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Application of PVC Membrane and Modified Carbon Nanotubes Paste as Electrochemical Sensors for Potentiometric Determination of Loperamide Hydrochloride

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ABSTRACT

Objectives: The main purpose of this work is to design a simple, sensitive, accurate and precise potentiometric membrane ion selective electrodes for selective determination of loperamide hydrochloride in bulk powder and in pharmaceutical preparation. **Methods:** Electrochemical behavior of loperamide hydrochloride were investigated using PVC membrane and modified carbon nanotubes paste sensors. The linearity of this developed method was established in the concentration range of 10^{-5} - 10^{-2} M and 10^{-6} - 10^{-2} M shows a Nernstian slope of 57.38 mV and 58.74 mV for PVC and Carbon paste sensor, respectively. **Results:** Validation parameters such as specificity, linearity, accuracy, precision, stability, limit of detection were found to be within the acceptance limit as studied according to IUPAC recommendation data. **Conclusion:** Both sensors ware successfully applied for potentiometric determination of loperamide hydrochloride in its pure form and pharmaceutical formulations.

Keywords: *Ion selective electrodes; Loperamide hydrochloride; Modified carbon nanotubes paste sensor; PVC membrane sensor*

INTRODUCTION

Loperamide hydrochloride, **Figure 1**, is 4-(4-*p*-Chlorophenyl-4-hydroxypiperidino)-*N*,*N*-dimethyl-2, 2-diphenylbutyramide hydrochloride. Its molecular weight is 513.5 and its molecular formula is $C_{29}H_{33}ClN_2O_2 \cdot HCl$. It is a white to slightly yellow powder. It is slightly soluble in water and in dilute acids; freely soluble in chloroform and in methyl alcohol; very slightly soluble in isopropyl alcohol.[1]

Loperamide is a synthetic derivative of pethidine that inhibits gut motility and may also reduce gastrointestinal secretions. It is given orally as an antidiarrhoeal drug as an adjunct in the management of acute and chronic diarrhoeas and may also be used in the management of colostomies or ileostomies to reduce the volume of discharge.[1]

Loperamide hydrochloride is an official drug in the United States Pharmacopoeias.[2] To date, various techniques have been utilized for the determination of

loperamide hydrochloride. It mainly includes: non-aqueous titration[3], spectrophotometry[4-6], colorimetry[7-10], spectrofluorimetry[4], chemiluminescence[11], voltammetry[12,13], high-performance liquid chromatography[14-29]. In recent decades potentiometric membrane ion-selective electrode (ISEs) have been widely used in several fields of modern analytical chemistry.[30] The simple design, low cost, relatively short response times, wide linear dynamic range (making sample concentration adjustments, to fit analyte concentration to the linear working range usually unnecessary), adequate selectivity, feasibility to analyse turbid and coloured samples and the low sample treatment (usually only an ionic strength adjustment step is required) are some of intrinsic advantages of potentiometric measurements that justify why these units have been the aim of several researches [31]. These sensors systems enable the development of an electrical potential at the surface of an electrode membrane when placed in contact with a solution containing the analyte. The extent of this potential change is related with the activity of the target species. Ion-selective electrodes can be classified according to the type and composition of the responsive membrane into glass electrodes, solid-state electrodes, liquid membrane electrodes, coated wire electrodes, gas sensing electrodes and enzyme substrate electrodes.[32]

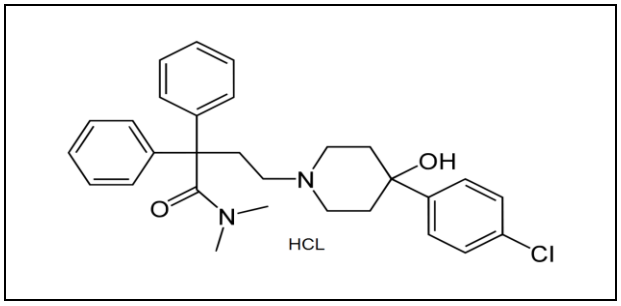


Figure 1. Structural formula of Loperamide hydrochloride

The aim of this work was to develop a new simple potentiometric ion selective membrane electrodes of two types: PVC membrane and carbon paste electrodes have been constructed for selective determination of loperamide hydrochloride.

MATERIAL AND METHODS

Materials and Chemicals

Pure loperamide hydrochloride (99.65%), the purity was checked by applying the reported method [6], was kindly provided by Alexandria Company for Pharmaceuticals and Chemical Industries – Alexandria–Egypt. **Imodium®** tablet: labeled to contain 2 mg loperamide hydrochloride per tablet, manufactured by Catalent UK Swindon Zydis Limited (batch number 8IV1331), purchased from local market. All chemicals and reagents used were of analytical grade and water used throughout the procedure was freshly distilled. For ISEs membranes preparation the following reagents were used: Tetrahydrofuran, dioctylphthalate (DOP), tributyl phosphate (TBP), polyvinyl chloride (PVC) of high relative molecular weight, graphite powder (synthetic 1–2 μm), multi walled carbon nanotubes (MWCNT), ammonium reineckate, methanol, boric, acetic and orthophosphoric acids, paraffin oil and petroleum ether (Sigma-Aldrich, Germany). Glucose, glycine, sucrose, urea, potassium chloride, calcium chloride, magnesium chloride, sodium chloride and nickel chloride (El-Nasr Company, Egypt). Britton Robinson buffer.[33]

Instruments

Jenway, 3510 pH meter (England) with Ag/AgCl reference electrode no 924017 -LO3-Q11C. Bandelin sonorox, Rx 510 S, magnetic stirrer (Hungarian). Hot plate (Torrey pines Scientific, USA). Thermostated water bath (Kotlermann Hanigsen, Germany). Analytical balance (Precisa125A, Switzerland).

Preparation of standard solution of loperamide hydrochloride

A stock standard solution of loperamide hydrochloride (10^{-2} M) was prepared by dissolving 513.5 mg of the drug powder in 80 ml of Britton Robinson buffer pH 5 and the volume was completed to 100 ml with the same solvent. Different working solutions of varying strengths were prepared by dilution of the stock standard solution with Britton Robinson buffer pH 5.

Preparation of the ion-exchanger

The ion-exchanger, loperamide-reineckate **(LOP-RKT)**, was prepared by mixing 50 ml of 10^{-2} M ammonium reineckate with 50 ml of 10^{-2} M loperamide hydrochloride. The mixture was left to react for 60 min under stirring at room temperature. The resulting precipitate was then filtered off on Whatman filter paper and washed several times with distilled water till chloride free (tested using $AgNO_3$ solution). The precipitate was left to dry for 12 hours at 60°C, washed with petroleum ether to remove any residual moisture, and then ground to fine powder.

Membrane preparation and sensor construction

PVC membrane sensor: In a glass petri dish (5-cm diameter), 0.17 ml of dioctylphthalate was mixed with 172 mg of PVC and 6 mg loperamide-reineckate. The mixture was dissolved in 10 ml of tetrahydrofuran.

Table 1. Regression, validation data and response characteristics of the PVC membrane and carbon paste loperamide hydrochloride sensors

Parameter	PVC membrane sensor	Carbon paste sensor
Linearity range (M)	10^{-5} - 10^{-2}	10^{-6} - 10^{-2}
LOD (M)	3.47 x10^{-6}	5.13 x10^{-7}
Regression Equation	$y^{a} = b\ x^{b} + a$	$y^{a} = b\ x^{b} + a$
- Slope (*b*)	-57.38	-58.74
- Intercept (*a*)	266.02	340.61
Coefficient of determination (r^2)	0.9996	0.9995
Working pH range	3–6	3–6
Response time (sec.)	40	25
Stability (days)	30	40
Accuracy (% R)[c]	100.83	99.52
Precision [d] (% RSD)		
- Repeatability	1.178	0.816
- Intermediate precision	0.953	1.412

[a] *The electrode potential in mV.*
[b] *the negative logarithmic value of the drug concentration in mole per liter.*
[c] *Average of nine determinations (three concentrations repeated three times).*
[d] *%RSD of nine determinations (three concentrations repeated three times).*

Table 2. Optimization of membrane composition (w/w %) of the PVC membrane loperamide hydrochloride sensor

Sensors	Composition % (w/w)			LOD (M)	Linearity rang (M)	Slope (mV/decade)	r^2
	LOP-RKT	PVC	Plasticizer				
1	2	49	49 (DOP)	6.32x10^{-6}	10^{-5}- 10^{-2}	-54.91	0.9993
2	4	48	48 (DOP)	4.65x10^{-6}	10^{-5}- 10^{-2}	-55.23	0.9994
3	**6**	**47**	**47 (DOP)**	**3.47x10^{-6}**	**10^{-5}- 10^{-2}**	**-57.38**	**0.9996**
4	8	46	46 (DOP)	3.81x10^{-6}	10^{-5} - 10^{-2}	-56.11	0.9995
5	2	49	49 (TBP)	6.53x10^{-6}	10^{-5} - 10^{-2}	-53.64	0.9992
6	4	48	48 (TBP)	5.04x10^{-6}	10^{-5} - 10^{-2}	-55.07	0.9993
7	6	47	47 (TBP)	4.16x10^{-6}	10^{-5}- 10^{-2}	-56.89	0.9995
8	8	46	46 (TBP)	4.25x10^{-5}	10^{-5}- 10^{-2}	-56.25	0.9991

Bold values for the optimum proposed sensor.

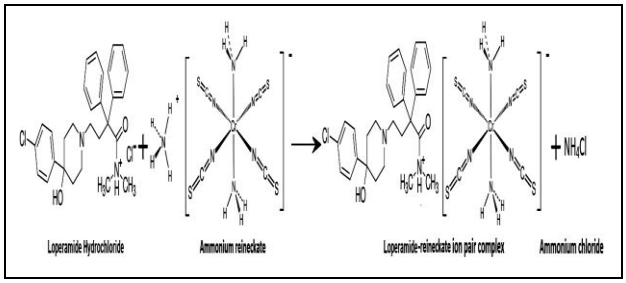
The petri dish was then covered with a Whatman No. 3 filter paper and left to stand overnight to allow for solvent evaporation at room temperature. A master membrane with a thickness of 0.1 mm was obtained.

Modified multi-wall carbon nanotubes carbon paste sensor: In a mortar 200 mg pure graphite powder, 16 mg loperamide-reineckate ion pair, 0.1 ml paraffin oil and 10 mg carbon nano particles were homogenously mixed well.

Sensors assembly

PVC membrane sensor: From the master membrane, 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 loperamide hydrochloride. The prepared sensor was preconditioned by soaking in 10^{-2} M drug solution for 18 hours.



Scheme 1. Proposed reaction pathway of loperamide hydrochloride and ammonium reineckate.

Modified multi-wall carbon nanotubes carbon paste sensor: The carbon paste was carefully packed in a piston driven teflon holder 3 mm in diameter. The prepared sensor was preconditioned by soaking in 10^{-2} M drug solution for 36 hours before measurements and electrode surface regeneration was performed by screwing the piston and polishing with a wet smooth paper.

Sensors calibration

The conditioned sensors were immersed in conjunction with Ag/AgCl reference electrode in solutions of loperamide hydrochloride in the range of 10^{-5} to 10^{-2} M for PVC membrane sensor and 10^{-6} to 10^{-2} M for carbon paste sensor. They were allowed to equilibrate while stirring until achieving a constant reading of the pH meter. Then, the electromotive forces values were recorded within ± 1 mV. Calibration graphs were plotted that related the recorded electrode potential versus negative logarithmic value of the drug concentration.

Measurement conditions

- For PVC membrane sensor, the electrochemical system can be represented as following: internal reference electrode/ internal filling solution/ PVC membrane/ test solution/ external reference electrode. Where the filling solution is a mixture of 10^{-2} M solutions of each of the drug and KCl.
- For carbon paste sensor the electrochemical system can be represented as following: reference electrode / test solution / carbon paste electrode.
- pH: 3 – 6 for the investigated sensors.
- Temperature: 20 - 40 °C for the investigated sensors.
- Soaking time: 18 hours for PVC membrane sensor and 36 hours for carbon paste sensor.
- Response time: 40 seconds for PVC membrane sensor and 25 seconds for carbon paste sensor.

Application to Pharmaceutical Preparation

Three **Imodium®** tablets (2 mg/tablet) were weighted, evacuated and finely powdered. Appropriate weight of powder equivalent to 5.135 mg was accurately weighed, transferred to 100 ml volumetric flask and the volume was made up to 75 ml with Britton Robinson buffer pH 5. The solution was shaken vigorously for 15 min then sonicated for 30 min and then filtered. The volume was completed to 100 ml with the same solvent. The concentration of this solution is claimed to be (10^{-4} M). Necessary dilutions of the filtrate were made with Britton Robinson buffer pH 5 to obtain different concentrations of loperamide hydrochloride.

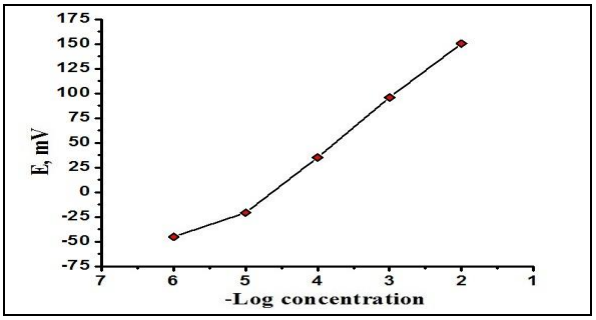


Figure 2. Profile of the potential in mV/- Log molar concentration of loperamide hydrochloride using PVC membrane sensor.

RESULTS AND DISCUSSION

The development and application of ion-selective electrodes is 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. [34]

In the present study, ion selective membrane electrodes of two types: PVC membrane and carbon paste electrodes have been constructed for selective determination of loperamide hydrochloride based on the fact that, loperamide behaves as a cation, due to the presence of (-N-) group. This property suggested the use of anionic type of ion exchanger such as ammonium reineckate as counter ions to prepare water insoluble association complex using precipitation based technique. The resulting precipitate has low solubility

Table 3. Effect of ion pair and modifier contents on the performance of loperamide hydrochloride carbon paste sensor

Ion-pair and modifier content		LOD (M)	Linearity rang (M)	Slope mV/decade	r^2
Ion-pair (mg)	Carbon nanotubes (mg)				
4	—	4.12×10^{-5}	5×10^{-5} - 10^{-2}	-46.25	0.9985
8	—	3.54×10^{-6}	10^{-5} - 10^{-2}	-51.19	0.9990
12	—	2.86×10^{-6}	10^{-5} - 10^{-2}	-53.34	0.9992
16	—	2.51×10^{-6}	10^{-5} - 10^{-2}	-55.93	0.9993
20	—	4.36×10^{-6}	10^{-5} - 10^{-2}	-50.66	0.9990
16	2	1.24×10^{-6}	10^{-5} - 10^{-2}	-55.94	0.9993
16	4	9.17×10^{-7}	10^{-6} - 10^{-2}	-56.21	0.9993
16	8	6.22×10^{-7}	10^{-6} - 10^{-2}	-57.45	0.9994
16	**10**	**5.13×10^{-7}**	**10^{-6} - 10^{-2}**	**-58.74**	**0.9995**
16	14	7.43×10^{-7}	5×10^{-6} - 10^{-2}	-57.58	0.9994

Bold values for the optimum proposed sensor

Table 4. Effect of soaking time on PVC membrane and carbon paste loperamide hydrochloride sensors at 20 ± 1 ^{O}C

Soaking time (h)	PVC membrane sensor slope (mV/decade)	Carbon paste sensor slope (mV/decade)
0	- 47.61	- 48.77
2	- 49.86	- 49.52
4	- 50.24	- 51.32
8	- 53.12	- 52.15
12	- 55.94	- 54.09
18	**- 57.38**	- 55.20
24	- 54.73	- 56.45
36	- 53.41	**- 58.74**
48	- 51.26	- 57.03

Bold values for the optimum proposed sensors

product, suitable grain size and physically compatible with the matrix. The low solubility product of loperamide-reineckate ion pair has a very important role in increasing the life span of the sensor by decreasing the leaching rate into the aqueous bathing solution. The reaction mechanism and the expected structure of the ion pair as shown in **Scheme 1.**

Electrochemical behaviour of loperamide hydrochloride with the investigated sensors

The electrochemical performance of the investigated sensors was evaluated according to IUPAC recommendation data [35, 36]. To obtain the electrochemical behavior, calibration was carried out by immersing the electrodes in conjunction with Ag/AgCl reference electrode in solutions of loperamide hydrochloride in the concentration range of 10^{-5} to 10^{-2} M for PVC sensor and 10^{-6} to 10^{-2} M for carbon paste sensor. They were allowed to equilibrate whilst stirring and recording the e.m.f. readings. The potential displayed by the proposed sensors for constructive measurements of standard drug solutions in the same day and from day to day did not vary by more than ± 1 mV. Calibration slopes did not change by more than ± 1 mV/decade concentration over a period of 30 and 40 days for PVC membrane and carbon paste sensors respectively. **Table 1** summarizes the performance, investigation, response characteristics and results obtained for the proposed sensors. The profile of the potential in mV versus –log molar concentration of loperamide hydrochloride by the investigated sensors was plotted as shown in **Figures 2, 3**.

Investigation and optimization of experimental conditions

Optimization of membrane composition for PVC membrane sensor

The sensitivity and selectivity of ion selective electrodes are known to be dependent not only on the nature of ionophores, but also significantly on the composition of the membrane ingredients. Therefore, it was of interest to study the effects of the membrane composition, ion exchange and type of plasticizer on the potential response of the proposed sensor.

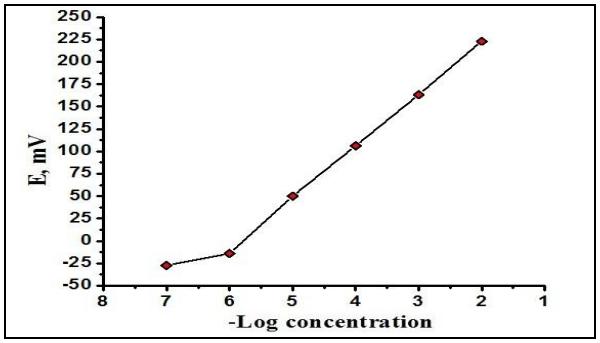


Figure 3. Profile of the potential in mV/- Log molar concentration of loperamide hydrochloride using carbon paste sensor

(i) Ion-exchanger percentage: The ion exchanger loperamide-reineckate was studied by varying the percentages of the ion exchanger, while keeping the percentages of the PVC and the plasticizer equal 1:1 as shown in **Table 2**. However, further addition of ion-pair displays somewhat smaller slopes and sensitivity.

(ii) Effect of plasticizer: The nature of the plasticizer influences key performance indicators of the ion selective electrodes such as slope, the domain of linear response and the selectivity. A plasticizer for the membrane preparation has to be compatible with the polymer, the ion exchanger, and has a high lipophilicity and low solubility in aqueous solution. In exploration for a suitable plasticizer, we used two plasticizers**,** dioctylphthalate and tributyl phosphate as shown in **Table 2**, the sensor plasticized with dioctylphthalate produced the best response. It is likely due to relatively high molecular weight, low dielectric constant and high lipophilicity that maybe avoid exudation and to considerably affect dissolution of ion-associations within the membrane. The best performances were obtained by using composition containing (6 LOP-RKT: 47 PVC : 47 DOP, by weight).

Optimization of the paste composition for carbon paste sensor

Due to the critical role of the matrix composition on the electrode performance, parallel studies were carried out on the two sensors matrices including influence of the ionophore and modifier to select the optimal sensor possessing the best sensitivity and selectivity.

(i) Ion-exchanger percentage: The ion exchanger loperamide-reineckate was used and tested by varying the amount of the ion exchanger (4, 8, 12, 16, and 20 mg) with fixed amounts of other paste components as shown in **Table 3**. The best performances were obtained by using composition containing 200 mg graphite powder and 16 mg loperamide-reineckate ion pair with 0.1 ml of paraffin oil. However, further addition of ion-pair displays some what smaller slopes and sensitivity, most probably due to some in homogeneities.

(ii) Effect of modifier: 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, 4, 8, 10 and 14 mg) were added to the paste matrix containing (200 mg pure graphite powder, 16 mg loperamide-reineckate ion pair and 0.1 ml of paraffin oil) and the results obtained were given in **Table 3**. The results showed that on using paste of optimum compositions (10 mg carbon nanotubes) exhibits the best performance. However, the consistence of pastes containing more than 10 mg 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.

Effect of soaking time

Freshly prepared sensor must be soaked to activate the surface of the membrane to form an infinitesimally thin gel layer at which ion exchange occurs. This preconditioning process requires different times depending on diffusion and equilibration at the electrode test solution interface; a fast establishment of equilibrium is certainly a condition for a fast potential response. For this purpose, the sensors were soaked in (10^{-2} M) loperamide hydrochloride. The slopes obtained from calibration curves were recorded after 0, 2, 4, 8, 12, 16 and 24 hours as shown in **Table 4**. The optimum soaking time was found to be 18 and 36 hours for PVC membrane and carbon paste sensors respectively. Soaking more than required hours is not recommended to avoid the leaching of the active ingredients (ion-exchanger and plasticizer) to the bathing solution [37].

Effect of temperature

The effect of temperature was studied by monitoring the potential response displayed by the sensor as a function of negative logarithmic value of the drug concentration at 20, 25, 30, 35 and 40 °C. It was found that the proposed sensor exhibited a gradual potential increase in the range of 20-40 °C; however, the calibration plots obtained at different temperatures were parallel. In spite of this, the limit of detection and response time did not significantly vary with variation of temperature; indicating thermal stability of the investigated sensors up to 40 °C as shown in **Figures 4, 5**.

Table 5. Selectivity coefficients for the PVC membrane and carbon paste loperamide hydrochloride sensors

Interferant	$K^{pot}_{Durg,J^{+z}}$ of PVC membrane sensor		$K^{pot}_{Durg,J^{+z}}$ of carbon paste sensor	
	SSM[a]	MPM[b]	SSM[a]	MPM[b]
Na^+	6.73×10^{-3}	——	3.16×10^{-3}	——
K^+	3.98×10^{-3}	——	2.51×10^{-3}	——
Ca^{++}	7.32×10^{-4}	——	6.12×10^{-4}	——
Mg^{++}	1.65×10^{-4}	——	4.03×10^{-4}	——
Ni^{++}	2.19×10^{-3}	——	5.60×10^{-3}	——
Glucose	——	5.32×10^{-4}	——	3.62×10^{-4}
Sucrose	——	3.96×10^{-4}	——	4.15×10^{-4}
Glycine	——	6.87×10^{-3}	——	5.37×10^{-3}
Urea	——	9.11×10^{-3}	——	8.96×10^{-4}

[a] *SSM: separate solution method*
[b] *MPM: matched potential method*

Table 6. Determination of loperamide hydrochloride in Imodium® tablet by PVC membrane, carbon paste loperamide hydrochloride sensors and reported methods

Parameters	PVC membrane sensor	Carbon paste sensor	Reported method[127]
Number of measurements	5	5	5
Mean % recovery of loperamide	99.48	100.16	99.79
% RSD	1.147	1.286	1.123
Variance	1.302	1.658	1.257
Student's *t*-test* (2.306)	0.442	0.485	——
F-value* (6.388)	1.036	1.319	——

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

Effect of pH

The effect of pH was investigated over a wide pH range to determine the working pH range of the proposed sensors. The investigations were performed in loperamide hydrochloride solutions (10^{-3} &10^{-4} M) prepared in Britton Robinson buffer pH (2-10)**.** Representative curves for effect of pH on the proposed sensors are shown in **Figures 6, 7.** The results revealed that, the change in pH does not affect the potential readings within the pH range of (3–6) for the proposed sensors**.** However, there is a slight deviation at pH values lower than 3 which may be due to H^+ interference. On the other hand, the potential decreases gradually at pH values higher than 6. The decrease may be attributed to the decrease in the concentration of protonated loperamide in the medium.

Sensors selectivity

The results of the calculated selectivity coefficients showed that the proposed sensors displayed high selectivity and no significant interference was observed from the interfering species as shown in **Table 5**. The high selectivity towards other interfering species can be attributed to the differences in polarity and to the lipophilic nature of their molecules relative to loperamide hydrochloride [38].

Response time of the proposed sensor

For analytical applications, the response time of a fabricated 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 loperamide hydrochloride solutions, each having a 10 fold difference in concentration, is investigated [36]. The dynamic response time for the proposed sensors were found to be 40 and 25 sec for PVC membrane and carbon paste sensors respectively as shown in **Figures 8, 9.**

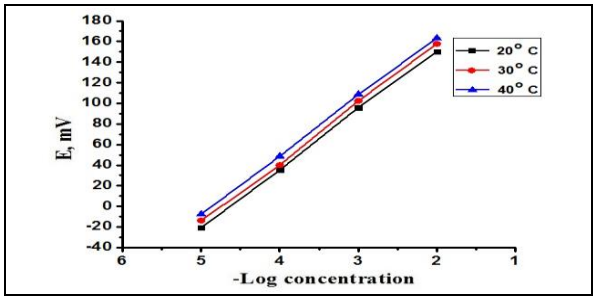


Figure 4. Effect of temperature on the response loperamide PVC membrane sensor.

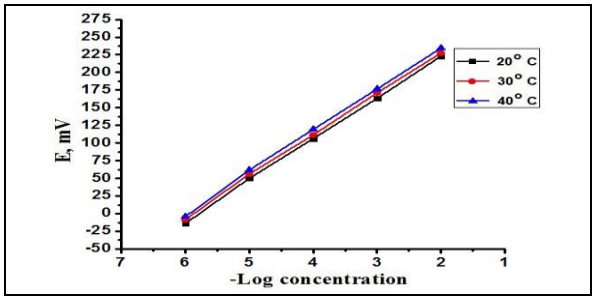


Figure 5. Effect of temperature on the response loperamide carbon paste sensor.

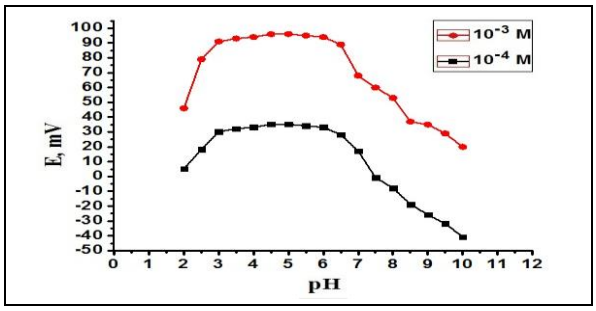


Figure 6. Effect of pH on the response of loperamide PVC membrane sensor.

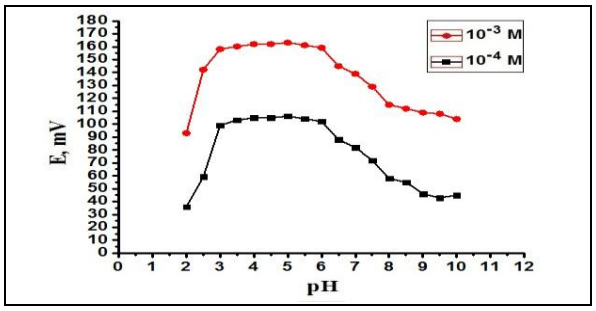


Figure 7. Effect of pH on the response of loperamide-carbon paste sensor.

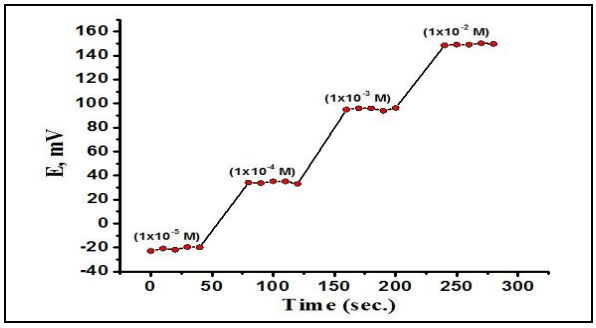


Figure 8. Response time of the loperamide-PVC membrane sensor.

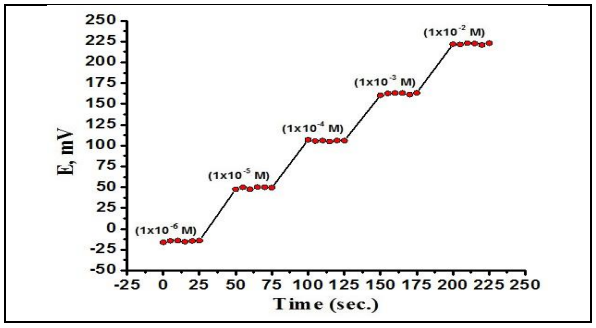


Figure 9. Response time of the of loperamide-carbon paste sensor.

METHOD VALIDATION

Linearity and range

Under the described experimental conditions, the calibration graph for each sensor was constructed by plotting the recorded electrode potential versus negative logarithmic value of the drug molar concentration. The regression plots were found to be linear over the range of 10^{-5}-10^{-2} M for PVC sensor and 10^{-6}-10^{-2} M for carbon paste sensor, as shown in **Figures 1, 2**. The regression data were presented in **Table 1**.

Limit of detection

Limit of detection measured by interception of the extrapolated arms of **Figures 1, 2** and the obtained results indicated the sensitivity of the proposed methods for the analysis of the studied drug as shown in **Table 1.**

Accuracy and precision

Accuracy of the proposed methods were indicated by the obtained good %R as shown in **Table 1.** While, the small values of %RSD indicated high precision of the methods as shown in **Table 1**.

Specificity

The results of the calculated selectivity coefficients indicated that the proposed sensors were highly selective towards the studied drug, **Table 5.**

Pharmaceutical applications

The proposed method was applied to the determination of loperamide hydrochloride in **Imodium®** tablet. 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[6]. No significant differences were found by applying student's *t*-test and *F*-test at 95% confidence level [39], indicating good accuracy and precision of the proposed method for the analysis of the studied drug in its pharmaceutical dosage form, as shown in **Table 6.**

CONCLUSION

In the present work, two types of potentiometric electrodes were constructed for determination of loperamide hydrochloride. The sensors demonstrated advanced performances with a fast response time, a lower detection limit of $3.47x10^{-6}$ M for PVC membrane electrodes and $5.13\ x10^{-7}$ M potential responses across the range of 10^{-5} - 10^{-2} M and 10^{-6} - 10^{-2} M. The best PVC membrane electrode performance was achieved by a membrane composition of 172 mg (PVC), 0.17 ml (DBP) and 6 mg (LOP-RKT). The best modified carbon electrode was composed of 16 mg (LOP-RKT), 10 mg MWCNTs, 0.1 ml paraffin and 200 mg graphite. Both sensors ware successfully applied to potentiometric determination of loperamide hydrochloride in its pure form and pharmaceutical formulations.

Conflict of interest

The authors declare that there is no conflict of interest regarding the publication of this paper.

REFERENCES

1. Sweetman, S.C. Martindale: The Complete Drug Reference, 36th Edn; Vol I. London, *The Pharmaceutical Press* **2009**.
2. United State Pharmacopoeia, 32th Edn; The United State Pharmacopeial Convention, Washington DC, *Board of Trustees* **2008**.
3. Elqudaby, H. M.; Mohamed, G. G.; and El Din, G. M. Utilization of phosphotungestic acid in the conductometric determination of loperamide hydrochloride and trimebutine antidiarrhea drugs. *J. Pharm. Res.* **2013**, *7* (8), 686-691.
4. Hewala, I. Spectrofluorimetric and derivative absorption spectrophotometric techniques for the determination of loperamide hydrochloride in pharmaceutical formulations. *J. Pharm. Biomed. Anal.* **1995**, *13* (6), 761-767.
5. Ravi, S.; Amandeep, K. Simultaneous estimation of loperamide hydrochloride and norfloxacin by validated UV-Spectrophotometric method. *World J. Pharm. Res.* **2014**, *3* (5), 693-703.
6. Rivai, H.; Puspita, R.; Misfadhila, S. Development and Validation of Loperamide Hydrochloride Tablet Analysis Method with Absorbance and Area under Curve Methods Spectrophotometrically. *JSFK* **2018**, *5* (2), 94-101.
7. El Sherif, Z. A.; Mohamed, A. O.; Walash, M. I.; Tarras, F. M. Spectrophotometric determination of loperamide hydrochloride by acid-dye and charge-transfer complexation methods in the presence of its degradation products. *J. Pharm. Biomed. Anal.* **2000**, *22* (1), 13-23.
8. Singh, L.; Nanda, S. Validated Spectrophotometric methods for estimation of Loperamide Hydrochloride from tablet dosage form. *Asian J. Pharm. Clin. Res.* **2010,** *3* (2), 121-122.
9. Kashyap, R.; Makavana, K. Development of new colorimetric method and validation for determination of loperamide in bulk and marketed formulation. *IJPCBS* **2013**, *3* (2), 215-226.
10. Elqudaby, H.M.; Mohamed, G.G.; El-Din, G. M. Analytical studies on the charge transfer complexes of loperamide hydrochloride and trimebutine drugs. Spectroscopic and thermal characterization of CT complexes. Spectrochimica Acta Part A: *Mol. Biomol. Spect.* **2014**, *129*, 84-95.
11. Zhang, H.; Nie, F.; Lu, J. Post-chemiluminescence method of the determination of loperamide hydrochloride in human plasma and pharmaceutical by using dichlorofluorescein as chemiluminescence reagent. *Anal. Lett.* **2007**, *40* (18), 3405-3416.
12. Radi, A.; Elmogy, T. Differential pulse voltammetric determination of loperamide in a pharmaceutical dosaqe form. *Sci. Pharm.* **2004**, *72* (3), 239-248.
13. Al-Qasmi, N.; Soomro, M. T.; Aslam, M.; Rehman, A. U.; Ali, S.; Danish, E. Y.; Hameed, A. The efficacy of the ZnO: α-Fe2O3 composites modified carbon paste electrode for the sensitive electrochemical detection of loperamide: A detailed investigation. *J. Electroanal. Chem.* **2016**, *783*, 112-124.
14. Ruddy, D. A.; Sherma, J. Determination of the active ingredient loperamide hydrochloride in pharmaceutical caplets by high performance thin layer chromatography with ultraviolet absorption densitometry of fluorescence quenched zones. *Acta Polon. Pharm.* **2002,** *59* (1), 15-18.
15. Leis, H. J.; Gleispach, H. Characterization of the antidiarrhoeal loperamide by gas chromatography-mass spectrometry and application of the Hofmann

degradation and Cope elimination reaction. *J. Chromatog. B* **1989**, *494*, 324–330.
16. Kabir, H.; Paul, R. K.; Rahaman, M. S.; Ahmad, M. F.; Bhattacharjya, D. K.; Rahaman, M. S. Method Validation for Assay of Loperamide Hydrochloride by HPLC in Loperamide Hydrochloride Tablets. *IJARCS* **2017,** *4* (4), 11-27.
17. Leung, C. P.; Au-Yeung, C. Y. High-performance liquid chromatographic determination of lopermide hydrochloride in pharmaceutical preparations. *J. Chromatog. A* **1988**, *449*,341-344.
18. He, H.; Sadeque, A.; Erve, J. C.; Wood, A. J.; Hachey, D. L. Quantitation of loperamide and N-demethyl-loperamide in human plasma using electrospray ionization with selected reaction ion monitoring liquid chromatography–mass spectro-metry. *J. Chromatog. B* **2000**, *744* (2), 323-331.
19. Ganssmann, B.; Klingmann, A.; Burhenne, J.; Tayrouz, Y.; Aderjan, R.; Mikus, G. Simultaneous determination of loperamide and its desmethylated metabolites in plasma and urine by high-performance liquid chromatographyAtmospheric-pressure lonization mass spectrometry. *Chromatographia* **2001**, *53* (11-12), 656-660.
20. Johansen, S.S.; Jensen, J. L. Liquid chromatography–tandem mass spectrometry determination of loperamide and its main metabolite desmethylloperamide in biological specimens and application to forensic cases. *J. Chromatog. B* **2004**. *811* (1), 31-36.
21. Yu, J. H.; Kim, H. J.; Lee, S.; Hwang, S. J.; Kim, W.; Moon, C. J. LC–MS determination and bioavailability study of loperamide hydrochloride after oral administration of loperamide capsule in human volunteers. *J. Pharm. Biomed. Anal.* **2004**, *36* (2), 421-427.
22. Streel, B.; Ceccato, A.; Klinkenberg, R.; Hubert,,Validation of a liquid chromatographic-tandem mass spectrometric method for the determination of loperamide in human plasma. *J. Chromatog. B* **2005**. *814* (2), 263-273.
23. Savić, I. M.; Nikolić, G. S.; Savić, I. M.; Marinković, V. D. Quantitative analysis of Loperamide hydrochloride in the presence its acid degradation products. *Hemijska Industrija* **2009**, *63* (1), 39-46.
24. Arafat, T.; Basil, A. Determination of loperamide in human plasma and saliva by liquid chromatography–tandem mass spectrometry. *J. Chromatog. B* **2014**, *972*,81-88.
25. Madhu, M. V. S.; Nagendra kumar, A. V. Validated RP - HPLC Method For The Determination of Loperamide Hydrochloride In Bulk and Pharmaceutical Formulation. *Asian J. Biomed. Pharm. Res.* **2014**, *4*, 102-111.
26. Sujatha, T.; Balmuralikrishna, K.; Raju, R. A validated RP-HPLC method for the estimation of loperamide hydrochloride in tablet dosage forms. *Int. J. Chem. Tech. Res.* **2014**, *6* (2), 1097-1102.
27. Kumar, K. P.; Satyanarayana, P.; Simultaneous estimation of tinidazole, ciprofloxacin and loperamide in bulk and pharmaceutical formulations by rp hplc method. *World J. Pharm. Pharm. Sci.* **2015**, *4* (10), 1513-1525.
28. Sonawane, A. M.; Dudhe,,B.; Chalke, N. H.; Bhagat, K. B. Development and validationrp-HPLC method for the simultaneous determinetion of loperamide hydrochloride and norfloxacin in pharmaceutical formulation. *Int. J. Pharm. Pharm. Sci Res.* **2016**, *7* (8), 34-41.
29. Suneetha, A.; Sharmila, N.; Purnima, M. Stability indicating RP-HPLC method for the determination &validation of loperamide hydrochloride & simethicone in pharmaceutical dosage form. *World J. Pharm. Pharm. Sci*. **2017**.
30. Frant, M. S. Historical Perspective. History of the Early Commercialization of Ion-Selec- tive Electrodes. *Analyst*, **1994**, *119* (11), 293-301.
31. García, M. S.; Ortuño, J.; Albero, M. I.; Cuartero, M. Application of a trazodone-selective electrode to pharmaceutical quality control and urine analyses. *Ana. Bioanal. Chem.* **2009**, *394* (6), 1563-1567.
32. Thévenot, D. R.; Toth, K.; Durst, R. A.; Wilson, G. S. Electrochemical biosensors: recommended definitions and classification. *Biosnse Bioelectron* **2001**, *16* (1), 121-131.
33. Britton, H. T. S.; Robinson. R. A. Universal buffer solutions and the dissociation constant of veronal. *J. Chem. Soc*. **1931**. 1456-1462.
34. Morf, W. E. The principles of ion-selective electrodes and of membrane transport, **2012**.
35. Buck, R. P.; Lindner, E. Recommendations for nomenclature of ion-selective electrodes. *Pure Appl. Chem.* **1994**, *66* (12), 2527-2536.
36. Buck, R. P.; Cosofret, V. V. Recommended procedures for calibration of ion-selective electrodes (Technical Report). *Pure Appl. Chem.* **1993**, *65*(8), 1849-1858.
37. Ali, T. A.; Mohamed, G. G.; Azzam, E. M. S.; Abd-elaal, A. A. Thiol surfactant assembled on gold nanoparticles ion exchanger for screen-printed electrode fabrication. Potentiometric determination of Ce (III) in environmental polluted samples. *Sens. Actuators B* **2014**, *191*, 192-203.
38. Bakker, E. Selectivity of liquid membrane ion selective electrodes. *Electroanalysis* **1997**, *9* (1), 7-12.
39. Armitage, P.; Berry, G. Statistical methods in medical research. 3rd Edn., Oxford (UK), Blackwell, **1994**.