Academic Sciences

International Journal of Current Pharmaceutical Research

ISSN- 0975-7066 Vol 5, Issue 4, 2013

Research Article

POTENTIOMETRIC CARBON PASTE ISEs FOR DETERMINATION OF FLUOXETINE HYDROCHLORIDE IN PHARMACEUTICAL PREPARATIONS

EMAD M. HUSSIEN, NAHLA S. ISMAIL AND FATMA M. ABDEL-GAWAD

National Organization for Drug Control and Research, Egypt. Email: emadhussien@yahoo.com

Received: 01 July 2013, Revised and Accepted: 28 July 2013

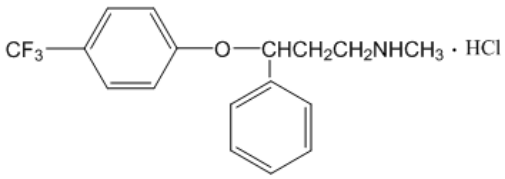
ABSTRACT

Carbon paste ion selective electrodes for fluoxetine hydrochloride (FXCl) were prepared and characterized in terms of composition, response time and usable pH range. The electrodes were applied to assay of FXCl in the drug substance and pharmaceutical product. The electrodes are based on fluoxetinium-phosphomolebdate (FX-PM) or fluoxetinium-tetraphenylborate (FX-TPB) as an ion exchanger dissolved in dioctylphthalate (DOP) as pasting liquid. The electrodes showed a sub-Nernestian slope of 52.0 mV/decade over the concentration ranges from 3 x 10^{-5} to 1 x 10^{-2} mol/L and a near-Nernestian slope of 56.5 mV/decade over the concentration range from 4 x 10^{-5} to 10^{-2} mol/L for (FX-PM) and (FX-TPB) based electrodes, respectively. The electrodes exhibited good selectivity for fluoxetine cations with respect to a large number of inorganic cations, organic cations, sugars and amino acids. The proposed electrodes offer the advantages of simplicity, accuracy and applicability to turbid solution

Keywords: Fluoxetine hydrochloride; Carbon paste ion selective electrodes; Potentiometric determination, Prozac capsule.

INTRODUCTION

Fluoxetine hydrochloride (FXCl) ((±)-N-methyl-3-phenyl-3-[(α,α,α-trifluoro-p-tolyl)-oxy]propyl-amine hydrochloride) (Scheme 1) is a selective serotonin reuptake inhibitor (SSRI) antidepressant drug, which has been widely prescribed for treatment of depression [1] and some other important disorders [2]. Fluoxetine overdoses may lead to seizures, rapid heartbeat and in worst cases to suicidal attempts.



Scheme 1

Several analytical methods for the determination of fluoxetine in pharmaceutical preparation have been developed such as chromatography [3-6], spectrophotometry [7-9], voltammetry [10, 11]. These method are either expensive or use undesirable solvent and reagents.

Previously, we reported on the construction of plastic membrane ion selective electrodes for fluoxetine [12]. A favorable characteristic of ion selective electrodes is the speed, electivity and ease of performing the assay. Herein, we extend this approach by the construction, potentiometric characterization, and analytical application of fluoxetine-selective carbon paste electrodes. The proposed electrodes have the advantage of easy preparation and generation of new active surface. The electrodes are based on the use of fluoxetinium-tetraphenylborate or fluoxetinium-phosphomolebdate as ion-exchangers and dioctylphthalate (DOP) as plasticizer.

MATERIALS AND METHODS

Materials and reagents

Fluoxetine hydrochloride drug substance was obtained from Amriya Company (Alexandria, Egypt). Prozac capsules were from Eli-Lilly Company (Lilly France S.A.S., France). Sodium tetraphenylborate (Na-TPB) and phosphomolybdic acid (PMA) were obtained from Fluka. Carbon powder and dioctylphthalate (DOP) were purchased from Aldrich. Tetrahydrofurane (THF) was purchased from Lab-Scan Analytical Science. All reagents were of chemically pure grades and bidistilled water was used throughout.

Preparation of the ion exchangers

The FX-TPB ion pair was prepared by mixing 100 ml of 10^{-2} mol/L solution of FXCl with 100 ml of 10^{-2} mol/L solution of NaTPB. The precipitate was filtered, washed thoroughly with bidistelled water, and dried at room temperature

The FX-PM ion-associate was prepared by the addition of one volume of 10^{-2} mol/L phosphomolybdic acid to three volumes of 10^{-2} mol/L fluoxetine hydrochloride solution. The precipitate was filtered, washed with bidistelled water and allowed to dry at room temperature.

Preparation of the electrodes

A Teflon holder (12 cm length) with a hole at one end (7 mm diameter, 3.5 mm deep) was as the electrode body. Electrical contact with carbon paste was made with a stainless-steel rod through the center of the holder. This rod can move up and down by screw movement. Modified carbon paste was prepared by mixing FX-PM or FX-TPB with DOP using 5 ml of THF. THF was allowed to evaporate at room temperature. Carbon powder was then added and intimate homogenization was achieved by careful mixing in a mortar. The paste was packed into the hole of the electrode body. The carbon paste was smoothed onto paper until it had a shiny appearance and was used directly for potentiometric measurements without preconditioning requirements.

Electrochemical system

Potentiometric measurements were carried out with HI 9321 microprocessor pH meter. A saturated Ag/AgCl electrode was used as an external reference electrode. The internal reference electrode was a coated wire Ag/AgCl electrode.

The electrochemical system is represented as follows:

Stainless steel/modified carbon paste/test solution//KCl salt brige/Ag/AgCl

Construction of calibration graph

The calibration graph for each electrode was constructed using solutions of different concentrations of fluoxetine hydrochloride covering the concentration range from 10^{-6} to 10^{-2} mol/L. The cell potential was recorded for each solution at constant stirring at room temperature and plotted against log [FXCl]. The slope of the calibration graph was calculated using Nernestain equation.

$$E = E^{\circ}_{ISE} + 2.303\frac{RT}{zF}\log[FXCl]$$

Where: R is the gas constant, F is the Faraday equivalent and z is the charge of the analyte. The term E°_{ISE} is a constant which is the sum of all invariants in the system.

Selectivity

Potentiometric selectivity coefficient $K^{pot}_{i,j}$ for different inorganic and organic cations were evaluated using the separate solution method (SSM) [13] and matched potential method (MPM) [14]. In the SSM the EMF value (E_i and E_j) of the electrode in pure solution of each of the primary and the interfering ion, of equal concentration, are used for calculating the selectivity coefficient. The selectivity coefficient $K^{pot}_{i,j}$ is calculated using Nickolsky-Eisenman equation.

$$\log K^{Pot}_{i,j} = \frac{(E_j - E_i)}{2.303RT/Z_i F} + \left(1 - \frac{Z_i}{Z_j}\right)\log a \qquad a_i = a_j$$

In the matched potential method the concentration of fluoxetine hydrochloride solution was increased from $a_i = 1 \times 10^{-6}$ mol/L (reference solution) to $a'_i = 1 \times 10^{-3}$ mol/L, and the change in potential (ΔE) was recorded. Then, small amounts of a solution of an interfering ion of concentration a_j (from 1×10^{-2} to 1×10^{-3} mol/L) was added to a new 1×10^{-6} mol/L reference fluoxetine hydrochloride solution until the same potential change (ΔE) is achieved. The selectivity coefficient was calculated using the following equation:

$$K^{Pot}_{i,j} = \frac{\Delta a_i}{a_j}$$

With

$$\Delta a_i = a'_i - a_i$$

Potentiometric determination of fluoxetine hydrochloride in the drug substance and in prozac capsules

Stock solution of fluoxetine hydrochloride drug substance was prepared into 100.0 mL measuring flask by dissolving 345.0 mg fluoxetine hydrochloride drug substance in 50 mL bidistilled water and diluting to mark with bidistilled water.

Stock sample solution of Prozac capsules was prepared into 100-mL measuring flask by dissolving an amount of the capsule powder (taken from average of 20 capsules), equivalent to 345.0 mg fluoxetine hydrochloride, in 50.0 ml bidistilled water. The solution was sonicated for 5 min and completed to mark with bidistilled water. The filtrate and washings were collected into a 100-ml standard volumetric flask and diluted to mark with bidistilled water.

An Aliquot of analyte solution containing 6.90, 10.35, and 17.25 mg of drug was pipette into a 100-mL beaker, and the solution was diluted to 50 mL with bidistilled water. The solution was titrated with 10^{-2} mol/L Na-TPB solution using the proposed electrodes. The volume of the titrant at the end point was obtained using the differential method.

RESULTS AND DISCUSSION

Composition and characteristics of the electrodes

Preliminary experiments showed that carbon paste electrodes, which are free from ion-associate modifier have no response toward fluoxetine. Consequently, the ion associates fluoxetinium-phsphomolebdate (FX-PM), fluoxetinium-phosphotungestate (FX-PT), fluoxetinium-renicate (FX-RC) and fluoxetinium-tetraphenylborate (FX-TPB) were prepared and investigated as modifiers for the paste. FX-PTA was practically insoluble in the pasting liquid (DOP), and FX-RC was soluble in water, therefore, these ion-associates were not useful as modifiers and were excluded. The ion-associates, FX-TPB and FX-PM, were used for the preparation of modified carbon paste electrodes. The effect of varying the composition of the paste on the response of the electrodes toward fluoxetine was investigated in terms of linear range, slope and detection limit. It was observed that the sensitivity and linearity depend significantly on the amount (w/w %) of the modifier in the paste. Table 1 summarizes the effect of varying the composition of the paste on the response of FX- PMA and FX-TPB based electrodes.

Table 1: Effect of changing the composition on the response of the electrodes at room temperature

Electrode	Composition % (w/w)				Slope (mV/decade)	Linear range (mol/L)	Detection limit (mol/L)	RSD[a] (%)
	Ion-pair	DOP	PVC	C				
FX-PM								
I	3.0	48.50	-	48.50	51.6	3.0×10^{-5} - 1.0×10^{-2}	3.0×10^{-5}	
II	5.0	47.50	-	47.50	52.0	3.0×10^{-5} - 1.0×10^{-2}	3.0×10^{-5}	0.68
III	7.5	46.25	-	46.25	50.0	3.0×10^{-5} - 1.0×10^{-2}	3.0×10^{-5}	-
IV	10.0	45.00	-	45.00	47.0	8.0×10^{-4} - 1.0×10^{-2}	6.0×10^{-5}	-
VI	13.0	43.50	-	43.50	45.0	1.0×10^{-4} - 1.0×10^{-2}	8.0×10^{-5}	-
FX-TPB								
I	5.00	47.50	47.50	-	56.5	1.0×10^{-5} - 1.0×10^{-2}	1.0×10^{-5}	0.36
II	7.50	46.25	46.25	-	55.0	4.0×10^{-5} - 1.0×10^{-2}	1.0×10^{-5}	-
III	10.00	45.00	45.00	-	51.0	1.0×10^{-4} - 1.0×10^{-2}	3.0×10^{-5}	-
IV	15.00	42.50	42.50	-	47.0	1.0×10^{-4} - 1.0×10^{-2}	6.0×10^{-5}	-

[a] Relative standard deviation (four preparations)

A carbon paste electrode containing 5.0% FX-PM, 47.5% carbon powder and 47.5% DOP, showed a sub-Nernestian slope of 52.0±0.68 mV/decade with a linear response in the concentration range from 3.0×10^{-5} to 1.0×10^{-2} mol/L and a detection limit of 3.0×10^{-5} mol/L. Whereas, a carbon paste modified with FX-TPB (5.0% FX-TPB, 47.5% carbon powder and 47.5% DOP), exhibited a near Nernestian response of 56.5±0.36 mV/decade. The linear range and the lower detection limit were 4.0×10^{-5} to 1.0×10^{-2} mol/L and 1.0×10^{-5}, respectively. The calibration curves of FX-PM and FX-TPB modified carbon paste electrodes are shown in Figure 1.

Calibration of the electrodes at different time intervals over four weeks showed that the electrodes retained their sensitivity to fluoxetine for 10 days and 16 days for FX-PM and FX-TPB electrodes, respectively. Afterwards, the slopes were decrease gradually to reach 42 mV and 48 mV/decade for FX-PM and FX-TPB electrodes, respectively.

Response time

The dynamic response time of the proposed electrodes was studied under stirring by measuring the time required to achieve a steady state potential (within ± 1 mV) after successive immersion of the electrode in a series of fluoxetine hydrochloride solutions from 1.0×10^{-6} to 1.0×10^{-2} mol/L, each having a 10-fold increase in concentration. A small potential drift (2 mV/min.) was observed for the FX-PM based carbon paste electrode at lower concentrations of fluoxetine hydrochloride, 10^{-6} and 10^{-5} mol/L. The cell potential remained constant (within ± 1 mV) for about 5 minutes at 10^{-4} and 10^{-3} mol/L. A drift in the cell potential of 1.4 mV/min was observed again when the electrode was immersed in 10^{-2} mol/L. Contrary to the FX-PM electrode, the FX-TPB electrode showed a small potential drift of 0.6 mV/min when the electrode was immersed in 10^{-6} mol/L. The cell potential was steady within ±1 mV at 10^{-5} mol/L and up to 10^{-2} mol/L fluoxetine hydrochloride

solution. Figure 2 shows the potential time response of FX-PM and FX-TPB based carbon paste electrodes.

Effect of pH

In order to check the dependence of the potential of the electrodes on the pH of the solution, potential-pH curves were constructed. The pH of 10^{-3} mol/L fluoxetine hydrochloride solution was altered by the addition of small volumes of 0.1 mol/L NaOH or 0.1 mol/L HCl. Fig. **2** shows that the potential of the electrodes is practically independent of the pH in the range from 4 to 7 for 10^{-3} mol/L fluoxetine hydrochloride solution. At higher pH (pH >7), the potential reading changes slightly due to the conversion of fluoxetine hydrochloride (pKa = 8.7) to the fluoxetine base. Further addition of NaOH (at pH >8.7) lead to a dramatic change in the potential of the electrodes due to further depletion of fluoxetine hydrochloride and diffusion of OH^- into the surface of the electrode. Interference from H^+ at lower pH (pH <4) was observed for both electrodes.

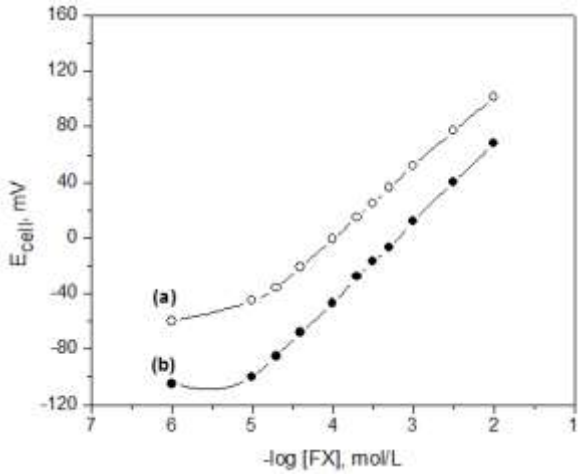
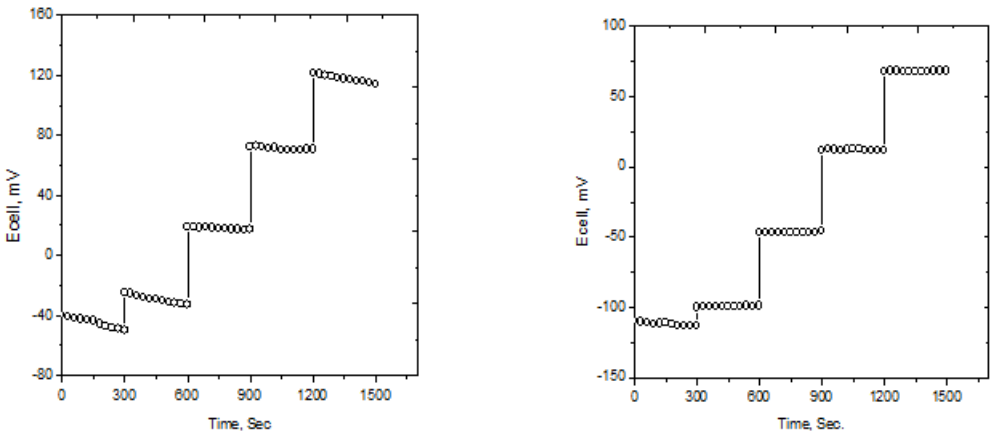


Fig. 1: Calibration curve of a) FX-PM and b) FX-TPB carbon paste electrodes.



(a) (b)

Fig. 1: Typical potential-time plot for the response of a) FX-PM and b) FX-TPB carbon paste electrodes.

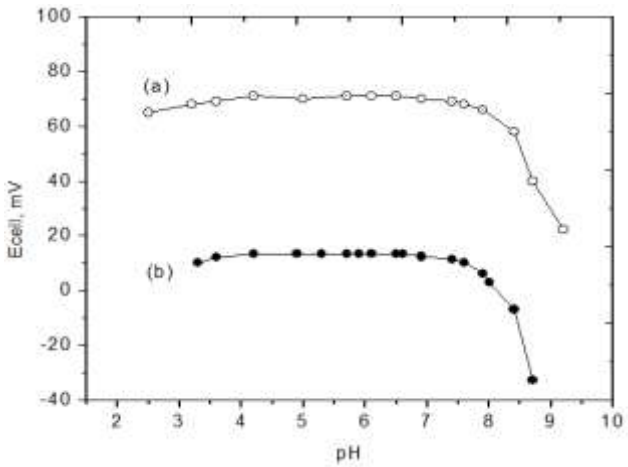


Fig. 2: Effect of pH change of 10^{-3} mol/L FXCl solution using a) FX-PM and b) Na-TPB based carbon paste electrodes.

Effect of interference

The interference of some common inorganic cations, sugars and amino acids was investigated using the separate and matched potential method [13, 14]; the two methods were recommended by the IUPAC in 1976 and 1995, respectively. The MPM was recommended as a method that gives analytically relevant practical selectivity coefficient values and overcome the limitation of the SSM. In case of MPM, the selectivity coefficient was calculated using the concentration of the interfering ion that induces a cell potential change of ≥10 mV. The selectivity coefficient were not calculated for interfering ions which induced a cell potential change of <10 mV. The selectivity coefficients are summarized in Table 2. Due to the very small values of $k^{MPM}_{i,j}$ they are tabulated as the negative logarithm $-\log k^{MPM}_{i,j}$ Practical calibration curves showed that there is small interference from Al^{3+}, Fe^{3+} and Ce^{4+} at high concentration (figure 4). The selectivity coefficient values obtained by the MPM confirms a small interference from Al^{3+}, Fe^{3+} and Ce^{4+} at high concentration whereas the SSM showed that the electrodes are extremely selective to FX ions for Al^{3+}, Fe^{3+} and Ce^{4+}, which is practically not correct.

The selectivity coefficient values recorded in Table 2 indicate that the electrode can be used for determination of fluoxetine in presence of high concentration of the interfering ions without fear of interference.

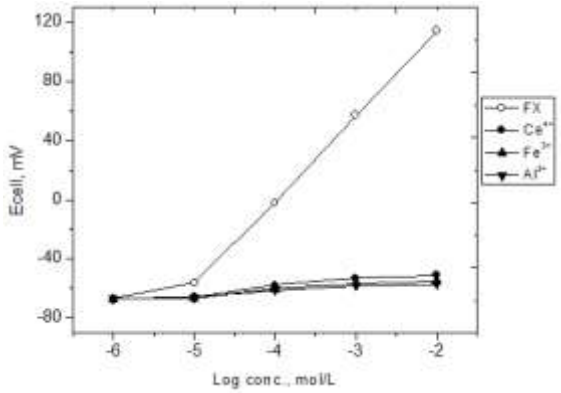


Fig. 4: E_{cell}-logc curves for determing the MPM selectivity coefficient of FX-PM carbon paste electrodes for FXCl against Al^{3+}, Fe^{3+} and Cr^{4+}. The initial reference solution of FXCl was 1 x 10^{-6} mol/L.

Table 2: Selectivity factor values $-\log K^{MPM}_{i,j}$ for FX- selective PVC membrane.

	FX-PM		FX-TPB	
Interferent	**MPM**	**SSM**	**MPM**	**SSM**
Na^{+}	3.8	3.17	2.05	2.78
K^{+}	3.49	3.31	-	2.97
NH_4^{+}	3.8	3.23	-	2.97
Ca^{++}	-	4.29	3.05	3.85
Cu^{++}	3.4	4.17	-	3.85
Co^{++}	3.24	4.20	2.05	3.87
Ba^{++}	2.97	4.31	3.05	3.97
Ni^{++}	3.12	4.29	-	4.12
Pb^{++}	-	4.17	-	4.10
Al^{3+}	1.4	4.54	1.05	4.83
Fe^{3+}	1.57	4.45	1.05	4.74
Ce^{4+}	1.75	4.44	2.05	4.72
Alanine	-	-	-	-
Glycin	-	-	-	-
D,L-Threonine	-	-	-	-
Maltose	-	-	-	-
Glucose	-	-	-	-

Analytical application

The proposed electrodes were proved useful for the assay of fluoxetine in the drug substance and pharmaceutical product by potentiometric titration using tetraphenylborate as a titrant. The end point was determined by the first derivative method. The accuracy and precision were tested at three different concentration levels (6.90-17.25 mg/50 mL), five samples were used at each level. The mean recovery obtained was within ± 2% for the drug substance and Prozac capsule, respectively. The relative standard deviation was ≤2.0%, indicate reasonable repeatability and reproducibility of the proposed methods. The accuracy and precision of the assay of fluoxetine hydrochloride in the drug substance and in Prozac capsule using the proposed electrodes are summarized in Table 3. Figure 5 shows the potentiometric titration curves of FXCl with Na-TPB using the FX-PM and FX-TPB electrodes.

Table 3: Accuracy and precision for quantification of fluoxetine hydrochloride in the drug substance and Prozac capsule using FX-PM and FX-TPB carbon paste electrodes.

		FX-PM			FX-TPB			
Fluoxetine hydrochloride	**Taken (mg/50 ml)**	**Found ± SD (mg/50 ml)**	**Recovery (%)**	**RSD (%)**	**Found ± SD (mg/50 ml)**	**Recovery (%)**	**RSD (%)**	**Reported method [8]**
Drug substance								
	6.90	6.85 ± 0.11	98.27	1.6	6.81 ± 0.09	98.7	1.32	
	10.35	10.41 ± 0.16	100.58	1.54	10.30 ± 0.12	99.52	1.16	
	17.25	17.28 ± 0.23	100.17	1.33	17.40 ± 0.22	100.17	1.26	
Prozac capsule								
	10.35	100.08 ± 1.4			99.56 ± 1.27			100.08 ± 1.4
		t=0.33			t=0.25			2.306
		F= 1.32			F= 1.47			6.39

Mean ± standard deviation of five determinations.

To compare the proposed methods to a reference method, fluoxetine in capsules was assayed by spectrophotometry using 2,3-dichloro-5,6-dicyano-p-penzoquinone (DDQ) [8]. Statistical comparison using Student's t- and F-ratio tests at 95% confidence level, the calculated t- and F- values did not exceed the critical values, indicating that there is no significant difference between the proposed and the spectrophotometric methods with regard to accuracy and precision.

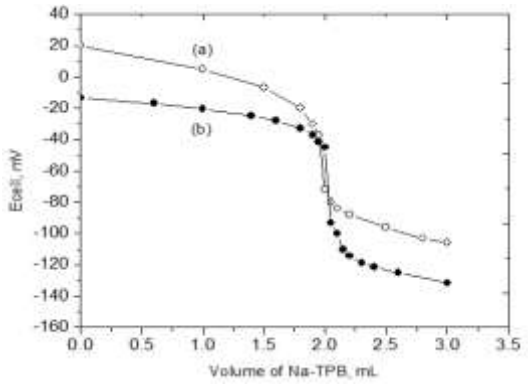


Fig. 5: Potentiometric titration of 6.90 mg FXCl against 10^{-2} mol/L Na-TPB using a) FX-PM and b) FX-TPB carbon paste electrodes.

CONCLUSION

The proposed carbon paste electrodes based on fluoxetinium-phosphomolebdate or fluoxetinium-tetraphenylborate as the electroactive compounds might be a useful analytical tool and an interesting alternative in the determination of FX the drug substance and pharmaceutical product. The present electrodes show high sensitivity, reasonable selectivity, fast static response, long-term stability and applicability over a wide pH range. The carbon paste electrode has the advantage of being easy to prepare and regeneration of the active surface.

REFERENCES

1. M. Asberg, P. Thoren, L. Traskman, L. Bertilsson, V. Ringberger, *Science,* 191 (1976) 478.
2. S. H. Y. Wong, S. S. Dellafera, R. Fernandes, H. Kranzler, *J. Chromatogr.,* 499 (1990) 601.
3. United States Pharmacopeia and National Formulary USP 34 NF 29 (2011), Fluoxetine Hydrochloride, p 2877
4. M. A. Raggi, F. Bugamelli, G. Casamenti, R. Mandrioli, D. De Ronchi, V. Volterra, *J. Pharmaceut. Biomed. Anal.,* 18 (1998) 699.
5. M. A. El-Dawy, M. M. Mabrouk, F. A. El-Barbary, *J. Pharmaceut. Biomed. Anal.*, 30 (2002) 561.
6. J. J. Berzas, C. Guiberteau, A. M. Contento, V. Rodriguez, *Chromatographia* 56 (2002) 545.
7. A. H. Prabhakar, V. B. Patel, R. Giridhar, *J. Pharmaceut. Biomed. Anal.,* 20 (1999) 427.
8. L. I. Bebawy, N. El-Kousy, J. K. Suddik, M. Shokry, *J. Pharmaceut. Biomed. Anal.,* 21 (1999) 133.
9. B. Starczewska, K. Mielech, *J. Pharmaceut. Biomed. Anal.,* 23 (2000) 243.
10. A. da Silva, J. C. Lima, M. T. O. Teles, A. M. O. Brett, *Talanta* 49 (1999) 611.
11. H. P. A. Nouws, C. Delerue-Matos, A. A. Barros, J. A. Rodrigues, A. Santos-Silva, F. Borges, *Analyt. Lett.,* 40 (2007) 1131.
12. E. M. Hussien, F. M. Abdel-Gawad, Y. M. Issa, *Biochem. Eng. J.,* 53 (2011) 210.
13. G. G. Guilbault, R. A. Durst, M. S. Frant, H. Freiser, E. H. Hansen, T. S. Light, E. Pungór, G. Rechnitz, N. M. Rice, T. J. Rohm, W. Simon, and J. D. R. Thomas, *Pure & Appl. Chem.*, 48 (1976) 127.
14. Y. Umezawa, K. Umezawa, H. Sato, *Pure & Appl. Chem.,* 67 (1995) 507.