

## Research Article



## Quantitative Analysis of Desvenlafaxine HCl by Ion Selective Electrode

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Accepted on: 20-07-2016; Finalized on: 30-09-2016.

### ABSTRACT

The construction and electrochemical response characteristics of a poly vinyl chloride (PVC) membrane selective electrode for the determination of desvenlafaxine HCl (DVN) are described. The electrode incorporates PVC membrane with desvenlafaxine-silicomolybdate (DVN-SMA) ion pair complex with dioctylphthalate (DOP) as a plasticizer. The influence of the electrode composition, conditioning time of the electrode and pH of the test solution, on the electrode performance were investigated. The drug electrode showed Nernstian response in the concentration range from  $1.0 \times 10^{-5}$  M to  $1.0 \times 10^{-2}$  M with slope of 58.0 mV decade<sup>-1</sup>, and was found to be very precise and usable within the pH range 4 –8.5. The electrode showed good selectivity towards DVN with respect to some inorganic and organic compounds. The electrode was successfully used for potentiometric determination of DVN both in pure solutions, urine and in pharmaceutical preparations.

**Keywords:** Desvenlafaxine hydrochloride (DVN), Ion-selective electrode, Potentiometry.

### INTRODUCTION

An ion-selective electrode (ISE) is defined as an electrode that is capable of measuring selectivity and activity of a given ion regardless of other ions present in the solution. It was used for determination of many drugs.<sup>1-3</sup>

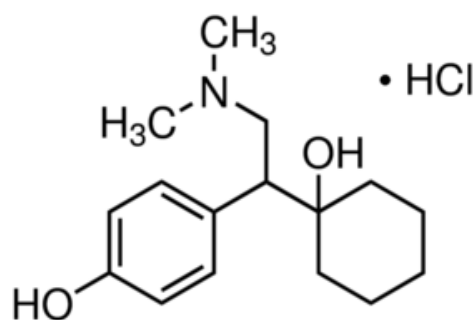
Compared with other analytical techniques, ISE has an impressive list of advantages such as being portable, suitable for either direct determination or using as a sensor in titrations besides, these membrane electrode don't affect the studied solutions.

In this part, the construction of plasticised PVC desvenlafaxine-ion selective electrode and its application in pharmaceutical analysis and in urine are described. Desvenlafaxine HCl (DVN), 1-2-(dimethylamino)-1-(4-methoxyphenyl) ethyl-cyclohexanol hydrochloride (Figure 1) is a new phenethylamine bicyclic antidepressant, which has a neuropharmacologic profile distinct from that of existing antidepressants including tricyclic compounds.

It imparts antidepressant effects by inhibiting the neuronal uptake of norepinephrine, serotonin and dopamine and lacks the adverse side effect profile of tricyclic antidepressants DVN is well absorbed in humans and undergoes extensive metabolism in the liver and has several metabolites, one of which is biologically active. DVN is extensively metabolized to O-desmethyl venlafaxine (ODV), a major metabolite with an activity profile similar to that of DVN. It is therefore important to monitor plasma concentration of DVN to establish pharmacokinetic parameters.

Several analytical procedures have been described for the determination of VEN in both pure and pharmaceutical samples including liquid chromatography–mass spectrometry LC-MS/MS<sup>4</sup>, UV spectroscopy<sup>5</sup>,

spectrophotometric<sup>6</sup>, LC–UV and LC–MS evaluation<sup>7</sup>, reverse phase high performance liquid chromatography HPLC–RP Method<sup>8</sup> and capillary electrophoresis.<sup>9-18</sup> Most of these methods use sophisticated instruments, time consuming or needs expensive reagents. Ion-selective electrodes have been increasingly used for quantitative measurement of drugs. Potentiometric methods based on this technique are simple, rapid, low cost, low detection limit, good accuracy, wide concentration range, applicability to coloured and turbid solutions and offer enough selectivity towards the drugs in the presence of various pharmaceutical excipients.<sup>19,20</sup>



**Figure 1:** Chemical Structure of Desvenlafaxine Hydrochloride

### MATERIALS AND METHODS

#### Reagents

All reagents were of analytical grade. Double distilled and deionized water was used throughout all experiments. Desvenlafaxine hydrochloride was provided by Sigma Co. (Pristiq® tablet) was obtained from local drug stores. Membrane components silicomolybdic acid (SMA)  $H_4SiO_4 \cdot 12MoO_3 \cdot H_2O$  and dioctylphthalate (DOP)  $C_{24}H_{38}O_4$  were obtained from Sigma-Aldrich. High molecular weight poly vinyl chloride (PVC), used as the electrode



membrane material, freshly distilled tetrahydrofuran (THF), used as a solvent for the membrane components, were obtained from Fluka. Stock DVN solution ( $10^{-2}$  M) was prepared daily by dissolving an appropriate amount of the drug in double distilled water. More dilute solutions were prepared by appropriate dilution. All DVN solutions were kept in dark brown bottles. To investigate the selectivity of the proposed electrode towards inorganic cations, amino acids and sugars,  $1.0 \times 10^{-2}$  M solution of each of the following ions were prepared:  $\text{Na}^+$ ,  $\text{NH}_4^+$ ,  $\text{Cu}^{2+}$ ,  $\text{Co}^{2+}$  and  $\text{Cr}^{3+}$ . Also  $1.0 \times 10^{-2}$  M solution of glucose, histidine and cysteine were prepared.

### Sensor Potential Measurement

Potentiometric measurements were carried out with an Orion (Cambridge, MA, USA) Model 701 A digital pH/mV-meter. A Techne circulator thermostat, Model C-100, was used to control the temperature of the test solution. The electrochemical system was as follows:

Ag/AgCl/internal solution/PVC membrane/test solution/SCE (sat. KCl).

### Preparation of DVN - SMA ion-pair Complex

DVN solution  $1.0 \times 10^{-2}$  M was mixed with an equal volume  $1.0 \times 10^{-2}$  M silico molybdic acid (SMA) solution with continuous stirring. The resulting precipitate was left in contact with their mother liquor over night to assure complete coagulation, was filtered, washed thoroughly with distilled water until chloride free (tested using  $\text{AgNO}_3$  solution) and dried at room temperature for 2 days. Elemental analyses were carried out to study the formation DVN-SMA ion-pair complex. The agreement between calculated and found values was very good confirming the postulated stoichiometry; the 4:1 (DVN - SMA) molar ratio stoichiometry.

### Preparation of PVC Membrane Electrode with an Internal Reference Solution

The general procedure to prepare the PVC membrane was as follow: different amounts of the ion-pair along with appropriate amounts of PVC, plasticizer and additive were dissolved in tetrahydrofuran (THF), Table 1, and the solution was mixed well. The resulting mixture was transferred into a glass dish of 5 cm diameter. The solvent was evaporated slowly until an oily concentrated mixture was obtained (about 2 days).

The thickness of the membrane was about 0.2 mm. In each case, prepared membrane and glued using PVC-THF paste to the end of a glass tube (17 mm in diameter). The electrode body was then filled with a mixture containing equal volumes of  $1.0 \times 10^{-3}$  M DVN and  $1.0 \times 10^{-1}$  M NaCl (as internal reference solution) in which the Ag/AgCl reference electrode was dipped. The electrode was finally conditioned for 3h by soaking in a  $1.0 \times 10^{-3}$  M VEN solution. When not in use the sensor was kept stored in a refrigerator showed a good preservation of the slope values and response properties extending to several months.

### General Procedure (Calibration of the Electrode)

Standard DVN solutions of  $1.0 \times 10^{-6}$  M –  $2.0 \times 10^{-2}$  M were prepared. The VEN-selective and reference electrodes were immersed and the potential of each sample solution was directly measured. The potential was recorded after stabilizing to  $\pm 1$  mV. The electrode was washed with double distilled water and dried between measurements. The electrode potential was plotted versus negative logarithmic concentration of DVN ( $P_{DVN}$ ). Slopes of the resulting calibration curves were calculated.

### Selectivity of the Electrode

Selectivity coefficients were determined by the separate solution method<sup>21</sup>, in which the following equation was applied.

$$\log K_{DVN, B^{z+}}^{pot.} = \frac{(E_2 - E_1)}{S} + \log [DVN] - \log [B^{z+}]^{1/z+} \quad \text{eq. (1)}$$

where  $E_1$  is the electrode potential in  $1 \times 10^{-3}$  M DVN and solution.  $E_2$  is the potential of the electrode in  $1.0 \times 10^{-3}$  M solution cation,  $B^{z+}$  and S is the slope of the calibration plot. The selectivity of the electrode towards sugars, amino acids, and certain cations was studied.

### Standard Addition Method

Small increments of a standard DVN solution  $1.0 \times 10^{-2}$  M were added to 50 ml aliquot samples of various drug concentrations. The change in potential reading at a constant temperature of  $25 \pm 1^\circ\text{C}$  was recorded for each increment and used to calculate the concentration of the drug sample solution using the following equation:

$$C_x = C_s \left( \frac{V_s}{V_s + V_x} \right) \left( 10^{n(\Delta E/S)} - \frac{V_x}{V_s + V_x} \right)^{-1} \quad \text{eq. (2)}$$

where  $C_x$  and  $V_x$  are the concentration and volume of the unknown, respectively,  $C_s$  and  $V_s$  are the concentration and volume of the standard, respectively, S is the slope of the calibration graph, and  $\Delta E$  is the change in potential due to the addition of the standards.

### Potentiometric Titration of VEN

An aliquot of DVN ( $1.0 \times 10^{-3}$  M -  $1.0 \times 10^{-5}$  M) was transferred into a 100 mL beaker, then titrated against a  $1.0 \times 10^{-3}$  M SMA using the investigated electrodes as indicator electrodes.

The same method was applied for the determination of DVN in the pharmaceutical preparations and urine.

### Determination of DVN in Pharmaceutical Preparations

A homogenized powder was prepared from ten accurately weighed DVN tablets.

An appropriate amount of this powder was dissolved in about 30 mL distilled water and filtered in a 50 mL measuring flask. The residue was washed three times with double distilled water, and the pH of the solution was adjusted to 5 by 0.1 M acetate buffer, and diluted to

the mark with water. The contents of the measuring flask were transferred into a 100 mL beaker and subjected to potentiometric determination of DVN.

#### Application to Spiked Urine Samples

Urine samples containing different DVN concentrations ( $1.0 \times 10^{-5}$  M to  $1.0 \times 10^{-3}$  M) were prepared by adding known amounts of DVN to 25 mL aliquots of blank urine sample, the DVN selective and reference electrodes were immersed and the DVN concentration was determined by direct potentiometry using the standard additions technique.

## RESULTS AND DISCUSSION

### Influence of Membrane Composition

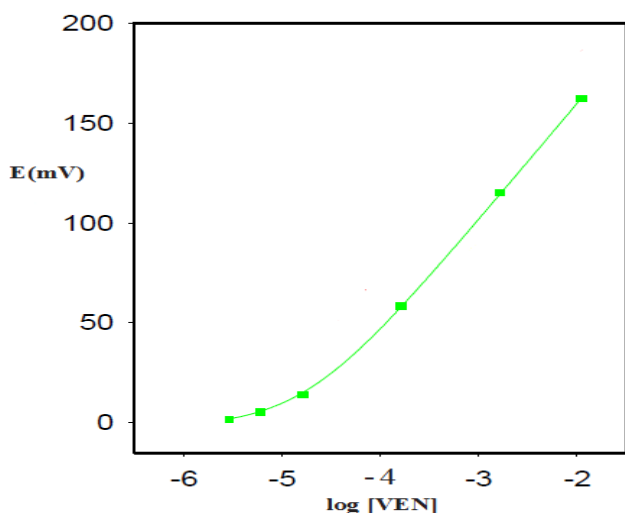
Five membranes of the different compositions (Table 1) prepared as described in the Experimental were tested. The results show that on using membranes of optimum compositions (assigned by *b* in the table), slope of 58.0 mV/concentration decade over a relatively wide range of DVN concentration ( $1.0 \times 10^{-5}$  M -  $1.0 \times 10^{-2}$  M). A typical calibration plot for electrode is shown in Figure 2. The limit of detection, as determined from the intersection of the two extrapolated segments of the calibration graph, was  $3.4 \times 10^{-6}$  M.

**Table 1:** Composition of different DVN - SMA membranes and slopes of the corresponding calibration graphs at  $25 \pm 0.1$  °C.

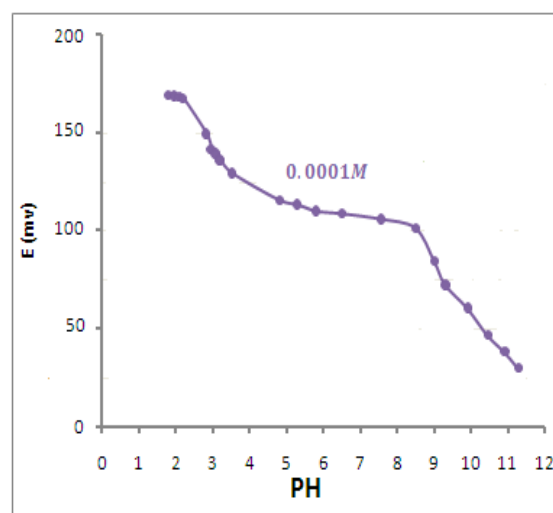
Composition % (w/w)			Slope (mV/decade)	Correlation Coefficient	RSD <sup>a</sup> (%)
Ion Pair	DOP	PVC			
3.0	48.0	48.0	56.7	0.991	0.067
5.0	47.5	47.5	53.5	0.987	0.045
7.0	46.5	46.5	51.8	0.994	0.050
10.0 <sup>b</sup>	45.0	45.0	58.0	0.998	0.079
13.0	43.5	43.5	49.0	0.993	0.031

<sup>a</sup>Relative standard deviation (three determinations)

<sup>b</sup>Optimum composition



**Figure 2:** Typical calibration graph of DVN -SMA-PVC membrane electrode.



**Figure 3:** Effect of pH on the optional response of DVN-SMA-PVC membrane electrode.

**Table 2:** Selectivity Coefficients of the DVN - Selective Electrode Calculated by the Separate Solution Method at 25 °C.

Interferent	$K_{DVN, B^{Z+}}^{pot}$	Interferent	$K_{DVN, B^{Z+}}^{pot}$
Na <sup>+</sup>	$2.8 \times 10^{-4}$	Cr <sup>3+</sup>	$1.1 \times 10^{-4}$
NH <sub>4</sub> <sup>+</sup>	$4.5 \times 10^{-3}$	Glucose	$2.2 \times 10^{-3}$
Cu <sup>2+</sup>	$3.1 \times 10^{-5}$	Histidine	$1.8 \times 10^{-2}$
Co <sup>2+</sup>	$3.3 \times 10^{-4}$	Cysteine	$3.6 \times 10^{-4}$

**Table 3:** Determination of DVN in Pure Form and in Pharmaceutical Preparations.

	Pure Solution		Pristiq Tablets	
	Standard Addition	Potentiometric Titration	Standard Addition	Potentiometric Titration
Taken (M)	$1.5 \times 10^{-5}$	$1.0 \times 10^{-5}$	$1.5 \times 10^{-5}$	$1.0 \times 10^{-5}$
	$1.0 \times 10^{-5}$	$1.0 \times 10^{-4}$	$1.0 \times 10^{-5}$	$1.0 \times 10^{-4}$
	$1.5 \times 10^{-4}$	$1.0 \times 10^{-3}$	$1.5 \times 10^{-4}$	$1.0 \times 10^{-3}$
Recovery (%)	98.88	103.13	98.90	103.52
	100.93	105.21	100.01	104.23
	103.44	99.08	97.98	101.23
R.S.D. (%)	0.72	0.26	0.65	0.29
	0.20	0.32	0.43	0.06
	0.12	0.05	0.22	0.04

\*RSD (three determination)

**Table 4:** Application of Proposed Electrode for the Determination of DVN in Urine.

Taken (M)		Recovery %	RSD*	Recovery %	RSD*
Human urine	1 x10 <sup>-5</sup>	98.5	0.63	100.2	0.83
	1 x10 <sup>-4</sup>	99.8	0.45	100.3	0.34
	1 x10 <sup>-3</sup>	97.9	0.88	99.8	0.57

\*RSD (three determinations)

### Response Time

The dynamic response time is an important factor with selective electrodes.

For the proposed ISE, the response time were obtained from the dynamic potential response corresponding to DVN concentration steps between  $1 \times 10^{-5}$  -  $1 \times 10^{-2}$  M.

This electrode exhibits a fast dynamic response of about 20 s. In spite of at the lower concentration below  $1 \times 10^{-3}$  M, the response time is expectedly sluggish about (25 – 30 s).

The electrode was used for a period of 35 days without significant change in the electrode parameters.

### Effect of pH

The influence pH on the response of PVC was checked by recording the potential reading of the cell for solutions containing  $10^{-4}$  M DVN at different pH values.

Variation of pH value was done by adding very small volumes of HCl and/or NaOH solution (0.1 – 1.0 M of each) to the drug solution.

The potential-pH curve for DVN concentrations were constructed as shown in Figure 3. As is obvious, within the pH range 4 – 8.5 the electrode potential is practically independent of pH, and in this range, the electrode can be safely used for DVN determination.

### Selectivity of the Electrode

The selectivity coefficients  $K_{DVN,J}^{Pot}$  presented in Table (2) clearly showed that the proposed PVC membrane

electrode is highly selective toward VEN with respect to many common inorganic cations, sugars, and amino acids which are frequently present in biological fluids and pharmaceutical preparations. The inorganic cations did not interfere due to the differences in their ionic size, mobility and permeability. Also, the smaller the energy of hydration of the cation facilitated a greater response of the membrane. In the case of sugar and amino acid, the high selectivity is mainly attributed to the difference in polarity and lipophilic nature of their molecules relative to trazodone hydrochloride.<sup>22,23</sup>

### Reproducibility

Reproducibility was tested by repeating each measurement at least three times.

However, for an electrode immersed in standard solutions with the same concentration from different batches or for several electrodes with the same composition immersed in the same standard solution, insignificant differences in potential readings were obtained. This indicated fairly good reproducibility.

### Analytical Applications

The aforementioned results proved that the proposed electrode can be used for analysis of drug in different real samples. The desvenlafaxine selective electrode was satisfactorily applied to the potentiometric determination of desvenlafaxine in pure solution, pharmaceutical preparations and in the urine by the standard additions method and potentiometric titration.



The results are shown in Tables 3, 4 and 5. These results revealed that the desvenlafaxine can be accurately determined using the proposed electrode. The results of the pure solutions and the pharmaceutical preparations were compared with the reference method.<sup>6</sup> The results are in good agreement with those obtained from the reference method.

## CONCLUSION

The proposed electrode is sufficiently simple and selective for the determination of DVN in pure form, pharmaceutical preparations and in urine. The use of the proposed electrode offers the advantage of fast response, elimination of drug pre-treatment or separation steps and accuracy over wide concentration range. They can therefore be used for the routine analysis of the drug in quality control laboratories.

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Source of Support: Nil, Conflict of Interest: None.

