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Research Article

COMPARATIVE STUDY OF DIFFERENT ELECTROCHEMICAL SENSORS FOR POTENTIOMETRIC DETERMINATION OF METOCLOPRAMIDE HYDROCHLORIDE IN BULK POWDER AND IN PHARMACEUTICAL PREPARATION

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ABSTRACT

Objective: Development and validation of three electrochemical sensors for determination of metoclopramide hydrochloride (MCP) in its bulk powder and in pharmaceutical preparaion. **Methods:** The three electrochemical sensors based on the use of metoclopramide **-** phosphomolybdate (MCP-PMA) ion pair as an electroactive material in plasticized PVC membrane, carbon paste and coated graphite sensors. **Results:** The suggested three-sensors show a near-Nernstian response for MCP over a wide concentration range of 1×10-5-1×10-2 M with detection limits of 8 x10-6 M for PVC and carbon paste sensors and 9×10-6 M for coated graphite sensor. The proposed sensors have a fast response time and can be used for 3-4 weeks without any considerable divergence in potentials. **Conclusion:** They exhibit comparatively good selectivity with respect to related substances, dosage form additives, alkaline earth and some heavy metal ions, the proposed sensors have been successfully applied for the determination of MCP in its pharmaceutical formulation. Also, the obtained results have been statistically compared to a reported method indicating no significant difference between the investigated methods and the reported one with respect to accuracy and precision.

Keywords: Metoclopramide, potentiometry, PVC, carbon paste, coated graphite.

INTRODUCTION

Metoclopramide monohydrochloride monohydrate (MCP) fig.1, 4-amino-5-chloro-2-methoxy-N-(2-diethylamino-ethyl), monohydrochloride, monohydrate is a dopamine receptor antagonist. It is a substituted benzamide used for its prokinetic and antiemetic properties in disorders of decreased gastrointestinal motility such as gastroparesis and ileus, as well as in gastro esophageal reflux disease, dyspepsia, nausea and vomiting, and for the prevention of cancer therapy-induced emesis [1]. It is official in British Pharmacopoeia (2009) and United States Pharmacopoeia (2007) which recommend acid-base titrations with potentiometric end point detection [2,3]. It is a white or almost white crystalline powder and it is odorless. At 25 °C, 1 g MCP is soluble in 0.7 g of water, 3 g of ethanol (96%) and 55 g of chloroform, though it is practically insoluble in ether. It is soluble in dilute hydrochloric acid. It shows two ionization constants; pK_1= 0.42 and pK_2= 9.71 [4].

Many analytical methods have been developed for analysis of MCP in both clinical and experimental medicine which has promoted extensive interest in its determination. Current analytical methods employed for the determination of MCP can involve potentiometry [5-17], spectrometry [18-34], fluorimetry [35-40], chromatography [41-51], capillary electrophoresis [52], gas chromatography-mass spectrometry (GC-MS) [53,54], voltammetry and amperometry [55], square wave anodic stripping voltammetry [56], fast stripping continuous cyclic voltammetry [57].

Most of the mentioned methods are complicated and need sophisticated instruments; as well as the chromatographic methods are costly and time-consuming, limiting their application. Other methods often are typically less sensitive or have their own intrinsic complexity or require expensive instrumentation. The present work establishes new simple, accurate, rapid and reproducible techniques for determination of MCP, by construction and electrochemical evaluation of novel potentiometric sensors. These sensors incorporate the ion association complexes of MCP cation with phosphomolybdic acid as a counter anion in each composition of the proposed three sensors. These sensors have fast response and near-Nernstian slopes. The proposed sensors have been demonstrated to be superior to the reported methods with respect to speed, simplicity, sensitivity, selectivity and cost-effectiveness, and have been successfully applied for the determination of MCP in simple and complex matrices

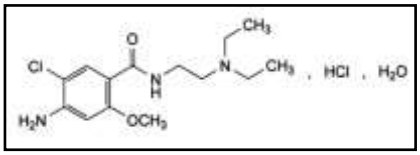

Fig. 1: Structural formula of metoclopramide hydrochloride.

EXPERIMENTAL

Instruments

- Bandelinsonorox, Rx 510 S, magnetic stirrer (Hungarian).
- Jenway, 3510 pH meter (England) with Ag/AgCl reference electrode no 924017 -LO3-Q11C.

Chemicals and solvents

All reagents used were of analytical grade and water used throughout the procedure was freshly distilled.

- Tetrahydrofuran, dioctylphthalate (DOP), graphite powder (synthetic 1–2µm), multi walled carbon nanotubes (MWCNT) and poly (vinyl chloride) of high relative molecular weight (Sigma-Aldrich, Germany).
- Phosphomolybdic acid (Sigma-Aldrich, Germany), prepared as 10^{-2} M aqueous solution.
- Glucose, glycine, sucrose, potassium chloride, calcium chloride, magnesium chloride, sodium chloride and nickel chloride (El-Nasr Company, Egypt), prepared as 10^{-3} M aqueous solution.
- Sodium hydroxide (El-Nasr Company, Egypt), prepared as (0.1-1) M aqueous solution.
- Hydrochloric acid (El-Nasr Company, Egypt), prepared as (0.1-1) M aqueous solution.

Pure and market samples

MCP was kindly supplied by Sanofi-aventis Egypt and certified to contain 99.99%.

Primperan® tablets with batch number 6EG022 manufactured by Sanofi Aventis Company. Each tablet was labeled to contain 10 mg of MCP, purchased from local market.

Standard and stock solutions of MCP

A stock standard solution of 10^{-2} M MCP was prepared by dissolving 0.35427 g of the drug powder in 50 ml of water and complete to 100 ml with water. Different working solutions of varying strengths ranging from (10^{-6} to 10^{-3} M) were prepared by suitable dilution from the stock standard solution with water.

PROCEDURES

Preparation of the ion-exchanger

The ion-exchanger, metoclopramide phosphomolybdate (MCP-PMA) was prepared by mixing of 150 ml of 10^{-2} M MCP solution to 50 ml of 10^{-2} M of phosphomolybdic acid. The resulting precipitate was left in contact with their mother liquor over night to assure complete coagulation, then the precipitate was filtered and washed thoroughly with distilled water and left to dry at room temperature for at least 3 days.

Preparation of membranes

PVC sensor

In a glass petri dish (5-cm diameter), 168 mg of dioctylphthalate was thoroughly mixed with 168 mg of PVC and 14 mg of MCP-PMA as an ion pair. The mixture was dissolved in 10 mL of tetrahydrofuran. The petri dish was then covered with a Whatman No. 3 filter paper and left to stand overnight to allow for solvent evaporation at room temperature. A master membrane with a thickness of 0.1 mm was obtained.

Coated graphite sensor

In a glass petri dish (5 cm diameter), 168 mg of DOP was thoroughly mixed with 168 mg of PVC and 14 mg of MCP-PMA. The mixture was dissolved in 10 ml of tetrahydrofuran and homogenized thoroughly. The solvent was slowly evaporated at room temperature until oily concentrated mixture was obtained.

Electrodes assembly

PVC sensor

From the master membrane, an 8-mm diameter disk was cut out from the prepared membrane and glued using tetrahydrofuran to a transposable PVC tip that was clipped into the end of the electrode glass part. The resulting electrode body was filled with equal portions of 10^{-2} M KCl and 10^{-2} M MCP. The prepared sensor was preconditioned by soaking in 10^{-2} M drug solution for 8 hours. When not in use, the sensor was stored in air.

Coated graphite sensor

It was fabricated using commercial graphite bar (2.5 cm length an, 3 mm diameter). One end of the bar was used for connection, while the other was dipped in the electro active membrane mixture. The process was repeated several times until a layer of proper thickness were formed covering the terminal of graphite bar. The electrode was left standing at room temperature to dry. The uncoated end of the graphite rod was sealed in a poly tetra ethylene tube; the tube was filled with metallic mercury into which a copper wire was dipped. The prepared sensor was preconditioned by soaking in 10^{-2} M drug solution for 12 hours. When not in use, the sensor was stored in air.

Preparation of carbon paste sensor modified with MCP-PMA/ multi walled carbon nanotubes composite (MWCNT/MCP-PMA)

115 mg pure graphite powder, 14 mg MCP-PMA and 5 mg multi walled carbon nanotubes (MWCNT) were transferred to mortar and mixed well with 150 mg of dioctylphthalate .The paste matrices were packed into a piston driven Teflon holder. The prepared sensor was preconditioned by soaking in 10^{-2} M drug solution for 8 hours before measurements and electrode surface regeneration was performed by screwing the piston and polishing with a moistened filter paper.

Measurement conditions

- pH: 3 - 8.
- Soaking time: 8 hours for both PVC and carbon paste sensors, but 12 hours for coated graphite sensor.
- Response time: 20, 45 and 60 seconds for PVC, carbon paste and coated graphite sensors, respectively.
- Sensor stability: 4 weeks for both PVC and carbon paste sensors, but 3 weeks for coated graphite sensor.

Sensors calibration

The prepared sensors were immersed in conjunction with Ag/AgCl reference electrode in solutions of MCP in the range of 10^{-6} to 10^{-2} M. They were allowed to equilibrate while stirring until achieving a constant reading of the potentiometer. Then, the electromotive force values were recorded within ± 1 mV. Calibration graphs were plotted that related the recorded electrode potential values versus the negative logarithmic values of the drug concentrations.

Validation of the methods

Limit of detection (LOD)

LOD was calculated by determining the concentration of the drug at the point of intersection of the extrapolated linear mid-range and final low concentration level segments of the calibration plot.

Accuracy and precision

Accuracy and precision of the sensors were determined by applying the procedures for determination of three different concentrations (10^{-2}, 10^{-3} and 10^{-5} M), each in triplicate, of MCP in pure form in the same day (intra-day) and in three successive days (inter-day), then the accuracy as percent recovery (R %) and precision as percent relative standard deviation (RSD %) were calculated.

Application to pharmaceutical preparation

Twenty **Primperan®** tablets (10 mg per tablet) were weighed and then finely powdered. Appropriate weight of powder equivalent to 0.17715 g of MCP was accurately weighed, transferred to 50 ml volumetric flask and the volume was made up to 30 ml with distilled water. The solution was shaken vigorously for 15 minutes then sonicated for 30 minutes and filtered through Whatman filter paper no 41. The volume was completed to 50 ml with water to produce a stock solution labeled to contain 10^{-2} M of MCP. Appropriate dilutions of the stock solution were made up with water to obtain different concentrations of MCP. Apply the described general procedures using aliquots covering the working concentration range. Determine MCP content of the tablets from the corresponding regression equation.

Results and discussion

The design and application of potentiometric sensors is of interest for quantitative pharmaceutical analysis because these sensors offer the advantages of simple design, higher selectivity, fast response and wide dynamic range with low detection limit. In the present study ion selective electrodes, of three types: PVC, carbon paste and coated graphite electrodes have been constructed for the selective determination of MCP in bulk powder and in its tablet formulation. The methods were based on the fact that, MCP behaves as a cation, due to the presence of tertiary amino group. This property suggested the use of anionic type of ion exchanger such as phosphomolybdic acid as a counter ion to prepare water insoluble association complex using precipitation based technique.

Electrochemical behavior of MCP with the investigated sensors

The electrochemical performance of the suggested sensors was evaluated according to IUPAC recommendation data [58,59]. Calibrations were achieved by immersing the sensors in conjunction with Ag/AgCl reference electrode in solutions of MCP in the concentration range of 10^{-6} to 10^{-2} M. They were allowed to equilibrate and recording the electromotive force values. The

performance, response characteristics, investigation and results obtained for the proposed sensors were summarized in **table (1)**. The profiles of the potential in mV versus negative log molar concentration of MCP by the proposed sensors were plotted as shown in **figure (2)**.

Table 1: The performance, investigation and response characteristics of the proposed sensors.

Parameter	PVC sensor	Carbon paste sensor	Coated graphite sensor
Regression parameters			
- Slope (b)	-57.89	-55.32	-52.67
- Intercept (a)	311.27	455.598	393.115
Regression coefficient	0.9999	0.9998	0.9996
Linearity range (M)	$1x10^{-5}$ - $1x10^{-2}$	$1x10^{-5}$ - $1x10^{-2}$	$1x10^{-5}$ - $1x10^{-2}$
Working pH range	3-7	3-7	3-7
Response time (sec.)	20	45	60
LOD (M)	8×10^{-6}	8×10^{-6}	9×10^{-6}
Life span (weeks)	4	4	3
Accuracy (% R)	100.06	100.11	100.66
Precision			
Repeatability	0.860	0.937	0.928
Intermediate precision (% RSD)	0.906	1.041	0.986

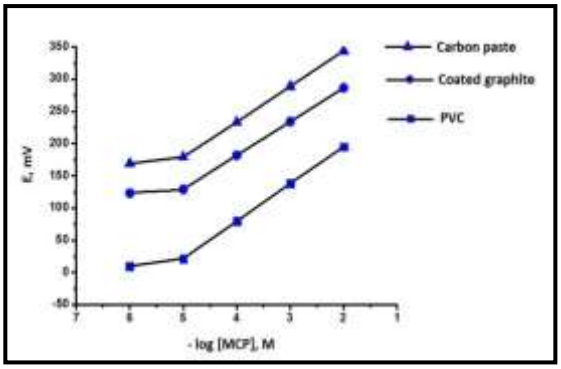

Fig. 2: Profile of the potential in mV/- Log molar concentration of MCP using PVC, carbon paste and coated graphite sensors.

Investigation and optimization of experimental conditions:

Optimization of the membrane composition for both PVC and coated graphite sensors

The ion exchanger, MCP-PMA, was tested as a modifier for the these two sensors. It was studied by varying the percentage of the MCP-PMA, while keeping the percentage of the PVC and DOP equal 1:1 as shown in tables (2,3). The sensors made of 4 % (w/w) MCP-PMA gave the best performance.

Table 2: Optimization of the membrane composition (w/w %) of the proposed PVC sensors

Sensor no.	Composition % (w/w)			LOD (M)	Linearity range (M)	Slope (mV/ decade)	r^2
	MCP-PMA	PVC	Plasticizer (DOP)				
1	1	49.5	49.5	3×10^{-5}	$5x10^{-5}$ - $1x10^{-2}$	-48.24	0.9956
2	2	49	49	2×10^{-5}	$5x10^{-5}$ - $1x10^{-2}$	-50.65	0.9942
3	3	48.5	48.5	8×10^{-6}	$1x10^{-5}$ - $1x10^{-2}$	-54.65	0.9984
4	4	48	48	8×10^{-6}	$1x10^{-5}$ - $1x10^{-2}$	-57.89	0.9999
5	5	47.5	47.5	3×10^{-5}	$5x10^{-5}$ - $1x10^{-2}$	-51.35	0.9987

Table 3: Optimization of membrane composition (w/w) coated graphite MCP sensors

Sensor no.	Composition % (w/w)			LOD (M)	Linearity range (M)	Slope (mV/ decade)	r^2
	MCP-PMA	PVC	Plasticizer (DOP)				
1	1	49.5	49.5	3×10^{-5}	$5x10^{-5}$ - $1x10^{-2}$	-47.24	0.9992
2	2	49	49	2×10^{-5}	$5x10^{-5}$ - $1x10^{-2}$	-49.65	0.9941
3	3	48.5	48.5	8×10^{-6}	$1x10^{-5}$ - $1x10^{-2}$	-50.65	0.9954
4	4	48	48	9×10^{-6}	$1x10^{-5}$ - $1x10^{-2}$	-52.67	0.9996
5	5	47.5	47.5	3×10^{-5}	$5x10^{-5}$ - $1x10^{-2}$	-48.35	0.9932

Optimization of the paste composition for carbon paste sensor

Incorporation of multi walled carbon nanotubes in the composition of the carbon paste will improve the conductivity and transduction of the chemical signal to electrical signal, which in turn improved the dynamic working range and response time. Different amounts of multi walled carbon nanotubes (2.5, 5, 7.5, 10 mg) were added to the paste matrix (containing 115 mg of pure graphite powder, 14 mg of MCP-PMA and 150 mg of dioctylphthalate) and the results obtained were given in **table (4)**.The results showed that on using paste of optimum compositions (5 mg MWCNT) exhibits the best performance. However, the consistence of pastes containing more than 5mg multi walled carbon nanotubes was difficult to be mixed with the paste showed lower Nernstian slopes with long response time. This may be due to the high surface area on the electrode surface and capturing ions on the surface of the paste.

Table 4: Effect of the ionophore and modifier contents on the performance chracterisics of MCP carbon paste sensors

Sensor no.	Composition (w/w)				LOD (M)	Linearity range (M)	Slope (mV/ decade)	r^2
	MCP-PMA	Graphite	MWCNTS	Plasticizer (DOP)				
1	14	115	2.5	150	8×10^{-6}	$1x10^{-5}$ - $1x10^{-2}$	-50.36	0.9991
2	14	115	5	150	8×10^{-6}	$1x10^{-5}$ - $1x10^{-2}$	-55.32	0.9998
3	14	115	7.5	150	3×10^{-5}	$5x10^{-5}$ - $1x10^{-2}$	-52.98	0.9985
4	14	115	10	150	4×10^{-5}	$5x10^{-5}$ - $1x10^{-2}$	-0.48.56	0.9947

Effect of soaking time

Freshly prepared sensor must be soaked to form thin gel layer at the surface of the membrane where ion exchange occurs. This process requires different times depending on diffusion at the electrode test solution interface. For this purpose, the sensors were soaked in 10^{-2} M MCP. The slopes obtained from calibration curves were recorded after 0, 2, 4, 8, 12, 16, 24 and 36 h as shown in **table (5)**. The optimum soaking time was found to be 8 hours for both PVC and carbon paste sensors, while for coated graphite sensor was 12 hours. Soaking more than the required hours should be avoided to prevent

the leaching of the active ingredients (MCP-PMA and DOP) to the bathing solution [60].

Table 5: Effect of soaking time on performance of the proposed three sensors at 25 ± 1 ^{0}C.

Soaking time/h	PVC sensor slope (mV/decade)	Carbon paste sensor slope (mV/decade)	Coated graphite sensor slope (mV/decade)
0	-51.65	-44.98	-44.32
2	-54.89	-47.58	-46.85
4	-56.25	-50.68	-48.58
8	-57.89	-55.32	-50.23
12	-54.69	-53.45	-52.67
16	-50.51	-50.87	-51.24
24	-48.54	-48.75	-47.25
36	-46.36	-45.87	-45.87

Effect of pH

In an approach to understanding the impact of pH on the electrodes response, the potential was measured at two particular concentrations of the metoclopramide solution (1×10^{-3} M and 1×10^{-4} M) from the pH value of 2 up to 11 (0.1-1 M sodium hydroxide or hydrochloric acid solutions were employed for the pH adjustment). Representative curves for the effect of pH on the proposed sensors using (1×10^{-3} M and 1×10^{-4}M) metoclopramide solution is shown in **figures (3-5)**. The results revealed that the potential remained constant despite the pH change in the range of 3 to 8, indicating the applicability of this electrode in the specific pH range. Relatively noteworthy fluctuations in the potential versus pH behavior took place below and above the formerly stated pH limits. In detail, the fluctuations above the pH value of 8 might be justified by removing the positive charge on the drug molecule (non-protonated form) and the fluctuations below the pH value of 3 were attributed to the removing the ion-pair in the membrane or due to an increased solution acidity which could lead to extraction of H^+ by the membrane, thus leading to noisy responses.

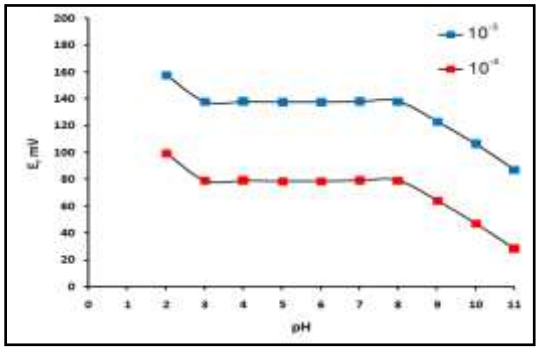

Fig 3: Effect of pH on the response of metoclopramide using PVC membrane sensor.

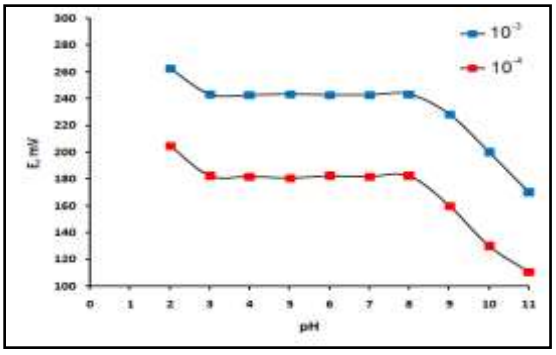

Fig 4: Effect of pH on the response of metoclopramide using coated graphite sensor.

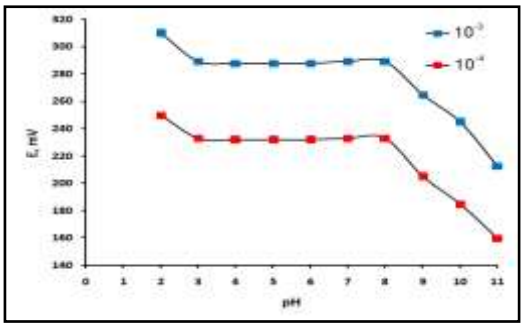

Fig5: Effect of pH on the response of metoclopramide using carbon paste sensor.

Sensor Selectivity

The potentiometric selectivity coefficients ($K^{pot}_{Drug,J^{+z}}$) of MCP sensors were measured by the separate solutions method (SSM) [61] for inorganic cations. In this method, the potentials of 1×10^{-3} M concentration of both MCP and the interfering species were determined separately. The selectivity coefficients were calculated using the following equation :

$$\text{Log } K^{pot}_{Drug,J^{+z}} = (E_2 - E_1)/S + \log[\text{drug}] - \log[J^{+z}]^{1/3}$$

where, E_1 and E_2 are the potential readings observed after exposing the sensors to the same concentration of MCP and interferentcation [J^{+Z}] in separate solutions, respectively, and S is the slope of the MCP calibration graph (mV/concentration decade).

While, for sugars and amino acids were determined using the matched potential method (MPM) using the following equation [62]:

$$a[S^1] = (aP' - aP)/aI$$

where a known activity [aP'] of the primary ion solution is added into a reference solution that contains afixed activity [aP] of primary ions and the corresponding potential change [ΔE] is recorded, and [aI] is the activity of the interfering ion that produced the same potential change [ΔE]. The selectivity coefficients obtained show that the proposed electrodes are highly selective towards the MCP ion. There is no interference from the inorganic cations due to the differences in their ionic size, mobility and permeability in comparison to the MCP ion. In the case of sucrose, glucose, urea and glycine the selectivity is most probably attributed to the difference in polarity and to the moderately hydrophobic nature of their molecules relative to the MCP ion **table (6)**.

Table 6: Potentiometric selectivity coefficients $K^{pot}_{Drug,J^{+z}}$ for some common cationswith the proposed sensors:

Interferents	$K^{pot}_{Drug,J^{+z}}$ of PVC sensor	$K^{pot}_{Drug,J^{+z}}$ of Carbon paste sensor	$K^{pot}_{Drug,J^{+z}}$ of Coated graphite sensor
SSM **			
Potassium chloride	1.2×10^{-3}	2.6×10^{-3}	2.1×10^{-3}
Calcium chloride	2.4×10^{-3}	3.2×10^{-3}	5.6×10^{-3}
Magnesium chloride	4.7×10^{-3}	2.8×10^{-3}	4.5×10^{-3}
Sodium chloride	1.8×10^{-3}	3.8×10^{-3}	6.5×10^{-3}
Nickel chloride	2.5×10^{-2}	5.2×10^{-3}	5.7×10^{-2}
MPM ***			
Glucose	3.4×10^{-2}	3.6×10^{-2}	6.3×10^{-2}
Sucrose	4.5×10^{-2}	9.6×10^{-3}	8.5×10^{-2}
Glycine	8.7×10^{-3}	5.8×10^{-3}	9.9×10^{-3}

****SSM: separate solution method.**
*****MPM: matched potential method.**

Response time of the proposed sensors

The response time of a prepared sensor is of critical importance. The average time required for the electrode to reach a steady potential response within ±1 mV of the final equilibrium value after successive immersion of a series of MCP solutions, each having a 10-fold difference in concentration, was investigated [59]. The dynamic response time for the proposed sensors to reach values within ± 1 mV of the final equilibrium potential after increasing the drug concentration 10-folds were found to be 20, 45 and 60 sec. for PVC, carbon paste and coated graphite sensors, respectively as shown in **figures (6-8)**.

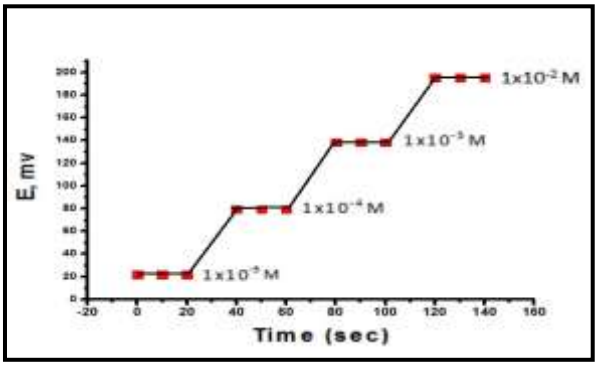

Fig. 6: Response time of the investigated PVC sensor.

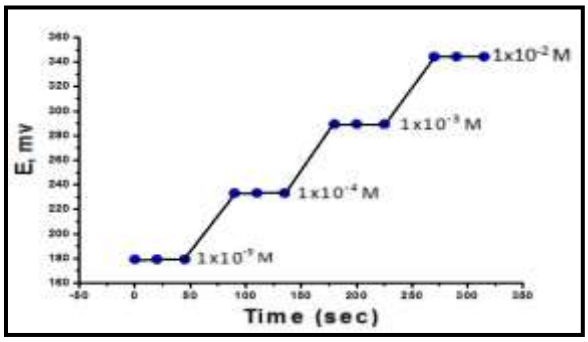

Fig. 7: Response time of the investigated carbon paste sensor.

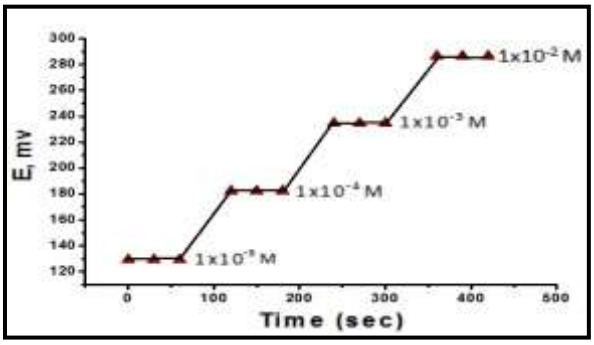

Fig. 8: Response time of the investigated coated graphite sensor.

Method validation

The proposed methods were validated in compliance with the ICH guidelines [63]. **Table (1)** shows the accuracy and precision, LOD, linearity and range of the proposed methods.

Application to pharmaceutical preparation

The proposed sensors were applied to the determination of MCP in **Primperan®** tablets. Satisfactory results were obtained in good agreement with the label claim, indicating no interference from excipients and additives. The obtained results were statistically compared to those obtained by the reported method [64] as could be seen from **table (7)**. The results revealed good agreement with the reported method.

Table 7: Determination of MCP in Primperan® tablets by the proposed sensors and reported method:

Parameters	PVC sensor	Carbon paste sensor	Coated graphite sensor	Reported method [a]
N *	5	5	5	5
Mean	99.18	100.15	99.58	99.81
SD	0.774	1.558	1.841	0.978
% RSD	0.780	1.555	1.849	0.979
t **	1.125 (2.306)	0.417 (2.306)	0.250 (2.306)	———
F **	0.627 (6.388)	2.540 (6.388)	3.548 (6.388)	———

*** Number of experiments.**

**** The values in parenthesis are tabulated values of "t "and "F" at (P = 0.05)**

a Reported zero order method using the absorbance at 272 nm (λ_{max}) for determination of MCP in pure form and solid pharmaceutical dosage form (tablets).

Conclusion:

The proposed methods were precise, specific and accurate. MCP could be determined in bulk powder and in pharmaceutical preparation without interference from common excipients using the proposed sensors. PVC and carbon paste sensors had shorter soaking and response time with lower detection limit than those of coated graphite sensor, attributed to the presence of an internal solution of the drug inside PVC glass electrode and the presence of multi walled carbon nanotubes as a modifier in carbon paste one, enhancing their electroactivity..

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