Anal. Bioanal. Electrochem., Vol. 8, No.1, 2016, 51-63

Analytical & Bioanalytical Electrochemistry

Full Paper

Novel Membrane Sensors for the Determination of Quetiapine Fumarate in Plasma and in Presence of its Related Compounds

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Received: 14 October 2015/Accepted: 26 January 2016 /Published online: 15 February 2016

Abstract- Two sensitive and selective polyvinyl chloride (PVC) matrix membrane sensors were developed and investigated for determination of the cationic drug Quetiapine Fumarate (QTF) in pure form, in plasma and in presence of its two related compounds namely Quetiapine N-oxide and Des-ethanol Quetiapine. The two sensors (I and II) were developed using sodium tetraphenyl borate as a cation exchanger with dioctyl phthalate (DOP) as a plasticizer. Selective molecular recognition component, β-cyclodextrin (β-CD), was used as ionophore to improve the selectivity of sensor II. The proposed sensors had a linear dynamic range of 1×10^{-6}-1×10^{-2} mol L^{-1} for sensor I and 1×10^{-7}-1×10^{-2} mol L^{-1} for sensor II with Nernstian slopes of 27.50±0.45 and 39.85±0.3 mV/decade for sensors I and II, respectively over the pH ranges of 2.5-7. The method was validated according to ICH guidelines. Statistical comparison between the results from the proposed method and the results from the reference HPLC method showed no significant difference regarding the accuracy and precision.

Keywords- Quetiapine Fumarate, Ion selective electrode, Membrane sensors, Cationic exchanger, Related compounds, Plasma

1. INTRODUCTION

Development of analytical methods for the determination of pharmaceuticals in the presence of related compounds without previous chemical separation is always a matter of interest. Our scientific motivation is developing a simple, accurate, low - cost, reproducible and rapid membrane sensor for the determination of QTF drug in pure form, in dosage form, plasma and in presence of its two related compounds; Des-ethanol Quetiapine (DQ) and Quetiapine N-oxide (QO) without the need for pretreatment or prior separation.

Quetiapine (QTF) (Fig. 1), is a dibenzothiazepine derivative and classified as an atypical antipsychotic with demonstrated efficacy in acute schizophrenia [1]. Several methods have been reported for the determination of QTF in bulk powder, pharmaceutical preparations and biological samples. These included UV-Visible spectrophotometric methods [2-4], HPLC methods [5-10], HPTLC-densitometric methods [11,12], Capillary electrophoresis [13,14], voltammetry [15,16] and potentiometry [17].

From the literatures, QTF was found to be most susceptible to oxidative degradation and shows no or minimal degradation to acid, base, thermal and photo degradation [18,19]. During stability studies, Quetiapine N-oxide (oxidation product) at level 0.1% was detected by ion-pair reversed-phase high performance liquid chromatography (HPLC) [20]. In the process of synthesis of QTF according to the Scheme (Warawa and Migler 1989); seven impurities were identified ranging from 0.05–0.15% by high performance liquid chromatography (HPLC). Based on the spectral data, one of them is des-ethanol quetiapine [21].

Most of the reported methods for determination of QTF involve complicated procedures, sample pretreatment, long analysis times, expensive instruments and extraction operations that are open to various interferences, and they are inapplicable to colored and turbid solutions. On the contrary, electrochemistry has always provided analytical techniques characterized by instrumental simplicity and moderate cost [22].

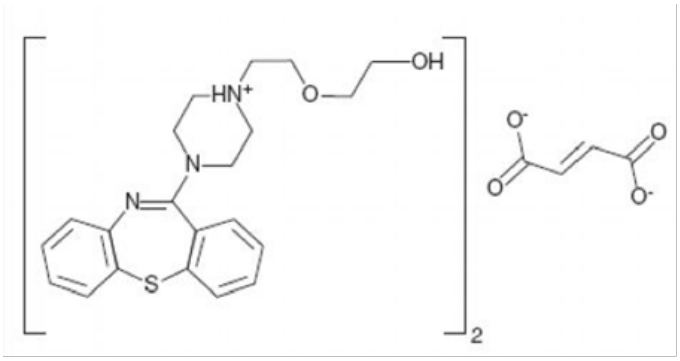


Fig. 1. Chemical structure of Quetiapine Fumarate (QTF)

The ion-selective electrodes (ISEs) application in pharmaceutical analysis have increased due to the advantages of portability, limited sample pretreatment, low energy consumption,

rapidity, and adaptability to small sample volumes[23,24]. Thus, the development of membrane sensors offering these advantages for the determination of QTF drug is desirable, especially given that there are no reported ISEs in the literature used for determination of QTF drug.

2. EXPERIMANTAL

2.1. Apparatus

A Jenway digital ion analyzer model 3330 (Essex, UK) with Ag/AgCl double junction reference electrode no. 924017-LO3-Q11C was used for potential measurements. A pH glass electrode Jenway (Essex, UK) no. 924005-BO3-Q11C was used for pH adjustment.

2.2. Materials

2.2.1. Reference samples

QTF, (99.4%) and its related compounds; DQ and QO (99.8%) were kindly supplied by National Organization of Drug Control and Research (NODCAR) institute, Cairo, Egypt.

2.2.2. Pharmaceutical formulation

Seroquel® tablets were manufactured by Astra Zeneca, Egypt. Each tablet was labeled to contain 25 mg of QTF.

2.3. Reagents

All chemicals and reagents used were of analytical grade and water was bi-distilled. Dioctyl phthalate (DOP) was obtained from Sigma (St. Louis, USA), sodium tetraphenylborate (NaTPB), tetrahydrofuran (THF) and poly vinyl chloride (PVC) were obtained from BDH (Poole, England), β-Cyclodextrin (β-CD) [Fluka,Steinheim, Germany]. Potassium chloride and hydrochloric acid 30-34% were obtained from El-Nasr pharmaceutical chemical company, Cairo, Egypt.

2.4. Standard solutions

2.4.1. QTF stock standard solution (1×10^{-2} mol L^{-1})

The solution was prepared by transferring 0.88 g of pure QTF into a 100-mL volumetric flask, which was dissolved in sufficient amount of a solvent consisting of 0.1 N HCl: distilled water in a ratio (1:1), and then the volume was brought up to the mark with the same solvent.

2.4.2. QTF working standard solutions (1×10^{-7}-1×10^{-3} mol L^{-1})

Prepared by suitable dilution from QTF stock standard solution and completed to the volume with bi-distilled water.

2.4.3. DQ and QO related compounds stock standard solutions (1×10^{-2} mol L^{-1})

The solutions were prepared by transferring 0.038 g and 0.039 g of DQ and QO, respectively into 100-mL volumetric flasks separately and completing the volume with the same solvent of 0.1 N HCl: bi-distilled water (1:1).

2.5. Procedures

2.5.1. Fabrication of PVC master membrane sensors

For the preparation of sensor I, 0.35 mL of (DOP) as plasticizer was mixed with 0.01 gm of the cation exchanger (NaTPB) and 0.19 gm PVC in a 5-cm Petri dish. The mixture was dissolved in 6 mL THF. For sensors II, 0.03 gm of β-CD was added to the previous components. The Petri dishes were covered with filter paper and left to stand overnight at room temperature to allow solvent evaporation. Master membranes 0.1 mm in thickness were obtained. From each master membrane, a disk (about 1.6 cm in diameter) was cut using a cork borer and pasted using THF to an interchangeable PVC tip that was clipped into the end of an electrode glass body. The electrodes were then filled with an internal solution of equal volumes of 10^{-2} mol L^{-1} QTF and 10^{-2} mol L^{-1} KCl. Ag/AgCl wire (1 mm diameter) was used as an internal reference electrode. The sensors were conditioned by soaking in 10^{-2} mol L^{-1} QTF solution for 24 h, and they were stored in the same solution when not in use. The electrochemical cells for potential measurements were: Ag/AgCl (internal reference electrode)/ 10^{-2} mol L^{-1} QTF solution, 10^{-2} mol L^{-1} KCl (internal reference solution) // PVC membrane// test solution // Ag/AgCl double junction reference electrode.

2.5.2. Sensors calibration

The conditioned sensors were calibrated by separately transferring 50 mL aliquots of solutions (1×10^{-8}-1×10^{-3} mol L^{-1}) of QTF into a series of 100-mL beakers. The membrane sensors, in conjunction with Ag/AgCl reference electrode, were immersed in the above test solutions and allowed to equilibrate while stirring. The potential was recorded after stabilizing to ±1 mV, and the electromotive force (emf) was plotted as a function of the negative logarithm of QTF molar concentration. The sensors were washed with bi-distilled water after each measurement.

2.5.3. Direct potentiometric determination of laboratory prepared mixtures containing different ratios QTF and its related compounds; DQ and QO

Aliquots of standard DQ and QO solutions (10^{-3} mol L^{-1}) were prepared using distilled water and mixed with standard drug solution (10^{-3} mol L^{-1}) in different ratios. The emf values of these laboratory-prepared mixtures were recorded and results were compared with the calibration plot.

2.5.4. Direct potentiometric determination of QTF in Seroquel tablets

A portion of Seroquel tablets powder equivalent to 0.088 gm QTF was transferred separately into 10-mL volumetric flask and filled to the mark with 0.1 N HCl: bi-distilled water (1:1) to obtain concentration of 1×10^{-3} mol L^{-1}. The potentiometric measurement was performed using the proposed sensors in conjunction with the Ag/AgCl reference electrode, and the potential reading was compared to the calibration plot.

2.5.5. Determination of QTF in plasma

One millilitre of each of 10^{-4}, 10^{-5} and 10^{-6} mol L^{-1} standard drug solution were added separately into three 20-mL stoppered shaking tubes each containing 9 mL of plasma and the tubes were shaken for 1 min. The membrane sensors were immersed in conjunction with the reference electrode in these solutions and then washed with water between measurements. The emf produced for each solution was measured by the proposed sensors, and the concentration of QTF was determined from the corresponding regression equation.

2.5.6. Estimation of the slope, response time and operative life of the proposed sensors

The electrochemical performance of the two proposed sensors was evaluated according to the IUPAC recommendations [25]. Sensor life span was examined by repeated monitoring of the slope of the drug calibration curve periodically. The detection limit was taken at the point of intersection of extrapolated linear segment of drug calibration graph.

The dynamic response time was recorded by increasing QTF concentration by up to 10-fold. The required time for the sensors to reach values within ±2.0 mV of the final equilibrium potential was measured.

2.5.7. Effect of pH

The effect of pH on the response of the investigated electrodes was studied using 10^{-3} and 10^{-4} mol L^{-1} solutions of QTF with pH ranging from 2 to 10. The pH was gradually increased

or decreased by adding aliquots of 0.1 N sodium hydroxide or 0.1 N hydrochloric acid solutions, respectively. The potential obtained at each pH value (1 pH interval) was recorded.

2.5.8. Sensors selectivity

The potentiometric selectivity coefficients ($K_{A.B}^{Pot}$) of the proposed sensors towards different substances were determined by a separate solution method using the following equation:

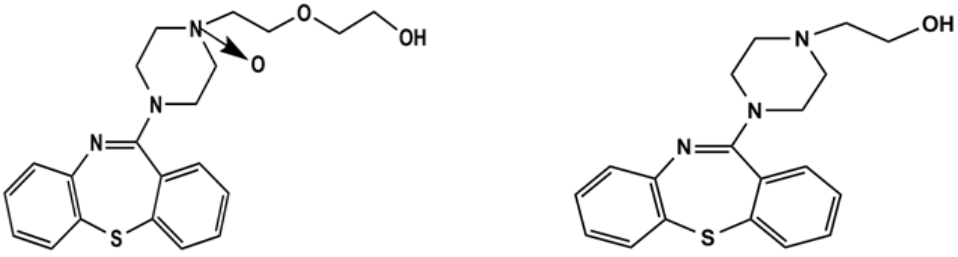
$$-log(K_{A.B}^{Pot}) = \frac{E_1 - E_2}{2.303RT/ZAF} + \left(1 - \frac{ZA}{ZB}\right) log\alpha_A$$

Where, ($K_{A.B}^{Pot}$) is the potentiometric selectivity coefficient, E_1 is the potential measured in 10^{-3} mol L^{-1} QTF solution, E_2 is the potential measured in 10^{-3} mol L^{-1} aqueous interferent solution, Z_A and Z_B are the charges of QTF and interfering ion, respectively, α_A is the activity of the drug and 2.303RT/ZAF represents the slope of the investigated sensor (mV/concentration decade).

3. RESULTS AND DISCUSSION

The development and application of ion-selective electrodes (ISEs) continue to be of interest for pharmaceutical analysis because these sensors offer the advantages of simple design and operation, fast response, reasonable selectivity, low detection limit, high accuracy, wide concentration range, applicability to colored and turbid solutions, and possible interfacing with automated and computerized systems [26].

Selective membranes in ion selective electrodes have shown both ion exchange and perm selectivity for the sensor ion [27]. Two selective membrane sensors with and without incorporation of ionophore were proposed for determination of QTF in its pure substance, drug product, plasma and in presence of its DQ, QO related compounds (Fig. 2).



(a) **(b)**

Fig. 2. Chemical structure of Quetiapine N-oxide (QO) (a) and Des-ethanol Quetiapine (DQ) (b)

3.1. Sensors fabrication

PVC was used as a matrix in the sensors fabrication being a regular support and reproducible trap for ion association complexes. PVC requires plasticization and places a constraint on the choice of mediator [28].Thus in the present work, the optimum available mediator for fabrication of sensors was found to be DOP and its proportion was optimized to minimize the electrical asymmetry of the membrane as to keep the sensor as clean as possible and to stop leaching into the aqueous phase [29]. The fact that QTF acts as a cation, suggests the use of the cationic ion exchanger such as sodium tetraphenylborate (NaTPB) for the fabrication of the two sensors.

Cyclodextrins have been applied as sensor ionophores in potentiometric ion selective electrodes for the determination of several drugs [30-36]. They are known to accommodate a wide variety of organic, inorganic and biologic guest molecules to form stable host–guest inclusion complexes or nanostructure supramolecular assemblies in their hydrophobic cavity while exhibiting high molecular selectivity and enantioselectivity [37]. In the case of natural CD, cooperative binding with certain guest molecules was mostly attributed to intermolecular hydrogen bonding between the CD molecules [38].

3.2. Sensors calibration and response time

Based on the IUPAC [25] recommendations the response characteristics of the designed sensors were assessed. Table 1 displays the results obtained over a period of three months for the two sensors. Typical calibration plots are shown in Fig. 3. The slope was computed from the linear part of the calibration graph.

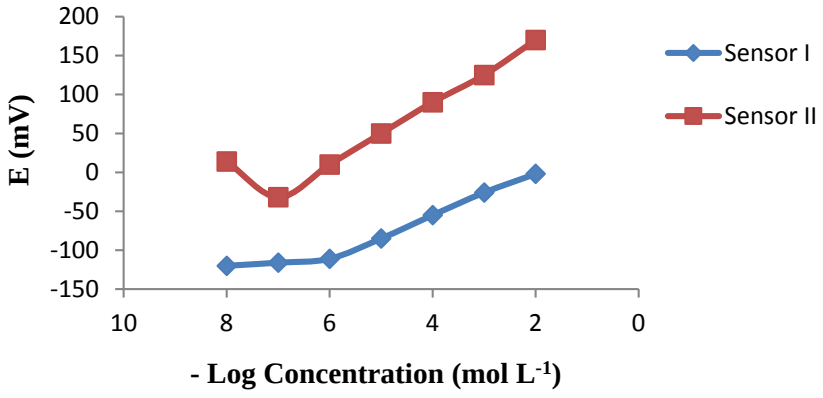


Fig. 3. Profile of the potential in mV versus –log concentration of QTF in mol L^{-1} obtained with sensors I and II

The slopes of the calibration plots were 27.5±1.0 and 39.85±1.0 mV/ concentration decades for sensor I and II, respectively. QTF reacts with TPB to form stable (1:2) water insoluble ion

association complexes, with low solubility product and suitable grain size precipitates. This ratio was confirmed by the elemental analysis data and by the Nernstian response of the suggested sensors, which was about 30 mV, the typical value for divalent drugs [25]. The deviation from the Nernstian slope is due to the fact that the electrodes respond to activities of the drug rather than the concentration. The sensors displayed constant potential readings within ±2 mV from day to day. The required time for the sensors to reach values within ±1 mV of the final equilibrium potential after increasing the drug concentration 10-fold was found to be 14 seconds for sensor I and 10 seconds for sensor II.

Table 1. Validation of the response characteristics of the two investigated sensors

Parameter		**Sensor I**	**Sensor II**
Slope (mV/ decade) [a]		27.50±0.45	39.85±0.3
Intercept (mV)		53.8±1.55	248.19±1.06
Correlation coefficient (r)		0.9994	0.9996
Linearity range (mol L^{-1})		1×10^{-6}-1×10^{-2}	1×10^{-7}- 1×10^{-2}
Response time (S)		14	10
Working pH range		2.5-7	2.5-7
Stability (weeks)		3	4
LOD (mol L^{-1})		1.8×10^{-6}	2.0×10^{-7}
Average Accuracy (%) ± S.D.[b]		98.99±1.12	99.34±0.56
Precision (RSD%, n=9)	Repeatability	1.5	0.65
	Reproducibility	2.3	1.34

[a] Average of five determinations.
[b] Limit of detection (measured by interception of the extrapolated arms of Fig. 3)

3.3. Effect of pH

For quantitative measurements with ISEs, studies were carried out to reach the optimum experimental conditions. The effect of pH on the response of the proposed sensors was studied to reach the optimum experimental conditions. Figs. 4 and 5 and show the potential-pH profile of 1×10^{-3} mol L^{-1} and 1×10^{-4} mol L^{-1} QTF for sensor I and II; respectively. It was apparent that the sensors responses were fairly constant in solutions of pH values 2.5-7; in this pH range, the drug is completely ionized, dissociated and sensed. Above pH 7, the potential showed a sharp decrease that could be due to the formation of non-protonated amino group of QTF. However, below pH 2.5, the potential displayed by the electrodes were noisy and unbalanced.

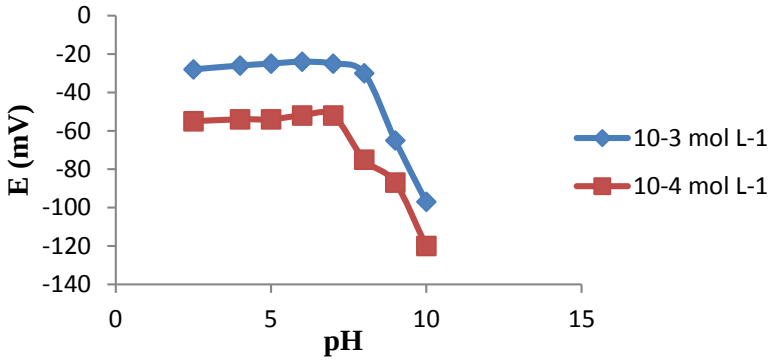


Fig. 4. Effect of pH on the response of suggested sensor I [working pH range 2.5-7]

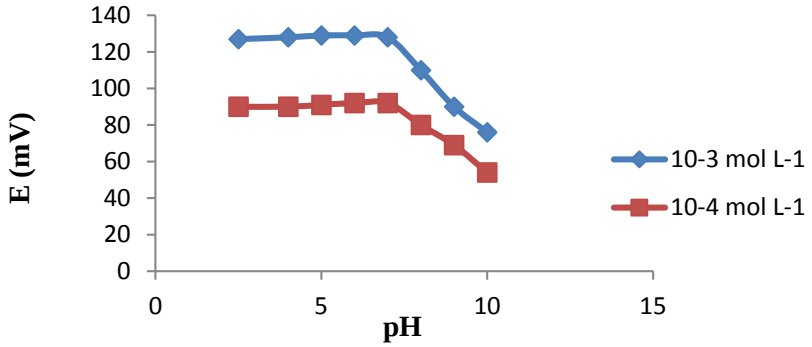


Fig. 5. Effect of pH on the response of suggested sensor II [working pH range 2.5-7]

Table 2. Potentiometric selectivity coefficients ($K_{A.B}^{Pot}$) of the proposed sensors

Interferent (10^{-3} mol L^{-1})	**Selectivity coefficient [a]**	
	Sensor I	**Sensor II**
N-oxide	1.9×10^{-3}	2.1×10^{-3}
Des-ethanol	1.5×10^{-3}	1.6×10^{-3}
NaCl	2.5×10^{-4}	1.3×10^{-4}
KCl	5.0×10^{-5}	1.9×10^{-5}
$CaCl_2$	3.8×10^{-4}	6.3×10^{-4}
$MgCO_3$	4.4×10^{-4}	1.8×10^{-4}
Sucrose	4.8×10^{-4}	7.9×10^{-4}
Mannitol	5.7×10^{-4}	3.0×10^{-4}
Urea	4.9×10^{-4}	8.3×10^{-4}

[a] Each value is the average of three determinations

3.4. Sensors selectivity

The effect of interfering substances on the performance of the sensors was studied by the separate method [26].

The response of the two sensors in the presence of susceptible tablet excipients, organic and inorganic related substances, was assessed. The calculated selectivity coefficients showed

that the proposed sensors displayed high selectivity, and no significant interference was observed from the interfering species, (Table 2).

3.5. Potentiometric determination of laboratory prepared mixtures

The results obtained upon analysis of synthetic mixtures containing different ratios of QTF to the two related compounds; DQ and QO show that sensors I and II can be successfully used for selective determination of intact drug in presence of its two related compounds with no need for prior separation, (Table 3).

Table 3. Determination of QTF in laboratory prepared mixtures containing different ratios of QTF and its related compounds by the proposed sensors

Ratio of QTF: N-oxide : Des-ethanol	**Drug recovery (%) ± S.D.[a]**	
	Sensor I	**Sensor II**
10:1:1	101.35 ±1.16	100.76±0.64
100:1:1	100.76±0.94	100.32±0.36
1000:1:1	102.24±0.97	101.32±1.01
1:1:1	102.41±1.23	101.59±1.24
1:10:10	101.32±0.94	102.76±1.43
1:100:100	120±1.64	104.42±2.05
1:1000:1000	122±1.86	117.47±2.12

[a] Average of three determinations

3.6. Potentiometric determination of QTF in plasma

The results obtained for the determination of QTF in spiked human plasma show that a wide concentration range can be determined by the investigated sensors with high precision and accuracy. The results presented in Table 4 show no interference from endogenous substances and that sensor Π is more sensitive so it is preferred to be used in plasma application as it can measure a concentration lower than QTF drug C_{max} (126.9 ng mL^{-1}) [39].

Table 4. Determination of QTF in spiked human plasma by the proposed sensors

Recovery% ± SD[a]		
Added (mol L^{-1})	**Sensor I**	**Sensor II**
10^{-5}	99.70±0.39	99.65±0.56
10^{-6}	98.40±0.97	98.37±1.65
10^{-7}	88.75±1.56	97.85±0.84

[a] Average of three determinations

3.7. Potentiometric determination of QTF in Seroquel tablets

The proposed sensors were applied for the analysis of QTF pharmaceutical formulation (Seroquel tablets). The results prove the applicability of the sensors, as demonstrated by the accurate and precise percentage recoveries. The susceptible tablet excipients did not show any interference. Thus, the determination of QTF was carried out without prior treatment or extraction by using the proposed sensors (Table 5).

Table 5. Determination of QTF in pharmaceutical preparation by the proposed sensors and the reference HPLC method

	Recovery%±SD[a]		
Item	**Sensor I**	**Sensor II**	**Reference method [b]**
Seroquel ® tablets labeled to contain 25.0mg QTF	99.67±0.71	99.81±0.82	99.21±0.97
Student's t-test [c]	1.29 (2.44)	0.147(2.201)	-
F-test [c]	3.18 (6.338)	2.086(8.845)	-

[a] Average of three determinations

[b] HPLC method supplied by Astra Zeneca company through personal communication ;C_{18} column and mobile phase; 0.02M dibasic ammonium phosphate: acetonitrile: methanol (39:7:54, v/v/v) and UV detection at 254 nm

[c] The values in parentheses are the corresponding theoretical values for t and F at P = 0.05

3.8. Statistical comparison of the obtained results with the reference method

To examine the validity of the proposed sensors, the obtained results were compared to HPLC reference method and no significant difference was observed in accuracy and precision. The results are shown in Table 5.

4. CONCLUSION

These two membrane sensors are the first in the literature for determination of QTF drug. The responses of the fabricated sensors are sufficiently precise and accurate, and they demonstrate the good selectivity and sensitivity of the sensors for the quantitative determination of QTF in pure form, in laboratory-prepared mixtures with two related compounds; N-oxide and Des-ethanol Quetiapine, in pharmaceutical formulation and in plasma. Sensor II with the ionophore inclusion is more sensitive and more stable than sensor I, so it is better to be used for plasma application. Moreover, the proposed sensors have the advantage of eliminating any need for drug pretreatment or separation steps and they are simple in design, low in cost and they could compete with the many sophisticated methods currently

available. Thus, the sensors can therefore be used for the routine analysis of QTF in quality-control laboratories.

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