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# Electrochemical Determination of Dapoxetine HCl in Biological Fluids Using Coated Wire Electrode

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**Abstract:** Coated wire sensor for potentiometric determination of DAP (dapoxetine HCl) in pure form and in biological fluids based on DAP-TPB (dapoxetine-tetraphenyl borate) as the sensing element in the presence of DOP (dioctylphthalate) as the plasticizing solvent mediator was prepared. The best performance was obtained with a membrane composition of 10.0% (w/w) ion-pair, 45.0% DOP (w/w) and 45.0% PVC (w/w). The electrode showed a Nernstian response (with a slope of 58.70 mV decade$^{-1}$) for the concentration range of $4.2 \times 10^{-5}$-$1.0 \times 10^{-2}$ mol/L. It illustrates a relatively fast response time in the whole concentration range (~15 s) in a pH range of 3.0-7.5. The selectivity coefficients were determined in relation to several inorganic and organic species. DAP is determined successfully in pure solutions and in biological fluids using the standard additions and potentiometric titrations methods.

**Key words:** DAP, coated wire electrode, biological fluids.

## 1. Introduction

DAP (Dapoxetine HCl) is designated chemically as (S)-N, N-dimethyl-3-(naphthalen-1-yloxy)-1 phenylpropan-1-amine with an empirical formula of $C_{21}H_{23}NO$. This drug is mainly useful in erectile dysfunction as SSRI (selective serotonin reuptake inhibitor) and it is the first drug approved for the on-demand treatment of premature ejaculation in men [1]. The chemical structure of DAP is shown in Fig. 1. Dapoxetine hydrochloride is not official in any pharmacopoeia. So, there is not any official method described for their estimation. It is estimated by spectrophotometry [2-4], HPLC [5, 6], fluorescence spectroscopy [7], and TLC [8] methods. Literature review shows that no potentiometric method has been reported so far for its estimation although ISEs have been used extensively for drug analysis over the last decades. Ion selective electrodes have been proven as an inexpensive and simple analytical technique with remarkable detection sensitivity, minimal sample pretreatment and ease of miniaturization rather than other analytical. Coated wire ion selective electrodes [9, 10], in which the membrane is casted onto a solid-like graphite, Ag, Cu, Pt, etc., can also be used as long as the matrix of the membrane does not react with the internal wire. The advantage of using coated wire is that they can be used in small volume of sample, simple design (absence of internal solution), mechanical flexibility, and the possibility of miniaturization and microfabrication. This work describes construction and investigation of performance characteristics of novel ISE based on coated wire electrode for the determination of DAP in pure solutions and in biological fluids.

## 2. Materials and Methods

The pure drug DAP was obtained as a gift sample from Inspire Pharma, Egypt. DOP (Dioctylphthalate), NaTPB (sodium tetraphenyl borate), THF (tetrahydrofuran) and high relative molecular weight PVC were purchased from the Merck and the Aldrich Chemical Companies. Stock DAP solution ($1.0 \times 10^{-1}$ mol/L) was prepared daily by dissolving an appropriate amount of the drug in distilled water. More dilute solutions were prepared by appropriate

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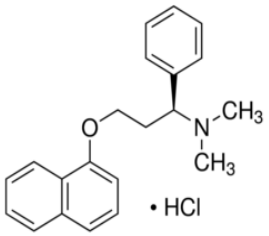


**Fig. 1 Structure of dapoxetine hydrochloride.**

dilution using double distilled water. Potentiometric measurements were carried out at 25 ± 0.1 °C on a digital pH/millivolt meter (Jenway, Model 3510). The electrochemical system may be represented as follows:

Copper (wire)-PVC membrane | sample solution || Ag-AgCl, KCl (sat.).

*2.1 Preparation of the Ion-Pair Complex*

The DAP-TPB ion pair was prepared by mixing 100 mL of $10^{-2}$ mol/L solution of DAP with 100 mL of $10^{-2}$ mol/L solution of NaTPB (sodium tetraphenyl borate). The precipitate that formed was filtered, washed thoroughly with water, and dried at room temperature. The composition of the precipitate was investigated by elemental analysis. The results indicated the formation of a 1:1 ion pair (DAP:TPB).

*2.2 Electrode Construction*

To make a wire coated electrode, pure copper wire of 12.0 cm length was tightly insulated by polyethylene tubes leaving 1.0 cm at one end of the coating and 0.5 cm at the other end for connection.

The electrode was polished with a fine emery paper and sonicated in bidistilled water. The copper wire was dipped for few seconds in a solution of THF containing PVC, ion pair and DOP several times (6 times). After each dip, the electrode was left to dry at room temperature for 5 min. Then, it was soaked in a $10^{-3}$ mol/L of DAP solution for 24 h.

*2.3 Construction of the Calibration Graphs*

Suitable increments of standard DAP solution were added to 50 mL of $1.0 \times 10^{-6}$ mol/L DAP solution so as to cover the concentration range from $1.0 \times 10^{-6}$ mol/L to $1.0 \times 10^{-2}$ mol/L. In this solution the sensor and the reference electrode were immersed and the *e.m.f.* was recorded after 10 s, at 25 °C, for each addition.

*2.4 Selectivity of the Electrode*

Selectivity coefficients were determined by the separate solution method [11], in which the Eq. (1) was applied.

$$\log K^{pot.}_{DAP,B^{z+}} = \left(E_2 - E_1\right)/S + \log\left[DAP\right] - \log\left[B^{z+}\right]^{1/z+} \quad (1)$$

where, $E_1$ and $E_2$ are the electrode potentials of solutions of the DAP and interfering cation, $B^{z+}$, respectively (both of the same concentration) and $S$ is the slope of the calibration graph.

*2.5 Potentiometric Determination of DAP*

Dapoxetine has been determined potentiometrically using the prepared electrode by the standard addition method. Small increments of a standard DAP 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 °C was recorded for each increment and used to calculate the concentration of the drug sample solution using the Eq. (2):

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

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.

*2.6 Determination of DAP in Biological Fluids*

5 mL of plasma or urine were collected from healthy person subsequently; different amounts of

DAP were added. The solution was diluted to 50 mL with bidistilled water and subjected to potentiometric analysis of DAP by standard addition method.

*2.7 Potentiometric Titration of DAP*

An aliquot of DAP solution was pipetted into a 100 mL titration vessel and the solution was diluted to 50 mL with bidistilled water. The resulting solution was titrated against a standard solution of $1 \times 10^{-2}$ mol/L NaTPB. The volume of the titrant at equivalence point was obtained using the conventional S-shaped curves. The differential graphs of the titration curves have also been constructed to obtain well defined and accurate end points.

## 3. Results and Discussion

*3.1 Composition of the Electrode*

Five electrodes containing 1.5, 3.5, 7.5, 10.0 and 13.5% of DAP-TPB ion pair were prepared as given in Table 1. Electrode with 10.0% DAP-TPB show the best Nernstian behaviour (slope = 58.70 mV decade$^{-1}$ within the usable concentration range $4.2 \times 10^{-5}$ – $1.0 \times 10^{-2}$ mol/L of DAP) as shown in Table 1. A typical calibration plot for electrode is shown in Fig. 2. The above optimum composition was used to prepare membrane electrode for all further subsequent investigations.

*3.2 Effect of Soaking*

The lifetime of the electrode was determined by soaking CWE in $1.0 \times 10^{-3}$ mol/L DPA solution. A calibration graph was constructed for electrode after optimum soaking time of 24 h. The measurements were stopped when the slope of the calibration graph deviated largely from the Nernstian value and the electrode become out of use. This behavior is attributed

**Table 1 Composition of different DAP-TPB membranes and slopes of the corresponding calibration graphs.**

| Ion pair | Composition % (w/w) DBP | PVC | Slope (mV/decade) | Correlation coefficient |
|---|---|---|---|---|
| 1.50 | 49.25 | 49.25 | 49.60 | 0.85 |
| 3.50 | 48.25 | 48.25 | 51.90 | 0.91 |
| 7.50 | 46.25 | 46.25 | 54.30 | 0.95 |
| 10.00[a] | 45.00 | 45.00 | 58.70 | 0.99 |
| 13.50 | 43.25 | 43.25 | 44.30 | 0.89 |

[a] Optimum composition.

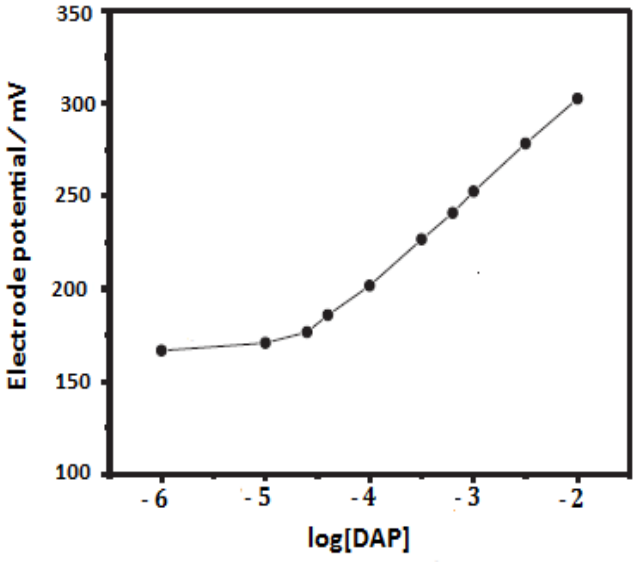


**Fig. 2 Calibration curve of DAP coated wire electrode.**

to the decomposition of the ion-pair and loss of other components in the membrane phase that was in contact with aqueous test solution containing DAP cation. The results showed that the slope of calibration curve of electrode in this way was found to 58.70 mV decade$^{-1}$ at 25 °C. It was observed that the slope sharply decreased to 47.8 mV/decade after daily use for 40 days.

*3.3 pH Effect on the Electrode Response*

To examine the effect of pH on electrode response, the potential was measured at a specific concentration of the DAP solution ($1.0 \times 10^{-2}$ M) from the pH value of 2.0 up to 12.0 (concentrated NaOH or HCl solutions were employed for the pH adjustment). The results showed that the potential remained constant despite the pH change in the range of 3.0 to 7.5, which indicates the applicability of this electrode in the specified pH range (Fig. 3). At pH higher than 7.5, the potential of electrode decreases with increasing pH of the working solution may be due to the deprotonation of DAP in the solution, which leads to a consequent decrease in its concentration [12].

These results were confirmed by pH-metric determination of the protonation constant of DAP, the mean *pKa* value obtained was 8.6, indicating that the decrease in pH outside the above the working range is due to the formation of the free base.

*3.4 Selectivity of DAP Electrode*

The influence of various basic substances on the response of DAP electrode was investigated by measuring the potentiometric interference from many sugars, inorganic cations and amino acids. The selectivity coefficients were determined by the separate solution method. The results obtained are summarized in (Table 2). The smaller the value of $K^{pot}_{DAP,B^{Z+}}$, the better the sensitivity of the electrode in the presence of the interfering ions. In case of a good ion-selective electrode, it should have a value of about $10^{-4}$. The inorganic cations do not interfere owing to the differences in ionic size and consequently their mobilities and permeabilities as compared with DAP ion. 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.

*3.5 Response Time*

The response time of the electrode were tested for concentrations of the drug from $10^{-4}$-$10^{-2}$ mol/L. The

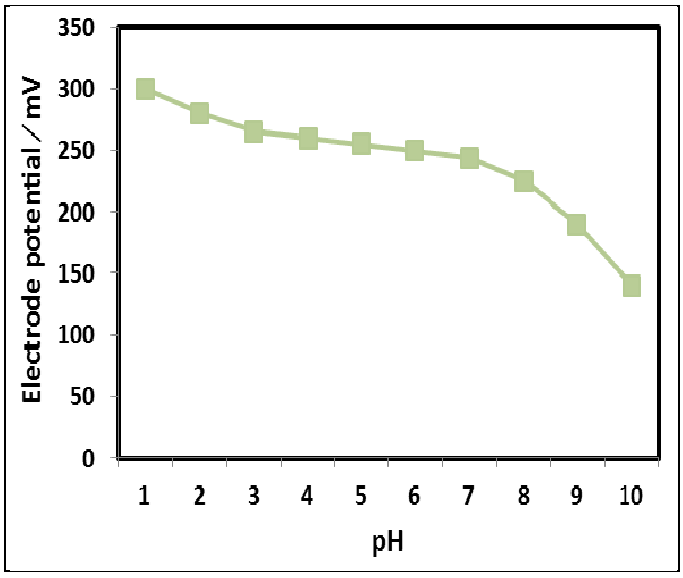


**Fig. 3 Effect of pH change of $10^{-2}$ mol/L DAP solution on the response of coated wire electrode.**

measurements were characterized by a fast stable response within 15 s over the whole concentration range. The potentials obtained for electrode remained constant for more than 4 min.

*3.6 Analytical Applications*

The proposed electrode was successfully employed for determination of DAP in pure solutions, spiked urine and plasma samples, by applying the standard additions and potentiometric titrations methods. The obtained average recovery and relative standard deviation values are summarized in Tables 3 and 4. Six replicate determinations at different concentration levels were carried out using the studied electrode to test the precision of the method. The mean % recovery found and % RSD, indicate that the proposed validated method could be adopted for the determination of the investigated drug in its in biological fluids.

## 4. Conclusion

The proposed coated wire selective electrode based on the DAP-TPB as a sensing element can be used for the determination of DAP over a wide range of concentration. The electrode showed a very good selectivity to DAP in the presence of various common inorganic cations, sugars and amino acids. The coated wire electrode has short response time ~15 s and it

**Table 2 Selectivity coefficients $K^{pot}_{DAP,\,B^{Z+}}$ of the DAP coated wire electrode calculated by the separate solution method ($1 \times 10^{-3}$ M of both DAP and the interferent) at 25 °C.**

| Interferent (B) | $K^{pot}_{DAP,\,B^{Z+}}$ | Interferent (B) | $K^{pot}_{DAP,\,B^{Z+}}$ |
|---|---|---|---|
| $NH_4^+$ | $2.9 \times 10^{-4}$ | Fructose | $3.6 \times 10^{-4}$ |
| $Na^+$ | $8.5 \times 10^{-4}$ | Glucose | $9.7 \times 10^{-4}$ |
| $Zn^{2+}$ | $1.6 \times 10^{-3}$ | Maltose | $2.1 \times 10^{-4}$ |
| $Ca^{2+}$ | $2.5 \times 10^{-3}$ | Glycine | $6.4 \times 10^{-5}$ |
| $Al^{3+}$ | $6.50 \times 10^{-4}$ | Valine | $6.4 \times 10^{-4}$ |
| Lactose | $1.6 \times 10^{-5}$ | Lysine | $8.0 \times 10^{-4}$ |

**Table 3 Application of proposed electrode for the determination of DAP in pure solutions applying the standard additions and potentiometric titrations methods.**

| Taken (μg/mL) | Standard addition | | | Potentiometric determination | | |
|---|---|---|---|---|---|---|
| | Found | Recovery (%) | RSD* (%) | Found | Recovery (%) | RSD* (%) |
| 5.00 | 5.20 | 104.00 | 1.45 | 4.84 | 96.80 | 1.35 |
| 10.00 | 9.88 | 98.80 | 1.33 | 10.03 | 100.30 | 1.12 |
| 15.00 | 14.97 | 99.80 | 1.18 | 14.92 | 99.45 | 1.41 |
| Mean | | 100.87 | 1.27 | | 98.85 | 1.21 |

* RSD (six determination).

**Table 4 Application of proposed electrode for the determination of DAP in spiked plasma and urine samples applying the standard addition method.**

| | Spiked urine | | Spiked plasma | |
|---|---|---|---|---|
| Taken (μg/mL) | recovery % | RSD* | Recovery % | RSD* |
| 5.00 | 99.90 | 0.37 | 97.90 | 0.76 |
| 10.00 | 98.67 | 0.55 | 101.50 | 0.13 |
| 15.00 | 100.05 | 0.21 | 100.40 | 0.23 |
| Mean | 99.54 | 0.38 | 99.93 | 0.37 |

* RSD (six determination).

can be used in pH range of 3.0-7.5. Additionally, the proposed method has some important advantages: the electrode proved to be successful, providing a rapid, simple and low cost potentiometric method for the determination of DAP in pure solutions and in biological fluids such as plasma and urine samples.

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