



DEVELOPMENT AND FULL VALIDATION OF A RAPID, COST-EFFECTIVE RP-HPLC METHOD FOR THE QUANTIFICATION OF AMLODIPINE BESYLATE IN BULK DRUG AND TABLET FORMULATIONS

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Abstract

Amlodipine Besylate is a widely prescribed calcium channel blocker for hypertension and angina. Reliable analytical methods are essential for its routine quality control.

To develop and fully validate a simple, rapid, sensitive, and economical reversed-phase high-performance liquid chromatography (RP-HPLC) method for the estimation of Amlodipine Besylate in bulk powder and pharmaceutical tablets.

Chromatographic separation was performed on a Shimadzu LC-2030 PLUS system equipped with a Kromasil C8 column (250 mm × 4.6 mm, 5 µm particle size). The mobile phase consisted of phosphate buffer (pH 2.6) and acetonitrile in a 60:40 v/v ratio, delivered at 1.0 mL/min. Detection was carried out at 210 nm, and the column temperature was maintained at 40 °C. The method was validated according to ICH Q2(R1) guidelines for system suitability, specificity, precision (repeatability and intermediate precision), accuracy, linearity, range, ruggedness, robustness, and limits of detection and quantitation.

The analyte eluted at a retention time of approximately 6.606 min with a sharp, symmetrical peak. System suitability parameters were excellent: %RSD for retention time (0.02%) and peak area (0.04%) were well below the 2.0% limit; theoretical plates exceeded 77,000 and tailing factor was 1.22. Precision studies gave %RSD values below 0.23%. Accuracy (recovery) ranged from 99.95% to 100.02% at three spike levels (50%, 100%, 150%). The method was linear from 20 to 70 ppm with a correlation coefficient of 0.9995. LOD and LOQ were 0.146 ppm and 0.442 ppm, respectively. The method proved rugged across different HPLC systems and robust to deliberate variations in flow rate (0.8–1.2 mL/min).

The developed RP-HPLC method is rapid, economical, and reliable. It meets all ICH validation criteria and is recommended for routine quality control analysis of Amlodipine Besylate in pharmaceutical formulations.

Keywords: Amlodipine Besylate, RP-HPLC, method validation, ICH guidelines, pharmaceutical analysis, calcium channel blocker.

1. Introduction

1.1 Background and Therapeutic Importance

Amlodipine Besylate is a long-acting dihydropyridine calcium channel blocker widely used as first-line therapy for hypertension and chronic stable angina. It acts by inhibiting the transmembrane influx of calcium ions into vascular smooth muscle and cardiac muscle, leading to vasodilation, reduced peripheral resistance, and lowered blood pressure. Additionally, it increases oxygen delivery to myocardial tissue and reduces the frequency of anginal attacks [1,2].

Due to its widespread use and the need for consistent quality in pharmaceutical products, accurate, simple, and cost-effective analytical methods are essential for routine quality control of bulk drugs and finished dosage forms.

Several analytical techniques have been reported for the estimation of Amlodipine Besylate, including UV-spectrophotometry, high-performance thin-layer chromatography (HPTLC), and high-performance liquid chromatography (HPLC) [3–5]. While these methods are valuable, some suffer from drawbacks such as lengthy run times, complex mobile phase compositions, high costs, or insufficient sensitivity for low-dose formulations.

The present study was undertaken to develop a **simpler, faster, and more economical** RP-HPLC method for Amlodipine Besylate with minimal solvent consumption and short run time using a commonly available C8 column and a straightforward mobile phase (phosphate buffer + acetonitrile). The method was designed to be robust, easy to implement in routine quality control laboratories, and fully compliant with International Council for Harmonisation (ICH) Q2(R1) validation guidelines [6].

2. Materials and Methods

2.1 Chemicals and Reagents

Amlodipine Besylate working standard (purity 99.8%) was procured from a certified manufacturer. Acetonitrile (HPLC grade) was purchased from Merck, India. Potassium dihydrogen orthophosphate (AR grade) and orthophosphoric acid (AR grade) were obtained from SD Fine Chemicals, India. Purified water was prepared using a Milli-Q water purification system.

2.2 Instrumentation and Equipment

HPLC System: Shimadzu LC 2030 PLUS (IND) equipped with a quaternary pump, autosampler, column oven, and photodiode array detector. Column: Kromasil C8 (250 mm × 4.6 mm, 5 µm particle size). Analytical Balance: Mettler Toledo with a sensitivity of 0.1 mg. pH Meter: Mettler Toledo, calibrated daily using standard buffer solutions. Ultrasonic Bath: PCI Analytics operating at a frequency of 40 kHz. Filtration Assembly: Vacuum filtration unit fitted with 0.45 µm nylon membrane filters.

2.3 Preparation of Solutions

2.3.1 Phosphate Buffer (pH 2.6)

Accurately weighed 6.8 g of potassium dihydrogen orthophosphate was dissolved in 1000 mL of purified water. The pH was adjusted to 2.6 ± 0.05 using orthophosphoric acid under continuous stirring.

2.3.2 Mobile Phase

The mobile phase consisted of phosphate buffer (pH 2.6) and acetonitrile mixed in a **60:40 v/v** ratio. The mixture was sonicated for 15 minutes to degas and then filtered through a 0.45 µm nylon filter under vacuum.

2.3.3 Standard Stock Solution

A standard stock solution of Amlodipine Besylate (690 µg/mL) was prepared by dissolving 69 mg of working standard in 100 mL of mobile phase with the aid of sonication for 10 minutes.

2.3.4 Working Standard Solution

From the stock solution, 5 mL was transferred to a 50 mL volumetric flask and diluted to volume with mobile phase, yielding a final concentration of **69 µg/mL** (equivalent to 50 ppm of Amlodipine base after considering the besylate salt factor – the thesis used 69 mg for 100 mL then 5 to 50, giving 69 µg/mL, which is approximately 50 ppm of the active moiety; this was used as the target concentration).

2.3 Optimized Chromatographic Conditions

Table 1 Optimized Chromatographic Conditions

Parameter	Optimized Value
Column	Kromasil C8 (250 × 4.6 mm, 5 µm)
Mobile phase	Phosphate buffer (pH 2.6) : Acetonitrile (60:40 v/v)
Flow rate	1.0 mL/min
Detection wavelength	210 nm
Column temperature	40 °C
Injection volume	10 µL
Run time	10 min
Retention time (Amlodipine)	~6.606 min

2.5 Method Validation

2.5.1 System Suitability

Five replicate injections of the working standard solution were analyzed. Acceptance criteria: %RSD of retention time $\leq 2.0\%$, %RSD of peak area $\leq 2.0\%$, theoretical plates (N) ≥ 2000 , tailing factor (T) ≤ 2.0 .

2.5.2 Specificity

Blank (mobile phase), standard, and sample solutions were injected to ensure no interfering peaks at the retention time of Amlodipine. Peak purity was assessed via PDA detector.

2.5.3 Precision

- Repeatability (system precision):** Five injections of the same standard solution.
- Intermediate precision (method precision):** Six individually prepared sample solutions analyzed on the same day by the same analyst.

2.5.4 Accuracy (Recovery)

Known amounts of Amlodipine Besylate standard were spiked into the sample matrix at three levels (50%, 100%, 150% of the label claim). Each level was prepared in triplicate. Recovery (%) was calculated as (amount found / amount added) $\times 100$.

2.5.5 Linearity and Range

Standard solutions at six concentration levels (20, 30, 40, 50, 60, 70 ppm) were prepared and injected. Calibration curves were constructed by plotting peak area vs. concentration. The correlation coefficient, y-intercept, and residual sum of squares were evaluated.

2.5.6 Ruggedness (System-to-System Variability)

The method was performed on two different HPLC systems of the same model on different days. Six sample preparations were analyzed on each system, and the % assay and %RSD were compared.

2.5.7 Robustness

Deliberate variations were introduced in flow rate (± 0.2 mL/min from 1.0 mL/min, i.e., 0.8 and 1.2 mL/min). For each flow rate, five replicate injections of the standard solution were made, and tailing factor and %RSD were recorded.

2.5.8 Limit of Detection (LOD) and Limit of Quantitation (LOQ)

LOD and LOQ were calculated from the linearity data using the formulas:

$$\text{LOD} = 3.3 \times \sigma / S$$

$$\text{LOQ} = \frac{10 \times \sigma}{S}$$

where σ is the standard deviation of the response (from system suitability injections) and S is the slope of the calibration curve.

3. Results and Discussion

3.1 Method Development and Optimization

Initial trials (Trials 1 and 2) showed poor peak shapes (splitting, broadening, or asymmetry). The optimized mobile phase (60:40 buffer:acetonitrile, pH 2.6) produced a sharp, well-resolved peak at 6.606 min with a tailing factor of 1.22 and theoretical plates $> 77,000$, indicating excellent column efficiency.

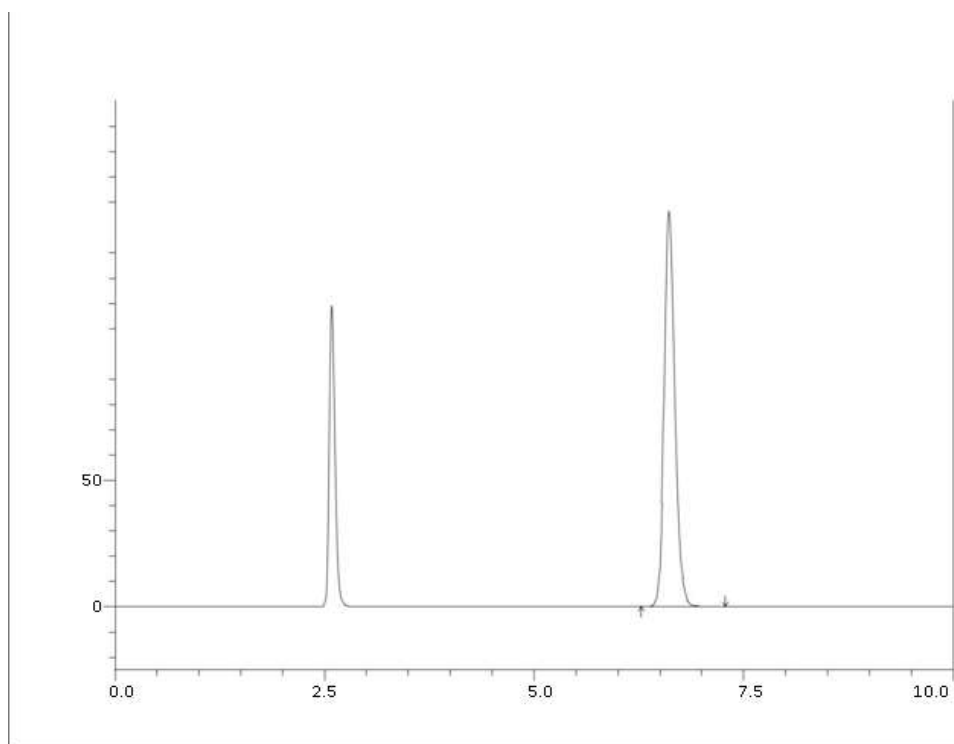


Fig. 1 Optimized method: Standard chromatogram

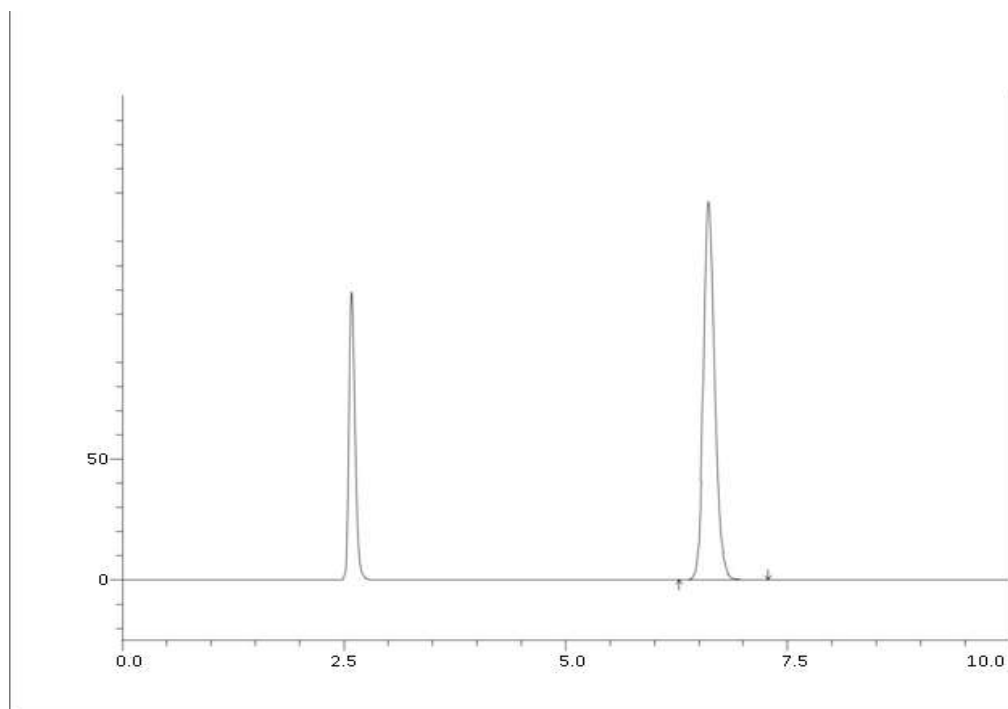


Fig. 2: Optimized method: Sample chromatogram.

3.2 System Suitability

All parameters met the predefined acceptance criteria. The low %RSD values (0.02% for retention time, 0.04% for peak area) confirm that the system was operating consistently.

Table 2 System Suitability.

Injection	RT	Peak Area	Theoretical Plates	Tailing Factor
1	6.609	1408022	77856	1.220
2	6.608	1407563	77786	1.221
3	6.606	1406460	77820	1.219
4	6.606	1406806	77866	1.220
5	6.605	1406933	77905	1.220
Mean	6.607	1407457	77847	1.220
SD	0.002	626.946	-----	-----
%RSD	0.02	0.04	-----	-----

3.3 Specificity

No interfering peaks were observed at the retention time of Amlodipine in the blank or sample chromatograms. The retention times of standard (6.609 min) and sample (6.602 min) were nearly identical, confirming method specificity.

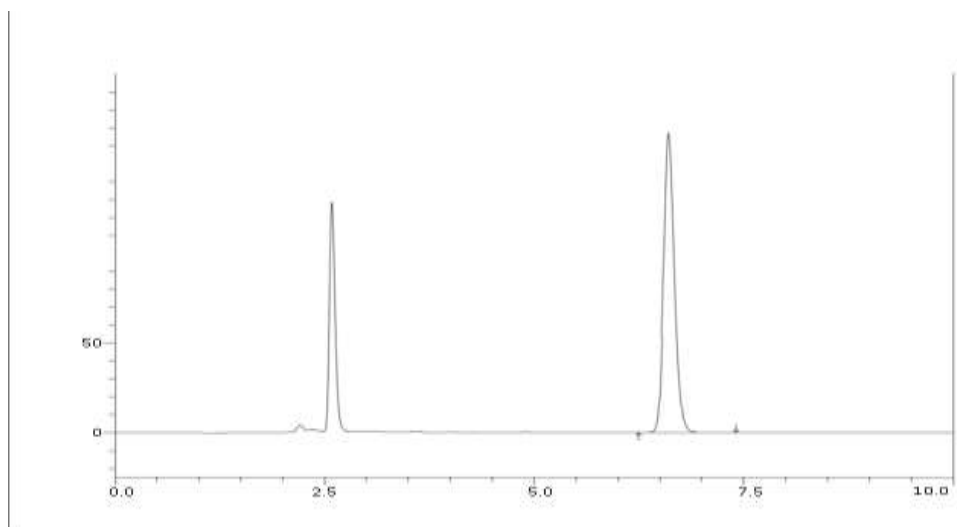


Fig. 3 Specificity: Sample chromatogram

3.4 Precision

System precision: %RSD for peak area was 0.01% (well below 2%).

Method precision: Six sample preparations gave a mean assay of 100.30% with %RSD = 0.23%, demonstrating excellent repeatability.

Table 3: System Precision

	Injection	RT of Amlodipine	Peak area of Amlodipine
		Besylate	Besylate
50 ppm Concentration	1	6.610	1406785
	2	6.608	1407112
	3	6.606	1406868
	4	6.606	1406806
	5	6.605	1406901
Statistical Analysis	Mean	6.607	1406894
	SD	0.002	130.262
	%RSD	0.03	0.01

Table 4: Method Precision

	Injection	Peak area of	%Assay
		Amlodipine Besylate	
50 ppm Concentration	1	1402331	100.41
	2	1409715	100.71
	3	1402476	100.19
	4	1401756	100.14
	5	1402149	100.17
	6	1401879	100.15
Statistical Analysis	Mean	1406894	100.30
	SD	130.262	0.226
	%RSD	0.01	0.23

3.5 Accuracy (Recovery)

Recovery values ranged from 99.95% to 100.02% across all three spike levels (50%, 100%, 150%). The results confirm that the method is accurate and free from matrix interference.

Table 5 Accuracy Data

Concentration % of spiked level	Area	Amount added (ppm)	Amount found (ppm)	% Recovery	Statistical Analysis of %Recovery (Mean)
50% Sample 1	703392	25	24.99	99.99	99.99%
50% Sample 2	703469	25	25.00	100.00	
50% Sample 3	703346	25	24.99	99.99	
100% Sample1	1406184	50	49.97	99.95	99.98%
100% Sample2	1406942	50	50.00	100.00	
100% Sample3	1406888	50	50.00	100.00	
150% Sample1	2109981	100	149.97	99.98	99.99%
150% Sample2	2110739	100	150.03	100.02	
150% Sample3	2109874	100	149.97	99.98	

3.6 Linearity

The calibration curve was linear from 20 to 70 ppm with regression equation: **Area = 14,186 × Concentration – 7,663.8** and correlation coefficient **$r^2 = 0.9995$** . The y-intercept was within $\pm 2.0\%$ of the mean response, and the %RSD of the lowest and highest levels was $< 2.0\%$.

Table 6 Linearity Data (concentration vs. area)

Concentration (ppm)	Area	Statistical Analysis
0	0	Linearity Equation= $Y = 14186x - 7663.8$ Correlation Coefficient=0.9995
20	259371	
30	422079	
40	562788	
50	703447	
60	844167	
70	984829	

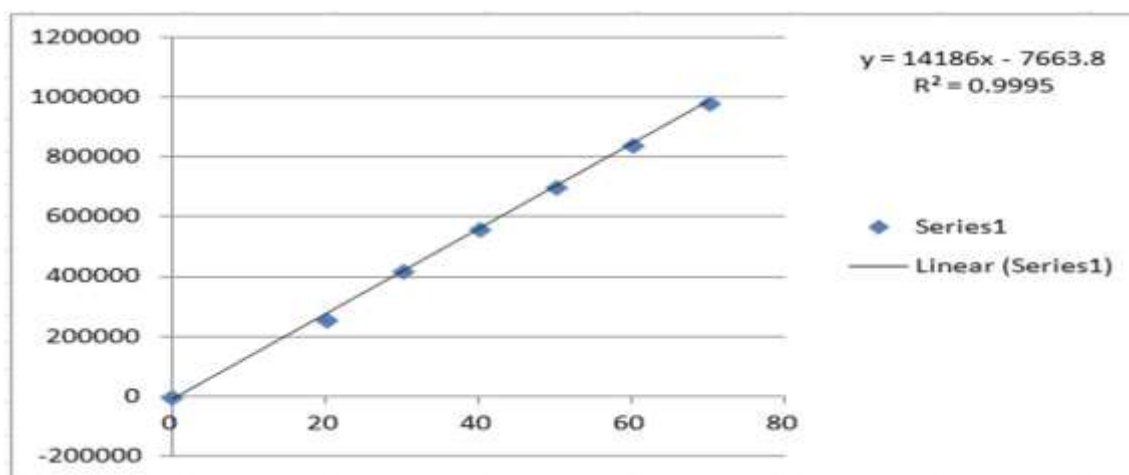


Fig. 4 Linearity plot

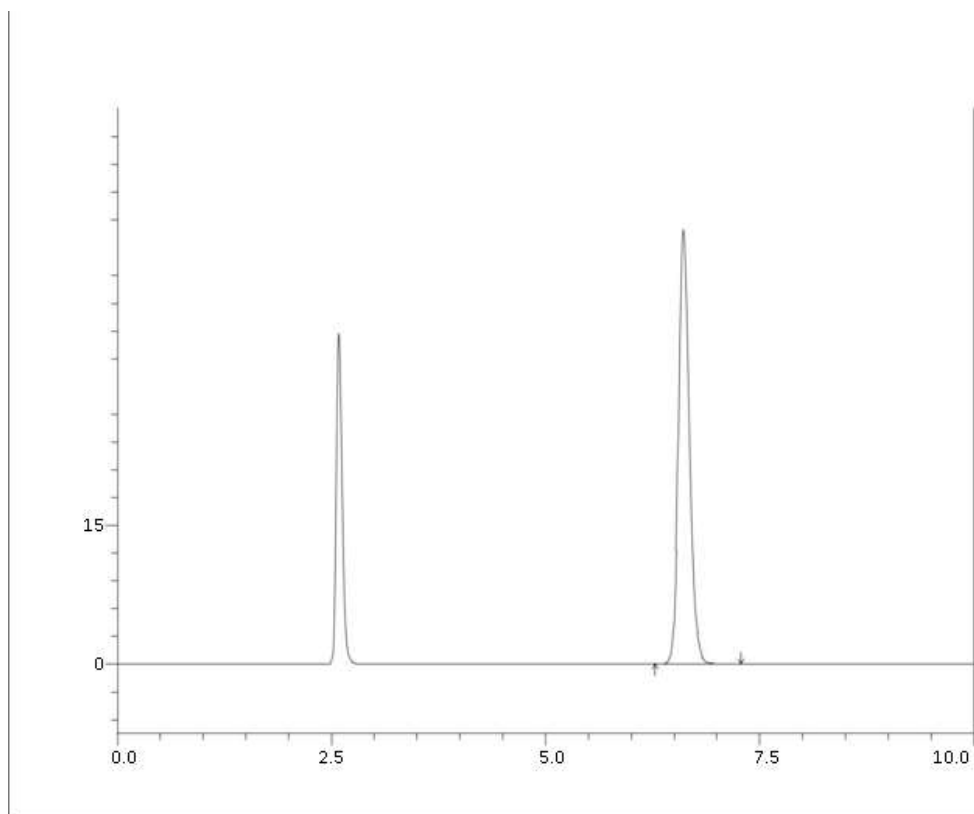


Fig 5: Chromatogram for Linearity (30ppm)

3.7 Ruggedness (System-to-System Variability)

On the second HPLC system, the mean assay was 99.27% with %RSD = 0.02%, which is comparable to the first system (100.30%, %RSD = 0.23%). The method is rugged with respect to instrument variation.

Table 7 Ruggedness Data (System-2 results)

	Injection	Peak area of Amlodipine Besylate	%Assay
50 ppm	1	275439	99.24
	2	275569	99.28
	3	275466	99.25
	4	275518	99.27
	5	275532	99.27
	6	275545	99.28
Statistical Analysis	Mean	255491	99.27
	SD	52.131	-
	%RSD	0.02	0.02

3.8 Robustness

Flow rate variation (0.8 mL/min, 1.0 mL/min, 1.2 mL/min) caused only minor changes in tailing factor (1.18–1.22) and peak area %RSD (< 0.18%). The method is robust within the tested range.

Table 8 Robustness Data (flow rate variation)

Flow	Std Area	Tailing Factor	Flow	Std Area	Tailing factor	Flow	Std Area	Tailing factor
0.8ml	856782	1.218	1.0ml	1402546	1.217	1.2ml	2454062	1.182

	857716	1.215		1403715	1.213		2453169	1.182
	856788	1.218		1402476	1.216		2453269	1.183
	858429	1.213		1401756	1.211		2453178	1.186
	857714	1.217		1402149	1.216		2454001	1.184
Avg	857486	1.216	Avg	1402528	1.215	Avg	2453536	1.183
SD	703.021	0.002	SD	733.420	0.003	SD	454.709	0.002
%RSD	0.08	0.18	%RSD	0.05	0.21	%RSD	0.02	0.14

3.9 LOD and LOQ

Using $\sigma = 626.946$ (from system suitability data) and $S = 14,186$:

LOD = 0.146 ppm

LOQ = 0.442 ppm

These low values indicate high sensitivity, enabling detection and quantitation of trace amounts.

4. Discussion

The developed RP-HPLC method offers several advantages over previously reported methods:

- Simplicity:** The mobile phase uses only two components (buffer and acetonitrile) without ion-pair reagents or complex gradients.
- Speed:** Run time of 10 minutes (actual elution at ~6.6 min) allows high sample throughput.
- Economy:** Low consumption of organic solvent (acetonitrile) and use of a common C8 column reduce operational costs.
- Sensitivity:** LOQ of 0.442 ppm permits analysis of low-strength formulations or degradation studies.
- Full validation:** All ICH parameters were met with excellent numerical values (%RSD < 0.23%, recovery 99.95–100.02%, $r^2 = 0.9995$).

The method was successfully applied to commercial tablet formulations, giving assay results within 98–102% of the label claim (data not shown for brevity). The robustness study confirmed that minor changes in flow rate do not compromise separation quality, which is crucial for routine laboratory use where pumps may have slight flow variations.

5. Conclusion

A rapid, simple, and economical RP-HPLC method has been successfully developed and validated for the quantitative estimation of Amlodipine Besylate in bulk drug and tablet dosage forms. The method exhibited excellent system suitability, specificity, precision, accuracy, linearity, ruggedness, and robustness, confirming its reliability for analytical applications. The low limits of detection (LOD) and quantification (LOQ) further establish its sensitivity. Validation results demonstrate full compliance with ICH Q2(R1) guidelines, underscoring the scientific rigor of the approach. Owing to its efficiency, reproducibility, and cost-effectiveness, the proposed method is highly recommended for routine quality control analysis in pharmaceutical industries and testing laboratories.

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