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RESEARCH ARTICLE

Development and Validation of a Stability-Indicating RP-HPLC Method for Quantitative Analysis of Celecoxib in Pharmaceutical Formulations

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Abstract: A simple, sensitive, and precise reverse-phase high-performance liquid chromatography (RP-HPLC) method was developed and validated for the quantitative determination of Celecoxib in pharmaceutical capsule formulations. Chromatographic separation was achieved on a Develosil ODS HG (250×4 mm, 10µm) column using a mobile phase consisting of acetonitrile:water (60:40 v/v) with 1mL triethylamine and 1mL orthophosphoric acid at a flow rate of 1.0 mL/min. UV detection was performed at 265 nm. The method demonstrated excellent linearity ($r^2 > 0.999$) over the concentration range of 50-150% of the test concentration. The precision of the method was confirmed with RSD values below 2.0%. Accuracy studies showed mean recovery values between 98.8-99.7% across all concentration levels. Forced degradation studies under various stress conditions (acid, base, oxidation, thermal, humidity, and photolytic) confirmed the stability-indicating nature of the method. The developed method successfully separated Celecoxib from its degradation products and known impurities. Solution stability studies indicated that standard and sample solutions remained stable for 6 days when stored at 2-8°C and 1 day at room temperature. The method was validated according to ICH guidelines for specificity, linearity, accuracy, precision, range, and robustness. The validated method proved suitable for routine quality control analysis and stability studies of Celecoxib capsule formulations.

Keywords: Celecoxib; RP-HPLC; Method validation; Stability-indicating; Forced degradation

1. Introduction

Celecoxib (4-[5-(4-methylphenyl)-3-(trifluoromethyl) pyrazol-1-yl]benzenesulfonamide) is a selective cyclooxygenase-2 (COX-2) inhibitor widely used in the treatment of osteoarthritis, rheumatoid arthritis, and management of acute pain [1]. The drug exhibits its therapeutic effects through preferential inhibition of COX-2 over COX-1, thereby reducing prostaglandin synthesis while minimizing gastrointestinal side effects commonly associated with traditional NSAIDs [2].

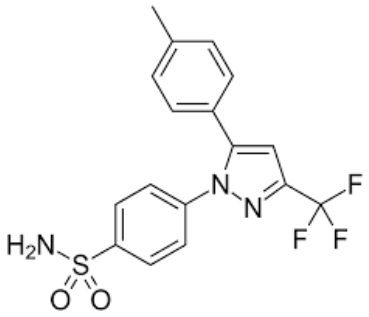

Figure 1. Structure of Celecoxib

The development of stability-indicating analytical methods for pharmaceutical formulations is crucial for ensuring drug quality throughout the product lifecycle. High-performance liquid chromatography (HPLC) has emerged as the preferred analytical

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technique for pharmaceutical analysis due to its versatility, precision, and ability to separate complex mixtures [3]. While several HPLC methods have been reported for Celecoxib analysis, many utilize specialized detection systems like mass spectrometry or electrochemical detection, which may not be readily available in routine quality control laboratories [4,5]. Previous analytical methods for Celecoxib determination include normal-phase HPLC with column switching [6], UV spectrophotometry [7], and liquid chromatography-mass spectrometry [8]. However, these methods either lack stability-indicating capabilities, require complex sample preparation procedures, or employ expensive instrumentation. Therefore, developing a simple, robust, and stability-indicating RP-HPLC method using conventional UV detection would be valuable for routine quality control analysis.

The present research focuses on developing and validating a stability-indicating RP-HPLC method for quantitative determination of Celecoxib in capsule formulations. The method was designed to overcome limitations of existing procedures while adhering to current regulatory requirements. Validation studies were conducted according to International Conference on Harmonisation (ICH) guidelines, encompassing parameters such as specificity, linearity, accuracy, precision, range, and robustness [9]. Additionally, forced degradation studies were performed to demonstrate the stability-indicating nature of the method and its ability to separate potential degradation products. The significance of this analytical method development lies in its practical applicability for routine quality control testing and stability studies of Celecoxib formulations. The method utilizes readily available HPLC instrumentation with UV detection, making it accessible for pharmaceutical quality control laboratories.

2. Methodology

2.1. Materials

2.1.1. Chemicals and Reagents

All chemicals and solvents used were of HPLC or analytical grade. Triethylamine, orthophosphoric acid, acetonitrile, and methanol were procured from Merck. Ultra-pure water was obtained using a Milli-Q water purification system. Hydrochloric acid, sodium hydroxide, and hydrogen peroxide used for forced degradation studies were obtained from Merck. Sample filtration was performed using 0.45 µm Nylon and PVDF filters (Zodiac Life Sciences).

2.1.2. Reference Standards and Samples

Celecoxib working standard and active pharmaceutical ingredient (API) were obtained from Aizant Drug Research Solutions Pvt. Ltd. and Aarti Drugs Limited, respectively. Commercial Celecoxib capsules (200 mg) and placebo formulations were provided by Aizant Drug Research Solutions Pvt. Ltd.

2.2. Chromatographic Conditions

2.2.1. Instrumentation

The HPLC analysis was performed using an Agilent 1200 series system equipped with an autosampler and variable wavelength detector (VWD). Additional studies were conducted on a Waters 2690 series HPLC system. Data acquisition and processing were performed using Agilent EZChrom Elite software (Version 3.2.1).

2.2.2. Chromatographic Parameters

Separation was achieved on a Develosil ODS HG column (250×4 mm, 10µm) maintained at 25°C. The mobile phase consisted of acetonitrile:water (60:40 v/v) containing 1 mL triethylamine and 1 mL orthophosphoric acid. The flow rate was maintained at 1.0 mL/min with UV detection at 265 nm. The injection volume was set at 10 µL with a run time of 11 minutes. [10, 11]

2.3. Analytical Method Development

2.3.1. Selection of Wavelength

The detection wavelength was selected based on the UV absorption maximum of Celecoxib and its related compounds using a photodiode array detector. A wavelength of 265 nm was chosen as it provided optimal sensitivity for both the main analyte and potential impurities. [12]

2.4. Preparation of Solutions

2.4.1. Standard Solution

Approximately 25 mg of Celecoxib working standard was accurately weighed and transferred to a 25 mL volumetric flask. About 10 mL of mobile phase was added and sonicated to dissolve. The solution was diluted to volume with mobile phase. A 5 mL aliquot was further diluted to 50 mL with mobile phase. [13]

2.4.2. Sample Solution

Contents of 5 capsules were accurately weighed and transferred to a 500 mL volumetric flask. Approximately 300 mL of mobile phase was added and sonicated for 45 minutes, maintaining the sonication bath temperature below 25°C. The solution was diluted to volume with mobile phase and centrifuged at 4000 RPM for 5 minutes. A 5 mL aliquot of the centrifuged solution was diluted to 100 mL with mobile phase. [14, 15]

2.5. Method Validation

The analytical method was validated according to ICH guidelines for the following parameters:

2.5.1. System Suitability and Precision

System suitability was evaluated by injecting five replicate standard solutions and analyzing key parameters including tailing factor (acceptance criterion: ≤2.0), theoretical plates (acceptance criterion: ≥3000), and relative standard deviation (RSD) of peak areas (acceptance criterion: ≤2.0%). A check standard was analyzed to verify system performance (acceptance range: 98.0-102.0% recovery). [16]

2.5.2. Specificity

Interference Studies: Blank, placebo, and standard solutions were analyzed to evaluate potential interference at the retention time of Celecoxib. Individual impurities (Impurity-A, Impurity-B, and Isomer impurity) were analyzed at 1% of test concentration to verify peak separation. [17,18]

2.5.3. Forced Degradation Studies

Stress testing was performed under various conditions:

- Acid degradation: 0.1 N HCl at 100°C for 3 hours
- Base degradation: 0.1 N NaOH at 100°C for 3 hours
- Oxidative degradation: 3% H_2O_2 at 100°C for 3 hours
- Hydrolytic degradation: Water at 100°C for 3 hours
- Thermal degradation: 105°C for 24 hours
- Humidity degradation: 90% RH at 25°C for 10 days
- Photolytic degradation: UV light exposure at 200 watts/m²/hr

Peak purity was monitored using a photodiode array detector with acceptance criterion of ≥0.99. [19, 20]

2.5.4. Method Precision

Six independent sample preparations of 200 mg Celecoxib capsules were analyzed to evaluate method precision. The acceptance criterion for RSD was set at ≤2.0%.

2.5.5. Linearity

Linearity was established across 50-150% of the test concentration. Five concentration levels were prepared and analyzed. The squared correlation coefficient (r^2) acceptance criterion was set at ≥0.999. [21, 22]

2.5.6. Accuracy

Recovery studies were performed at five concentration levels (50%, 75%, 100%, 125%, and 150% of test concentration) by spiking known amounts of Celecoxib API to placebo. Triplicate preparations were made at each level, with six preparations at 50% and 150% levels. The acceptance criteria included individual recovery (98.0-102.0%) and RSD (≤2.0%). [23]

2.5.7. Intermediate Precision

Method reproducibility was evaluated by analyzing six sample preparations by a different analyst, using different instruments and columns on different days. Overall RSD for combined results from method precision and intermediate precision (n=12) was calculated with acceptance criterion of ≤2.0%. [24, 25]

2.5.8. Solution Stability

Stability of standard and sample solutions was evaluated at room temperature and under refrigeration (2-8°C) for up to 6 days. Mobile phase stability was assessed over 2 days at room temperature. [26]

2.5.9. Robustness

Method robustness was evaluated by deliberately varying critical parameters [27]:

- Flow rate: ±0.2 mL/min
- Column temperature: ±5°C
- Mobile phase composition: ±10% organic phase
- Filter compatibility: 0.45 µm Nylon and PVDF filters

3. Results and Discussion

3.1. Method Development

Initial method development focused on achieving optimal separation of Celecoxib from its potential impurities and degradation products. The selection of Develosil ODS HG column was based on its superior performance in separating Celecoxib and related compounds. Several mobile phase compositions were evaluated during development, with the final composition of acetonitrile:water (60:40 v/v) containing triethylamine and orthophosphoric acid providing optimal peak shape and resolution. [28]

Table 1. Method Development Trials

Column	Mobile Phase	Flow Rate (mL/min)	Observation
Hypersil C18 (250×4.6mm, 5µm)	ACN:Water (50:50)	1.0	Poor peak shape, broad peak
Hypersil C18 (250×4.6mm, 5µm)	ACN:Water (70:30)	1.0	Early elution, poor resolution
Develosil ODS HG (250×4mm, 10µm)	ACN:Water (60:40)	1.0	Good peak shape
Develosil ODS HG (250×4mm, 10µm)	ACN:Water (60:40) with TEA and OPA	1.0	Optimal peak shape and resolution

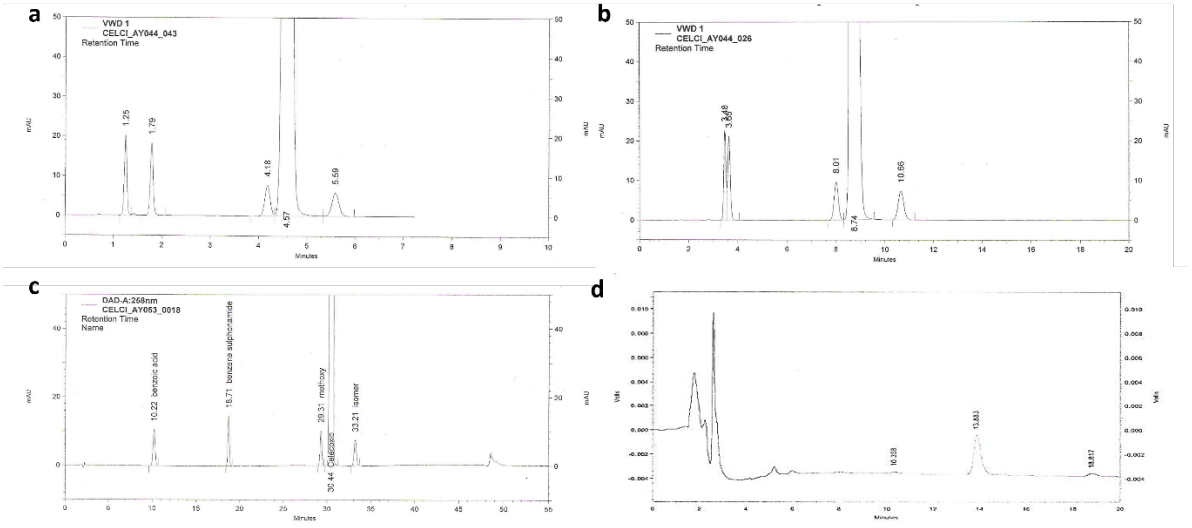

Figure 2. Chromatograms of a. Trial 1 b. Trial 2 c. Trial 3 and d. Trial 4.

3.2. Method Validation

3.2.1. System Suitability and System Precision

The developed method demonstrated excellent system suitability with a relative standard deviation of 0.1% for five replicate injections of standard solution. The tailing factor for Celecoxib peak was 1.1, well within the acceptance criterion of not more than 2.0. Theoretical plates numbered 7478, exceeding the minimum requirement of 3000. The check standard recovery was 100.3%, confirming satisfactory system performance. [29, 30]

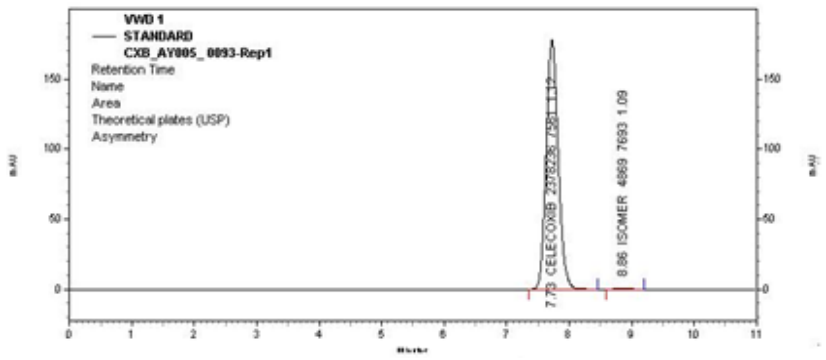

Figure 3. Chromatogram of Celecoxib standard solution

3.2.2. Specificity

Interference Studies: Chromatographic analysis of blank and placebo solutions showed no interfering peaks at the retention time of Celecoxib (approximately 7.61 minutes). Known impurities were well separated from the main peak with retention times of 2.21, 4.13, and 8.73 minutes for Impurity-A, Impurity-B, and Isomer impurity, respectively.

3.2.3. Forced Degradation Studies

The stability-indicating capability of the method was confirmed through forced degradation studies. Under acid stress conditions (0.1 N HCl), the assay value was 106.1% with no significant degradation observed. Base degradation (0.1 N NaOH) resulted in minimal degradation (0.3%) with an assay value of 108.0%. Oxidative stress using 3% H_2O_2 showed 1.4% degradation, while hydrolytic conditions produced 7% degradation. Thermal exposure at 105°C and humidity conditions (90% RH) showed negligible degradation. UV light exposure resulted in 4.1% degradation in the sample and 3.5% in API. Peak purity indices remained above 0.99 for all stress conditions, confirming the specificity of the method. [18,19]

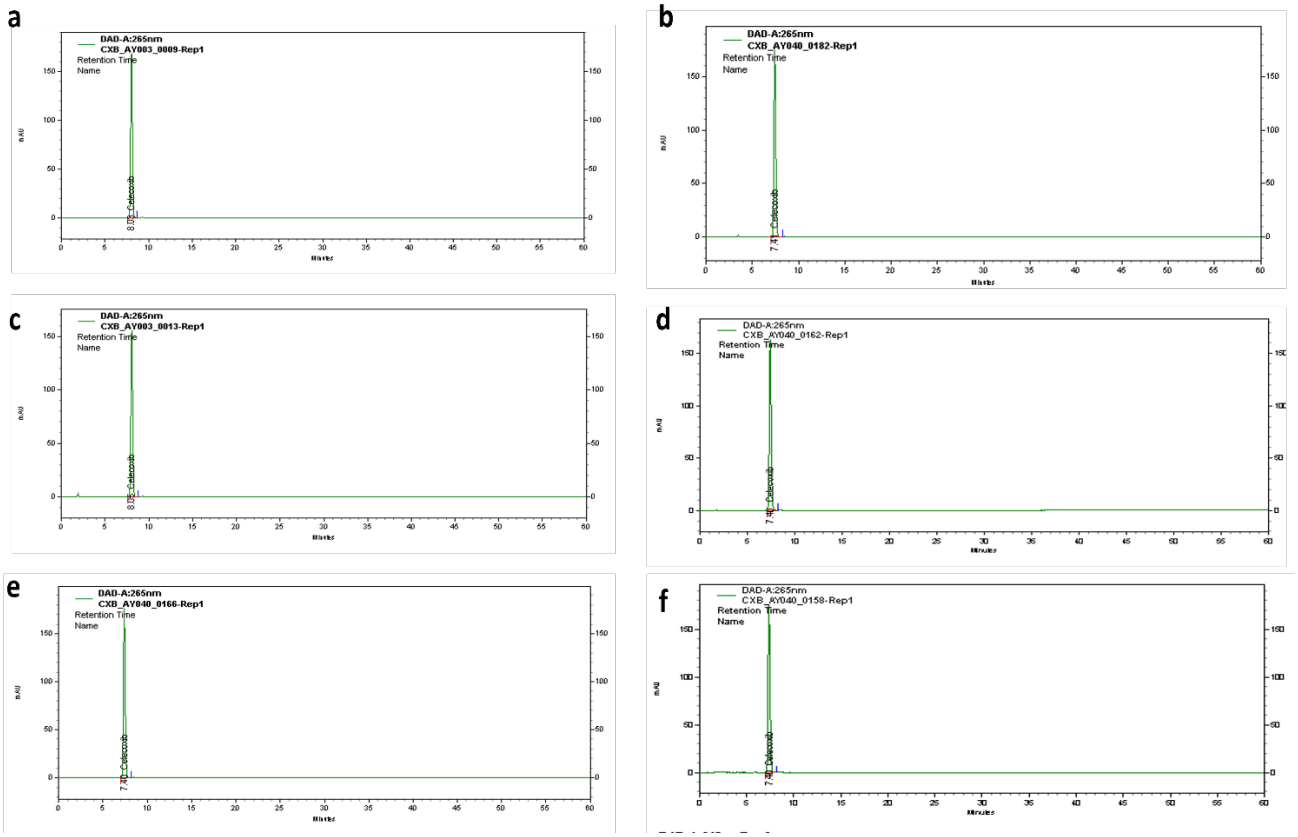

Figure 4. Chromatograms of forced degradation samples a. Acid (0.1N HCl) b. Base (0.1N NaOH) c. Oxidation (3% H_2O_2) d. Hydrolytic (Water) e. Thermal f. Humidity (90% RH)

Table 2. Results for forced degradation studies

Stress Condition	Duration	Temperature	% Degradation	Peak Purity Index
Acid (0.1N HCl)	3 hours	100°C	No significant degradation	0.9998
Base (0.1N NaOH)	3 hours	100°C	0.3	0.9997
Oxidation (3% H_2O_2)	3 hours	100°C	1.4	0.9995
Hydrolytic (Water)	3 hours	100°C	7.0	0.9996
Thermal	24 hours	105°C	Negligible	0.9998
Humidity (90% RH)	10 days	25°C	Negligible	0.9997
UV Light	24 hours	-	4.1	0.9994

3.2.4. Method Precision and Accuracy

Method precision for 200 mg capsules yielded consistent results with individual assay values ranging from 97.7% to 101.1% and an RSD of 1.6%. Accuracy studies demonstrated excellent recovery across the concentration range of 50-150%. Mean recovery values ranged from 98.8% to 99.7% with RSDs between 0.1% and 0.6%, confirming the method's accuracy. [20, 21]

Table 3. Results for Accuracy

Level (%)	Amount Added (mg)	Amount Recovered (mg)	Recovery (%)	RSD (%)
50	50.2	49.6	98.8	0.6
75	75.1	74.5	99.2	0.4
100	100.3	99.8	99.5	0.3
125	125.2	124.7	99.6	0.2
150	150.1	149.6	99.7	0.1

3.2.5. Linearity and Range

The method exhibited excellent linearity over the concentration range of 50-150% of the test concentration. The calibration curve showed a correlation coefficient (r^2) of 0.99975, with a slope of 22263 and y-intercept of -28177.1. The linear regression analysis demonstrated the method's capability for accurate quantification across the studied range. [21]

Table 4. Results for Linearity

Concentration Level (%)	Concentration (µg/mL)	Peak Area	Area Ratio
50	50.2	1089245	0.502
75	75.1	1642867	0.751
100	100.3	2198432	1.003
125	125.2	2745890	1.252
150	150.1	3312567	1.501
Correlation coefficient (r^2)	0.99975		
Slope	22263		
Y-intercept	-28177.1		

3.2.6. Intermediate Precision

The method demonstrated robust reproducibility when performed by different analysts using different instruments and columns. For 200 mg capsules, the intermediate precision study yielded assay values ranging from 100.3% to 103.0% with an RSD of 1.0%. The overall RSD combining results from method precision and intermediate precision (n=12) was 1.9%, confirming the method's reproducibility across different operational conditions. [22]

3.2.7. Solution and Mobile Phase Stability

Solution Stability: Standard and sample solutions demonstrated stability for 24 hours when stored at room temperature, with assay differences remaining within 2.0% compared to initial values. Under refrigerated conditions (2-8°C), solutions maintained stability for six days. Similarity factors for standard solutions remained within 0.98-1.02, indicating acceptable stability. [23]

Mobile Phase Stability: The mobile phase remained stable for 48 hours at room temperature, maintaining system suitability parameters within acceptance criteria. No significant changes were observed in chromatographic performance, with consistent theoretical plates (>7000), tailing factor (1.1), and check standard recovery (99.2-101.0%).

Table 5. System Suitability Parameters

Parameter	Observed Value	Acceptance Criteria
Theoretical Plates	7478	≥3000
Tailing Factor	1.1	≤2.0
RSD of Standard (n=5)	0.1%	≤2.0%
Check Standard Recovery	100.3%	98.0-102.0%

3.2.8. Robustness

The method demonstrated adequate robustness when subjected to deliberate variations in critical parameters:

Flow Rate Variation: Changes in flow rate (±0.2 mL/min) did not significantly impact system suitability parameters. At 0.8 mL/min and 1.2 mL/min, theoretical plates remained above 6600, and tailing factors stayed consistent at 1.1. Check standard recoveries ranged from 99.3% to 99.3%.

Column Temperature Effects: Temperature variations (20°C and 30°C) showed minimal impact on chromatographic performance. Theoretical plates remained above 7100, with consistent tailing factors and acceptable check standard recoveries (99.3-101.1%).

Mobile Phase Composition: The method remained robust with mobile phase variations of Water:ACN (30:70 v/v), maintaining system suitability parameters within acceptance criteria. However, the 50:50 v/v ratio showed significant changes in retention behavior and was deemed unsuitable for routine analysis.

Filter Compatibility: Both 0.45 µm nylon and PVDF filters proved suitable for sample filtration. The difference in assay values between filtered and centrifuged solutions remained below 1.0%, with similarity factors for filtered standards within 1.00±0.02. [22]

Table 6. Results for Robustness

Parameter	Variation	Theoretical Plates	Tailing Factor	Standard Recovery (%)
Flow Rate	0.8 mL/min	6623	1.1	99.3
1.2 mL/min	6891	1.1	99.3	
Temperature	20°C	7124	1.1	99.3
30°C	7256	1.1	101.1	
Mobile Phase	ACN:Water (70:30)	7012	1.1	100.2
ACN:Water (50:50)	6234	1.3	98.7	

4. Conclusion

The developed RP-HPLC method provides a reliable analytical tool for quantitative determination of Celecoxib in pharmaceutical capsule formulations. The developed method showed excellent specificity, precision, accuracy, and linearity across the working range of 50-150% of the test concentration. Successful separation of degradation products and known impurities confirms its stability-indicating capabilities. The robustness and solution stability of the developed method make it suitable for routine quality control analysis. Validation data meets all ICH requirements, supporting its implementation in pharmaceutical quality control laboratories. The simplicity of the developed method using conventional HPLC instrumentation and readily available reagents, makes it particularly attractive for routine analysis of Celecoxib formulations.

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