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# Towards disposable sensors for drug quality control: Dextromethorphan screen- printed electrodes

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**A simple, rapid, reliable, and reproducible method for mass production of disposable sensors using screen-printing technology is described. Homemade printing has been characterized and optimized on the basis of effects of the modifier and plasticizers. The fabricated bi-electrode potentiometric strip containing both working and reference electrode was used as dextromethorphan (DXM) sensor. The proposed sensors worked satisfactorily in the concentration range from $10^{-5}$ to $10^{-2}$ mol $L^{-1}$ with detection limit reaching 6 × $10^{-6}$ mol $L^{-1}$ and adequate shelf life of 8 months. DXM was determined in pharmaceutical formulations under batch and flow injection analysis (FIA) conditions with sampling output 120 $h^{-1}$. Copyright © 2010 John Wiley & Sons, Ltd.**

**Keywords:** disposable screen-printed carbon electrode; potentiometry; dextromethorphan; flow injection analysis (FIA); pharmaceutical preparations

## Introduction

Drug quality control is a branch of analytical chemistry that has a wide impact on public health; therefore, the development of reliable rapid and accurate procedures for active ingredient quantification is welcomed. Electrochemical techniques are of choice since they possess the advantages of simplicity, accuracy, and low cost without separation or pretreatment procedures.[1–4]

The conventional polyvinylchloride (PVC) membrane electrodes have found a wide range of applications in pharmaceutical analysis;[5–7] however, they still have certain inherent limitations due to the difficulty of miniaturization and their short lifetime. To overcome the aforementioned difficulties in PVC membrane electrodes, new kinds of all solid-state ones (without internal reference solution) allowing electrode miniaturization capability were introduced. Coated-wire electrodes (CWE) and coated graphite electrodes are examples of these sensors design;[8–9] however, the potential drift and the poor adhesion of the membrane to the metal substrate are main drawbacks of these electrodes.[10–11]

Carbon pastes have been employed as useful materials for the fabrication of sensors by mixing the sensing material with carbon powder and a suitable pasting liquid. Carbon pate electrodes (CPEs) have the advantages of low Ohmic resistance with short response time and the ease of fabrication and regeneration. Although considerable attention has been given to the preparation of CPEs, their applications in analytical chemistry have been mainly based on selective preconcentration followed by voltammetric determination of the target specie[12,13] and just a few of these electrodes have been used as potentiometric sensor.[14–16]

As the demand for on-the-spot monitoring in clinical, environmental, and industrial analysis increases, both practical and economic interests have driven the development of various kinds of disposal electrochemical sensors based on screen-printing technology.[17–19] As CPEs continued to play a major role in the development of analytical procedures or testing new analytical methodology, screen-printed electrodes (SPEs) could be considered a solution for the lack of commercial availability of CPEs. Screen printing seems to be one of the most promising technologies providing high versatility, reproducibility, and large-scale production for commercialization. SPEs have been used for the potentiometric determination of various species using different commercial printing inks;[20–22] however, the ink compositions are usually unknown in many respects and some of the ink components may interfere with the electrochemical measurements.[23] Homemade printing ink (prepared by mixing carbon powder, plasticizer, and binding material) was optimized and successfully applied for fabrication of potentiometric SPCEs sensors.[24,25]

In the previous work,[26] the conventional CPEs and PVC electrodes were optimized for FIA potentiometric determination of DXM. The present work aimed to introduce disposable screen-printed carbon electrodes (SPCEs) as potentiometric sensors using homemade carbon ink. SPCEs were fabricated in plain and modified forms, and subjected to a series of tests to select the sensor possessing the most favourable analytical characteristics for their application as quality control potentiometric sensor for DXM determination in pharmaceutical formulations under batch and FIA conditions.

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## Experimental

### Reagents and chemicals

All reagents were of analytical grade and bidistilled water was used throughout the experiments. *o*-Nitrophenyloctylether (o-NPOE, Sigma 73732, St. Louis, USA), dibutylphthalate (DBP, BDH), dioctylphthalate (DOP, Sigma 6699 St. Louis, USA), dioctylsebacate (DOS, Avocado 122-62-3, *Heysham, Lancs*, UK) and tricresylphosphate (TCP, Fluka 1330-78-5, Switzerland) were used as electrode plasticizers. PVC (relative high molecular weight, Aldrich 389293, Steinheim, Germany) and graphite powder (synthetic 1–2 μm, Aldrich 28, 286-3, Dorset, UK) were applied in electrode fabrication.

### Authentic samples

Authentic dextromethorphan HBr monohydrate sample ($C_{18}H_{26}BrNO.\ H_2O$ assigned to be 99%) was kindly provided from National Organization of Drug Control and Research (Giza, Egypt). Stock drug solution ($1 \times 10^{-2}$ mol $L^{-1}$) was prepared by dissolving the appropriate amount of DXM in bidistilled water and kept at 4 °C.

### Pharmaceutical preparations

Tussilar tablets and drops (Kahira Pharm. and Chem. Ind. Co., Cairo, Egypt, 10 mg/tablet and 1g/100 mL solution, respectively) were purchased from local drug stores. Ten tablets were weighed, ground, and an accurate weight of the powder assigned to contain 100 mg DXM was dissolved in bidistilled water, filtered and completed to 50 mL with bidistilled water.

### Apparatus

Potential measurements were carried out using a 692-pH meter (Metrohm, Herisau, Switzerland) with a combined pH glass electrode. Single-line flow injection system composed of Perspex wall-jet cell, four channel peristaltic pump (MCP Ismatec, Zurich, Switzerland) and sample injection valve (ECOM, Ventil Prague C, Czech Republic) with exchangeable sample loops (5–200 μL) was used. The change of electrode potential was monitored using 46-Range Digital Multimeter (Radioshack) with PC interface. JXA 840A electron probe microanalyzer (JEO-Japan) was used for surface structures studies.

### Procedures

*Sensors construction*

The potentiometric strips were fabricated in arrays of six couples consisting of the working and reference electrodes (each 5 × 35 mm) following the procedures described elsewhere.[24,25] Ag/AgCl pseudo-reference electrode was first printed using homemade ink (prepared by mixing 0.9 g Ag/AgCl mixture (65 : 35%) with 0.8 g of 8% PVC solution in acetone-cyclohexanone mixture) and cured at 60 °C for 30 min. The plain carbon electrode was printed using carbon ink (prepared by mixing 0.45 g *o*-NPOE, 1.25 g of 8% PVC solution and 0.75 g carbon powder), cured at 50 °C for 30 min and soaked in freshly prepared DXM-ion pair suspensions for 24 h. The modified electrodes were fabricated in the same manner with incorporation of either 20 mg of DXM-tetraphenylborate ion-pair[26] or 50 mg of sodium teteraphenylborate (NaTPB) as sensing materials and used directly in the potentiometric measurements after 10 min preconditioning in $1 \times 10^{-3}$ mol $L^{-1}$ DXM solution.

*Sensors calibration*

In batch measurements, the fabricated sensors were calibrated by immersing the bi-electrode strip in 5 mL aliquots of $1 \times 10^{-6}$ to $1 \times 10^{-2}$ mol $L^{-1}$ DXM solutions and the potential readings were plotted against drug concentration (log [DXM]).

For FIA measurements, 50 μL of freshly prepared DXM solutions covering the concentration range from $1 \times 10^{-5}$ to $1 \times 10^{-2}$ mol $L^{-1}$ was injected in the flow stream (12.6 mL $min^{-1}$) and the corresponding peak heights were plotted against the drug concentration to establish the calibration graphs.

*Analytical applications*

In standard addition method, known increments of $1 \times 10^{-2}$ mol $L^{-1}$ standard DXM solution were added to 5 mL aliquot of sample solution where the change in potential readings was recorded for each increment and used to calculate the concentration of DXM in sample solution.

Under FIA conditions, 50 μL of sample solutions were injected where the peak heights were measured at the optimum conditions and compared to those obtained from injecting standard solutions with the same concentration.

In the potentiometric titration methods, aliquots of the sample solutions containing 0.27–13.5 mg DXM were titrated with standard NaTPB solution[27] and the electrode potential values were plotted against volume of the titrant added to estimate the end point.

## Results and Discussion

SPCEs are heterogeneous carbon electrodes having a composite structure since the printing ink matrix colligates different phases (carbon powder, plasticizer polymeric binder which is PVC dissolved in a proper organic solvent). After printing and curing, carbon tracks were deposited on the substrate with a final composition of 34.6% plasticizer, 57.7% carbon and 7.7% polymeric binder.[25] This composition combines those of both carbon pastes (28.6% plasticizer and 71.4% carbon) and PVC membranes (50% plasticizer, and 50% PVC). Scanning electron microscopy (SEM) indicated that addition of the plasticizer into the printing carbon ink produced a semi-liquid phase with smooth electrode surface (Figure 1). Such unique composition makes the SPCEs to combine the electroanalytical behavior of both PVC and CPE.

Owing to the low Ohmic resistance of the printed electrodes (about 1.5 k Ω), there is no need to print a conductive silver track underneath the carbon layer simplifying the printing of the working electrodes to a one-step process.

### Optimization of the electrode performance under batch condition

Both unmodified and modified electrodes (either with DXM ion pairs or ion pairing agents) were prepared and tested for the effect of nature and content of modifier, type of plasticizer, pH, response time, interferents, and applications.

*Electrodes modified with DXM ion pairs*

DXM forms water-insoluble ion pair complexes with NaTPB, reineckate ammonium salt (RAS), phosphotungstic acid (PTA), phosphomolybdic acid (PMA) or silicotungstic acid (STA), which

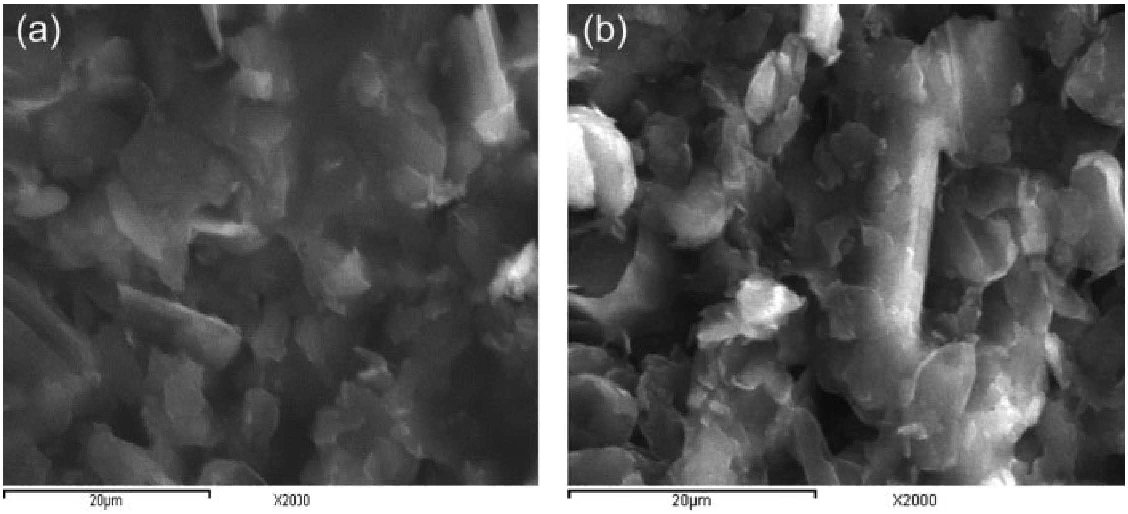

**Figure 1.** Scanning electron micrographs of electrode surface. a) carbon ink containing *o*-NPOE, b) carbon ink without o-NPOE.

can be used as electroactive materials for DXM sensors.[26] SPCEs incorporated with different DXM ion-pairs gave Nernstian responses with different slope and sensitivity depending on the nature of the ion-pair used. Incorporation of DXM-TPB showed the best performance (slope 53.1 ± 2.1 mV decade$^{-1}$) compared to other DXM-ion pairs modified electrodes. The content of DXM-TPB in the printing ink was varied from 5 to 50 mg; incorporation of 20 mg was found to be the best (58.1 ± 0.5 mV decade$^{-1}$) as further addition of this ion-pair resulted in decreasing of the electrode slope as it reached 45.7 mV decade$^{-1}$ at 50 mg.

### *Electrode modified with the ion pairing agents (in situ mode)*

Incorporation of a suitable ion pairing agent in the printing ink followed by soaking of the printed electrodes in DXM solution has led to the formation of DXM-IPs at the electrode surface which were subsequently extracted by the electrode mediator (plasticizer) into the electrode bulk. From different incorporated ion pairing agents, NaTPB showed superior sensitivity indicated by the highest slope (52.2 ± 2.1 mV decade$^{-1}$) compared to the other ion pairing agents. Carbon inks containing 10 to 100 mg NaTPB were prepared and used in printing of electrodes and calibration results revealed that SPCEs containing 50 mg of NaTPB showed the highest slope (54.7 ± 3.5 mV decade$^{-1}$).

### *Plain (soaked) electrodes*

Homemade carbon ink was prepared by mixing of carbon powder, plasticizer, and PVC binder dissolved in a proper organic solvent.[25] It is expected that during soaking of such electrode in the aqueous DXM-IPs suspension, the electrode plasticizer extracts these IPs and the electrode bulk becomes gradually saturated with such IPs, and hence there is no need to incorporate the ion exchanger into the electrode during its preparation.

The plain SPCEs were soaked in different DXM-IPs suspensions and used in potentiometric determination of DXM. Results showed that the electrodes soaked in DXM-TPB gave the best performance indicated by the highest slope (56.3 ± 0.6 mV decade$^{-1}$) which may be attributed to the difference in solubility products of these IPs and their extraction into the electrode bulk.[14,26]

**Table 1.** Analytical performances* of various DXM-SPCEs

| Parameter | Modified | In situ | Plain (Soaked) |
|---|---|---|---|
| Concentration range (mol L$^{-1}$) | $10^{-5} - 10^{-2}$ | $10^{-5} - 10^{-2}$ | $10^{-5} - 10^{-2}$ |
| Slope (mV decade$^{-1}$) | 58.1 ± 0.5 | 54.7 ± 3.5 | 56.3 ± 0.6 |
| r | 0.9988 | 0.9998 | 0.9987 |
| LOD (mol L$^{-1}$) | $6 \times 10^{-6}$ | $1 \times 10^{-5}$ | $6 \times 10^{-6}$ |
| Response time (s) | 1.6 | 3 | 1.6 |
| Operational lifetime (day) | 28 | 21 | 21 |
| Shelf lifetime (months) | 8 | 8 | 8 |
| Working pH range | 3–7 | 3–7 | 3–7 |

* Results are average of five different calibrations

### *Plasticizer effect*

The influence of the plasticizer on the electrode performance has been studied by comparing the o-NPOE plasticized electrode with those plasticized with DBP, DOP, DOS, DBS, or TCP. The obtained calibration graphs of plain SPCEs clarified that, using *o*-NPOE as plasticizer offers better sensitivity indicated by the highest slope (slope values were 56.3±0.6, 54.5±0.8, 52.2±1.3, 51.5±2.5, 50.5±0.2, and 50.0±0.5 mV decade$^{-1}$ for *o*-NPOE, DOP, TCP, DBS, DBP and DOS, respectively) which may be related to the dielectric constant of plasticizers and their abilities to extract DXM-TPB into the electrode matrices ($\varepsilon$ = 24, 3.8, 17.6, 4.5, 5.2 and 4.7 for the tested plasticizers, respectively).

## Sensors performance

The potentiometric response characteristics of various DXM-SPCEs were evaluated according to IUPAC recommendations.[28] Sensors displayed (Table 1) linear response from $1 \times 10^{-5}$ to $1 \times 10^{-2}$ mol L$^{-1}$ DXM with a Nernstian cationic slopes depending on the mode of preparation. Both SPCEs modified with the DXM-TPB and plain electrodes showed better performance relative

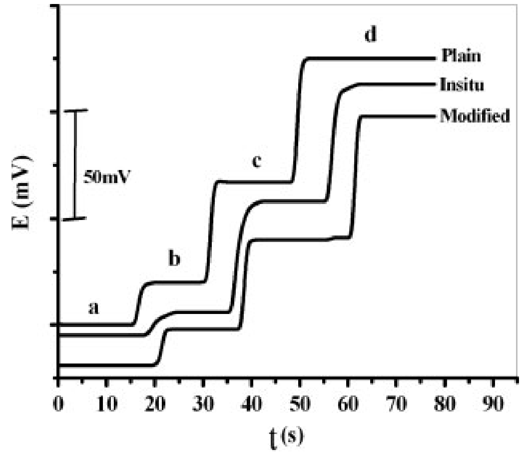

**Figure 2.** Dynamic response of DXM SPCEs: a) 1 × $10^{-6}$, b) 1 × $10^{-5}$, c) 1 × $10^{-4}$, d) 1 × $10^{-3}$ mol $L^{-1}$ DXM.

to those incorporated with the ion pairing agent indicated by higher slopes (58.1 ± 0.5 and 56.3 ± 0.6 mV $decade^{-1}$) with lower detection limit reaching 6 × $10^{-6}$ mol $L^{-1}$.

Screen-printing technology offers production reproducibility, versatility, and large-scale production for commercialization. Concerning the fabrication reproducibility, modification with DXM-TPB was the best as the average slope values for ten electrodes within the same batch were 58.1 ± 0.5 mV $decade^{-1}$ with standard potential 409.8 ± 7.0 mV. The corresponding values between three different batches were 58.9 ± 1.2 mV $decade^{-1}$ and 412 ± 8.1 mV, respectively.

The lifetimes of the different fabricated electrodes were tested by performing day-to-day calibration. SPCEs showed a useful lifetime of 4 weeks of daily measurement, during which the average slopes were reproducible (within ±2 mV/decade). Moreover, the SPCEs showed shelf life of more than 8 months when stored dry at 4 °C without significant change in the electrode performance.

The dynamic response time of the electrode was tested by measuring the time required to achieve a steady state potential (within ±1 mV) after sudden increase in the DXM concentration from 1 × $10^{-6}$ to 1 × $10^{-3}$ mol $L^{-1}$ (Figure 2). The response time of both plain and DXM-TPB modified SPCEs was fast as (about 1.6 s); while electrodes modified with the ion pairing agents gave a stable potential reading after 3 s.

The influence of pH on the response of SPCEs was also checked by recording the potential readings of the cell in solutions containing 1 × $10^{-4}$ to 1 × $10^{-2}$ mol $L^{-1}$ DXM at different pH values (pH 2–9). The plots of E (mV) versus pH indicated that the electrodes responses were found to be pH independent in the range 3–7.

Selectivity coefficients of DXM-SPCEs were determined using Matched Potential Method (MPM).[29] Additives and fillers commonly introduced in pharmaceutical formulations (such as glycine, caffeine, citrate, maltose, sucrose, and starch) as well as inorganic cations, $Na^+$, $K^+$, $Li^+$, $Ca^{2+}$, $Mg^{2+}$, and $NH_4{}^+$ did not show significant interference and selectivity coefficients were similar to that obtained with DXM CPEs.[26]

## Potentiometric titration

In addition to the application of SPCEs in direct potentiometric determination of DXM, the developed sensors were also used as end-point indicator electrodes in the potentiometric titration of DXM with NaTPB. The effect of electrode plasticizer on the titration performance was also investigated. Generally, the printed electrodes plasticized with *o*-NPOE gave the highest total potential change ($\Delta$E=304 mV) compared with those plasticized with TCP, DOP, DOS, DBS or DBP ($\Delta$E= 161, 126, 70, 80 and 74 mV for the plasticizers in the same order). Moreover, plain SPCEs showed the best titration curve (Figure 3A) comparable to those modified with either the DXM-TPB or ion-pairing agent. Under the same conditions, SPCEs showed titration curve better than that obtained with CPEs and similar to PVC electrode (Figure 3B).[26]

The titration curves were symmetrical with very well-defined inflexion points of potential jumps indicating the high sensitivity of the electrode. The titration process was highly reproducible with average recoveries 99.1 ± 1.1 and 98.7 ± 0.8% for 1.9 and 8.1 mg DXM, respectively. It is noteworthy to leave out, the same electrode was successfully applied for more than 30 titration processes over 20 days with non-significant drift in the total potential change ($\Delta$E= 266 ± 2.8 mV) and average recovery of 103.1 ± 0.9%.

## Electrode response under FIA conditions

The application of online systems with potentiometric detectors has the advantages of high sampling output with high reproducibility and sensitivity.[30–32] In the present study, the

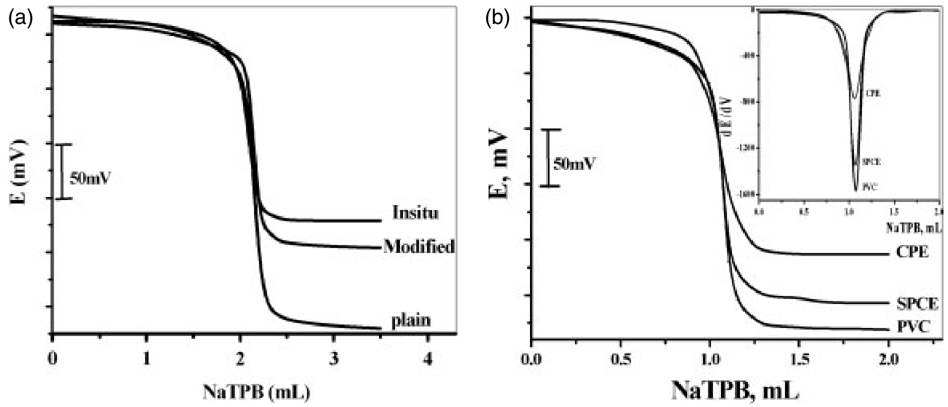

**Figure 3.** Potentiometric titration of DXM with 9.4 × $10^{-3}$ mol $L^{-1}$NaTPB using; a) SPCEs fabricated with different modes (2 mL of 1 × $10^{-2}$ mol $L^{-1}$ DXM), b) SPCE, PVC and CPEs (1 mL of 1 × $10^{-2}$ mol $L^{-1}$ DXM).

**Table 2.** Potentiometric determination of DXM in pharmaceutical preparations using SPCPEs

| | | Found | | | | | |
|---|---|---|---|---|---|---|---|
| | | Pure solution | | Tussilar drops | | Tussilar tablets | |
| | Taken mg | Recovery* | RSD* | Recovery | RSD | Recovery | RSD |
| Standard addition | 0.27 | 98.5 | 0.9 | 99.4 | 0.7 | 97.5 | 1.5 |
| | 1.89 | 99.1 | 1.1 | 100.1 | 1.0 | 98.0 | 1.2 |
| | 8.14 | 98.7 | 0.8 | 99.4 | 0.9 | | |
| Titration | 0.27 | 101.6 | 1.5 | 102.2 | 0.8 | 101.1 | 1.3 |
| | 1.89 | 96.3 | 0.9 | 99.6 | 0.9 | 95.8 | 0.64 |
| | 8.14 | 98.6 | 1.3 | 101.4 | 1.4 | | |
| FIA | 0.014 | 102.0 | 0.9 | 97.6 | 1.1 | 96.6 | 1.4 |
| | 0.135 | 97.6 | 0.8 | 99.8 | 0.9 | 99.8 | 0.95 |

* Mean recovery and relative standard deviations of five determinations in %

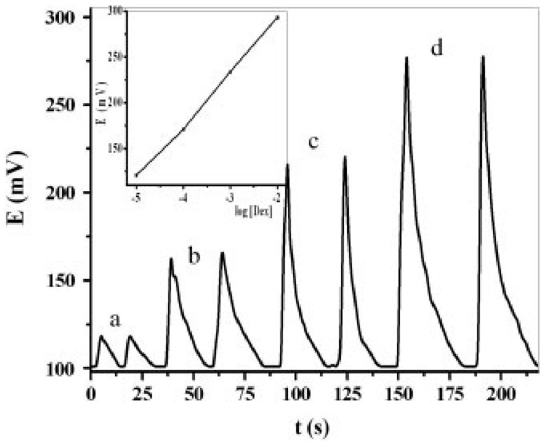

**Figure 4.** Flow injection potentiometric determination of DXM using SPCEs: a) 1 × $10^{-5}$, b) 1 × $10^{-4}$, c) 1 × $10^{-3}$, d) 1 × $10^{-2}$ mol $L^{-1}$.

performance of the bi-electrode strip containing both the working and reference electrodes fabricated by screen-printing technology was investigated under FIA conditions.

The influence of the sample volume was investigated by injecting of 5 to 200 µL of 1 × $10^{-2}$ mol $L^{-1}$ DXM solution into water carrier stream. It was observed that the larger the sample volume, the higher the peak height and the longer the residence time. A sample volume of 50 µL was selected which gave the maximum peak height and suitable residence time. In addition, the dependence of the peak heights and the time to reach the base line on the flow rate was studied by monitoring the sensor responses at different flow rates (6.30–22.05 mL $min^{-1}$). It was found that at a fixed injected volume (50 µL), both the residence time and the peak height were inversely proportional to the flow rate, and the flow rate of 12.6 mL $min^{-1}$ was chosen to compromise between the peak height and the analysis time. Under the optimum conditions, a limited dispersion coefficient of 1.13 was obtained with sampling output of 120 sample $h^{-1}$.

Figure 4 shows the peaks from the proposed electrode when 50 µL of DXM solutions at various concentrations were injected in the flowing stream (12.60 mL $min^{-1}$). The calibration graph was linear in the concentration range from $1 \times 10^{-5}$ to $1 \times 10^{-2}$ mol $L^{-1}$ with Nernstian slopes of 57.9±1.9 mV/decade and lower detection limit of 7.2 × $10^{-6}$ mol $L^{-1}$. Reproducibility was evaluated from repeated 12 injections of 50 µL of 1 × $10^{-2}$ mol $L^{-1}$ DXM solution and the average peak heights were found to be 293.0 ± 2.1 mV.

## Analytical applications

The proposed electrodes were successfully employed for the assay of DXM in their authentic samples as well as pharmaceutical formulations applying standard addition, FIA, and potentiometric titration methods. The results (Table 2) clearly indicate satisfactory agreement between the DXM contents in different samples determined by the developed sensor and official method. The time required for sample analysis was short in case of FIA (about 1 min) compared with about 10 min for the standard and potentiometric titration methods.

# Conclusion

Novel SPCEs were characterized, optimized, and successfully applied for the potentiometric determination of DXM using the procedures adapted in the application of the ordinary CPEs and PVC electrodes. The developed disposable strips have several advantages including simplicity, versatility, reproducibility of the preparation, and low cost mass production. Moreover, the amenability of construction the bi-electrode system offers availability of integration in FIA using small sample volume.

SPCEs are produced more easily and rapidly, saving large amounts of reagents, especially sensing material; 20 mg DXM-TPB is sufficient for printing more than 30 electrodes with the highest reproducibility in the sensor fabrication. The different DXM sensors presented in this study showed fast dynamic response times and longer lifetimes when compared with all previously published sensors.

The proposed methods of electrode modification (*in situ* and soaked) allow the potentiometric determination of more cationic and anionic drugs. The electroanalytical performance of the developed SPCEs rivaled or was even better than that obtained by conventional ones and can be regarded as the base for further research on drug quality control via incorporation of different sensing materials (ionophores or IPs) as well as commercialization of such disposable electrodes.

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