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Preparation and Characterization of a Codeine Responsive Electrode

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Summary. The behaviour of codeine reineckate and codeine tetraphenylborate membrane electrodes has been observed with a respective *Nernst*ian response of 58 and 56 mV/decade for 9.3×10^{-5}–1.3×10^{-3} *M* codeine sulfate solutions. The working *pH* ranges were 5–8 and 4–8, respectively. The selectivity towards sugars, amines, amino acids, cations, and some pharmaceutical compounds was found to be satisfactory. The isothermal temperature coefficient was 0.0014 V/°C. The electrodes were applied successfully for the determination of codeine in some pharmaceutical dosage forms with a relative standard deviation range of 0.16–0.30% and an average recovery of 98.6 ± 0.6%.

Keywords. Codeine electrode; Codeine reineckate; Plastic codeine membrane.

Herstellung und Charakterisierung einer codeinselektiven Elektrode

Zusammenfassung. Das Verhalten von Codeinreineckat- und Codeintetraphenylboratmembranelektroden in 9.3×10^{-5}–1.3×10^{-3} *M* Codeinsulfatlösungen wurde untersucht (*Nernst*scher Response: 58 bzw. 56 mV/Dekade). Der verwendete *pH*-Bereich für die beiden Elektroden war 5–8 bzw. 4–8. Ihre Selektivität gegenüber Zuckern, Aminen, Aminosäuren, Kationen und einigen pharmazeutisch aktiven Verbindungen ist zufriedenstellend. Der isotherme Temperaturkoeffizient beträgt 0.0014V/°C. Die Elektroden wurden erfolgreich zur Bestimmung von Codein in einigen pharmazeutischen Präparaten eingesetzt (relative Standardabweichung: 0.16–0.30%).

Introduction

Codeine sulfate (morphinan-6-ol, 7,8-dihydro-4,5-epoxy-3-methoxy-17-methyl-, (5α,6α)-sulfate 2:1 salt) trihydrate [1] has moderate analgesic and weak cough suppressant effects. It is also used to check diarrhoea. It is less depressant to the respiratory centre and causes much less nausea and vomiting than morphine.

Different methods were applied for the determination of free codeine in biological fluids or in different pharmaceutical preparations. Many chromatographic techniques have been widely used for codeine analysis like HPLC [2], GC [3], and TLC [4]. Spectroscopic methods are very important for codeine determination, including spectropolarimetry [5], spectrophotometry [6], colorimetry [7], and absorptimetry [8]. *Radecki* and *Wesolowski* have applied thermogravimetry and differential thermal analysis for codeine determination [9]. Several titrimetric

methods using perchloric acid [10, 11], toluene-4-sulfonic acid [12], or sodium tetraphenyl borate [13] as titrants have been applied. Complexometric methods have also been used [14]. Codeine has been extracted as a pictrate ion-pair [15] or by electrodialytic extraction [16]. Tetraphenyl borate [17] or arenesulfonic acids [18] are good reagents for the gravimetric determination of codeine. Voltammetric analysis of codeine has been performed using a modified electrode based on carbon and a polymer [19]. Potentiometric titrations in non-aqueous media can also be utilized for codeine analysis [20–22].

Biosensors for the determination of drugs including codeine have been reviewed and discussed by *Guilbault* and *Schmid* [23]. A liquid membrane selective electrode for codeine based on a codeine dipicrylamine complex in nitrobenzene has been reported [24, 25]. It had a working concentration range of 1 μ*M* to 0.1 *M* of codeine. Its response time varied largely with the drug concentration. Direct potentiometry for the determination of some amine drugs including codeine has been applied using a PVC membrane containing dibutyl phthalate as plasticizer [26].

In the present work, a codeine electrode with a short and constant response time independent of the drug concentration is presented. The introduced electrode is of a plastic nature; it can easily be prepared and used in comparison to previously reported liquid membranes [24, 25]. The electrode measures the concentration of codeine down to 9.3×10^{-5} *M*. Its application for the direct potentiometric determination of codeine in some pharmaceutical dosage forms is demonstrated.

Results and Discussion

Membrane composition and behaviour

A stable and reproducible *Nernst*ian behaviour of the electrode has been observed; this may be explained by the ionic nature of the codeine sulfate molecule used for the ion pair preparation by precipitation with ammonium reineckate:

$$[(C_{18}H_{21}NO_3)H_2]^{2+}SO_4^{2-} + 2NH_4^+[Cr(NH_3)_2(SCN)_4]^-$$
$$\rightarrow [(C_{18}H_{21}NO_3)_2H_2]^{2+}[Cr(NH_3)_2(SCN)_4]_2^{2-} + (NH_4)_2SO_4$$

The electrochemical cell can be represented as Ag–AgCl/inner filling solution/membrane//test solution//double junction reference electrode. The effects of ion pair (IP) and dioctylphthalate (*DOP*) concentration were studied. Table 1 shows the changes occurring by using different percentages of IP (2, 5, 10, and 15%). The values of the *Nernst*ian slope and the usable linear part increase with the amount of IP. The percentage of *DOP* also influences the electrode behaviour: different slope values (12, 60, and 56 mV/decade for 30%, 45%, and 60% *DOP*, respectively) are obtained. In case of using codeine-*TPB*, a similar *Nernstian* behaviour was obtained (Table 2). *DOPP* was tried as a solvent for the membrane preparation when codeine reineckate was used as an ion pair.

Interferent effects and selectivity coefficients

The selectivity of an ion pair complex depends on the ion exchange process at the membrane–test solution interface. The selectivity coefficients $K^{\mathrm{Pot}}_{Cod\mathrm{H}^+,J^{z+}}$ of both

Table 1. Effect of membrane composition on codeine responsive electrode

Membrane composition			Linear part (M)	Slope (mV/decade)
IP (%)	*PVC* (%)	*DOP* (%)		
2	49	49	9.6×10^{-5}–1.3×10^{-3}	58
5	47.5	47.5	1.1×10^{-5}–1.3×10^{-3}	58
10	45	45	9.6×10^{-5}–1.3×10^{-3}	60
15	42.5	42.5	3.4×10^{-5}–1.3×10^{-3}	70
10	60	30	9.6×10^{-5}–4.3×10^{-4}	12
10	30	60	4.9×10^{-5}–1.3×10^{-3}	56

Table 2. Response characteristics of codeine electrodes (according to IUPAC recommendations)

Parameter	Codeine-*TPB* *DOP*	Codeine reineckate	
		DOP	*DOPP*
Slope (mV/log$C$)	56	58	66
Intercept (mV)	$+96 \pm 0.5$	54 ± 0.4	33 ± 0.5
Lower limit of detection (M)	4.0×10^{-5}	7.6×10^{-5}	2.0×10^{-4}
Response time (sec) in 10^{-3} M solution	5	8	4
Working acidity range (pH)	4–8	5–8	5–8

electrode versions (*TPB* and reineckate) towards different substances have been calculated (Table 3). From the obtained results we conclude that most of the common cations, amines, amino acids, and sugars do not affect the electrode behaviour; only ephedrine and phenylephrine greatly interfere. Ephedrine can form an insoluble reineckate salt, whereas the phenylephrine interference may be attributed to the presence of the amine and the hydroxyle groups competing with the same groups in the codeine molecule. Thus, any measurements should be performed in their abscence. From the results we report that the codeine reineckate membrane electrode has better selective properties than the codeine *TPB* type.

Electrode aging

The electrode has a long working period extending up to 75 days and is ready for measurements after a short preconditioning period (1 h, *Nernst*ian slope: 60 mV/decade). Small changes were observed up to a soaking time of 12 h, the slope varying between 56 and 60 mV/decade. The electrode response deviates very little from the *Nernstian* value for soaking periods from 16 h to 75 days (slope range: 54–50 mV/decade). For soaking periods of 75 days and longer, a deviation from the *Nernst*ian slope was observed (44 mV/decade). These changes may be explained by the leaching of the ion pair component from the membrane surface. The sensitivity of

Table 3. Selectivity coefficient values for codeine selective electrode

Interferent	$K^{Pot}_{Cod_2H_2^{2+},J^{z+}}$		Interferent	$K^{Pot}_{Cod_2H_2^{2+},J^{z+}}$	
	Cod.-*TPB*	Cod. reineckate		Cod.-*TPB*	Cod. reineckat
NaCl	2.9×10^{-2}	1.2×10^{-2}	Ephedrine HCl	1.6	1.7
KNO_3	3.0×10^{-2}	1.4×10^{-2}	Phenylephrine HCl	9.2×10^{-2}	1.9
$MgCl_2$	7.5×10^{-4}	8.9×10^{-4}	Glycine	1.7×10^{-2}	1.2×10^{-2}
$Cu(NO_3)_2$	1.3×10^{-3}	1.0×10^{-3}	Lysine	2.4×10^{-2}	3.0×10^{-2}
$NiCl_2$	3.4×10^{-3}	8.9×10^{-4}	Arginin	7.3×10^{-3}	4.2×10^{-4}
$CaCl_2$	8.9×10^{-4}	1.3×10^{-3}	Tryptophan	1.1×10^{-1}	1.6×10^{-2}
$BaCl_2$	8.9×10^{-4}	1.8×10^{-3}	Cystine	7.9×10^{-2}	7.9×10^{-2}
$ZnCl_2$	8.1×10^{-4}	2.3×10^{-3}	Sucrose	4.2×10^{-2}	8.5×10^{-3}
NH_4Cl	1.9×10^{-2}	1.1×10^{-2}	Dextrose	1.5×10^{-2}	3.3×10^{-2}
Pyridoxine HCl	20.4	1.5×10^{-1}	Maltose	1.4	3.9×10^{-2}
Thiamphenicol glycinate	7.9×10^{-2}	7.3×10^{-1}			

the electrode towards codeine did not change largely during the different soaking periods extending from 0.5 h to 75 days. The lower concentration limit of the calibration graph varied between 9.3×10^{-5} and 1.5×10^{-4} *M* of codeine sulfate for 0.5 to 32 h preconditioning periods. For soaking intervals above 7 days, an increase in the sensitivity of the electrode was observed, the lower limit of the calibration curve being now 7.3×10^{-5} *M* codeine sulfate.

The response times of different electrode compositions (2, 5, 10, and 15% IP) were tested at different codeine concentrations (1.0×10^{-3} and 4.0×10^{-4} *M*) and calculated according to *Fleet* and coworkers [27] who defined the response time as the interval within which the electrode potential reaches 95% of the steady state value. The response time of the electrode is below 10 seconds which allows the direct reading of the electrode potential. It is also shown that the response time decreases with increasing ion pair percentage due to the enhancement of the ion exchange process.

pH Effect

The effect of different *pH* values on the electrode potential was studied for 1.3×10^{-3} and 4.0×10^{-4} *M* $cod_2 \cdot H_2SO_4$. Stable potential values were observed for the *pH* ranges of 5–8 and 4–8 for codeine reineckate and codeine-*TPB* membranes, respectively. Below *pH* 5 or 4, potential deviations were observed due to H^+ interference. Above *pH* 8, a decrease in potential occurs due to the liberation of free codeine base. H^+ and OH^- ions may attack the membrane when the *pH* of the codeine solution is out of the optimum range of both electrode types. H^+ ions may dissolve the IP at the membrane surface below *pH* 5, whereas the sorption of OH^- ions on the membrane surface interferes with the ion exchange process above *pH* 8.

Table 4. Effect of temperature on the codeine responsive electrode

Temperature (°C)	mV/decade		Usable concentration range (M)	E^0 (mV)
	*Nernst*ian	Electrode		
25	59.2	60	9.3×10^{-5}–1.3×10^{-3}	+243
35	61.1	60	9.3×10^{-5}–1.3×10^{-3}	+227
45	63.0	60	7.4×10^{-5}–1.3×10^{-3}	+237
55	65.0	60	3.4×10^{-5}–1.3×10^{-3}	+261
65	67.9	67	7.4×10^{-5}–1.3×10^{-3}	+284
75	68.9	74	7.4×10^{-5}–1.3×10^{-3}	+304
85	71.8	79	7.4×10^{-5}–1.3×10^{-3}	+313
95	71.9	77	9.3×10^{-5}–1.3×10^{-3}	+317

Effect of temperature

After soaking the electrode for 1 h, calibration graphs at different temperatures (25–95 °C) were recorded. Their slopes and their usable linear ranges are shown in Table 4. Comparing the obtained values with the theoretical *Nernst*ian slopes at different temperatures, only small changes were observed at 75–95 °C. Thus, we can state that the electrode can be used for measurements at temperatures up to 65 °C. This advantage was not available for other codeine selective electrodes [23–25].

The linear part of the calibration graphs did not vary largely with temperature. A maximum sensitivity was observed at 55 °C (3.4×10^{-5}–1.3×10^{-3} M); at 25, 75, and 95 °C, the ranges of linearity are 9.3×10^{-5}–1.3×10^{-3} M, 7.4×10^{-5}–1.3×10^{-3} M and 9.3×10^{-5}–1.3×10^{-3} M, respectively. At 45, 65, and 85 °C, similar ranges of linearity were recorded (7.4×10^{-5}–1.3×10^{-3} M). The deviation of the electrode from the *Nernst*ian behaviour upon heating above 75 °C may be due to the dissociation and/or dissolution of the IP by heating.

The isothermal temperature coefficient (dE^0/dT) was calculated using the equation

$$E^0 = E^0_{25} + (dE^0/dT)(t - 25)$$

where E^0 values are the intercepts of the calibration graphs at $pE = 0$.

The value of the isothermal temperature coefficient is 0.0014 V/°C for the temperature range 25–95 °C. This means that only slight changes in the potential readings are observed over a wide temperature range.

Determination of codeine in pharmaceutical preparations

The electrode was successfully applied for the selective determination of codeine in pharmaceutical preparations (Codacetine (tablets), Vegaskine (tablets), Nova-C-retard (tablets), Bepro (syrup), and Diarrest (liquid)). The average recovery is $98.6 \pm 6\%$, and the relative standard deviation range is 0.16–0.30% (Table 5). The results agree with those obtained by the colorimetric procedure [7].

Table 5. Determination of codeine in pharmaceutical preparations by codeine selective electrode

Pharmaceutical preparation	Lable	Weight found (mg)		S (%)[b]
		Colorimetric procedure[a]	Proposed procedure	
Codacetine (tablets; Kahira Pharm. & Chem. Ind. Co., Cairo, Egypt)	Salicylamide 300 mg, paracetamol 250 mg, codeine phosphate 10 mg	9.92	9.80	0.16
Vegaskine (tablets; Alexanderia Co. for Pharm. and Chem. Ind., Alexandria, Egypt)	Acetylsalicylic acid 300 mg, paracetamol 200 mg, codeine phosphate 10 mg	10.1	9.91	0.30
Nova-C-retard (tablets; Nile Co. for Pharm. and Chem. Ind., Cairo, Egypt)	Paracetamol 450 mg, phenyl propanolamine HCl 25 mg, chlorpheniramine maleate 5 mg, caffeine anhyd. 40 mg, codeine 15 mg	14.95	14.81	0.23
Bepro (syrup; Wallace Chem., U.K.)	5 ml contains; 6.25 mg codeine sulfate, papaverine HCl 625 µg, calcium iodide 50 mg, glycerol 250 mg	6.15	6.20	0.19
Diarrest (liquid; Galen, U.K.)	5 ml contains; 5 mg codeine phosphate, 2.5 mg dicyclomine HCl, 50 mg NaCl, 40 mg KCl, 50 mg sodium citrate	4.89	4.92	0.28

[a] W. Li. and Y. Li, Yaoxue Tongbao, 16 (1981) 8; [b] 4 determinations

Experimental

Reagents and Materials

All solutions were prepared from high purity chemicals and deionized water. Codeine sulfate ($cod_2 \cdot H_2SO_4$) was provided by the local Center of Toxicology. Polyvinyl chloride (*PVC*, Fluka), ammonium reineckate (*BDH*), tetraphenylborate (*TPB*, Prolabo), dioctylphenylphosphonate (*DOPP*, Aldrich), and dioctylphthalate (*DOP*, Aldrich) were used. The ion pair (IP) was obtained by mixing 50 ml 10^{-2} *M*, ammonium reineckate or *TPB* with 25 ml 10^{-2} *M* codeine sulfate. The formed precipitate was filtered, washed with a dilute solution of ammonium reineckate, and dried on air. Codacetine (tablets), Vegaskine (tablets), and Nova-C-retard (tablets) are products of local drug companies; Bepro (syrup) and Diarrest (liquid) are products of Wallace Chem. and Galen (UK), respectively.

Membrane and electrode preparation

Six membrane compositions were prepared as explained previously [28] either by varying the IP or the *DOP* percentages (Table 1). Also, codeine-*TPB* was tried as an ion pair, and *DOPP* was applied as a membrane solvent instead of *DOP* (Table 2). The electrode was prepared by cutting a disk of 12 mm diameter out of the membrane and glueing it to a quicfit female socket (10/19). This was fixed to a glass tube into which 1.3×10^{-3} *M* codeine sulfate and 10^{-1} *M* NaCl were filled. An internal reference electrode (Ag–AgCl) was immersed into the inner filling solution. The Ag–AgCl wire was connected to a cable through a solder joint which passed through a male quickfit cone to the outside of the electrode body.

Electrode calibration

The electrochemical cell consists of the codeine sensitive electrode and a double junction Ag–AgCl reference electrode (Orion model 90-02-00) filled with KNO_3 in the outer compartment. A *pH*/mV meter (Cole-Parmer Series 5986) was used for potential measurements. Also, an Orion Ionalyzer (model 407) with its glass electrode was employed for *pH* adjustments. Codeine sulfate solutions were prepared to cover a concentration range of 10^{-7}–1.3×10^{-3} ($pk_a = 8.2$) [29].

Electrode selectivity

The selectivity coefficients $K^{Pot}_{CodH^+,J^{z+}}$ of the electrodes towards several interferents (J^{z+}) including amines, aminoacids, sugars, and different drug excipientes were calculated by the separate solution method [28] using equation

$$\log K^{Pot}_{CodH^+,J^{z+}} = (E_2 - E_1)/S + \log[CodH^+] - \log[J^{z+}]^{1/z}$$

where E_1 and E_2 are the electrode potentials in 10^{-3} *M* $cod_2 \cdot H_2SO_4$ and interferent solutions, respectively, and *S* is the slope of the calibration graph at room temperature.

Application for the determination of codeine

Samples of Codacetine (tablets), Vegaskine (tablets), Nova-C-retard (tablets), Bepro (syrup), and Diarrest (liquid) containing 10, 10, 15, 6.25, and 5 mg codeine were dissolved in 25 ml water and put in the electrochemical cell containing the codeine selective electrode; the potential readings were recorded. Results were compared with a previously established calibration graph to find the concentration of codeine in each of the tested samples using a guide of two standard solutions [30] where the unknown concentration is found by the following equation:

$$\text{Unknown codeine concentration} = \text{antilog}\frac{\text{mV reading of Std. 1} - \text{mV reading of unknown}}{\text{mV reading of Std. 1} - \text{mV reading of Std. 2}}$$

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