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Method Development and Validation For The Simultaneous Estimation of Telmisartan and Azelnidipine In Bulk and Tablet Dosage Form By Using HPLC

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Abstract:
We established a simple, accurate, and exact approach to estimate the simultaneous pharmacological dose forms of Telmisartan and Azelnidipine. A 4.6*250mm, 5µ Inertsil ODS chromatogram was used for the analysis. A 1 ml/min flow rate was used to pump a mobile phase across the column, which contained a 70:30 ratio of phosphate buffer to acetonitrile. The temperature was kept at room temperature. For Telmisartan and Azelnidipine, the optimal wavelength was 225 nm. Telmisartan had a retention duration of 2.726 minutes and azelnidipine of 3.568 minutes. Telmisartan had a purity level of 100.25% and Azelnidipine of 98.99%. Telmisartan and azelnidipine were determined to have system suitability values of 3458.72, 2381.56, 1.13, and 1.11, respectively. Mean recovery rates of 99.59% and 100.01%, respectively, were discovered in the linearity research for Telmisartan and Azelnidipine, with correlation coefficients (r2) of 0.999 and 0.999.For repeatability, the RSD was 0.7 and for intermediate precision, it was 0.1; for both measurements, the RSD was 0.2 percent. There was accuracy, robustness, and repeatability in the precision research. The linear optical density (LOD) was 3 and the linear optical density (LOQ) was 2.98 and 10.0, respectively. This study's findings suggest that the suggested RP-HPLC technique might be effective for routinely estimating the pharmaceutical dose forms of Telmisartan and Azelnidipine, since it is straightforward, accurate, exact, sturdy, robust, quick, and repeatable.

Keywords: Telmisartan, Azelnidipine, RP-HPLC, Simultaneous estimation.

INTRODUCTION:

Telmisartan is an ARB used to treat hypertension, diabetic nephropathy, and congestive heart failure. Telmisartan is an angiotensin II receptor antagonist (ARB) used in the management of hypertension[1]. Generally, angiotensin II receptor blockers (ARBs) such as telmisartan bind to the angiotensin II type 1 (AT1) receptors with high affinity, causing inhibition of the action of angiotensin II on vascular smooth muscle, ultimately leading to a reduction in arterial blood pressure. Recent studies suggest that telmisartan may also have PPAR-gamma agonistic properties that could potentially confer beneficial metabolic effects[2].IUPAC name of Telmisartan is 2-[4-[[4-methyl-6-(1-methylbenzimidazol-2-yl)-2-propylbenzimidazol-1-yl] methyl] phenyl] benzoic acid. Molecular Formula is $C_{33}H_{30}N_4O_2$. Molecular Weight is 514.6. Telmisartan is soluble in organic solvents such as DMSO and dimethyl formamide (DMF), which should be purged with an inert gas. The solubility of telmisartan in DMSO is approximately 1 mg/ml and approximately 1.6 mg/ml in DMF. Telmisartan is sparingly soluble in aqueous buffers.

Azelnidipine is a dihydropyridine calcium channel blocker. It has a gradual onset of action and produces a long-lasting decrease in blood pressure, with only a small increase in heart rate, unlike some other calcium channel blockers[3]. It is currently being studied for post-ischemic stroke management. Azelnidipine inhibits trans-membrane Ca2+ influx through the voltage-dependent channels of smooth muscles in vascular walls. Ca2+ channels are classified into various categories, including L-type, T-type, N-type, P/Q-type, and R-type Ca2+ channels. The L-type Ca2+ channels[4]. Normally, calcium induces smooth muscle contraction, contributing to hypertension. When calcium channels are blocked, the vascular smooth muscle does not contract, resulting in relaxation of vascular smooth muscle walls and decreased blood pressure. IUPAC name of Azelnidipine is 3-O-(1-benzhydrylazetidin-3-yl) 5-O-propan-2-yl 2-amino-6-methyl-4-(3-nitrophenyl)-1,4-dihydropyridine-3,5-dicarboxylate. Molecular formula is $C_{33}H_{34}N_4O_6$. Molecular Weight is 582.6. Azelnidipine is soluble in organic solvents such as ethanol, DMSO, and dimethyl formamide (DMF), which should be purged with an inert gas. The solubility of azelnidipine in ethanol is approximately 15 mg/ml and approximately 30 mg/ml in DMSO and DMF. Azelnidipine is sparingly soluble in aqueous buffers.

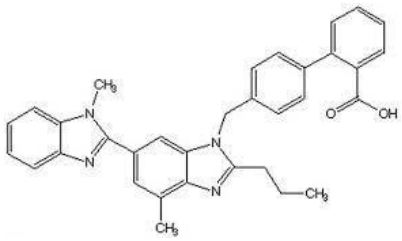


Figure 1: Structure of Telmisartan

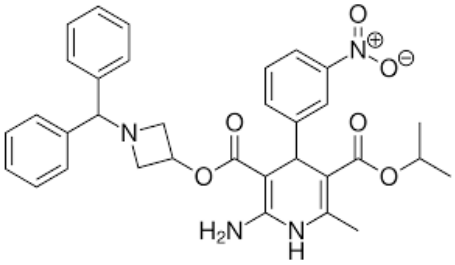


Figure 2: Structure of Azelnidipine

Literature survey shows that a number of methods have been reported for estimation of Telmisartan And Azelnidipine individually or in combination with other drugs Those are UV [5],HPTLC [6], UPLC [7],HPLC[10-27] However, there is only few HPLC methods are reported for the simultaneous estimation of these drugs in combined dosage forms. I got better results than already published one. The aim of the present study was A New Rp-Hplc Method for Simultaneous Estimation of Telmisartan and Azelnidipine in Its Bulk and Tablet Dosage Form and Its Force Degradation Studies as Per Ich.

MATERIALS AND METHODS:

Chemicals and Reagents: Telmisartan and Azelnidipine were Purchased from Hetero drugs. NaH_2PO_4 was analytical grade supplied by Finerchem limited, Orthophosphoric acid (Merck), and Water and Methanol for HPLC (Lichrosolv (Merck).

Equipment and Chromatographic Conditions: The chromatography was performed on a Waters 2695 HPLC system, equipped with an auto sampler, UV detector and Empower 2 software. Analysis was carried out at 225 nm with column Inertsil ODS (4.6*250mm, 5µ), dimensions at 25^0C temperature. The optimized mobile phase consists of Phosphate buffer and Acetonitril in the ratio of 70:30. Flow rate was maintained at 1 ml/min.

Preparation of solutions:

Preparation of Phosphate buffer:

3.4g of Potassium di hydrogen ortho phosphateis taken in 1000 ml of HPLC water pH was adjusted with 0.1M NAOH up to 3.0. final solution was filtered through 0.45 µm Membrane filter and sonicate it for 10 mins.

Preparation of mobile phase:
Accurately measured 700 ml (70%) of above buffer and 300 ml of Acetonitrile HPLC (30%) were mixed and degassed in an ultrasonic water bath for 10 minutes and then filtered through 0.45 µ filter under vacuum filtration.

Diluent Preparation:
The Mobile phase was used as the diluent.

Standard Solution Preparation:
Accurately weigh and transfer 40 mg of Telmisartan and 8 mg of Azelnidipine working standard into a 10 ml clean dry volumetric flask add about 7 mL of Diluent and sonicate to dissolve it completely and make volume up to the mark with the same solvent. (Stock solution)
Further pipette 0.75 ml of the above stock solutions into a 10ml volumetric flask and dilute up to the mark with diluent**.**

Sample Solution Preparation:
Accurately weigh and transfer the equivalent weight of 40 mg of Telmisartan and 8 mg of Azelnidipine Tablet powder into a 10 ml clean dry volumetric flask add about 7 mL of Diluent and sonicate to dissolve it completely and make volume up to the mark with the same solvent. (Stock solution)
Further pipette 0.75 ml of the above stock solutions into a 10ml volumetric flask and dilute up to the mark with diluent.
Procedure:
Inject 20 µL of the standard, sample into the chromatographic system and measure the areas for Telmisartan and Azelnidipine peaks and calculate the %Assay by using the formulae**.**

RESULTS AND DISCUSSION
METHOD:
The developed chromatographic method was validated for system suitability, linearity accuracy, precision, ruggedness and robustness as per ICH guidelines.
System suitability parameters: To evaluate system suitability parameters such as retention time, tailing factor and USP theoretical plate count, the mobile phase was allowed to flow through the column at a flow rate of 1.0 ml/min to equilibrate the column at ambient temperature. Chromatographic separation was achieved by injecting a volume of 10 µL of standard into Inertsil ODS (4.6*250mm, 5µ), the mobile phase of composition 70% buffer 30% CAN was allowed to flow through the column at a flow rate of 1.0 ml per minute. Retention time, tailing factor and USP theoretical plate count of the developed method are shown in table 1.

Table 1: System suitability parameters

Parameter	Telmisartan	Azelnidipine
Theoretical plates	3458.72	2381.56
Retention time	2.726	3.568
Tailing factor	1.13	1.11

Assay of pharmaceutical formulation: The proposed validated method was successfully applied to determine Telmisartan and Azelnidipine in their tablet dosage form. The result obtained for was comparable with the corresponding labeled amounts and they were shown in Table-2.

Table 2: Assay results for Telmisartan and Azelnidipine

	Label Claim (mg)	% Assay
Telmisartan	40	100.25
Azelnidipine	8	98.99

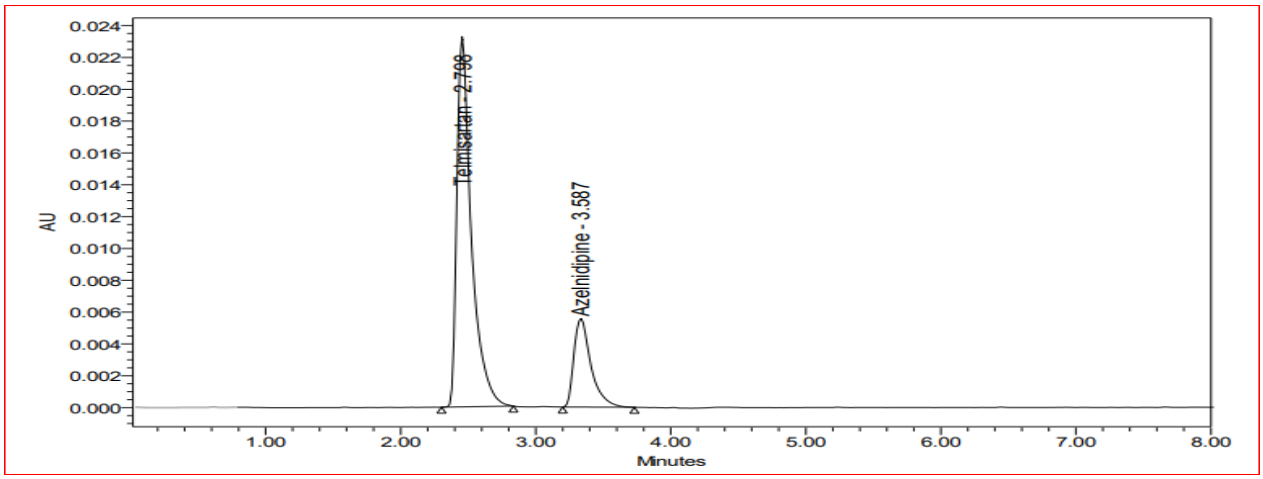


Figure 3: Standard chromatogram

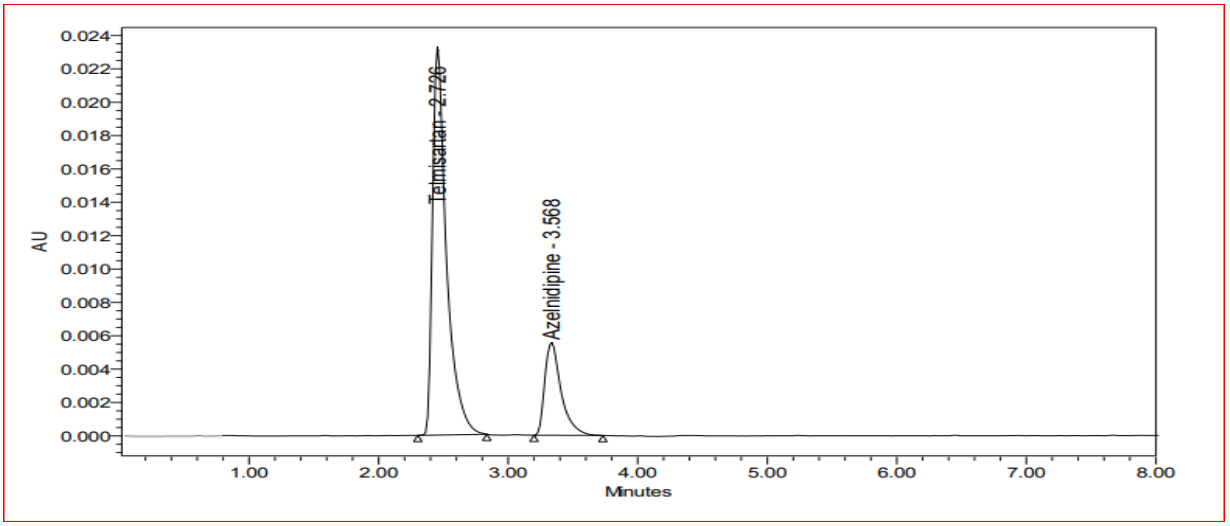


Figure 4: Sample chromatogram

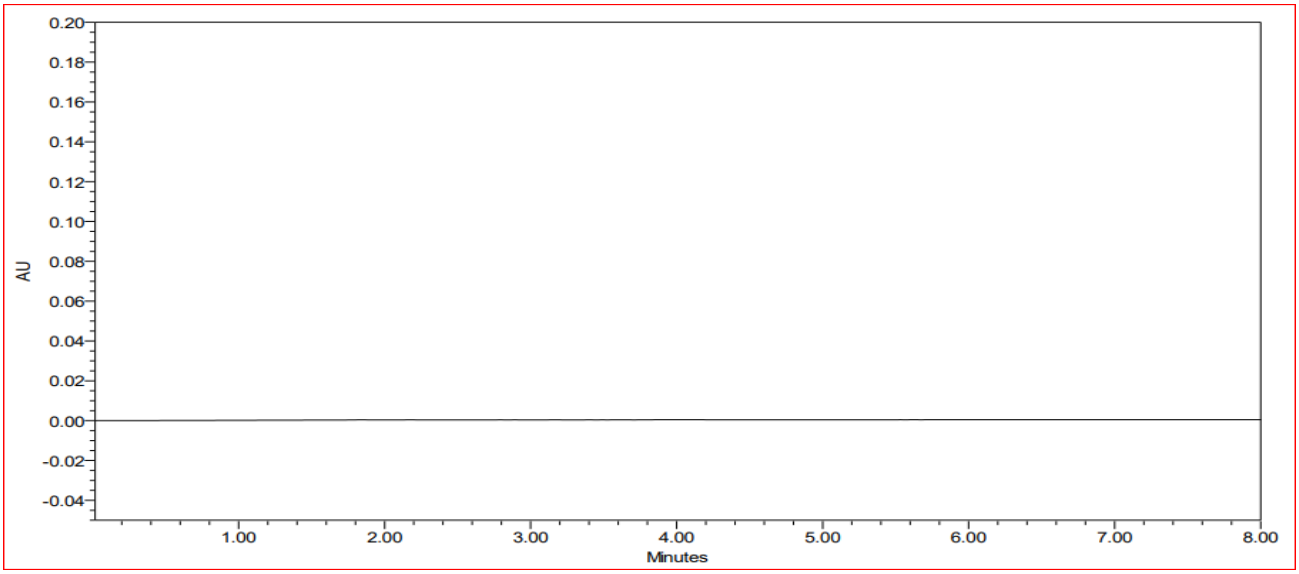


Figure 5: Blank chromatogram

Validation of Analytical method:

Linearity: The linearity study was performed for the concentration of 100 ppm to 500 ppm and 40.5 ppm to 202.5 ppm level. Each level was injected into chromatographic system. The area of each level was used for calculation of correlation coefficient. Inject each level into the chromatographic system and measure the peak area. Plot a graph of peak area versus concentration (on X-axis concentration and on Y-axis Peak area) and calculate the correlation coefficient. The resulte are shown in table 3,4.

Table 3: Linearity results of Telmisartan

S. No	Linearity Level	Concentration	Area
1	I	100	65787
2	II	200	131783
3	III	300	194311
4	IV	400	256245
5	V	500	317748
Correlation Coefficient			0.999

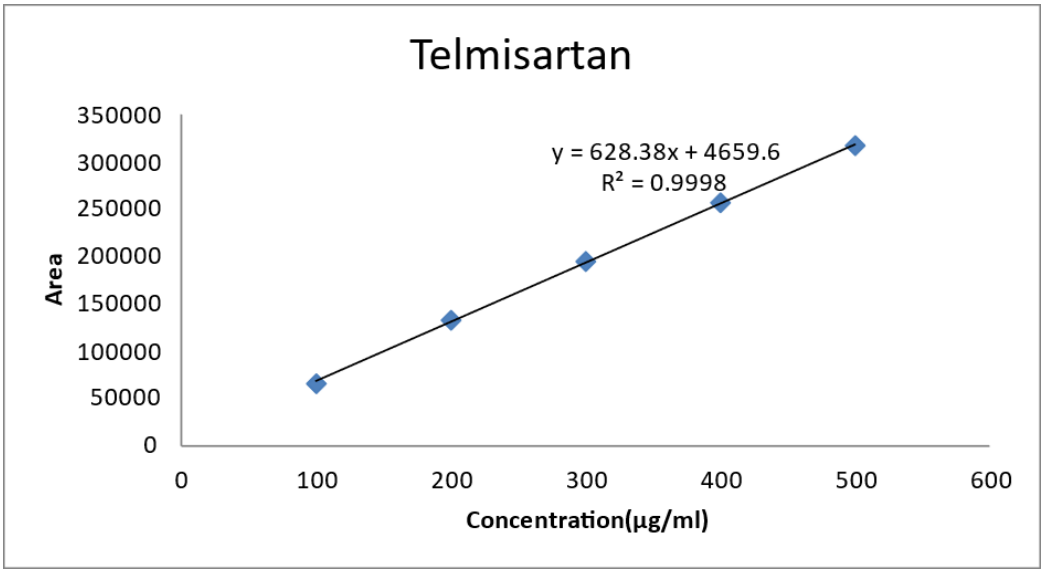
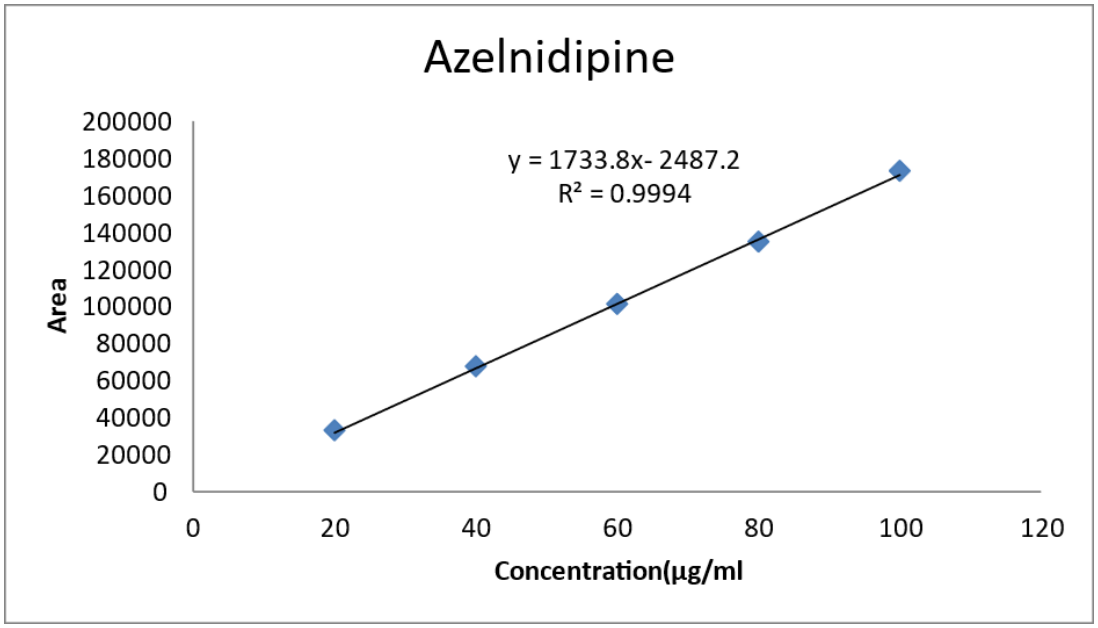


Figure 6: Linearity graph for Telmisartan

Table 4: Linearity results of Azelnidipine

S. No	Linearity Level	Concentration	Area
1	I	40.5	32441
2	II	81	67728
3	III	121.5	100630
4	IV	162	134448
5	V	202.5	172463
Correlation Coefficient			0.999



Accuracy studies: The accuracy was determined by help of recovery study. The recovery method carried out at three level 50%, 100%, 150% and 50%, 100%, 150% Inject the standard solutions into chromatographic system. Calculate the Amount found and Amount added for Telmisartan and Azelnidipine and calculate the individual recovery and mean recovery values. The results are shown in table 5,6.

Table 5: Showing accuracy results for Telmisartan

%Concentration (at specification Level)	Area	Amount Added (mg)	Amount Found (mg)	% Recovery	Mean Recovery
50%	95505	10	9.97	99.67	99.59
100%	191399	20	19.97	99.87	
150%	285309	30	29.77	99.25	

Table 6: Showing accuracy results for Azelnidipine

%Concentration (at specification Level)	Area	Amount Added (mg)	Amount Found (mg)	% Recovery	Mean Recovery
50%	53846	4.05	4.06	100.23	100.01
100%	107344	8.1	8.09	99.90	
150%	159676	12.04	12.04	99.89	

Precision Studies: precision was caliculated from Coefficient of variance for six replicate injections of the standard. 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. The resulte are shown in table 7.

Table 7: Precision results for Telmisartan and Azelnidipine

Injection	Area for Telmisartan	Area for Azelnidipine
Injection-1	191345	107339
Injection-2	191232	107232
Injection-3	191671	107131
Injection-4	191999	107399
Injection-5	192898	107018
Injection-6	194679	107089
Average	192304.0	107201.3
Standard Deviation	1308.1	148.4
%RSD	0.7	0.1

Ruggedness: To evaluate the intermediate precision of the method, Precision was performed on different day. 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. The resulte are shown in table 8.

Table 8: Ruggedness results of Telmisartan and Azelnidipine

Injection	Area for Telmisartan	Area for Azelnidipine
Injection-1	192345	104533
Injection-2	192432	104232
Injection-3	192971	104531
Injection-4	192899	104399
Injection-5	192898	104018
Injection-6	192333	104689
Average	192646.3	104400.3

Robustness: As part of the Robustness, deliberate change in the Flow rate, Mobile Phase composition, Temperature Variation was made to evaluate the impact on the method. The flow rate was varied at 0.8 ml/min to 1.2 ml/min. The resulte are shown in table 9,10,11,12.

Table 9: Flow variation results for Telmisartan

S. No	Flow Rate (ml/min)	System Suitability Results	
		USP Plate Count	USP Tailing
1	0.9	3828.18	1.21
2	1	3417.62	1.14
3	1.1	3328.18	1.11

Table 10: Flow variation results for Azelnidipine

S. No	Flow Rate (ml/min)	System Suitability Results		
		USP Plate Count	USP Tailing	USP Resolution
1	0.9	3213.92	1.23	4.96
2	1	2381.56	1.11	4.42
3	1.1	3415.92	1.21	4.96

Table 11: Change in Organic Composition in the Mobile Phase for Telmisartan

S. No	Change in Organic Composition in the Mobile Phase	System Suitability Results	
		USP Plate Count	USP Tailing
1	10% less	3726.18	1.21
2	*Actual	3417.62	1.14
3	10% more	3343.64	1.34

Table 12: Change in Organic Composition in the Mobile Phase for Azelnidipine

S. No	Change in Organic Composition in the Mobile Phase	System Suitability Results		
		USP Plate Count	USP Tailing	USP Resolution
1	10% less	3175.92	1.31	4.96
2	*Actual	2381.56	1.11	4.42
3	10% more	34445.92	1.23	4.96

LOD and LOQ: The sensitivity of RP-HPLC was determined from LOD and LOQ. Which were calculated from the calibration curve using the following equations as per ICH guidelines. The results are shown in table 13.

LOD = 3.3σ/S and

LOQ = 10 σ/S, where

σ= Standard deviation of y intercept of regression line,

S = Slope of the calibration curve

Table 13: LOD, LOQ of Telmisartan and Azelnidipine

Drug	LOD	LOQ
Telmisartan	3	9.98
Azelnidipine	2.98	10.0

DEGRADATION STUDIES:

The International Conference on Harmonization (ICH) guideline entitled stability testing of new drug substances and products requires that stress testing be carried out to elucidate the inherent stability characteristics of the active substance. The aim of this work was to perform the stress degradation studies on the Telmisartan and Azelnidipine using the proposed method. The results are shown in table 14,15.

Preparation of stock: Accurately weigh and transfer 40 mg of Telmisartan and 8 mg of Azelnidipine working standard into a 10 ml clean dry volumetric flask add about 7 mL of Diluent and sonicate to dissolve it completely and make volume up to the mark with the same solvent. (Stock solution)

Hydrolytic degradation under acidic condition: Pipette 0.75 ml of above solution into a 10ml volumetric flask and 3 ml of 0.1N HCl was added. Then, the volumetric flask was kept at 60ºC for 24 hours and then neutralized with 0.1 N NaOH and make up to 10ml with diluent. Filter the solution with 0.44 microns syringe filters and place in vials.

Hydrolytic degradation under alkaline condition: Pipette 0.75 ml of above solution into a 10ml volumetric and add 3ml of 0.1N NaOH was added in 10ml of volumetric flask. Then, the volumetric flask was kept at 60ºC for 24 hours and then neutralized with 0.1N HCl and make up to 10ml with diluent. Filter the solution with 0.44 microns syringe filters and place in vials.

Thermal induced degradation: Telmisartan and Azelnidipine sample was taken in Petri dish and kept in Hot air oven at 110^0 C for 3 hours. Then the sample was taken and diluted with diluents and injected into HPLC and analyzed.

Oxidative degradation

Pipette 0.75 ml above stock solution into a 10ml volumetric flask and 1ml of 30% w/v of hydrogen peroxide added in 10 ml of volumetric flask and the volume was made up to the mark with diluent. The volumetric flask was then kept at room temperature for 15 min. Filter the solution with 0.45 microns syringe filters and place in vials.

Table 14: Degradation results for Telmisartan

Sample Name	Telmisartan	
	Area	% Degraded
Standard	191642	
Acid	183252	4.38
Base	183532	4.23
Peroxide	183253	4.38
Thermal	187552	2.13
Photo	186452	2.71

Table 15: Degradation results for Azelnidipine

Sample Name	Azelnidipine	
	Area	% Degraded
Standard	107223	
Acid	98959	7.71
Base	98921	7.74
Peroxide	98978	7.69
Thermal	98851	7.81
Photo	98789	7.87

CONCLUSION:

The validated HPLC method developed for the quantitative quality control determination of Telmisartan and Azelnidipine in combination was evaluated for system suitability, specificity, sensitivity, linearity, range, accuracy (recovery), precision (repeatability and intermediate precision), and robustness. All the validation results were within the allowed specifications of ICH guidelines. The developed method has proven to be rapid, accurate, and stability-indicating for the simultaneous determination of combined Telmisartan and Azelnidipine in tablet dosage form in the presence of excipients and the degradation products. There was always a complete separation of both ingredients from their degradation products and from the placebo. As a result, the proposed HPLC method could be adopted for the quantitative quality control and routine analysis of the tablet dosage form.

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