Original articles

Simultaneous determination of lisinopril and amlodipine besylate in tablets by high performance liquid chromatography

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Abstract

Background: Hypertension is a common disease, and the fixed-dose combination of lisinopril and amlodipine is widely used to improve blood pressure control, enhance patient adherence, and reduce treatment costs. However, no specific monographs are currently available in the Vietnamese Pharmacopoeia V or other reference pharmacopoeias for quality control of this combination. Objective: Development and validation of a high performance liquid chromatography (HPLC) method for the simultaneous determination of lisinopril and amlodipine besylate in combined tablets.

Materials and Methods: *Material:* The fixed-dose combination tablets containing lisinopril dihydrate and amlodipine besylate. *Method:* Investigation of chromatographic conditions, development and validation of the HPLC method according to ICH guidelines.

Results: Chromatographic conditions: InertSustain® C18 column (250 × 4.6 mm, 5 µm) using gradient elution with methanol and 0.1% trifluoroacetic acid in water (pH 2), detection wavelength at 210 nm, column temperature of 40 °C, flow rate of 1.0 mL/min, injection volume of 10 µL. LIS and AML were completely separated, with retention times of 3.897 and 9.393 min, respectively. The method was validated for system suitability, specificity, linearity, accuracy, and precision in accordance with ICH Q2 (R2) guidelines. Analysis of commercially available tablets showed assay values of 98.1% for LIS and 96.5% for AML.

Conclusion: The method for the simultaneous determination of lisinopril and amlodipine besylate was successfully developed and met the validation requirements. The method was applied to commercially available tablet samples.

Keywords: *lisinopril; amlodipine besylate; high performance liquid chromatography; simultaneous determination.*

1. INTRODUCTION

Hypertension is one of the most prevalent diseases and a leading cause of premature mortality worldwide. According to the World Health Organization (WHO), an estimated 1.28 billion adults aged 30 - 79 years are affected by hypertension, of whom only one in five has the condition under control [1].

According to the treatment guidelines of the European Society of Cardiology (ESC), four major classes of drugs are recommended for the management of hypertension, including angiotensin-converting enzyme inhibitors (ACEIs), angiotensin II receptor blockers (ARBs), calcium channel blockers (CCBs), and diuretics [2]. Among these, initial combination therapy using either an ACEI or ARB in combination with a CCB or a diuretic has been shown to improve blood pressure control, enhance treatment adherence, and reduce medication costs. Especially, lisinopril (LIS) and amlodipine besylate (AML) are active pharmaceutical ingredients commonly combined in tablet dosage forms that have been approved for marketing in Vietnam by the Drug Administration of Vietnam, Ministry of Health.

At present, the Vietnam Pharmacopoeia V and major reference pharmacopoeias, including the European Pharmacopoeia (EP 11.6), British Pharmacopoeia (BP 2025), and United States Pharmacopeia (USP 2025), have not yet established a specific monograph for the quality control of this fixed-dose combination. In the world, there have been several studies [3-8] reporting the simultaneous determination of LIS and AML using UV-Vis spectrophotometry, derivative spectroscopy, and RP-HPLC methods. In Vietnam, there have been no published studies on the simultaneous quantification of these two active ingredients in tablet dosage forms using an HPLC method.

Therefore, the development of a method for the simultaneous quantification of both active ingredients in combined tablet formulations is necessary to ensure rapid and accurate quality control, reduce analysis time compared with the separate determination of individual components,

and facilitate the development of generic medicines by pharmaceutical companies in Vietnam, thereby contributing to the establishment of in-house quality standards. In addition, the proposed chromatographic conditions were developed without the use of buffer systems, which simplifies mobile phase preparation, reduces potential column contamination, and improves method cost-effectiveness for routine analysis. Furthermore, the applicability of the method under laboratory conditions in Vietnam may provide practical value for domestic pharmaceutical quality control and support the development of locally applicable analytical procedures.

2. MATERIALS AND METHODS

2.1. Materials

Preparation: Tablet samples containing two active ingredients, amlodipine besylate and lisinopril dihydrate, were developed at the Department of Pharmaceutical Technology, School of Pharmacy, University of Medicine and Pharmacy at Ho Chi Minh City.

Reference standard: Lisinopril with batch number QT268 0423 with 91.0% content, amlodipine besylate with batch number QT145 0124 with 99.0% content, origin from National Institute of Drug Quality Control, Viet Nam.

Solvents and chemicals: methanol (HPLC grade) and acetonitrile (HPLC grade) were purchased from Fisher; acetic acid (analytical grade), formic acid (analytical grade) and trifluoroacetic acid (analytical grade) were from Xilong.

Equipment: Analytical equipment was Waters ACQUITY Arc system, Waters 2996 PDA detector; InertSustain column packed particle (250 × 4.6 mm; 5 µm); 5-digit analytical balance (CP225D, Sartorius); pH meter (WTWpH7110, Inolab); ultrasonic bath (WUC-D10H, Daihan Scientific); drying oven (Memmert WM 500CO, Memmert); 0.22 µm membrane filters (Membrane Solutions) and all glassware met the requirements for analytical work.

2.2. Methods

2.2.1. Preparation of samples

Diluent: Methanol - water (70:30, v/v).

Stock standard solution: Accurately weigh approximately 21.8 mg of lisinopril reference standard (equivalent to 20.0 mg of lisinopril) and 13.9 mg of amlodipine besylate reference standard (equivalent to 10.0 mg of amlodipine) into separate 50 mL volumetric flasks. Each was dissolved in about 30 mL of sample solvent with sonication for 10 min, cooled to room temperature, and diluted to volume with the same solvent to obtain stock standard solutions containing approximately 400 µg/mL of lisinopril and 278 µg/mL of amlodipine besylate (equivalent to about 200 µg/mL of amlodipine), respectively.

Standard mixture solution: An aliquot of 5.0 mL each of lisinopril and amlodipine besylate stock standard solutions was transferred into a 20 mL volumetric flask and diluted to volume with sample solvent to obtain a mixed standard solution containing approximately 100 µg/mL of lisinopril and 70 µg/mL of amlodipine besylate (equivalent to about 50 µg/mL of amlodipine).

Sample solution: Twenty tablets were weighed and finely powdered. An amount equivalent to approximately 21.8 mg of lisinopril and 13.9 mg of amlodipine besylate was transferred into a 50 mL volumetric flask, dissolved in about 30 mL of sample solvent with sonication for 10 min, cooled, diluted to volume, mixed well, and filtered, discarding the first 5 mL of filtrate. Then, 5.0 mL of the filtrate was diluted to volume in a 20 mL volumetric flask with sample solvent to obtain a test solution containing approximately 100 µg/mL of lisinopril and 70 µg/mL of amlodipine besylate (equivalent to about 50 µg/mL of amlodipine).

Placebo solution: An accurately weighed amount of excipients equivalent to approximately 21.8 mg of lisinopril dihydrate and 13.9 mg of amlodipine besylate was transferred into a 50 mL volumetric flask, dissolved in about 30 mL of sample solvent with sonication for 10 min, cooled, diluted to volume, mixed well, and filtered, discarding the first 5 mL of filtrate. Then, 5.0 mL of the filtrate was diluted to volume in a 20 mL volumetric flask with sample solvent and mixed well.

All samples were passed through 0.22 µm membrane filters prior to injection into the chromatographic system. Samples were prepared on the same day and stored at room temperature.

2.2.2. Chromatographic conditions

In this study, the following mobile phase compositions under isocratic and gradient elution conditions were investigated (Table 1-3). The condition, under which the analyte peaks would be pure and completely separated (resolution ≥ 1.5), the tailing factor would be between 0.8 and 1.8, and the apparent number of theoretical plates would be ≥ 2000, would be selected.

Table 1. The chromatographic conditions were carried out

Experiment no.	Elution mode	Mobile phase	Figure
1	Isocratic	Methanol - trifluoroacetic acid 0.1% at ratio 70:30 (v/v)	1a
2	Isocratic	Methanol - trifluoroacetic acid 0.1% at ratio 60:40 (v/v)	1b
3	Isocratic	Methanol - trifluoroacetic acid 0.1% at ratio 50:50 (v/v)	1c
4	Isocratic	Methanol - trifluoroacetic acid 0.1% at ratio 40:60 (v/v)	1d
5	Isocratic	Methanol - trifluoroacetic acid 0.1% at ratio 30:70 (v/v)	1e
6	Gradient 1	Gradient program 1 *(details in Table 2)*	1f
7	Gradient 2	Gradient program 2 *(details in Table 3)*	1g

Table 2. Gradient program 1

Time	Methanol (%)	Trifluoroacetic acid 0.1% pH 2 (%)
0	50	50
3.5	50	50
4.0	60	40
14.5	60	40
15.0	50	50
20.0	50	50

Table 3. Gradient program 2

Time	Methanol (%)	Trifluoroacetic acid 0.1% pH 2 (%)
0	50	50
3.5	50	50
4.0	70	30
14.5	70	30
15.0	50	50
20.0	50	50

The study further investigated the effects of factors such as mobile phase compositions, mobile phase pH, and column temperature (Table 4) on peak characteristics to select the suitable quantitative analytical method.

Table 4. Investigated factors affecting the quantitative method

Experiment no.	Factor varied	Mobile phase	Figure
1	Mobile phase composition	Acetonitrile - trifluoroacetic acid 0.1%	2a
2		Methanol - water	2b
3		Methanol - formic acid 0.1%	2c
4		Methanol - acetic acid 0.1%	2d
5	Mobile phase pH	Methanol - trifluoroacetic acid 0.01%	2e
6	Column temperature	25 ^{o}C	2f

2.2.3. Validation of the quantitative analytical method

The procedure for simultaneous determination of LIS and AML by HPLC method with PDA detector was validated according to ICH guidelines [9], including investigation of system suitability, specificity, linearity, precision and accuracy.

System suitability

Chromatographic analysis was performed by injecting the standard solution six consecutive times according to the analytical procedure. The chromatograms were recorded, and the retention times, mean peak areas, and other peak parameters (resolution, tailing factor, number of theoretical plates, etc.) were determined.

Specificity

Chromatographic analysis was performed sequentially for the following samples: blank, mixed standard solution, test solution, placebo solution, spiked placebo solution, and degraded samples under selected chromatographic conditions. The chromatograms were recorded, and the chromatographic parameters in analysed samples were evaluated. All peaks were clearly separated, impurity peaks generated under harsh conditions did not overlap with the main peaks, and peak purity was achieved (purity angle < purity threshold).

Forced degradation study

Photodegraded sample: Approximately 1 g of powdered tablets was weighed and spread in a petri dish, then exposed to sunlight for 12 hours. An accurately weighed amount of the degraded powder equivalent to 21.8 mg of lisinopril dihydrate and 13.9 mg of amlodipine besylate was transferred into a 50 mL volumetric flask and prepared in the same manner as the test solution.

Thermally degraded sample: Approximately 1 g of powdered tablets was weighed and placed in a petri dish, then kept in an oven at 60 ± 2 °C for 12 hours. An accurately weighed amount of the degraded powder equivalent to 21.8 mg of lisinopril dihydrate and 13.9 mg of amlodipine besylate was transferred into a 50 mL volumetric flask and prepared as described for the test solution.

Oxidatively degraded sample: An accurately weighed amount of powdered tablets equivalent to 21.8 mg of lisinopril dihydrate and 13.9 mg of amlodipine besylate was transferred into a 50 mL volumetric flask. About 30 mL of the sample solvent was added, and the mixture was sonicated for 10 min and allowed to cool to room temperature. Then, 5 mL of 30% hydrogen peroxide solution was added, and the solution was diluted to volume with the sample solvent, mixed well, and kept at room temperature for 12 hours. The solution was subsequently prepared in the same manner as the test solution.

Linearity

The samples were analysed at five concentration levels of 80, 90, 100, 110 and 120%. The chromatograms were recorded, and peak responses were determined. The linear regression equation and correlation coefficients between the standard solution concentration and the peak response were calculated.

Precision

Six test samples were analysed, each injected once. The content of active ingredients was determined as a percentage of the labelled claim. Method repeatability was evaluated based on the %RSD of the assay results.

Accuracy

Three types of spiked placebo samples were prepared by adding known amounts of standard substances at concentration levels of 80, 100, and 120%. At each level, at least three independent samples were analysed.

3. RESULTS

3.1. Investigation of quantitative analytical conditions

The UV spectra of lisinopril and amlodipine besylate were recorded over the range of 200–400 nm. Based on the results, 210 nm provided optimal peak height and peak area, and was therefore selected as the detection wavelength for further chromatographic optimization.

Using a mobile phase of methanol and 0.1% trifluoroacetic acid (70:30, v/v), two peaks corresponding to AML and LIS were observed (Figure 1a). However, the LIS peak co-eluted with the solvent front and both peaks showed very short retention times (< 5 min).

At a 60:40 ratio (Figure 1b), retention times improved, but LIS was still not fully separated from the solvent front. When the aqueous phase was further increased from 50:50 to 30:70 (Figure 1c - 1e), LIS was completely separated; however, increased TFA content led to higher baseline noise, and peak distortion was observed at 30:70, with an increased tailing factor (1.8 - 2.2). In addition, AML was not eluted within a 20-minute run. Therefore, a gradient elution was required.

Gradient program 1 (Table 2) was applied with an initial 50:50 composition held for 3.5 min, followed

by an increase in the organic phase. Results (Figure 1f) showed complete separation of LIS and AML, acceptable system suitability parameters, and peak purity. However, the long interval (~10 min) between LIS and AML peaks remained.

To improve analysis time, the methanol proportion was further increased in Gradient program 2 (Table 3). As shown in Figure 1g, the retention time of AML decreased to approximately 10 min, while LIS performance remained unchanged. Therefore, Gradient program 2 was selected for simultaneous determination of LIS and AML.

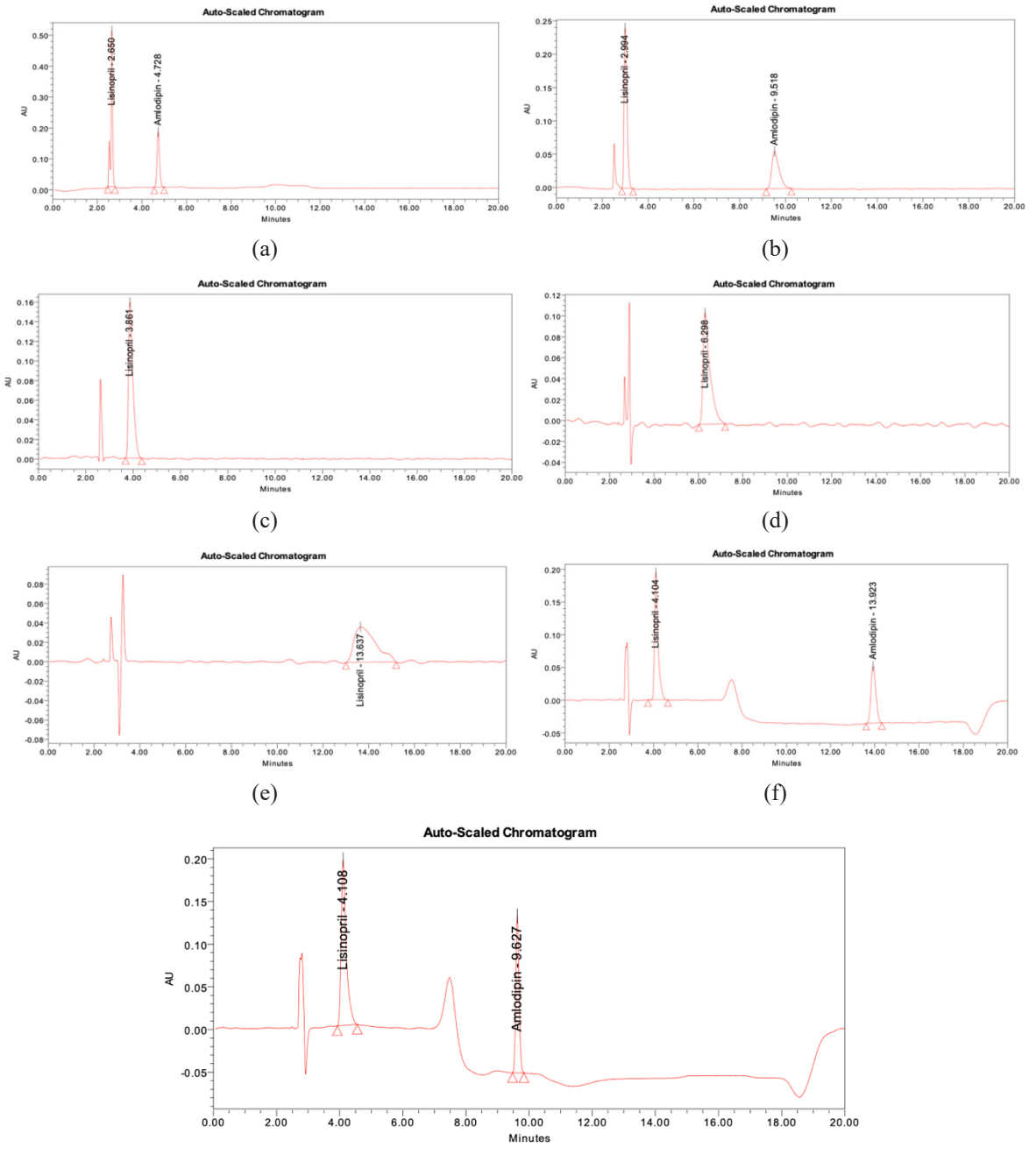


Figure 1. Chromatograms obtained when analysing the standard mixture using different mobile phase compositions (a: 70:30, b: 60:40, c: 50:50, d: 40:60, e: 30:70) and elution mode (f: gradient 1, g: gradient 2)

As shown in Figure 2a, when methanol was replaced with acetonitrile, the analyte peaks were eluted more efficiently, resulting in a significant decrease in the retention times of LIS and AML. In particular, LIS showed minimal interaction with the stationary phase and was therefore not detected on the chromatogram. In addition, when 0.1% trifluoroacetic acid aqueous solution was replaced with water, 0.1% acetic acid or 0.1% formic acid (Figures 2b - 2d), the peaks were also eluted rapidly; however, the tailing factors increased and peak purity criteria were not met. Therefore, methanol and trifluoroacetic acid were selected as the suitable mobile phase components for the quantitative analytical method.

The study further adjusted the mobile phase pH from 2.0 to 2.9 by changing the TFA concentration from 0.1% to 0.01%. The results (Figure 2e) showed a decrease in retention times and an increase in tailing factors. In addition, the column temperature was reduced to 25 °C, which resulted in no significant changes in the chromatographic parameters. However, to protect the chromatographic system and extend column lifetime, a TFA concentration of 0.1% and a column temperature of 40 °C were selected for the quantitative analytical method.

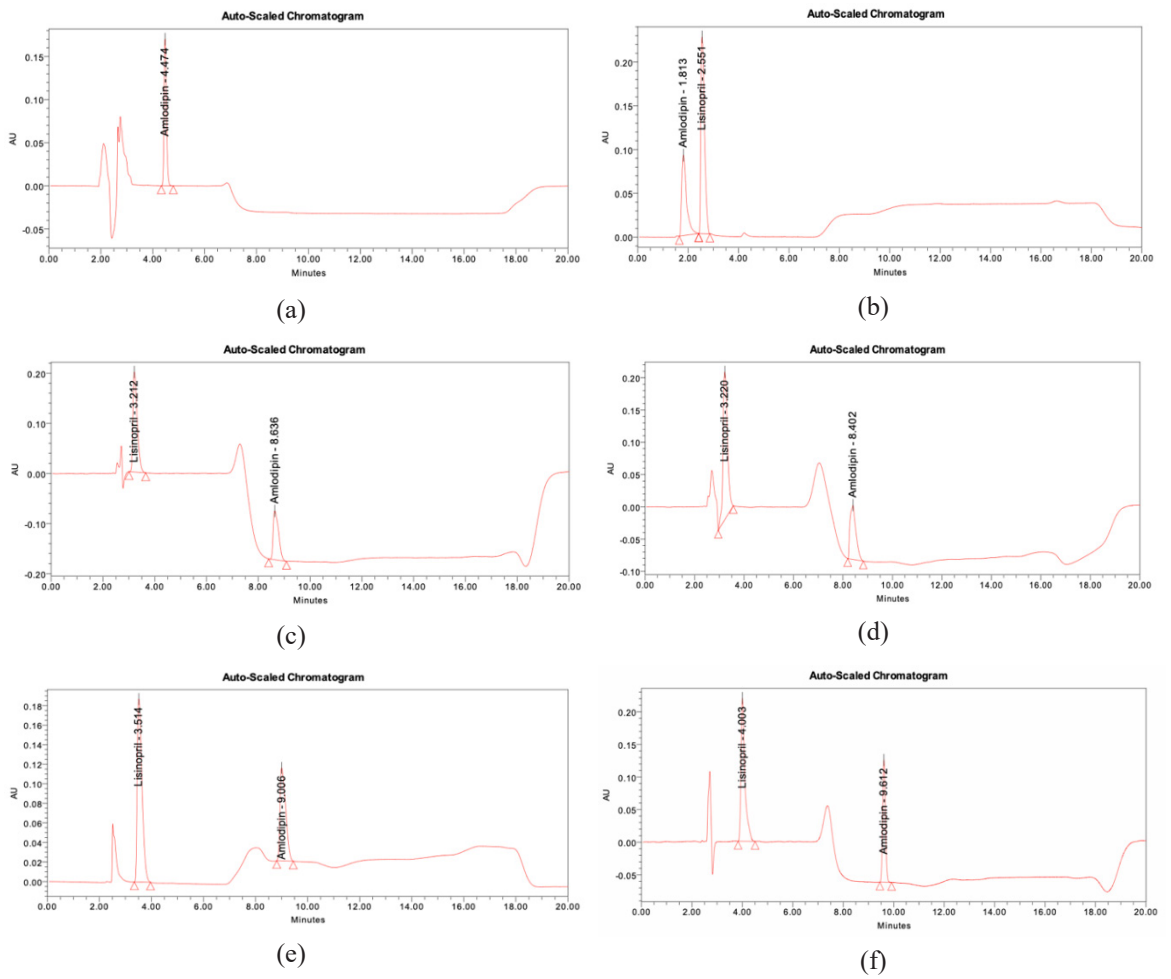
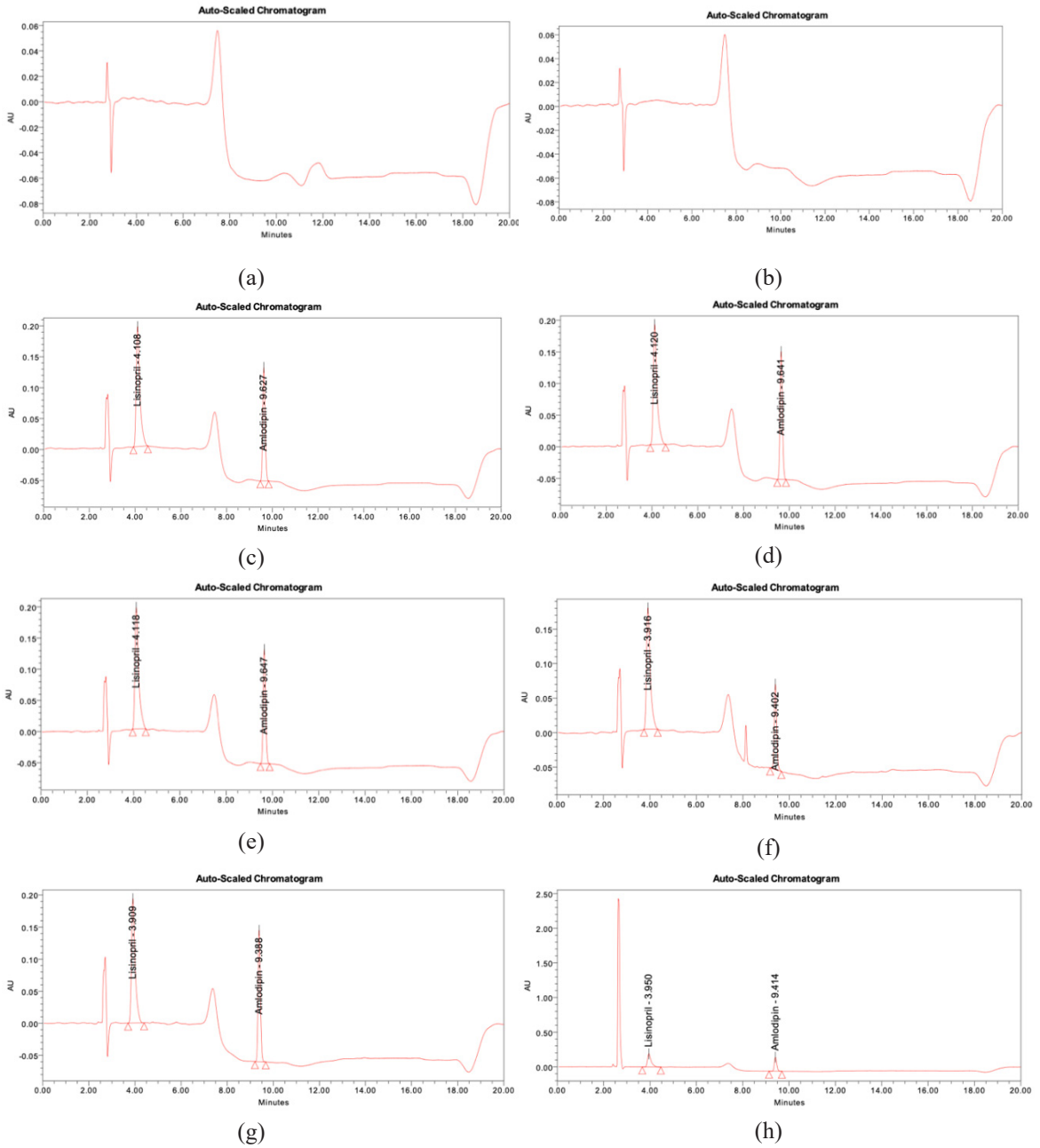
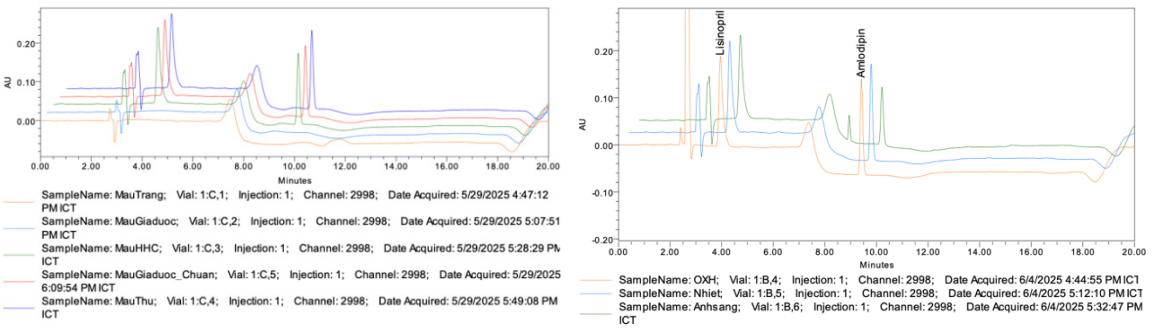


Figure 2. Chromatograms obtained with different factors

3.2. Validation of the quantitative analytical method

The validation results showed that the procedure for simultaneous quantification of AML and LIS using HPLC-PDA method met all the requirements according to the ICH guidelines.





(i) (j)

Figure 3. Chromatograms for specificity evaluation

a. Blank solution; b. Placebo solution; c. Standard mixture solution; d. Test solution; e. Spiked placebo solution; f. Photodegraded solution for 12 hours; g. Thermally degraded solution for 12 hours; h. Oxidatively degraded solution for 12 hours; i. Overlay chromatograms for samples; j. Overlay chromatograms for degraded samples

System suitability

The %RSD values of retention time and peak area were ≤ 2.0%, resolution between peaks was ≥ 1.5, tailing factor ranged from 0.8 - 1.8 and the number of theoretical plates was ≥ 2000.

Table 5. Results of system suitability*

Compound	Retention time	%RSD of retention time	%RSD of area	Tailing factor	Theoretical plates
LIS	3.914	0.1	1.4	1.6	3181
AML	9.393	0.1	0.4	1.2	39515

**Average of 6 readings*

Specificity

All peaks were clearly separated, impurity peaks generated under harsh conditions did not overlap with the main peaks (Figure 3), and peak purity was achieved (Figure 4).

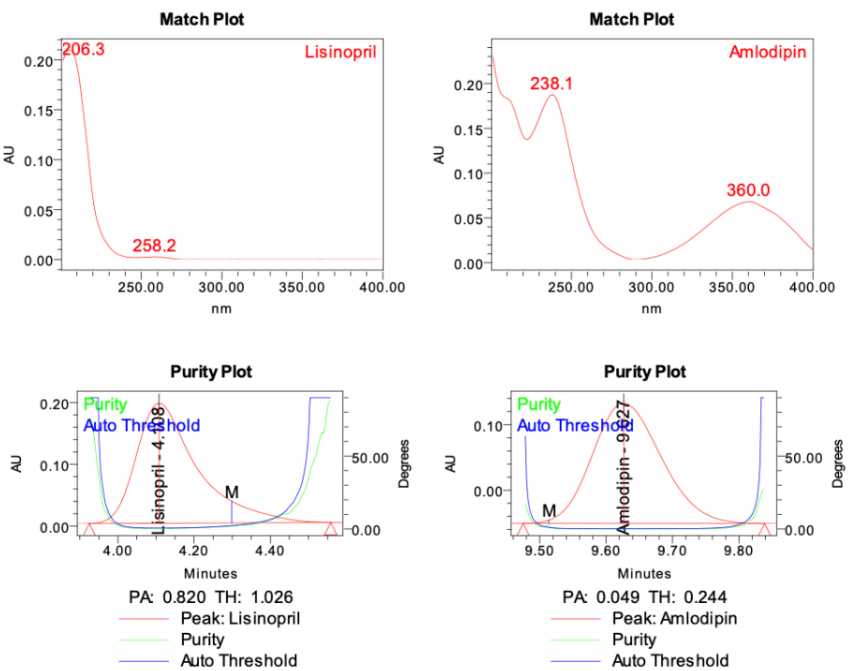


Figure 4. Peak purity of the standard mixture solution

Linearity range

The correlation coefficient (R) was ≥ 0.999, with linearity ranges of 80 – 120 µg/mL for LIS and 56 – 84 µg/mL for AML.

Accuracy

The recovery rates of both substances were in the range of 98.0 - 102.0%.

Table 6. Recovery rates

Amount of standard added to the analyte (%)	LIS recovery (%)	Mean recovery (%)	Mean RSD (%)
80	99.2		
100	99.6	99.7	0.6
120	100.1		
Amount of standard added to the analyte (%)	**AML recovery (%)**	**Mean recovery (%)**	**Mean RSD (%)**
80	98.9		
100	99.6	99.5	0.6
120	99.7		

Precision

Precision includes repeatability and intermediate precision, with RSD values not exceeding 2.0%.

Table 7. Precision results*

Compound	Repeatability (%)	%RSD	Intermediate precision (%)	%RSD
LIS	100.8	1.7	99.2	1.3
AML	113.4	1.4	110.2	0.8

**Average of 6 readings*

3.3. Application of the simultaneous determination procedure

Preparation: The tablet formulation containing a combination of lisinopril and amlodipine besylate was manufactured by company X using the same formulation composition.

Result: Assay results for the marketed tablet formulation (Table 8), with an average tablet weight of 204 mg, showed LIS and AML contents of 98.1% and 96.5%, respectively.

Table 8. Assay results for the marketed tablet formulation

Sample	Lisinopril		Amlodipine besylate	
	Peak area	Percentage content	Peak area	Percentage content
1	2299872	98.4	1359007	96.4
2	2282325	97.7	1361241	96.6
Average	-	98.1	-	96.5

4. DISCUSSION

High-performance liquid chromatography is one of the most widely used analytical techniques in various fields. This technique is based on the separation of analytes on a chromatographic column, followed by detection using suitable detectors such as PDA, UV, fluorescence, or mass spectrometric detectors [10]. Among various chromatographic modes, reversed-phase liquid chromatography is the most used due to its versatility, robustness, good reproducibility, compatibility with aqueous–organic mobile phases, and its applicability to a wide range of analytes with different polarities. However, chromatographic separation efficiency depends on multiple factors, including the composition of the mobile phase, the type of stationary phase, flow rate, column temperature, and other operational parameters. Therefore, investigating different mobile phase compositions to select suitable solvents and ratios for effective separation of the analytes is necessary.

Currently, most studies worldwide on the simultaneous or individual determination of LIS

and mainly employ reversed-phase columns with C18 – bonded silica columns (particle size 5 µm). These studies predominantly use HPLC – PDA systems, with mobile phases composed of organic solvent, such as methanol, combined with acetate or phosphate buffer at controlled pH values [3–8]. However, prolonged use of buffer systems may adversely affect the chromatographic system and reduce column lifetime. Therefore, in this study, an aqueous phase containing organic acids was selected as an alternative to buffered systems for initial chromatographic investigation.

According to the Henderson – Hasselbalch equation, maintaining analytes predominantly in their molecular form requires adjusting the mobile phase pH relative to the pKa values of their functional group. LIS contains two carboxyl groups (- COOH), one primary amine (- NH_2), and one secondary amine (- NH -), with experimentally determined pKa values of 2.5, 4.0, 6.7 and 10.1 [11], respectively. These values indicate that pH significantly influences the ionic forms of LIS (Figure 5), thereby affecting its interaction with the stationary phase. In contrast, AML contains one primary amine group (- NH2) with an experimentally determined pKa value of 8.6 [12]. Overall, AML is a moderately polar compound and generally exhibits stronger interactions with the stationary phase than lisinopril, even under varying mobile phase pH conditions.

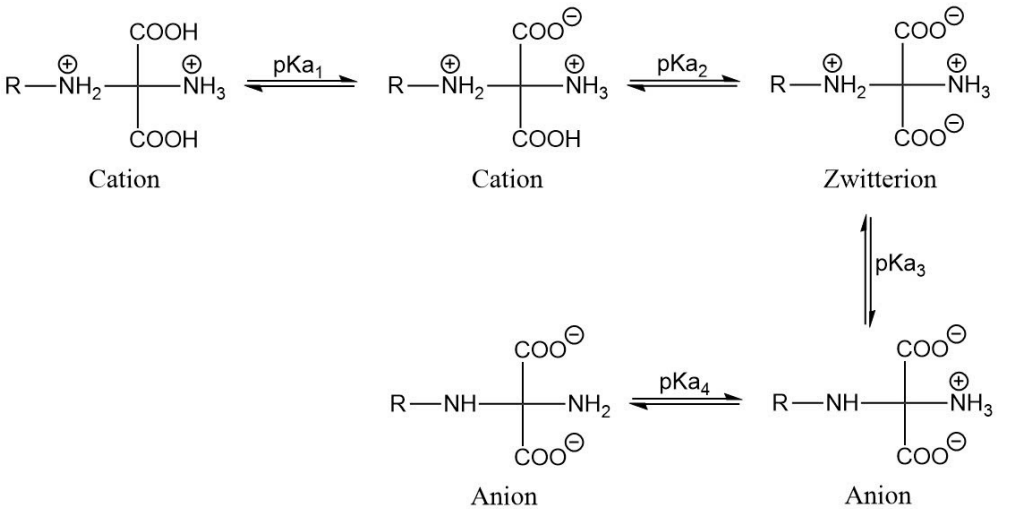


Figure 5. Ionization forms of lisinopril

When investigating mobile phase systems with different pH values, increased peak tailing was mainly attributed to undesirable interactions between ionic analyte species and free silanol groups on the stationary phase. Silanol groups are weakly acidic (pKa = 3.8 - 4.2) [13]; thus, when the mobile phase pH is above 5, they predominantly exist in the anionic form (SiO-), leading to enhanced peak tailing peak tailing. Conversely, at pH values below 3, silanol groups mainly exist in the molecular form (SiOH), minimizing interactions with the analytes.

Accordingly, mobile phases consisting of 0.1% formic acid (pH = 2.8), 0.1% acetic acid (pH = 3.3), and water (pH = 6.8 - 7.0) were evaluated. Increasing mobile phase pH altered the ionic states of LIS and AML, resulting in changes in retention time, resolution, and theoretical plates, and particularly increasing peak tailing. Consequently, trifluoroacetic acid (TFA) was selected to adjust the mobile phase pH to below pKa_1, ensuring that the carboxyl groups of LIS remained predominantly in their molecular form. In addition, TFA acts as an ion – pairing agent with the amino groups of LIS and AML, reducing undesirable interactions with free silanol groups and improving retention and peak symmetry.

The elution strength of organic solvents was further investigated using methanol and acetonitrile. Acetonitrile resulted in earlier elution of LIS and AML, attributed to its lower viscosity at a column temperature of 40°C; increased mobile phase mobility further facilitated elution. Although reducing the column temperature to 25°C did not significantly affect retention time or other chromatographic parameters, a column temperature of 40°C was maintained to reduce mobile phase viscosity, system backpressure, and to protect the chromatographic

systems and column lifespan.

Robustness was determined by the variation in peak area and resolution with small adjustments of pH, mobile phase composition, temperature, and flow rate. The results showed %RSD < 2% and Rs > 1.5, demonstrating the method's high reliability and its lack of significant impact from experimental errors. Therefore, the process meets the required roughness standard, ensuring stability in practical applications.

This study contributes to the limited literature in Vietnam on the simultaneous quantification of LIS and AML in tablets using HPLC. Compared with previously published studies, the developed procedure offers notable advantages: (i) it avoids the use of phosphate or acetate buffers and inorganic acids such as phosphoric acid, thereby minimizing salt formation, reducing the risk of column contamination, and extending the lifetime of the HPLC system and column; (ii) it systematically investigates the effects of different organic acids and chromatographic parameters, providing a more comprehensive understanding of their influence on the chromatographic behaviour of LIS and AML; (iii) it employs a simplified mobile phase composition, which facilitates easier preparation, improves method reproducibility, and reduces potential errors associated with buffer preparation; and (iv) it enables efficient simultaneous determination of both analytes within a reasonable analysis time, making the method suitable for routine quality control applications.

5. CONCLUSION

High performance liquid chromatography method with PDA detection for the simultaneous quantification of LIS and AML in tablets was successfully developed and validated in accordance with ICH guidelines. Chromatographic separation was achieved using gradient elution with methanol and 0.1% trifluoroacetic acid in water (pH 2), detection wavelength at 210 nm, column temperature of 40 °C, flow rate of 1.0 mL/min, injection volume of 10 µL. The validated method demonstrated satisfactory system suitability and showed good specificity, accuracy, precision, and linearity, confirming its reliability and suitability for routine quality control analysis of pharmaceutical preparations containing LIS and AML.

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