Analytical applications of electrode sensitive to labetalol in pharmaceuticals

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Abstract: The analytical properties of an ion-selective electrode sensitive to labetalol with a liquid membrane, based on ion-pair complexes with sodium tetraphenylborate (TPB-Na⁺) are described. The studied electrode can be used for the determination of labetalol hydrochloride as a protonated form of labetalol in pharmaceuticals. The calibration curve, e.g. EMF=f(pC_LabHCl) is linear in the range from 10⁻⁵ to 10⁻² mol L⁻¹ with a correlation coefficient of 0.9992 and slope of 61.13 mV/decade, which is close to the Nernstian slope. The detection limit of the examined electrode is 7.20×10⁻⁶ mol L⁻¹. The influence of pH of the tested solutions on the formulation of the electrode is not as considerable since the electrode works correctly in the pH range 3.0-8.0. The main attributes of the developed electrode are: stability, good reproducibility of EMF and short response time, close to 30 seconds depending on labetalol concentration in the solution. The electrode shows good selectivity for many inorganic ions. The selectivity for drug cations is weaker due to the structural similarity of the interfering cations to labetalol. The results of labetalol determination using direct potentiometry in drugs such as Pressocard (Polpharma) and Trandate (GlaxoWellcome) were compatible with the quantity of labetalol declared by the manufacturer, and with parallel UV spectrophotometric and HPLC determinations.

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1 Introduction

The analysis of pharmaceuticals requires alternative systems in order to develop faster, cheaper methods or reference methods. Determination with ion-selective electrodes can meet these requirements since these methods are relatively simple and rapid; they do not require the use of any sophisticated apparatus, they may be readily automated, and they can also be used for continuous measurements. Consequently, the membrane electrodes have been increasingly applied in the pharmaceutical industry and in clinical analysis, making it possible to carry out routine determinations at short time intervals while maintaining high precision. This interest is confirmed by numerous works on ion-selective electrodes sensitive to ionic substances used in pharmaceuticals e.g. [1-5].

![Scheme 1](image)

**Scheme 1** The chemical formula of labetalol hydrochloride (LabHCl).

Labetalol hydrochloride (LabHCl) (scheme 1), which is the protonated form of labetalol (2-hydroxy-5-{1-hydroxy-[(1-methyl-3-phenylpropyl)-amino]-ethyl}-benzamide) is an important component of pharmaceuticals called adrenolitics. Due to its molecular structure and chemical properties labetalol blocks $\alpha_1$ and $\beta$-receptors ($\beta$ blockade is stronger) in the treatment of chronic and peracute hypertension.

A number of labetalol determinations have previously been described in the literature for e.g. UV spectrometry [6], TLC [7], electrophoresis [8], colorimetrically [9]. Labetalol has also been determined in plasma, urine and blood [10-12]. An ion-selective membrane electrode with a PVC matrix has been applied [13]. However, the majority of these methods are very elaborate and time consuming requiring expensive apparatus to apply them.

Thus, the problem of finding a new, relatively simple, and rapid potentiometric method of labetalol determination is timely. In order to develop such a method it is advisable to test a range of solvents and compounds forming ion-pairs with labetalol.

The aim of this work is to elaborate a new ion-selective electrode sensitive to labetalol. The studied electrode will be applied for labetalol determination in pharmaceuticals which are used in the treatment of hypertension. The liquid membrane of the electrode is a tetrachloroethane-water interface and labetalol tetraphenylborate is used as an active compound.
2 Experimental

2.1 Reagents and apparatus

Labetalol hydrochloride (SIGMA-ALDRICH, USA), promazine hydrochloride (DOLDER, Switzerland), ephedrine hydrochloride (CEFARM, Poland), ethaverine hydrochloride (SIGMA-ALDRICH, USA), verapamil hydrochloride (ALDRICH, Germany), papaverine hydrochloride (SCHUETZ & CO, Germany), prometazine hydrochloride (SPECIAPARIS, France), fluphenazine dihydrochloride (P.F. JELFA S.A., Poland), pyrantel citrate (SIGMA, USA), acetonitrile gradient grade for liquid chromatography (MERCK), TRANDATE ampoules (0.1 g, GLAXOWELLCOME, UK), PRESSOCARD pills (0.2 g, POLPHARMA, Poland) were used.

Other reagents used in this work were of analytical grade (POCh Gliwice, Poland). Water was deionized with Mili-Q (Milipore) apparatus. All solvents used in the experiment were deoxidized with a Polsonic ultrasonic cleaner.

The ion-selective electrode potential was measured with an N-5172 pH-meter (TELEKO Wroclaw, Poland) connected to a computer. This system made it possible to measure the cell potential (EMF) with ±0.1 mV accuracy.

Spectrophotometric measurements were carried out with a diode spectrophotometer from Hewlett-Packard, type 8452A.

HPLC analysis was done with a Merck, model L-4500, liquid chromatograph.

2.2 Preparation of active compound

The labetalol cation forms an ion pair with tetraphenylborate anion in a 1:1 molar ratio. The compound is barely soluble in water and soluble in some organic solvents. Labetalol tetraphenylborate (LabH\(+\).TPB\(^-\)) was prepared by mixing 25 mL of 0.01 mol L\(^{-1}\) aqueous solutions of labetalol hydrochloride (LabH\(+\).Cl\(^-\)) and sodium tetraphenylborate (TPB-Na\(^+\)). The precipitate was filtered under pressure, washed with small portions of distilled water, dried at room temperature and then powdered. The membrane solution was prepared by mixing 16.2 mg of labetalol tetraphenylborate in 25 mL of 1,1,2,2-tetrachloroethane.

2.3 Electrode construction

A teflon casing was used for the ion-selective electrode (Fig. 1). The construction made it possible to saturate a porous ring made of hydrophobized cellulose nitrate (Type 11307 membrane filter from SARTORIUS) with the membrane solution. The membranes were 0.1 mm thickness and 5.5 mm diameter. In comparison with the PVC membrane electrodes, the liquid membranes are better because the membrane preparation methods are faster and easier. The presence of an active compound in liquid membrane results in keeping its concentration constant.
The membrane separated the examined solution from the inner solution of the electrode, which consisted of $1 \times 10^{-3}$ mol L$^{-1}$ labetalol hydrochloride solution in $1 \times 10^{-2}$ mol L$^{-1}$ lithium chloride solution. The potential was measured against a silver/silver chloride electrode (RADELKIS) containing 1 mol L$^{-1}$ potassium chloride as the inner solution with an electrolyte bridge containing 1 mol L$^{-1}$ lithium chloride. The measuring cell used in the measurements can be represented by the following scheme:

![Scheme 2 The scheme of measuring cell.](image)

The phase border between the membrane solution and the analysed solution was the decisive border for the response of the electrode to the analyte concentration. Other phase borders were reversible and potentials on these phase borders did not change.

The membrane solution was $1 \times 10^{-4}$ mol L$^{-1}$ labetalol tetrphenylborate solution in tetrachloroethane.

### 2.4 Determination of selectivity coefficients

The selectivity coefficients were determined following the Nikolsky-equation [14]:

$$K_{Lab/j} = \frac{a_{Lab} \left(10^{\Delta E/S} - 1\right)}{a_{j}^{1/n_{j}}}$$

where $a_{Lab}$ and $a_{j}$ are the activities of the labetalol cation (LabH$^+$) and interfering cation, respectively, $n_{j}$ is the interfering ion valence, $\Delta E = E_{Lab/j} - E_{Lab}$, $E_{Lab/j}$ is the electrode potential in the solution containing the interfering cations beside the LabH$^+$ cation, $E_{Lab}$ is the electrode potential in the solution containing the LabH$^+$ cation only, and $S$ is the slope of labetalol electrode characteristic.

The measurements of the potential were carried out in one solution containing labetalol of constant activity ($E_{Lab}$) and interfering cations of variable activities ($E_{Lab/j}$). The ionic strength of the tested solutions was set to the value of $I=0.1$ and it was controlled with NaNO$_3$. The selectivity coefficient values against the inorganic and organic cations were determined at $1 \times 10^{-4}$ mol L$^{-1}$ LabH$^+$ concentration. The measurements were carried out at such pH values that the effect of the H$^+$ or OH$^-$ ions of the electrode potential was not observed.
2.5 Procedure determination

Labetalol hydrochloride was determined in pharmaceuticals such as *Pressocard* and *Trandate* by the proposed potentiometric method and in parallel by two reference methods: UV spectrophotometry and high performance liquid chromatography (HPLC).

2.5.1 Potentiometric determination

The potentiometric method carried out by direct potentiometry did not require a special sampling process. The drug solution (obtained from tablets) was prepared by powdering the tablets in a porcelain mortar, dissolving the powder in water and doubly filtering under pressure. The final concentration of drug solution was $1.10 \times 10^{-3} \text{ mol L}^{-1}$. The solution of Trandate ampoules was prepared in a similar way. The ampoule was diluted and the potential was measured. The final concentration of the tested solution was $1.37 \times 10^{-3} \text{ mol L}^{-1}$.

2.5.2 UV spectrophotometric determination

At the beginning the labetalol absorption spectra was determined. The intense band was 238 nm. No special sample preparation was needed. The drug (e.g. tablets and ampoules) was dissolved and appropriately diluted. The absorbance was measured at $\lambda=238 \text{ nm}$ using the labetalol hydrochloride solutions and water as blank.

2.5.3 HPLC determination

In the HPLC method, labetalol aqueous solution was introduced into the RP-18 (250 x 4 mm) column. The eluent was 35% acetonitrile in $4.5 \times 10^{-4} \text{ mol L}^{-1} \text{ KH}_2\text{PO}_4$, adjusted to pH=3.0 with phosphoric acid. The flow-rate of the mobile phase was 0.5 mL/min and chromatograms were recorded at 238 nm wavelength. Labetalol concentration was read out from the calibration curve ($5 \times 10^{-5}-2 \times 10^{-3} \text{ mol L}^{-1}$) obtained by using the pure substance solution.

3 Results and discussion

3.1 Choice of solvent and active compound concentration

The properties of a liquid-membrane ion selective electrode depend, to a great degree, on the choice of membrane solution solvent; particularly on solvent electric permittivity, its miscibility with water, the influence on the material stabilising the interface and solubility of the active compound. Membrane selectivity, the stability of potential, and calibration curve parameters are all dependant on the properties of the solvent. The essential parameters characterising the calibration curves obtained for the studied membrane solvents are collected in Table 1.

The choice of solvent and active compound concentration was done by plotting curves for membranes saturated with the active compound in the tested solvent. It is well known
that the best parameters of ion-selective electrodes calibration curves are where the is slope close to the Nernstian, have a wide linearity range and the correlation coefficient close to 1. The shape of the calibration curves tested for the solvents are very specific. The EMF value at $10^{-6}$ mol L$^{-1}$ was higher than at $10^{-5}$ mol L$^{-1}$. This was caused by the detection limit which limits the dependence between EMF and the labetalol hydrochloride concentration.

The calibration curves of chlorobenzene, dichlorobenzene and chloroform were not reproducible and their slopes differed markedly from the Nernstian value (e.i. 0.059 V/decade). In the case of the calibration curves of chloroform, the values were probably due to the low boiling point of the solvent, where evaporation from the membrane resulted in subsequent changes in the membrane properties. Fairly good miscibility of this solvent with water is also a factor for consideration. However, dichloroethane was characterised by too much unstable potential and a longer response time than in the case of tetrachloroethane.

The slope of the curve obtained for dichloroethane was too large, i.e. 0.075 V/decade. This of course is against the thermodynamic laws and why the electrode with this solvent is not reversible. Hence, the solvent was not used for further measurements. The number of organic solvents possessing suitable physical properties for liquid electrode construction is limited. Tetrachloroethylene was not used in the experiments due to weak solubility of the active compound (LabH$^+$TPB$^-$) in the solvent, which could provoke an increase in the membrane resistance. In the case of the three studied alcohols (1-heptanol, 1-octanol, 1-decanol) the main reason for not using these solvents for further measurements, was leakage through the membrane. The solvents with a nitro group in the structure were not tested because these solvents destroy the cellulose nitrate membrane filter.

Tetrachloroethane, however, was found to be suitable. Its calibration curve had the biggest linearity range, its slope was similar to the theoretical, it’s response time was satisfactory (about 30 s), stability was good and the potentials were reproducible. The calibration curve obtained with tetrachloroethane in the concentration range $1 \times 10^{-5}$- $1 \times 10^{-2}$ mol L$^{-1}$ is described by the equation:

$$\text{EMF}[V] = -0.061pC_{LabHCl} + 0.279$$

The concentration effect of the active compound on the electrode performance was checked. The measurements were done in the liquid ion exchanger concentration range $1 \times 10^{-3}$- $1 \times 10^{-5}$ mol L$^{-1}$. The small deterioration of the electrode detection limit was observed with the increasing membrane solution concentration. Concurrently, the potential gradually decreased at higher concentration ($1 \times 10^{-3}$ mol L$^{-1}$), probably because of the washing out of the active compound to the aqueous phase, whereas an unstable potential was observed at a low membrane solution concentration due to membrane resistance. The $1 \times 10^{-4}$ mol L$^{-1}$ ion exchanger concentration was chosen as optimal.
3.2 Response time and electrode stability

Response time depending on the studied compound concentration in the solution is close to 30 s in the $1\times10^{-4}$-$1\times10^{-2}$ mol L$^{-1}$ concentration range, and about 60 s for lower concentrations.

The electrode did not require conditioning before use, but was assembled before each measurement because of the ease of fitting (about 5 min) and easy membrane solution preparation.

3.3 Effect of pH

The dependence of the electrode potential on the pH of the solution is presented in Figure 2 for various labetalol hydrochloride concentrations.

From the shape of the curves it may be concluded that the pH range in which the electrode works correctly narrows stepwise with the decreasing potential or increasing ion concentration. The potential drop observed in the solutions of pH above 8.0 is caused by the decreasing labetalol cation concentration caused by hydrolysis and the increase in potential observed at pH below 3.0 is due to the effect of hydrogen ions of the electrode. The linear potential increase observed in this potential range indicates the change in the properties of the membrane which becomes reversible to the hydrogen ion. The pH range 3.0-8.0 is useful in the analysis.

3.4 Selectivity

The selectivity coefficient is the most important parameter of an ion-selective electrode as it determines its usefulness in the analysis. The selectivity of the proposed electrode to various metal cations and selected organic cations used as drugs was tested and the experimental medium selectivity coefficients were collected in Table 2.

Inorganic ions examined as potential interfering ions are present in body fluids and these cations often occur in many pharmaceutical samples. Examined organic cations were used in this work because of their similarity to the labetalol structure, although these ions are not present simultaneously with labetalol in pharmaceuticals. The selectivity coefficients do not have the constant values. They depend on ion activity (Fig. 4 and Fig. 5). The fact that the selectivity of interferented ion is much better at low concentrations ($1\times10^{-4}$ mol L$^{-1}$) than at higher concentrations seems to be particularly significant.

The selectivity of the labetalol electrode to the tested metal cations is satisfactory, apart from the potassium cation.

Various values of selectivity coefficients and various shapes of curves $pK_{i/j} = f(pa_j)$ may indicate differences in electrode mechanism.
3.5 Analytical applications of the electrode

Constant pH and ionic strength value of the studied and reference solutions are required in the determinations. The direct potentiometry method is characterised by the good precision, which results from small standard deviation. This is why this procedure is an appropriate one.

The proposed electrode was applied to the determination of labetalol in a drug by the direct potentiometry method. The results of the method used and of comparative determinations (spectrophotometric and chromatographic) are presented in Table 3.

Summarising the obtained results, the developed electrode is useful in the analysis of labetalol and can be applied in many other pharmaceutical analyses. Also, this kind of analysis is not as costly as HPLC and UV spectrophotometry. The developed electrode may be easily and cheaply prepared. Therefore, the determination of labetalol using this electrode may be applied as an interesting alternative or reference method. Additionally, similar ion-selective electrodes with liquid membrane may be used to determine other pharmaceutical components which are similar to labetalol.

4 Conclusions

The developed electrode and the electrode described in the literature [13] are characterised by many different parameters. In the first case the calibration curve slope is 0.061 V/decade and it is higher than the Nerstian slope. The difference between these slopes is smaller than in the case of the PVC matrix electrode. An identical situation occurs while comparing the pH effect on EMF. The range of constant dependence of pH on EMF is wider for the developed electrode than the electrode described in the literature. The rest of the parameters, like response time and detection limit, are better for PVC matrix electrodes. However, the analytical properties of the electrode described in the literature are worse. The standard deviation values show that the precision of labetalol determination made by using the solid-state electrode is smaller in opposition to the electrode with liquid membrane. The assays carried out with the studied electrode are characterised by good precision and small determination error.

Besides, the assays carried out with direct potentiometry were better than the applied parallel determinations such as UV spectrophotometry and HPLC methods, especially because of the low costs of the apparatus and reagents as well as the shorter experimental time. A good agreement between results obtained by these methods indicates that the proposed electrode is suitable for labetalol determination in simple pharmaceuticals.

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| Solvent            | Slope of calibration curve [mV/decade] | Correlation coefficient | Linearity range of calibration curve [mol L\(^{-1}\)] |
|--------------------|----------------------------------------|-------------------------|-----------------------------------------------------|
| 1,1,2-trichloroethane | 0.061 ± 0.000                          | 0.9992                  | 1 \times 10^{-5} - 1 \times 10^{-2}                |
| 1,2-dichloroethane  | 0.074 ± 0.001                          | 0.9992                  | 1 \times 10^{-5} - 1 \times 10^{-2}                |
| chlorobenzene      | 0.058 ± 0.003                          | 0.9945                  | 5 \times 10^{-5} - 5 \times 10^{-2}                |
| 1,2-dichlorobenzene| 0.061 ± 0.006                          | 0.9976                  | 5 \times 10^{-5} - 5 \times 10^{-2}                |
| chloroform         | 0.078 ± 0.002                          | 0.9969                  | 5 \times 10^{-5} - 1 \times 10^{-2}                |

**Table 1** Analytical parameters of the electrodes containing studied membrane solvents.
| Interfering ion | Medium selectivity coefficient |
|----------------|-------------------------------|
| K$^+$          | 0.526 ± 0.717                |
| Na$^+$         | 2.91×10$^{-2}$± 1.37×10$^{-2}$ |
| NH$_4^+$       | 5.56×10$^{-2}$± 4.28×10$^{-2}$ |
| Ca$^{2+}$      | 1.91×10$^{-3}$± 0.44×10$^{-3}$ |
| Mg$^{2+}$      | 6.97×10$^{-4}$± 5.44×10$^{-4}$ |
| Fe$^{2+}$      | 1.64×10$^{-2}$± 0.79×10$^{-2}$ |
| Cu$^{2+}$      | 8.30×10$^{-3}$± 3.46×10$^{-3}$ |
| Ephedrine      | 0.288 ± 0.128                |
| Ethaverine     | 4.328 ± 1.230                |
| Fluphenazine   | 0.166 ± 0.109                |
| Papaverine     | 0.193 ± 0.090                |
| Promazine      | 10.265 ± 2.413               |
| Prometazine    | 0.232 ± 0.133                |
| Pyrantel       | 3.272 ± 4.026                |
| Verapamil      | 0.125 ± 0.053                |

Table 2 Medium selectivity coefficient values of selected cations (labetalol hydrochloride concentration: 1×10$^{-4}$mol L$^{-1}$).
| Sample | Declared quantity [mg] | Determined quantity [mg] | Mean results ± standard deviation [mg] | Determination error [%] | Declared quantity [mg] | Determined quantity [mg] | Mean results ± standard deviation [mg] | Determination error [%] | Declared quantity [mg] | Determined quantity [mg] | Mean results ± standard deviation [mg] | Determination error [%] |
|--------|------------------------|--------------------------|----------------------------------------|------------------------|------------------------|--------------------------|----------------------------------------|------------------------|------------------------|--------------------------|----------------------------------------|------------------------|
| 1      | 100                    | 102.3                    | 101.9 ± 0.9                            | + 1.9                  | 105.0                  | 104.1 ± 2.3              | + 4.1                                  | 102.7                  | 103.0                  | 103.6 ± 1.3              | + 3.6                                  |
|        | 100.9                  |                          |                                        |                        | 105.9                  |                          |                                        |                        | 105.0                  |                          |                                        |                        |
|        | 102.4                  |                          |                                        |                        | 101.5                  |                          |                                        |                        |                       |                                        |                        |
| 2      | 100                    | 100.9                    | 101.4 ± 1.1                            | + 1.4                  | 105.1                  | 101.3 ± 1.4              | + 4.3                                  | 103.6                  | 105.7 ± 1.8              | + 5.7                                  |
|        | 100.6                  |                          |                                        |                        | 102.7                  |                          |                                        |                        | 106.7                  |                          |                                        |                        |
|        | 102.6                  |                          |                                        |                        | 105.2                  |                          |                                        |                        | 106.7                  |                          |                                        |                        |
| 3      | 100                    | 101.7                    | 102.4 ± 0.8                            | + 2.4                  | 100.1                  | 100.8 ± 1.9              | + 0.8                                  | 106.7                  | 104.3 ± 2.2              | + 4.3                                  |
|        | 103.2                  |                          |                                        |                        | 99.3                   |                          |                                        |                        | 102.4                  |                          |                                        |                        |
|        | 102.4                  |                          |                                        |                        | 103.0                  |                          |                                        |                        | 103.7                  |                          |                                        |                        |
| Sample | Declared quantity [mg] | Determined quantity [mg] | ± Standard deviation [mg] | Error [%] | Potentiometric method | HPLC method | Spectrophotometric method |
|--------|------------------------|--------------------------|--------------------------|-----------|-----------------------|-------------|--------------------------|
|        |                        |                          |                          |           |                       |             |                          |
| 1      | 200                    | 195.6 ± 0.3              | -2.2                     | 204.6 ± 0.9 | +2.3                  | 201.5       | 204.7                    |
| 2      |                        | 195.3 ± 0.3              | -1.8                     | 202.6 ± 1.9 | +1.1                  | 200.4       | 202.3                    |
| 3      |                        | 196.1 ± 0.2              | -1.9                     | 201.7 ± 1.7 | +1.2                  | 201.5       | 201.2                    |

Table 4 Results of labetalol hydrochloride determination in (Pressocard tablets).
Fig. 1 The electrode construction:
1 – the electric lead,
2 – electric contact,
3 – silver – silver chloride electrode,
4 – electrode inner solution,
5 – spring,
6 – membrane solution,
7 – porous membrane,
A – nut,
B – middle casing part,
C – the electrode core,
D – lower casing part.
Fig. 2 Calibration curve obtained with 1,1,2,2-tetrachloroethane.
Fig. 3 Effect of pH on the labetalol electrode potential (labetalol hydrochloride concentrations: $1 \times 10^{-3}$ mol L$^{-1}$, $5 \times 10^{-4}$ mol L$^{-1}$, $1 \times 10^{-4}$ mol L$^{-1}$).
Fig. 4 The curves of changes of electrode selectivity coefficient for several inorganic cations.
Fig. 5 The curves of changes of electrode selectivity coefficient for several drug organic cations.