

## Preparation, Comparison and Characterization of Dual Drug (Promethazine & Oxymetazoline) Selective Electrode

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### Abstract

A dual drug ion selective electrode has been constructed for the first time, based on promethazine hydrochloride (PMH) and Oxymetazoline hydrochloride (OMH) using phosphotungstic acid as ionophore and di-butyl phosphate (DBPH) as a plasticizer. The major objective is to find a new polyvinyl chloride (PVC) matrix combination that allows two ions or drugs to be tested within the same membrane and accounted as a modification for Moody and Thomas theory. Many combinations have been tested but the most successful one was in electrode no. 2 with 1% of each active material. The resulting membrane gives a linear range ( $1 \times 10^{-4}$ – $1 \times 10^{-1}$ ) M with respect to (PMH) and ( $5 \times 10^{-4}$ – $1 \times 10^{-2}$ ) M with respect to (OMH). The slope for the linear range obtained was 57.68 and 56.64 mV/decade with a correlation coefficient 0.9995 and 0.9999 while the detection limit was  $1 \times 10^{-4}$  and  $3 \times 10^{-4}$  M for the (PMH) and (OMH), respectively. The obtained results were very reliable compared with the original results obtained for single drug ion selective electrode. The pH effect was studied using different concentrations of the two active materials, and the interferences were also studied using separated solution method in the presence of ( $\text{Li}^+$ ,  $\text{Na}^+$ ,  $\text{K}^+$ ,  $\text{Ca}^{+2}$ ,  $\text{Mg}^{+2}$ ,  $\text{Zn}^{+2}$ ,  $\text{Fe}^{+3}$ ,  $\text{Al}^{+3}$ , and  $\text{Cr}^{+3}$ ) as interfering ions, given a remarkable results. The constructed electrode has been also successfully applied in the determination of sample using direct method, standard addition (SA) method, multi standard addition (MSA) method and precipitation titration (PT) method.

Keywords: Ion selective electrode, electrode comparison, electrode selectivity, precipitation titration.

### Introduction

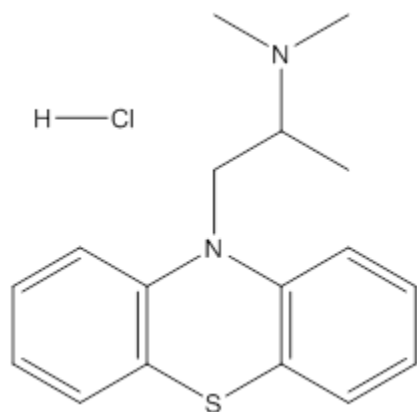
Ion-selective electrodes are mainly membrane-based devices, consisting of perm-selective ion-conducting materials, which separate the sample from the inside of the electrode. In the inside is a filling solution containing the ion of interest at a constant activity, the membrane is usually nonporous, water insoluble, and mechanically stable. The composition of the membrane is designed to yield a potential that is primarily due to the ion of interest (via-selective binding processes, e.g., ion exchange, which occur at the membrane–solution interface). The trick is to find a membrane that will selectively bind the analyte ions, leaving co-ions behind. Membrane materials, possessing different ion recognition properties, have thus been developed to impart high selectivity<sup>[1]</sup>.

The ion-discriminating ability depends not only on the nature of the recognition element but also on the exact membrane composition, including the membrane solvent and the nature and content of the plasticizer. The extraction properties of the membrane can be further

improved by adding ion-pairing agents to the plasticizer. The PVC matrix provides mechanical strength and permits diffusion of analytes to the recognition sites<sup>[1]</sup>.

According to Moody and Thomas<sup>[2]</sup>, typical polymeric membranes are based on (PVC), it approximately 66% of plasticizer and 33% of PVC and 1% active material. An appropriate plasticizer is added to membrane in order to ensure the mobility of the free and complex ionophore.

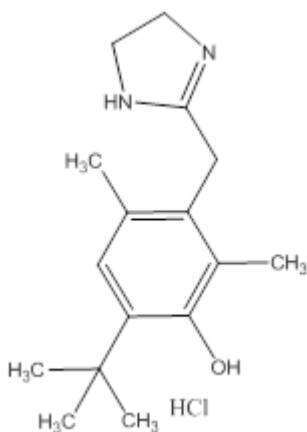
Promethazine hydrochloride (PMH) is an antihistamine used for the symptomatic relief of hypersensitivity reactions for the control of nausea, vomiting, the vertigo of various causes, as a sedative and hypnotic and common ingredient of cough and cold preparations<sup>[3]</sup>. (PMH)<sup>[4]</sup> is [N, N-dimethyl-1-(10H-phenothiazin-10-yl)propan-2-amine hydrochloride] with a chemical formula:  $\text{C}_{17}\text{H}_{21}\text{ClN}_2\text{S}$  and a molecular weight:  $320.88 \text{ g mol}^{-1}$ .



***Promethazine hydrochloride.***

Oxymetazolinehydrochloride [3] (OMH) is a decongestant. It works by constricting (shrinking) blood vessels (veins and arteries) in your body. The nasal formulation acts directly on the blood vessels in your nasal tissues. Constriction of the blood vessels in your nose and sinuses leads to drainage of these areas and a decrease in congestion.

Oxymetazolinenasal is used to treat congestion associated with allergies, hay fever, sinus irritation, and the common cold.



***Oxymetazoline hydrochloride.***

OMH) [4] is [6-tert-butyl-3-((4,5-dihydro-1H-imidazol-2-yl)methyl)-2,4-dimethylphenol hydrochloride] with a chemical formula:  $C_{16}H_{25}ClN_2O$  and a molecular weight: 296.84, g mol<sup>-1</sup>.

Many methods have been attempted in determination of PMH, like spectrophotometric method for PMH bulk powders and its dosage forms [5-7]. Other method is Silica gel thin layer chromatography plates [8.]

While the methods applied in determination of (OMH) is by using HPLC with UV detector [9], reversed-phase [10] and also using a strong cationic exchange [11]. Also flow injection technique [12] was used in determination of (OMH).

In this paper we anticipate constructing ion selective electrode that can detect two compounds (drugs) using two active materials instead of one, trying different percent of active materials, and study the prosperities of the new constructed electrode .

## Experimental

### Equipment

1. Expandable ion analyzer, Microprocessor based Bench pH/ mV/ C° Meter, HANNA Instruments, PH211, Made in Romania.
2. Calomel reference electrode type Gallen Kamp (USA).
3. Combined glass electrode type HANNA Instruments, HI131.
4. The (PMH-OMH) electrode used was handiwork constructed as follows: The Ag-AgCl wire was immersed in internal filling solution of 0.1 M PMH and 0.1 M OMH solution, respectively and used as the reference electrode. One side of a piece of PVC tube (1-2 cm long) was flattened and smoothed by placing it on a glass plate moistened with THF. A disk of the membrane was cut equal to the external diameter of the PVC tubing and mounted on the polished end. The other side of the PVC tubing was then connected to the electrode body. The assembled electrodes were conditioned by soaking in 0.1 M of the calculated ion solution for at least 3 h before the use of the electrodes.

### Chemicals

1. Promethazine hydrochloride and Oxymetazolinehydrochloride standards were a gift from the state company of drug industries and medical appliances (IRAQ-SDI-Samarra).
2. Plasticizer, di-butyl phosphate (DBPH) was obtained from Fluka AG. Other chemicals and reagents of analytical grade quality were obtained from Fluka, BDH and Aldrich.
3. Stock solutions of 0.1 M for each of LiCl, NaCl, KCl, CaCl<sub>2</sub>, MgCl<sub>2</sub>, ZnCl<sub>2</sub>, FeCl<sub>3</sub>,

$AlCl_3$ , and  $CrCl_3$  were prepared. More diluted solutions were prepared by subsequent dilution of the stock solutions.

### Preparation of ion-pair compound

Two ion pair compound were prepared, 1st one was PMH-PT prepared by mixing 50mL of 0.01M PMH with 50mL of 0.01M phosphotungsticacid while stirring .

The 2nd ion-pair OMH-PT was prepared by mixing 0.01M acidified aqueous solution of PMH with 0.01M phosphotungsticacid, with stirring. The resultant precipitate was filtered, washed with water, and dried at 60 °C.

### Casting the membrane

The method of immobilizing the matrix in to the PVC matrix membrane as described by Moody et al.[2] was modified by mixing two active materials in the membrane trying many combinations, but the most successful two combinations were 0.5% in electrode no.1 and 1% in electrode no. 2.

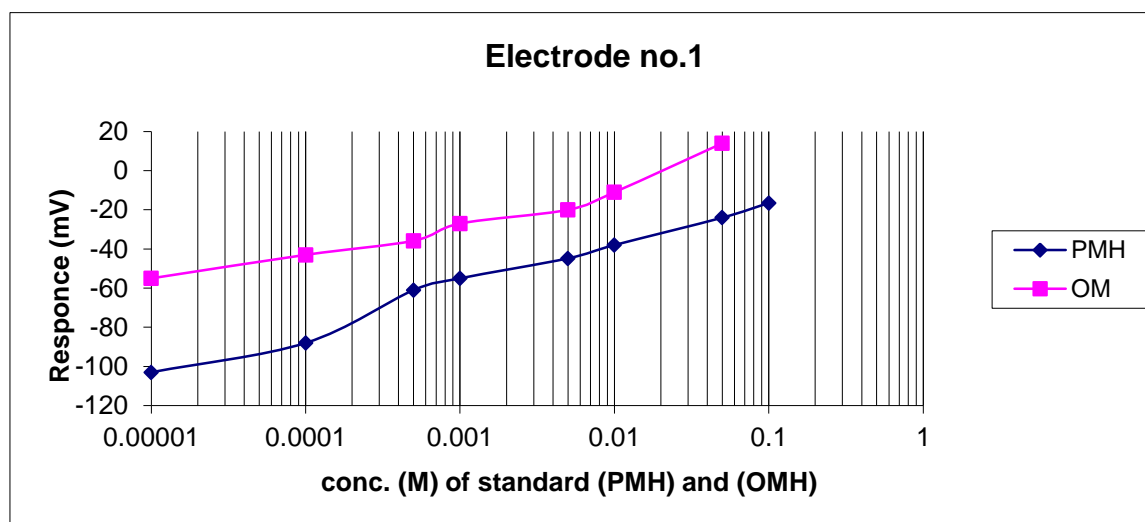
- Electrode no.1: was made by mixing 0.02g of OMH-PT, 0.02g PMH-PT matrixes and mixed with 0.36g of plasticizer (DBPH) and 0.17g of PVC powder after that 6 or 7mL of THF was added with stirring until the formation of viscous solution .
- Electrode no.2: was made by mixing 0.04g of OMH-PT, 0.04g PMH-PT matrixes and mixed with 0.36g of plasticizer (DBPH) and 0.17g of PVC powder after that 6 or 7mL of THF was added with stirring until the formation of viscous solution .

The above solutions poured into glass casting ring about 30 mm length and 35 mm in diameter. The assembly was left for 2 to 3 days to allow graduate evaporation of the solvent.

### Results and Discussion

Calibration curves (for the two electrodes) were prepared by plotting the potential versus the concentration of (PMH& OMH).

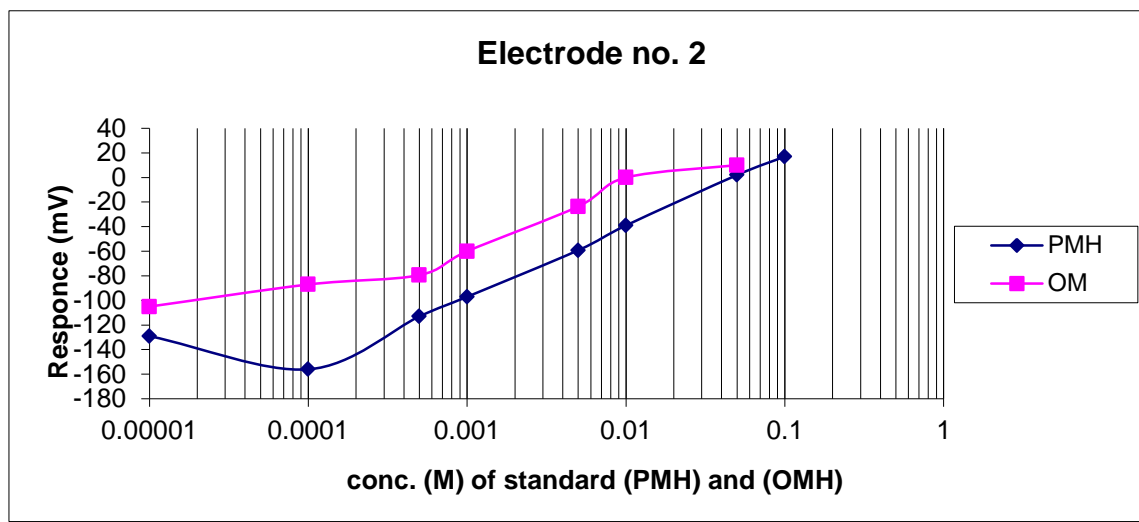
### Calibration Curve of Electrode no.1:



*Fig. (1) Calibration curve for electrode no. 1 using promethazinehydrochloride(PMH) and oxymetazolinehydrochloride (OMH) standards.*

The electrode no.1 shows un-reliable and non-Nuristian curve as shown in the Table (1)

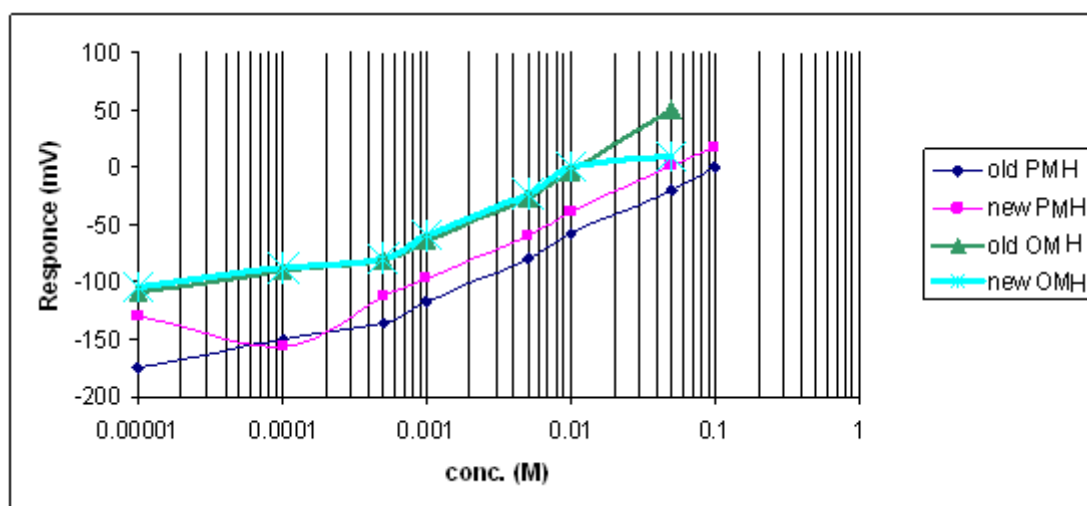
### Calibration Curve of Electrode no.2:



**Fig. (2) Calibration curve for electrode no. 2 using promethazine hydrochloride (PMH) and oxymetazolinehydrochloride(OMH) standards.**

The electrode no.2 shows a relatively good and reliable Nernstian slope as shown in the Table (1). The curve that obtained from electrode no.2 which is di-ionic was compared

with original results obtained by Nassory et.al. [13, 14] for single ion selective electrode as shown in Fig.(3).



**Fig. (3) Calibration curve comparison between the old (single ion) electrode prepared by Nassory et.al.<sup>[13, 14]</sup> and the new (di-ion) electrode.**

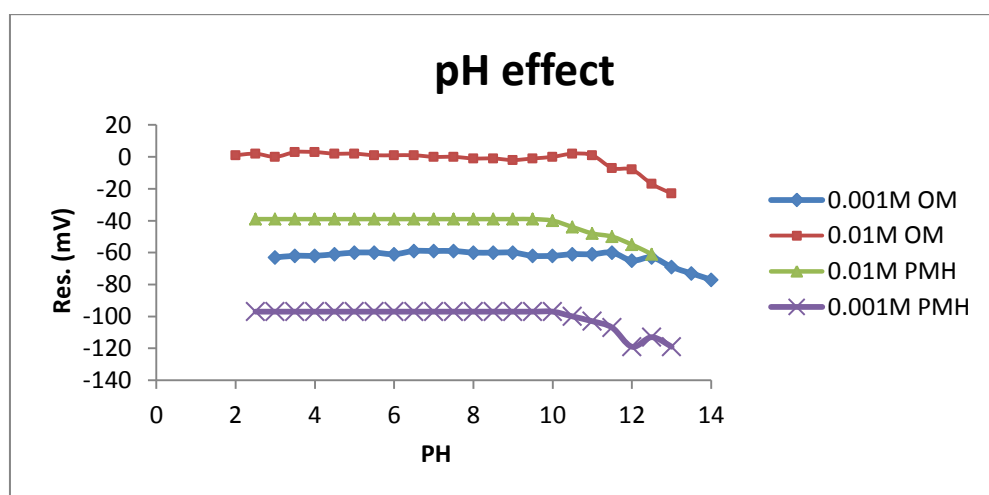
**Table (1)**  
**Comparison of electrode no. 1, electrode no.2 and the old single ion electrodes.**

Electrode	Standard used	slope	correlation coefficient	Linearity range (M)	Detection limit (M)	Life time (day)
Electrode no.1	PMH	21.84	0.9850	$5 \times 10^{-3}$ - $5 \times 10^{-1}$	$5 \times 10^{-3}$	{ ~53
	OM	17.44	0.9320	$5 \times 10^{-3}$ - $5 \times 10^{-2}$	$5 \times 10^{-3}$	
Electrode no.2	PMH	57.68	0.9995	$1 \times 10^{-4}$ - $1 \times 10^{-1}$	$1 \times 10^{-4}$	{ ~37
	OM	56.64	0.9999	$5 \times 10^{-4}$ - $1 \times 10^{-2}$	$3 \times 10^{-4}$	
Old PMH electrode <sup>[13]</sup>	PMH	56.17	0.9993	$5 \times 10^{-4}$ - $1 \times 10^{-1}$	$2 \times 10^{-4}$	~72
Old OMH electrode <sup>[14]</sup>	OM	57.60	0.9995	$5 \times 10^{-4}$ - $1 \times 10^{-1}$	$3 \times 10^{-4}$	~49

The comparison between the electrodes shows a very close data obtained especially in slope, detection limit and linearity range but with a smaller life time with electrode no.2 which may be caused to the increase in the amount of ion-pair compound that immobilized into the membrane make it easier to leak out, and decrease the life time of electrode.

#### Effect of pH

The pH effect on electrode no.2 has been studied using different concentrations of OMH & PMH, the pH was adjusted with dilute solutions of sodium hydroxide and hydrochloric acid using pH meter as shown in Fig.(4).



**Fig. (4) pH effect study for OMH ( $1 \times 10^{-3}$ ,  $1 \times 10^{-2}$ ) M and PMH ( $1 \times 10^{-3}$ ,  $1 \times 10^{-2}$ ) M.**

The obtained results has been compared with original results for single selective electrode as described in Table (2), the

comparison shows better range than the old single electrodes.

**Table (2)**  
**Working pH range comparison of electrode no.2 and the old single ion electrodes.**

Electrode	Working pH range	
	0.01 M	0.001 M
New electrode no.2	PMH	2.5-10.5
	OMH	2-11
Old PMH electrode <sup>[13]</sup>		3.9-6.8
Old OM electrode <sup>[14]</sup>		3-9.9

### Selectivity measurements

One of the most important factors that represent the good electrodes is the selectivity for the ion of interest. In this work separated solution method<sup>[15]</sup> was used to calculate the selectivity. The method description is to estimate potential using a standard ion (PMH and OMH) with conc. of  $1 \times 10^{-3} \text{M}$ , also estimate potential using standard 0.1M interfere ion ( $\text{Li}^{+1}$ ,  $\text{Na}^{+1}$ ,  $\text{K}^{+1}$ ,  $\text{Ca}^{+2}$ ,  $\text{Mg}^{+2}$ ,  $\text{Zn}^{+2}$ ,  $\text{Fe}^{+3}$ ,  $\text{Al}^{+3}$ , and  $\text{Cr}^{+3}$ ), then the selectivity

potential can be measured using the following equation

$$\log K_{\text{pot}} = \frac{(E_B - E_A)}{(2.303RT/zF)} + (1 - \frac{z_A}{z_B}) \log a_A$$

$E_A$ ,  $E_B$ ;  $z_A, z_B$ ; and  $a_A$ ,  $a_B$  are the potentials, charge numbers, and activities for the primary A and interfering B ions, respectively, at  $a_A = a_B$ . The results obtained shown in Table (3).

**Table (3)**  
*Selectivity comparison of electrode no.2 and the old single ion electrodes.*

Interfering ion	<i>K<sub>pot.</sub> using <math>1 \times 10^{-3} \text{M}</math> standard</i>			
	<i>Electrode no.2 PMH</i>	<i>Electrode no.2 OMH</i>	<i>Old single PMH<sup>[5]</sup></i>	<i>Old single OMH<sup>[6]</sup></i>
$\text{Li}^{+1}$	$1.469 \times 10^{-2}$	$2.103 \times 10^{-2}$	$2.5 \times 10^{-2}$	0.061
$\text{Na}^{+1}$	$2.359 \times 10^{-2}$	$5.471 \times 10^{-2}$	$6.4 \times 10^{-2}$	0.1722
$\text{K}^{+1}$	$8.735 \times 10^{-2}$	$8.119 \times 10^{-3}$	$5.7 \times 10^{-2}$	0.111
$\text{Ca}^{+2}$	$3.242 \times 10^{-3}$	$1.786 \times 10^{-5}$	$3.8 \times 10^{-3}$	$1.821 \times 10^{-4}$
$\text{Mg}^{+2}$	$1.367 \times 10^{-4}$	$1.450 \times 10^{-4}$	$1.1 \times 10^{-2}$	$3.452 \times 10^{-4}$
$\text{Zn}^{+2}$	$6.225 \times 10^{-3}$	$2.433 \times 10^{-5}$	$9.2 \times 10^{-3}$	$1.973 \times 10^{-4}$
$\text{Fe}^{+3}$	$6.768 \times 10^{-3}$	$1.719 \times 10^{-6}$	$8.2 \times 10^{-3}$	$8.590 \times 10^{-5}$
$\text{Al}^{+3}$	$8.1719 \times 10^{-4}$	$3.827 \times 10^{-6}$	$1.0 \times 10^{-2}$	$4.716 \times 10^{-5}$
$\text{Cr}^{+3}$	$5.923 \times 10^{-5}$	$1.467 \times 10^{-6}$	$6.1 \times 10^{-3}$	$1.281 \times 10^{-4}$

The obtained results were reliable and even better than the old electrodes so the new constructed electrode gave a better selectivity than the old single ion electrode.

### Using electrode for samples analysis

The constructed electrode has been successfully applied in the calculation of concentration of PMH & OM in sample using the following methods:

- **Direct method:** The calibration curve was constructed and the concentration of the unknown was calculated by linear equation of the calibration curve and the results are listed in Table 4.
- **Standard addition (SA) method:** In this method concentration of  $1 \times 10^{-3} \text{M}$  of PMH and OMH standards were used. The absolute error, standard deviation and relative standard deviation were calculated from the results obtained for each method are given in Table (4).

- **Multi standard addition (MSA) method:** In this method two synthetic solutions of (PMH and OMH) standards at concentrations of  $1 \times 10^{-3}$  were used to plot antilog E/S versus volume of standard (PMH and OMH), respectively. The results of the concentrations of (PMH and OMH) calculated using the electrode is shown in Table (4).
- **Precipitation titration (PT) method:** In this method a solution of  $1 \times 10^{-3} \text{M}$  of phosphotungstic acid was used for precipitate  $1 \times 10^{-3} \text{M}$  (PMH and OMH) samples and calculates responses.

The results were statistically studied as shown in Table (4).

**Table (4)**  
**Samples analysis of electrode no.2 for (PMH and OMH) respectively.**

Sample used	Sample Conc.	Direct method	SA method	MSA method	PT method
PMH	1x10 <sup>-3</sup>	1.03x10 <sup>-3</sup>	9.91x10 <sup>-4</sup>	1.16x10 <sup>-3</sup>	1.29x10 <sup>-3</sup>
		E=0.03X10 <sup>-3</sup>	E=-0.009X10 <sup>-3</sup>	E=0.16X10 <sup>-3</sup>	E=0.29X10 <sup>-3</sup>
	1x10 <sup>-3</sup>	1.11x10 <sup>-3</sup>	1.01x10 <sup>-3</sup>	1.43x10 <sup>-3</sup>	1.22x10 <sup>-3</sup>
		E=0.11 x10 <sup>-3</sup>	E=0.01 x10 <sup>-3</sup>	E=0.43 x10 <sup>-3</sup>	E=0.22 x10 <sup>-3</sup>
	1x10 <sup>-3</sup>	1.15x10 <sup>-3</sup>	1.13x10 <sup>-3</sup>	1.15x10 <sup>-3</sup>	1.19x10 <sup>-3</sup>
		E=0.15 x10 <sup>-3</sup>	E=0.13 x10 <sup>-3</sup>	E=0.15 x10 <sup>-3</sup>	E=0.19 x10 <sup>-3</sup>
Method SD		0.6 x10 <sup>-3</sup>	4.8 x10 <sup>-3</sup>	1.6 x10 <sup>-3</sup>	0.5 x10 <sup>-3</sup>
Method RSD		0.632	1.393	0.644	0.220
OM	1x10 <sup>-3</sup>	1.25x10 <sup>-3</sup>	1.17x10 <sup>-3</sup>	1.17x10 <sup>-3</sup>	1.20x10 <sup>-3</sup>
		E=0.25 x10 <sup>-3</sup>	E=0.17 x10 <sup>-3</sup>	E=0.17 x10 <sup>-3</sup>	E=0.2 x10 <sup>-3</sup>
	1x10 <sup>-3</sup>	1.07x10 <sup>-3</sup>	9.89x10 <sup>-4</sup>	1.12x10 <sup>-3</sup>	1.14x10 <sup>-3</sup>
		E=0.07 x10 <sup>-3</sup>	E=-0.011 x10 <sup>-3</sup>	E=0.12 x10 <sup>-3</sup>	E=0.14 x10 <sup>-3</sup>
	1x10 <sup>-3</sup>	1.08x10 <sup>-3</sup>	9.66x10 <sup>-4</sup>	1.01x10 <sup>-3</sup>	1.05x10 <sup>-3</sup>
		E=0.08 x10 <sup>-3</sup>	E=0.034 x10 <sup>-3</sup>	E=0.01 x10 <sup>-3</sup>	E=0.05 x10 <sup>-3</sup>
Method SD		1 x10 <sup>-3</sup>	0.9 x10 <sup>-3</sup>	0.8 x10 <sup>-3</sup>	0.8 x10 <sup>-3</sup>
Method RSD		0.759	1.199	0.819	0.581

*E= Absolute Error.*

*SD= Standard Deviation.*

*RSD=Relative Standard Deviation.*

### Conclusion

In the light of the present study the Moody theory for the ion selective electrode membrane combination could be modified to give many other combinations, So that electrodes could be synthesized with more than one drug, by injecting more than one active material into the membrane.

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### الخلاصة

تم تحضير ولأول مرة اقصاب بوليميرية حساسة لنوعين من الأدوية هما هيدروكلوريد البروميثازين وهيدروكسيد الاوكسي ميتازولين كمعقد مع حامض الفوسفوتتكتستك وفوسفات ثنائي البيوتيل كملدن. الفكرة الاساسية هي بإيجاد خلطة لغشاء الكلوريد بولي فايناييل تسمح بقياس نوعين من الادوية في غشاء واحد، كتعديل على نظرية مودي وثوماس. تم تجريب مجموعة من الخلطات ولكن الانجح كانت في القطب رقم ٢ مع ١% من كل مادة. وقد اختبرت الخلطة الناجحة وأعطت مدى تركيز جيد ( $1 \times 10^{-4}$  -  $1 \times 10^{-1}$ ) مولارياً بالنسبة لهيدروكسيد الاوكسي ميتازولين و ( $5 \times 10^{-4}$  -  $1 \times 10^{-2}$ ) مولارياً بالنسبة لهيدروكلوريد البروميثازين. فيما كان منحنى الانحدار يساوي تقريباً 57.68 و 56.64 ملي فولت ادبيكايد ومعامل التصحيح 0.9995 و 0.9999 فيما كان اقل حد للتحسس هو  $1 \times 10^{-4}$  و  $3 \times 10^{-4}$  مولارياً لكل من هيدروكلوريد البروميثازين وهيدروكلوريد البروميثازين بالتوالي. النتائج كانت ذات اعتمادية عالية جدا عند مقارنتها مع النتائج الأصلية بالنسبة لقطب الأيون الواحد. وقد تم دراسة الدالة الهيدروجينية باستخدام تراكيز مختلفة من المادة الفعالة، كما تمت دراسة المتداخلات من الايونات الاخرى مثل

(  $Li^{+1}$  و  $Na^{+1}$  و  $K^{+1}$  و  $Ca^{+2}$  و  $Mg^{+2}$  و  $Zn^{+2}$  و  $Fe^{+3}$  و  $Cr^{+3}$  و  $Al^{+3}$  ) باستخدام طريقة المحاليل المنفصلة واعطت نتائج باهرة، وقد طبق القطب المحضر بنجاح بقياس مجموعة من العينات باستخدام طرق مختلفة منها الطريقة المباشرة وطريقة الإضافات القياسية و طريقة الإضافات القياسية المتعددة بالإضافة الى طريقة التسحيح بالترسيب.