IJMPR 2023, 7(11), 27-35

International Journal of Modern Pharmaceutical Research

www.ijmpronline.com

ISSN: 2319-5878
IJMPR
Research Article

SJIF Impact Factor: 5.273

SIMULTANEOUS ESTIMATION OF CILNIDIPINE AND TELMISARTAN BY RP-HPLC IN PHARMACEUTICAL DOSAGE FORM

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Received on: 07/09/2023
Revised on: 27/09/2023
Accepted on: 17/10/2023

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ABSTRACT

An accurate, precise, simple, efficient and reproducible, isocratic Reversed Phase-High Performance Liquid Chromatography (RP-HPLC) method was developed and validated for the simultaneous estimation of Cilnidipine and Telmisartan in bulk and combined pharmaceutical tablet dosage forms. Cilnidipine and Telmisartan were separated by using a Symmetry ODS C18 (4.6mm×150mm) 5µm Particle Size; Waters Alliance e2695 HPLC system with 2998 PDA detector and the mobile phase contained a mixture of Methanol: 0.1%Orthophosphoric acid (64:36% v/v). The flow rate was set to 1 ml/min with the responses measured at 224 nm. The retention time of Cilnidipine and Telmisartan was found to be 2.808 min and 3.880 min respectively with resolution of 5.68. Linearity was established for Cilnidipine and Telmisartan in the range of 20-100 µg/ml for Cilnidipine and 60-140 µg/ml for Telmisartan with correlation coefficient 0.999. The percentage recovery was found to be 100.30% for Cilnidipine and 100.21% for Telmisartan respectively. Validation parameters such as specificity, linearity, precision, accuracy and robustness, limit of detection (LOD) and limit of quantitation (LOQ) were evaluated for the method according to the International Conference on Harmonization (ICH) Q2 R1 guidelines. The developed method was successfully applied for the quantification of bulk and active pharmaceutical ingredient present and in combined tablet dosage form.

KEYWORDS: Cilnidipine, Telmisartan, RP-HPLC, Validation, Accuracy, Robustness.

INTRODUCTION

Chromatography is a laboratory technique for the separation of a mixture. The mixture is dissolved in a fluid called the mobile phase, which carries it through a structure holding another material called the stationary phase. The various constituents of the mixture travel at different speeds, causing them to separate. The separation is based on differential partitioning between the mobile and stationary phases. Subtle differences in a compound's partition coefficient result in differential retention on the stationary phase and thus affect the separation.[1-10]

Chromatography may be preparative or analytical. The purpose of preparative chromatography is to separate the components of a mixture for later use, and is thus a form of purification. Analytical chromatography is done normally with smaller amounts of material and is for establishing the presence or measuring the relative proportions of analytes in a mixture. The two are not mutually exclusive.[11-18]

High-pressure liquid chromatography (HPLC)

Using this chromatography technique, it is possible to perform structural and functional analysis, and purification of many molecules within a short time, this technique yields perfect results in the separation, and identification of amino acids, carbohydrates, lipids, nucleic acids, proteins, steroids and other biologically active molecules. In HPLC, mobile phase passes through columns under 10–400 atmospheric pressure, and with a high (0.1–5 cm//sec) flow rate. In this technique, use of small particles, and application of high pressure on the rate of solvent flow increases separation power, of HPLC and the analysis is completed within a short time.[19-24]

DRUG PROFILE

Table 1: Drug profile of Cilnidipine.[25]

Drug	**Cilnidipine**
Synonym	Cilnidipine, Cinalong, Atelec, Siscard
Category	Calcium channel blockers
IUPAC	3-(E)-3-Phenyl-2-propenyl 5-2- methoxyethyl 2,6-dimethyl-4-(m- nitrophenyl)-1,4-dihydropyridine-3,5- Dicarboxylate
Molecular formula	$C_{27}H_{28}N_2O_7$
Molecular Weight	492.528
Melting Point	110^{o}c
pKa	11.39
Log p	4.7

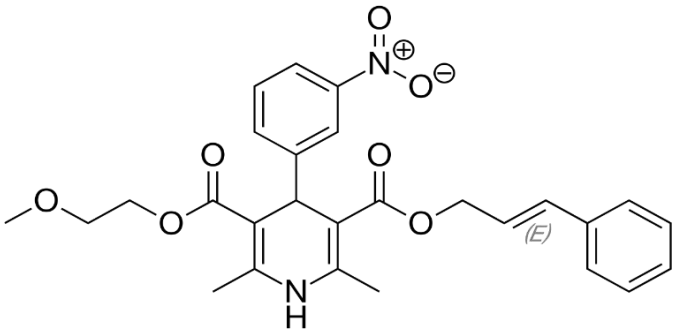

Fig. 1: Structure of Cilnidipine.

Table 2: Drug profile of Telmisartan.[26]

Drug	**Telmisartan**
Category	Angiotensin 2 receptor blocker
IUPAC	2-(4-{[4-methyl-6-(1-methyl-1H-1,3- benzodiazol-2-yl)-2-propyl-1H-1,3- benzodiazol-1-yl]methyl}phenyl)benzoicAcid
Molecular Formula	$C_{33}H_{30}N_4O_2$
Molecular Weight	514.6169 gm/mole.
Melting Point	$261\text{-}263^{0}$C
pKa	3.65
Log P	7.7

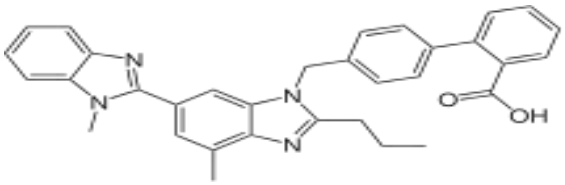

Fig. 2: Structure of Telmisartan.

METHODS AND MATERIALS

Table 3: Instruments used.

S. No.	**Instruments and Glass wares**	**Model**
1	HPLC	WATERS Alliance 2695 separation module, Software: Empower 2, 996 PDA detector.
2	pH meter	Lab India
3	Weighing machine	Sartorius
4	Volumetric flasks	Borosil
5	Pipettes and Burettes	Borosil
6	Beakers	Borosil
7	Digital ultra sonicator	Labman

Table 4: Chemicals used.

S. No.	Chemical	Brand names
1	Cilnidipine (Pure)	Sura labs
2	Telmisartan (Pure)	Sura labs
3	Water and Methanol for HPLC	LICHROSOLV (MERCK)
4	Acetonitrile for HPLC	Merck

HPLC METHOD DEVELOPMENT TRAILS

Preparation of standard solution

Accurately weighed and transferred 10 mg of Cilnidipine and Telmisartan working standard into a 10 ml of clean dry volumetric flasks, added about 7 ml of Methanol and sonicated to dissolve and removal of air completely and made the volume up to the mark with the same Methanol.

Further pipetted 0.6 ml of Cilnidipine and 1 ml of Telmisartan from the above stock solutions into a 10 ml volumetric flask and diluted up to the mark with Methanol.

Procedure

Injected the samples by changing the chromatographic conditions and recorded the chromatograms, noted the conditions of proper peak elution for performing validation parameters as per ICH guidelines.

Mobile Phase Optimization

Initially the mobile phase tried was Methanol: Water and ACN: Water with varying proportions. Finally, the mobile phase was optimized to Methanol: 0.1% Orthophosphoric acid in proportion 64:36 v/v respectively.

Optimization of Column

The method was performed with various C18columns like Symmetry, X terra and ODS column. Symmetry ODS C18 (4.6mm×150mm) 5µm Particle Size was found to be ideal as it gave good peak shape and resolution at 1ml/min flow.

METHOD VALIDATION

Preparation of mobile phase

Accurately measured 640 ml of Acetonitrile (64%) and 360 ml of HPLC Water (36%) were mixed and degassed in a digital ultrasonicater for 15 minutes and then filtered through 0.45 µ filter under vacuum filtration.

Diluent Preparation

The Mobile phase was used as the diluent.

VALIDATION PARAMETERS SYSTEM SUITABILITY

Accurately weighed and transferred 10 mg of Cilnidipine and Telmisartan working standard into a 10 ml of clean dry volumetric flasks, added about 7 ml of diluents and sonicated to dissolve it completely and made volume up to the mark with the same solvent. (Stock solution).

Further pipetted out 0.6 ml of Cilnidipine and 1 ml of Telmisartan from the above stock solutions into a 10ml volumetric flask and diluted up to the mark with diluent.

Procedure

The standard solution was injected for five times and measured the area for all five injections in HPLC. The %RSD for the area of five replicate injections was found to be within the specifiedlimits.

SPECIFICITY STUDY OF DRUG

Preparation of Standard Solution

Accurately weighed and transferred 10 mg of Cilnidipine and Telmisartan working standard into a 10 ml of clean dry volumetric flasks, added about 7 ml of Diluents and sonicated to dissolve it completely and made volume up to the mark with the same solvent. (Stock solution) Further pipetted out 0.6 ml of Cilnidipine and 1 ml of Telmisartan from the above stock solutions into a 10 ml volumetric flask and diluted up to the mark with diluent.

Preparation of Sample Solution

Taken average weight of Tablet and crushed in a mortar by using pestle and weighed 10 mg equivalent weight of Cilnidipine and Telmisartan sample into a 10 ml clean dry volumetric flask and added about 7 ml of Diluent and sonicated to dissolve it completely and made volume up to the mark with the same solvent. Filtered the sample solution by using injection filter which contains 0.45µ pore size.

Further pipetted out 0.6 ml of Cilnidipine and 1 ml of Telmisartan from the above stock solutions into a 10 ml volumetric flask and diluted up to the mark with diluent.

PREPARATION OF DRUG SOLUTIONS FOR LINEARITY

Accurately weighed and transferred 10 mg of Cilnidipine and Telmisartan working standard into a 10ml of clean dry volumetric flasks added about 7 ml of Diluents and sonicate to dissolve it completely and made volume up to the mark with the same solvent. (Stock solution).

Preparation of Level – I (20 ppm of Cilnidipine and 60 ppm of Telmisartan)

Pipetted out 0.2 ml of Cilnidipine and 0.6 ml of Telmisartan into a 10 ml volumetric flask and made the volume upto mark by using diluent and sonicated for air entrapment.

Preparation of Level – II (40 ppm of Cilnidipine and 80 ppm of Telmisartan)
Pipetted out 0.4 ml of Cilnidipine and 0.8 ml of Telmisartan into a 10 ml volumetric flask and made the volume up to mark by using diluent and sonicated for air entrapment.

Preparation of Level – III (60 ppm of Cilnidipine and 100 ppm of Telmisartan)
Pipetted out 0.6 ml of Cilnidipine and 1 ml of Telmisartan into a 10 ml volumetric flask and made the volume up to mark by using diluent and sonicated for air entrapment.

Preparation of Level – IV (80 ppm of Cilnidipine and 120 ppm of Telmisartan)
Pipetted out 0.8 ml of Cilnidipine and 1.2 ml of Telmisartan into a 10 ml volumetric flask and made the volume up to mark by using diluent and sonicated for air entrapment.

Preparation of Level – V (100 ppm of Cilnidipine and 140 ppm of Telmisartan)
Pipetted out 1 ml of Cilnidipine and 1.4 ml of Telmisartan in to a 10 ml volumetric flask and made the volume up to mark by using diluent and sonicated for air entrapment.

Procedure
Injected each level into the chromatographic system and measure the peak area.

Plotted a graph of peak area versus concentration (on X-axis concentration and on Y-axis Peakarea) and calculated the correlation coefficient.

PRECISION REPEATABILITY
Preparation of Cilnidipine and Telmisartan Product Solution for Precision
Accurately weighed and transferred 10 mg of Cilnidipine and Telmisartan working standard into a 10 ml of clean dry volumetric flasks, added about 7 ml of Diluents and sonicated to dissolve it completely and made volume up to the mark with the same solvent. (Stock solution).

Further pipetted out 0.6 ml of Cilnidipine and 1 ml of Telmisartan from the above stock solutions into a 10ml volumetric flask and diluted up to the mark with Diluent.

The standard solution was injected for five times and measured the area for all five injections in HPLC. The %RSD for the area of five replicate injections was found to be within the specifiedlimits.

INTERMEDIATE PRECISION
To evaluate the intermediate precision (also known as Ruggedness) of the method, Precisionwas performed on different days by maintaining same conditions.

Procedure
DAY 1
The standard solution was injected for six times and measured the area for all six injections in HPLC. The %RSD for the area of six replicate injections was found to be within the specifiedlimits.

DAY 2
The standard solution was injected for six times and measured the area for all six injections in HPLC. The %RSD for the area of six replicate injections was found to be within the specifiedlimits.

ACCURACY
For preparation of 50% Standard stock solution:
Accurately weighed and transferred 10 mg of Cilnidipine and Telmisartan working standard into a 10 ml of clean dry volumetric flasks added about 7 ml of diluents and sonicated to dissolve it completely and made volume up to the mark with the same solvent. (Stock solution).

Further pipetted out 0.3 ml of Cilnidipine and 0.5 ml of Telmisartan from the above stock solutions into a 10 ml volumetric flask and diluted up to the mark with diluent.

For preparation of 100% Standard stock solution
Accurately weighed and transferred 10 mg of Cilnidipine and Telmisartan working standard into a 10 ml of clean dry volumetric flasks add about 7ml of diluents and sonicated to dissolve it completely and made volume up to the mark with the same solvent. (Stock solution).

Further pipetted out 0.6 ml of Cilnidipine and 1 ml of Telmisartan from the above stock solutions into a 10 ml volumetric flask and diluted up to the mark with diluent.

For preparation of 150% Standard stock solution
Accurately weighed and transferred 10 mg of Cilnidipine and Telmisartan working standard into a 10 ml of clean dry volumetric flasks added about 7 ml of diluents and sonicated to dissolve it completely and made volume up to the mark with the same solvent. (Stock solution).

Further pipetted out 0.9 ml of Cilnidipine and 1.5 ml of Telmisartan from the above stock solutions into a 10 ml volumetric flask and diluted up to the mark with diluent.

Procedure
Injected the three replicate injections of individual concentrations (50%, 100%, 150%) were made under the optimized conditions. Recorded the chromatograms and measured the peak responses. Calculated the amount found and amount added for Cilnidipine and Telmisartan and calculated the individual recovery and mean recovery values.

Robustness
The analysis was performed in different conditions to find the variability of test results. The following conditions are checked for variation of results.

For preparation of Standard solution
Accurately weighed and transferred 10 mg of Cilnidipine and Telmisartan working standard into a 10 ml of clean dry volumetric flasks added about 7 ml of diluents and sonicated to dissolve it completely and made volume up to the mark with the same solvent. (Stock solution).

Further pipetted out 0.6 ml of Cilnidipine and 1 ml of Telmisartan from the above stock solutions into a 10 ml volumetric flask and diluted up to the mark with diluent.

Effect of Variation of flow conditions
The sample was analysed at 0.9 ml/min and 1.1 ml/min instead of 1ml/min, remaining conditions are same. 20µl of the above sample was injected and chromatograms were recorded.

Effect of Variation of mobile phase organic composition
The sample was analyzed by variation of mobile phase i.e., Methanol: 0.1% Orthophosphoric acid (64:36% v/v) was taken in the ratio and 69:31, 59:41 instead of 64:36 remainingconditions are same. 20µl of the above sample was injected and chromatograms were recorded.

RESULTS AND DISCUSSIONSYSTEM SUITABILITY

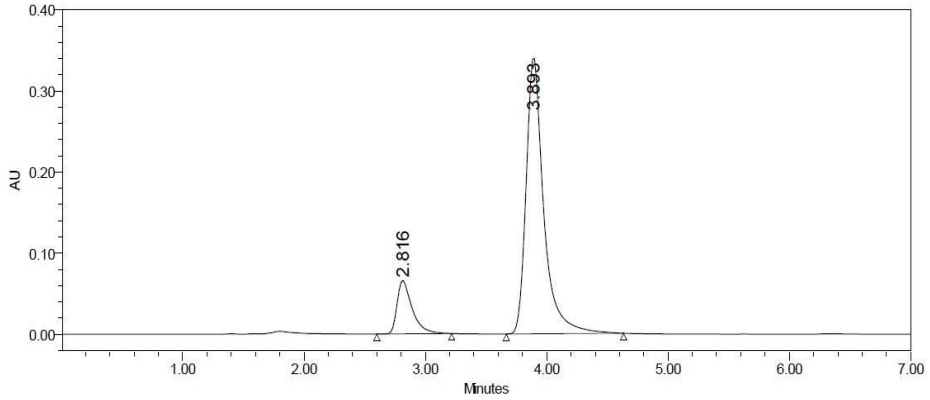

Figure 3: Chromatogram for system suitability.

Table 5: Results of system suitability parameters for Cilnidipine and Telmisartan.

S. No.	Name	Retentiontime(min)	Area (µV sec)	Height(µV)	USP resolution	USP tailing	USP platecount
1	Cilnidipine	2.816	65358	4536		1.08	5689.6
2	Telmisartan	3.893	8658746	658985	5.69	1.42	6892.4

Method Validation Parameters
Assay

Table 6: Assay Results.

S. No.	Name of Compound	Label Claim	Amount Taken (from Combination Tablet)	% Purity
1	Cilnidipine	10 mg	59.84	99.68%
2	Telmisartan	40 mg	499.63	99.46%

Precision
Precision of the method was carried out for both sample and standard solutions as describedunder experimental work. The corresponding chromatograms and results are shown below.

Table 7: Results of method precision for Cilnidipine.

S. No.	Name	R_t	Area	Height	USP plate count	USP Tailing
1	Cilnidipine	2.808	65898	4365	5682.2	1.08
2	Cilnidipine	2.808	65487	4375	5628.6	1.09
3	Cilnidipine	2.808	65324	4395	5649.7	1.08
4	Cilnidipine	2.808	65982	4328	5638.4	1.09
5	Cilnidipine	2.808	65248	4371	5698.3	1.08
6	Cilnidipine	2.808	65734	4391	5682.7	1.09
Mean			65612.17			
Std. Dev			304.8425			
% RSD			0.464613			

Table 8: Results of method precision for Telmisartan Intermediate Precision.

S. No.	Name	R_t	Area	Height	USP platecount	USP Tailing	USP Resolution
1	Telmisartan	3.880	8659824	658784	6859.4	1.42	5.68
2	Telmisartan	3.880	8658547	657489	6824.6	1.43	5.69
3	Telmisartan	3.880	8659824	652368	6829.3	1.42	5.68
4	Telmisartan	3.880	8659875	658745	6892.7	1.43	5.69
5	Telmisartan	3.880	8658745	658213	6875.2	1.42	5.68
6	Telmisartan	3.880	8659862	652354	6859.8	1.42	5.69
Mean			8659446				
Std. Dev			623.2924				
% RSD			0.007198				

There was no significant change in assay content and system suitability parameters at different conditions of ruggedness like day to day and system to system variation.

Table 9: Results of Intermediate precision for Cilnidipine.

S. No.	Name	R_t	Area	Height	USP plate count	USP Tailing
1	Cilnidipine	2.808	66895	4468	5784.2	1.09
2	Cilnidipine	2.808	66986	4523	5835.1	1.09
3	Cilnidipine	2.808	66258	4475	5864.4	1.10
4	Cilnidipine	2.808	66457	4514	5864.6	1.09
5	Cilnidipine	2.808	66539	4489	5784.9	1.10
6	Cilnidipine	2.808	66298	4565	5748.5	1.10
Mean			66572.17			
Std. Dev			304.536			
% RSD			0.457452			

Table 10: Results of Intermediate precision for Telmisartan.

S. No.	Name	Rt	Area	Height	USP platecount	USP Tailing	USP Resolution
1	Telmisartan	3.882	8758568	669583	6982.4	1.43	
2	Telmisartan	3.882	8756982	665984	6935.3	1.44	5.69
3	Telmisartan	3.882	8746925	665345	6984.7	1.44	
4	Telmisartan	3.882	8723654	665325	6952.8	1.43	5.70
5	Telmisartan	3.882	8754982	669852	6898.9	1.44	
6	Telmisartan	3.882	8754698	665874	6976.5	1.43	5.69
Mean			8749302				
Std. Dev			13188.56				
% RSD			0.150738				

Accuracy

Sample solutions at different concentrations (50%, 100%, and 150%) were prepared and the % recovery was calculated.

Accuracy Sample

Table 11: Accuracy (recovery) data for Cilnidipine.

%Concentration (at specification Level)	Area	Amount Added (mg)	Amount Found (mg)	% Recovery	Mean Recovery
50%	35921.67	30	30.134	100.446%	100.30%
100%	70894.33	60	60.205	100.341%	
150%	105654.7	90	90.093	100.103%	

Table 12: Accuracy (recovery) data for Telmisartan.

%Concentration (at specificationLevel)	Area	Amount Added (mg)	Amount Found (mg)	% Recovery	Mean Recovery
50%	4276302	50	50.208	100.416%	100.21%
100%	8484717	100	100.148	100.148%	
150%	10160609	150	150.091	100.060%	

LINEARITY

The linearity range was found to lie from 20-100 ppm of Cilnidipine, 60 µg/ml to 140 µg/ml of Telmisartan and chromatograms are shown below.

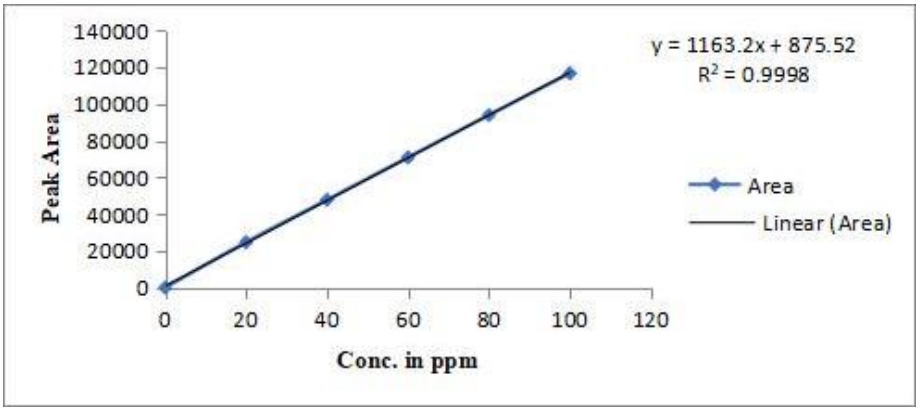

Figure 4: Calibration graph for Cilnidipine

Table 13: Linearity Results: (for Cilnidipine).

S. No.	Linearity Level	Concentration (ppm)	Area
1	I	20	24759
2	II	40	47859
3	III	60	70898
4	IV	80	93985
5	V	100	116698
Correlation Coefficient			0.999

Linearity Results: (for Telmisartan)

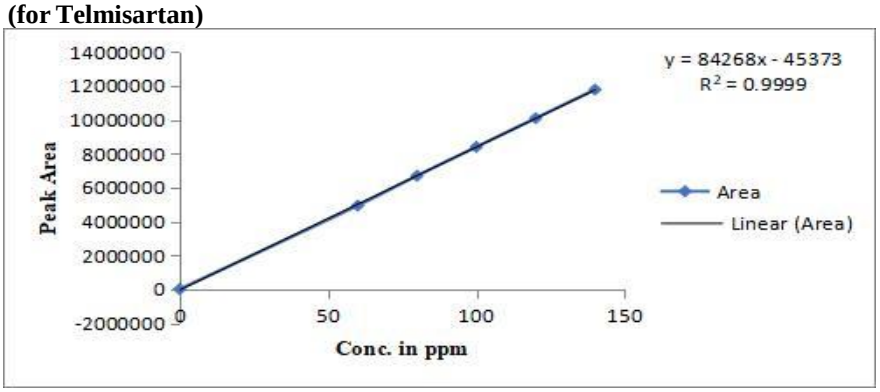

Figure 5: Calibration graph for Telmisartan

Table 14: Linearity Results (for Telmisartan).

S. No.	Linearity Level	Concentration(ppm)	Area
1	I	60	4928578
2	II	80	6687842
3	III	100	8389878
4	IV	120	10085847
5	V	140	11769854
Correlation Coefficient			0.999

Table 15: Analytical performance parameters of Cilnidipine and Telmisartan.

Parameters	Cilnidipine	Telmisartan
Slope (m)	1163	84268
Intercept (c)	875.5	45373
Correlation coefficient (R^2)	0.999	0.999

LIMIT OF DETECTION

The detection limit of an individual analytical procedure is the lowest amount of analyte ina sample which can be detected but not necessarily quantitated as an exact value.

LOD = 3.3 × σ / s

Where

σ = Standard deviation of the response S = Slope of the calibration curve **Cilnidipine Result** = 0.97 µg/ml **Telmisartan Result =** 2.06 µg/ml

LIMIT OF QUANTITATION LIMIT

The quantitation limit of an individual analytical procedure is the lowest amount of analyte in a sample which can be quantitatively determined.

LOQ = 10 × σ/S

Where

σ = Standard deviation of the response S = Slope of the calibration curve **Cilnidipine Result** =2.91 µg/ml **Telmisartan Result** = 6.18 µg/ml

ROBUSTNESS

The standard and samples of Cilnidipine and Telmisartan were injected by changing the conditions of chromatography. There was no significant change in the parameters like resolution, tailing factor, asymmetric factor, and plate count.

Variation in flow

Table 16: Robustness results for Cilnidipine.

S. No	Flow Rate(ml/min)	Robustness Results		
		USP Plate Count	USP Tailing	Retention Time (min)
1	0.9	5784.6	1.06	3.091
2	1.0	5685.4	1.08	2.813
3	1.1	5869.5	1.09	2.553

Table 17: Robustness results for Telmisartan.

S. No	Flow Rate(ml/min)	Robustness Results		
		USP Plate Count	USP Tailing	Retention Time (min)
1	0.9	6698.3	1.46	4.274
2	1.0	6895.7	1.42	3.886
3	1.1	6983.6	1.49	3.538

CONCLUSION

The study is focused to develop and validate HPLC methods for estimation of Cilnidipine and Telmisartan in bulk and tablet dosage form.

For routine analytical purpose it is desirable to establish methods capable of analysing huge number of samples in a short time period with good robustness, accuracy and precision without any prior separation steps. HPLC method generates large amount of quality data, which serve as highly powerful and convenient analytical tool. The method shows good reproducibility and good recovery. From the specificity studies, it was found that the developed methods were specific for Cilnidipine and Telmisartan.

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