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RESEARCH ARTICLE

Development and Validation of a Stability-Indicating RP-HPLC Method for Simultaneous Quantification of Cilnidipine and Telmisartan in Pharmaceutical Formulations

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Abstract: A rapid, sensitive, and precise reverse-phase high-performance liquid chromatographic (RP-HPLC) method was developed and validated for simultaneous quantification of Cilnidipine and Telmisartan in pharmaceutical formulations. The chromatographic separation was achieved using an Agilent C18 column (2.5 µm; 4.6×100 mm) with an isocratic mobile phase consisting of methanol:0.1% triethylamine (pH 6.0 adjusted with orthophosphoric acid) in the ratio of 60:40 v/v at a flow rate of 0.9 mL/min. Detection was carried out at 251 nm wavelength. The retention times for Cilnidipine and Telmisartan were 2.382 and 3.315 minutes, respectively. The method demonstrated linearity over concentration ranges of 2-10 µg/mL for Cilnidipine and 1.5-7.5 µg/mL for Telmisartan with correlation coefficients (R^2) of 0.999. The limits of detection were 0.0843 and 0.0084 µg/mL, while the limits of quantification were 0.255 and 0.025 µg/mL for Cilnidipine and Telmisartan, respectively. The method was validated according to ICH guidelines for accuracy, precision, specificity, linearity, robustness, and ruggedness. Forced degradation studies revealed that both drugs underwent significant degradation under oxidative conditions (6.02% for Cilnidipine and 21.15% for Telmisartan), while showing minimal degradation under neutral conditions. The developed method found to be suitable for routine quality control analysis of Cilnidipine and Telmisartan in pharmaceutical formulations.

Keywords: Cilnidipine; Telmisartan; RP-HPLC; Stability-indicating method; Method validation.

1. Introduction

Chromatographic techniques play a pivotal role in pharmaceutical analysis, offering precise separation and quantification of drug components. High-performance liquid chromatography (HPLC) has emerged as an indispensable analytical tool in pharmaceutical research and quality control, providing superior resolution and sensitivity compared to conventional methods [1]. The technique's versatility in analyzing diverse chemical compounds, coupled with its ability to provide rapid and accurate results, makes it particularly valuable for pharmaceutical applications [2]. High-performance liquid chromatography operates on the principle of differential migration of compounds between a mobile phase and stationary phase. The separation mechanism relies on various molecular interactions, including adsorption, partition, ion exchange, and size exclusion [3]. The advent of high-pressure systems and refined column technology has significantly enhanced separation efficiency and resolution [4]. Reverse-phase HPLC, utilizing non-polar stationary phases and polar mobile phases, has become particularly prominent in pharmaceutical analysis due to its broad applicability and reproducibility [5].

Cilnidipine, a dihydropyridine calcium channel blocker, exhibits dual L/N-type calcium channel blocking activity. Its chemical structure comprises 1,4-dihydropyridine with a cinnamyl group at position 2 and a methoxyethyl group at position 5 [6]. The compound demonstrates significant antihypertensive effects through its action on both vascular smooth muscle and sympathetic nerve terminals [7]. Telmisartan functions as an angiotensin II receptor antagonist, specifically blocking the AT1 receptor subtype. It has a benzimidazole core with a biphenyl substituent, contributing to its high receptor affinity and long duration of action [8]. The drug's lipophilic nature results in excellent tissue penetration and bioavailability [9].

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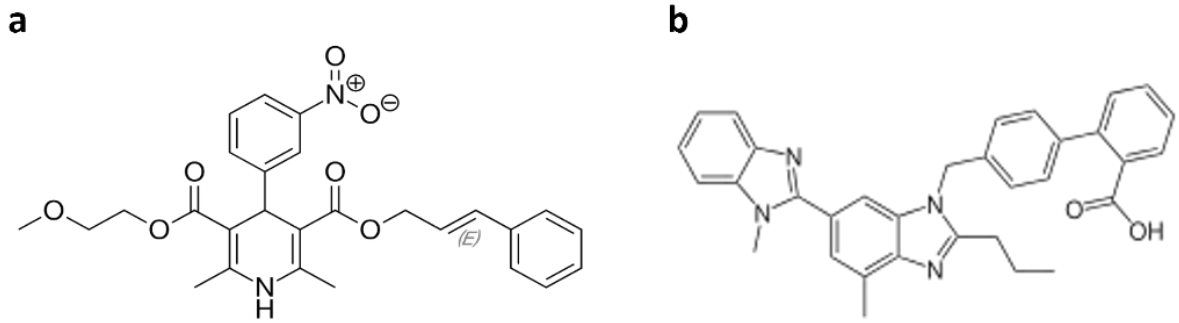

Figure 1. Structure of a. Clinidipine and b. Telmisartan

The simultaneous determination of Cilnidipine and Telmisartan presents several analytical challenges due to their different physicochemical properties and potential interference from excipients and degradation products [10]. Previous analytical methods for these drugs individually or in combination with other compounds have shown limitations in terms of separation efficiency, analysis time, or sensitivity [11, 12]. Therefore, developing a stability-indicating method capable of simultaneous quantification of both drugs while resolving their degradation products becomes crucial for pharmaceutical quality control [13]. Various analytical techniques have been reported for the individual analysis of Cilnidipine and Telmisartan, including spectrophotometry, HPLC, and liquid chromatography-mass spectrometry [14, 15]. However, methods for their simultaneous determination are limited, particularly those addressing stability-indicating aspects [16]. The development of a validated RP-HPLC method for simultaneous quantification would provide significant advantages in terms of time, cost, and analytical efficiency [17].

2. Materials and Methods

2.1. Chemicals and Instruments

The chromatographic analysis was performed using a Shimadzu HPLC system equipped with a quaternary pump, autosampler, and UV-visible detector. Data acquisition and processing were accomplished using LC Solution software. Other instrumentation included a Shimadzu UV-Vis spectrophotometer, VSI pH meter, Labman ultrasonicator, and Mettler-Toledo analytical balance [18]. Reference standards of Cilnidipine and Telmisartan (API grade) were obtained from Swapnroop Drugs Pvt. Ltd., Aurangabad. HPLC-grade methanol, triethylamine, and orthophosphoric acid were procured from established chemical suppliers. All other reagents used were of analytical grade.

2.2. Chromatographic Conditions

The separation was achieved using an Agilent C18 column (2.5 µm; 4.6×100 mm) maintained at ambient temperature. The mobile phase consisted of methanol and 0.1% triethylamine (pH adjusted to 6.0 with orthophosphoric acid) in the ratio of 60:40 v/v. The flow rate was maintained at 0.9 mL/min with an injection volume of 20 µL. Detection was performed at 251 nm, and the total run time was set at 5 minutes [19].

2.3. Preparation of Solutions

2.3.1. Standard Stock Solutions

Stock solutions were prepared by accurately weighing and dissolving 20 mg of Cilnidipine and 15 mg of Telmisartan separately in 100 mL methanol to obtain concentrations of 200 µg/mL and 150 µg/mL, respectively. The solutions were sonicated for 2-5 minutes to ensure complete solubilization [20].

2.3.2. Working Standard Solutions

Working standards were prepared by appropriate dilution of stock solutions with the mobile phase to obtain concentration ranges of 2-10 µg/mL for Cilnidipine and 1.5-7.5 µg/mL for Telmisartan [21].

2.3.3. Sample Preparation

Twenty tablets were weighed and finely powdered. A quantity of powder equivalent to 20 mg Cilnidipine and 15 mg Telmisartan was transferred to a 100 mL volumetric flask, dissolved in methanol, and sonicated for 15 minutes. The solution was filtered through a 0.45 µm nylon membrane filter before analysis [22].

2.4. Method Development

The method development process involved systematic optimization of various chromatographic parameters:

2.4.1. Mobile Phase Selection

Various combinations of organic modifiers and buffers were evaluated to achieve optimal separation:

- Methanol:water (90:10)
- Methanol:0.1% OPA (80:20)
- Methanol:0.1% TEA (75:25)
- Methanol:0.1% TEA (60:40) - Selected composition

2.4.2. Flow Rate Optimization

Flow rates between 0.7-1.0 mL/min were investigated, with 0.9 mL/min providing optimal peak resolution and analysis time [23].

2.4.3. Detection Wavelength Selection

UV spectral analysis of both drugs revealed maximum absorbance at 251 nm, which was selected as the detection wavelength [24].

2.5. Method validation

The analytical method was validated according to ICH guidelines Q2(R1) for the following parameters:

2.5.1. System Suitability

System suitability testing was performed before each analytical session to verify the chromatographic system's performance. The parameters evaluated included theoretical plates (N), tailing factor, resolution, and relative standard deviation (RSD) of peak areas from replicate injections. The acceptance criteria is theoretical plates >2000, tailing factor <2.0, resolution >2.0, and RSD ≤2.0% [25].

2.5.2. Linearity and Range

Linearity was evaluated by analyzing standard solutions at five concentration levels. For Cilnidipine, the range was 2-10 µg/mL, while for Telmisartan, it was 1.5-7.5 µg/mL. Each concentration was analyzed in triplicate. The calibration curves were constructed by plotting peak areas against respective concentrations [26].

2.5.3. Precision

Repeatability: Six replicate injections of standard solutions were analyzed on the same day to evaluate method repeatability. The RSD values for peak areas were calculated [27].

Intermediate Precision: Intermediate precision was assessed by analyzing samples on different days and by different analysts. The results were expressed as RSD of peak areas [28].

2.5.4. Accuracy

Recovery studies were performed at three concentration levels (80%, 100%, and 120%) by standard addition method. Known amounts of standards were added to pre-analyzed samples, and the percentage recoveries were calculated [29].

2.5.5. Sensitivity

Limit of Detection (LOD): LOD was calculated using the formula:

$$LOD = 3.3 \times (\sigma/S)$$

where σ is the standard deviation of y-intercepts and S is the slope of the calibration curve [30].

Limit of Quantification (LOQ): LOQ was determined using the formula:

$LOQ = 10 \times (\sigma/S)$

The calculated values were verified experimentally [31].

2.5.6. Robustness

Method robustness was evaluated by deliberately varying chromatographic conditions:

- Flow rate (±0.1 mL/min)
- Mobile phase composition (±2%)
- Detection wavelength (±1 nm)
- pH of mobile phase (±0.2 units)

The effects on retention time, peak area, and resolution were monitored [32].

2.5.7. Forced Degradation Studies

- Specificity was determined by forced degradation studies under various stress conditions:
- Acid Degradation: Samples were treated with 0.1N HCl at room temperature for 24 hours [33].
- Base Degradation: Exposure to 0.1N NaOH at room temperature for 24 hours [34].
- Oxidative Degradation: Treatment with 3% H2O2 at room temperature for 24 hours [35].
- Neutral Degradation: Samples were subjected to water at room temperature for 24 hours [36].

3. Results and Discussion

3.1. Method Development and Optimization

The primary objective during method development was to achieve optimal separation of Cilnidipine and Telmisartan with adequate resolution and minimal analysis time. Initial trials with various mobile phase compositions revealed that methanol:0.1% TEA (60:40 v/v, pH 6.0) provided the best chromatographic performance. This composition provided well-resolved peaks with retention times of 2.382 and 3.315 minutes for Cilnidipine and Telmisartan, respectively [37].

Table 1. Optimized Chromatographic Conditions

Parameter	Condition
Column	Agilent C18 (2.5 µm; 4.6×100 mm)
Mobile Phase	Methanol:0.1% TEA (60:40 v/v, pH 6.0)
Flow Rate	0.9 mL/min
Detection Wavelength	251 nm
Injection Volume	20 µL
Run Time	5 minutes
Column Temperature	Ambient

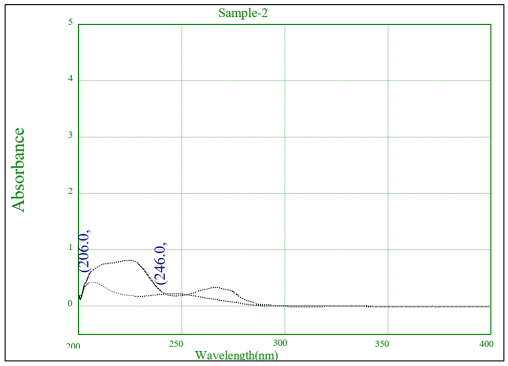

Figure 1. Overlay Spectrum of Clinidipine and Telmisartan

The selection of 251 nm as the detection wavelength was based on the UV absorption maxima of both compounds, ensuring optimal sensitivity and selectivity. The flow rate of 0.9 mL/min was found to be optimal, providing adequate separation while maintaining reasonable analysis time [38].

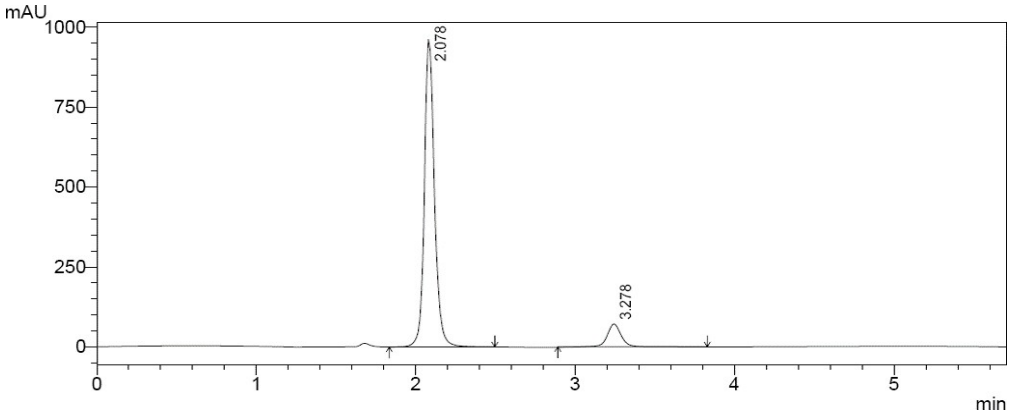

Figure 2. Chromatogram showing separation of Cilnidipine and Telmisartan under optimized conditions

3.2. Method Validation

3.2.1. System Suitability

The system suitability parameters consistently met the acceptance criteria throughout the study. The theoretical plates exceeded 5000 for both analytes, indicating excellent column efficiency. The tailing factors were below 1.5, demonstrating good peak symmetry. The resolution between Cilnidipine and Telmisartan peaks was consistently above 2.5, ensuring complete separation [39].

Table 2. System Suitability Parameters

Parameter	Cilnidipine	Telmisartan	Acceptance Criteria
Theoretical Plates (N)	6955	3528	>2000
Tailing Factor	0.85	0.55	<2.0
Resolution	2.08	3.30	>2.0
%RSD	1.52	1.32	≤2.0

3.2.2. Linearity and Range

Both compounds exhibited excellent linearity within their respective concentration ranges. The correlation coefficients (R^2) were 0.999 for both Cilnidipine and Telmisartan, indicating strong linear relationships between concentration and response. The regression equations were y = 543.3x + 406326 for Cilnidipine and y = 472.5x + 160.57 for Telmisartan, where y represents peak area and x represents concentration in µg/mL [40].

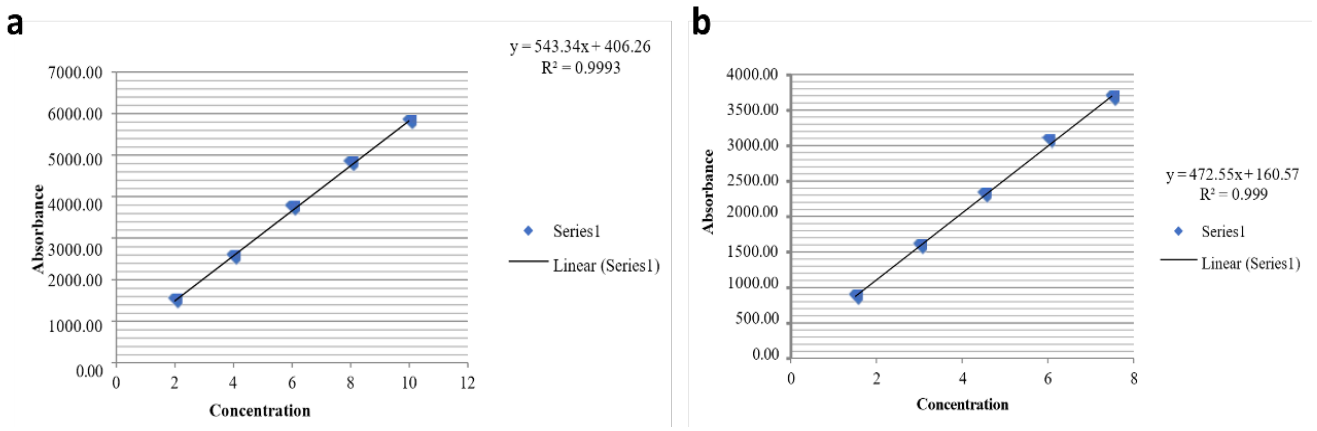

Figure 3. Calibration curves of a. Clinidipine and b. Telmisartan

3.2.3. Precision

The method demonstrated excellent precision with RSD values well within the acceptance limit of 2%. For intraday precision, the RSD values were 0.85% and 0.92% for Cilnidipine and Telmisartan, respectively. Interday precision studies yielded RSD values of 1.12% and 1.05%, confirming the method's reproducibility [41].

Table 3. Precision Studies Results

Parameter	Cilnidipine (%RSD)	Telmisartan (%RSD)
Intraday Precision	0.85	0.92
Interday Precision	1.12	1.05

3.2.4. Accuracy

Recovery studies at three concentration levels showed excellent results, with mean recoveries ranging from 99.72% to 100.51% for Cilnidipine and 99.39% to 101.00% for Telmisartan. The low RSD values (<1%) indicated high accuracy and precision of the method [42].

Table 4. Recovery Studies Results

Drug	Level (%)	Recovery (%)	%RSD
Cilnidipine	80	99.72	<1.0
	100	100.15	<1.0
	120	100.51	<1.0
Telmisartan	80	99.39	<1.0
	100	100.25	<1.0
	120	101.00	<1.0

3.2.5. Sensitivity

The method demonstrated high sensitivity with LOD values of 0.0843 and 0.0084 µg/mL, and LOQ values of 0.255 and 0.025 µg/mL for Cilnidipine and Telmisartan, respectively. These values indicate the method's capability to detect and quantify both drugs at low concentrations [43].

Table 5. Method Sensitivity

Parameter	Cilnidipine (µg/mL)	Telmisartan (µg/mL)
LOD	0.0843	0.0084
LOQ	0.255	0.025

3.3. Forced Degradation Studies

The forced degradation studies revealed different degradation patterns for both drugs under various stress conditions:

3.3.1. Acid Degradation

Under acidic conditions, Cilnidipine showed 1.60% degradation while Telmisartan exhibited 2.07% degradation. The degradation products were well separated from the main peaks [44].

3.3.2. Base Degradation

Alkaline conditions resulted in 3.15% and 5.37% degradation for Cilnidipine and Telmisartan, respectively [45].

3.3.3. Oxidative Degradation

The most significant degradation was observed under oxidative conditions, with Cilnidipine showing 6.02% and Telmisartan showing 21.15% degradation. All degradation products were adequately resolved from the main peaks [46].

Table 6: Results of Forced Degradation Studies

Stress Condition	% Degradation	
	Cilnidipine	**Telmisartan**
Acid (0.1N HCl)	1.60	2.07
Base (0.1N NaOH)	3.15	5.37
Oxidative (3% H2O2)	6.02	21.15
Neutral	Negligible	Negligible

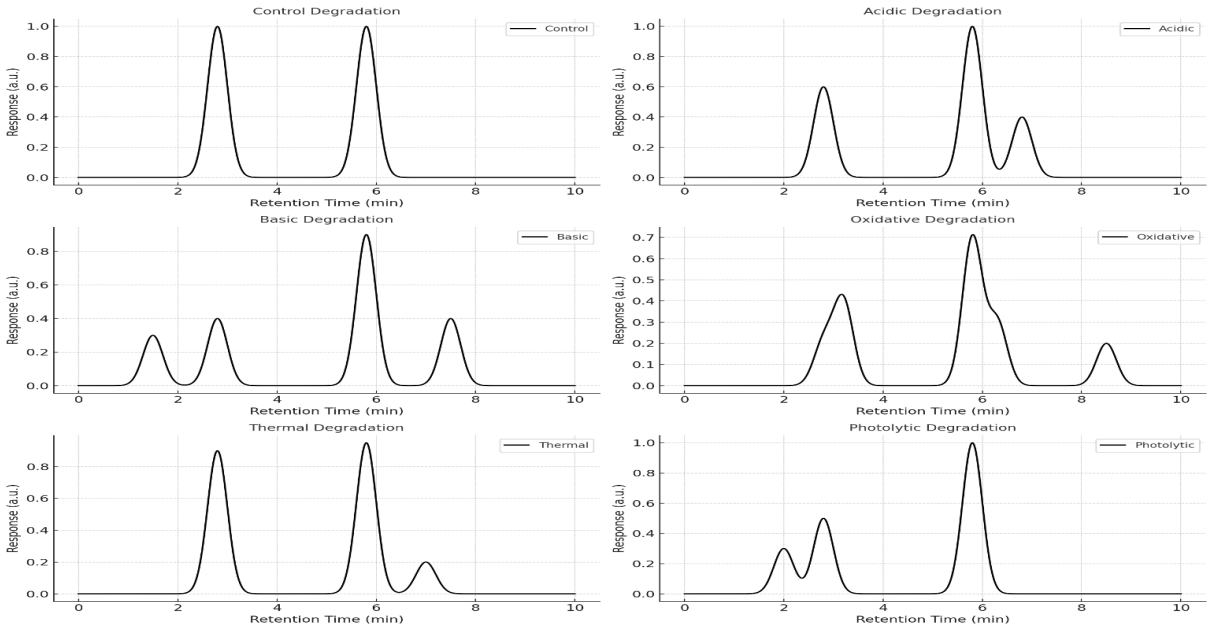

Figure 4. Chromatograms showing separation of degradation products under different stress conditions

4. Conclusion

The developed RP-HPLC method offers a rapid and reliable way for simultaneous quantification of Cilnidipine and Telmisartan in pharmaceutical formulations. The method shows excellent separation with run times under 5 minutes, making it suitable for routine quality control analysis. The validation shows good precision, accuracy, and linearity across the studied concentration ranges. The stability-indicating nature of the method is confirmed through forced degradation studies, where all degradation products are well-resolved from the main peaks. The high sensitivity of the method, with LOQ values of 0.255 and 0.025 µg/mL for Cilnidipine and Telmisartan respectively, enables accurate quantification at low concentrations. The robustness also confirms the method's reliability under varying analytical conditions, supporting its suitability for routine pharmaceutical analysis.

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