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All-solid-state polymeric screen printed and carbon paste ion selective electrodes for determination of oxymetazoline in pharmaceutical dosage forms

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ABSTRACT

All-solid state potentiometric ion selective electrodes have the merits of being portable, small and suitable for small volume samples. Herein, disposable home-made screen printed polymeric ion selective electrode (SPE) is developed for determination of oxymetazoline (OXM) in pharmaceutical nasal drops and drug substance. Ion selective electrodes with optimal potentiometric response were achieved by careful selection of the ion exchanger and plasticizer. A screen printed electrode utilizing oxymetazoline-tetraphenyl borate (OXM-TPB) as an ion exchanger and dibutyl phthalate (DBP) as a plasticizer exhibited a Nernstian slope of 59.5±0.5 mV/decade (n=3) over the concentration range from 1×10^{-5} to 1×10^{-2} M OXM (r = 0.9999) with a detection limit of 5.0×10^{-6} M. The electrode is useful over a wide pH range from 4.0 to 8.0. The electrode showed a high selectivity for OXM against several common interfering ions. The potential interference from benzalkonium chloride was easily eliminated by treatment the sample with KI. Comparable potentiometric characteristics including linearity, detection limit, pH range and selectivity pattern were obtained with a carbon paste electrode (CPE) comprising same ion exchanger and plasticizer. The electrodes were successfully used for the assay of OXM in the drug substance and in the dosage form in presence of benzalkonium chloride with high accuracy (±2%) and precision (%RSD <2.5). The proposed method is simple, accurate and precise.

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1. Introduction

Oxymetazoline hydrochloride (Figure 1) is the common name for 3-[(4,5-dihydro-1*H*-imidazol-2-yl) methyl]-6-(1,1-dimethylethyl)-2,4-dimethylphenol hydrochloride [1]. It is a direct acting sympathomimetic used as a vasoconstrictor to relieve nasal congestion. It acts on alpha receptors in the arterioles of the conjunctiva and nasal mucosa to produce constriction [2]. Oxymetazoline should not be used more than 2 to 3 times daily for five consecutive days, prolonged use increases the probability of occurrence of rebound congestion [3]. Oxymetazoline should be prescribed with great caution to avoid potential adverse effects. Thus, there has been always great demand for reliable and simple methods for controlling the concentration of oxymetazoline in the pharmaceutical dosage forms and drug substances.

Consequently, spectrophotometric [4-7], high performance liquid chromatographic (HPLC) [8-12], chemiluminescence [13, 14] and potentiometric methods [15] have been suggested for the determination of OXM. Some of the proposed spectrophotometric methods use either tedious lengthy calculations or they are highly dependent on the selection of the wavelength region which critically affects the precision and accuracy.

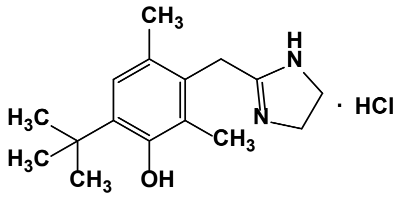

Figure 1. Structure of oxymetazoline hydrochloride.

The other spectrophotometric method [5] is based on an oxidation reaction and suffers from a narrow linear range. On the other hand, the chromatographic methods are time and solvent consuming, while, the suggested chemiluminescence methods [13,14] require instrumentations with limited applications which make them not available in most laboratories for routine analysis. Although potentiometric ion selective

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electrodes (ISEs) represent a cost-effective approach for measuring ionic compounds in turbid and colored solutions, the proposed polyvinyl chloride (PVC) plastic membrane requires large volumes of the sample and special skills for construction and handling.

A possible way to circumvent these difficulties is represented in the development of solid-state ion selective electrodes. The electrodes have the advantages of small size, easy construction and can be used in different space position with easy rotation and vibration. They have no inner filling solution where the ion selective membrane is in direct contact with the solid transducer surface [16,17]. Recently, mass production of inexpensive, portable and reliable all-solid-state electrodes for environmental and pharmaceutical analysis has attracted great attention [18]. Such electrodes are commonly produced via screen printing technology and are suitable for small volume samples [16,19].

The present work aims to the fabrication of disposable screen printed ion selective electrode for the determination of OXM in pharmaceutical nasal drops. The potentiometric response was optimized by careful selection of the ion exchanger and the plasticizer. The potentiometric response of the electrode was characterized according to the IUPAC recommendation [20]. The potentiometric performance of proposed electrode was evaluated by comparison to carbon paste electrode. The electrodes were employed as potentiometric indicator electrodes for the assay of OXM in pharmaceutical dosage forms.

2. Experimental

2.1. Reagents and chemicals

Oxymetazoline hydrochloride drug substance and Oxymet Nasal drops (0.5% Oxymetazoline HCl) was obtained from Pharaonia Pharmaceuticals, Alexandria, Egypt. Poly(vinyl chloride) (PVC) of high molecular weight, dibutylphthalate (DBP) and dioctylphthalate (DOP) were from Sigma-Aldrich, St. Louis, USA. Tricresylphosphate (TCP) was purchased from Fluka, Switzerland. Graphite powder (particle size <50 µm) and sodium tetraphenyl borate (Na-TPB) were purchased from Merck, Darmstadt, Germany. Phosphomolybdic acid (PMA) was purchased from S D Fine-Chem Limited, Mumbai, India. Ammonium reineckate (RKT) was from Riedel-De Haen AG, Hannover, Germany. All reagents were of analytical grade and bidistilled water was used throughout the experiments.

2.2. Apparatus

All potential measurements were performed using Ag/AgCl reference electrode and a Cyberscan 500 digital pH/mV meter (Eutech Instruments, Thermo Scientific, USA). The cell assembly for the potentiometric measurements was as follows: Ag / AgCl / 3 M KCl // Sample / SPE. The pH measurements were performed using a Jenway 3510 pH meter (England).

2.3. Preparation of ion-exchangers (IP)

The ion-exchangers (IP) were obtained by addition of 50 mL of 0.01 M solution of Na-TPB, phosphomolybdic acid or ammonium reineckate to 50 mL of 0.01 M of OXM.HCl solution. Each solution was stirred for 10 min and filtered through a Whatman filter paper. The precipitate was washed several times with bidistilled water and left to dry for 2 days at room temperature.

2.4. Construction of screen printed electrodes (SPEs)

The potentiometric screen printed strips (3×25 mm) were fabricated manually using a home-made polyester screen. The electrodes were printed in array of eight electrodes on a flexible PVC support (≃200 µm thick). First, a conductive carbon track was printed using home-made ink (graphite/PVC ink) and cured at 60 °C for 2 h. Afterwards, the sensing membrane cocktail SPE2 (5% OXM-TPB, 47.5% plasticizer and 47.5% PVC in 1:1 cyclohexanone: acetone) was printed over the graphite track. The electrodes were dried at 40 °C in a vacuum oven for 2 hours. The electrodes were covered with an insulating tape leaving a rectangular area (3×3 mm) at the two terminals as a sensing part and conductive parts.

2.5. Construction of carbon paste electrode (CPEs)

The carbon paste electrode (CPE3) was prepared by mixing 55% graphite powder, 38% binder (DBP) and 7% ion-exchanger in a glass mortar. An empty 50 µL plastic tip was used as the electrode body. The tip was completely filled with paste. Complete and compact packing of the paste was confirmed by pressing the tip (at its wide opening) into the paste several times. The back connection was made by inserting a copper wire into the paste through the apex of the tip. The wide opening of the tip served as the electrode surface. The carbon paste was packed into the hole of the electrode body and smoothed on a filter paper until it has a shiny appearance.

2.6. Calibration graph

The SPEs were conditioned in 0.01 M OXM for 30 min before any measurements. The calibration graphs were constructed by successive addition of 0.01 M OXM solution to 50 mL bidistilled water to cover the concentration range from 1×10^{-6}- 1×10^{-3} M OXM. The potential of higher concentration solutions 3×10^{-3} and 1×10^{-2} M were measured by dipping the electrode in each solution separately. We do so to avoid large dilution of the sample in the measuring cell, the measuring cell has a limited volume of 100 mL. All measurements were performed under constant stirring. Calibration graphs were constructed by plotting the potential values (mV) *vs.* -log [OXM]. The selectivity coefficient was measured by the separate solution method.

2.7. Selectivity

The potentiometric selectivity coefficient $\log k_{i,j}^{pot.}$ of different inorganic and organic cations was evaluated using the separate solution method [21]. In this method, the electromotive force value (E_i and E_j) of the electrode in pure solution for the primary (OXM; a_i) and the interfering ion (a_j), of equal concentration ($a_i = a_j = 1\times10^{-3}$ M), were used to calculate the selectivity coefficient. The selectivity coefficient $\log k_{i,j}^{pot.}$ was calculated using Nicolsky-Eisenman equation.

$$\log k_{i,j}^{pot.} = (E_j - E_i)\, z_i F / 2.303\, RT + (1-(z_i/z_j))\, \mathrm{Log}\, a_i \qquad (1)$$

2.8. Potentiometric titration

Drug substance: Aliquots of 0.01 M OXM drug substance solution (1, 2 and 3 mL) were transferred each into 50-mL volumetric flask and diluted to mark with bidistilled water. Each concentration was prepared in triplicate. Each solution was titrated against 0.01 M PMA using the proposed screen printed and carbon paste electrodes. The end point was determined by the derivative method.

Oxymet finished product: Appropriate volumes of Oxymet Nasal Drops (0.05% Oxymetazoline HCl) were diluted each with 25 mL bidistilled water and treated with 1 mL of 0.01 M KI solution, then diluted to mark with bidistilled water.

Table 1. Potentiometric response characteristics of OXM screen printed electrode with variable composition of the sensing layer *.

Sensor	Composition% (w/w)			Slope, mV/decade	Linear range, M	R
	IP%	Plasticizer%	PVC%			
Effect of ion-exchanger						
OX-TPB						
SPE 1	2.5	47.5% DBP	50.0	59.0	1×10^{-5}- 1×10^{-2}	0.9991
SPE 2	5.0	47.5% DBP	47.5	59.9	1×10^{-5}- 1×10^{-2}	0.9999
SPE 3	7.5	38.0% DBP	54.5	60.0	1×10^{-5}- 1×10^{-2}	0.9999
SPE 4	10.0	37.0% DBP	53.0	60.1	1×10^{-5}- 3×10^{-2}	0.9999
OX-RKT						
SPE 5	5.0	48.0% DBP	50.0	46.1	1×10^{-4}- 3×10^{-2}	0.9999
OX-PMA						
SPE 6	5.0	40.0% DBP	55.0	50.5	1×10^{-4}- 1×10^{-2}	0.9997
Effect of plasticizers						
SPE 7	5.0	40.0% DOP	55.0	46.2	1×10^{-5}- 1×10^{-2}	0.9997
SPE 8	5.0	40.0% TCP	55.0	55.5	1×10^{-5}- 1×10^{-2}	0.9997

* IP%: ion pair.

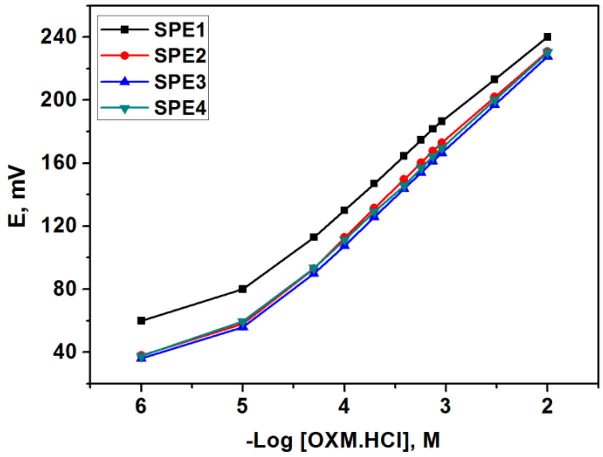


Figure 2. Calibration curves for OXM screen printed electrodes with different concentrations of the ion exchanger in the sensing membrane. SPE 1, SPE 2, SPE 3 and SPE 4 contain 2.5, 5.0, 7.5 and 10% of OXM-TPB, respectively.

Each solution was prepared in triplicate and titrated with PMA and the end point was determined by the derivative method as before.

3. Results and discussion

3.1. Effect of membrane composition

Construction of polymeric membrane ISEs with optimal potentiometric response is governed by several factors including the type of ion exchanger and the type of plasticizer. The ion exchanger is the key element for the establishment of thermodynamic ion exchange equilibrium at the membrane/ solution interface. Thus, it should be hydrophobic, practically insoluble in water and stable over a wide pH range. Meanwhile, the plasticizer should be immiscible with water, nonvolatile and capable of dissolving the ion exchanger. In this work, screen printed polymeric ISE electrodes with variable membrane compositions were prepared using OXM-TPB as ion exchanger and DBP as a plasticizer (Table 1). A calibration curve was constructed for each membrane composition and the slope, linear range and the detection limit were obtained. Typical calibration graphs are shown in Figure 2. As we have noticed, the electrodes (SPE1-SPE4) exhibited a Nernstian slope of 59.5± 1 mV/decade (r = 0.999) over the concentration range from 1×10^{-5}-1×10^{-2} M. The slope was nearly independent of the amount of OXM-TPB in the membrane indicating the robustness of the prepared electrode; and that any deliberate change in the amount of OXM-TPB (5±2.5%, *w/w*) is not affecting the potentiometric characteristics of the electrode. Other ion exchangers such as OXM-RKT and OXM-PMA were tested. Both OXM-RKT and OXM-PMA based electrodes exhibited sub Nernstian responses of 46.1 and 50.5 mV/decade, respectively, over the concentration range from 1×10^{-4}-1×10^{-2} M. The potentiometric characteristics of OXM-RKT and OXM-PMA based electrodes are included in Table 1. The sub-Nernstian response would be due to leaching the OXM-RKT and OXM-PMA from the membrane when the electrode is brought in contact with the solution. Furthermore, the effect of the plasticizer on the potentiometric response of OXM-TPB based electrode was studied using DOP and TCP plasticizers. The slope was dropped to 46.2 and 55.5 mV/decade (SPE 7 and SPE 8; Table 1) when DOP and TCP were used as plasticizers, respectively. This would be to the limited solubility of the ion exchanger (OXM-TPB) in both DOP and TCP; we noticed that mixing OXM-TPB with either DOP or TCP resulted in a turbid solution. Therefore, screen printed ISEs (SPE 2; Table 1) with OXM-TPB (5% w/w) and DBP as a plasticizer was considered for further characterization.

3.2. Carbon paste electrodes

Carbon paste electrodes with variable ratios of the OXM-TPB were also prepared and their potentiometric response characteristics were compared to the SPEs. Interestingly, all carbon paste electrodes (Table 2) gave potentiometric response comparable to those of the SPEs. Changing the amount of the ion exchanger from 2 to 10% exhibited Nernstian slopes from 58.2 to 61.5 mV/decade. Thus, all compositions are useful for preparation of carbon paste electrodes for sensitive determination of OXM.

Table 2. Potentiometric response characteristics of OXM carbon electrodes with variable composition *.

Sensor	Composition w/w%			Slope, mV/decade	Linear range, M	R
	IP%	Plasticizer%	C%			
OXM-TPB						
CPE 1	2.0	48.0% DBP	50.0	61.5	1×10^{-5}- 1×10^{-2}	0.9996
CPE 2	5.0	40.0% DBP	55.0	60.0	1×10^{-5}- 1×10^{-2}	0.9996
CPE 3	7.0	38.0% DBP	55.0	59.4	1×10^{-5}- 1×10^{-2}	0.9996
CPE 4	10.0	37.0% DBP	53.0	58.2	1×10^{-5}- 1×10^{-2}	0.9999

* C%: Carbon percentage.

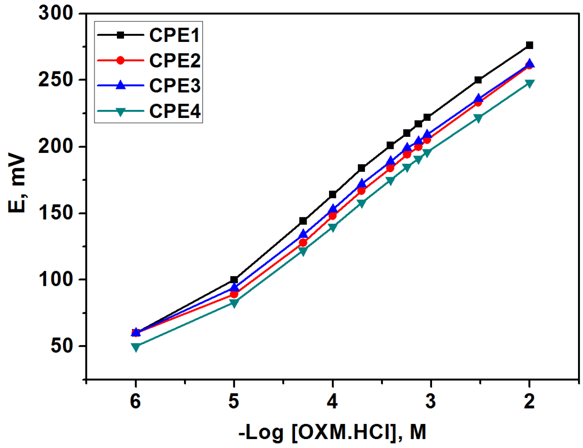


Figure 3. Calibration curves for OXM-selective carbon paste sensors with variable compositions. DBP was used as a binder; CPE 1, CPE 2, CPE 3 and CPE 4 contain 2, 5, 7 and 10% of OXM- TPB, respectively.

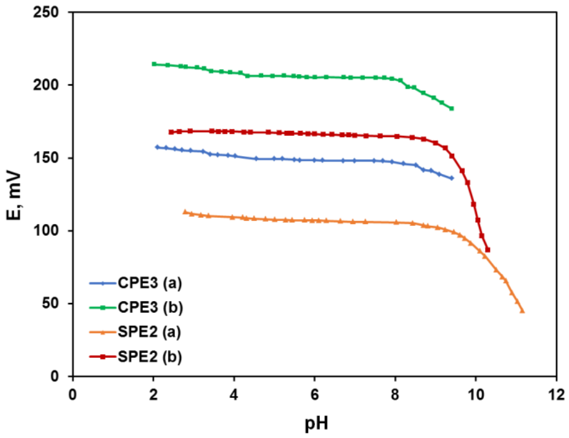


Figure 4. Effect of pH on the response of carbon paste (CPE 3) and screen printed (SPE 2) electrodes using (a) 1×10^{-4} and (b) 1×10^{-3} M oxyemtazoline HCl solutions.

Typical calibration graph is shown in Figure 3. CPE3 was chosen as it gives the best Nernstian slope.

3.3. Effect of pH

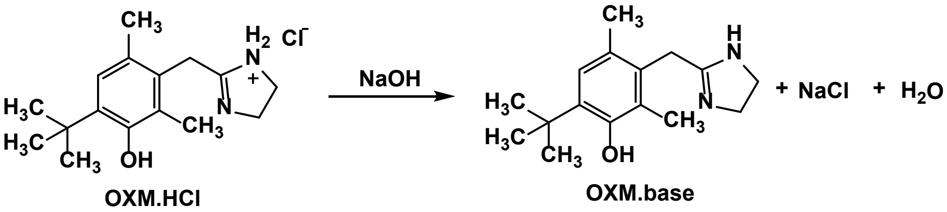
The potentiometric measurements should be performed within a pH range where the potentiometric response is pH-independent. The effect of pH on the sensor response was studied at two different concentrations of OXM, 1×10^{-4} and 1×10^{-3} M. The pH of the measuring solution was changed using HCl and/or NaOH solutions. Figure 4 shows the effect of changing the pH of the measuring solution on the potentiometric response of the sensors. The emf was independent of pH in the pH range from 4-8. A very slight change in emf readings was observed at pH < 4; this would be due to H^+ interference. A dramatic change in emf values was observed at pH > 8; this can be explained by the depletion of OXM ions and formation of OXM base as shown in the following scheme (Scheme 1). The formation of a white precipitate at pH > 8 is an evidence of the formation of water-insoluble OXM base.

3.4. Response time and emf stability

Figure 5 shows the dynamic response time and the emf stability of the proposed CP and SP sensors. The emf reading was monitored for 2 minutes at different concentration levels from 1×10^{-5}-1×10^{-2} M. The sensors revealed a fast response time. A stable emf reading was achieved in a few seconds. The emf showed a high stability and the change was within ±0.1 mV. There was no drift observed for the SP sensor; this could be explained by the well connection between the sensing layer and the conductive carbon track since the two layers are prepared using the same binder. Such configuration impedes the uptake and formation of water layer at the interface and increases the sensor stability.

Table 3. Selectivity coefficients of CPE and SPE electrodes using the separate solution method.

Interferant	log $k^{pot.}_{i,j}$	
	CPE3	**SPE2**
Na^+	-2.54	-3.36
K^+	-2.56	-3.40
Ca^{2+}	-3.61	-4.52
Mg^{2+}	-3.61	-4.55
Alanine	-2.67	-3.08
Glycine	-2.58	-3.14
Glutamine	-2.53	-3.34
Leucine	-2.39	-3.26
Lycine	-2.40	-3.39



Scheme 1. Interaction of OXM.HCl with NaOH and formation of OXM base.

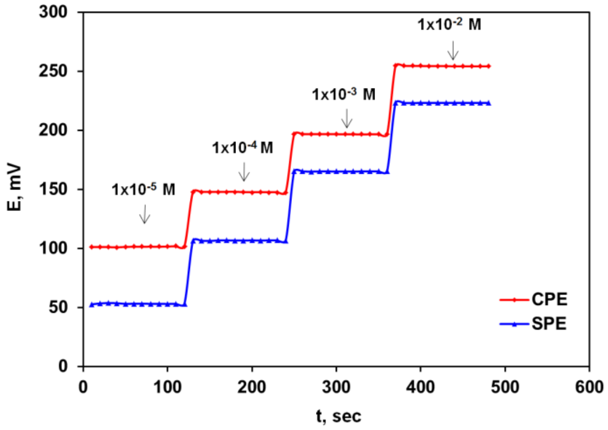


Figure 5. Dynamic response time of the screen printed (SPE 2) and carbon paste (CPE 3) electrodes at different-concentrations.

3.5. Selectivity interference

The selectivity coefficient $K^{Pot.}_{I,j}$ is defined as the ability of an ISE to discriminate between the target analyte I and an interferent j. The selectivity coefficients of the OXM sensors to a variety of interfering compounds were calculated using the separate solution method [21]. The selectivity coefficients of CP and SP sensors towards common mono-, divalent and amino acids are summarized in Table 3. The small values of $K^{Pot.}_{I,j}$ reflect the high selectivity of the proposed sensors to OXM over the interfering compounds. The values are tabulated as $\log K^{Pot.}_{I,j}$. The electrode showed a high interference from benzalkonium chloride; a preservative cationic surfactant commonly present in nasal and eye drops. Nevertheless, this interference can be eliminated by precipitation of benzalkonium chloride using a proper amount of KI [2].

3.6. Validation parameters

The proposed method was validated according to the International Conference on Harmonization (ICH) guidelines and the IUPAC recommendation [20,22].

3.6.1. Linearity and range

Linear relationship between the potential and the drug concentration was found to be in the concentration range from 1×10^{-5}-1×10^{-2} M for both CPE3 and SPE2 electrodes. The regression parameters were computed and presented in Table 4. Statistical analysis of the data gave high values of correlation coefficient (R^2) and small values of standard deviation (SD) and relative standard deviation (RSD) which figures out the low scattering of the points around the calibration graph and proved linearity of the method over the specified concentration range.

3.6.2 Detection limit

The limits of detection (LOD) for the CPE and SPE electrodes were calculated according to the IUPAC recommendation [20]. The LOD is the concentration at the intersection of the two segments of the calibration plot (Figure 6). The LOD was found to be 2.8×10^{-6} and 5.0×10^{-6} M for CPE3 and SPE2, respectively. The calculated values are presented in Table 4.

Table 4. Response characteristics of CPE3 and SPE2.

Parameters	**CPE 3**	**SPE2**
Slope (mV/decade)	59.5	59.9
Intercept	391.0	353.2
Correlation coefficient (R^2)	0.9996	0.9999
Linearity range (mol/L)	1×10^{-5} - 1×10^{-2}	1×10^{-5}- 1×10^{-2}
Detection limit (mol/L)	2.8×10^{-6}	5.0×10^{-6}
Quantitation limit (mol/L)	1×10^{-5}	1×10^{-5}
%Mean recovery (±SD)	100.38±0.9	99.12±1.0
Relative standard deviation (%RSD)	0.911	1.017

Table 5. Acurracy and precision for determination of oxymetazoline HCl in the drug substance and oxymet nasal drops.

Sensor	**Taken mg/50 mL**	**Conc. found** [a]	**Recovery** [a]
Drug substance			
CPE	2.97	2.96	99.66
	5.94	6.12	103.03
	8.90	8.74	98.16
		Average	100.33
		%RSD	2.48
SPE	2.97	2.93	98.8
	5.94	5.92	99.75
	8.90	8.68	97.53
		Average	98.69
		%RSD	1.12
Oxymet nasal drops			
CPE	1.5	1.503	100.2
	2.0	1.945	97.23
	2.5	2.412	96.5
		Average	97.97
		%RSD	2.00
SPE	1.5	1.533	102.2
	2.0	2.088	104.4
	2.5	2.64	105.6
		Average	104.06
		%RSD	1.65

[a] Average of three determination.

[b] Average of nine determinations; three determinations at each concentration level.

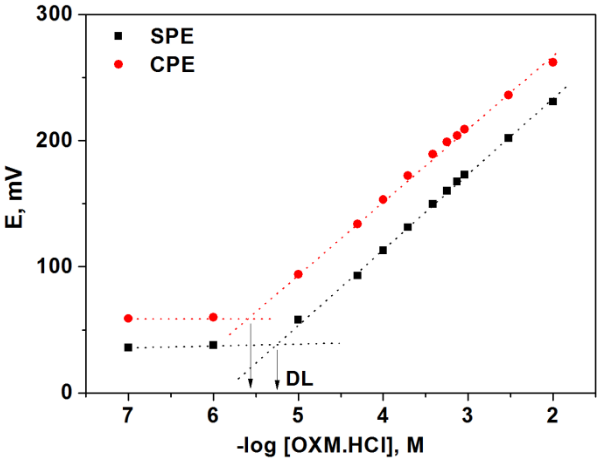


Figure 6. Determination of the detection limit of SPE2 and CPE3 electrodes. The intersection of the two segments of the calibration graph shows the detection limit of the electrode [20].

3.6.3. Accuracy and precession

The proposed electrodes were successfully applied for the assay of OXM in pure substance using the potentiometric titration method. Potentiometric titration curves together with the first derivative curves are shown in Figure 7. The average recovery was between 98.0 and 102.0% with %RSD <2.5% for the drug substance. However, direct potentiometric titration for the finished product turned out to be difficult due to potential interference of benzalkonium chloride. Most of precipitating agents including Na-TPB and PMA react with both the active ingredient and benzalkonium chloride. Yet, treatment of the sample with KI and using PMA as a titrant enabled successful determination of OXM in presence of benzalkonium chloride. The average recovery was not less than 90.0% and not higher than 110.0% using the proposed SP and CP electrodes. The %RSD was <2.5%. This wide range is acceptable for the finished product.

The accuracy and precision results are presented in Table 5. The obtained results were compared statistically by a Student's t-test and F-ratio with the official method [1] at the 95 % confidence level with five degrees of freedom. The results in Table 6 showed that there was no significant difference between the proposed and official method.

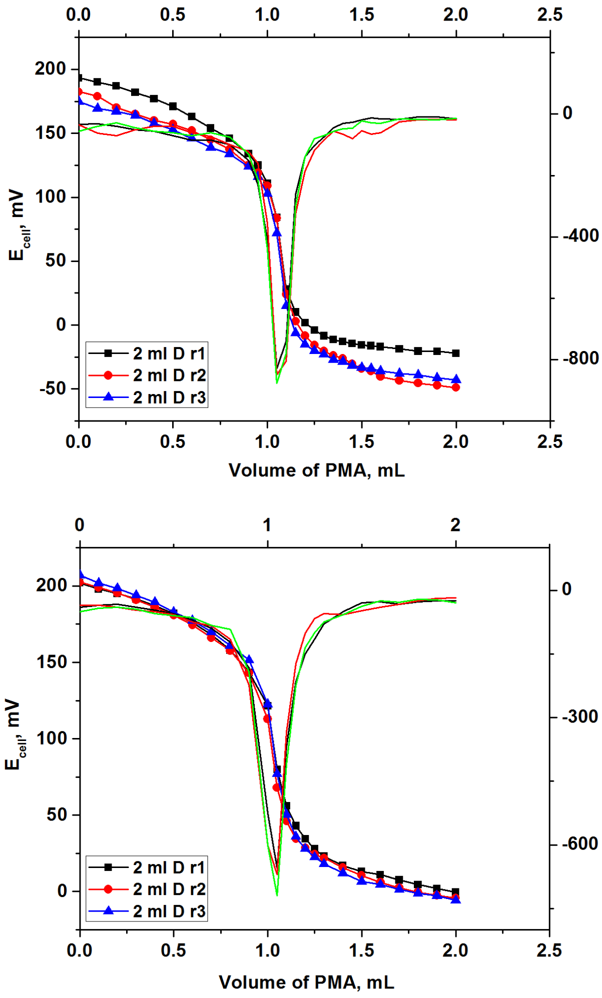
Table 6. Statistical comparison between the results of an analysis of OXM in drug substance and pharmaceutical preparation of Oxymet Nasal Drops (0.05%) applying the proposed and official methods:

Item	Proposed CPE method		Proposed SPE method		Official method
	Drug substance	Oxymet nasal drops	Drug substance	Oxymet nasal drops	
Mean recovery, % [a]	100.38	99.59	99.12	101.28	100.25
SD	0.914	0.634	1.008	0.936	0.791
RSD	0.911	0.636	1.017	0.924	0.789
T-test [b]	0.229	1.468	1.988	1.874	
F-test [c]	1.335	1.557	1.622	1.399	

[a] Average of five determinations for the proposed and official methods, SD: Standard deviation, SD: Relative standard deviation.

[b] Tabulated t values at 95% confidence level is 2.306 (n = 5).

[c] Tabulated F values at 95% confidence level is 6.39 (n = 5).



(a)

(b)

Figure 7. Potentiometric titration and first derivative curves for 50 mL of 2×10^{-4} M OXM-HCl solution using and SPE2 (**a**) and CPE3 (**b**). Phosphomolybdic acid 0.01 M was used as a titrant. The symbol (D) refers to drug substance and (r) refers to first derivative. Overload curves: The experiment is repeated three times for the same concentration.

4. Conclusion

A simple, inexpensive and reproducible home-made screen printed ion selective electrode is described for the assay of oxymetazoline HCl. Oxymetazoline-tetraphenyl borate ion associate and dibutylphthalate exhibited the best sensitivity among the tested ion associates and plasticizers. The electrode exhibited a Nernstian slope of 59.5 mV/decade over a wide concentration range from 1×10^{-5} to 1×10^{-2} M (r = 0.9999). The electrode is useful over a wide pH range from 4 to 8. Similar potentiometric response was obtained with a carbon paste electrode comprising oxymetazoline-tetraphenyl borate ion associate and dibutylphthalate as plasticizer. Treatment of the finished product with KI was necessary to avoid interference from benzalkonium chloride. The electrodes were used for the assay of Oxymetazoline HCl in the drug substance and in the finished product with high accuracy (±2%) and precision (%RSD <2.5). The proposed method does not need expensive solvents or tedious calculations as for chromatographic and spectrophotometric methods.

Disclosure statement DS

Conflict of interests: The authors declare that they have no conflict of interest.

Author contributions: Corresponding author contributed mainly to this work.

Ethical approval: All ethical guidelines have been adhered.

Sample availability: Samples of the compounds are available from the author.

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