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Scientific paper

Electrochemical Quantitative Assessment of Labetalol Hydrochloride in Pure Form and Combined Pharmaceutical Formulations

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Abstract

This work describes how to utilize the electrochemical technique to determine labetalol hydrochloride (Lab) in pure form and combined pharmaceutical formulation for quality control purposes. Four membrane sensors were developed using two plasticizers, dioctyl phthalate with 2-hydroxypropyl-β-cyclodextrin and ammonium reineckate (RNC) for sensors 1a and 2a, and tributyl phthalate with 2-hydroxypropyl-β-cyclodextrin and ammonium reineckate for sensors 1b and 2b as ionophores in polyvinyl chloride (PVC) matrix. Fast response and stable Nernstian slopes of 59.60, 57.58, 53.00 and 55.00 mV/decade for sensors 1a, 2a, 1b, and 2b, respectively, were obtained by developed sensors within a concentration range 10^{-4} M–10^{-2} M over pH range 2.00–5.10. Developed sensors showed good selectivity for Lab in pure form, in the presence of co-administered drugs, many of interfering ions, and excipients present in pharmaceutical formulation. No remarkable difference was detected upon the statistical comparison between the results of proposed sensors and the official method.

Keywords: Ammonium reineckate; 2-hydroxypropyl-β-cyclodextrin; ion-selective electrode; labetalol hydrochloride; tributyl phthalate; dioctyl phthalate.

1. Introduction

Labetalol hydrochloride (Lab), Fig (1), known chemically as 5-[1-hydroxy-2-[(1-methyl-3-phenylpropyl)-amino]-ethyl]-salicylamide monohydrochloride,[1] is a mixed α- and β-adrenoceptor blocking agent that works by blocking the action of epinephrine on heart and blood vessels. It is considered one of the major therapeutic drugs for the treatment of hypertension either alone or combined with other antihypertensive drugs or diuretics. It is also used to induce hypotension during surgery as Lab reduces blood pressure more rapidly than other α- or β-receptor blockers. Lab is a well-known doping agent in sports and hence has been banned for Olympic players by the International Olympic Committee.[2–4]

Literature survey revealed that various analytical techniques were employed to estimate the concentration of Lab in pharmaceutical preparations, either alone or in combination with hydrochlorothiazide, and in biological fluids. These techniques include spectrofluorimetry,[5–10] chromatography,[11–18] capillary electrophoresis,[19,20] capillary isotachophoresis,[21] NMR spectroscopy,[22] ion-selective electrode using ion-pair complex,[23] and adsorptive voltammetry,[24] methods which in comparison to proposed electrodes require sample manipulation, are affected by various interferences, inappropriate for colored or turbid solutions, and more expensive as they require sophisticated equipment and software for data processing.

Ion-selective electrode (ISE) as a new analytical technique offers an accurate quantitative estimation of active drug substance in pharmaceutical formulation regardless of turbidity or color of sample media due to its relatively high selectivity which is determined by the nature and composition of the membrane materials used in the fabrication of the electrode.[25]

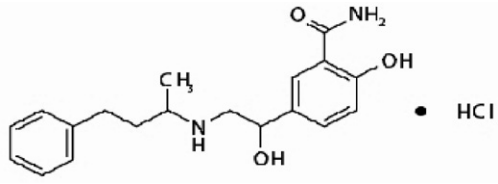

Fig. 1. Chemical structure of labetalol hydrochloride

This work describes the advantage of utilization of ion-selective sensors prepared in PVC matrix using 2-hydroxypropyl-β-cyclodextrin and ammonium reineckate (RNC) with two different plasticizers for the determination of Lab in pure form and combined pharmaceutical formulation having equal efficiency as the previously developed spectrophotometric and HPLC methods,[10,18] with superiority of elimination of sample pretreatment, working over wide pH range, devoid of several preparation steps as in HPLC and being eco-friendly.

2. Experimental

2. 1. Apparatus

- pH meter 3510 pH /mV /°C (Jenway, UK)
- pH glass electrode (Jenway, UK)
- Ag/AgCl double junction reference electrode (Jenway, UK)
- 5-digit electronic balance model XA60/220 (RADWAG, Poland)
- water purification system (Milli Q, France)
- magnetic stirrer: model 34532 (Snijders, Holland)
- thermometer
- sonicator (Falc, Japan)

2. 2. Samples and Pharmaceutical Formulations

- Pure labetalol hydrochloride was kindly supplied by El-debiky Co., Cairo, Egypt. Its purity was found to be 100.48% ± 0.84 according to the official HPLC method.[1]
- Labipress plus® tablets produced by El-debiky Pharmaceutical Company, Cairo, Egypt: Batch No: (141019). Each tablet is labeled to contain 100 mg of labetalol hydrochloride and 25 mg of hydrochlorothiazide.

2. 3. Chemicals and Reagents

All chemicals and reagents used were obtained from Sigma Aldrich.

- 2-hydroxypropyl-β-cyclodextrin (βC), tetrahydrofuran (THF), and ammonium reineckate (RNC)
- polyvinyl chloride (PVC), tributyl phthalate (TBP), and dioctyl phthalate (DOP)
- deionized water
- potassium chloride (KCl)

2. 4. Standard Solutions

- Standard stock solution (10^{-2} M) was prepared by dissolving 364.87 mg of Lab in 100 ml deionized water.
- Serial dilutions from the stock solution were made in deionized water to prepare (10^{-7} M–10^{-3} M) working standard solutions of Lab.

2. 5. Procedures

2. 5. 1. Preparation of Membrane Sensors

(a) Membrane 1a&b

For the preparation of membrane 1a, 0.04 g 2-hydroxypropyl-β-cyclodextrin was mixed with 0.40 g of DOP and 0.19 g of PVC. This mixture was dissolved in 5 ml THF in a 5 cm diameter glass petri dish and covered with filter paper to allow for solvent evaporation at room temperature for 24 h. 0.1 mm thickness master membrane was obtained and used for the construction of the electrode. Membrane 1b was prepared similarly but with the use of TBP instead of DOP.

(b) Membrane 2a&b

For the preparation of membrane 2a, 0.01 g ammonium reineckate (RNC) was mixed with 0.40 g of DOP and 0.19 g of PVC. This mixture was dissolved in 5 ml THF in a 5 cm diameter glass petri dish and covered with filter paper to allow for solvent evaporation at room temperature for 24 h. 0.1 mm thickness master membrane was obtained and used for the construction of the electrode. Membrane 2b was prepared similarly but with the use of TBP instead of DOP.

Disks of about 12 mm diameter were cut from each master membrane with a cork borer and glued to an interchangeable PVC tip (fixed to the end of an electrode glass body) using THF and left to dry for 24 h. Then the prepared electrodes were filled with equal volumes of 10^{-3} M Lab and 10^{-3} M KCl as an internal solution and a 1 mm diameter Ag/AgCl wire was used as an internal reference electrode. Electrodes were soaked in 10^{-3} M aqueous solution of Lab for 24 h for conditioning and kept in the same solution when not in use.

2. 5. 2. Sensors Calibration

Calibration of conditioned sensors was performed by immersing prepared electrodes, in conjunction with the Ag/AgCl reference electrode, into a set of 100 ml beakers containing 50 ml separate aliquots of (10^{-7} M–10^{-2} M) solutions of Lab and allowed to equilibrate under stirring with washing with deionized water between measurements. The potential difference (emf) between each of the prepared membrane sensors (indicator electrode) and Ag/AgCl reference electrode was measured and plotted as a function of the negative logarithm of Lab concentration. Regression equations were calculated for the linear part of the curves and used for the estimation of Lab concentrations.

2. 5. 3. Sensors Selectivity

Potentiometric selectivity coefficient ($K^{Pot.}_{lab,\ interferent}$) was estimated following IUPAC guidelines,[27] using separate solution method (SSM),[26] in which the potential of two separate solutions, A (Lab) and B (interfering ion) at a concentration of 10^{-3} M, was measured by prepared membrane electrode conjugated with reference electrode.

$$\mathrm{Log}K^{Pot.}_{A,B} = [(E_B - E_A) / (2.303\ RT/Z_AF)] + \\ + [1 - (Z_A / Z_B)\ \log[A]$$

Where E_A is the potential measured in 1×10^{-3} M standard Lab solution, E_B is the potential measured in 1×10^{-3} M interfering ion solution, Z_A and Z_B are the charges of Lab and interfering ion, respectively, and $2.303\ RT/Z_AF$ represents the slope of the calibration curve.

2. 5. 4. Application to Pharmaceutical Formulations

Twenty tablets of Labipress plus® tablets were pulverized and the accurate weight of powdered tablets was dissolved in 100 ml deionized water for 15 min to prepare 10^{-2} M solution of Lab. Prepared sensors, conjugated with Ag/AgCl reference electrode, were immersed in the prepared solution. The measured potential was used to estimate the concentration of Lab in solution by substitution in the regression equation of the corresponding electrode.

3. Results and Discussion

3. 1. Sensors Preparation

Ion-selective electrodes' use in quantitative estimation of active drug substances in pharmaceuticals has shown superiority over other analytical techniques because of high selectivity and suitability for the analysis of turbid or colored test solutions over wide ranges of pH and concentrations with high accuracy and fast response.

In the present work, a cationic type of ion exchangers, 2-hydroxypropyl-β-cyclodextrin and ammonium reineckate, was used in electrode preparation based on the fact that Lab in aqueous solution behaves as a cation; also, 2-hydroxypropyl-β-cyclodextrin and ammonium reineckate are physically compatible with PVC polymeric matrix that was used to produce highly stable complexes as PVC has the advantages of chemical inertness and low cost but its use raises a need for a plasticizer.[24]

Dioctyl phthalate and tributyl phthalate were selected as plasticizers because of their chemical asymmetry that results in unique electrical properties as they allow PVC membranes to operate with less energy input than with other plasticizers, relatively non-volatile under heat and maintain flexibility at low temperature combined with a resistance to high temperature.[27]

3. 2. Sensors Calibration and Response Time

IUPAC recommendation data[28] were used for evaluating the electrochemical performance characteristics of proposed sensors, Table 1. Calibration graphs are presented in Fig. 2, showing stability, consistency of potential readings and stability of calibration slopes over 1 month. A fast, stable response was obtained within 10–15 s for sensors 1a, 1b, and 15–20 s for sensors 2a, 2b using concentrations of Lab from 10^{-4} M–10^{-2} M for estimation of the response time of prepared electrodes. The pro-

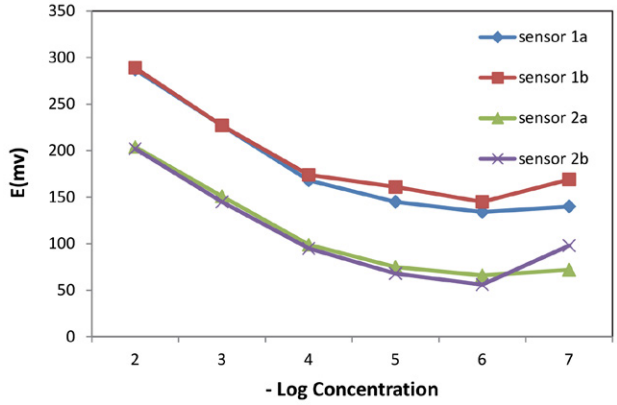

Fig. 2. Profile of the potential in mV versus –log(concentration of Lab) using the investigated sensors.

Table 1. Response characteristics of the investigated sensors.

Parameter	Sensor 1a	Sensor 1b	Sensor 2a	Sensor 2b
Slope (mV/decade)	–59.60	–57.58	–53.00	–55.00
Intercept (mV)	406.40	403.34	310.60	310.60
Correlation coefficient	0.9999	0.9997	0.9999	0.9999
Response time (s)	10–15	10–15	15–20	15–20
Working pH range	2.00–5.10	2.00–5.10	2.00–5.10	2.00–5.10
Concentration range (M)	10^{-4}–10^{-2}	10^{-4}–10^{-2}	10^{-4}–10^{-2}	10^{-4}–10^{-2}
Life span (weeks)	2–4	2–4	2–3	2–3
Average recovery[a] ± SD	100.12 ± 0.27	99.74 ± 0.35	99.83 ± 0.25	99.87 ± 0.52
LOD(M)	4.17×10^{-5}	3.98×10^{-5}	3.98×10^{-5}	3.16×10^{-5}

[a]Average of three determinations

posed sensors displayed good long term potential stability for 2–4 weeks.

3. 3. Effect of pH and Temperature

Conditions affecting the response of ion-selective electrodes were studied to determine the optimum conditions for quantitative measurement. The effect of pH was studied considering both sensor function and chemical form of Lab. It was concluded from Fig. 3–6, that sensors response is fairly steady over pH range 2.00–5.10 where Lab exists in the cationic form and is detectable by the electrodes; outside this pH range, the potentials measured by the electrodes were unstable. The temperature effect was also studied, where the proposed membrane sensors

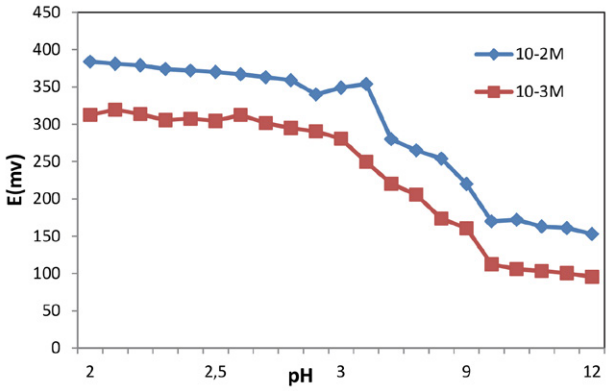

Fig. 3. Effect of pH on the response of Lab sensor 1a

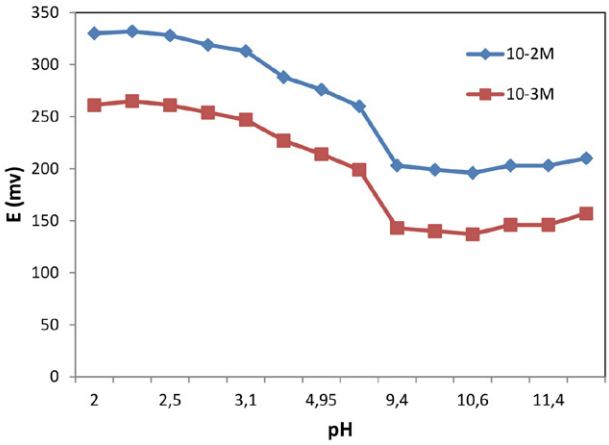

Fig. 4. Effect of pH on the response of Lab sensor 1b

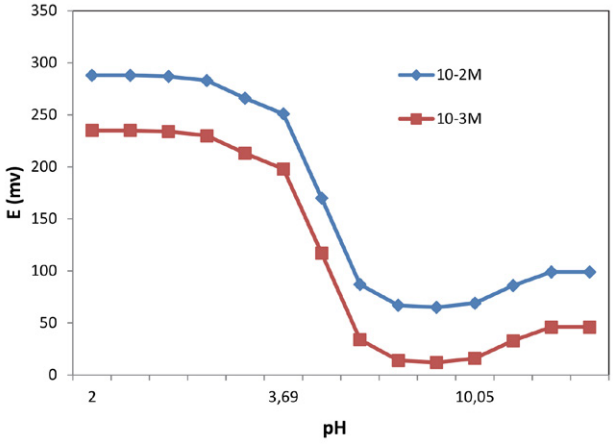

Fig. 5. Effect of pH on the response of Lab sensor 2a

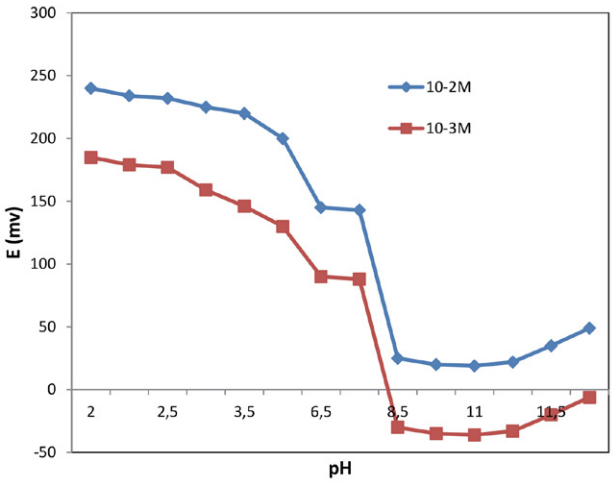

Fig. 6. Effect of pH on the response of Lab sensor 2b

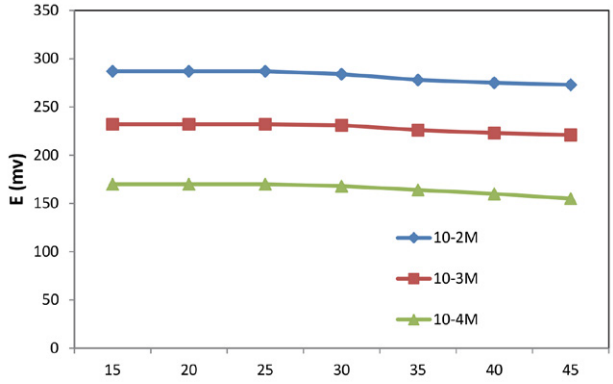

Fig. 7. Effect of temperature on the response of Lab sensor 1a

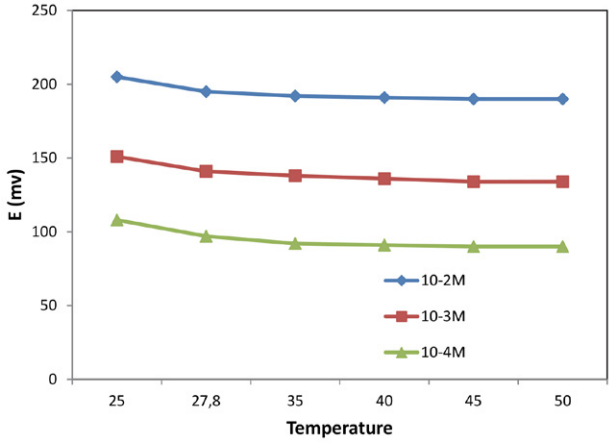

Fig. 8. Effect of temperature on the response of Lab sensor 1b

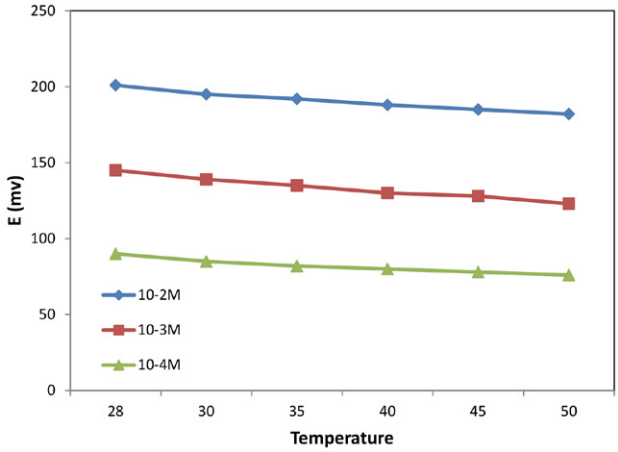

Fig. 9. Effect of temperature on the response of Lab sensor 2a

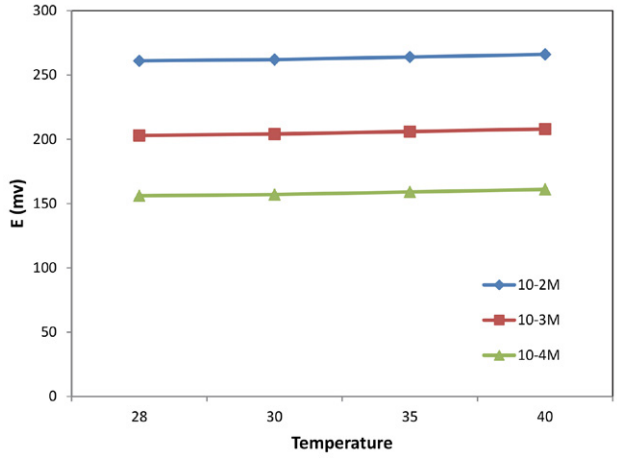

Fig. 10. Effect of temperature on the response of Lab sensor 2b

displayed thermal stability up to 35 °C indicated by a steady potential response, Fig. 7–10.

3. 4. Sensors Selectivity

The potentiometric selectivity coefficient was determined for several excipients, co-administered drugs, and related substances by the proposed sensors. Table 2: the results revealed high selectivity for Lab and that no significant interference was observed.

3. 5. Application to Pharmaceutical Formulations

The proposed sensors were used for determination of Lab in Labipress plus® tablets without pretreatment and no interference was observed from excipients or hydrochlorothiazide as a co-formulated drug, Table 3.

No remarkable difference was detected upon the statistical comparison between results of the proposed electrodes and the official method,[1] for determination of the pure form of Lab, Table 4.

3. 6. Application to Biological Fluids

Trials were made to use the proposed sensors for determination of Lab in biological fluids since Lab is absorbed rapidly after oral administration with peak plasma concentration achieved within 2 h and its bioavailability varies from 10% to over 80% correlating with age. But also approximately 50% of Lab is bound to the plasma proteins which prevented direct determination of Lab in human plasma using proposed sensors.[29] Lab is eliminated mainly by hepatic metabolism with the production of several biologically inactive glucuronides which in turn are excreted in the urine and bile. Approximately 85% of Lab in the blood is removed during a single passage through the liver which also prevented its determination in human urine using proposed sensors.[29]

4. Conclusion

The described sensors displayed fast, selective and accurate potential response for Lab over concentration range (10^{-4} M–10^{-2} M) and have equal efficiency to previously developed methods[10,18] used for quantitative estima-

Table 2. Potentiometric selectivity coefficients of the proposed electrodes using a separate solution method.

Interferents [a]	Selectivity Coefficient			
	Sensor 1a	Sensor 1b	Sensor 2a	Sensor 2b
Hydrochlorothiazide	3.26×10^{-5}	5.62×10^{-5}	2.76×10^{-5}	4.42×10^{-5}
Chlorothiazide	1.76×10^{-4}	4.54×10^{-4}	2.49×10^{-5}	3.95×10^{-5}
Benzothiadiazine	1.59×10^{-5}	3.90×10^{-5}	2.06×10^{-5}	3.17×10^{-5}
KCl	1.90×10^{-4}	3.68×10^{-4}	2.19×10^{-5}	6.31×10^{-5}
NaCl	1.83×10^{-4}	4.49×10^{-4}	3.37×10^{-5}	7.31×10^{-5}
$CuSO_4$	1.31×10^{-3}	3.23×10^{-3}	2.14×10^{-3}	3.66×10^{-3}
Lactose	1.63×10^{-4}	4.08×10^{-4}	2.48×10^{-4}	2.14×10^{-4}
Ammonium dihydrogen phosphate	8.28×10^{-3}	9.06×10^{-3}	8.92×10^{-3}	5.92×10^{-3}
$CaCO_3$	4.87×10^{-4}	3.93×10^{-4}	5.11×10^{-4}	1.43×10^{-6}
Starch	2.49×10^{-4}	3.58×10^{-4}	2.00×10^{-5}	4.33×10^{-5}

[a] Aqueous Solutions of 1×10^{-3} M were used

Table 3. Determination of Lab in Labipress plus® tablets by the proposed sensors

Preparation	Company method [b]	Sensors			
		Sensor 1a	Sensor 1b	Sensor 2a	Sensor 2b
Labipress Plus tablets Each tablet contains 100 mg labetalol HCl, 25 mg hydrochlorothiazide B.N.: 141019	Found [a] ± RD 99.91 ± 0.91	Assay Found [a] ± RD 99.96 ± 0.89	Assay Found [a] ± RD 99.70 ± 1.34	Assay Found [a] ± RD 99.90 ± 0.84	Assay Found [a] ± RD 99.20 ± 0.58

[a]Average of three determinations. [b]HPLC method using C_{18} (250 mm × 4.6 mm, 5 µm) analytical column, with mobile phase acetonitrile:phosphate buffer (pH = 3.5):triethylamine in ratio (40:60:0.1 *v/v/v*) with flow rate 1.0 ml/min at 230 nm.

Table 4. Statistical comparison of results obtained by the proposed sensors and the official method for determination of Lab in pure form.

Items	Offical method[1]	sensor 1a	sensor 1b	sensor 2a	sensor 2b
Mean[a]	100.48	100.12	99.74	99.83	99.87
S.D	0.84	0.27	0.35	0.25	0.52
Variance	0.71	0.07	0.12	0.06	0.27
n	5	3	3	3	3
S.E	0.38	0.16	0.20	0.14	0.30
t-test (2.447)	–	0.87	1.72	1.81	1.26
F-ratio (19.25)	–	10.14	5.92	11.83	2.63

[a] Official HPLC method using C_{18} (200 mm × 4.6 mm, 5 µm) analytical column, with mobile phase methanol:phosphate buffer in the ratio (35:65 *v/v*) with flow rate 1.5 ml/min, 60 °C at 230 nm.[1S]

tion of Lab in pure and combined pharmaceutical formulation and more, they are eco-friendly, require minimum preparations for test measurement and show long term stability in response which suggests their use for quality control purpose as proposed electrodes enable determination of Lab over concentration range that covers its concentration in pharmaceutical formulation with reasonable sensitivity and are easily fabricated in comparison to other membranes.[30]

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Povzetek

Članek opisuje uporabo elektrokemijske tehnike za določanje labetalol hidroklorida (Lab) v čisti obliki in v kombiniranih farmacevtskih pripravkih z namenom kontrole kakovosti. Razvili smo štiri membranske senzorje na osnovi dveh plastifikatorjev, dioktil ftalata z 2-hidroksipropil-β-ciklodekstrinom in amonijevim reinekatom (RNC) za senzorja 1a in 2a, ter tributil ftalata z 2-hidroksipropil-β-ciklodekstrinom in amonijevim reinekatom za senzorja 1b in 2b, ki služita kot ionoforja v matrici polivinil klorida (PVC). Za vse senzorje smo znotraj koncentracijskega območja 10^{-4} M–10^{-2} M in pH-območja 2,00–5,10 ugotovili hiter odgovor in stabilen Nernstov naklon 59,60 mV/dekado za 1a, 57,58 mV/dekado za 2a, 53,00 mV/dekado za 1b in 55,00 mV/dekado za 2b. Razviti senzorji so pokazali dobro selektivnost za Lab v čisti obliki in v prisotnosti drugih zdravil, mnogih interferenčnih ionov ter polnil, prisotnih v farmacevtskih pripravkih. Pri statistični primerjavi rezultatov, dobljenih s predlaganimi senzorji in z uradno metodo, nismo ugotovili znatnih razlik.