Quantitative determination of Lisinopril Dihydrate in pharmaceutical preparations by direct potentiometry

S Bozhanov¹, M Smerikarova¹ and V Maslarska*¹
¹Department of Chemistry, Faculty of Pharmacy, Medical University-Sofia, Sofia, 1000, Bulgaria
*Corresponding author’s e-mail: vmaslarska@mail.bg

Abstract. A direct potentiometric titration method was applied for determination of Lisinopril Dihydrate. The method was based on the treatment of the primary data with nonlinear regression procedure. An accessible and easy-to-use algorithm for the evaluation (quantification) of a system with acid-base properties has been developed to provide a quick and unambiguous answer for the quantitative content of Lisinopril Dihydrate. The acid-base constants of Lisinopril Dihydrate were determined in aqueous solutions (at constant ionic strength 0.2 mol/l KCl and temperature 25ºC). The potentiometric method developed was validated according to ICH and shows very good accuracy and precision. The present approach can be successfully used in routine analysis of the drug in quality control laboratories.

1. Introduction
Combination therapy with Lisinopril – a potent ACE inhibitor (chemically known as (2S)-1-[(2S)-6-amino-2-[(1S)-1-carboxy-3-phenylpropyl]amino]hexanoyl]pyrroloidine-2-carboxylic acid) and Hydrochlorothiazide – a diuretic from the group of thiazides (chemically known as 6-chloro-1,1-dioxo-3,4-dihydro-2H-1,2,4-benzothiadiazine-7-sulfonamide) has been shown to be effective in treating high blood pressure and heart failure [1]. Chemical structures of both drugs are shown in figure 1.

Figure 1. Chemical structures of Lisinopril (1) and Hydrochlorothiazide (2).

Wide use of such drugs requires reliable methods for quality control of bulk substances and pharmaceutical formulations. Various methods such as titrimetry [2], voltammetry [3, 4], spectrophotometry [5, 6] and spectrofluorimetry [7, 8] have been reported for determination of the two drugs. Analysis
based on HPTLC [9] and HPLC [10-13] methods are also available. Despite the variety of techniques, direct potentiometry probably remains the simplest method in terms of materials used, equipment availability and labor intensity.

Complex interactions were established in each acid-base system, that is why the acid-base equilibrium depends on many factors. Such complicated relations can be described by regression methods. Most often linear or nonlinear regression was applied to equations of the type \( V = f (h) \) or \( V = f (E) \) for \( pH / ml \) data and \( V / E \) data respectively. This work was based on the earlier developed approach for data processing of potentiometric titration of substances with acid - base properties [14-16]. Using the mass balance equations and proton stability of the species, a well-defined formula valid for each titration of mono- and polyfunctional protoliths was derived - Equation (1)

\[
V = V_o * \left( h - K_w / h + \sum_{m=1}^{M} \sum_{n=1}^{N} B_{o,m} * \bar{n}_{H,m} \right) / (C_t - h + K_w / h)
\]

where, \( V \) - is volume of the added titrant, ml; \( V_o \) - initial volume of the titrated solution, ml; \( h \) - concentration of protons, mol/l; \( K_w \) - autoprotolysis constant of water; \( M \) - number of components; \( N \) - maximum number of protons that a protolyte can accept or release; \( B_o \) - concentration of the analyzed base (resp. \( A_o \) for acid), mol/l; \( C_t \) - total concentration of the titrant, mol/l.

As a result, the proton stability acid-basic constants \( \beta_n \) (resp. \( pK \)), autoprtolysis constant \( (K_w) \) of the water and the concentration of the analysed substance \( (B_o) \) were obtained.

The theoretical foundations of the proposed method were based on the fact that acid - base interactions were represented as complex formation process between the base (B) or the acid (A) and the ligand H (protons). Steady-state equilibrium represents interaction in a mononuclear system. The aim of this study is to develop and validate an analytical method for routine analysis of Lisinopril Dihydrate in pharmaceutical preparations using direct potentiometry.

2. Material and methods

2.1. Measurements

2.2. The measurements were carried at constant ionic strenght (KCl, 0.2 mol/l) in thermostated vessel (25°C). A 713 Metrohm pH-meter, equipped with combined electrode (ref. 6.0228.000 Pt1000) with temperature sensor and auto burette “Radiometer” ABU 80 were used. Reagents and solutions

Sodium hydroxide – p.a. and Potassium chloride – p.a. (Merck, Darmstadt, Germany) were used without purification. Lisinopril Dihydrate standard was obtained from Sigma Aldrich. Tablet formulation containing Lisinopril Dihydrate 20 mg and Lisinopril 20 mg + Hydrochlorothiazide 12.5 mg in VITOPRIL plus tablets STADA were obtained commercially. All chemicals investigated, corresponded to p.a. purity and were used without purification.

Sodium hydroxide (0.01 mol/l) in water was prepared by dilution of certified volumetric solutions with carbon-dioxide free redistilled water. The solution of sodium hydroxide was standardized with standard solution of hydrochloric acid.

2.3. Preparation of the standard solution

Aqueous solution (0.01 mol/l) of Lisinopril Dihydrate standard was prepared. The titrant used was a standard solution of sodium hydroxide (0.01 mol/l).

2.4. Sample Preparation

2.4.1. Procedure for Lisinopril Dihydrate. A solution of the analyzed substance at concentration of 0.01 mol/l and a constant ionic strength 0.2 mol/l was prepared. Aliquot samples of 10.0 ml and 90.0 ml 0.2 mol/l KCl were titrated at 25±0.1°C with a standard0.01mol/l NaOH.
2.4.2. **Procedure for Lisinopril Dihydrate in Tablets.** Twenty tablets were weighed accurately and ground into a fine powder. One portion of the powder equivalent to 300 mg of Lisinopril Dihydrate (0.01 mol/l) was accurately weighed into a 100 ml volumetric flask. The extraction was done by adding 40 ml of water and shaking for 20 minutes. After that the volume was adjusted to the mark with distilled water and the solution was filtrated using a filter paper. Aliquot samples of 10.0 ml were mixed with 90.0 ml 0.2 mol/l KCl and titrated according to the above described scheme.

### 3. Results and discussion

The Equation 1 was applied to the analysis of Lisinopril Dihydrate substance. With the help of non-linear regression pKₐ values were calculated, than were set as constants for further data processing and calculating of the analytical results. Analysis of Lisinopril Dihydrate according to European Pharmacopoeia 8.0 was also performed. The results obtained by the two methods were in very good agreement (table 1). Further, in order to validate the method, the procedure was applied for the analysis of synthetic mixtures of the pharmaceutical form of Lisinopril Dihydrate as well as placebo sample.

| Substance       | pKₐ₁ | pKₐ₂ | Found, % | Ph.Eur.8 |
|-----------------|------|------|----------|----------|
| Lisinopril Dihydrate | 3.49 | 4.40 | 99.53    | 99.80    |

All of the analytical validation parameters for this proposed method were determined according to ICH guidelines [17, 18] as follows:

#### 3.1. Selectivity

A placebo blank containing calcium hydrogen phosphate dehydrate, magnesium stearate, cornstarch, mannitol and colloidal anhydrous silica was prepared, extracted and solution made as described under “procedure for tablets”. Aliquot samples were titrated according to the recommended procedure. It was found that there was no interference between the analyte and placebo.

#### 3.2. Accuracy

Accuracy studies were performed by titration of samples at three different concentration levels. The accuracy was evaluated as percentage relative standard deviation (%) between the measured and taken amounts/concentrations. Relative standard deviation was found to be less than 2% which was within the limits according to ICH. The results of this study are compiled in table 2.

| Lisinopril Dihydrate, taken, mg | Intra-day accuracy | Inter-day accuracy |
|---------------------------------|--------------------|--------------------|
|                                 | Lisinopril Dihydrate found*, mg | %, RSD          | Lisinopril Dihydrate found*, mg | %, RSD          |
| 10.0                            | 10.21               | 0.684              | 10.12                          | 1.135            |
| 20.0                            | 19.78               | 0.345              | 20.03                          | 0.432            |
| 30.0                            | 29.93               | 0.231              | 29.56                          | 0.324            |

* Average of three independent procedures.

#### 3.3. Precision

Precision of the proposed method was established by six-time analysis of Lisinopril Dihydrate in substance and tablets. The results obtained are presented in table 3.
Table 3. Results of the Precision analysis of Lisinopril Dihydrate and tablets 20 mg.

| №  | Substance, % | Tablets, mg |
|----|--------------|-------------|
| 1  | 99.95        | 20.13       |
| 2  | 100.05       | 19.89       |
| 3  | 99.87        | 20.34       |
| 4  | 99.29        | 20.16       |
| 5  | 99.86        | 20.11       |
| 6  | 100.5        | 19.56       |

Parameter

- Mean: 99.92, 20.03
- Stand.Deviation: 0.389, 0.272
- Rel.SD,:% 0.389, 1.358
- Conf. Interval: 0.408, 0.285
- % Error: 0.408, 1.424

3.4. Application to combined dosage form

The proposed method was applied to combined dosage form. Results of the statistical processing of the obtained method (table 4) repeat data for the analysis of Lisinopril 20 mg and Hydrochlorothiazide 12.5 mg in VITOPRIL plus tablets STADA.

| №  | Lisinopril, mg | Hydrochlorothiazide, mg |
|----|----------------|-------------------------|
| 1  | 19.90          | 12.51                   |
| 2  | 20.10          | 12.48                   |
| 3  | 19.96          | 12.42                   |
| 4  | 20.11          | 12.55                   |
| 5  | 20.03          | 12.48                   |
| 6  | 20.06          | 12.53                   |

Parameter

- Mean: 20.03, 12.49
- Stand.Deviation: 0.082, 0.046
- Rel.SD,:% 0.411, 0.368
- Conf. Interval: 0.086, 0.048
- % Error: 0.431, 0.386

4. Conclusions

The applied approach provides an accessible procedure for processing the experimental data in order to quantify substances with acid-base properties. A quantitative method suitable for routine laboratory analysis of Lisinopril Dihydrate substance, Lisinopril Dihydrate with Hydrochlorothiazide in tablets was developed. The method was validated and has been proven to have very good reproducibility and accuracy.

Acknowledgements

The authors are thankful to Faculty of Pharmacy, Medical University-Sofia, Bulgaria for providing lab facilities.

References

[1] Sukalo, A., Deljo, D., Krupalija, A., Zjajo, N., Kos, S., Curic, A., Divkovic, G., Hubjar, S., Smailagic, M., Hodzic, E., Marjanovic, D., Medjedovic, S. (2016) Treatment of hypertension with combination of lisinopril/hydrochlorothiazide. Med. Arch., 70(4): 299-302.
[2] Olalowo, A.W., Adegbolagun, O.M., Bamiro, O.A. (2015) Simple potentiometry and phenolphthalein-based titrimetric methods of analysis for Lisinopril tablets. Afr. J. Pharm. Pharmacol., 9(6): 165-172.

[3] González-Vargas, C., Serrano, N, Ariño, C., Salazar, R., Esteban, M., Díaz-Cruz, J.M. (2017) Voltammetric determination of anti-hypertensive drug hydrochlorothiazide using screen-printed electrodes modified with l-glutamic acid. Chemosensors, 5: 25-36.

[4] Valezi, C.F., Eisele, A.P.P., Sartori, E.R. (2017) Versatility of a carbon paste electrode coupled to differential pulse voltammetry for determination of lisinopril with its associations (hydrochlorothiazide and amlodipine). Anal. Methods, 9: 4599-4608.

[5] Shraihat, M., Okdeh, M.M.S. (2016) New method for spectrophotometric determination of lisinopril in pure form and in pharmaceutical formulations. Mod. Chem. Appl., 4(1): 172-175.

[6] Patel, N., Prabhu, P., Walia, S. (2015) Spectrophotometric quantitative estimation of hydrochlorothiazide and lisinopril in bulk drugs and pharmaceutical dosage form. World J. Pharm. Res., 4(9): 1684-1701.

[7] Derayea, S.M., Badr El-din, K.M., Mohammed, F.F. (2018) An innovative validated spectrofluorimetric method for determination of lisinopril in presence of hydrochlorothiazide; application to content uniformity testing. Spectrochim. Acta A, 188: 318-323.

[8] Derayea, S.M., Badr El-din K.M., Mohammed, F.F. (2017) Selective spectrofluorimetric method for determination of Lisinopril in pharmaceutical preparations and in presence of hydrochlorothiazide: Application to content uniformity testing. Luminescence, 32(8): 1482-1487.

[9] Pandya, J.J., Sanyal, M., Shrivastav, P.S. (2017) Simultaneous densitometric analysis of amlodipine, hydrochlorothiazide, lisinopril, and valsartan by HPTLC in pharmaceutical formulations and human plasma. J. Liq. Chromatogr. Relat. Technol., 40(9): 467.

[10] Mohammed, N.S., Mohammed, A.J. (2016) Development and validation of RP-HPLC method for the determination of hydrochlorothiazide in bulk drug and pharmaceutical dosage form. Chromatogr. Res. Int., 2016, Article ID 1693024, pp. 1-7.

[11] Shah, J.V., Shah, P.A., Shah, P.V., Sanyalc, M., Shrivastava, P.S. (2017) Fast and sensitive LC-MS/MS method for the simultaneous determination of lisinopril and hydrochlorothiazide in human plasma. J. Pharm. Anal., 7:163–169.

[12] Eid, M., El-Shabrawy, Y., El-Shaheny, R. (2017) Green micellar HPLC analysis of three angiotensin - converting enzyme inhibitors in their mixtures with hydrochlorothiazide and modeling of their retention behavior by fitting to Foley's model. J. Sep. Sci., 40(18): 3646-3654.

[13] Dawud, E.R., Shakya, A.K. (2019) HPLC-PDA analysis of ACE-inhibitors, hydrochlorothiazide and indapamide utilizing design of experiments. Arab. J. Chem., 12: 718–728.

[14] Maslarska, V., Tencheva, J., Budevsky, O. (2003) New approach in the treatment of data from an acid–base potentiometric titration I. Monocomponent systems of monofunctional acids and bases. Anal. Bioanal. Chem., 375(2): 217–222.

[15] Maslarska, V., Tencheva, J., Budevsky, O. (2005) A new approach to data treatment in acid-base potentiometric titration II. Determination of polyprotic acids and bases. Chem. Anal. (Warsaw), 50(5): 815-823.

[16] Maslarska, V., Tencheva, J., Budevsky, O. (2011) Potentiometric analysis of mixtures of acids or bases. Der Chemica Sinica, 2(6): 325-330.

[17] International Conference on Harmonization (2005) ICH harmonized tripartite guideline Validation of analytical procedures: text and methodology Q2 (R1) ICH. Geneva, Nov; 2005.

[18] European Pharmacopoeia 8th Edition, Vol. 2, 2014.