Spectrophotometric methods for the determination of lisinopril in medicines

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Abstract

Two simple, rapid and green spectrophotometric methods are described for the determination of lisinopril medicines. The determination is based on the reaction of the primary amino group of the lisinopril with ninhydrin in aqueous medium (Method I) and reaction on the carboxylic group of the lisinopril with copper (II) sulfate (Method II). For both methods, optimal spectrophotometric conditions were established. The linear relationship was found between absorbance at λmax and concentration of drug in the range 40–60 µg/mL (Method I) and 0.592–2.072 mg/mL (Method II). Regression analysis of Beer’s law plot at 400 nm yielded the regression equation, $y = 7.4929x – 0.0545$ (Method I) and at 730 nm $y = 0.0443x – 0.0832$ (Method II). High values of correlations coefficient ($R^2 = 0.9917$ (Method I) and $R^2 = 0.999$ (Method II)) and small values of intercept validated the linearity of calibration curve and obedience to Beer’s law. The LOD and LOQ values were calculated to be 6.91 µg/mL and 23.01 µg/mL respectively (Method I) and 0.11 mg/mL and 0.36 mg/mL respectively (Method II). Intra-day and inter-day accuracy and precision were in acceptable limits. The proposed methods were applied for the quantification of lisinopril in tablets pertaining to three commercial formulations. Analytical eco-scale for greenness assessment of the proposed spectrophotometric methods showed that both methods correspond to excellent green analysis.

Keywords

Analytical Eco-Scale, Copper (II) sulfate, Lisinopril, Ninhydrin, Spectrophotometry

Introduction

Nowadays, hypertension is becoming a worldwide problem. Several medicines used for treatment hypertension. Lisinopril is a competitive inhibitor of angiotensin-converting enzyme (ACE) and prevents the conversion of angiotensin I to angiotensin II, which is a potent vasoconstrictor (https://www.ncbi.nlm.nih.gov/books/NBK482230/). The chemical name of lisinopril is (2S)-1-[(2S)-6-amino-2-[[1S]-1-carboxy-3-phenylpropyl]amino]hexanoyl]pyrrolidine-2-carboxylic acid (Fig. 1) (European Pharmacopoeia 2020). Physico-chemical methods of analysis are increasingly being introduced into basic pharmaceutical research and the practice of pharmaceutical analysis, given their high sensitivity, accuracy, specificity and expressiveness. Chemists-analysts constantly work on the development of new methods for the analysis of API in drugs and biological fluids and on their optimization in order to save time and materials, which also ensures the effectiveness of the developed methodology. European Pharmacopoeia 2020 has a monograph on the substance of
lisinopril dihydrate. Identification of lisinopril dihydrate EPh regulates to perform the absorption spectrophotometry in the infrared region and specific optical rotation and the quantitative determination – alkalimetry.

Analytical methods of analysis such as HPLC (El Gindy et al. 2001; Beasley et al. 2005; Ivanovic et al. 2007; Chauhan et al. 2011; Sultana et al. 2011; Naveed et al. 2012; Arayne et al. 2013; Peleshok et al. 2021a; Shulyak et al. 2021), LC/MS (Andreas et al. 2003; Huang et al. 2006; Drapak et al. 2019a, b), gas chromatography with mass detection (Leis et al. 1998, 1999), spectrophotometry (El-Emam et al. 2004; Rahman et al. 2005a, b; Basavaiah et al. 2009; Jamakhandi et al. 2011; Sbârcea et al. 2014) have been developed for the determination of lisinopril in medicines and biological liquids. Spectrophotometry as a quantitative analytical methodology belongs to the foremost oft-used analytical techniques in pharmaceutical analysis. It provides sensible and significant economic benefits over alternative ways. Visible spectrophotometry is the technique of choice even today because of its inherent simplicity, selectivity, sensitivity, precision, accuracy and cost-effectiveness. In the available sources, several different spectrophotometric methods have been reported for quantification of lisinopril in medicines using different reagents (El Gindy et al. 2001; El-Emam et al. 2004; Rahman et al. 2005a, b; Basavaiah et al. 2009; Jamakhandi et al. 2011; Sbârcea et al. 2014). However, many of these methods are limited in their applications or rather much tedious and time consuming. There is, therefore, a need for a rapid simple spectrophotometric methods for the assay of lisinopril in medicinal products.

The present paper describes a rapid, simple and green spectrophotometric methods for the determination of lisinopril in medicines using different reagents (El Gindy et al. 2001; El-Emam et al. 2004; Rahman et al. 2005a, b; Basavaiah et al. 2009; Jamakhandi et al. 2011; Sbârcea et al. 2014). However, many of these methods are limited in their applications or rather much tedious and time consuming. There is, therefore, a need for a rapid simple green spectrophotometric methods for the assay of lisinopril in medicinal products.

The present paper describes a rapid, simple and green spectrophotometric methods for the determination of lisinopril in medicines. The determination is based on the reaction of the primary amino group of the lisinopril with ninhydrin in aqueous medium (Method I) and reaction on the carboxylic group of the lisinopril with copper (II) sulfate (Method II).

Aim of work

We aimed to develop and validate rapid, simple and green spectrophotometric methods for the determination of lisinopril in medicines.

Materials and methods

Apparatus

A double – beam Shimadzu UV-Visible spectrophotometer, with spectral bandwidth of 1 nm wavelength accuracy ±0.5 nm, Model –UV 1800 (Japan), Software UV-Probe 2.62, and a pair of 1 cm matched quartz cells, was used to measure absorbance of the resulting solution. Designed in accordance with the governing Japanese and European Pharmacopoeia, the new UV-1800 UV-VIS spectrophotometer achieves a resolution of 1 nm, the highest in its class, in a compact design.

Reagents and standards

All the chemicals were used of analytical reagent grade.

0.2% solution of ninhydrin

200 mg of chemical (Sigma-Aldrich) were dissolved in water and brought to 100 mL with water. Freshly prepared ninhydrin solution was always used.

0.02 M Copper (II) sulfate

The solution was prepared by dissolving 319 mg of chemical (Honeywell Fluka) in water and diluting to 100 mL in a calibrated flask.

Pharmacopeial standard sample of lisinopril dihydrate was provided by Sigma-Aldrich (≥ 98%, HPLC).

The used dosage forms of lisinopril: Lisinopril – Astrapharm (Ukraine) (20 mg), Lisinopril-KRKA (Slovenia) (20 mg), Lisinopril-Teva (Germany) (20 mg).

Spectrophotometric method I

Proposed procedure for the determination of lisinopril with ninhydrin

Different aliquots of 100 µg/mL lisinopril methanol solution (40–60 µg/mL) were accurately measured and transferred in heating tubes. 1.1 mL of 0.2% solution of ninhydrin was added to each tube. The mixture was kept in a water bath at 95 ± 2 °C for 25 minutes, then cooled to room temperature and transferred into a 25 mL volumetric flask. The volume was made up to the mark by adding water. The absorbance was measured at 400 nm against the reagent blank, which was similarly prepared by omitting the drug. The calibration curve was performed by plotting the measured absorbance values versus concentration.

Procedure for pharmaceutical formulation for the determination of lisinopril with ninhydrin

Twenty tablets were accurately weighed and powdered. A quantity of powder containing 25 mg of lisinopril was transferred into a 25 mL volumetric flask with 15 mL methanol. The mixture was shaken for 15 min, diluted to volume with methanol and then filtered using 0.2 µm Nylon.
filter membrane. The filtrate was subsequently subjected to analysis using the above described procedure.

**Spectrophotometric method II**

*Proposed procedure for the determination of lisinopril with copper (II) sulfate*

Different aliquots of 10 mg/mL lisinopril aqueous solution (0.5–2.1 mg/mL) were accurately measured and transferred into a 25 mL volumetric flask. 10.0 mL of 0.02 M solution of copper (II) sulfate was added to each tube. The volume was made up to the mark by adding water. The absorbance was measured at 730 nm against the reagent blank, which was similarly prepared by omitting the drug. The calibration curve was performed by plotting the measured absorbance values versus concentration.

**Procedure for pharmaceutical formulation for the determination of lisinopril with copper (II) sulfate**

Thirty tablets were accurately weighed and powdered. A quantity of powder containing 0.37 g of lisinopril was transferred into a 50 mL volumetric flask with 35 mL water. The mixture was shaken for 15 min, diluted to volume with water and then filtered using 0.2 µm Nylon filter membrane. The filtrate was subsequently subjected to analysis using the above described procedure. Aliquots of 5 mL lisinopril aqueous solution was accurately measured and transferred into a 25 mL volumetric flask. 10.0 mL of 0.02 M solution of copper (II) sulfate was added to each tube. The volume was made up to the mark by adding water. The absorbance was measured at 730 nm against the reagent blank, which was similarly prepared by omitting the drug. The calibration curve was performed by plotting the measured absorbance values versus concentration.

**Results and discussion**

**Method development**

**Spectrophotometric method I**

The ninhydrin has been known as a reagent for the detection of amino acids and amines for many years and therefore, a number of theories have been put forward to explain the mechanism of its reaction. It was suggested that the reactions of ninhydrin with amine, amino acids and imino acids all proceed by the same mechanism (Mccaldin 1960) to give diketohydrindylidene–diketohydrindane. This compound would further react with amino group to give the product which absorbed maximally at 400 nm and 560 nm. Results of experiments suggested that a higher sensitivity could be achieved at λmax 400 nm, which was selected for the following studies (Fig. 2 and Scheme I).

Different parameters such as the temperature, heating time, reagents concentration have been analyzed, in order to render the optimal conditions for reaction. It has been noted that the complete color development was attained at 95 ± 2 °C. Optimum reaction time has been determined by heating the reaction mixture on a water bath at 95 ± 2 °C. A heating time of 25 minutes was found as optimal for the development of the purple color product (Fig. 3).
been measured against reagent blank. The optimum value was found to be 1.1 mL of 0.2% ninhydrin (Fig. 4).

To establish the analytical sensitivity of valsartan with ninhydrin, the sensitivity of the reaction was calculated. The molar absorption index ($\varepsilon$) was $2.44 \times 10^3$, the specific absorption ($a$) was $6.02 \times 10^{-1}$, and the Sendel coefficient ($W_5$) was $1.66 \times 10^{-4}$.

**Spectrophotometric method II**

In neutral media lisinopril forms with Cu$^{2+}$ ions a blue complex compound. Figure 5 shows the spectrum of this compound with an absorption maximum at $\lambda = 730$ nm. Schemes II, III present proposal of the reaction pathway between lisinopril and copper (II) sulfate and suggested reaction mechanism for reaction between lisinopril and copper (II) sulfate.

The stoichiometry of the reaction was determined using Job’s method of continuous variation (Job 1936). Master equimolar solutions ($1 \times 10^{-3}$ M) of copper (II) sulfate with lisinopril were prepared. The method revealed 1:2 ratio (copper (II) sulfate:lisinopril). The results obtained from molar ratio studies were in agreement with the suggested reaction mechanism (Scheme III) (Fig. 6).

To establish the analytical sensitivity of valsartan with copper (II) sulfate, the sensitivity of the reaction was calculated. The molar absorption index ($\varepsilon$) was $0.13 \times 10^3$, the specific absorption ($a$) was $3.08 \times 10^{-3}$, and the Sendel coefficient ($W_5$) was $2.40 \times 10^{-3}$.

**Method validation**

**Linearity**

Beer’s law limit, molar absorptivity, detection limit, regression equation and correlation coefficient were obtained by least square treatment of results (ICH 2005). The linear relationship was found between absorbance at $\lambda_{max}$ and concentration of drug in the range 40–60 µg/mL.
(Method I) and 0.592–2.072 mg/mL (Method II). Regression analysis of Beer’s law plot at 400 nm yielded the regression equation, $y = 7.4929x - 0.0545$ (Method I) and at 730 nm $y = 0.0443x + 0.0832$ (Method II). High values of correlation coefficient ($R^2 = 0.9917$ (Method I) and $R^2 = 0.999$ (Method II)) and small values of intercept validated the linearity of calibration curve and obedience to Beer’s law. Calibration curves are presented in Figure 7A, B. The range of application for Method I was narrow but these results did affect other validation parameters.

**Limits of detection and quantification**

The ICH guidelines were followed in order to determine the LOD and LOQ. Accordingly, the method based on the standard deviation of the response and the slope has been applied, so that 3.3 and 10 times the standard deviation values of y-intercept of regression line and the regression equation were used to calculate the LOD and LOQ. The LOD and LOQ values were calculated to be 6.91 μg/mL and 23.01 μg/mL respectively (Method I) and 0.11 mg/mL and 0.36 mg/mL respectively (Method II).

**Selectivity**

The proposed methods were tested in order to assess its selectivity using the artificial mixture for analysis. It has been confirmed that the measured absorbance was only produced by the analyte. A synthetic mixture was prepared, containing lisinopril (20 mg), calcium hydrogen phosphate, mannitol (E 421), corn starch, magnesium stearate, colloidal anhydrous silica. The extract was yielded according to the procedure that was described for tablets and subsequently analyzed using the procedure previously described. The replicate analysis ($n = 5$) for a concentration level of 52 μg/mL lisinopril has yielded the % lisinopril recovery at 100.42 ± 1.25 (Method I) and for a concentration level of 1.78 mg/mL has yielded the % lisinopril recovery at 100.85 ± 1.41 (Method II), and thus revealed that the inactive ingredients did not interfere with lisinopril determination.

**Precision and accuracy**

Intra- and inter-day precision values have been calculated by replicate analysis ($n = 5$) of calibration standard, at three different concentration levels, during the same day, and then during 5 consecutive days. The RSD (%) values of intra- and inter-day measurements have indicated a good precision. (Table 1). Accuracy, defined as the closeness between the reference and the found values, has been evaluated, on the other hand, as percentage relative error between the measured and theoretical concentration of lisinopril. The results are presented in Table 1, and show good accuracy for developed methods.

**Application to pharmaceutical formulation**

The proposed methods were applied for the quantification of lisinopril in tablets pertaining to three commercial formulations. The results as presented in Table 2 reveal no significant differences between the proposed methods. The Student’s t- and the F-values at 95% confidence level are less than the theoretical one, but nevertheless confirming a good agreement between the results obtained by the proposed methods.

**Table 1. Intra-day and inter-day accuracy and precision.**

| Method | Lisinopril taken, μg/mL (Method I), mg/mL (Method II) | Intra-day accuracy and precision | Inter-day accuracy and precision |
|--------|------------------------------------------------------|---------------------------------|---------------------------------|
|        | Lisinopril found, μg/mL (Method I), mg/mL (Method II) | RE, % | RSD, % | Lisinopril found, μg/mL (Method I), mg/mL (Method II) | RE, % | RSD, % |
| I      | 40 | 39.97 | 0.65 | 1.09 | 40.11 | 0.74 | 1.06 |
|        | 50 | 50.07 | 0.60 | 1.18 | 49.86 | 0.85 | 1.14 |
|        | 60 | 60.13 | 1.09 | 1.31 | 60.07 | 0.56 | 1.01 |
| II     | 0.59 | 0.5901 | 0.74 | 1.06 | 0.5904 | 0.36 | 1.02 |
|        | 1.48 | 1.4795 | 0.49 | 1.53 | 1.4803 | 0.45 | 1.08 |
|        | 2.07 | 2.0689 | 0.82 | 1.37 | 2.0692 | 0.51 | 1.04 |

RE – Relative error; RSD – Relative standard deviation.
Robustness

The evaluation of robustness was carried out at the stage of development of spectrophotometric methods for the determination of valsartan during the establishment of optimal conditions for the course of reactions and determination of factors that may affect the optical density (stability of solutions over time). It was found that the studied solutions were stable for at least 45 minutes (Figs 8, 9).

Analytical eco-scale for greenness assessment

Analytical eco-scale is a semi-quantitative assessment tool commonly used for examining the greenness of analytical methods in a comparative manner (Van Aken et al. 2006; Peleshok et al. 2021b, 2021c; Galuszka et al. 2012). It is based on assigning a numerical score, penalty points, for every step in the whole analytical method of analysis that may affect the green system such as solvents, reagents, their amounts, energy consumption, occupational risk and waste generated hazards.

Table 3 summarizes the results of developed methods found to be an excellent green analysis with a score of 89 (Method I) and 93 (Method II).

Conclusion

Two simple, rapid and green spectrophotometric methods were developed for the determination of lisinopril medicines. The determination was based on the reaction of the primary amino group of the lisinopril with ninhydrin in aqueous medium (Method I) and reaction on the carboxylic group of the lisinopril with copper (II) sulfate (Method II). Optimal spectrophotometric conditions were established. As a result of calculations of analytical indicators of sensitivity of reactions it was established that reaction of valsartan with ninhydrin has higher sensitivity, than reaction of valsartan with copper (II) sulphate that was testified by high value of molar coefficient of absorption and low value of an opening minimum. The proposed methods were validated for selectivity, linearity, limits of detection and quantification, precision and accuracy. The results of the assay of medicines of the developed methods are highly reliable and reproducible and are in good agreement with the label claim of the drugs. The developed methods can help research studies, quality control and routine analysis with lesser resources available.

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