

Potentiometric Determination of Oxymetazoline Hydrochloride Using Modified Carbon Paste Electrodes

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Received 20/12/2018; accepted 02/03/2021

<https://doi.org/10.4152/pea.2021390505>

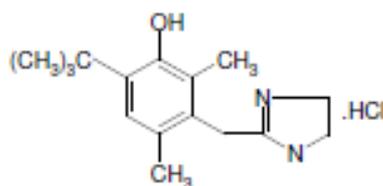
Abstract

Two carbon paste electrodes for oxymetazoline hydrochloride were constructed based on ion pair complexes of this drug, with sodium tetrphenylborate (NaTPB) or ammonium reineckate, using dibutyl phthalate and dioctyl phthalate as solvent mediators, respectively. The developed electrodes displayed a fast, stable response over the concentration range from 3.98×10^{-5} to 1×10^{-2} M oxymetazoline hydrochloride, with a near-nernstian slope of 59.0, 58.2 mV of concentration decade⁻¹ and a limit of detection (LOD) of 3.31×10^{-5} and 3.72×10^{-5} M, in the oxymetazoline-tetrphenylborate and oxymetazoline-reineckate cases, respectively. The developed electrodes have been successfully applied for oxymetazoline hydrochloride determination in the Afrin nasal drop pharmaceutical formulation.

Keywords: Oxymetazoline hydrochloride; modified carbon paste electrode; potentiometry; and pharmaceutical formulation.

Introduction

Oxymetazoline hydrochloride (OMCl), phenol, 3-[4,5-dihydro-1H-imidazol-2-yl)methyl]-6-(1,1-dimethylethyl)-2,4-dimethylmonohydrochloride [2315-02-8] (Scheme 1) is an adrenergic (nasal) drug [1].



Scheme 1. Structural formula of oxymetazoline hydrochloride.

A review of the literature revealed that several methods have been used for oxymetazoline hydrochloride determination. These include high performance liquid

chromatography (HPLC) [2-13], gas chromatography [14], a two phase titration method [15], flow injection chemiluminometry [16,17], spectrophotometry [18-33] and spectrofluorimetry [34]. A plastic PVC membrane ion selective electrode method, based on oxymetazoline-phosphotungstate, has been reported [35]. Carbon paste electrodes (CPEs) have attracted attention as ion selective electrodes, mainly due to their advantages over membrane electrodes, such as renewability, stable response, low ohmic resistance and no need of an internal solution [36]. The aim of this work is to describe the construction and performance characteristics of oxymetazoline modified carbon paste electrodes based on oxymetazoline-tetraphenylborate and oxymetazoline-reineckate as electroactive materials, using dibutyl phthalate and dioctyl phthalate as solvent mediators, respectively. The developed carbon paste selective electrodes were used for OMCl determination in Afrin nasal drops pharmaceutical preparation (0.05%).

Experimental

Reagents and materials

All chemicals were of analytical grade. Double distilled water was used throughout all experiments. Pure grade oxymetazoline hydrochloride and the Afrin nasal drops (0.05%) pharmaceutical preparation were provided by Medical Union Pharmaceuticals Co., Abou Sultan, Egypt. Sodium tetraphenylborate (NaTPB), ammonium reineckate, dioctyl sebacate (DOS) and tricresyl phosphate (TCP) were obtained from Fluka. Dibutyl phthalate (DBP) and dioctyl phthalate (DOP) were obtained from Merck. Graphite powder (1-2 micron) was obtained from Aldrich Co.

Apparatus

Potentiometric and pH measurements were carried out using a Seibold G-103 digital pH/mV meter (Vienna, Austria). A C-100 Techne circulator thermostat model was used to control the test solutions temperature. A saturated calomel electrode (SCE) was used as the reference electrode. The electrode electrochemical system may be represented as follows: OM-carbon paste electrode / test solution // KCl salt bridge // saturated calomel electrode.

Ion pair preparation

The ion pairs, OM-TPB and OM-reineckate, were prepared by mixing a 100 mL of a 10^{-2} M OMCl solution with 100 mL of 10^{-2} M of sodium tetraphenyl borate or ammonium reineckate. The formed precipitates were filtered, washed thoroughly with bidistilled water and dried at room temperature. The composition of the ion pair was found to be 1:1, both for OM-TPB and OM-reineckate, as confirmed by elemental analysis data done at Microanalytical Center, Faculty of Science, Cairo University. The found percentage values were 82.54, 7.40 and 4.73, and the calculated values were 82.89, 7.65 and 4.83, for C, H and N, respectively, in the OM-TPB case, while in the OM-reineckate case, the found percentage values were 40.56, 4.93 and 18.62, and the calculated were 40.25, 5.40 and 18.77, for C, H and N, respectively.

Electrode assembly

Carbon paste was prepared by mixing the required amount of the ion pair with graphite powder (Aldrich, 1-2 micron) and dibutyl phthalate (DBP) or dioctyl phthalate (DOP) with a pasting liquid (the ratio of graphite powder to pasting liquid was 1:1) in a mortar, until it was uniformly wetted. The carbon paste electrode was prepared by successive packing of the carbon paste into the tip end of a home-made Teflon holder (2 mm), and electrical contact was achieved by a stainless steel rod (2 mm) connecting the paste to the mV meter.

Electrodes selectivity

The electrodes selectivity coefficients towards different J^{z+} cationic species were determined by a separate solution method [37], in which the Nicolsky Eisenman equation was used:

$$\log K_{OM, J^{z+}}^{\text{pot}} = \frac{(E_2 - E_1)}{S} + \log[OM] - \log[J^{z+}]^{\frac{1}{z}}$$

where E_1 and E_2 are the electrode potentials in 1×10^{-3} mol L⁻¹ OMCl and J^{z+} interfering ions, respectively, and S is the slope in mV. In case of ions without charges, the selectivity coefficients were determined by the matched potential method (MPM) [38]. In this method, a known activity of the oxymetazoline ion solution was added into a reference solution containing a fixed activity of oxymetazoline ion, α_{OM} ($\alpha'_{OM} - \alpha_{OM}$ is the change in activity), and the corresponding potential change (ΔE) was recorded. Then, a solution of the interfering ion was added to the reference solution, until the same potential change (ΔE) was reached. The change in potential produced at the constant background of the primary ion must be the same in both cases:

$$K_{OM, J}^{\text{pot}} = \frac{\alpha'_{OM} - \alpha_{OM}}{\alpha_J}$$

where α_J is the added interferent activity.

OMCl potentiometric determination

OMCl has been potentiometrically determined using the investigated electrodes by the standard addition method [39] and by potentiometric titration with a standard solution of NaTPB.

OMCl determination in Afrin nasal drops (0.05%)

The request amount of nasal drop solution (0.05%) was transferred to a separating funnel, 25 mL of a saturated solution of sodium borate were added and extracted with four 25 mL portions of chloroform, and then the extracts were combined in a second separating funnel. The combined chloroform extracts were extracted with two 20 mL portions of dilute hydrochloric acid (20 fold dilution), the acid extracts were combined in a 50 mL volumetric flask, and dilute hydrochloric acid was added to the mark and mixed. The contents of the measuring flask were transferred to a 100 mL beaker, and subjected to OMCl potentiometric determination, by

using the standard addition method, as previously described in the pure drug solution case.

Results and discussion

Carbon paste electrodes composition

Four compositions containing the OM-TPB or OM- reineckate ion pairs, in the ratio of 5, 10, 12 and 15%, were prepared; the ratio of graphite to liquid mediators (DBP) was 1:1, after the electrodes soaking for 30 min in a 10^{-3} M OMCl solution (Table 1). Results indicated that the carbon paste electrode with an ion pair ratio of 10% exhibited the best performance characteristic, with slopes of 59.00 and 53.20 mV of concentration decade, at 25°C, for OM-TPB and OM-reineckate, respectively. The performance characteristics of the selective electrodes were primarily affected by the plasticizers, due to their effect on migration, ion pair formation and diffusion coefficient [40]. The plasticizers effect type on the OM electrodes performance characteristic was investigated by using four plasticizers with different polarities (DBP, DOP, DOS, and TCP), as shown in Table 2. The results indicate that DBP and DOP are the best solvent mediators for OM-TPB and OM-reineckate electrodes, respectively. Poor sensitivities for the electrodes using other plasticizers as liquid mediators are due to low distributions of the OM-TPB or OM- reineckate electroactive complexes in these solvents [41].

Table 1. Composition of oxymetazoline carbon paste electrodes and the slope of their calibration graphs, at $25 \pm 1^\circ\text{C}$, and 30 min soaking in 1×10^{-3} M OMCl solution.

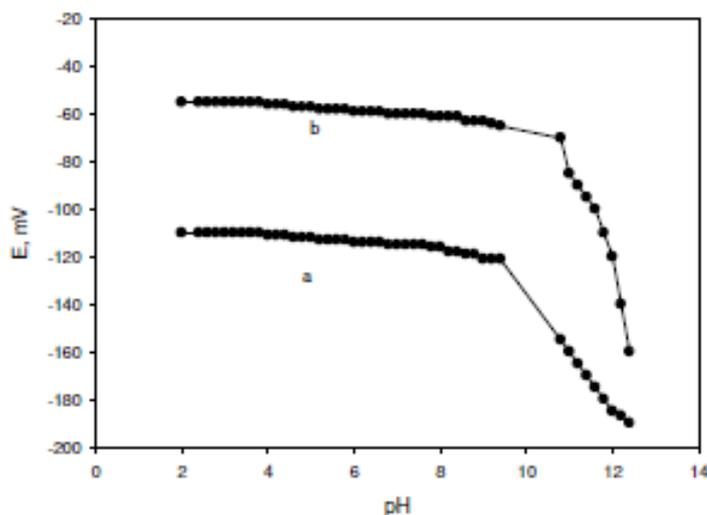
Electrode	Composition (% w/w)			Slope (mV decade ⁻¹)	RSD
	Ion pair	graphite	solvent mediator		
<u>OM-TPB electrode</u>					
I	5.0	47.5	47.5	57.0	0.46
II	10.0	45.0	45.0	59.0	0.53
III	12.0	44.0	44.0	52.0	0.30
IV	15.0	42.5	42.5	40.0	2.50
<u>OM- reineckate electrode</u>					
I	5.0	47.5	47.5	45.7	0.37
II	10.0	45.0	45.0	53.2	0.42
III	12.0	44.0	44.0	46.3	1.07
IV	15.0	42.5	42.5	30.0	0.78

Effect of pH

The effect of the solution pH on the electrode response was checked for two OMCl concentrations (1×10^{-4} and 1×10^{-3} M), by following the variation in potential with change in pH, by the addition of very small volumes of hydrochloric acid and sodium hydroxide (0.1-1.0 M). The results indicate that the investigated electrodes showed no pH response over the pH range from 2.0 to 9.4, for the two proposed electrodes. Fig. 1 represents potential versus pH profiles for OM-TPB electrode. The decrease in potential occurring at higher pH values is most probably attributed to the free oxymetazoline base formation in the solution, leading to a decrease in the oxymetazoline cation concentration ($\text{pK}_a = 10.6$ [43]).

Table 2. Effect of solvent mediator on 10% OM-TPB and 10% OM-reineckate electrodes, and the slopes of their calibration graphs, at 25 °C, and 30 min soaking in a 10^{-3} M OMCl solution.

Solvent mediators	Slope (mV decade ⁻¹)	Concentration range (M)	LOD ⁴² (M)
<u>OM-TPB electrodes</u>			
DBP	59.00	$3.98 \times 10^{-5} - 1 \times 10^{-2}$	3.31×10^{-5}
DOP	43.00	$3.98 \times 10^{-5} - 1 \times 10^{-2}$	1.00×10^{-6}
DOS	36.30	$3.98 \times 10^{-5} - 1 \times 10^{-2}$	7.94×10^{-5}
TCP	50.30	$3.98 \times 10^{-5} - 1 \times 10^{-2}$	3.31×10^{-5}
<u>OM-reineckate electrodes</u>			
DBP	53.20	$3.98 \times 10^{-5} - 1 \times 10^{-2}$	3.16×10^{-5}
DOP	58.23	$3.98 \times 10^{-5} - 1 \times 10^{-2}$	3.72×10^{-5}
DOS	55.13	$3.98 \times 10^{-5} - 1 \times 10^{-2}$	3.55×10^{-5}
TCP	22.26	$3.98 \times 10^{-5} - 1 \times 10^{-2}$	3.63×10^{-5}

**Figure 1.** pH effect of the test solution on the OM-TPB electrode potential response: (a) 1×10^{-4} M and (b) 1×10^{-3} M OMCl solutions.

Electrode life span

The life span of the proposed electrodes was investigated by periodically performing the calibration graphs, and calculating the response slope after the electrode was left in air without soaking in the drug; the electrode was preconditioned by soaking in 1×10^{-3} M OMCl, for 30 min, before use. The results indicate that, in the OM-TPB electrode case, the calibration graph slope remained constant, near $59.0 \text{ mV decade}^{-1}$, for 1 day; then, it slightly decreased, reaching about 56.0 , 55.0 , 53.0 , 52.0 , 51.0 and $50.0 \text{ mV decade}^{-1}$, after 8, 21, 30, 45, 60 and 90 days, respectively. In the OM-reineckate electrode case, the calibration graph slope remained constant near $58.0 \text{ mV decade}^{-1}$, for 1 day; then, it slightly decreased, reaching about 52.0 and $50.0 \text{ mV decade}^{-1}$, after 8 and 15 days, respectively. The response time of the proposed OM carbon paste electrodes was found to be < 10 seconds.

Effect of test solution temperature

To study the investigated electrodes thermal stability, calibration graphs were constructed at different test solution temperatures, and the isothermal coefficients (dE/dt) of these electrodes were calculated [44] to be 0.0010 and 0.0020 V/ °C, for OM-TPB and OM-reineckate electrodes, respectively.

Selectivity

The influences of some inorganic cations, sugars, amino acids and vitamins, on the OM electrodes response, were investigated according to IUPAC recommendations, using the separate solution method (SSM) [37] or matched potential method [38]. The selectivity coefficients values, $-\log K_{OM,J^{z+}}^{pot}$, presented in Table 3, indicate that the proposed carbon paste electrodes are highly selective towards the oxymetazoline cation. The inorganic cations do not interfere, because of the difference in their mobility and permeability, as compared to the oxymetazoline cation. In the sugars and amino acids case, the high selectivity is related to the difference in polarity and lipophilic nature of their molecules relative to the oxymetazoline cation.

Table 3. Selectivity coefficients, $-\log K_{OM,J^{z+}}^{pot}$, for the OM electrodes.

Interferent	OM-TPB		OM-reineckate	
	SSM	MPM	SSM	MPM
Na ⁺	2.21	-	1.66	-
K ⁺	2.28	-	2.16	-
Ca ²⁺	3.78	-	3.09	-
Mg ²⁺	2.41	-	3.07	-
Zn ²⁺	3.78	-	3.05	-
Co ²⁺	3.73	-	2.99	-
NH ₄ ⁺	2.26	-	1.59	-
VitaminB ₁	2.12	-	1.47	-
VitaminB ₆	2.17	-	1.52	-
Glucose	-	2.33	-	2.33
Fructose	-	2.42	-	2.36
Lactose	-	2.33	-	2.33
Maltose	-	2.42	-	2.44
Glycine	-	2.17	-	2.15
Alanine	-	2.19	-	2.13
Urea	-	2.19	-	1.97

Analytical applications

The usefulness of the investigated electrodes was examined by using them for the OMCl potentiometric determination in pure solutions and in the Afrin nasal drops pharmaceutical preparation (0.05%). Standard addition and potentiometric titration methods were used in the pure solutions case. In the Afrin nasal drops pharmaceutical preparation case (0.05%), the standard addition method was used. The potentiometric titration method could not be used, because it had a lower OMCl concentration (0.5 mg / mL of the drops), and the potentiometric titration method needs a higher drug concentration. Fig. 2A and Fig. 2B represent the potentiometric titration methods using the OM-TPB electrode and OM-reineckate electrode, respectively.

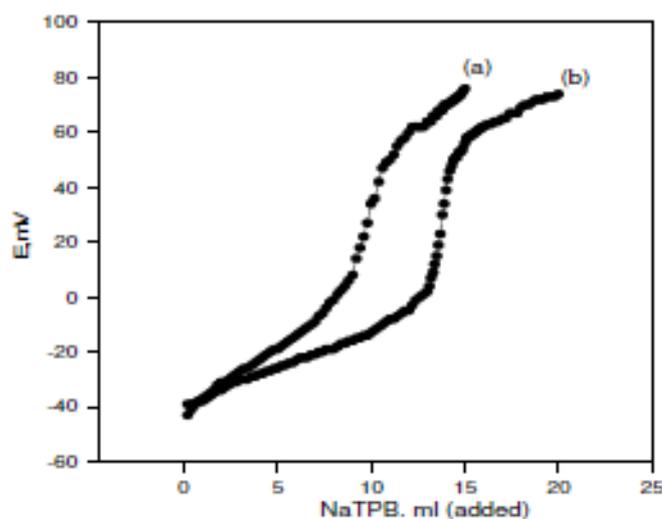


Figure 2A. Potentiometric titrations of (a) 10 and (b) 15 mL of the 10⁻²M OMCl drug in a 10⁻² M NaTPB solution using OM-TPB electrode.

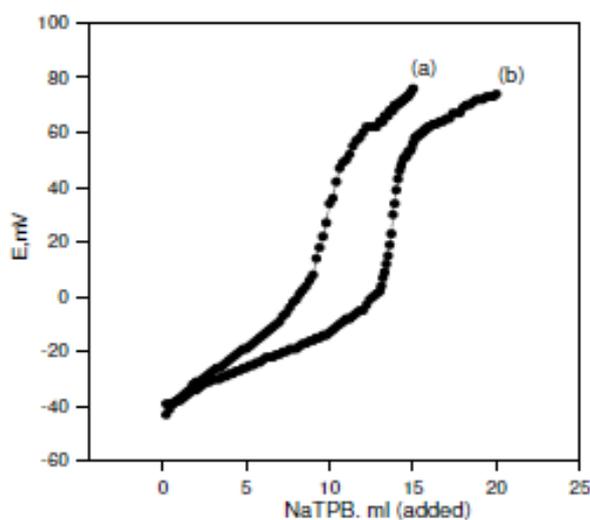


Figure 2B. Potentiometric titrations of (a) 10 and (b) 15 mL of the 10⁻²M OMCl drug in a 10⁻² M NaTPB solution using an OM-reineckate electrode.

The mean recovery and relative standard deviation values are briefed in Table 4. The results were in good agreement with the label claims and with the values obtained using the official United States Pharmacopeia¹ (Table 5). Statistical comparison of the accuracy and precision of the proposed methods with the official method was performed using Student's t- and F-ratio tests, at a 95% confidence level [45].

Table 4. OMCl determination by applying OM-TPB and OM-reineckate responsive electrodes.

Sample	Standard addition method			Potentiometric titration method		
	Taken (mg)	Mean recovery (%)	RSD (%)	Taken (mg)	Mean recovery (%)	RSD (%)
OM-TPB						
Pure solution	1.84	99.11	0.70	22.9	99.40	0.45
	2.30	98.40	0.62	34.5	98.40	0.55
	4.60	99.00	1.40			
	11.50	98.90	0.88			
Afrin nasal drops (0.05%)	0.50	97.70	0.93			
	1.00	98.20	0.25			
	1.50	99.11	0.12			
	2.00	98.50	0.24			
OM-reineckate						
Pure solution	1.84	97.70	1.11	22.9	99.60	0.50
	2.30	98.50	1.22	34.5	98.30	0.32
	4.60	98.30	1.49			
	11.50	97.90	1.22			
Afrin nasal drops (0.05%)	0.50	98.11	0.79			
	1.00	98.40	0.15			
	1.50	99.40	0.45			
	2.00	99.30	0.36			

Relative standard deviation (four determinations).

Table 5. Statistical comparison between the results of the analysis of an Afrin nasal drop pharmaceutical preparation (0.05%), applying the proposed standard addition method and the official method, using carbon paste electrode.

Parameter	Standard addition method	Official method [1]
OM-TPB electrode		
Mean Recovery %	98.37	99.22
SD	0.378	0.598
RSD	0.385	0.603
F-ratio		2.45 (9.28) ^a
t-test		2.37 (2.447) ^b
OM-reineckate electrode		
Mean Recovery %	98.80	99.43
SD	0.42	0.598
RSD	0.43	0.602
F-ratio		1.96 (9.28) ^a
t-test		1.70 (2.447) ^b

SD: Standard deviation; RSD: Relative standard deviation; ^a Tabulated F-ratio value at 95% confidence level; ^b Tabulated t-value at 95% confidence level and six degrees of freedom.

Conclusions

The proposed oxymetazoline modified carbon paste electrodes based on OM-TPB and OM-Rein ion pairs, as electroactive materials, are useful sensors for this drug determination in its pharmaceutical formulation, Afrin nasal drops (0.05%). These sensors have advantages of high selectivity, low cost and fast response and wide applicable range.

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