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Research Article

Comparative Study of Different Electrochemical Sensors for Potentiometric Determination of Mepivacaine Hydrochloride in Bulk Powder and in Pharmaceutical Preparation

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Abstract

Objective: Development and validation of three electrochemical sensors for determination of mepivacaine hydrochloride (MC) in its bulk powder and in pharmaceutical preparation.

Methods: The three electrochemical sensors based on the use of mepivacaine- reineckate (MC-RT) 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 MC over a wide concentration range of 1×10^{-5}-1×10^{-2} M with detection limits of $7.2x10^{-6}$, $7.4x10^{-6}$ and $7.5x10^{-6}$ M for PVC, coated graphite and carbon paste sensors. The proposed sensors have a fast response time and can be used for 2-4 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 MC 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: Mepivacaine; Potentiometry; PVC; Coated graphite; Carbon paste

Introduction

Mepivacaine hydrochloride, (Figure 1), is (1-methyl-2-piperidyl) formo-2′, 6′-xylidide hydrochloride. Its molecular weight is 282.80 and its molecular formula is $C_{15}H_{23}ClN_2O$. It is white or almost white crystalline powder. It is freely soluble in water and alcohol [1]. It is official in United States Pharmacopoeia which recommend a titration for determination of MC in pure form using 0.1N perchloric acid as a titrant and crystal violet as indicator [2]. Different analytical methods have been reported for the determination of mepivacaine including very few spectroflurometric [3], electrochemical [4], chromatographic [5-15] and capillary electrophoretic methods [16,17] in both clinical and experimental medicine.

The present work establishes simple, accurate, rapid and reproducible sensors for determination of MC. These sensors incorporate the ion association complexes of MC cation with ammonium reineckate 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 MC in simple and complex matrices.

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), poly (vinyl chloride) (PVC) of high relative molecular weight, paraffin oil and graphite powder (synthetic 1–2 μm), (Sigma-Aldrich, Germany).
- Ammonium reineckate (Sigma-Aldrich, Germany), prepared as 10^{-2}M aqueous solution.
- Glucose, glycine, sucrose, urea, calcium chloride, magnesium chloride, sodium chloride, potassium chloride and nickel chloride (El-Nasr Company, Egypt), prepared as 10^{-3}M aqueous solution.

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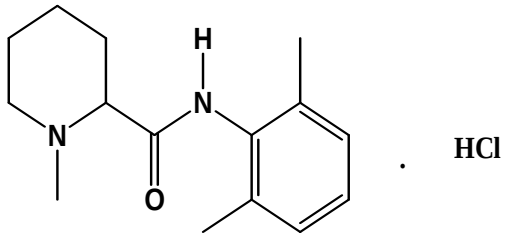

Figure 1: Structural formula of mepivacaine hydrochloride.

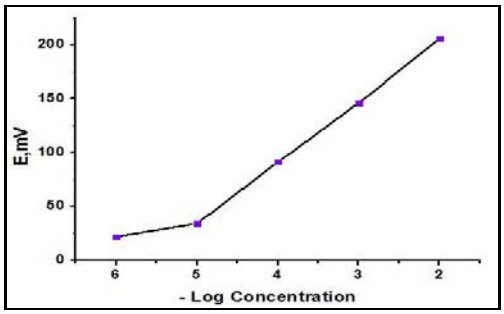

Figure 2: Profile of the potential in mV/- Log molar concentration of mepivacaine hydrochloride using PVC membrane sensor.

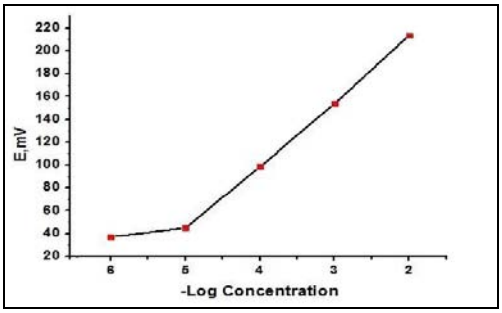

Figure 3: Profile of the potential in mV/- Log molar concentration of mepivacaine hydrochloride using coated graphite sensor.

- Orthophosphoric acid prepared as 0.04M aqueous solution (Prolabo, Paris, France).

- Boric and acetic acids were prepared as 0.04M aqueous solutions (Sigma-Aldrich, Germany).

- Sodium hydroxide prepared as 0.2M aqueous solution (El-Nasr Company, Egypt).

- Britton Robinson (BR) buffer was prepared by mixing the acid mixture containing 0.04M phosphoric acid, 0.04M acetic acid and 0.04M boric acid. Buffer solutions were adjusted with the appropriate amount of 0.2M sodium hydroxide to get the desired pH.

Pure and market samples

- Pure mepivacaine hydrochloride (99.45%) certified by the manufacturer was kindly supplied by Alexandria for Pharmaceuticals, Alexandria, Egypt.

- Mepecaine 3%® carpules: each 1ml is claimed to contain 30mg mepivacaine hydrochloride (B. NO: 5413064, manufactured by Alexandria for Pharmaceuticals, Alexandria, Egypt), purchased from local market.

Standard solution of mepivacaine hydrochloride

A stock standard solution of mepivacaine hydrochloride (10^{-2}M) was prepared by dissolving 0.283g of the drug powder in 50ml of distilled water and completed to 100ml with the same solvent. Other solutions (10^{-3} - 10^{-6} M) were prepared by serial dilution from the stock solution either in Britton Robinson (BR) buffer pH (2-10) for studying pH effect or in water for the calibration and other experimental conditions.

Procedures

Preparation of the ion association complex: The ion association complex, mepivacaine-reineckate (MC-RT) was prepared by mixing 50ml of 10^{-2}M of both mepivacaine hydrochloride and ammonium reineckate solutions. The resulting precipitate was left in contact with its mother liquor for 6h, then the precipitate was filtered and washed thoroughly with distilled water and left to dry at room temperature for 24hour.

Preparation of the membrane

- Preparation of mepivacaine hydrochloride PVC membrane sensor: In a glass petri dish (5-cm diameter), 185mg of DOP was thoroughly mixed with 185mg of PVC and 30mg of MC-RT. The mixture was dissolved in 5mL of tetrahydrofuran. The petri dish was 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 0.1mm was obtained. From the master membrane, 8mm 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 mepivacaine hydrochloride. The prepared sensor was preconditioned by soaking in 10^{-2}M drug solution for 2 hours.

- Preparation of mepivacaine hydrochloride coated graphite sensor: In a glass petri dish (5-cm diameter), 180 mg of DOP was thoroughly mixed with 180mg of PVC and 40mg of MC-RT. The mixture was dissolved in 5ml of tetrahydrofuran and homogenized thoroughly. The solvent was slowly evaporated at room temperature until oily concentrated mixture was obtained. One end of the commercial graphite bar (2.5cm length, 3mm diameter) was dipped in the electro active membrane mixture and the process was repeated several times until a layer of a proper thickness was formed covering the terminal end of graphite bar. The electrode was left standing at room temperature to dry. The other 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 and used for connection. The prepared sensor was preconditioned by soaking in 10^{-2}M drug solution for 6 hours.

- Preparation of mepivacaine hydrochloride carbon paste sensor: In a mortar, 0.2mL of paraffin oil was thoroughly mixed with 240mg of pure graphite powder and 40mg of MC-RT. Then the carbon paste was carefully packed in a piston driven teflon holder 3mm in diameter. The prepared sensor was preconditioned by soaking in 10^{-2}M drug solution for 4 hours before measurements and

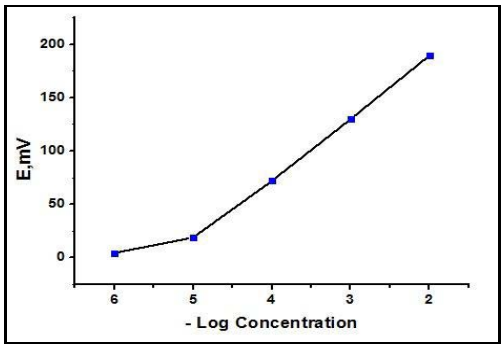

Figure 4: Profile of the potential in mV/- Log molar concentration of mepivacaine hydrochloride using carbon paste sensor.

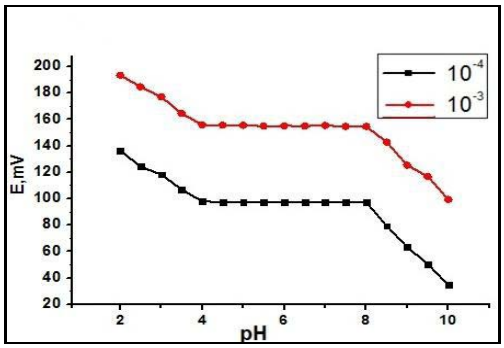

Figure 6: Effect of pH on the response of mepivacaine hydrochloride using coated graphite sensor.

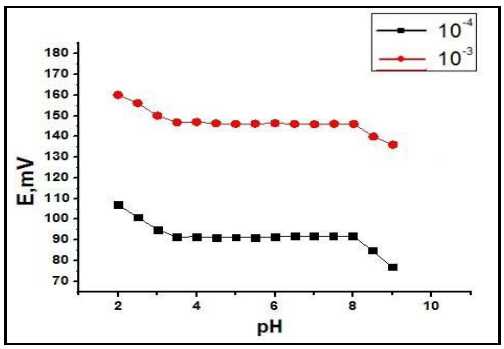

Figure 5: Effect of pH on the response of mepivacaine hydrochloride using PVC membrane sensor.

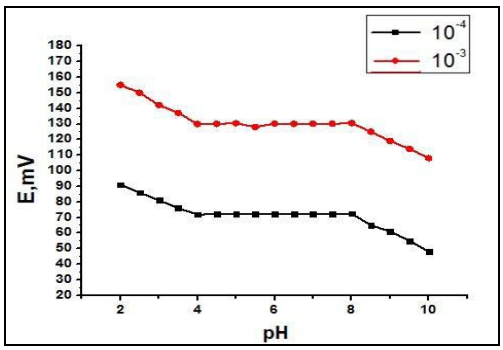

Figure 7: Effect of pH on the response of mepivacaine hydrochloride using carbon paste sensor.

electrode surface regeneration was performed by screwing the piston and polishing with a wet smooth paper.

Potential measurement conditions

- The electrochemical system can be represented as following:

1. Internal reference electrode/internal filling solution/ PVC membrane/test solution/external reference electrode, for PVC membrane sensor.

2. Reference electrode/test solution/graphite electrode, for coated graphite sensor.

3. Reference electrode/test solution/carbon paste electrode, for carbon paste sensor.

- pH range: 3.5-8 for PVC membrane sensor and 4 – 8 for both coated graphite and carbon paste sensors.

- Soaking time: 2, 6 and 4 hours for PVC membrane, coated graphite, carbon paste sensors.

- Response time: 25s for PVC membrane sensor and 30s for both coated graphite and carbon paste sensors.

Sensors calibration: The prepared PVC, coated graphite and carbon paste sensors, were immersed in conjunction with Ag/AgCl reference electrode in the solutions of mepivacaine hydrochloride in the range of 10^{-6} to 10^{-2} M. They were allowed to equilibrate while stirring until achieving constant reading of the pH meter. Then, the electromotive force values were recorded within ±1mV. Calibration graphs were plotted that related the recorded electrode potential values versus the negative logarithmic value of the drug concentration.

Validation of the methods

The methods were tested for linearity, range, limit of detection, acuracy, precision and specificity [18-20].

Application to pharmaceutical preparation

Contents of 20 Mepecaine 3%® carpules were mixed well. A volume equivalent to 0.283 of mepivacaine hydrochloride was dissolved in 50mL distilled water and completed to 100mL with the same solvent to produce a stock solution labeled to contain (10^{-2})M of mepivacaine hydrochloride. Necessary dilutions of the stock solution were made. Apply the described general procedures using aliquots covering the working concentration range. Determine MC content of the carpules from the corresponding regression equation.

Reported method

Ion selective coated wire sensor, based on ion-pair complex of mepivacaine hydrochloride with tetra phenyl borate [4].

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, coated graphite and carbon paste electrodes have been constructed for the selective determination

Table 1: The performance characteristics of the proposed sensors.

Parameter		PVC	Coated graphite	Carbon paste
- Regression equation		$y^{*}= b\ x^{**}+ a$	$y^{*}= b\ x^{**}+ a$	$y^{*}= b\ x^{**}+ a$
- Slope (b)		-57.36	-56.17	-56.93
- Intercept (a)		318.95	304.37	301.93
Coefficient of determination (r^2)		0.9997	0.9996	0.9996
Linearity range (M)		10^{-5}- 10^{-2}	10^{-5}- 10^{-2}	10^{-5}- 10^{-2}
Working pH range		3.5-8	4–8	4–8
Response time (s)		25	30	30
LOD (M)		7.2 x10^{-6}	7.4x10^{-6}	7.5x10^{-6}
Stability (weeks)		4	2	3
Accuracy (%R)***		99.15	100.23	99.07
Repeatability	Precision (%RSD)***	1.124	0.856	0.729
Intermediate precision		1.544	1.008	1.336

y^{*} is the electrode potential in mV.
x^{**} is the negative logarithmic value of the drug concentration in mole per liter.
*** Values for 3 determinations of 3 different concentrations.

of MC in bulk powder and in its carpules. The methods were based on the fact that, MC 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 ammonium reineckate as a counter ion to prepare water insoluble association complex using precipitation based technique.

Electrochemical behavior of MC with the investigated sensors

The electrochemical performance of the suggested sensors was evaluated according to IUPAC recommendation data. Calibrations were achieved by immersing the sensors in conjunction with Ag/AgCl reference electrode in solutions of MC 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 MC by the proposed sensors were plotted as shown in Figures 2-4.

Optimization of the sensors composition

Effect of ion association complex percentage:

- **PVC membrane sensor**

The main components of PVC membrane sensor are ion association complex, PVC and plasticizer (DOP). For the preparation of the membrane, the ion association complex, plasticizer and PVC should be taken in the appropriate percentage-weight ratios to improve the performance of the developed sensor. MC-RT was prepared and tested as a modifier for the proposed sensor. It was studied by varying the percentages of the ion association complex, while keeping the percentages of the PVC and the plasticizer equal 1:1 as shown in Table 2. The best performances were obtained by using composition containing 185mg PVC and 30 mg MC-RT ion pair with 185mg of DOP.

- **Coated graphite sensor**

The ion association complex, MC-RT, was prepared and tested as a modifier for the proposed sensor. It was studied by varying the percentages of the ion association complex, while keeping the percentages of the PVC and the plasticizer equal 1:1 as shown in Table 2. The best performances were obtained by using composition containing 180mg PVC and 40mg MC-RT ion pair with 180mg of DOP.

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

	Composition % (w/w)			Linearity rang	Slope (mV/ decade)	r^2
PVC membrane sensor	MC-RT	PVC	DOP	(M)		
	4	48	48	1x10^{-5}-1x10^{-2}	-55.21	0.9994
	7	**46.5**	**46.5**	**1x10^{-5}-1x10^{-2}**	**-57.36**	**0.9997**
	10	45	45	1x10^{-5}-1x10^{-2}	-56.09	0.9995
	12	44	44	1x10^{-5}-1x10^{-2}	-52.75	0.9993
	Composition % (w/w)			Linearity rang	Slope (mV/ decade)	r^2
Coated graphite sensor	MC-RT	PVC	DOP	(M)		
	4	48	48	1x10^{-5}-1x10^{-2}	-51.0.3	0.9992
	7	46.5	46.5	1x10^{-5}-1x10^{-2}	-55.05	0.9995
	10	**45**	**45**	**1x10^{-5}-1x10^{-2}**	**-56.17**	**0.9996**
	12	44	44	1x10^{-5}-1x10^{-2}	-52	0.9994
	Composition % (w/w)			Linearity rang	Slope (mV/ decade)	r^2
Carbon paste sensor	MC-RT	PVC	DOP	(M)		
	4	70	26	1x10^{-5}-1x10^{-2}	-52.0.3	0.9993
	7	65	28	1x10^{-5}-1x10^{-2}	-54.85	0.9996
	10	**60**	**30**	**1x10^{-5}-1x10^{-2}**	**-56.93**	**0.9996**
	12	55	33	1x10^{-5}-1x10^{-2}	-54.27	0.9995

- **Carbon paste sensor**

The ion association complex**,** MC-RT was used and tested by varying the amount of the ion exchanger and other paste components as shown in Table 2. The best performances were obtained by using composition containing 240mg graphite powder and 40mg MC-RT ion pair with 120mg of DOP.

Effect of soaking time: Freshly prepared sensors must be soaked to activate the surface of the membrane to form an infinitesimally thin gel layer at which ion exchange occurs. The investigated sensors were soaked in 10^{-2}M solution of mepivacaine hydrochloride. Calibration graphs were constructed for the sensor after different time intervals (0, 2, 4, 6, 8 and 12 hour) till the slope of the calibration graph deviated largely from the Nernstian value and the sensor become out of use. The results indicated that the optimum soaking time was 2, 6 and 4 hours for PVC membrane, coated graphite and carbon paste sensors, respectively as shown in Table 3.

Effect of pH: The effect of pH was investigated over a wide pH range (2 – 10) to determine the working pH range of the proposed sensors. The investigations were performed using 10^{-3} and 10^{-4} M of mepivacaine hydrochloride prepared in Britton Robinson buffer**.** The potential obtained at each pH value was recorded. Representative curves for the effect of pH on the proposed sensors are shown in Figures 5-7. For PVC membrane sensor the potential remained constant in the pH range of (3.5-8) while in the case of coated graphite

Table 3: Effect of soaking time on the described sensors.

Soaking time/h	Slope (mV/decade)		
	PVC	Coated graphite	Carbon paste
0	-47.39	-42.19	-46.44
2	**-57.36**	-49.08	-53.12
4	-57.05	-52.28	**-56.93**
6	-55.24	**-56.17**	-55.15
8	-54	-55.78	-53.1
10	-53.18	-54.37	-52.19
12	-52.42	-53.62	-51.38

Table 4: Selectivity coefficients of the described sensors.

Interferant*	log K		
	PVC membrane	Coated graphite	Carbon paste
KCl	-3.41	-2.75	-3.64
$CaCl_2$	-3.11	-3.41	-3.68
$MgCl_2$	-2.52	-3.15	-2.52
NaCl	-3.01	-2.82	-2.82
$NiCl_2.6H_2O$	-3.72	-3.65	-3.51
Glucose	-3.65	-3.58	-3.76
Urea	-2.98	-2.25	-2.52
Glycine	-3.49	-3.74	-3.12
Sucrose	-3.52	-3.25	-3.16

*all interferant are in the concentration of 1×10^{-3} molL^{-1}

and carbon paste sensors the potential remained unchanged in the pH range (4-8).

Sensors selectivity: The influence of the related interfering compounds on the response of the investigated sensors towards the drug was studied. The separate solution method (SSM) was applied when determining the selectivity coefficient for inorganic cations based on measuring the potential of 10^{-3}M solution of the drug and the interfering ions separately. Then the selectivity coefficients log $K^{pot}_{Durg,J^{+z}}$ were calculated by applying the following equation [21]:

$$\log K^{pot}_{Durg,J^{+z}} = \frac{E_2 - E_1}{S} + \log [drug] - \log [J^{+z}]^{\frac{1}{z}}$$

where E_1 and E_2 are the electrode potential of 10^{-3}M solution of each of investigated drug and interferent ion [J^{+Z}], respectively, and S is the slope of calibration curve. For neutral molecules, such as glucose, urea and sucrose the selectivity coefficient was calculated using the matched potential method [MPM] [22,23]. This method does not depend on the Nicolsky-Eisenman equation at all, in this method; the selectivity coefficient is defined as the activity ratio of primary and interfering ions that give the same potential change under identical conditions. At first, a known activity (aA') of the primary ion solution is added into a reference solution that contains a fixed activity (aA) of primary ions and the corresponding potential change (ΔE) is recorded. Next, a solution of an interfering ion is added to the reference solution until the same potential change (ΔE) is recorded, where (aB) is the activity of the interfering ion that produced the same potential change (ΔE). The change in potential produced at the constant background of the primary ion must be the same in both cases. K^{POT} = *(aA'-aA)/Ab,* then potentiometric selectivity coefficients were calculated. The interfering compounds were; potassium chloride, calcium chloride, magnesium chloride, sodium chloride, nickel chloride, glucose, urea, glycine and sucrose.

The results of the calculated selectivity coefficients indicated that the proposed sensors were highly selective towards the studied drug as shown in Table 3.

Response time of the proposed sensors: For analytical applications, the response time of the prepared sensors is of critical importance. The average time required for the electrode to reach a steady potential response within ±1mV of the final equilibrium value after successive immersion of a series of the drug solutions, each having a 10-fold difference in concentration, was investigated. Stable responses were achieved within 25s for PVC membrane sensor and 30s for both coated graphite and carbon paste sensors.

Method validation

Linearity and range: Under the described experimental conditions, the calibration graph for each sensor was constructed by plotting the recorded sensor potential versus negative logarithmic value of the drug concentration.

The regression plots were found to be linear over the range of 10^{-5}-10^{-2} M for the studied drug, as shown in Figures 2-4.

Limit of detection: Limit of detection was measured by interception of the extrapolated arms of Figures 2-4. It was found to be 7.2×10^{-6} for PVC membrane sensor, 7.4×10^{-6} for coated graphite sensor and 7.5×10^{-6} M for carbon paste sensor. The small values of LOD indicate good sensitivity of the described sensors.

Accuracy and precision: Accuracy of the described methods, calculated as the mean percent recovery (%R), was assessed by applying the described procedure for triplicate determination of three concentration levels covering the linearity range of each drug (10^{-5}, 10^{-3} and 10^{-2} M). The results in Table 1 indicated the accuracy of the proposed method.

Precision of the methods, calculated as the percent of relative standard deviation (%RSD), was assessed by triplicate determination of three concentration levels covering the linearity range of each drug (10^{-5}, 10^{-3} and 10^{-2} M) within one day for repeatability and on three successive days for inter mediate precision. The small values of %RSD indicated high precision of the method as shown in Table 4.

Pharmaceutical application

The described electrochemical methods were applied for the determination of mepivacaine hydrochloride in Mepecaine 3%® carpules. 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 [4]. No significant differences were found by applying *t*-test and *F*-test at 95% confidence level [24], 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 5.

Conclusion

The proposed methods were precise, specific and accurate. MC could be determined in bulk powder and in pharmaceutical

Table 5: Determination of mepivacaine hydrochloride in Mepecaine 3%® carpules by the described sensors and reported method.

Parameters	PVC membrane	Coated graphite	Carbon paste	Reported method [4]
n*	5	5	5	5
Average (%Recovery)	100.19	100.06	99.49	99.89
%RSD	0.913	1.269	1.293	1.115
Variance	0.837	1.612	1.655	1.24
Student-t-test (2.306)**	0.468	0.222	0.523	——
F-value (6.388)**	1.481	1.299	1.335	——

**Number of measurements*

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

preparation without interference from common excipients using the proposed sensors. PVC and carbon paste sensors had shorter soaking time than the 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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