

Ion Selective Poly(vinyl) chloride Membrane Electrode for the Determination of Dapoxetine Hydrochloride in Tablets

Samar O. Aljazzar

Department of Chemistry, College of Science, Princess Nourah bint Abdul Rahman University, Riyadh, Saudi Arabia

Abstract

Aim: To fabrication and characterization of liquid membrane ion selective electrode for the determination of dapoxetine (DAP) in pure form and in tablets. **Materials and Methods:** The membranes compositions were studied by varying the percentages (w/w) of the ion-pair, poly(vinyl) chloride (PVC) and dioctyl phthalate (DOP) until an optimum composition was obtained based on its performance characteristics. The membranes of 0.4-mm thickness were glued to one end of a Pyrex glass tube by careful removal from the glass plate. The electrode was filled with a mixture of 10^{-2} mol/L NaCl and 10^{-2} mol/L DAP as an internal filling solution and then preconditioned by soaking in 10^{-3} mol/L DAP for 3 h before use. **Results and Discussion:** A new DAP ion-selective PVC membrane electrode was fabricated based on the use of DAP-phosphomolybdate as the electroactive substance, and DOP as the plasticizing agent. The performance characteristics of the electrode were evaluated according to IUPAC recommendations reveal a fast, stable and linear response over the concentration range 2.0×10^{-5} – 1.0×10^{-2} mol/L for DAP. The electrode was successfully applied to the determination of DAP hydrochloride in pure solutions and in tablets by standard addition potentiometry. **Conclusion:** The proposed electrode is sufficiently simple and selective for the determination of DAP hydrochloride in pure form and pharmaceutical preparations. This electrode is sensitive and accurate to be a privilege for applications in DAP HCl determination and its quality control.

Key words: Dapoxetine hydrochloride, ion-selective electrode, pharmaceutical analysis, potentiometry

INTRODUCTION

Dapoxetine HCl (DAP, Figure 1) is designated chemically as (S)-N, dimethyl-3-(naphthalen-1-ylxy)-1N- phenylpropan-1-amine. This drug is mainly useful in erectile dysfunction as selective serotonin reuptake inhibitor (SSRI).^[1] SSRI's are a class of compounds typically used as antidepressants in the treatment of depression, anxiety disorders, and some personality disorders. The drug's mechanism of action is thought to be related to inhibition of neuronal reuptake of serotonin and subsequent potentiation of serotonin activity and increase the ejaculation time.^[2] Various analytical techniques have been employed for the quantitative analysis of DAP. Most of these analytical methods are based on high-performance liquid chromatography (HPLC) which is applied for the determination of DAP in combined tablet formulation,^[3,4] spectrophotometry,^[5-7] fluorescence spectroscopy,^[8] and thin layer

chromatography^[9] methods. Most of these methods, however, utilize expensive instrumentation, suffer from lack of selectivity, involve careful control of the reaction conditions or derivatization reactions, and require time-consuming pretreatment steps, which affect their usefulness for routine analysis. On the other hand, applications of potentiometric sensors in the field of pharmaceutical and biomedical analysis have been advocated.^[10] Electrochemical techniques are of choice since they possess the advantages of simplicity, accuracy, low cost without separation, or pretreatment procedures and selective technique for determination of various drugs.^[11,12]

Address for correspondence:

Samar O. Aljazzar, Department of Chemistry, College of Science, Princess Nourah bint Abdul Rahman University, Riyadh, Saudi Arabia.
E-mail: drjazzar1971@hotmail.com

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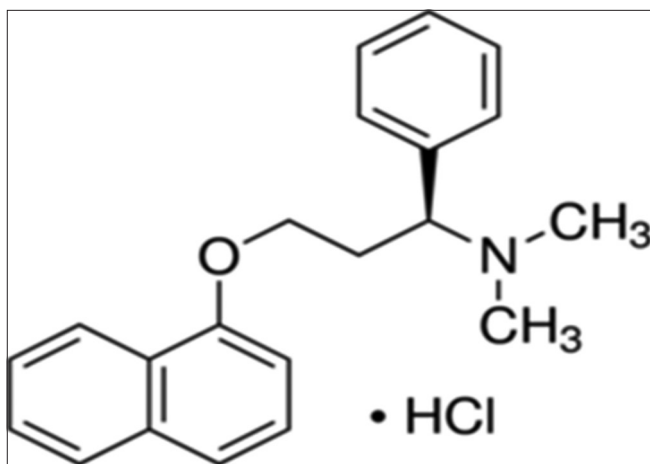


Figure 1: Structure of dapoxetine hydrochloride

The present investigation deals with the fabrication and characterization of liquid membrane ion selective electrode for the determination of DAP. The electrochemical sensitivity of the electrode is based on the incorporation of DAP-phosphomolybdic acid (PMA) as a sensing element. The electrode was used successfully for the determination of DAP in the pharmaceutical dosage form without any prior separation.

MATERIALS AND METHODS

All chemicals used were of analytical reagent grade, distilled water (DW) was used throughout all the experiments. DAP hydrochloride and its tablets (Joybox), 60 mg of DAP in each tablet, were obtained from Inspire Pharma, Egypt. PMA, dioctyl phthalate (DOP), sodium tetraphenylborate (NaTPB), tetrahydrofuran (THF), and high relative molecular weight poly(vinyl) chloride (PVC) were purchased from the Merck and the Aldrich Chemical Companies.

Stock DAP HCl solution (1.0×10^{-1} mol/L) was prepared daily by dissolving an appropriate amount of the drug in DW. More dilute solutions were prepared by appropriate dilution using DW. The DAP-PMA (ion pair) was prepared by a method similar to that described previously.^[13] The chemical composition of each ion pair was confirmed by elemental analysis.

Potentiometric measurements were carried out at $25 \pm 0.1^\circ\text{C}$ on a digital pH/millivoltmeter (Jenway, Model 3510). A (WTW) packed saturated calomel electrode (SCE) was used as an external reference electrode. The electrochemical system may be represented as follows:

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

Construction of electrode

The membranes compositions were studied by varying the percentages (w/w) of the ion-pair, PVC and DOP until an

optimum composition was obtained based on its performance characteristics. For each composition the ion-pair, PVC and DOP were dissolved in 5 ml THF. The resulting mixture was transferred into a glass dish of 5 cm diameter, and the THF was allowed to evaporate at room temperature (about 2 days). The membranes of 0.4-mm thickness were glued to one end of a Pyrex glass tube by careful removal from the glass plate. The electrode was filled with a mixture of 10^{-2} mol/L NaCl and 10^{-2} mol/L DAP as an internal filling solution and then preconditioned by soaking in 10^{-3} mol/L DAP for 3 h before use.

Electrode calibration

The calibration of the electrode was preceded using standard solutions of DAP ranging from 1.0×10^{-6} – 1.0×10^{-2} mol/L. The sequence of measurements was carried out from low concentration to a higher one. The prepared electrode in conjunction with the reference electrode was immersed in the above test solutions and allowed to equilibrate while stirring. The potential was recorded after stabilizing to ± 1 mV. The electrode potential was plotted versus negative logarithmic concentration of DAP, slopes of the resulting calibration curves were calculated.

Effect of pH on the electrode response

The effect of pH on the potential values of the DAP electrode was studied over the pH range of 2–10 at 1-pH interval. This is done by immersing the electrode in 10^{-3} mol/L DAP solution. The pH was gradually increased or decreased by adding aliquots of diluted sodium hydroxide or hydrochloric acid solutions, respectively. The potential obtained at each pH was recorded.

Selectivity

Potentiometric selectivity factors for the proposed electrode were evaluated by the modified form of the matched potential method (MPM),^[14] then potentiometric selectivity coefficients were calculated using the following equation:

$$K_{A,B}^{\text{pot}} = \frac{\Delta a_A}{a_B} = \frac{a'_A - a_A}{a_B}$$

In this method, the specified activity of the primary ion ($a_A = 1.0 \times 10^{-6}$ mol/L of drug) is added to reference solution ($a'_A = 1.0 \times 10^{-3}$ mol/L) of drug, and the potential is measured. In a separate experiment interfering ion concentrations ($a_B = 1.0 \times 10^{-2}$ mol/L) were added to an identical reference solution, until the measured potential matched that obtained before the addition of the primary ions. The selectivity coefficients were then given by the resulting primary to interfering ion activity ratio.

Potentiometric determination of DAP

DAP was determined potentiometrically using the fabricated electrode by the standard addition method.^[15] In the standard addition method, known small increments of 1.0×10^{-2} mol/L standard DAP solution were added to 50.0 ml aliquot samples of various concentrations of pure drug and pharmaceutical preparations. The change in potentials was recorded for each increment and used to calculate the concentration of DAP sample solution.

Analysis of Joybox® tablet

Ten tablets of Joybox® (60 mg/tablet) were finely powdered. An accurate weight equivalent to 600 mg of DAP was transferred to a beaker and diluted to 50 ml with DW. The mixture was filtered through a filter paper and washed with water. The filtrate and washings were collected in a 100-ml standard volumetric flask and diluted to volume with DW and subjected to the potentiometric determination using the proposed electrode.

RESULTS AND DISCUSSION

The response characteristics of DAP electrode are listed in Table 1.

Table 1: Critical response characteristics of DAP electrode

Parameter	Value
Slope (mV/decade)	59.30
Correlation coefficient (r)	0.996
Linear range (mol/L)	2.0×10^{-5} – 1.0×10^{-2}
Detection limit (mol/L)	3.7×10^{-5}
Response time/s	20
Lifetime/day	38
Working pH range	4.0–7.8

DAP: Dapoxetine

Composition of the membranes

Several membranes of varying ratios of ion pair /PVC/ plasticizer were prepared for the systematic investigation of the membranes compositions, and the results are summarized in Table 2. The results showed that the membrane prepared with 10% DAP-PMA ion pair exhibits the best performance characteristics slope 59.30 mV concentration decade⁻¹ at $25 \pm 0.1^\circ\text{C}$, the highest value of the correlation coefficient, usable concentration range 2.0×10^{-5} – 1.0×10^{-2} mol/L of DAP. Electrochemical performance characteristics of the proposed sensors were systematically evaluated according to IUPAC standards.^[16,17]

Effect of soaking

The preconditioning process requires different soaking intervals depending on the diffusion and equilibration at the interface. Fast establishment of equilibrium is certainly a sufficient condition for fast response.^[18] The investigated electrode was soaked in 10^{-3} mol/L solution of the drug at room temperature. A calibration graph was constructed for electrode after time intervals covering the range 5 h up to 38 days; the measurements were stopped when the slope of the calibration graph deviated largely from the Nernstian value and the electrode become out of use. The results indicate that the slope of the calibration graph was found to be 59.20 mV/concentration decade after 5 h of soaking and then it till it reaches about 48.30 mV/decade after 38 days of continuous soaking for electrode. The decrease in the efficiency of the electrode is due to a diminished exchange rate of the cations of the drugs on the membrane gel layer test solution interface, which is responsible for the membrane potential.

Dynamic response time

The response time is the time which elapses between the instant when an ion-selective electrode and a reference electrode (ISE cell) are brought into contact with a sample solution. The dynamic response time of the electrode

Table 2: Optimization of membrane composition (w/w %) of DAP electrode and slopes of the corresponding calibration graphs at 25.0°C

Composition % (w/w)			Slope mV/decade	RSD ^a (%)
Ion pair	PVC	DOP		
1.0	49.50	49.50	48.90	0.90
3.0	48.50	48.50	54.20	0.56
5.0	47.50	47.50	53.20	0.77
7.0	46.50	46.50	55.00	0.42
10.0 ^b	45.00	45.00	59.30	0.23
12.0	44.00	44.00	43.30	1.12

^aRelative standard deviation (three determinations), ^b Optimum composition, DAP: Dapoxetine

systems was tested for 1.0×10^{-5} – 1.0×10^{-3} mol/L DAP solutions. The electrode yielded steady potential within 20 s. The potential readings stayed constant, to within ± 1 mV for at 40 s.

Effect of pH

The effect of pH of the 10^{-3} mol/L DAP hydrochloride on the electrode potential was investigated over the pH range 2.0–10.0 by adding aliquots of diluted sodium hydroxide or hydrochloric acid solutions. The potential was independent of pH in the range 4.0–8.0 [Figure 2]. At pH higher than 7.8, the potential reading changes slightly due to the conversion of DAP hydrochloride ($pK_a = 8.6$) to the DAP base. Further, addition of NaOH (at pH >8.6) lead to a dramatic change in the potential of the electrode due to further depletion of DAP hydrochloride and diffusion of OH⁻ into the surface of the electrode. Interference from H⁺ at lower pH (pH <4) was observed for the electrode.

Selectivity

The interference of some common inorganic cations, sugars and amino acids was investigated using the MPM.^[14] The

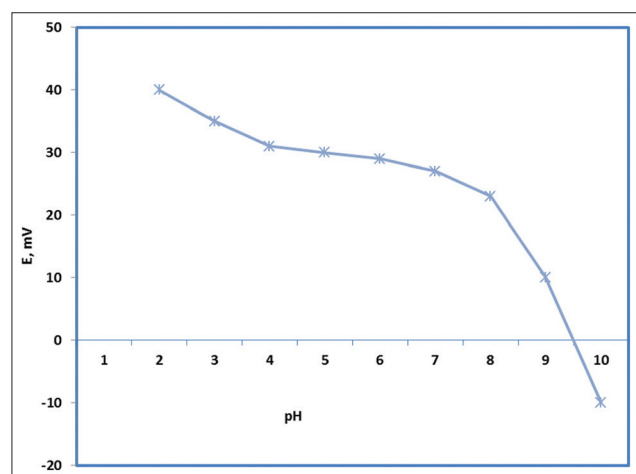


Figure 2: Effect of pH change of 10^{-3} mol/L DAP solution on the response of DAP electrode

selectivity coefficient values recorded in Table 3 indicate that the electrode can be used for determination of DAP presence of high concentration of the interfering ions without fear of interference. The inorganic cations did not interfere due to the differences in their mobilities and permeabilities as compared with DAP hydrochloride. In the case of sugars and amino acids, the high selectivity is mainly attributed to the difference in polarity and lipophilic character of their molecules relative to DAP hydrochloride.

Analytical applications

The proposed electrode was proved useful for the assay of DAP in the drug substance and pharmaceutical product by standard addition method. The accuracy and precision were tested at three different concentration levels (4.0–18.0 mg/50 mL). The recovery and standard deviation values are given in Table 4. The relative standard deviation was $\leq 2.0\%$, indicate reasonable repeatability and reproducibility of the proposed methods. To compare the proposed method to a reported method, DAP in pure solutions was assayed by spectrophotometric method using BTB.^[19] Statistical comparison of the results of the proposed and reported methods [Table 4] was performed with regard to accuracy and precision using the t- and F-ratio tests. At 95% confidence level, the calculated t- and F-values did not exceed the theoretical values, indicating that there is no significant difference between the proposed method and spectrophotometric method with regard to accuracy and precision.

CONCLUSION

The proposed electrode is sufficiently simple and selective for the determination of DAP hydrochloride in pure form and pharmaceutical preparations. Ion-selective electrode has shown good performance characteristics with time stability up to 5 weeks. This electrode is sensitive and accurate to be a privilege for applications in DAP HCl determination and its quality control.

Table 3: Selectivity coefficients $K_{DAP^+,B}^{pot}$ for the DAP electrode at 25.0°

Interfering ions (B)	$K_{DAP^+,B}^{pot}$	Interfering ions (B)	$K_{DAP^+,B}^{pot}$
Na ⁺	2.67×10^{-4}	Ce ⁴⁺	5.14×10^{-4}
K ⁺	8.21×10^{-4}	Glucose	-
Co ²⁺	-	Maltose	3.44×10^{-3}
Cu ²⁺	7.54×10^{-4}	Histidine	1.17×10^{-4}
Cr ³⁺	1.87×10^{-3}	Cysteine	1.85×10^{-3}
Al ³⁺	-	Threonine	9.72×10^{-4}

–: Negligible interference, DAP: Dapoxetine

Table 4: Potentiometric determinations of DAP in pure form and joybox tablets using DAP electrode by the standard addition method, at 25°C

Sample	Taken (mg/50 mL)	Found	Recovery (%)	RSD ^a (%)	Reported method ^[13]
Drug substance	4.0	4.0	100.00	0.99	99.96±2.12 (2.571) ^b (6.39) ^b
	12.0	11.95	99.60	1.16	
	18.0	17.60	97.78	1.34	
	Mean		99.14	1.16	
	<i>t</i> =1.45				
	<i>F</i> =1.18				
Joybox tablets (60 mg DAP/ tab.)	4.0		99.90	1.12	
	6.0		98.80	1.32	
	12.0		99.70	1.18	
	Mean		99.13	1.20	

^aRSD (five determinations), ^bspectrophotometric method using BTB, ^ctheoretical values of *t*- and *F*-tests at 95% confidence, DAP: Dapoxetine

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