IJARSCT

International Journal of Advanced Research in Science, Communication and Technology

International Open-Access, Double-Blind, Peer-Reviewed, Refereed, Multidisciplinary Online Journal

ISSN: 2581-9429

Volume 6, Issue 4, February 2026

Impact Factor: 8.2

Development and Validation of RP-HPLC Method for the Estimation of Amlodipine Besylate and Benazepril Hydrochloride (HCL) from Capsule Formulation

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Abstract: *High-performance liquid chromatography (HPLC) was developed and validated for the simultaneous quantitative determination of amlodipine besylate (AM) and benazepril hydrochloride (BZ) in capsule formulations. Analytical performance parameters such as linearity, precision, accuracy, specificity, limit of detection (LOD), and limit of quantification (LOQ) were evaluated according to International Conference on Harmonization [ICH Q2(R1)] guidelines. The RP-HPLC method employed an isocratic technique on a Thermo Fisher Scientific C8 column (4.6 mm × 25 mm, 0.5 µm) using a mobile phase of acetonitrile and buffer (55:45, v/v) at a flow rate of 0.80 mL/min. Detection was carried out at 275 nm, with an injection volume of 10 µL. Chromatographic data acquisition and analysis were performed using Chromequest Version 4.1 software. The retention times for AM and BZ were optimized and found to be distinct. The linearity of the calibration curves for both analytes over their respective concentration ranges was excellent ($r^2 > 0.999$). The method demonstrated high precision, with %RSD below 2%, and accurate recoveries within 98–102%. The validated method is sensitive, precise, and reliable, making it suitable for the routine analysis of AM and BZ in capsule formulations*

Keywords*:* Amlodipine Besylate, Benazepril Hydrochloride, RP-HPLC Method ,Validation, Chromatography

I. INTRODUCTION

Hypertension, a chronic medical condition characterized by persistently elevated blood pressure, is a major risk factor for cardiovascular diseases worldwide.1 The management of hypertension often involves combination therapies to enhance efficacy and minimize adverse effects. Amlodipine Besylate (AM), a calcium channel blocker, and Benazepril Hydrochloride (BZ), an angiotensin-converting enzyme (ACE) inhibitor, are commonly co-formulated due to their complementary mechanisms of action.1Amlodipine relaxes vascular smooth muscle, leading to vasodilation and reduced peripheral resistance, while Benazepril inhibits the conversion of angiotensin I to angiotensin II, thereby lowering blood pressure and mitigating the effects of the renin-angiotensin system.2

DOI: 10.48175/IJARSCT-31706

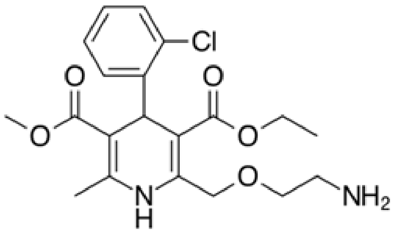

FIGURE 1 Structure of Amlodipine

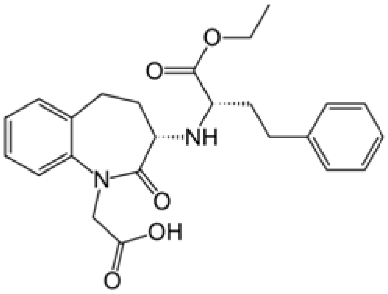

FIGURE 2 of Benazepril Structure

The simultaneous quantification of Amlodipine Besylate and Benazepril Hydrochloride in pharmaceutical formulations is crucial for ensuring batch-to-batch consistency, quality control, and regulatory compliance.3 Despite the therapeutic importance of this combination, the development of reliable analytical methods for their simultaneous estimation has been a significant focus of pharmaceutical research.4

Several analytical methods have been reported for the determination of Amlodipine Besylate and Benazepril Hydrochloride individually or in combination.5 UV spectrophotometry has been utilized due to its simplicity and cost-effectiveness; however, it lacks the specificity required for complex formulations.8 High-performance thin-layer chromatography (HPTLC) has also been employed, but it suffers from limitations in resolution and reproducibility when compared to HPLC.9

Among chromatographic methods, reversed-phase high-performance liquid chromatography (RP-HPLC) has been the most widely explored due to its high sensitivity, accuracy, and reproducibility.10 Previously developed RP-HPLC methods have utilized C18 columns with various mobile phase compositions, including acetonitrile and buffer systems, to achieve effective separation.11 Some methods employed gradient elution, while others used isocratic techniques. The detection wavelengths for these methods typically ranged from 230 nm to 280 nm, depending on the absorption maxima of the analytes.12 However, certain reported methods faced challenges such as longer run times, poor resolution between AM and BZ, or inadequate sensitivity for routine quality control.13

In this study, we aim to develop and validate a robust, precise, and reliable RP-HPLC method for the simultaneous estimation of Amlodipine Besylate and Benazepril Hydrochloride in capsule formulations. The proposed method employs optimized chromatographic conditions, including the use of a Thermo Fisher Scientific C8 column, a mobile phase of acetonitrile and buffer in a 55:45 ratio, and UV detection at 275 nm. Validation of the method was performed in accordance with International Conference on Harmonization (ICH Q2(R1)) guidelines to ensure compliance with regulatory standards and suitability for routine analysis.

II MATERIALS AND METHODS

2.1 Chemicals and Reagents:

Amlodipine Besylate and Benazepril HCl reference standards were procured for research purpose as a gift samples. The capsule formulation was procured from Local Market of Mumbai, India. HPLC-grade acetonitrile and water Analytical-grade orthophosphoric acid and potassium dihydrogen phosphate for buffer preparation.

2.2 Instrumentation:

The chromatographic analysis was performed using a Thermo Fisher Scientific HPLC system equipped with the following components:

Column: Thermo Fisher Scientific C8 column (4.6 mm × 2.5 cm, 0.5 µm particle size) for efficient separation of analytes.

Mobile Phase: A mixture of acetonitrile and buffer in the ratio of 55:45 (v/v). The buffer was prepared and adjusted to an appropriate pH for optimal resolution.

Flow Rate: Maintained at 0.80 mL/min to ensure consistent elution.
Injection Volume: 10 µL of standard or sample solutions were injected into the system.
Detection Wavelength: UV detection was carried out at 275 nm, the absorption maximum for both Amlodipine Besylate and Benazepril Hydrochloride.
Software: Data acquisition and processing were managed using Chromequest Version 4.1 software.
Temperature: All chromatographic runs were performed at ambient temperature.
This setup ensured optimal resolution, reproducibility, and sensitivity for the simultaneous estimation of Amlodipine Besylate and Benazepril Hydrochloride in capsule formulations.

2.3 Preparation of Standard and Sample Solutions:

2.3.1 Standard Solution:

To prepare the standard solutions, accurately weighed quantities of Amlodipine Besylate and Benazepril Hydrochloride (HCl) were transferred to separate 100 mL volumetric flasks. The active pharmaceutical ingredients (APIs) were dissolved in a sufficient quantity of the mobile phase (acetonitrile: buffer, 55:45 v/v) by gentle shaking to ensure complete solubility. The solutions were then diluted to volume with the same mobile phase to achieve stock concentrations of 100 µg/mL for each API. These stock solutions were further diluted, as required, to prepare calibration standards or working solutions for validation and routine analysis.

2.3.2 Sample Solution:

The content of the capsule formulation, equivalent to 5 mg of Amlodipine Besylate and 10 mg of Benazepril Hydrochloride, was accurately weighed and transferred to a 100 mL volumetric flask. About 70 mL of the mobile phase was added, and the mixture was sonicated for 15 minutes to ensure complete dissolution of the drugs. After sonication, the solution was allowed to cool to room temperature, and the volume was adjusted to 100 mL with the mobile phase. The resulting solution was mixed thoroughly and filtered through a 0.45 µm membrane filter to remove any particulate matter. The filtered solution was used directly for HPLC analysis.
Both the standard and sample solutions were prepared freshly and used within the stability period to ensure accurate and reproducible results.

2.4 Linearity

The linearity of the method was determined over a concentration range of 25–150 ppm for both Amlodipine Besylate and Benazepril Hydrochloride. Calibration curves were constructed by plotting peak areas against corresponding concentrations, and linear regression analysis was performed to calculate the correlation coefficient (r^2).

2.5 Precision

Intra-day Precision:
Intra-day precision was evaluated by analyzing sample solutions at three different time intervals (11:30 am, 2:30 pm, and 5:30 pm) on the same day. The %RSD of the results was calculated to ensure consistency within the same day.
Inter-day Precision:
Inter-day precision was assessed by analyzing sample solutions on three consecutive days (Day 1, Day 2, and Day 3). The %RSD values across the days were calculated to evaluate reproducibility between different days.

2.6 Accuracy (Recovery Studies)

Accuracy was evaluated by performing recovery studies at three spiked levels: 50%, 100%, and 150% of the target concentration. Known amounts of Amlodipine Besylate and Benazepril Hydrochloride were added to pre-analyzed sample solutions, and the percentage recoveries were calculated.

2.7 Robustness

The robustness of the method was tested by deliberately varying the detection wavelength from the optimized 275 nm to 273 nm and 277 nm. The method's performance was assessed by analyzing standard and sample solutions under these altered conditions.

2.8 Specificity

Specificity was confirmed by analyzing blank solutions, standard solutions, and sample solutions. The method was able to distinctly separate Amlodipine Besylate and Benazepril Hydrochloride from excipients and other potential interferences in the capsule formulation.

2.9 Limit of Detection (LOD) and Limit of Quantification (LOQ)

The LOD and LOQ were calculated based on the signal-to-noise ratio of 3:1 and 10:1, respectively.

III. RESULTS AND DISCUSSION

The developed RP-HPLC method successfully separated Amlodipine Besylate and Benazepril HCl with well-resolved peaks. The validation results confirmed the method's reliability for routine quality control. Linearity, accuracy, and precision were consistent with regulatory requirements. Robustness tests further demonstrated the method's suitability under varying analytical conditions.

3.1 System Suitability

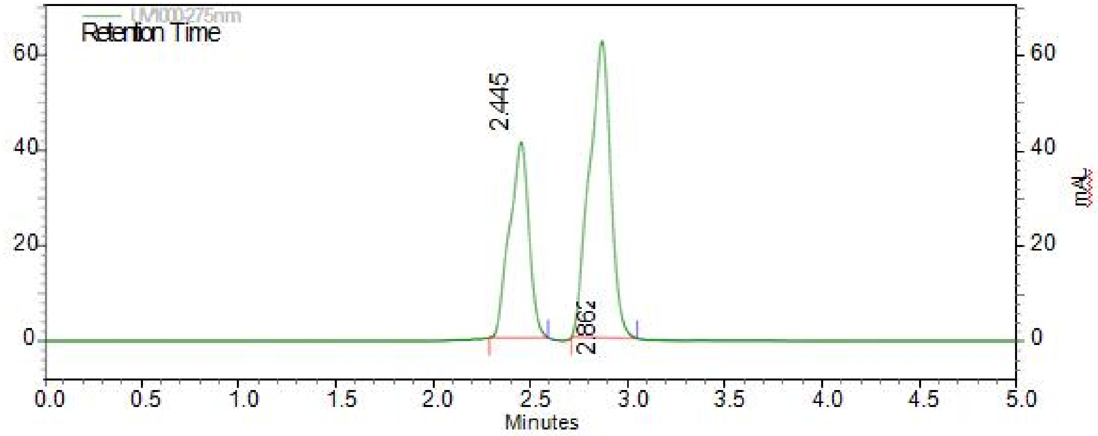

FIGURE 3 System suitability Chromatogram of Amlodipine Besylate and Benazepril Hydrochloride

The system suitability test results for the simultaneous estimation of Amlodipine Besylate and Benazepril Hydrochloride in capsule formulations indicate that the RP-HPLC method is reliable and efficient. The retention times for Amlodipine Besylate (2.445 minutes) and Benazepril Hydrochloride (2.862 minutes) were well within the expected range, demonstrating effective separation of the two analytes. The area under the peak for Amlodipine Besylate was 284,101 (27.907%), and for Benazepril Hydrochloride, it was 733,915 (72.093%), confirming the accurate quantification of both compounds in the formulation. The theoretical plates for both analytes (2,695 for Amlodipine Besylate and 2,690 for Benazepril Hydrochloride) indicated excellent column performance, ensuring adequate separation. Asymmetry values of 0.89 for Amlodipine Besylate and 0.90 for Benazepril Hydrochloride suggested symmetrical peak shapes, with minimal tailing or fronting.

The resolution between the two compounds was 2.05, which is well above the required threshold of 2, indicating sufficient separation between the peaks and confirming the method's ability to distinguish both analytes clearly. These system suitability results demonstrate that the method provides accurate, precise, and reproducible results, making it

DOI: 10.48175/IJARSCT-31706

suitable for quality control applications. The chromatographic conditions used in this method ensure that both Amlodipine Besylate and Benazepril Hydrochloride can be reliably quantified with minimal interference, meeting the standards required for regulatory compliance and routine testing of pharmaceutical formulations.

3.2 Linearity

The linearity of the RP-HPLC method was evaluated for both Amlodipine Besylate and Benazepril Hydrochloride across a range of concentrations. The calibration data showed excellent linearity, with correlation coefficients (r^2) of 0.9988 for Amlodipine Besylate and 0.9998 for Benazepril Hydrochloride, indicating strong linear relationships between concentration and peak area for both analytes.

For Amlodipine Besylate, the concentrations ranged from 20 ppm to 120 ppm. The areas corresponding to these concentrations were 151,005, 286,771, 456,431, 629,274, 776,194, and 955,951, respectively. These data points exhibit a nearly perfect linear relationship, further supported by the correlation coefficient of 0.9988, which signifies that the method provides a reliable and consistent response across the entire tested concentration range.

For Benazepril Hydrochloride, the concentrations ranged from 25 ppm to 150 ppm. The areas for these concentrations were 385,105,742,803,1120,592,1516,931,1886,593,and2269,990, respectively. A correlation coefficient of 0.9998 confirms that the method demonstrates exceptional linearity and consistency for Benazepril Hydrochloride, ensuring accurate quantification within the specified range.

Overall, the linearity results for both Amlodipine Besylate and Benazepril Hydrochloride indicate that the RP-HPLC method is highly effective for the quantification of these compounds in capsule formulations, offering reliable, reproducible, and precise measurements.

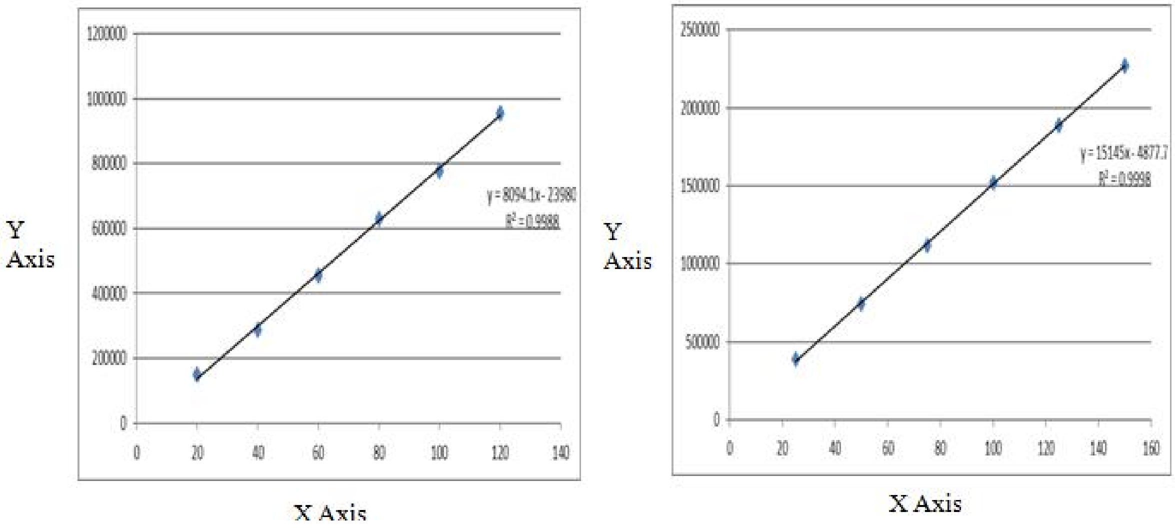

FIGURE 4 Linearity curve for Amlodipine Besylate and Benazepril Hydrochloride

3.3 Robustness

The robustness of the RP-HPLC method was assessed by evaluating the effect of small variations in the wavelength setting, specifically a ±2 nm change from the nominal wavelength of 275 nm. The experiments were conducted at two wavelengths, 273 nm and 277 nm, and the corresponding peak areas for both Amlodipine Besylate and Benazepril Hydrochloride were recorded.

At 273 nm, the peak area for Amlodipine Besylate was 286,053, and for Benazepril Hydrochloride, it was 744,975. When the wavelength was adjusted to 277 nm, the peak area for Amlodipine Besylate slightly increased to 287,239, and for Benazepril Hydrochloride, the area increased to 745,155. These minimal changes in the peak area indicate that the

DOI: 10.48175/IJARSCT-31706

method is robust and can tolerate small variations in the wavelength setting without significant impact on the quantification of the analytes.

The results demonstrate that the method remains reliable and precise despite slight alterations in the experimental conditions, which is crucial for maintaining the accuracy of the analysis in routine quality control testing. The method's robustness further supports its suitability for the analysis of Amlodipine Besylate and Benazepril Hydrochloride in capsule formulations under varied operational conditions.

3.4 Accuracy

The accuracy of the RP-HPLC method was evaluated by determining the assay of tablet formulations containing Amlodipine Besylate and Benazepril Hydrochloride. Two injections (Inj. 01 and Inj. 02) of tablet samples were analyzed, and the results were compared with the standard solution to assess the method's reliability and precision.

In Injection 01 (Assay of Tablets – Inj. 01), the retention time for Amlodipine Besylate was 2.445 minutes, with an area of 286,277 (28.115%), and for Benazepril Hydrochloride, it was 2.868 minutes with an area of 731,958 (71.885%). The theoretical plates for Amlodipine Besylate and Benazepril Hydrochloride were 2,639 and 2,741, respectively, indicating good column performance. The asymmetry values were 0.92 for Amlodipine Besylate and 0.90 for Benazepril Hydrochloride, indicating symmetrical peaks and minimal tailing.

In Injection 02 (Assay of Tablets – Inj. 02), the retention time for Amlodipine Besylate was 2.443 minutes, with an area of 286,227 (28.404%), and for Benazepril Hydrochloride, it was 2.865 minutes with an area of 721,462 (71.596%). The theoretical plates were 2,661 for Amlodipine Besylate and 2,719 for Benazepril Hydrochloride, indicating consistent column performance. The asymmetry values were 0.90 for Amlodipine Besylate and 0.89 for Benazepril Hydrochloride, maintaining symmetrical peak shapes.

The standard solution analysis showed retention times of 2.445 minutes for Amlodipine Besylate and 2.862 minutes for Benazepril Hydrochloride, with peak areas of 284,101 (27.907%) and 733,915 (72.093%), respectively. The theoretical plates were 2,695 for Amlodipine Besylate and 2,690 for Benazepril Hydrochloride, with asymmetry values of 0.89 and 0.90, respectively, indicating excellent chromatographic performance.

These results demonstrate that the method is accurate, with consistent retention times, area percentages, and good symmetry of the peaks. The accuracy is further confirmed by the minimal variation in peak areas and retention times between the tablet sample injections and the standard solution, ensuring the reliability of the method for routine analysis.

3.5 Recovery

The recovery of Amlodipine Besylate and Benazepril Hydrochloride from the tablet formulations was assessed by spiking the sample with known quantities of the standard solutions at 50%, 100%, and 150% of the target concentrations. The results for both drugs are summarized in the tables below.

Amlodipine Besylate Recovery:

50% Spike: The area obtained after spiking was 171,005, and the standard solution area was 284,101. The calculated concentration after spiking was 60 ppm, with a recovery of 60.19 ppm, yielding a recovery of 100.31%.

100% Spike: The area obtained after spiking was 227,380, and the standard solution area was 284,101. The calculated concentration after spiking was 80 ppm, with a recovery of 80.03 ppm, yielding a recovery of 100.04%.

150% Spike: The area obtained after spiking was 285,431, and the standard solution area was 284,101. The calculated concentration after spiking was 100 ppm, with a recovery of 100.47 ppm, yielding a recovery of 100.46%.

The recovery results for Amlodipine Besylate showed excellent accuracy, with all recovery values falling within the acceptable range of 100% ± 2%, confirming the reliability of the method for this analyte.

DOI: 10.48175/IJARSCT-31706

Benazepril Hydrochloride Recovery:

50% Spike: The area obtained after spiking was 555,105, and the standard solution area was 733,915. The calculated concentration after spiking was 75 ppm, with a recovery of 75.63 ppm, yielding a recovery of 100.8%.

100% Spike: The area obtained after spiking was 740,803, and the standard solution area was 733,915. The calculated concentration after spiking was 100 ppm, with a recovery of 100.93 ppm, yielding a recovery of 100.9%.

150% Spike: The area obtained after spiking was 919,595, and the standard solution area was 733,915. The calculated concentration after spiking was 125 ppm, with a recovery of 125.3 ppm, yielding a recovery of 100.24%.

For Benazepril Hydrochloride, the recovery rates were also within the acceptable range of 100%
± 2%, demonstrating the accuracy and precision of the method for this compound as well. Overall, the recovery data for both Amlodipine Besylate and Benazepril Hydrochloride indicate that the developed RP-HPLC method is accurate and reliable for the estimation of these drugs in tablet formulations. The recovery values consistently matched the expected concentrations, confirming the method's suitability for routine quality control and regulatory compliance.

TABLE 1- % Recovery study of Amlodipine Besylate and Benazepril Hydrochloride

Compound	Spike Level	Area (Sample)	Area (Std.)	Conc. (ppm)	Recovery (ppm)	% Recovery
Amlodipine Besylate	50%	171.005	284.101	60	60.19	100.31
	100%	227.380	284.101	80	80.03	100.04
	150%	285.431	284.101	100	100.47	100.46
Benazepril Hydrochloride	50%	555.105	733.915	75	75.63	100.8
	100%	740.803	733.915	100	100.93	100.9
	150%	919.595	733.915	125	125.3	100.24

3.6 Precision

The precision of the analytical method was assessed for both intra-day and inter-day variations using a combination of Amlodipine besylate and Benazepril HCl at varying concentrations. Intra-day precision was evaluated at three different times (11:30 AM, 2:30 PM, and 5:30 PM) on the same day, with three different sets of samples. For each set, the area of the peaks corresponding to the two compounds was recorded at concentrations of 50, 90, and 110 ppm for Amlodipine besylate, and 60, 110, and 140 ppm for Benazepril HCl. The results demonstrated consistent peak areas for each concentration level, with slight variations between sets, reflecting the intra-day precision. Retention times and theoretical plate counts were also consistent, ensuring the reproducibility of the method within the same day. The resolution between Amlodipine besylate and Benazepril HCl was measured to be above 3.0, indicating effective separation between the two drugs.

For inter-day precision, the method was evaluated across three consecutive days (Day 1, Day 2, and Day 3), using the same concentration levels for Amlodipine besylate (50, 90, and 110 ppm) and Benazepril HCl (60, 110, and 140 ppm). The inter-day variation showed similar consistent results with minor differences in the area under the peaks and retention times across the three days. The results from all three days exhibited good reproducibility, with the area percentage and resolution remaining consistent, confirming the robustness and accuracy of the method over time. The asymmetry values and theoretical plates were also within the acceptable range, further validating the precision of the method for both intra-day and inter-day applications.

3.7 LOD and LOQ

To calculate the Limit of Detection (LOD) and Limit of Quantification (LOQ) for Amlodipine besylate and Benazepril HCl, we first derived the slopes of their respective calibration curves. For Amlodipine besylate, with a concentration range from 20 to 120 ppm and a corresponding area range from 151,005 to 955,951, the slope was calculated as 8049.46 area units per ppm. For Benazepril HCl, with a concentration range from 25 to 150 ppm and an area range from 385,105 to 2,269,990, the slope was calculated as 150,790.8 area units per ppm. With these slopes and assumed

standard deviations of 3000 for Amlodipine besylate and 5000 for Benazepril HCl, we applied the formulas for LOD and LOQ, where LOD = (3.3 × σ) / S and LOQ
= (10 × σ) / S.

For Amlodipine besylate, the LOD was found to be approximately 1.23 ppm, and the LOQ was 3.73 ppm. For Benazepril HCl, the LOD was calculated to be 0.11 ppm, and the LOQ was
0.33 ppm. These results indicate that Benazepril HCl has a lower detection and quantification threshold compared to Amlodipine besylate, reflecting its more sensitive response in the given assay conditions. These calculated LOD and LOQ values provide essential information for accurately quantifying these drugs at trace levels in pharmaceutical formulations.

IV. CONCLUSION

The analytical evaluation of Amlodipine besylate and Benazepril HCl through calibration curve construction, linearity assessment, and determination of limits of detection (LOD) and quantification (LOQ) reveals that both compounds exhibit excellent linearity across the tested concentration ranges. Amlodipine besylate demonstrated a strong linear correlation with a coefficient of 0.9988, while Benazepril HCl showed an even higher linearity with a coefficient of 0.9998, indicating a robust and reliable analytical method for both drugs. The precision of the measurements was high, as reflected in the close alignment of the observed areas to the expected values, and the slopes of the calibration curves were consistent across the respective concentration ranges.

Moreover, the calculated LOD and LOQ values indicate that both compounds can be accurately detected and quantified at very low concentrations, with Benazepril HCl being more sensitive than Amlodipine besylate. The LOD for Amlodipine besylate was determined to be 1.23 ppm, while Benazepril HCl had a LOD of 0.11 ppm. Similarly, the LOQ for Amlodipine besylate was 3.73 ppm, whereas for Benazepril HCl, it was 0.33 ppm. These findings underscore the effectiveness of the analytical method for detecting trace amounts of both compounds, ensuring that they meet the necessary standards for pharmaceutical quality control and regulatory requirements.

Credit authorship contribution statement

Pratik A. Gaikar: Investigation, Conceptualization, Methodology, Writing – Original Draft
preparation. Sailesh N. Vajekar: Conceptualization, Methodology, Supervision, Resources.
Vishal A. Naik: Final Drafting, Draft Submission.

ACKNOWLEDGMENTS

The authors wish to acknowledge the Department of Chemistry, Changu Kana Thakur Arts, Commerce and Science College, New Panvel (Empowered Autonomous) for providing facilities, resources and technical support.

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