

1-1-2000

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ARZUM ERDEM

DİLŞAT ÖZKAN

KAĞAN KERMAN

BURCU MERİÇ

TAYFUN DALBASTI

*See next page for additional authors*

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# Ion-Selective Membrane Electrode for the Determination of a Novel Phenylpiperazine Antidepressant, Nefazodone

Arzum ERDEM, Dilşat ÖZKAN, Kağan KERMAN, Burcu MERİÇ

*Faculty of Pharmacy, Analytical Chemistry Department,  
Ege University, 35100 Bornova, İzmir-TURKEY*

Tayfun DALBASTI

*Faculty of Medicine, Neurosurgery Department,  
Ege University, 35100 Bornova, İzmir-TURKEY*

Mehmez ÖZSÖZ\*

*Faculty of Pharmacy, Analytical Chemistry Department,  
Ege University, 35100 Bornova, İzmir-TURKEY*

Received 25.04.2000

The construction and performance characteristics of ion-selective membrane electrodes for a newly found phenylpiperazine antidepressant, Nefazodone (NFN), based on its ion-pair complexes with phosphotungstate (PT), tetraphenylborate (TPB), tungstosilicate (TS) and reineckate (RN) in a poly(vinyl chloride) (PVC) matrix are described. The best ion-selective electrode for determination of NFN contains NFN-PT as the active material. This electrode exhibits a Nernstian response (62.6 ± 0.4 mV per decade) in the range  $1.5 \times 10^{-5}$  to  $1.0 \times 10^{-2}$  M NFN.HCl in solutions. The selectivity of this electrode to NFN in the presence of a number of sugar molecules, cations and drugs is reported. The potentiometric standard addition method and the argentometric titration method are used to determine the NFN amount in pure solution.

## Introduction

Voltammetric methods have been widely used for selective and sensitive measurements of several important groups of drugs<sup>1-7</sup>. Because of the widespread clinical use of many drugs, effective procedures for their measurements are essential. Most of these compounds are electrochemically active and such activity has been exploited previously for developing adsorptive stripping<sup>1-4</sup> and amperometric<sup>5,6</sup> schemes for their quantification.

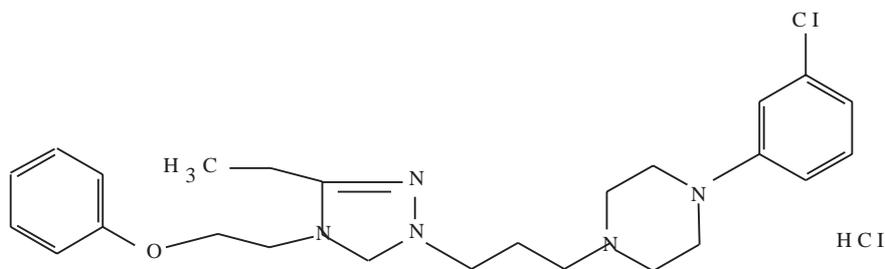
The applications of potentiometric schemes have also expanded over the past two decades with the rapid development of new selective electrodes and more sensitive and stable electronic components<sup>7</sup>. Ion-selective electrodes (ISEs) have become important and reliable devices for chemical, pharmaceutical and

\*Author to whom correspondence should be addressed. e-mail:ozsozs@eczacilik.ege.edu.tr

biomedical analysis; they are inexpensive and easy to use, and have a wide range of application<sup>8,9</sup>. One of the many existing principles for the construction of ion-selective membranes is the addition of a lipophilic ion-pair complex into a highly plasticized polymer membrane. Most of the ISEs, which are sensitive to medically important ionic compounds such as psychopharmacological drugs, alkaloids and muscle relaxants, belong to the class of ion-pair based liquid membrane electrodes<sup>10,11</sup>.

Suitable ISEs for drugs have enough selectivity towards the drugs over pharmaceutical excipients and they can be useful in the quantitative analysis of the drugs in pharmaceutical preparations without prior separations. In particular, ISEs are very useful in the case of drugs which are unstable during prior separation<sup>12,13</sup>.

**Nefazodone Hydrochloride** (2-[3-[4-(3-chlorophenyl)-1-piperazinyl]propyl]-5-ethyl-4-(2-phenoxyethyl)-3H-1,2,4-triazol-3-one hydrochloride, see Scheme 1) is a novel phenylpiperazine antidepressant, which has a potent effect on serotonergic (5-HT<sub>2</sub>) receptors. This newly developed drug is used in the treatment of depression as an alternative to more conventional antidepressants such as the tricyclics, because NFN shows no cardiotoxicity or anticholinergic activity<sup>14,15</sup>.



**Scheme 1-** Chemical structure of Nefazodone Hydrochloride.

To the best of our knowledge, no ISE has been described for the rapid and inexpensive potentiometric determination of NFN. In this study, NFN-selective membrane electrodes have been constructed using various ion-pair complexes of this new drug, and their performances have been compared. The electrode which is based on the incorporation of the NFN-PT ion-pair complex in a PVC membrane is used as a sensor to determine the amount of NFN.HCl in pure solution.

## Experimental

### Apparatus

Potentiometric measurements were carried out using an Orion Model 420A digital pH/millivolt meter. An electrode was used in conjunction with an Ingold (10303001 type) calomel electrode (SCE). The electrochemical system may be represented as follows:



### Reagents and Materials

All chemicals used were of analytical grade. Solutions were prepared with double distilled water. NFN.HCl was supplied by Bristol-Myers Squibb Co. Pharm. Ind. (Turkey). Other materials and reagents, such as

sodium tetraphenylborate (NaTPB), sodium phosphotungstate (Na-PT), tungstosilicic acid hydrate (TSA) and ammonium reineckate were obtained from Sigma. Bis(2-ethylhexyl)-sebacate (DOS), PVC of relative high molecular mass and tetrahydrofuran (THF) for ISEs were obtained from Fluka.

## Construction of the Electrodes

The ion-pair complex (IPC) was prepared by mixing 25 mL of  $10^{-2}$  M NFN.HCl with 25 mL of  $10^{-2}$  M solution of counter ion. The precipitate was filtered, washed thoroughly with double distilled water and dried at room temperature. The membrane composition (w / w) was 10.3% IPC, 37.2% PVC, 52.5% DOS. The components were dissolved in 2 ml THF.

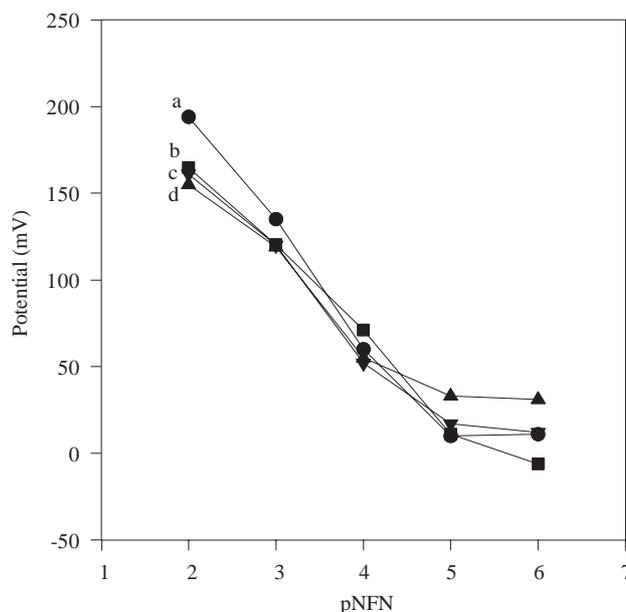
The solution containing the IPC, PVC and DOS dissolved in THF as given above was poured into a 30.5 mm i.d. glass ring on a petri dish. The solvent was allowed to evaporate at room temperature. A disk (5 mm i.d.) was cut from the membrane and fixed to the end of a 30 mm Tygon tube using a PVC-DOS-THF solution as adhesive. The electrode was then filled with  $1 \times 10^{-3}$  M NFN.HCl solution and an Ag/AgCl wire was immersed in this solution. The prepared electrode was preconditioned by soaking in  $1 \times 10^{-3}$  M NFN.HCl solution for 30 minutes. It was stored dry in a well-closed vessel in a refrigerator at  $4^{\circ}\text{C}$  when not in use.

## Results and Discussion

### Electrode Response

A typical calibration plot for each NFN-selective membrane electrode was obtained with NFN.HCl standard solutions in the range of  $10^{-2}$  -  $10^{-6}$  M.

Comparison of the response characteristics of the four kinds of electrodes under investigation are summarized in Table 1, and representative curves are shown in Figure 1.



**Figure 1.** Calibration plot for the NFN-selective membrane electrodes with NFN-PT (a), NFN-TPB (b), NFN-RN (c) and NFN-TS (d) ion-pair complexes with internal filling solution of  $10^{-3}$  M NFN.HCl.

As seen in Table 1, the NFN-PT type membrane electrode has the best Nernstian response, and thus is the most suitable, one and was chosen for all the potentiometric studies about NFN determination.

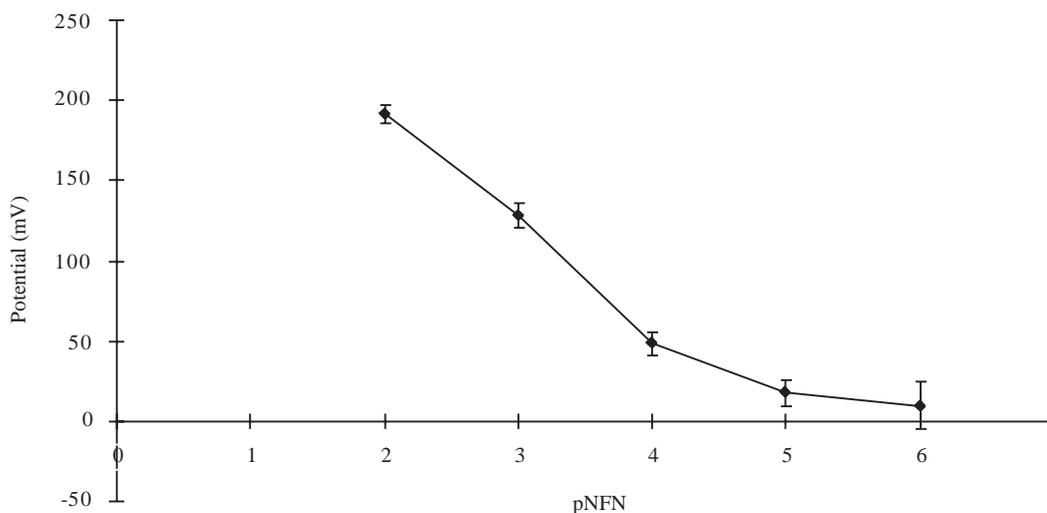
The calibration plot was obtained with the four NFN-selective membrane electrodes based on the NFN-PT ion-pair complex (Figure 2). The average slope value was found with the electrodes (n = 4) prepared from different membrane compositions, as  $60 \pm 3$  mV (CV% = 5%).

The response time was short at higher concentrations ( $10^{-2}$ - $10^{-4}$  M). Only 3 mins were required for solutions of  $1.0 \times 10^{-5}$  and  $1.0 \times 10^{-6}$  M.

**Table 1.** Comparison of the response characteristics for NFN-selective membrane electrodes.

NFN- Counter ion complex	Slope (mV/decade)	Detection Limit (M)	Response Time(sec)
NFN-PT	$62.6 \pm 0.4^*$	$1.5 \times 10^{-5}$	$\leq 20$
NFN-TPB	$47 \pm 6^*$	$1.0 \times 10^{-5}$	30
NFN-RN	$50.3 \pm 0.4^*$	$1.5 \times 10^{-5}$	30
NFN-TS	$43 \pm 6^*$	$7.0 \times 10^{-4}$	$\geq 30$

\*Standard deviation of values obtained with the identical electrodes (n=3) prepared from the same membrane composition.



**Figure 2.** Calibration plot obtained by using the four NFN-selective membrane electrodes based on NFN-PT ion-pair complex with internal filling solution of  $10^{-3}$  M NFN.HCl.

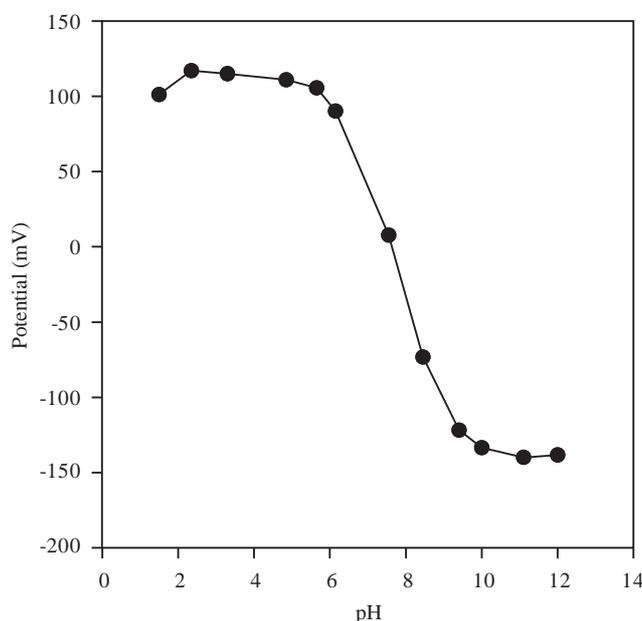
### Life-span of the electrode

The period through which the electrode retains a Nernstian response is known as the *electrode age* or *life-span*<sup>16</sup>. The electrode which was constantly used during the experiments was found to have an operative life of about 2 weeks, with the slope ranging with 17.5% from 60.0 to 70.3 mV per decade and a linear concentration range from  $1.0 \times 10^{-5}$  to  $1.0 \times 10^{-2}$  M NFN.

The electrode, which was prepared a year ago has never been used for experimental studies, and been kept dry in a well-closed vessel in the refrigerator at 4°C. This electrode was only used in the calibration plot three times during this period. The slope range changed by 29.23%, from 54.4 to 70.3 mV per decade.

### Effect of pH

The effect of pH of the test solution ( $10^{-3}$  M NFN.HCl) on the electrode potential was investigated by following the variation in potential with change in pH. The change in pH had a negligible effect in the pH range 2.0-5.5, and thus in this range the electrode can safely be used for NFN determination (Figure 3). The pKa of NFN was calculated<sup>17</sup> and found to be 6.2. At lower acidities (higher pH), free base precipitated in the aqueous test solution and, consequently, the concentration of unprotonated species gradually increased. As a result, lower e.m.f. readings were recorded.



**Figure 3.** Effect of pH on potential response of the NFN-selective membrane electrode. Other conditions are as in Figure 2.

### Selectivity of the Electrode

The selectivity of an ion-pair complex based membrane electrode depends on the selectivity of the ion exchange process at the membrane-test solution interface and the mobilities of the respective ions in the membrane, and hydrophobic interactions between the primary ion and the organic membrane. The selectivity of the NFN-selective membrane electrode is related to the free energy of transfer of the drug cation between the aqueous and organic phases. The response of the electrode towards different substances was checked and the selectivity coefficients  $K_{NFN^+, J^{z+}}^{Pot}$  were used to evaluate the degree of interference.

The values given in Table 2 were obtained using the separate solution method,<sup>18</sup> in which the following equation was applied:

$$\log K_{NFN^+, J^{z+}}^{Pot} = \frac{(E_2 - E_1)}{S} + \log[NFN^+] - \log[J^{z+}]$$

where  $E_1$  is the electrode potential in a  $10^{-3}$  M NFN.HCl solution and  $E_2$  is the electrode potential in a  $10^{-3}$  M solution of the interferent  $J^{z+}$ .

The substances and ions, listed in Table 2, are sugar molecules, the amino acid glycine, and monovalent and divalent cations, which might be frequently present in biological fluids or with NFN in pharmaceutical preparations.

The obtained results show that the electrode is reasonably selective towards NFN. Only Trifluoperazine HCl and Chlorpromazine HCl cause serious interference. This is expected from electrodes based on ion-pairing agents where highly lipophilic species will also be efficiently extracted into the membrane<sup>19</sup>. Imipramine HCl and Fluphenazine HCl also cause interference but not as serious as the interference caused by Trifluoperazine HCl and Chlorpromazine HCl.

**Table 2.** Selectivity coefficients for the NFN-selective membrane electrode.

Interferent	$K_{NFN^+, J^{z+}}^{Pot}$ (Separate Solutions Method)
$K^+$	0.0132
$Na^+$	0.0153
$Ca^{2+}$	$4.49 \times 10^{-4}$
$NH_4^+$	0.0202
Trisodium citrate-5,5' dihydrate	$4.6 \times 10^{-3}$
Ascorbic acid	0.1371
Glycine	0.0701
Lactose	0.0955
Sucrose	0.0476
Ephedrine HCl	0.0811
Imipramine HCl	0.9400
Fluphenazine HCl	0.7580
Chlorpromazine HCl	2.0070
Trifluoperazine HCl	2.0584

## Analytical Applications

### The determination of NFN. HCl in pure solutions

The pure solution contains 100.0 mg of NFN.HCl in 250 mL. 10 mL is taken as a sample. This process is repeated three times (n=3) for the experiments below.

The investigated electrode was shown to be useful in the potentiometric determination of the amount of NFN in pure solution by direct potentiometry using the standard addition method.

The argentometric titration method<sup>17</sup> was also used to determine the amount of NFN indirectly by the precipitation of  $Cl^-$  in the NFN sample. The same procedure above (n=3) is also used for this method in the same NFN pure solution. The results obtained by using potentiometric standard addition method and by argentometric titration method are  $3.8 \pm 0.3$  mg and  $3.2 \pm 0.1$  mg, respectively.

The comparison of potentiometric standard addition method and argentometric titration method was made on the basis of **Fisher-Snedecor distribution**<sup>19</sup>. It can be concluded that both the potentiometric standard method and the argentometric titration method gave identical results for the chosen probability ( $p=0.95$ ,  $n=3$ ). It was observed that the difference was not statistically significant.

The proposed potentiometric method for the determination of NFN using the NFN-selective membrane electrode has the advantages of simplicity, rapidity, reproducibility and specificity. This method requires no extraction procedure with both studies of pure solution.

The results obtained by direct potentiometry using the NFN-selective electrode are in good agreement with the argentometric titration determinations, demonstrating that it can be advantageously used in pharmaceutical analysis.

Work in this laboratory is continuing towards exploring the scope of the other applications of NFN-selective membrane electrodes.

## Acknowledgements

The authors would like to thank Bristol-Myers Squibb Co. Pharm. Ind. (Turkey) and Bristol-Myers Squibb Research Centre (USA) for supplying Nefazodone Hydrochloride. A. E. acknowledges a scholarship from the Scientific and Technical Research Council of Turkey (TUBITAK), Munir Birsal Foundation. B. M. acknowledges a scholarship for graduate students from TUBITAK.

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