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Full Paper

Ion Selective Membrane Electrodes for Determination of Citalopram Hydrobromide in Drug Product and in Presence of Its Degradation Products

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Abstract- This paper presents a comparative study between three sensors developed to determine Citalopram Hydrobromide (CT) in the presence of its alkaline hydrolysis and oxidation induced degradation products using different ion association complexes. Sensor 1 was fabricated using phosphomolybdic acid, Sensor 2 used phosphotungestic acid and sensor 3 used the sodium tetraphenyl borate. Linear responses of CT were obtained within the concentration ranges of 1×10^{-6} to 1×10^{-2} mol L^{-1} for sensor 1 and 2 and 1×10^{-5} to 1×10^{-2} mol L^{-1} for sensor 3 over the pH range of 3.0–6.0. The selectivity coefficients of the developed sensors indicated excellent selectivity for CT. The proposed sensors displayed useful analytical characteristics for the determination of CT in bulk powder, pharmaceutical formulation, and in the presence of its degradation products and thus could be used for stability-indicating methods. 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 accuracy and precision.

Keywords- Citalopram Hydrobromide, Ion selective electrode, Degradation products, Cation exchanger, PVC

1. INTRODUCTION

Citalopram (CT) (Fig. 1), 1-(3-dimethylaminopropyl)-1-(4-fluorophenyl)-5-phthalan carbonitrile, is an antidepressant drug used to treat depression associated with mood disorders. CT belongs to a class of drugs known as selective serotonin reuptake inhibitors (SSRIs). It affects the neurotransmitters, the chemical transmitters within the brain. It works by preventing the uptake of serotonin by nerve cells after it has been released. Such uptake is an important mechanism for removing released neurotransmitters and terminating their actions on adjacent nerves. The reduced uptake caused by CT results in stimulation of the nerve cells by the free serotonin in the brain [1].

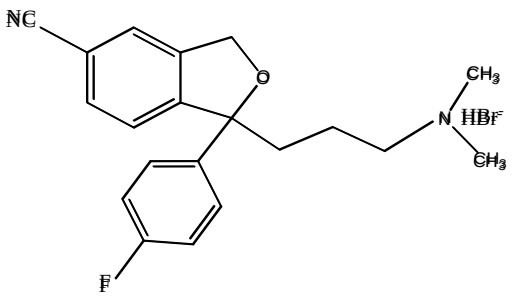


Fig. 1. Chemical structure of Citalopram Hydrobromide

Several methods have been reported for the determination of CT including spectrophotometry [2-5], capillary electrophoresis [6-8], gas chromatography [9], thin layer chromatography [10] and high performance liquid chromatography [11-13].

However, these reported methods involve long procedures, sample pretreatment, utilization of expensive instruments and they are inapplicable to colored and turbid solutions. On the contrary, electrochemistry offers instrumental simplicity, portability and moderate cost [14].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 [15,16] . Furthermore, they show rapid response to changes in concentration and are tolerant to small changes in pH.

Various reports have been published which highlight the important contribution of ion selective sensors for quantification of drugs [17,18]. Thus, the development of reliable ISEs offering these advantages for the determination of CT in presence of its alkaline hydrolysis and oxidation induced degradation products is desirable, especially given that the literature

reveal only two papers for determination of CT using ion exchanger [19,20]. The first paper developed citalopram-tetraphenyl borate ion-pair PVC membrane with sensitivity of (1×10^{-5} to 1×10^{-2} mol L^{-1}) which is less than our developed sensors 1 and 2 and the second paper developed screen-printed ISEs using homemade carbon ink with shorter life time. Both previous published sensors are not stability–indicating methods as our sensors.

The aim of this work was to develop simple easily prepared ion selective electrodes for rapid, reproducible, selective, sensitive, accurate and low-cost estimation of the cationic drug CT in the presence of its degradation products, in its pure form and pharmaceutical formulation without the need of preliminary extraction or separation steps.

2. EXPERIMENTAL

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 sample

A pure sample of Citalopram hydrobromide (CT) (purity 99.87%) was supplied by SEDICO Company for pharmaceuticals and chemical industries (Cairo, Egypt).

2.2.2. Pharmaceutical formulation

Citalo® tablets. Each tablet is claimed to contain 20 mg of CT. they were manufactured by Delta Pharma Company, Cairo, Egypt.

2.3. Chemicals and reagents

All chemicals and reagents used were of analytical grade and water was bi-distilled. Dioctyl phthalate (DOP), dibutyl phthalate (DBP) were obtained from Sigma (St. Louis, USA), sodium tetraphenylborate (NaTPB), phosphotungestic acid (PTA), phosphomolybdic acid (PMA), tetrahydrofuran (THF), poly vinyl chloride (PVC) were obtained from BDH (Poole, England). Orthophosphoric acid for adjusting the phosphate buffer to pH 5.3 (Riedel-dehaen, Sigma-Aldrich, Germany). Potassium chloride, sodium hydroxide pellets, hydrochloric acid 30-34%, hydrogen peroxide 30% , Potassium dihydrogen orthophosphate (ADWIC, Egypt).

2.4. Standard solutions

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

The solution was prepared by transferring 0.405 gm of pure CT into a 100-mL volumetric fask, which was dissolved in sufficient amount of phosphate buffer pH (5.3), and then the volume was brought up to the mark with the same solvent.

2.4.2. CT working standard solutions (1×10^{-7}-1×10^{-2} mol L^{-1})

CT working solutions were freshly prepared by serial dilutions from the CT stock solution using phosphate buffer (pH 5.3) as a solvent.

2.5. Procedures

2.5.1. Preparation of the PVC master membrane sensors

A 50 mL aliquot of 1.0×10^{-2} mol L^{-1} aqueous CT solution was mixed with 50 mL of 1.0×10^{-2} mol L^{-1} aqueous solution of phosphomolybdic acid (PMA) for sensor 1, phosphotungestic acid (PTA) for sensor 2 and sodium tetraphenyl borate (NaTPB) for sensor 3 and continuously stirred. Each ion pair complex was precipitated, filtered, washed thoroughly with bi-distilled water, dried at room temperature and ground to a fine powder. A 10 mg portion of CT ion pair was mixed with 0.35 mL of DOP plasticizer and 190 mg of PVC powder and dissolved in 6 mL of THF. The solution was poured into Petri dishes (5 cm diameter). The petri dishes were covered with whatman NO.3 filter paper and left to stand overnight to allow solvent evaporation at room temperature. Master membranes with thickness of 0.1 mm were obtained and used for the construction of the sensors.

2.5.2. Preparation of the electrodes assemblies

From each prepared master membrane, a disk (≈1.6 cm diameter) was cut using a cork borer and pasted using THF to an interchangeable PVC tip that was clipped into the end of the glassy electrode body. Equal volumes of 10^{-2} mol L^{-1} CT and 10^{-2} mol L^{-1} KCl (prepared in phosphate buffer, pH 5.3) were mixed and this solution was used as internal solution for electrodes. Ag/AgCl wire (1mm diameter) was immersed in the internal reference solution as an internal reference electrode. The electrodes were conditioned by soaking in 1×10^{-2} mol L^{-1} stock standard CT solution for 24 hours and were stored in the same solution when not in use. The electrochemical cell for potential measurements was: Ag/AgCl (internal reference electrode) / 1.0×10^{-2} mol L^{-1} CT solution, 1.0×10^{-2} mol L^{-1} KCl (internal reference solution) // PVC membrane//test solution // Ag/AgCl double junction reference electrode.

2.5.3. Sensors calibration

Each sensor was separately conjugated with a double junction Ag/AgCl reference electrode, calibrated by being immersed in drug solutions covering the concentration range of (1×10^{-7}-1×10^{-2} mol L^{-1}) and allowed to equilibrate while stirring until achieving a constant reading of the potentiometer. The electrodes were washed with phosphate buffer, pH 5.3 between measurements. The developed potentials were plotted versus negative logarithmic concentration of CT standard solutions. The regression equations of the obtained calibration plots were used for subsequent measurements of unknown samples of CT.

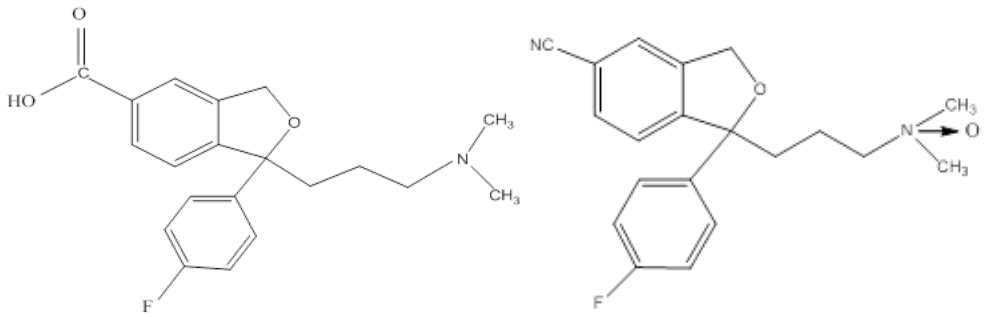
2.5.4. Preparation of degradation products

2.5.4.1. Alkaline degradation

CT alkaline degradation product was obtained by heating 0.02 gm CT with 20 mL 5.0 M sodium hydroxide at 80°C in oven for three hours. The resulting solution was neutralized with HCl, transferred into 50-mL volumetric flask and completed to the mark with bi-distilled water to obtain concentration of 1×10^{-3} mol $L^{-1}$and tested for complete degradation by the thin layer chromatography (TLC) technique using ethyl acetate: formic acid: acetic acid: methanol in a ratio (12:1:1:1, v/v/v/v) as a mobile phase and detecting the spots at 254 nm.

2.5.4.2. Oxidative degradation

CT oxidative degradation product was obtained by heating 0.02 gm CT with 20 mL 30% H_2O_2 at 70 °C in oven for five hours. The resulting solution transferred into 50-mL volumetric flask and completed to the mark with bi-distilled water to obtain concentration of 1×10^{-3} mol $L^{-1}$and tested for complete degradation with the same mobile phase system of TLC.



(a) **(b)**

Fig. 2. Structures of alkaline (a) and oxidative (b) degradation products of Citalopram

2.5.5. Determination of CT in its pharmaceutical formulation

The contents of 10 tablets were accurately weighed, their average weight was calculated, and then finely powdered. An amount equivalent to 0.02 gm CT was accurately weighed and transferred into 50-mL beaker. Thirty mL of bi-distilled water were added and the solution was sonicated for 30 min. Then filtered into 50-mL volumetric flask, and the volume was completed with bi-distilled water 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, the resulting potential was recorded, and the respective concentration was calculated from the corresponding regression equations.

2.5.6. Determination of CT in the presence of its degradation products

Aliquots of standard drug solution (10^{-3} mol L^{-1}) were mixed with its alkaline and oxidative degraded sample (10^{-3} mol L^{-1}) in different ratios. The emf values of these laboratory-prepared mixtures were recorded and the concentration of the drug was calculated from the corresponding regression equations.

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

The slope, response time and operative life of the three proposed sensors were evaluated according to the IUPAC recommendations [21].

2.5.8. Effect of pH

The effect of pH on the potential values of the three sensors was studied over pH ranges of 2-12. This was manipulated by adding diluted aliquots of 0.1 mol L^{-1} hydrochloric acid and 0.1 mol L^{-1} sodium hydroxide solutions to 1×10^{-3} mol L^{-1} solution of CT solution. The potential obtained at each pH value was recorded.

2.5.9. Effect of interfering substances on the electrode selectivity

The potential response of the three proposed sensors in the presence of interfering substances was studied, and the potentiometric selectivity coefficient $\left(k_{A.B}^{pot}\right)$ was calculated to estimate the degree to which a foreign substance would interfere with the response of the electrode to their primary ion. The selectivity coefficients were calculated by separate solution method (SSM) [22] from the rearranged Nicolsky Eisenman equation:

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

Where, $\left(k_{A.B}^{pot}\right)$ is the potentiometric selectivity coefficient, E_1 is the potential measured in 10^{-3} mol L^{-1} CT solution, E_2 is the potential measured in 10^{-3} mol L^{-1} interferent solution, Z_A and Z_B are the charges of CT 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

In ion selective electrodes, the selective membranes show both ion exchange and perm selectivity for the sensor ion [23]. Taking this in account it is considered advantageous to create new fabricated electrodes with competitive properties for the determination of CT drug in its pure substance, drug product and in presence of its alkaline and oxidative degradation products.

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 [24]. 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 [25]. The present study originates from the fact that CT behaves as cation in acid medium as it has dissociation constant (p*K*a=9.5). This fact suggests the use of cationic exchangers as PTA, PMA, NaTPB in acid medium as they form insoluble ion association complexes with suitable grain size with CT. The ratio of CT to the ion exchangers in the formed complexes was found to be 1:1 as proven by elemental analysis and the obtained Nernestian slopes (about 60 mV/decade) so CT acts as a monoionic species.

3.2. Sensors calibration and response time

Based on the IUPAC [21] recommendations the response characteristics of the designed sensors were assessed. Table 1 displays the results obtained over a period of three months for the three sensors. Typical calibration plots are shown in Fig. 3. The slope was computed from the linear part of the calibration graph. The slopes of the calibration plots were 49.8±0.45, 52.8±1.0and 47.4±0.30 mV/concentration decades for sensors 1, 2 and 3 respectively. The deviation from the ideal Nernstian slope (60 mV/ decade), is due to the fact that the electrodes respond to activities of the drug rather than the concentration. The suggested electrodes displayed constant potential readings for day to day measurements, and the calibration slopes did not change by more than ±1.4 mV/decade over a period of 8 weeks. The dynamic response time is the required time for the sensor to reach values within ±1 mV

of the final equilibrium potential after increasing the drug concentration 10-fold. The sensors were able to quickly reach its equilibrium response (10-14 seconds).

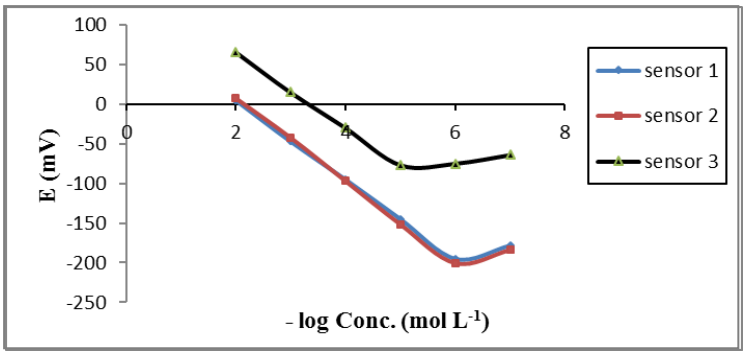


Fig. 3. Profile of the potential in mV versus –log concentration of CT in mol L^{-1} obtained with sensors 1, 2 and 3

3.3. Precision

To evaluate the precision of measurements, three concentrations within the linear concentration range ($10^{-4,}$ 10^{-3} and 10^{-2}, mol L^{-1} solutions) of CT were chosen. Three solutions of each concentration were prepared and analyzed in triplicate (repeatability assay). This assay was repeated on three different days (reproducibility assay), (Table 1).

3.4. Robustness

The method demonstrated efficient stability when the plasticizer was changed to DBP instead of DOP for sensors 1 and 2. Also, the wide range of pH (3.0-6.0) made the method robust. Results proved the robustness of the method upon changing the type of the plasticizer (Table 1).

3.5. Effect of pH

The effect of pH on the response of the proposed sensors was studied. The results showed that the potential remained constant despite the pH change in the range of 3.0-6.0, which indicates the applicability of this electrode in the specified pH range. Fig. 4.

Relatively noteworthy fluctuations in the potential versus pH behavior took place below and above the formerly stated pH limits. In detail, the decrease in potential above the pH value of 6.0 was due to the gradual decrease in the concentration of the CT mono-cation due to the formation of the non-protonated dimethyl amino group. Below pH 3, the electrode response increased with the increase of analyte acidity; the membrane may extract H^{+}, leading to noisy responses.

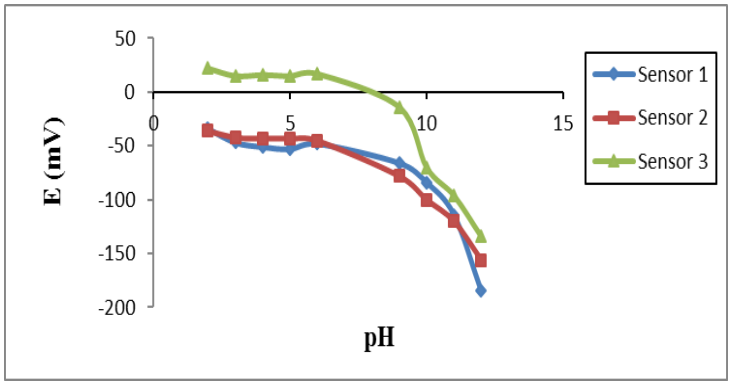


Fig. 4. Effect of pH on the response of the suggested sensors in 10^{-3} mol L^{-1} CT

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

Parameter		**Sensor 1 CT-PMA**	**Sensor 2 CT-PTA**	**Sensor 3 CT- NaTPB**
Slope (mV/ decade) [a]		49.8±0.45	52.8±1.0	47.4±0.30
Intercept (mV)		103.8±2.0	114.4±1.0	159.4±2.0
Correlation coefficient (r^2)		0.9999	0.9996	0.9994
Linearity range (mol L^{-1})		1×10^{-6}-1×10^{-2}	1×10^{-6}-1×10^{-2}	1×10^{-5}-1×10^{-2}
Response time (S)		14	14	10
Working pH range		3.0-6.0	3.0-6.0	3.0-6.0
Stability (weeks)		8	8	6
LOD (mol L^{-1})		1×10^{-6}	1×10^{-6}	1×10^{-5}
Average Accuracy (%)±S.D.[b]		99.8±1.3	99.9±2.3	98.8±2.1
Precision (RSD%, n=9)	Repeatability	1.5	1.0	2.0
	Reproducibility	2.9	2.0	2.3
Robustness[c]		2.5	2.8	-

[a]Results of six determinations
[b]Average recovery % of five concentration levels ,each repeated three times.
[c]Relative standard deviation % of the potential produced by 10^{-3} mol L^{-1} solution (n=3) using DBP as plasticizer instead of DOP for sensors 1 and 2.

3.6. Sensors selectivity

The selectivity of an ion-pair based membrane electrodes depend on the physico-chemical characteristics of the ion-exchange process at the membranes. The response of the three

sensors in the presence of susceptible tablet excipients, organic and inorganic related compounds, was assessed. As it was obvious from Table 2, none of the tested interfering species had a significant influence on the potentiometric responses of the electrodes towards CT.

3.7. Potentiometric determination of CT in the presence of its degradation products

CT was completely degraded when heated with 5.0 M NaOH for three hours and when heated with 30% H_2O_2 for five hours. Fig. 2 shows the reported alkaline and oxidative degradation of the drug [26,27]. Table 3 shows the results obtained upon analysis of synthetic mixtures containing different ratios of intact drug and degradation products. From the presented results it was obvious that the proposed sensors could be used for selective determination of intact drug in the presence of up to 20 % degradates.

Table 2. Potentiometric selectivity coefficients $\left(k_{A.B}^{pot}\right)$ for CT sensors by separate solution method

Interferent (10^{-3} mol L^{-1})	**Selectivity coefficient** [a]		
	Sensor 1 CT-PMA	**Sensor 2 CT-PTA**	**Sensor 3 CT- NaTPB**
Alkaline degradate	5.8×10^{-2}	2.6×10^{-2}	2.3×10^{-2}
Oxidative degardate	1.1×10^{-3}	3.0×10^{-2}	2.1×10^{-2}
NaCl	2.1×10^{-4}	2.3×10^{-3}	5.12×10^{-3}
KCl	5.3×10^{-4}	1.5×10^{-4}	3.3×10^{-3}
$CaCl_2$	3.7×10^{-4}	3.3×10^{-4}	2.13×10^{-3}
$MgCO_3$	5.8×10^{-4}	4.1×10^{-4}	2.2×10^{-3}
Sucrose	9.3×10^{-4}	1.0×10^{-5}	2.45×10^{-3}
Mannitol	1.4×10^{-5}	9.5×10^{-4}	9.7×10^{-4}
Urea	1.0×10^{-5}	7.2×10^{-4}	8.9×10^{-4}

[a]Each value is the average of three determinations

3.8. Potentiometric determination of CT in pharmaceutical formulation

As none of the commonly used CT tablet additives show significant interference with the determination of CT, the new proposed sensors were successfully applied for CT determination in tablet without prior extraction as shown in Table 4. Results obtained proved the applicability of the method as demonstrated by the accurate and precise recovery percentages.

Table 3. Determination of CT in laboratory prepared mixtures containing different ratios of CT and its alkaline and oxidative degradation products by the proposed sensors

Ratio of drug: alkaline deg.: oxidative deg.	Drug recovery (%) ± S.D.[a]		
	Sensor 1 CT-PMA	**Sensor 2 CT-PTA**	**Sensor 3 CT- NaTPB**
100: 0: 0	99.8±0.8	99.4±1.2	98.3±0.6
90: 5: 5	100.5±1.4	100.6±0.9	100.3±1.4
80: 10: 10	101.3±1.7	100.6±1.2	100.8±1.2
70: 15: 15	101.8±0.9	101.5±0.8	99.7±2.0
60: 20: 20	102.6±1.4	101.8±2.3	98.8±1.7
50: 25: 25	120±2.3	125±2.1	143±1.3

[a]Average of three determinations

3.9. Statistical comparison

The results obtained for the determination of CT in tablets were statistically compared to the reference HPLC method for analysis of CT in pharmaceutical preparation as shown in Table 4. The calculated t & F values are less than the tabulated ones which reveals that there is was no significant difference between the compared methods with respect to accuracy and precision, respectively.

Table 4. Statistical analysis between the results obtained for the determination of CT in tablets by the proposed sensors and those by the HPLC method

Pharmaceutical preparation	Drug recovery (%) ± S.D.[a]			
	Sensor 1 CT-PMA	**Sensor 2 CT-PTA**	**Sensor 3 CT- NaTPB**	**HPLC method [b]**
Citalo® tablets labeled to contain 20.0 mg CT	99.6±0.92	99.8±1.5	99.4±1.7	99.60±0.42
t-test [c]	1.5 (2.77)	1.06 (4.3)	1.9 (4.3)	
F [c]	2.4 (4.3)	4.6 (8.9)	7.4 (8.9)	

[a]Average of five determinations
[b]HPLC method supplied by SEDICO company through personal communication, using C_{18} column, mobile phase; water: acetonitrile: trifluoroacetic acid (67:33:0.2, v/v/v) and UV detection at 238 nm
[c]The values between parenthesis are the theoretical values of *t*- and F-at P=0.05

4. CONCLUSION

The responses of the fabricated sensors are sufficiently precise, accurate, and they demonstrate good selectivity for quantitative determination of CT in pure powder, in

pharmaceutical formulation and in presence of alkaline and oxidative degradation products. The sensors offer the advantages of fast response, simplicity, elimination of drug pretreatment or separation steps. Further advantages offered by the PMA and PTA sensors over the TPB membrane are the higher sensitivity, selectivity and the longer lifetime. The proposed three sensors can be used as stability indicating for determination of CT in presence of its degradation products. They can therefore be used for routine analysis of CT in quality-control laboratories and could compete with the many sophisticated methods currently available.

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