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Development and Validation of A Robust RP-HPLC Method For Simultaneous Estimation of Telmisartan and Cilnidipine In Bulk and Tablet Dosage Form

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ABSTRACT

A simple, accurate, precise, and cost-effective reversed-phase high-performance liquid chromatography (RP-HPLC) method has been developed and validated for the simultaneous estimation of Telmisartan and Cilnidipine in bulk and marketed tablet dosage form. Chromatographic separation was achieved using an Agilent C18 column (250mm × 4.6mm, 5 µm) with a mobile phase consisting of Acetonitrile and phosphate buffer (pH 3.0) in a 90:10 v/v ratio, at a flow rate of 1.0 mL/min and detection wavelength of 254 nm. Method validation followed ICH Q2 (R1) guidelines for system suitability, linearity, accuracy, precision, robustness, LOD, and LOQ. The method showed linearity over the range of 40–240 µg/mL for Telmisartan and 10–60 µg/mL for Cilnidipine, with correlation coefficients (R^2) of 0.9998 for both drugs. The method was found to be accurate, precise (%RSD < 2%), robust, and suitable for routine quality control analysis in pharmaceutical formulations.

Keywords: Telmisartan, Cilnidipine, RP-HPLC, Method Validation, ICH Q2(R1), Fixed-Dose Combination

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INTRODUCTION

Hypertension is a major global health concern and a key risk factor for cardiovascular diseases, necessitating lifelong pharmacological intervention in many patients. The use of fixed-dose combinations (FDCs) has gained prominence in clinical practice due to improved therapeutic efficacy, patient compliance, and reduced pill burden. Among these, the combination of Telmisartan, an angiotensin II receptor blocker (ARB), and Cilnidipine, a dual L-/N-type calcium channel blocker, has shown promising results in managing essential hypertension [1, 2]. Telmisartan selectively inhibits the binding of angiotensin II to the AT1 receptor, thereby preventing vasoconstriction and promoting vasodilation, while Cilnidipine inhibits calcium influx through L-type calcium channels in vascular smooth muscle and also blocks N-type channels on sympathetic nerve terminals, reducing norepinephrine release [3]. This combination offers complementary mechanisms of action, resulting in enhanced blood pressure control and a reduced risk of adverse cardiovascular outcomes [4].

Given the pharmacological significance of this combination, there is a growing need for reliable and validated analytical methods to ensure the quality, efficacy, and safety of Telmisartan and Cilnidipine in pharmaceutical preparations. Reversed-phase high-performance liquid chromatography (RP-HPLC) remains the most widely used analytical technique in pharmaceutical industries due to its high precision, sensitivity, and reproducibility [5]. However, literature review reveals a limited number of methods available for simultaneous estimation of Telmisartan and Cilnidipine, and many of them are either costly, time-consuming, lack sensitivity, or are not adequately validated as per regulatory standards [6, 7]. Moreover, some reported methods focus on forced degradation or stability-indicating studies rather than straightforward quantitative estimation suitable for routine quality control [8].

In this context, the present study aims to develop a simple, rapid, and cost-effective RP-HPLC method for the simultaneous estimation of Telmisartan and Cilnidipine in bulk and fixed-dose combination tablets. The method is rigorously validated according to ICH Q2 (R1) guidelines for various parameters including linearity, precision, accuracy, specificity, robustness, and sensitivity [9,10]. Furthermore, the developed method was applied to commercially available tablet formulations to evaluate its real-world applicability. The results provide a reliable and reproducible tool suitable for routine quality control and regulatory compliance in pharmaceutical industries.

MATERIALS AND METHOD

Chemicals and Reagents

Telmisartan and Cilnidipine APIs were procured from Emcure Pharmaceuticals Ltd. HPLC-grade Acetonitrile, Triethylamine, Ortho-phosphoric acid, and Sodium dihydrogen phosphate monohydrate were used. Commercial tablets (Cilacar-T, J.B. Chemicals Ltd.) were analyzed.

Instrumentation and Chromatographic Conditions

The RP-HPLC analysis was performed using a chromatographic system equipped with a UV detector and an Agilent C18 column (250 mm x 4.6 mm i.d., 5 µm). The mobile phase comprised acetonitrile and phosphate buffer (pH 3.0) in the ratio of 90:10 (v/v). The flow rate was maintained at 1.0 mL/min with a run time of 12 minutes. Detection was carried out at 254 nm with an injection volume of 10 µL at ambient temperature.

Preparation of Standard and Sample Solutions

A stock solution of Telmisartan (400 µg/mL) and Cilnidipine (100 µg/mL) was prepared by accurately weighing and dissolving 40 mg and 10 mg of each drug, respectively, in the mobile phase and diluting to 100 mL. Working standard solutions (40 µg/mL Telmisartan and 10 µg/mL Cilnidipine) were prepared by appropriate dilution with mobile phase. All solutions were filtered through 0.45 µm membrane filters and sonicated for 30 minutes before injection.

Sample solutions from tablets were prepared by accurately weighing powdered tablet material equivalent to 40 mg Telmisartan and 10 mg Cilnidipine. The powder was transferred to a 100 mL volumetric flask, dissolved in mobile phase, filtered, sonicated, and diluted to volume to obtain a stock solution. Further dilutions were made to prepare test solutions.

METHOD VALIDATION

The developed method was validated following ICH Q2 (R1) guidelines for linearity, precision, accuracy, specificity, robustness, LOD, and LOQ.

System Suitability

System suitability was evaluated using six replicate injections of standard solutions (40 µg/mL Telmisartan and 10 µg/mL Cilnidipine). Parameters like retention time (RT), peak area, number of theoretical plates (N), tailing factor (T), and %RSD were assessed.

Linearity

Linearity was determined in the concentration range of 40–240 µg/mL for Telmisartan and 10–60 µg/mL for Cilnidipine. Calibration curves were plotted between mean peak areas and corresponding concentrations.

Precision

Repeatability (intra-day) and intermediate precision (inter-day) were evaluated using three quality control (QC) standards across the linearity range: 60, 140, and 220 µg/mL for Telmisartan and 15, 35, and 55 µg/mL for Cilnidipine.

Accuracy

Accuracy was assessed by recovery studies at 80%, 100%, and 120% of test concentrations by spiking known quantities of standard into pre-analyzed samples. % Recovery was calculated.

Robustness

Robustness was tested by making deliberate changes to method parameters, including flow rate (±0.1 mL/min), detection wavelength (±1 nm), and organic phase composition (±2%).

LOD and LOQ

LOD and LOQ were calculated using standard deviation of response and slope of calibration curve: LOD = 3.3 × (σ/S); LOQ = 10 × (σ/S)

RESULTS AND DISCUSSION

System Suitability

The system suitability parameters were found to be within the acceptable limits: number of theoretical plates (>2000), tailing factor (<2), and %RSD for retention time (<0.5%) and peak area (<2%). Retention times for Telmisartan and Cilnidipine were approximately 4.74 and 7.57 minutes, respectively.

Table 1: System suitability study of Telmisartan and Cilnidipine

Name	RT (min)	Area	%Area	NOP	TF
Telmisartan 40 ppm	4.745	90153	100%	11091	1.03
Cilnidipine 10 ppm	7.593	35293	100%	14556	0.96

Linearity

The method exhibited excellent linearity over the tested concentration ranges. The correlation coefficient (R^2) was found to be 0.9998 for both drugs. The regression equations were:

Telmisartan: $y = 2336.9x - 2408.5$

Cilnidipine: $y = 4036.2x - 4621.5$ These results indicate a strong linear relationship between concentration and peak area.

Table 2: Linearity of Telmisartan and Cilnidipine

Sr. No.	Conc. of SBL std. solution (µg/mL)	Mean peak Area*	Conc. of VAL std. solution (µg/mL)	Mean peak Area*
1	40	90759	10	36042
2	80	184024	20	77375
3	120	276925	30	115112
4	160	373413	40	155475

5	200	468034	50	197368
6	240	555386	60	238511

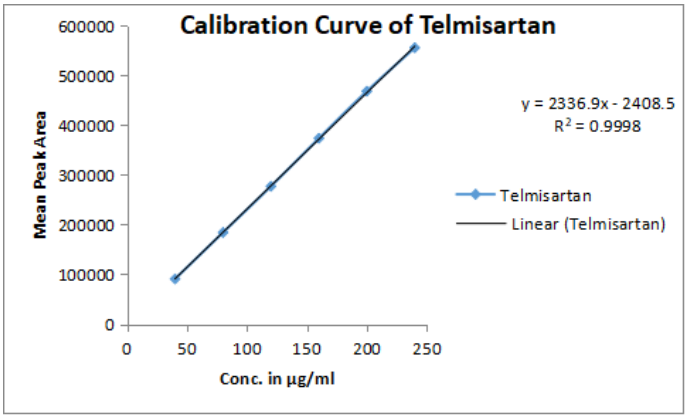

Figure 2: Calibration curve for Telmisartan

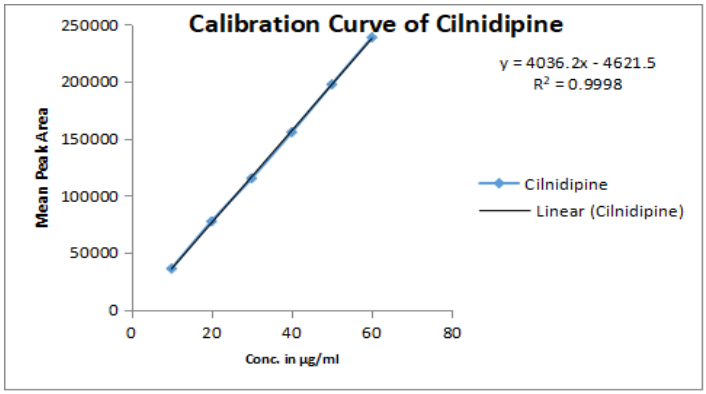

Figure 3: Calibration cure for Cilnidipine

Precision

Intra-day and inter-day precision studies showed %RSD values well within the acceptance criteria (≤2%). For Telmisartan, %RSD ranged from 0.86 to 1.46; for Cilnidipine, 0.35 to 1.94. These results confirm that the method is precise and reproducible.

Table 3: Repeatability and intermediate precision for Telmisartan

Conc.(µg/mL)	Intra-day precision (Repeatability)			Inter-day precision (Intermediate precision)		
	Mean area ± SD	%RSD	Inference	Mean area ± SD	% RSD	Inference
60	124563.67 ±1308.90	1.05	Complied	126535.00 ± 1846.77	1.46	Complied
140	282762.00 ±3808.78	1.35	Complied	286921.00 ± 1696.41	0.59	Complied
220	453024.33 ±3898.30	0.86	Complied	469698.00 ±11429.40	2.43	Not Complied

Table 4: Repeatability and intermediate precision for Cilnidipine

Conc.(µg/mL)	Intra-day precision (Repeatability)			Inter-day precision (Intermediate precision)		
	Mean area ± SD	% RSD	Inference	Mean area ± SD	% RSD	Inference
15	50347.00 ± 580.49	1.15	Complied	51372.00 ± 942.77	1.84	Complied
35	115131.33±1558.27	1.35	Complied	116504.33± 409.92	0.35	Complied
55	183867.67±2074.01	1.13	Complied	190357.00 ± 3696.19	1.94	Complied

Accuracy

Accuracy was demonstrated through recovery studies. %Recovery for Telmisartan ranged from 98.27% to 99.81%, and for Cilnidipine, from 108.32% to 111.47%. These values were within pharmacopoeial specifications, confirming the method's accuracy.

Table 5: % Accuracy calculated from precision data of Telmisartan

Sr. No	Conc. (µg/mL)	Mean Peak Area*	Mean Measured Conc. (µg/mL)	% Accuracy	Inference (90-110% w/w)
1	60	126535	55.18	91.96	Complied
2	140	286921	123.81	88.44	Not Complied
3	220	469698	202.02	91.83	Complied

Table 6: % Accuracy calculated from precision data of Cilnidipine

Sr. No	Conc. (µg/mL)	Mean Peak Area*	Mean Measured Conc. (µg/mL)	% Accuracy	Inference (85-115% w/w)
1	15	51373.00	13.87	92.49	Complied
2	35	116504.33	30.01	85.74	Complied
3	55	190357.00	48.31	87.83	Complied

Robustness

The method remained unaffected by small deliberate variations in chromatographic conditions. All results were within acceptable limits, demonstrating that the method is robust.

Table 7: Robustness with variation in the detector wavelength for mixture of Telmisartan and Cilnidipine at 40 and 10ppm respectively

'λ' in nm	Mean peak area		Mean measured conc. (µg/mL)		% Assay (w/w)		Inference (90-110% w/w)	
	TML	CIL	TML	CIL	TML	CIL	TML	CIL
245	90759	36042	39.87	10.07	99.67	100.75	Complied	Complied
246	95427	37772	41.87	10.50	104.66	105.03	Complied	Complied
244	99632	38075	43.66	10.58	109.16	105.78	Complied	Complied

Table 8: Robustness for variation in the organic concentration of mobile phase for mixture of Telmisartan and Cilnidipine at 40 and 10ppm respectively

Org. Conc. (%)	Mean peak area		Mean measured conc. (µg/mL)		% Assay (w/w)		Inference (90-110% w/w)	
	TML	CIL	TML	CIL	TML	CIL	TML	CIL
90	90759	36042	39.87	10.07	99.67	100.75	Complied	Complied
92	86516	35127	38.05	9.85	95.13	98.48	Complied	Complied
88	100143	38448	43.88	10.67	109.71	106.71	Complied	Complied

TML: Telmisartan; CIL: Cilnidipine

LOD and LOQ

The LOD and LOQ for Telmisartan were found to be 3.46 µg/mL and 10.48 µg/mL, respectively, while for Cilnidipine, they were 1.03 µg/mL and 3.11 µg/mL, respectively. These low values indicate the high sensitivity of the method.

Table 11: LOD and LOQ of Telmisartan and Cilnidipine

Standard Drug Solution	LOD (µg/mL)	LOQ (µg/mL)
Telmisartan	3.46	10.48
Cilnidipine	1.03	3.11

Application to Marketed Formulation

The method was successfully applied for the estimation of Telmisartan and Cilnidipine in marketed tablet dosage forms. The results confirmed the method's applicability for routine quality control with no interference from tablet excipients

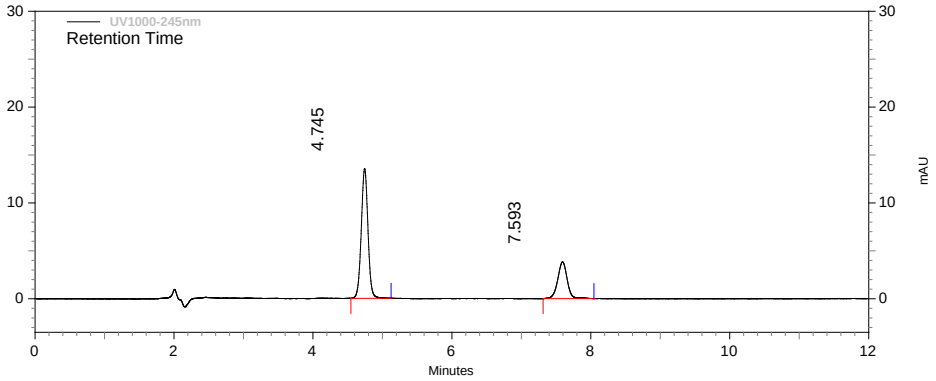

Figure 1: Chromatogram for simultaneous estimation of Telmisartan and Cilnidipine in SST

Table 9: Percent Recovery of Telmisartan at three levels

% Recovery Level	Conc. of standard spiked (µg/mL)	Conc. of sample (µg/mL)	Total mean peak area (test conc.)	Mean peak Area of sample conc.	Amount recovered (µg/mL)	% Recovery (w/w)	Inference (90-110% w/w)
80	40	32	167527	76768	33.88	99.07	Complied
100	40	40	185942	95183	41.76	98.27	Complied
120	40	48	206805	116046	50.69	99.81	Complied

Table 10: Percent Recovery for Cilnidipine at three levels

% Recovery Level	Conc. of standard spiked (µg/mL)	Conc. of sample (µg/mL)	Total mean peak area (test conc.)	Mean peak Area of sample conc.	Amount recovered (µg/mL)	% Recovery (w/w)	Inference (85-115% w/w)
80	10	8	69250	33208	9.37	111.47	Complied
100	10	10	76380	40338	11.14	108.32	Complied
120	10	12	85852	49810	13.49	111.43	Complied

CONCLUSION

In the present study, a robust, reliable, and economical RP-HPLC method was successfully developed and validated for the simultaneous estimation of Telmisartan and Cilnidipine in bulk drugs and marketed fixed-dose combination tablets. The method employed a simple mobile phase consisting of acetonitrile and phosphate buffer (pH 3.0), with optimized chromatographic

conditions ensuring clear resolution and short retention times for both analytes. Validation of the method was performed according to ICH Q2(R1) guidelines and covered critical parameters such as system suitability, linearity, accuracy, precision, robustness, sensitivity (LOD and LOQ), and applicability to commercial formulations.

The method demonstrated excellent linearity with correlation coefficients of 0.9998 for both drugs across their respective concentration ranges. It was also found to be precise, with %RSD values well within acceptable limits, and accurate, as demonstrated by high recovery values. The robustness study confirmed the method's resilience to small deliberate changes in analytical parameters, and the low LOD and LOQ values underscored its sensitivity. Importantly, the method was effectively applied to a marketed formulation, verifying its practical suitability for routine quality control and regulatory purposes. Overall, the developed RP-HPLC method provides a significant contribution to pharmaceutical analysis by offering a validated, reproducible, and cost-effective tool for the simultaneous estimation of Telmisartan and Cilnidipine in quality control laboratories. This method can be confidently adopted in both industrial and academic settings for routine analysis and stability assessment of this important antihypertensive drug combination.

Declaration of Competing Interest

The authors declare no conflict of interest.

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