

*Full Paper*

## **Poly(Pyrrole) Conducting Polymer Solid-State Sensor for Potentiometric Determination of Fluoxetine**

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*Received: 26 December 2018 / Received in revised form: 4 March 2019 /*

*Accepted: 18 March 2019 / Published online: 31 May 2019*

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**Abstract-** An electrochemical potentiometric sensor was introduced for Fluoxetine (FLX) analysis in pharmaceutical formulations using conducting polymer coated on a solid-state contact. FLX is one of the antidepressant of the selective serotonin reuptake inhibitor (SSRI) class. For this purpose, pyrrole was electrochemically polymerized on the surface of a solid contact made of graphite to form a thin layer of poly(pyrrole) (PPy). After this step, a thin layer of another polymeric composite composed of poly(vinyl chloride), dibutyl phthalate and ion-pair compound of FLX and phenyl borate was covered on the treated surface. The modified graphite rod was finally used as a working electrode in a potentiometric cell assembly. Linear concentration range of  $1.0 \times 10^{-6}$  to  $1.0 \times 10^{-3}$  mol L<sup>-1</sup>, lower detection limit of  $6.3 \times 10^{-7}$  mol L<sup>-1</sup>, 8s response time, and two months lifetime were the characterizations of the proposed sensor. Finally, FLX content of some pharmaceutical samples were analyzed by the prepared sensor accurately and precisely.

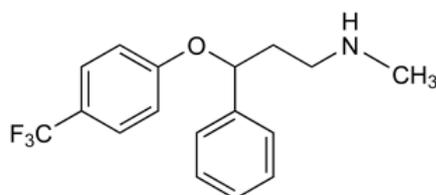
**Keywords-** Fluoxetine; Sensor; Potentiometry; Conducting Polymer; Poly(pyrrole)

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### **1. INTRODUCTION**

Fluoxetine (here abbreviated as FLX), N-Methyl-γ-[4-(trifluoromethyl)phenoxy] benzene propanamine (Scheme 1), is an antidepressant of the selective serotonin reuptake inhibitor (SSRI). FLX does not substantially inhibit norepinephrine or dopamine reuptake at therapeutic

doses but it can delay reuptake of serotonin and causing the released serotonin persevering longer. It is usually prescribed medication for depressive disorder, obsessive-compulsive disorder (OCD), bulimia nervosa, panic disorder, and premenstrual dysphoric disorder [1]. FLX is on the World Health Organization's List of Essential Medicines and is a popular medication [2].



**Scheme 1.** Fluoxetine chemical structure

Because of the great importance and extensive prescription of FLX, its determination is essential in pharmaceutical industries and medical purposes. However, similar to most of the drug, generally it is analyzed by instrumental methods such as chromatographic methods [3-7]. Designing electrochemical sensors for determination of drug molecules especially in pharmaceutical formulation can be a replace for sophisticated and expensive instruments [8-12].

For designing an electrochemical potentiometric sensor, there is a need to place a PVC membrane containing a suitable sensing element on a suitable transducer. Ion-to-electron transfer when just a PVC membrane is in contact with a solid conductor cannot be performed effectively. Hence, many researches have focused to introduce intermediate materials for improvement of this phenomenon. In this regards, conducting polymers (CPs), polymers possessing efficient electrical and ionic conductivity, can be a right choice [13-15]. Beside, using a layer of CP on the solid transducer surface causes a better adherence of the PVC layer (the sensing layer of the sensor). In a traditional PVC membrane electrode, the sensing membrane is placed between two inner and outer solutions [16] but in a new electrode design, the membrane is placed on a graphitic or metallic conductor. The former has defect of drift in potential as a result of high charge-transfer resistance while in the second one, this phenomenon is improved through a better ion-to-electron transducer between the conducting layer and the membrane. The conducting polymer layer and the sensing layer can be used as separately layer by layer or in a composite form. However, the electrochemically deposition of the conducting layer and then physically placing the sensing layer leads to better adherence to the solid contact and improve the sensor performance.

Poly(pyrrrole)s (PPy) with high electrochemical conductivity can be a good choice in this case [13]. PPy is categorized as "quasi-unidimensional" polymer in contrast with one-dimensional ones, because some crosslinking and chain occurs during its polymerization. PPy

film is typically insoluble in water and can be stable in air up to 150 °C [17]. PPy is an insulator but its oxidized derivatives can be good electrical conductors. The conductivity of PPy depends on the conditions and reagents used in the oxidation process. Conductivities can range from 2 to 100 S/cm. Higher conductivities can be achievable using larger anions during its polymerization.

In this work, a solid-state potentiometric PVC membrane sensor based on conducting polymer of PPy was introduced for the determination of FLX in some pharmaceutical formulations. PPy is utilized as an ion-to-electron transducer and ion-pair compound of FLX-tetraphenyl borate is used as a sensing material.

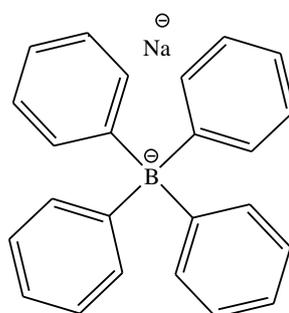
## 2. EXPERIMENTAL

### 2.1. Chemical and Reagents

High-molecular weight poly(vinylchloride) (PVC), pyrrole (>98%), sodium tetraphenylborate (NaTPB), dibutyl phthalate (DBP), and tetrahydrofuran (THF), and all inorganic salts, which were analytical reagent grade, were from Merck Co. and used as received. Fluoxetine hydrochloride and its pharmaceutical formulations were obtained from a local pharmaceutical company (Tehran, Iran). All aqueous solutions were prepared using deionized distilled water.

### 2.2. Preparation of the ion-pair compound

The ion-pair of the FLX-Tetraphenyl borate was synthesized as follow. Mixing about 20 mL of 0.01 mol L<sup>-1</sup> solution of fluoxetine hydrochloride with 20 mL of 0.01 mol L<sup>-1</sup> solution of NaTPB resulted an insoluble precipitate which was then filtered, washed and dried to be used. NaTPB (Scheme 2) is an organic salt with hydrophobic large anions and small inorganic cations. This salt is typically precipitating reagents for making ion-pair.



**Scheme 2.** Chemical structure of NaTPB ionic additives

### 2.3. Devices and instruments

Electro-polymerization of pyrrole was done in a three-electrode electrochemical cell setup by aid of a DropSens  $\mu$ Stat400 Bipotentiostat/Galvanostat (Asturias, Spain). Working electrode was a graphite rod electrode (GE), an Ag/AgCl Azar-electrode was used as reference electrode and a platinum wire as an auxiliary electrode. Potentiometric measurements were done in a cell assembly composed of an Ag/AgCl 1M KCl reference electrode and the prepared working electrode both connected to a mili-voltmeter ( $\pm 0.1$ ).

### 2.4. Sensor preparation

Pyrrole was electro-polymerized on the surface of a graphite rod to form a thin layer of Poly(pyrrole) in potentiodynamic modes in electrolyte solution of  $1.0 \times 10^{-1}$  mol L<sup>-1</sup> of pyrrole and  $1.0 \times 10^{-1}$  mol L<sup>-1</sup> of KI as described elsewhere [13]. Polymerization was done in the potential range of 0.0-1.0 V vs. Ag/AgCl with a scan rate of 20 mVs<sup>-1</sup> for 5 cycles on graphite electrode (GE). The resulting electrode was indicated as PPy/GE. For making the sensing membrane, a certain amount of PVC (30 mg) and optimized amounts of ion-pair of FLX-tetraphenyl borate (7 mg), with 63 mg DBP plasticizer were dissolved in 2mL THF and slowly heated to evaporate the solvent and an oily concentrated mixture was formed. The PPy/GE was dipped in the above prepared cocktail for about 10s and dried in room temperature for 5h. Next, it was conditioned in a  $1.0 \times 10^{-3}$  mol L<sup>-1</sup> of FLX hydrochloride solution for one day. The final prepared electrode (PVC membrane/PPy/GE) was used as FLX sensor in a potentiometric cell assembly for further studies.

## 3. RESULTS AND DISCUSSION

### 3.1. Electro-polymerization of pyrrole on the graphite rod

Electro-polymerization (EP) is a coating process in which a conducting polymer film is formed and deposited from a monomer solution onto a conducting substrate (here the electrode). Selecting the EP condition, such as applied potential is very important. The applied potential should be high enough to be able to oxidize and polymerize the monomer, and low enough to avoid induce corrosion of the electrode. EP is performed in a three-electrode electrochemical cell assembly. The solution generally contains the monomer and the supporting electrolyte. EP can be done in potentiodynamic, galvanostatic or potentiostatic modes. In the first mode, EP is done through the potential cyclic sweep between the monomer oxidation potential and the reduction potential of the polymerized conducting polymer. In this way, the polymer film continuously changes from its neutral state to its conducting state as the potential is swept back and forth. In two other modes, a constant potential was applied to the electrode. However, in galvanostatic mode at start of the EP process, the potential rises for a

short period and then decreases. PPy film which is formed through potentiostatic or galvanostatic modes is dendritic type and have low adhesion strength on the electrode surface. While PPy which is polymerized using potentiodynamic mode, is shiny black and adheres strongly on the surface, and also has a smooth and homogenous morphology [18]. This is due to the formation of a large number of equivalent nucleation sites during the growth process.

PPy which chemically synthesized is usually yellow however because of oxidation in air it changes to brown. PPy thin film electro-polymerized on a surface is observed as dark-blue to black depending on the degree of polymerization and the thickness of the film. Here, the electro-deposition of PPy films on the graphite electrode was done in a potentiodynamic mode as described above and a shiny black film was formed on the GE surface. Cyclic voltammetry also showed an obvious and increase capacitive current at PPy/GE in comparison with bare GE. The higher capacitive current in PPy/GE can causes a better potential stability in potentiometric sensor.

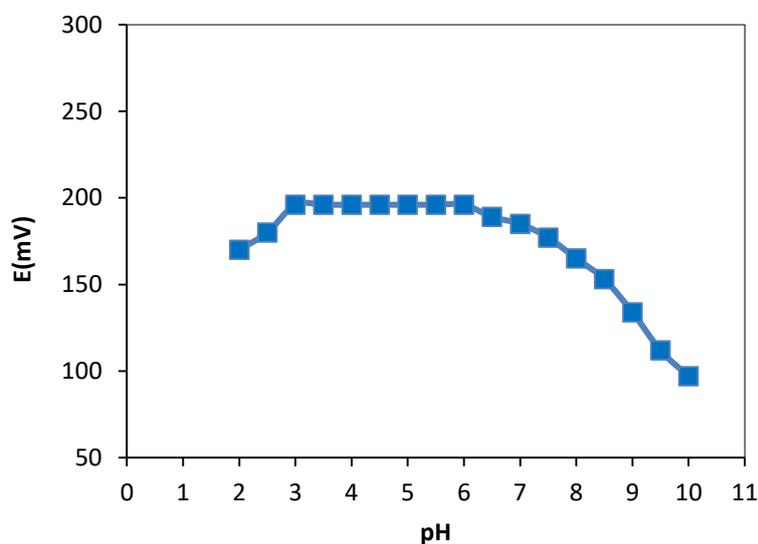
### 3.2. Sensor Characterization

After EP of the pyrrole on the surface of the GE, a layer of sensing element was placed on the modified surface as described above, and the prepared working electrode was assembled in a potentiometric cell.

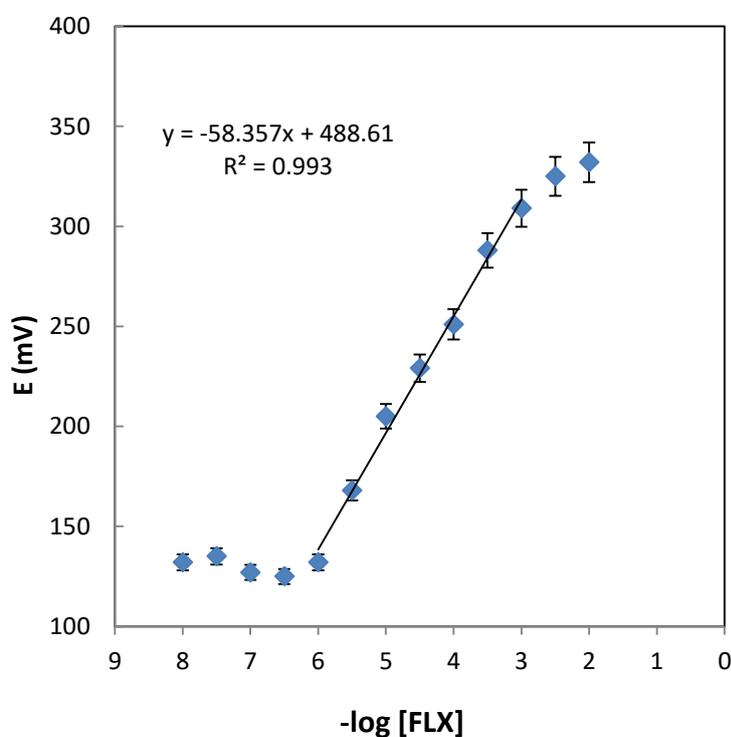
To study the effect of membrane ingredients on the sensor response, various amounts of ion-pair compound, PVC, DBP as plasticizer and NaTPB as additives were selected [19-25] and the potential response of each electrodes in terms of Nernstian slope was recorded. The optimized amount of membrane ingredients were 30% PVC, 7% ion-pair of FLX-TPB, and 63% DBP which showed a slope of  $58.3 \pm 0.4$  mV decade<sup>-1</sup>. Furthermore, membrane with no sensing element was studied and showed a poor response (slope of  $4.6 \pm 0.8$  mV decade<sup>-1</sup>) toward FLX. DBP, a rather non-polar solvent with dielectric constant of 6.4 was selected as the best plasticizer to improve the membrane plasticize ability and help the better extraction of FLX from an aqueous solution to the sensing membrane. Ionic additives are components applied in the membrane in order to diminish the electrical resistance. However, the presence of PPy in the electrode construction leads to the remarkable decrease in charge-transfer resistance during the potential measurement. As a result there was no need to use ionic additives in the sensor fabrication.

Working pH range of any sensor is an important parameter which should be studied. The effect of pH on the response of the proposed sensor was studied in FLX solutions ( $1.0 \times 10^{-5}$  mol L<sup>-1</sup>) over a pH range of 2-10. The pH of the solution was adjusted at the required value by addition of concentrated HCl or NaOH. Fig. 1 shows the potential changes in this pH range. As can be seen, the sensor can be performed in the range of 3.0-6.0. Fluctuation above the pH 6.0 is due to the removing positive charge on the drug molecule.

A standard series of FLX concentration (from  $1.0 \times 10^{-8}$  to  $1 \times 10^{-2}$  mol L<sup>-1</sup>) was prepared and the performance of the proposed sensor based conducting polymer with optimized membrane composition was studied. The obtained calibration curve was shown in Fig. 2. As can be seen, the measuring range of the sensor is linear in the range of  $1.0 \times 10^{-6}$  to  $1.0 \times 10^{-3}$  mol L<sup>-1</sup>.



**Fig. 1.** Potential changes of the FLX sensor vs. pH in a solution of FLX ( $1.0 \times 10^{-5}$  mol L<sup>-1</sup>)



**Fig. 2.** Potential changes of the conducting polymer based sensor vs. concentration of FLX

Detection limit for a potentiometric drug sensor is defined as the concentration at which the measured potential varies from the Nernstian response. According to the IUPAC recommendation, the detection limit is measured by the cross-section of the two extrapolated linear parts of the ion-selective electrode calibration curve [26-30]. Based on the calibration curve in Fig. 2, the lower detection limit of the proposed sensor to FLX is  $6.3 \times 10^{-7}$  mol L<sup>-1</sup>.

Response time of a potentiometric sensor is defined as the required time at which the potential of the cell has gotten to 90% of the final value after immersing the electrodes in the solution [26-30]. Relatively short analysis times can make a method applicable as a detection tool. A short response of 8s was observed in the whole concentration range. The lifetime of the proposed FLX sensor is two months. During this period of time, the sensor can work probably and the changes in its characterization was less than 3.7%. Using conducting polymer as an interface between solid graphite contact and the polymeric membrane, mechanical stability and shelf life of the sensor was improved extremely.

Selectivity of the new sensor was calculated through the matched potential method (MPM) [26-30]. As shown in Table 1, the selectivity coefficients for all interferences tested is not significant, which indicates the high selectivity of the proposed sensor toward FLX drug molecule.

**Table 1.** Selectivity coefficients for Tramadol ion selective electrode

Interference	Log K <sub>MPM</sub>
Na <sup>+</sup>	-4.9
K <sup>+</sup>	-4.7
Mg <sup>2+</sup>	-4.5
Ca <sup>2+</sup>	-4.9
NH <sub>4</sub> <sup>+</sup>	-3.6
Cl <sup>-</sup>	-4.6
NO <sub>3</sub> <sup>-</sup>	-4.4
Lactose	-
Glucose	-

Repeatability and reproducibility of the proposed sensor was also studied. For repeatability, 5 replicate standard samples of FLX were measured by a certain sensor. RSD value of less than 3.3% was obtained for these replicate measurements. For reproducibility, 5 sensors were prepared with the same condition. Then certain concentration of FLX was analyzed by these sensors. The RSD among the results was less than 5.2%.

Comparison of the obtained results with the only report [31] on FLX potentiometric determination was done in Table 2.

**Table 2.** Comparison of the developed sensor for FLX determination with a previous reported sensors

The electrode	Detection Limit (mol L <sup>-1</sup> )	Linear Range (mol L <sup>-1</sup> )	Response Time (s)	pH range	Life-time	Ref.
PVC membrane electrode	1.0 × 10 <sup>-5</sup>	1.0 × 10 <sup>-5</sup> - 1.0 × 10 <sup>-2</sup>	25	3.2-7.2	6 weeks	[31]
Ion-pair-MWCNT-Nanosilica Carbon paste electrode	5.0 × 10 <sup>-6</sup>	5.0 × 10 <sup>-6</sup> - 5.0 × 10 <sup>-2</sup>	20	3.2-7.2	8 weeks	[31]
PVC membrane/PPy/GE	6.3 × 10 <sup>-7</sup>	1.0 × 10 <sup>-6</sup> - 1.0 × 10 <sup>-3</sup>	8	3.0-6.5	8 weeks	This work

As it can be obviously seen, the proposed sensor is comparable to the previous report in terms of important characterization of a sensor.

### 3.3. Pharmaceutical Analysis

To test the analytical ability of the prepared sensor, it was utilized in the determination of FLX in some pharmaceutical capsules (Table 3). The active ingredient of the capsules was determined using standard addition method. For this assay, 20 capsules of FLX.HCl were opened and the powders thoroughly mixed. Amounts equivalent to the weight of 5 tablets (each capsule contain 20 mg FLX) were weighed carefully and transferred into a 100-mL volumetric flask, shaken thoroughly and diluted with acetate buffer (0.05 mol L<sup>-1</sup>; pH=4.7). Suitable amounts of this solution were filtered through a Millipore filter (0.45 mm). This solution was used as a standard solution. The same samples were also analyzed by HPLC method as standard method. As t-test shows, there is no significant difference between the results of the proposed sensor and HPLC standard method [4].

**Table 3.** Potentiometric determination of fluoxetine in pharmaceutical formulations

Sample	Found* by the sensor	Found* by HPLC method	t-test (p-value: 0.05; t <sub>theoretical</sub> : 2.31)
1	21.13±2.55	19.02±1.29	t <sub>experimental</sub> =1.65
2	19.07±1.45	20.11±0.33	t <sub>experimental</sub> = 1.18
3	23.17±0.93	21.77±1.05	t <sub>experimental</sub> = 2.23

\*the number of replicates was 5.

#### 4. CONCLUSION

A solid state potentiometric sensor was made for Fluoxetine (FLX) quantification in pharmaceutical formulation. Electro-polymerization of pyrrole was done in aqueous potassium iodide solution to modify the surface of a graphite rod. Using PPy in the designed sensor improved the ion to electron transduction. The proposed solid contact based conducting polymer sensor is in comparison with traditional symmetric PVC membrane electrodes or even asymmetric coated wire ones, showed superior performance. The proposed sensor possessed long term lifetime in a wide linear range of  $1.0 \times 10^{-6}$ - $1.0 \times 10^{-3}$  mol L<sup>-1</sup>) with a Nernstian slope of  $58.3 \pm 0.4$  mV decade<sup>-1</sup>. Real sample analyses confirmed the applicability of the sensor in quantification of FLX active ingredients of pharmaceutical formulation accurately and precisely.

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