} of NaTPB and $3.3x10^{-3}$ mol L^{-1} of PT were prepared by dissolving the accurately weighed amounts of the pure solid in double distilled water. Solutions of sodium hydroxide and hydrochloric acid of concentrations within the range 10^{-1}-1.0 mol L^{-1} were used for adjusting the pH of the medium.

Venlafaxine and Desvenlafaxine standard solutions

Fresh stock solutions of 0.01 mol L^{-1} V.HCl and DVS were prepared by dissolving 0.3139 and 0.3815 g in 100 mL double distilled water; which stored in dark bottle and kept in a refrigerator for no more than a few days.

The working standard solutions of V.HCl and DVS (1×10^{-6}-1×10^{-2} mol L^{-1}) were then prepared by accurate dilution of the stock solution with double distilled water.

Preparation of the ion-pairs

V-TPB or DV-TPB ion-pairs were prepared by mixing 50 mL of 1×10^{-2} mol L^{-1} V.HCl or 50 mL of 1×10^{-2} mol L^{-1} DVS with 50 mL of 1×10^{-2} mol L^{-1} NaTPB .

V-PT or DV-PT ion-pairs were prepared by mixing 150 mL of 1×10^{-2} mol L^{-1} of V.HCl or DVS with 50 mL of 1×10^{-2} mol L^{-1} PTA.

The resulting precipitates were left in contact with their mother liquor overnight to assure complete coagulation. The precipitates were then filtered through filter paper Whatmann no.1, washed thoroughly with distilled water, dried at room temperature and then ground to fine powder to be used in the construction of the sensors.

Preperation of the sensors

The modified paste was prepared by mixing various amounts of V-TPB, DV-TPB, V-PT and DV-PT (5-10%, w/w) and an appropriate amount of spectroscopic graphite powder (<50 μm particle size) with plasticizer (ratio of graphite powder to plasticizer was 1:1, w/w for V-TPB, V-PT, and DV-PT electrodes but the ratio was 1.5:1, w/w for DV-TPB electrode). The mixture was carefully homogenized using agate pestle in agate mortar. After homogenization of the mixture, the paste was moved to a hole (7 mm diameter and 3.5 mm depth) at one end of a teflon holder (12 cm) and to the other end a stainless steel rod was inserted through the center of the holder to make electrical contact. This rod can move up and down by screw movement to press the paste down when renewal of the electrode surface is needed. The external surface of the carbon paste was smoothed with soft paper.

Instruments

Potentiometric and pH measurements were carried out using a digital JENWAY meter, Model 3510, UK. A saturated calomel electrode (SCE) that filled with saturated KCl solution (satd.) was used as the external reference. The electrochemical system of the VH^+ and DV^+ cations carbon paste electrodes may be represented as:

Carbon paste working electrode || V^+ or DV^+ solution ||saturated reference electrode $Hg/HgCl_2$ ||.

These measurements were done using calibration method with several standard solutions.

Construction of calibration graphs

Suitable increments of standard drug

solution 1x10^{-2} mol L^{-1} of V.HCl or DVS were added to 50 mL bidistilled water so as to cover the concentration range 1×10^{-6}-1×10^{-2} mol L^{-1}. The working sensors and reference sensor were immersed in the solution and the emf values were recorded at 25±1.0 ºC, after each addition. The recorded values were plotted versus -log [V^{+}] or -log [DV^{+}].

The performance of the electrodes

Effect of pH

Aliquots of drug solution (50 mL) were transferred to the titration cell and the tested sensor in conjunction with a saturated calomel electrode was immersed in this solution. The emf and pH readings were simultaneously recorded. The pH of the solution was varied over range of 1.0-12.0 by addition of very small volumes of 1.0 mol L^{-1} HCl or 0.1-1.0 mol L^{-1} NaOH solutions. The effect of pH of the drug solution on the cell emf values in concentrations, 1.00×10^{-4}, and 1.00×10^{-3} mol L^{-1} of V.HCl and 1.00×10^{-3} and 5.00×10^{-3} mol L^{-1} of DVS were studied. The emf readings were plotted against the pH for the different drug concentrations.

Selectivity coefficient of the electrodes

The selectivity coefficients were determined by the modified separate solution method using the rearranged Nicolsky equation [36]:

$$\mathbf{Log\ K_{D,B}^{pot} = [(E_1\text{-}E_2)/S)] + [1 + (z_1/z_2)]\ log\ a}$$

Where, E_1 is the potential measured in 1×10^{-3} mol L^{-1} of V.HCl or DVS (D), E_2 the potential measured in 1x10^{-3} mol L^{-1} of the interfering compound (B), z_1 and z_2 are the charges of the V.HCl or DVS (D) and interfering compound (B), respectively and S is slope of the electrode calibration plot.

Response time

The response time of the proposed sensors were tested by measuring the time required to achieve a steady state potential (within±1 mV) after successive immersion of the sensors in a series of drug V.HCl and DVS solutions each having a 10-fold increase in concentration from 1×10^{-4} to 1×10^{-2} mol L^{-1} for V.HCl electrodes and 1×10^{-3}, 1×10^{-2} mol L^{-1} for DVS electrodes. Typical potential-time plots for the response characteristics of the V.HCl and DVS sensors.

Standard addition method

The standard addition method was applied, in which small increments of standard V.HCl or DVS solution was added to 50 mL aliquot of samples of various concentrations of pure drug, or its pharmaceutical preparation. The change in potential reading was recorded for each increment and used to calculate the concentration of the drug in sample solution using the following equation [37]:

$$C_x = C_s \left(\frac{V_s}{V_x + V_s} \right) \left[10^{n(\Delta E/S)} - \frac{V_x}{V_s + V_x} \right]^{-1}$$

Where C_x is the concentration to be determined, V_x is the volume of the original sample solution, V_s and C_s are the volume and concentration of standard solution added to the sample to be analyzed, respectively, ΔE is the change in potential after addition of a certain volume of standard solution and S is the slope of the calibration graph.

Potentiometric titration

Different aliquots of the investigated drug solutions (1.00×10^{-2} mol L^{-1} V.HCl or DVS) were transferred into 100 mL titration cell and diluted to 50 mL with bidistilled water and the resulting solutions were titrated against 1.00×10^{-2} mol L^{-1} Na-TPB and PTA solutions. The emf values were recorded against the volume of the titrant added (V) and plotted as E (mV) vs V (mL) graph. The end points were determined from the conventional S-shaped curves and by the first derivative. The same procedure was applied for tablet.

Analysis of tablets

Ten Tablets were accurately weighed and ground to fine powder in mortar and appropriate weight from this powder was taken and dissolved in 30 mL of bidistilled water and the mixture was filtered in 50 mL measuring flask. The residue was washed three times with bidistilled water and the volume was completed to the mark using bidistilled water. After that, the standard addition method and potentiometric titration were applied.

Results and Discussion

Sensors characterization:

Different carbon paste sensors were prepared by varying the percentages of the ion-pairs (V-TPB, and V-PT or DV-TPB, and DV-PT), using different plasticizer mediators with different polarities (o-NPOE, DOP, and DBP). to obtain the optimum compositions of the sensors which give the best performance characteristics **(Table 1)**. Fig. 1 shows Potential profile of the optimized DV-TPB/CMCP selective electrodes for determination of DV using a) 5% DV-TPB,38%DOP, 57% C, b) 7% DV-TPB:37.2%DBP: 55.8% C, and C) 5% DV-TPB:38%%o-NPOE: 57%.

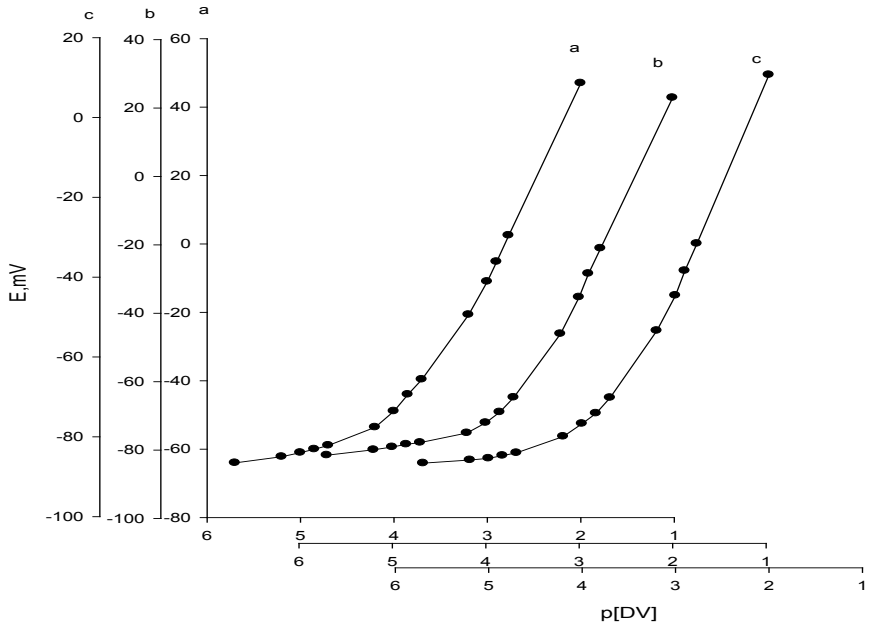


Fig. 1. Potential profile of the optimized DV-TPB/CMCP selective electrodes for determination of DV using a) 5% DV-TPB,38%DOP, 57% C, b) 7% DV-TPB:37.2%DBP: 55.8% C, and C) 5% DV-TPB:38%%o-NPOE: 57%

TABLE 1. Composition and slope of calibration curves for V-TPB, V-PT, DV-TPB and DV-PT CMCP sensors at 25 C°±1.

Ion-pair %	G%	Solvent mediator	Slope mV decade^{-1}	Linear range mol L^{-1}	LOD	RSD* %	r^2
			V-TPB				
5	47.5	47.5 DOP	42.39±1.56	1.99×10^{-6}-9.09×10^{-4}	1.99×10^{-5}	3.68	0.9992
5	38	47 DOP	56.7±0.41	1.99×10^{-5}-1.0×10^{-2}	1.99×10^{-5}	0.72	0.9997
7	46.5	46.5 DOP	39.15±1.73	1.99×10^{-5}-1.0×10^{-2}	1.99×10^{-5}	4.42	0.9994
7	37.2	55.8 DOP	50.4±1.45	5.96×10^{-5}-1.00×10^{-2}	1.99×10^{-5}	2.88	0.9989
5	47	38 o-NPOE	58.381±0.9	5.96×10^{-5}-1.00×10^{-2}	1.99×10^{-5}	1.54	0.9996
5[a]	47.5	47.5o-NPOE	59.18±0.64	5.96×10^{-5}-1.00×10^{-2}	1.06×10^{-6}	1.08	0.9986
			V-PT				
5[b]	47.5	47.5o-NPOE	59.981.09±	5.96×10^{-5}-1.00×10^{-2}	5.01×10-5	1.82	0.9999
5	47.5	47.5DOP	44.5±0.59	5.96×10^{-5}-1.00×10^{-2}	5.01×10-5	1.33	0.9998
5	57	38 DOP	54.91±0.64	5.96×10^{-5}-1.00×10^{-2}	5.01×10-5	1.17	0.9990
7	47.5	47.5o-NPOE	52±1.54	5.96×10^{-5}-1.00×10^{-2}	5.01×10-5	2.96	0.9994
5	47.5	47.5o-DBP	52.3±0.89	5.96×10^{-5}-1.00×10^{-2}	5.01×10-5	1.70	0.9989
			DV- TPB				
5	47.5	47.5 DBP	56.53±0.77	5.66×10^{-4} – 1.00×10^{-2}	9.12×10^{-5}	1.36	0.9994
5	57	38 DBP	56.49±0.64	5.66×10^{-4} – 1.00×10^{-2}	1.20×10^{-4}	1.13	0.9996
7	46.5	46.5 DBP	56.34±0.84	5.66×10^{-4} – 1.00×10^{-2}	1.33×10^{-4}	1.49	0.9993
7[c]	55.8	37.2 DBP	57.98±0.31	5.66×10^{-4} – 1.00×10^{-2}	1.58×10^{-4}	0.53	0.9999
5	47.5	47.5 DOP	52.17±0.32	5.66×10^{-4} – 1.00×10^{-2}	1.1×10^{-4}	0.62	0.9999
5	57	38 DOP	43.44±0.24	5.66×10^{-4} – 1.00×10^{-2}	5.75×10^{-5}	0.55	0.9999
5	38	57 DOP	49.87±0.28	5.66×10^{-4} – 1.00×10^{-2}	8.91×10^{-5}	0.56	0.9999
7	46.5	46.5 DOP	55.83±0.30	5.66×10^{-4} – 1.00×10^{-2}	1.13×10^{-4}	0.54	0.9999
7	55.8	37.2 DOP	53.16±0.39	5.66×10^{-4} – 1.00×10^{-2}	1.38×10^{-4}	0.73	0.9998
5	57	38 o-NOPE	53.90±0.98	5.66×10^{-4} – 1.00×10^{-2}	1.99×10^{-4}	1.82	0.9990
			DV-PT				
5	47.5	47.5 DBP	55.24±0.47	5.66×10^{-4} – 1.00×10^{-2}	7.76×10^{-5}	0.85	0.9997
5	57	38 DBP	53.66±1.18	5.96×10^{-5} – 1.00×10^{-2}	2.75×10^{-5}	2.19	0.9992
7	55.8	37.2 DBP	48.97±0.60	5.66×10^{-4} – 1.00×10^{-2}	4.47×10^{-5}	1.22	0.9995
7[d]	46.5	46.5 DBP	59.23±0.56	5.66×10^{-4} – 1.00×10^{-2}	6.31×10^{-5}	0.94	0.9997
5	47.5	47.5 DOP	48.86±0.84	1.96×10^{-4} – 1.00×10^{-2}	3.31×10^{-5}	1.72	0.9994
7	46.5	46.5 DOP	49.53±1.01	1.96×10^{-4} – 1.00×10^{-2}	3.47×10^{-5}	2.04	0.9989
7	55.8	37.2 DOP	40.32±0.78	5.96×10^{-5} – 1.00×10^{-2}	2.15×10^{-5}	1.93	0.9974
7	46.5	46.5 DBP	51.95±0.63	9.90×10^{-5} – 1.00×10^{-2}	5.89×10^{-5}	1.22	0.9991
10	45	45 DBP	57.850.64±	5.66×10^{-4} – 1.00×10^{-2}	6.76×10^{-5}	1.11	0.9996
10	54	36 DBP	55.53±1.19	5.66×10^{-4} – 1.00×10^{-2}	4.79×10^{-5}	2.14	0.9986

a, b, c, and d: Selected CMCPEs. *RSD of four replicate measurements. r^2: correlation coefficient. G: graphite powder.

The plasticizer mediator acts as a fluidizer allowing homogenous dissolution and diffusion mobility of the ion-pairs inside the paste. For each composition, the trial was repeated four times and the preparation process was highly reproducible as revealed by the low RSD% values of the obtained slopes. **Fig 2 (A, B)** shows calibration curves of V-TPB, V-PT, DV-TPB and DV-PT CMCPEs. The electrodes were used for a period of 60-70 for all prepared electrodes days without significant change in the electrode parameters (Long life span).

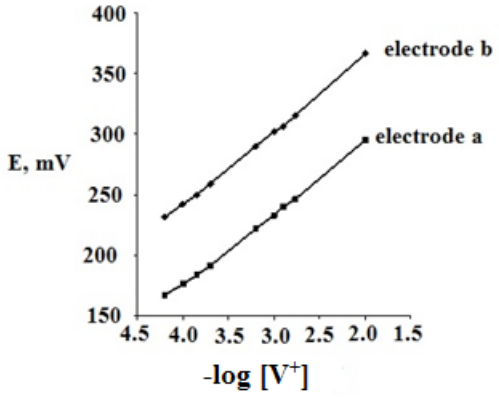


Fig. 2A

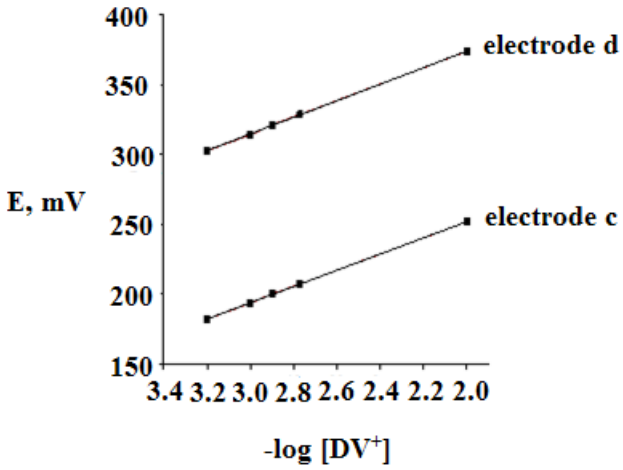


Fig. 2B

Fig. 2 (A, B). Calibration curves of V-TPB (a), V-PT (b), DV-TPB (c), and DV-PT (d) CMCPEs at 25 C°±1.

Effect of pH

The effect of pH on the sensor response was checked for concentrations of V.HCl ($1\times10^{-3}$and 1×10^{-4} mol L^{-1}) and DVS (1×10^{-3} and $5\times\mathbf{10}^{-3}$ mol L^{-1}) by measuring the variation in emf values with change in the solution pH by addition of very small volumes of hydrochloric acid and sodium hydroxide (each 0.1-1.0 molL^{-1}). The results indicate that, the sensors show no response to the pH change in the range of (2.50 - 7.00), and (2.00 - 6.00) using DV-TPB, and V-TPB sensors, respectively. Effect of pH of the test solutions on the potential response of the CMCPEs is shown in **Fig. 3 (A, B).**

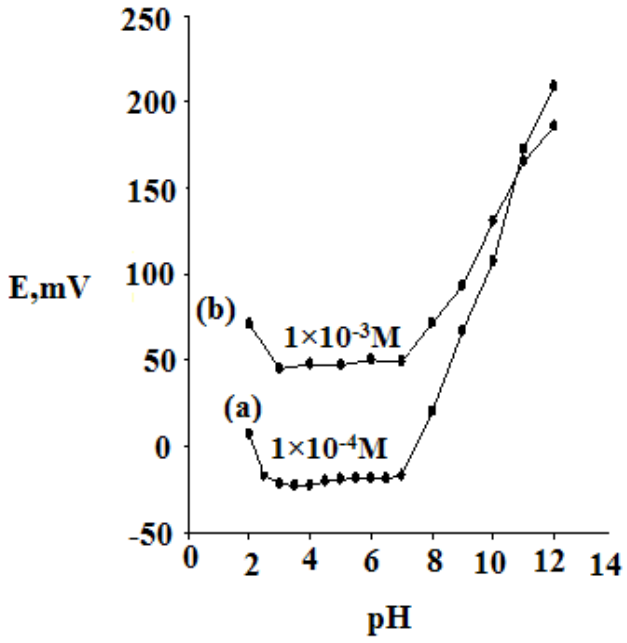


Fig. 3A

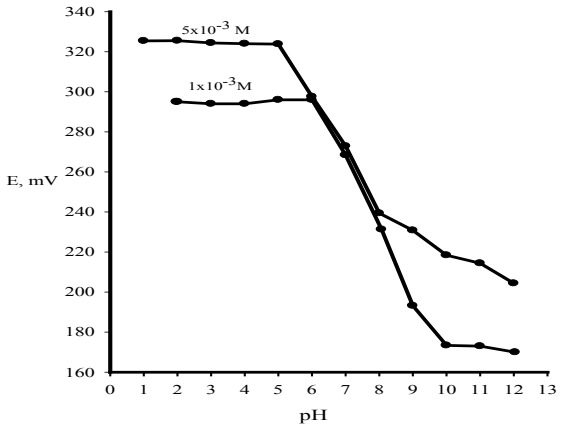


Fig. 3B

Fig. 3 (A, B): Effect of pH on 1×10^{-3} M (a), 1×10^{-4} M (b) and 5x10^{-3} (c), 1×10^{-3} M (d) V and DV solutions on the potential response of (A) V-TPB and (B) DV-TPB CMCPEs respectively.

The potential pH profile obtained indicates that the responses of the two electrodes were fairly constant over wide pH range. At higher pH values, the potentials displayed by the electrodes sharply decrease or increase due to formation of non-protonated V or DV.

Resonse time

The response time [38] of the proposed sensors were tested by measuring the time required to achieve a steady state potential (within±1 mV) after successive immersion of the sensors in a series of drug V.Cl and DV solutions each having a 10-fold increase in concentration from 1×10^{-4} to 1×10^{-2} mol L^{-1} for V electrodes and 1×10^{-3}, 1×10^{-2} mol L^{-1} for DV electrodes. The sensors showed steady state potentials within 5-12 s for V-TPB, V-PT and DV-PT sensors and 8-14 s for DV-TPB sensor. The e.m.f stay constant (within±1 mV) for at least 1 min for V-PT and DV-PT sensors and 47 s for V-TPB and DV-TPB sensors, respectively. Typical potential-time plots for the response characteristics of the V and DV sensors were shown in **Fig. 4.**

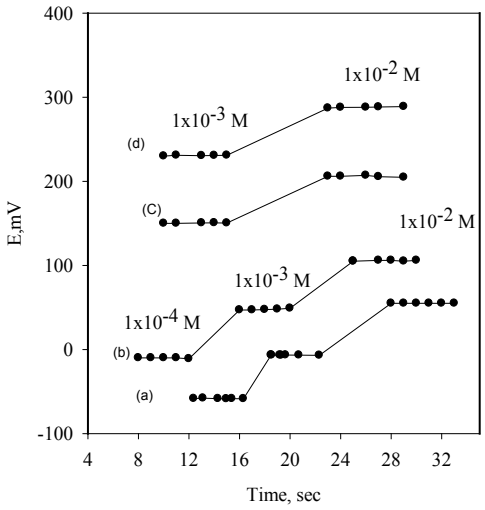


Fig. 4: Potential-time plot for the response of V-TPB (a) and V-PT (b), DV-TPB (c), and DV-PT (d) CMCPEs.

Selectivity of the electrode:

The influence of some inorganic cations and amino acids on the V and DV-electrodes were investigated, **Table 2**.

The selectivity coefficients values of the CMCPEs reflect a very high selectivity of the investigated electrodes for the V and DV cations using the modified separate solution method (SSM) [36,39]. The inorganic cations do not interfere owing to the differences in ionic size and consequently their mobilities and permeabilities as compared with V^+ and DV^+. The selectivity sequence significantly differs from the so called Hofmeister selectivity sequence [39] (i.e. selectivity solely based on lipophilicity of cation).

TABLE 2. Potentiometric selectivity coefficients values $K_{D, Bpot}$ of V and DV CMCPEs:

Interfering species	$K_{D, B}^{pot}$ (V-TPB)	$K_{D, B}^{pot}$ (V-PT)	$K_{D, B}^{pot}$ (DV-TPB)	$K_{D, B}^{pot}$ (DV-PT)
L-Threonine	2.057×10^{-3}	2.01×10^{-2}	3.35×10^{-3}	2.04×10^{-2}
L- Ornithine L-Aspartate	2.37×10^{-3}	3.50×10^{-3}	3.03×10^{-3}	4.57×10^{-2}
L- Carnitine	2.59×10^{-3}	2.25×10^{-3}	3.28×10^{-3}	2.45×10^{-2}
L- Arginine monohydrochloride	3.23×10^{-3}	1.61×10^{-2}	3.07×10^{-3}	1.86×10^{-2}
Cu^{2+}	2.50×10^{-5}	2.67×10^{-5}	3.99×10^{-5}	2.24×10^{-5}
Na^{+}	9.88×10^{-6}	1.98×10^{-5}	1.6×10^{-6}	0.891×10^{-5}
K^{+}	7.09×10^{-6}	3.46×10^{-5}	1.6×10^{-6}	0.741×10^{-5}
Zn^{2+}	2.03×10^{-4}	2.02×10^{-5}	2.3×10^{-5}	3.02×10^{-5}
Fe^{2+}	3.2×10^{-3}	1.22×10^{-10}	1.9×10^{-6}	1.62×10^{-10}
Mg^{2+}	2.50×10^{-5}	2.37×10^{-4}	1.1×10^{-6}	2.09×10^{-4}

In case of non-ionic species, the high selectivity is mainly attributed to the difference in polarity and to the lipophilic nature of their molecules relative to V and DV cations. The mechanism of selectivity is mainly based on the stereospecificity 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 [40].

Potentiometric determination of V and DV in pure, and pharmaceutical preparations

The proposed V and DV-CMCPEs were successfully applied for determination of V.HCl in pure form and in pharmaceutical preparations (Effegad 75, 86 mg/cap) and DVS in pure form and in pharmaceutical preparations (Pristiq 76 mg/tablet) using the standard additions and potentiometric titration methods. The results are shown in **Table 3.**

TABLE 3: Determination of V.HCl and DVS in their pure solutions and in pharmaceutical formulations applying the potentiometric titration and the standard addition method using V and DV CMCPEs.

Potentiometric titration						Standard addition method				
	DV-TPB/DBP			DV-PT/DBP			DV-TPB/DBP		DV-PT/DBP	
Taken (mg)	Recovery (%)		RSD*	Recovery	RSD*	Taken (mg)	Recovery	RSD*	Recovery	RSD* (%
DV Pure solution										
3.81	99.25		0.97	102.28	0.92	4.57	101.42	2.05	99.25	0.096
11.44	99.58		1.51	103.36	1.78	7.62	96.73	1.96	99.94	1.09
38.1		99.76	1.40	101.80	1.09	15.24	98.95	2.29	100.76	1.37
						38.10	97.70	0.75	99.77	0.57
Pristiq tablet (76 mg/tablet)										
3.81	100.60		1.29	102.50	0.79	4.57	98.73	1.48	101.86	1.59
11.44	100.67		1.19	103.02.	0.35	7.62	100.20	2.26	103.14	1.06
38.1		98.76	1.40	101.20	1.09	15.24	100.04	1.55	102.60	1.01
						38.10	99.33	1.76	100.40	1.02
V Pure solution										
		V-TPB/ o-NPOE		V-PT/ o-NPOE			V-TPB/ o-NPOE		V-PT/ o-NPOE	
3.13		98.2	0.43	102.20	0.93	0.63	99.20	0.56	97.98	1.23
9.39		98.7	0.85	100.50	0.67	3.10	98.12	0.94	99.51	1.70
18.78		99.6	0.31	99.20	0.89	6.20	97.85	1.69	98.67	0.92
Effegad tablet (86 mg/tablet)										
		V-TPB/ o-NPOE		V-PT/ o-NPOE			V-TPB/ o-NPOE		V-PT/ o-NPOE	
3.13		103.20	1.19	101.85	2.14	0.63	99.70	0.62	97.98	0.59
9.39		102.49	0.94	101.29	2.36	3.10	99.1	0.57	99.55	0.71
18.78		101.85	0.98	101.50	1.11	----------				

* Relative standard deviation of four repetitive measurements.

Statistical treatment of the obtained data

Venelafaxine and desvenelafaxine results were statistically compared with HPLC official method [33]and in house EVA-Pharma Potentiometric titration method (non-aqueous titration method) [41], respectively, using t- and F-tests, **Table 4**.

TABLE 4: Statistical treatment of the obtained data for the determination of DV and V applying the potentiometric titration and the standard addition method using the constructed CMCPEs in comparison with official [33] **and reported** [40] **methods.**

Reported method [40]		DV-TPB		DV-PT	
	Pure solution	Pure solution	Pristiq tablet(76 mg)		
	Pristiq tablet(76 mg)				
		Potentiometric titration			
X±S.D	99.92±0.58	99.25±1.29	100.63±1.21	102.44±1.76	101.78±1.45
RSD%*	0.58	1.30	1.20	1.72	1.42
t-test		0.92	1.04	2.29	2.28
F-test		2.05	1.93	2.80	2.30
		Standard addition method			
X±S.D	99.92±0.58	98.70±2.03	99.58±0.68	99.93±0.63	101.50±1.29
RSD%*	0.58	2.06	0.68	0.63	1.27
t-test		1.16	0.77	0.02	2.23
F-test		3.23	1.08	0.99	2.05
		V-TPB		V-PT	
Official method[33]		Pure solution	Effegad 86 mg/cap	Pure solution	Effegad 86 mg/ cap
		Potentiometric titration			
X±S.D	100.50±0.68	98.54±1.80	100.83±1.51	101.44±1.10	99.78±1.64
RSD%*	0.66	1.82	1.50	1.08	1.64
t-test		1.66	0.14	2.35	2.03
F-test		7.00	4.93	2.62	5.16
		Standard addition method			
X±S.D	100.5±0.68	98.8±0.78	98.2±1.9	98.9±1.60	98.7±0.91
RSD%*	0.66	0.79	1.34	1.62	0.94
t-test		3.26	1.80	1.63	2.28
F-test		1.30	3.65	5.50	1.78

X± S.D: Recovery± standard deviation, F-tabulated is 9.28 at 95.0% confidence limit, t-tabulated is 2.353 at 95.0% at 3 degrees of freedom.USP monograph of Venelafaxine HCl, HPLC assay using Mobile phase: Acetonitrile and Buffer (3:7).

At 95% confidence level for 4 replicate measurements, the calculated t- and F-values did not exceed the critical values, indicating that there is no significant difference between the proposed method and the official method with regard to accuracy and precision.

Conclusion

The electrodes prepared with the ion-pairs of V-TPB or V-PT and DV-TPB or DV-PT the electro active materials in the carbon paste electrode have been successfully applied to the determination of V. HCl and DVS in pure and pharmaceutical preparation. The proposed methods possess many advantages such as fast response, long life span, lower detection of limits, good accuracy, adequate selectivity in the presence of related species and simple analytical procedures for the determination of V. HCl and DVS in tablet preparations without the need for any sample preparation. They can be applied for routine analyses for these drugs in their formulations especially in NODCAR (National Organization for Drug Control and Research).

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تقديركهروكيميائي للفينبلافاكسين هيدروكلورايد و الديسفينبلافاكسين سكسينات بإستخدام أقطاب أيونية أنتقائية من عجينة الكربون

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البحث المقدم يشرح تحضير وتحديد فاعلية وخواص العديد من الأقطاب الأيونية الانتقائية من عجينة الكربون المعدلة للمركبات الدوائيه المضاده للأكتئاب فينبلافاكسين هيدروكلورايد أو الديسفينبلافاكسين سكسينات مع خليط رباعى فينيل بورات الصوديوم أو خليط الفوسفومولبدات والتى تم إستخدامهم فى تقدير المركبات الدوائيه فينبلافاكسين هيدروكلورايد و الديسفينبلافاكسين سكسينات كهروكيميائيا.

هذه الأقطاب هى من أنواع عجينة الكربون المعدلة. كان العامل الفعال بالنسبة لهذه الأقطاب هى ميكانيكية التبادل الأيونى تعتمد على واحد من التجمعات الأيونية من فينبلافاكسين هيدروكلورايد أو الديسفينبلافاكسين سكسينات مع خليط رباعى فينيل بورات الصوديوم أو الفوسفومولبيدات والمدمجة فى غشاء عجينة الكربون مع مادة ملينة مناسبة.

وتم دراسة العوامل المؤثرة على فاعلية هذه الأقطاب . ثم تم إستنباط طريقة تم فيها إستخدام هذه الأقطاب الأيونية الانتقائية فى تقدير المركبات الدوائيه فينبلافاكسين هيدروكلورايد و الديسفينبلافاكسين سكسينات فى العمل الرقابى.

وتم إجراء دراسه إحصائية لنتائج الطرق المقترحة ومقارنتها بنتائج الطرق المنشورة أوالدستورية.