New Polymeric Potentiometric Coated Wire Sensors for Determination of Montelukast Sodium in Commercial Products

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Herein the study concerns with the construction of new potentiometric coated wire sensors by incorporating the montelukast sodium (MON) with phosphomolybdic (PMA) and phosphotungstic acids (PTA). The formed ion-pair complexes MON-PM, MON-PT and MON-PM/PT was utilized to analyze MON in commercial products. After optimizing the method parameters, the linearity between the potential/mV and -log [MON] of the suggested sensors were obtained in the range of 1.0×10^{-8}-1.0×10^{-2}, 1.0×10^{-8}-1.0×10^{-3} and 1.0×10^{-9}-1.0×10^{-2} mol L^{-1} for the designed MON-PM, MON-PT and MON-PM/PT sensors, respectively. The derived linear equations were found to be $E_{(mV)} = (58.21 \pm 0.5)$ log [MON] + 641.79, $E_{(mV)} = (57.37 \pm 0.5)$ log [MON] + 670.54 and $E_{(mV)} = (58.82 \pm 0.5)$ log [MON] + 714.14, with correlation coefficients 0.9997, 0.9998 and 0.9998 for the three sensors respectively. The content uniformity assay was carried out to ensure the quality control of tablets. To evaluate also the validity of the suggested sensors, accuracy, precision, linearity, robustness and ruggedness were studied. The proposed potentiometric technique can be exploited in the determination of MON in its pure and commercial products.

1. INTRODUCTION

Asthma is known as a chronic inflammation disorder usually associated with airway hyper responsiveness that causes many symptoms such as chest tightness, breathlessness, wheezing and continuous coughing, particularly in the morning or night. Asthma always ranges from mild to severe attack with more inflamed airways. In some cases, the airways are completely blocked [1].

Montelukast (MON) is a therapeutic medication acts as a leukotriene receptor antagonist. It is recommended in the treatment of asthma symptoms and reduces the seasonal allergy symptoms. It acts

by blocking the effects of leukotrienes which affected the airways in the lungs by narrowing and swelling them [2].

The literature review focused on theoretical and experimental studies of MON, in pure form, pharmaceuticals and in biological fluids. It included three main sections, chromatographic methods [3-15], voltammetry [16-18] and spectroscopic analysis [19-23].

Potentiometric analysis is a common technique usually applied for the determination of various compounds. This technique is simply based on the measurement of potential responses of the indicator sensors towards the tested ions [24]. This technique is suitable for direct determination of a large number of samples with low concentrations and covering a wide detection range without pre-complicated procedures.

The objective view of this study is to suggest a simple, fast, inexpensive and high sensitivity technique to prepare new coated wire membrane sensors based on different electroactive materials such as MON-PM, MON-PT and MON-PM/PT for the quantification of MON in its authentic samples, and its commercial formulations. The sensitivity of the suggested sensors towards the quantification of MON was evaluated. Also the effects of different experimental parameters were studied such as: effect of pH, interfering of the electrodes towards some foreign substances was studied. Also, the suggested potentiometric was validated with respect the recommended guidelines ICH [25].

2. EXPERIMENTAL

2.1. Reagents and solvents

The authentic montelukast sodium drug has been provided from Tabuk pharmaceuticals. Co. (Tabuk, Saudi Arabia). Commercial Singulair® 10 mg coated film tablets were supplied by Pharma Pharmaceutical industries. (Riyadh, Saudi Arabia). It was purchased from local pharmacies. Tetrahydrofuran (THF) 97 %, polyvinyl chloride (PVC), phosphomolybdic acid (PMA), phosphotungstic acid (PTA), methanol, chloroform, acetone, sodium hydroxide, hydrochloric acid, and di-octylphthalate (DOP) were provided by Sigma-Aldrich, Hamburg, Germany.

2.2. Instruments

All recorded potentials were measured using a digital pH-mV (HANNA, model 211) with an indicator sensor and a silver/silver chloride reference electrode. Also, the pH values were adjusted using pH- meter (Metrohm, model 744).

2.3. Stock MON supplier

The analytical stock supplier of 1.0×10^{-2} mol L^{-1} MON was obtained by adding 0.6 g to 100 mL of ultrapure water. All analytical samples were obtained by preparing the required diluted samples with the same dissolution solvent.

2.4. Ion associate complex

The ion-associate MON-PM or MON-PT was obtained by mixing the same quantity and concentration of MON and precipitating agent PMA and PTA (1.0×10^{-2} mol L^{-1}, 50 mL) solutions. The formed ion-associates were collected using Whatman paper No. 40, rinsed with ultrapure water and kept aside overnight at ambient degree to dry. The mixed ion associate (MON-PM/PT) was prepared by mixing 5 mg of each previously prepared ion-associate.

2.5. Membrane composition

The mixture of coated membrane was obtained by dissolving 190 mg of (PVC) powder and 0.35 mL of fluidizing agent DOP and 10 mg of each (MON-PM), (MON-PT) and (MON-PM/PT) complex in 5 mL of organic solubilizing solvent THF. Each solution was streamed into a small glass dish and the THF was slowly dry up at ambient degree until a polymeric mixture was obtained.

2.6. Preparation of the indicator sensor

The indicator sensor was prepared by insulating 5 cm Al wire with polyethylene tube. The wire surface was cleaned using a detergent and distilled water, followed by acetone and chloroform. After drying the wire was coated from one edge with the polymeric membrane mixture by repeating its dipping several times. The obtained coated wire was left hanging to dry and then soaked in aliquot of 1.0×10^{-3} mol L^{-1} of MON overnight.

2.7. Evaluation of pH effect

One of the most critical parameters which are greatly affecting the potential performance of the potentiometric sensor is the pH of the tested sample. This parameter was investigated using 1.0×10^{-3} and 1.0×10^{-4} mol L^{-1} of MON solutions. The pH values were changed from acidic to alkaline by adding a few drops of 1.0×10^{-1} mol L^{-1} HCl or NaOH. The pH graph of each sensor was plotted using the recorded potential readings vs. pH values.

2.8. Sensors calibration graphs

About 10 mL of 1.0×10^{-9} - 1.0×10^{-2} mol L^{-1} MON solutions were analyzed using each constructed coated wire sensor (MON-PM), (MON-PT) and (MON-PM/PT) in connection with the reference one. The potential was measured and recorded within mV. The potential readings of each sensor were plotted against –log concentration of the analyzed drug and slopes of calibration graphs was calculated.

2.9. Standard addition method

This method was accomplished by detecting the potential of unknown drug concentration and then small known increments were added. The potentials before E_1 and after addition, E_2 were determined and the drug concentration was determined from the equilibrium potential ΔE (E_2-E_1) [26].

2.10. Interferent study

The effect of interference on the designed sensors was evaluated by following the previously recommended method [27]. The tolerable quantities were calculated by measuring separately the potentials of each 1.0×10^{-3} mol L^{-1} of MON and foreign items including some cations, amino acids, sugars, co-additives and pharmacological related compounds. The following equation was used:

$$\text{Log } K_{pot} \text{ MON } J^{z+} = (E_2 - E_1)/S + \log [\text{MON}] - \log (J \text{ } z+)^{1/z}$$

Where, E_1 and E_2 are the recorded potential using 1.0×10^{-3} mol L^{-1} of MON and foreign species, whereas S is the slope of the linear graph.

2.11. Response time

The lifetimes of the designed coated wire sensors were detected using 1.0×10^{-9}- 1.0×10^{-2} mol L^{-1} MON samples. The designed sensors gave fast dynamic responses in 20, 45 and 20 s and used through periods of 35, 27 and 45 days for (MON-PM), (MON-PT) and (MON-PT/PM) respectively without remarkable changes in sensor performance.

2.12. Determination of MON in its pharmaceutical preparation

Five tablets of Singulair$^{®}$ (10 mg/tablet) were finely powdered and mixed well. Appropriate weight of the fine powder was shaken with 30 mL methanol and filtered. The filtrate was completed with water to 100 mL. The obtained stock labeled to contain 1.7×10^{-2} mol L^{-1} of MON. Required analytical samples were obtained by diluting the as-prepared drug solution using distilled water.

2.13. Quality control study

About 10 separate tablets of Singulair$^{®}$ (10 mg/tablet) were put down separately in 100 mL of distilled water. The proposed sensors were dipped into each sample and the potential/mV was measured for five times. The mean recoveries were considered to assess the content uniformity of the tablets using the linear graphs.

3. RESULTS AND DISCUSSION
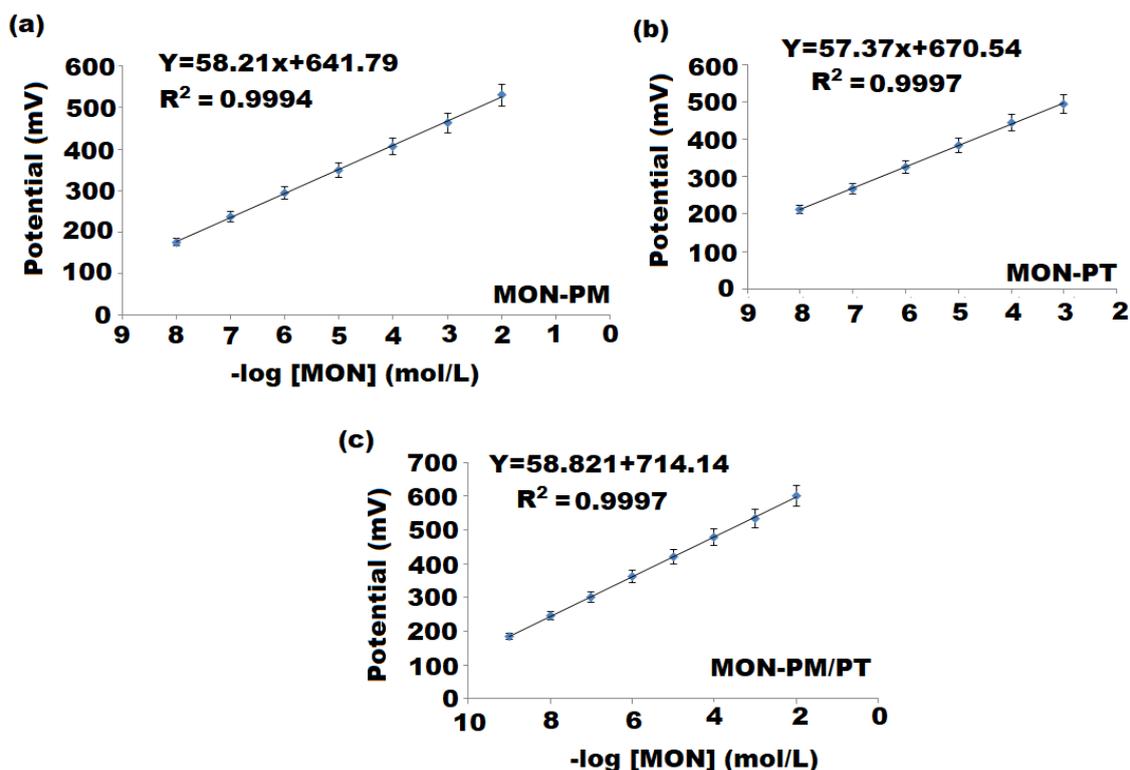
3.1. Polymeric membrane mixture

Figure 1. Calibration graphs of the suggested (a) MON-PM, (b) MON-PT and (c) MON-PM/PT coated wire sensors for the determination MON

The membranes of MON-PM, MON-PT and MON-PM/PT were prepared using 2% ion associate, 35% PVC and 63% DOP (0.35 mL). This membrane composition was reported previously for some sensors used in pharmaceutical analysis [28-30].

3.2. Sensor performance

MON reacts with PMA, PTA and PMA/PTA to form stable MON-PM, MON-PT and MON-PM/PT complexes which were water insoluble but freely soluble in THF. The ion-associate complexes were produced and examined as electroactive sites with DOP a fluidizing matrix in the presence of PVC. The analytical response properties of the proposed MON-PM, MON-PT and MON-PM/PT sensors were evaluated (Table 1).

Table 1. Critical response characteristics of MON-PM, MON-PT and MON-PM/PT coated wire sensors for the determination of MON

Parameter	MON-PM coated wire sensor	MON-PT coated wire sensor	MON-PM/PT coated wire sensor
Slope (mV decade^{-1})	58.21±0.5	57.37±0.8	58.82±0.3
Intercept	641.79	670.54	714.14
Correlation coefficient, r	0.9997	0.9998	0.9998
Linear range (mol L^{-1})	1.0×10^{-8}-1.0×10^{-2}	1.0×10^{-8}-1.0×10^{-3}	1.0×10^{-9}-1.0×10^{-2}
LOD	5.0×10^{-9}	5.01×10^{-9}	5.0×10^{-10}
Response time/s	30	45	20
Working pH range	6-10	6-10	6-10
Lifetime/(day)	35	27	40
Temperature ˚C	25˚C	25˚C	25 ˚C
Accuracy (%)	99.34± 0.6	99.31 ± 0.5	99.94±0.3
Robustness[b]	99.22± 0.5	99.12 ± 0.3	99.38±0.4
Ruggedness[c]	99.58±0.3	99.35 ± 0.5	99.65±0.6

[a] Mean of six measurements
[b] Small variation in method parameters were studied using phosphate buffer pH 6±1
[c] Comparing the results by those obtained by a different sensor

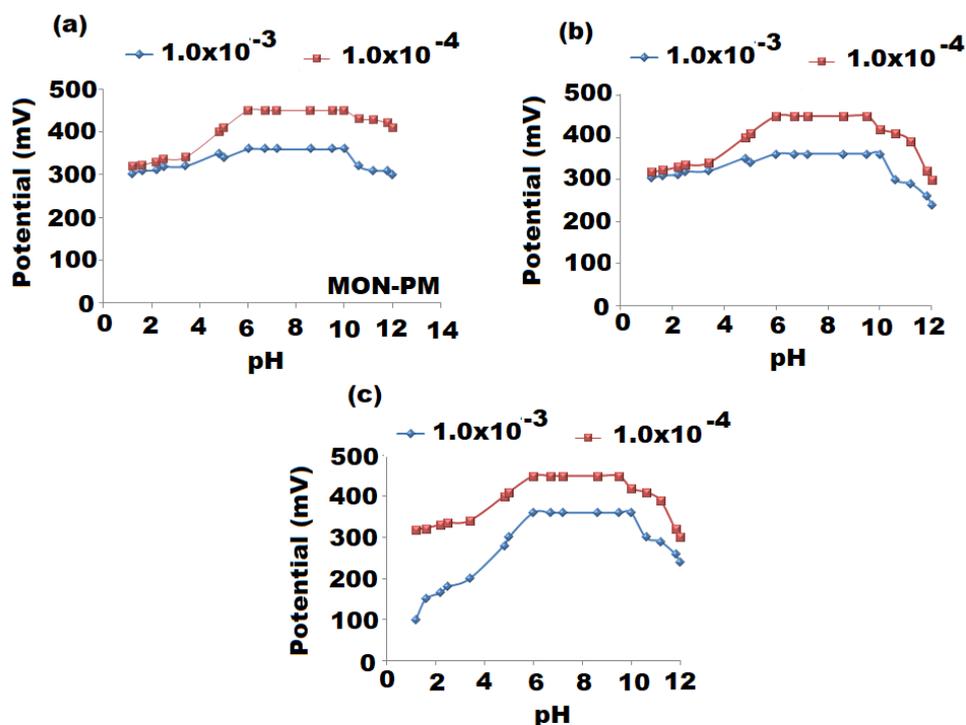The typical calibration graphs were illustrated in Figure 2.

Figure 2. pH effect on the response of the suggested (a) MON-PM, (b) MON-PT and (c) MON-PM/PT coated wire sensors using 1.0×10^{-3} and 1.0×10^{-4} mol L^{-1} MON solutions

3.3. Dynamic and lifetime response

The dynamic sensation time of each sensor was recognized using 1.0×10^{-9}- 1.0×10^{-2} mol L^{-1} of MON standard samples. The proposed sensors exhibit fast dynamic responses of 30, 45 and 20 s for MON-PM, MON-PT and MON-PM/PT, respectively. The sensors were used for a period of 35, 27 and 40 days without significant changes in the sensor performance as shown in Table 1.

3.4. pH evaluation

The three designed sensors were used to measure the potential reading in 1.0×10^{-3} and 1.0×10^{-4} mol L^{-1} of MON samples after changing the pH values from acidic to alkaline (Figure 3).
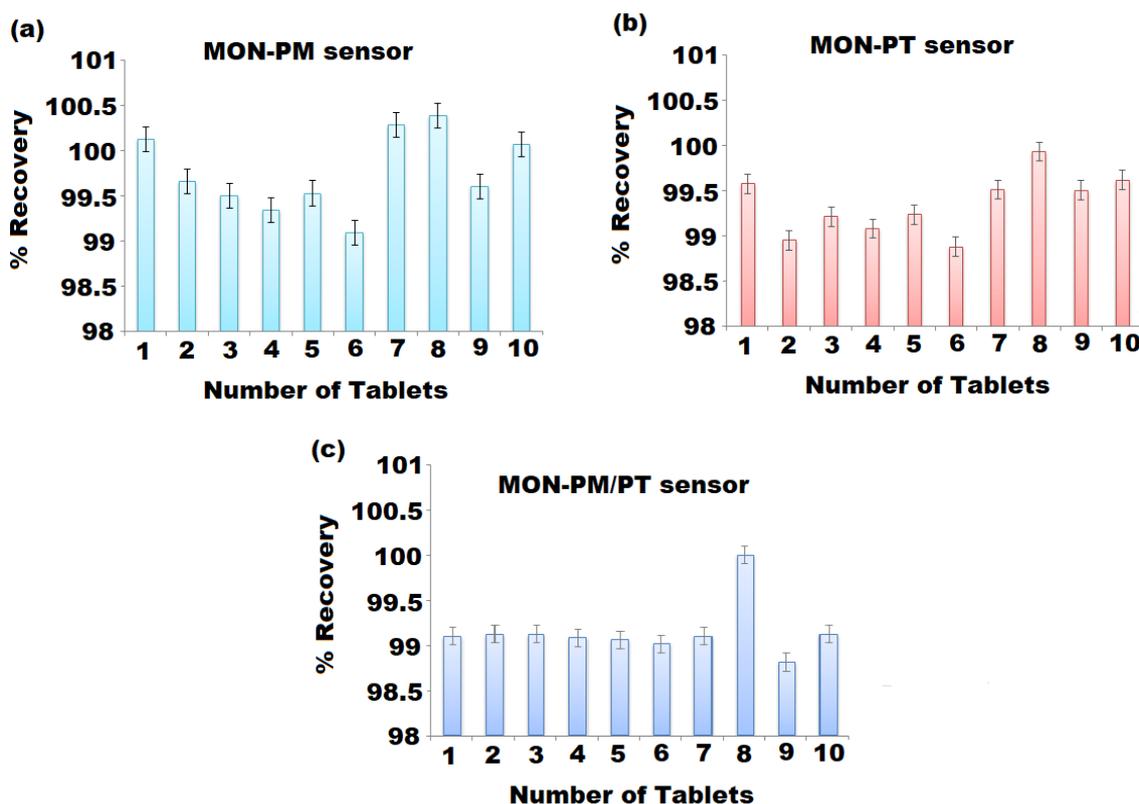
Figure 3. Content uniformity assay of MON in tablets using the suggested (a) MON-PM, (b) MON-PT and (c) MON-PM/PT coated wire sensors

The suitable pH range was estimated from the pH graphs and was found to be 6-10. In pH less than 6, the hydrogen ions interfered in the response of the sensors causing an increase in the measured potential. However, the alkaline medium the sensors safely worked up to pH 10. The increase of pH more than 10 may induce some interferent from hydroxyl ions causing a gradual decrease in the recorded potential [31].

3.5. Interferent study

The effect of various foreign items on each coated wire sensor response was evaluated by determining the interferent effect of inorganic cations such as Na^+, K^+, Fe^{3+}, Ag^+, Ni^{2+}, Cu^{2+}, Ca^{2+}, Zn^{2+} and Sn^{2+} sugars including glucose and lactose. Furthermore, some amino acids were tested such as serine, ornithine and histidine. Additionally, aminophylline as related pharmacological action was analyzed. All outcomes are presented in Table 2.

Table 2. Selectivity coefficient K_{pot} MON^+ of MON-PM, MON-PT and MON-PM/PT coated wire sensors calculated by separate solution method (1.0×10^{-3} mol L^{-1}) of both drug and interferent species at 25° C

Interferents	MON-PM coated wire sensor K_{pot}^{MON+}	MON-PT coated wire sensor K_{pot}^{MON+}	MON-PM/PT coated wire sensor K_{pot}^{MON+}
Na^+	1.2×10^{-3}	2.8×10^{-3}	2.3×10^{-6}
K^+	2.7×10^{-4}	2.6×10^{-2}	6.8×10^{-6}
$Fe3^+$	5.2×10^{-3}	7.9×10^{-2}	2.6×10^{-6}
Ag^+	2.5×10^{-4}	7.5×10^{-3}	7.6×10^{-6}
Ni^{2+}	5.8×10^{-4}	4.1×10^{-2}	1.5×10^{-3}
Cu^{2+}	1.5×10^{-3}	3.5×10^{-3}	5.6×10^{-5}
Ca^{2+}	4.2×10^{-3}	2.4×10^{-2}	5.8×10^{-6}
Zn^{2+}	3.4×10^{-3}	1.1×10^{-3}	7.6×10^{-6}
Sn^{2+}	2.3×10^{-3}	2.6×10^{-3}	4.6×10^{-6}
Ascorbic acid	7.4×10^{-3}	9.7×10^{-2}	2.9×10^{-7}
Serine	4.1×10^{-3}	2.1×10^{-2}	3.5×10^{-6}
Ornithine	9.8×10^{-4}	1.6×10^{-3}	7.1×10^{-5}
Aminophylline	3.4×10^{-3}	1.2×10^{-3}	3.8×10^{-6}
Histidine	2.0×10^{-3}	2.2×10^{-3}	3.8×10^{-6}
Glycine	5.2×10^{-4}	4.9×10^{-2}	2.9×10^{-6}
Glucose	9.0×10^{-4}	1.9×10^{-3}	2.0×10^{-6}
Lactose	6.8×10^{-4}	1.5×10^{-3}	5.2×10^{-5}

The selectivity the designed coated wire membrane sensors were based on the physical and chemical features of the ion associate sites inside the membranes such as the tested ion movement, hydrophobicity of the polymeric matrix and the free energy transferred between the tested drug and the membrane phases [30]. No significant interferences were observed.

3.6. Quantification of MON in pure drug

The MON was directly quantified in its authentic samples using the proposed MON-PM, MON-PT and MON-PM/PT sensors accord average percentage values of 99.64±0.8, 99.38±0.7 and 99.29±1.02 for the designed sensors, respectively. The collected results were compared with those previously reported [21]. No significant difference with respect to precision and accuracy was observed between the suggested and reported methods (Table 3).

Table 3. Determination of MON in its bulk drug using the constructed MON-PM, MON-PT and MON-PM/PT sensors in comparison with the results of reported method [21]

Type of sensor	Tested conc. range (mol L^{-1})	Mean ±SD	n	Variance	% SE	% RSD	t-test	F-test
MON-PM	1.0×10^{-8} - 1.0×10^{-2}	99.64±0.8	7	0.64	0.30	0.80	0.278(2.228)*	1.31(5.05)*
MON-PT	1.0×10^{-8} - 1.0×10^{-3}	99.38±0.7	6	0.49	0.28	0.70	0.909(2.262)*	1.00(5.19)*
MON-PM/PT	1.0×10^{-9} - 1.0×10^{-2}	99.29±1.02	9	1.10	0.35	1.05	1.00 (2.179)*	2.24(3.84)*
Reported method [21]	1.0×10^{-6} - 1.0×10^{-2}	99.76±0.7	5	0.49	0.31	0.70		

* The figures between parentheses are the theoretical values of t- and F- tests at p = 0.05 [32].

3.7. Validity study

The progressed potentiometric technique for the analysis of MON was justified according to analytical requirement guidelines [25]. Under optimized analytical parameters, a linearity between the potential/mV and -log [MON] was obtained in the range of 1.0×10^{-8}-1.0×10^{-2}, 1.0×10^{-8}-1.0×10^{-3} and 1.0×10^{-9}-1.0×10^{-2} mol L^{-1} for MON-PM, MON-PT and MON-PM/PT sensors, respectively. The linear estimated equations were found to be $E_{(mV)} = (58.21 \pm 0.5)$ log [MON] + 641.79, $E_{(mV)} = (57.37 \pm 0.5)$ log [MON] + 670.54 and $E_{(mV)} = (58.82 \pm 0.5)$ log [MON] + 714.14, with correlation coefficients 0.9997, 0.9998 and 0.9998 for the three sensors respectively as indicated in Table 1.

The IUPAC recommendation was applied to determine the detection limit of MON sample when the response of the sensor deviates from the primary response by 17.8 mV [26]. The calculated LOD of the suggested sensors were found to be 5.0×10^{-9}, 5.01×10^{-9} and 5.01×10^{-10} mol L^{-1} (Table 1).

The analytical method accuracy was tested by analyzing nine MON authentic samples. The estimated results were presented as percentage standard error (% SE) as shown in Table 4.

Table 4. Accuracy data for MON determination using MON-PM, MON-PT and MON-PM/PT coated wire sensors

Type of sensor	Tested conc. range (mol L^{-1})	Mean ±SD	n	Variance	% SE	% RSD
MON-PM	1.0×10^{-8} - 1.0×10^{-2}	99.34±0.6	9	0.36	0.20	0.60
MON-PT	1.0×10^{-8} - 1.0×10^{-3}	99.32±0.5	9	0.25	0.16	0.50
MON-PM/PT	1.0×10^{-9} - 1.0×10^{-2}	99.94±0.3	9	0.09	0.10	0.30

The results obtained revealed the high accuracy for the three constructed sensors with mean percentage recoveries 99.34±0.6, 99.32±0.5 and 99.94±0.3 and low percentage errors 0.20, 0.16 and 0.10, respectively. The presence of mixed ion-pair complex MON-PM/PT enhances the sensitivity of the sensor towards the determination of MON. This can be attributed to the synergistic enhancement

effect of the electroactive material MON-PM/PT rather than the constructed sensors of MON-PM and MON-PT.

The intermediate precision of the current procedure was evaluated as relative standard deviations (% RDS) by analyzing of the investigated MON-PM, MON-PT and MON-PM/PT sensors in intra and inter day detection (Table 5).

Table 5. Precision data for MON determination using MON-PM, MON-PT and MON-PM/PT coated wire sensors

Parameters		MON-PM coated wire sensor		
	Taken (mol L^{-1})	% Recovery	% RSD	% SE
Inter-day	1.0×10^{-8} - 1.0×10^{-4}	99.9-100.3	0.2-0.8	0.1-0.5
Intra-day	1.0×10^{-8} - 1.0×10^{-4}	99.3-100.0	0.4-1.1	0.2-0.6
	Taken (mol L^{-1})	MON-PT coated wire sensor		
		% Recovery	% RSD	% SE
Inter-day	1.0×10^{-7} – 3.0×10^{-5}	98.6-100.0	0.01-0.14	0.01-0.08
Intra-day	1.0×10^{-7} – 3.0×10^{-5}	99.17-99.71	0.16-0.32	0.09-0.18
	Taken (mol L^{-1})	MON-P/PT coated wire sensor		
		% Recovery	% RSD	% SE
Inter-day	1.0×10^{-7} - 1.0×10^{-3}	99.60-100.20	0.1-0.3	0.05-0.17
Intra-day	1.0×10^{-7} - 1.0×10^{-3}	98.80-100.20	0.1-0.4	0.05-0.23

The % RSD of the suggested three sensors were 0.2-0.8, 0.01-0.14 and 0.1-0.3 % for inter-day assay. However, the % RSD of the intra-day assay were 0.4-1.1, 0.16-0.32 and 0.1-0.4 %, respectively. All results were within the permission value <2.0 %, suggesting high precision of the proposed technique.

System robustness were investigated by reproducing the suggested method with a small changing in analytical variables such as change in pH value using phosphate buffer (pH 6 ± 1). The method remained unaffected and provided results 99.22 ± 0.5, 99.12 ± 0.3 and 99.38 ± 0.4 for MON-PM, MON-PT and MON-PM/PT coated wire sensors, respectively. The results are closely related to that previously obtained.

The current method ruggedness was performed to test the reproducibility degree of the obtained data. Therefore, the same working samples were analyzed using another with a pH-meter (Jenway 3510) and were matched with those recorded by another model of pH-meter (HANNA, model 211), and the provided results were 99.58 ± 0.3, 99.35 ± 0.5 and 99.65 ± 0.3, the above mentioned coated wire sensors, respectively for (Table 1).

Int. J. Electrochem. Sci., 16 **(2021)** Article ID: 210634

11

3.8. Analytical applications

3.8.1. Analysis of MON in Singulair tablets

The MON-PM, MON-PT and MON-PM/PT sensors were applied to estimate the MON in Singulair® (10 mg/tablet). Standard addition method was used and the obtained data were summarized in Table 6.

Table 6. Determination of MON in Singulair 10 mg\tablet using the constructed MON-PM, MON-PT and MON-PM/PT sensors in comparison with the results of reported method [21]

Type of sensor	Tested conc. range (mol L^{-1})	Mean ±SD	n	Variance	% SE	% RSD	t-test	F-test
MON-PM	1.0×10^{-8} - 1.0×10^{-2}	99.61±0.3	9	0.09	0.10	0.30	1.280(2.210)*	1.77(3.44)*
MON-PT	1.0×10^{-8} - 1.0×10^{-3}	99.65±0.4	6	0.16	0.16	0.40	1.213(2.160)*	1.00(3.69)*
MON-PM/PT	1.0×10^{-9} - 1.0×10^{-2}	99.71±0.4	9	0.16	0.13	0.40	1.686(2.120)*	1.00(3.44)*
Reported method [21]	2.0-10.0 µg mL^{-1}	99.40±0.4	9	0.16	0.13	0.40		

* The figures between parentheses are the theoretical values of t- and F- tests at p = 0.05 [32]

Table 7. Comparative study between the previously published analytical methods and the suggested potentiometric method

Type of method	Linear range	LOD	LOQ	Ref.
Reversed phase high performance liquid chromatography (RP-HPLC)	50 – 300 µg mL^{-1}	3.15 µg mL^{-1}	9.55 µg mL^{-1}	[3]
Liquid chromatography coupled with mass spectrometry (LC/MS)	6.098–365.855 ng mL^{-1}	-	6.098 ng mL^{-1}	[11]
High performance thin layer chromatography (HPTLC)	100-500 ng spot^{-1}	131.01 ng spot^{-1}	597.82 ng spot^{-1}	[14]
Voltammetry	5.0×10^{-8}- 1×10^{-6} mol L^{-1}	4.0×10^{-9} mol L^{-1}	-	[17]
Present work	1.0×10^{-9} 1.0×10^{-2} mol L^{-1}	5.0×10^{-10} mol L^{-1}	-	-

The estimated mean recoveries were calculated as 99.61 ± 0.3, 99.65 ± 0.4 and 99.71 ± 0.4 for the three constructed sensors, respectively. All results were assessed by carrying out t-test and F-test analysis. The overcome data were excellent in matching with others estimated from a spectrophotometric method [21]. Furthermore, relative study was accomplished to evaluate the sensitivity of the current method and the previously addressed analytical methods (Table 7).

The comparative study revealed the high sensitivity of the suggested sensors towards the determination MON in its pure form and pharmaceutical tables.

3.8.2. Content uniformity assay

The quality control of the tables with respect to content uniformity of the active ingredient MON in its commercial products was tested. The results of this assay were expressed as the mean percentage recoveries ± standard deviations. The outcomes were found to be 99.76±0.43, 99.67±0.41 and 100.0±0.1for MON-PM, MON-PT and MON-PM/PT, respectively (Figures 3a-c).

4. CONCLUSION

The described potentiometric method displayed a simple, fast and high sensitivity towards the analysis of MON in its authentic and tablets. The suggested electrochemical method using MON-PM, MON-PT and MON-PM/PT showed linear relationships over 1.0×10^{-8}-1.0×10^{-2}, 1.0×10^{-8}-1.0×10^{-3} and 1.0×10^{-9}-1.0×10^{-2} mol L^{-1}, respectively, with limit of detection of 5.0×10^{-9}, 5.01×10^{-9} and 5×10^{-10} mol L^{-1} within safe pH range of 6-10 for the suggested sensors. The method validation study indicated good accuracy, precision and the suggested sensors showed high response for 35, 45, and 40 days without significant change in their responses. The suggested potentiometric method provided high sensitivity and suitability for the quantification of MON drug.

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Int. J. Electrochem. Sci., 16 **(2021)** Article ID: 210634

13

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