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A NEW RP-UPLC METHOD DEVELOPED FOR THE SIMULTANEOUS DETERMINATION OF TELMISARTAN AND AZELNIDIPINE IN DOSAGE FORMS

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Keywords:

Telmisartan, Azelnidipine, RP-UPLC, ICH, Force Degradation

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ABSTRACT: A new, precise, and sensitive ultra-performance liquid chromatography method for simultaneous estimating Telmisartan and Azelnidipine in bulk and tablet dosage form was developed and validated. The chromatographic separation was achieved by using the HSS C18 (100 x 2.1 mm, 1.8µ) column. A mixture of buffer and ACN (70:30 v/v) was pumped through the column at a flow rate 0.3 mL/min. The temperature was maintained at 30 °C, eluents were monitored at 260 nm, and Telmisartan and Azelnidipine retention time was 1.636 min. and 1.153 min. The method obeys the Beer-Lambert's law in the range of 20-120 µg/mL (Telmisartan) and 2-12 µg/mL (Azelnidipine) with regression equations as y = 15673x + 11440 and y = 16761x + 597.17 respectively. Assay (%) was obtained as 99.94 % w/w and 98.96 % w/w for Telmisartan and Azelnidipine, respectively. The force degradation studies were performed under conditions like acidic, alkaline, oxidation, thermal, photolytic, and water. According to ICH guidelines, the methods were validated for system suitability, linearity, accuracy, precision, sensitivity, robustness, LOD, and LOQ. They can be conveniently used for the regular quality control analysis of the drugs in bulk and tablets.

INTRODUCTION: Telmisartan [1] ($C_{33}H_{30}N_4O_2$) is a benzimidazole derivative and a non-peptide angiotensin II receptor antagonist used as an antihypertensive. It selectively binds to the AT1 receptor (located in vascular smooth muscle and adrenal gland), which inhibits angiotensin II, resulting in vasodilation and subsequently reducing the blood pressure. The IUPAC name of Telmisartan is 2-[4-[[4-methyl-6-(1-methyl-benzimidazol-2-yl) - 2 - propyl-benzimidazol-1-yl] methyl] phenyl] benzoic acid.

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Azelnidipine [2] ($C_{33}H_{34}N_4O_6$) is an isopropyl ester and dihydropyridine calcium channel blocker used as an antihypertensive. It inhibits trans-membrane Ca^{2+} influx through the voltage-dependent channels of smooth muscles in vascular walls. The calcium channels are blocked, resulting in the relaxation of vascular smooth muscle walls, which reduces blood pressure.

The IUPAC name of Azelnidipine is 3-*O*-(1-benzhydryl-azetidin-3-yl) 5-*O*-propan-2-yl 2-amino -6 - methyl-4-(3-nitrophenyl)-1, 4-dihydropyridine-3, 5-dicarboxylate. A literature survey revealed that various analytical methods like UV, NMR, MASS, IR spectroscopic, HPLC, UPLC, HPTLC, TLC, LC/MS [3-27] had been reported to estimate Telmisartan and Azelnidipine alone or simultaneously with other combination. But there is

no single UPLC method available for this combination of drugs. Hence, the present work aims to develop a novel, precise, economic, and stable indicating RP-UPLC method for simultaneous estimating Telmisartan and Azelnidipine in the tablet dosage form.

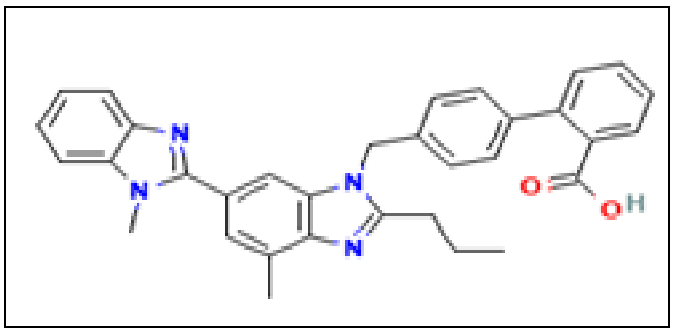

FIG. 1: CHEMICAL STRUCTURE OF TELMISARTAN

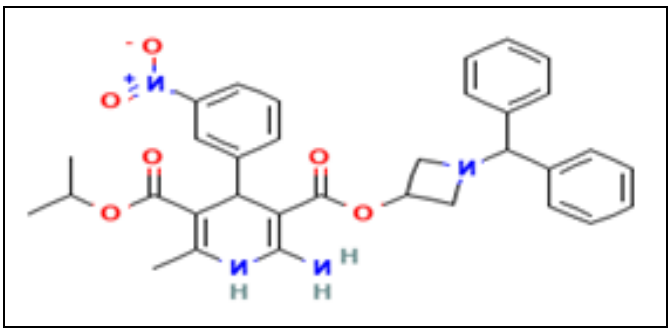

FIG. 2: CHEMICAL STRUCTURE OF AZELNIDIPINE

Instrument: The chromatographic separation was performed using ultra-performance liquid chromatography (UPLC), Waters ACQUITY TUV detector integrated with Empower 2 Software, equipped with Auto Sampler and HSS C_{18} Column (100 x 2.1 mm, 1.8µ).

TABLE 1: CHROMATOGRAPHIC CONDITIONS

Parameter	Optimized condition
Column	HSS C18100x 2.1mm, 1.8µ.
Detector	TUV
Mobile phase	0.01N Potassium dihydrogen ortho phosphate: ACN (70:30, % v/v))
Diluent	Water: Acetonitrile (50:50, % v/v)
Flow rate	0.3 mL/min
Elution	Isocratic mode
Injection volume	2 µL
Run time	7 min.
RT	3.2 ± 0.41 min
UV detection	260 nm
Column temperature	30 °C

Preparation of 0.01N Potassium Dihydrogen ortho phosphate Buffer: Accurately weighed 1.36gm of potassium dihydrogen orthophosphate was transferred to 1000 mL of the volumetric flask, about 900 mL of milli-Q water was added, sonicated to degas and finally made up the volume with water then added 1mL of Triethylamine. The pH was adjusted to 3.0 with a dilute orthophosphoric acid solution.

Preparation of Mobile Phase: Potassium dihydrogen orthophosphate buffer, 0.01N (70 %), and ACN (30 %) were mixed and used in the mobile phase.

Preparation of Diluent: Based upon the solubility of drugs, water and acetonitrile (50:50 % v/v) were selected as diluent.

Preparation of Standard Stock Solution and Working Solution: Accurately weighed and transferred 40.0 mg of Telmisartan and 4.0 mg of Azelnidipine into 50 mL clean dry volumetric flasks, respectively, 10 mL of diluent was added, sonicated for 10 minutes and made up the final volume with diluent (800 µg/mL Telmisartan, and 80 µg/mL of Azelnidipine). For working standard solution, 1mL of the solution was pipetted from the above stock solutions into 10 mL volumetric flasks and made up to volume with diluent (80µg/mL Telmisartan and 8 µg/mL of Azelnidipine).

Assay of Telmisartan and Azelnidipine: Accurately weighed equivalent weight of the admixture sample transferred into a 100 mL of the volumetric flask, then 50 mL of diluent was added and sonicated for 25 min; further, the volume was made up with diluent and filtered by milli-Q filters (800 µg/mL Telmisartan, and 80 µg/mL of Azelnidipine). The working solution was prepared by taking 0.5 mL of filtered sample stock solution

into 10 mL of volumetric flask and made up the final volume with diluent. (80 µg/mL Telmisartan and 8 µg/mL of Azelnidipine).

Method Validation [28-30]: The method validation study for the simultaneous estimation of Telmisartan and Azelnidipine in pharmaceutical dosage form was carried out according to ICH guidelines which include various parameters like system suitability, linearity, precision, accuracy, specificity, the limit of detection, the limit of quantification and robustness.

System Suitability Parameters: The system suitability was performed by injecting six times a standard solution of Telmisartan and Azelnidipine and the parameters like peak tailing, resolution and USP plate count were determined. The % RSD for the area of six standard injections should not be more than 2 %.

Accuracy: The method's accuracy was achieved by recovery studies performed by preparing spiked solutions at different levels (50%, 100%, and 150%). The standard stock solution was spiked to the sample stock solution, and the % recovery for each level was calculated.

Precision: Precision studies were performed in terms of repeatability and intermediate precision. Solutions containing 80 µg/mL of Telmisartan and 8 µg/mL of Azelnidipine in diluent were prepared and analyzed six times. The area of each peak was measured and the % RSD obtained was calculated to establish the precision of the developed method.

Repeatability: It is the measurement over a short interval of time under same operating condition. Six replicate samples were injected, area of each peak was observed, and the % RSD obtained was calculated to establish the precision of the developed method.

Intermediate Precision: The intermediate precision is the measurement that expresses within-laboratories variations like different days, different analysts, different equipment, *etc*.

Six replicate samples were prepared and injected in multiples on different days; the % RSD of the peak area obtained was used to establish the precision of the developed method.

Linearity: The linearity of the method was studied in terms of regression analysis. A series of dilutions were prepared from standard stock solutions, made up of diluents ranging from 20-120 µg/mL (Telmisartan) and 2-12 µg/mL (Azelnidipine). Chromatograms were observed, and the calibration curves were plotted for area vs concentration for both the drugs and the peak area.

Robustness: It is the measure of the capacity of the developed method to remain unaffected by small, deliberate variations made in the optimized method conditions like flow rate (± 0.1 mL/min.), mobile phase (± 5), and temperature (± 5 °C). The sample solution was injected under each altered condition in duplicate, and % RSD for the peak areas obtained was calculated.

LOD and LOQ: Accurately pipetted about 0.25 mL each from two standard stock solutions, transferred to two separate 10 mL volumetric flasks, and made up with diluent. From the above solutions, 0.1mL and 0.3 mL of Telmisartan and Azelnidipine solutions were transferred to 10 mL volumetric flasks and made up with the same diluent. The LOD and LOQ were assessed at the signal-to-noise ratio of 3:1 and 10:1, respectively, by injecting a dilute solution of the drug into the chromatograph.

Specificity: The optimized method was checked for the interferences in the presence of excipients. Blank, placebo, and standard drug solutions were injected and observed for interfering peaks at Telmisartan and Azelnidipine retention times.

Degradation Studies: The simultaneous RP-UPLC method for the determination of Telmisartan and Azelnidipine was tested for its stability-indicating nature. The degradation studies were conducted at 60 °C, and relative humidity was maintained 75%. Telmisartan and Azelnidipine solution was exposed to acidic, alkali, thermal, oxidative and photolytic stress and analyzed for the % degradation.

Acid Degradation Studies: About 1mLof 2N hydrochloric acid was added to 1mL stock solution of Telmisartan and Azelnidipine, refluxed for 30 min. at 60 °C; the resultant solution was cooled, neutralized, and diluted. A 10 µL solution was injected into the system, and the chromatograms were recorded to assess sample stability.

Alkali Degradation Studies: About 1 mL of 2N sodium hydroxide was added to 1 mL stock solution of Telmisartan and Azelnidipine and refluxed for 30 min. at 60 °C; the resultant solution was cooled, neutralized, and diluted. A10 µL was injected into the system and the chromatograms were recorded to assess sample stability.

Oxidation: 1 ml of 20 % hydrogen peroxide (H_2O_2) was added to 1 mL stock solution of Telmisartan and Azelnidipine. The solutions were kept for 30 min. at 60 °C. The resultant solution was diluted to obtain 80 µg/mL and 8 µg/mL solutions, 10 µL was injected into the system. The chromatograms were recorded to assess the stability of the sample.

Thermal: The standard drug solution was placed in an oven at 105 ^{0}C for 6 hr. to study dry heat degradation. For the UPLC study, the resultant solution was diluted to 80 µg/mL and 8 µg/mL solutions, and a 10 µL was injected into the system. The chromatograms were recorded to assess the stability of the sample**.**

Photo-Stability Studies: The photochemical stability of the drug was studied by exposing the Telmisartan and Azelnidipine solutions (800 µg/mL and 80 µg/mL) to ultraviolet light by keeping the beaker in UV Chamber for 7 days or at 200-Watt hours/min. in a photostability chamber. The resultant solution was diluted, and a 10 µL was injected into the system. The chromatograms were recorded to assess the stability of the sample.

Neutral Degradation Studies: Stress testing under neutral conditions was studied by refluxing the drug in water for 6 hr. at a temperature of 60 ºC. The resultant solution was diluted to 80µg/mL and 8µg/mL solutions, and 10 µL was injected into the system. The chromatograms were recorded to assess the stability of the sample**.**

RESULTS AND DISCUSSION:

Method Development: Different chromatographic conditions were performed by changing mobile phase ratio, buffers, diluents, *etc*., to develop an optimized condition for the simultaneous estimation of Telmisartan and Azelnidipine using RP-UPLC. After many trials, the optimized condition was obtained with 0.01N Potassium dihydrogen orthophosphate: Acetonitrile (70:30 % v/v) as mobile phase at 0.3 mL/min. flow rate on a HSS C18 column (100x 2.1mm, 1.8µ) maintained at 30 °C. Water and acetonitrile in the ratio 50:50 v/v were used as the diluent, the peaks for Telmisartan and Azelnidipine were eluted at 1.636 min. and 1.153 min. respectively. Tailing factor, theoretical plate count, and resolution were considered for the selection of mobile phase and flow rate in the developed method.

Method Validation: The developed method was successfully validated according to ICH guidelines, and force degradation studies were also performed. The system suitability parameters were within the range and satisfactory, as shown in **Table 2**. The linear concentrations of Telmisartan and Azelnidipine were found to be 20-120µg/mL and 2-12µg/mL, respectively (after triplicate injections). Average areas were measured, and the calibration curves were constructed from which the linearity equation obtained for Telmisartan and Azelnidipine was y = 15673x + 11440 (0.9996) and y = 16761x + 597.17 (0.9997), respectively as shown in **Table 3**.

Telmisartan and Azelnidipine samples were prepared by standard addition method at three levels (80, 100, and 120%) for validating accuracy. Triplicate injections were given for each level, and mean % recovery was obtained as 100.40-101.16 % and 99.53- 100.18 % for Telmisartan and Azelnidipine, respectively as shown in **Table 4**. Precision **Table 5** was validated by system, repeatability and intermediate precision. % RSD calculated for peak areas in system precision (six injections) was obtained as 0.8 and 0.2, respectively, for Telmisartan and Azelnidipine. For repeatability, replicates of six standard working solutions of the same concentration prepared by multiple sampling from a stock solution were injected. Average area, standard deviation, and % RSD were calculated for the drugs and found to be within limits (0.89 and 0.50). Similarly, six standard working solutions of the same concentration were prepared and analysed on different days to validate intermediate precision. The peak areas and % RSD values were obtained as 0.33 and 0.59 for both drugs. LOD and LOQ of the method were calculated and found to be 0.55 and 0.07 µg/mL (LOD), while it was 1.66 and 0.21 µg/mL (LOQ), respectively, for Telmisartan and

Azelnidipine **Table 6**. Robustness was conducted by deliberately varying the chromatographic conditions like flow rate (0.2 mL/min. and 0.4 mL/min.), mobile phase composition (65A:25B and 75A:35B), and temperature (25°C and 35°C) from which the % RSD calculated and was within the limit **Table 7**. **Table 8** of Telmisartan and Azelnidipine were expressed as a percentage of label claims in Telma Az (80 mg, 8 mg) tablets. It was found that there is no interaction from the excipients commonly present, and this method was said to be specific as no interfering peaks were found in the blank and placebo chromatograms at the retention times of the drugs (chromatogram is shown in **Fig. 3**. Degradation studies were conducted under various conditions like acidic, basic, peroxide, UV, thermal, and water hydrolysis. Small peaks at 1.264 min. (acidic), 1.267 min. (basic) and 1.329 min. (peroxide) were observed in the degraded samples. The degradation from both the analytes was found to be less than 5.0 %, and percentage drug degraded was reported in **Table 9.**

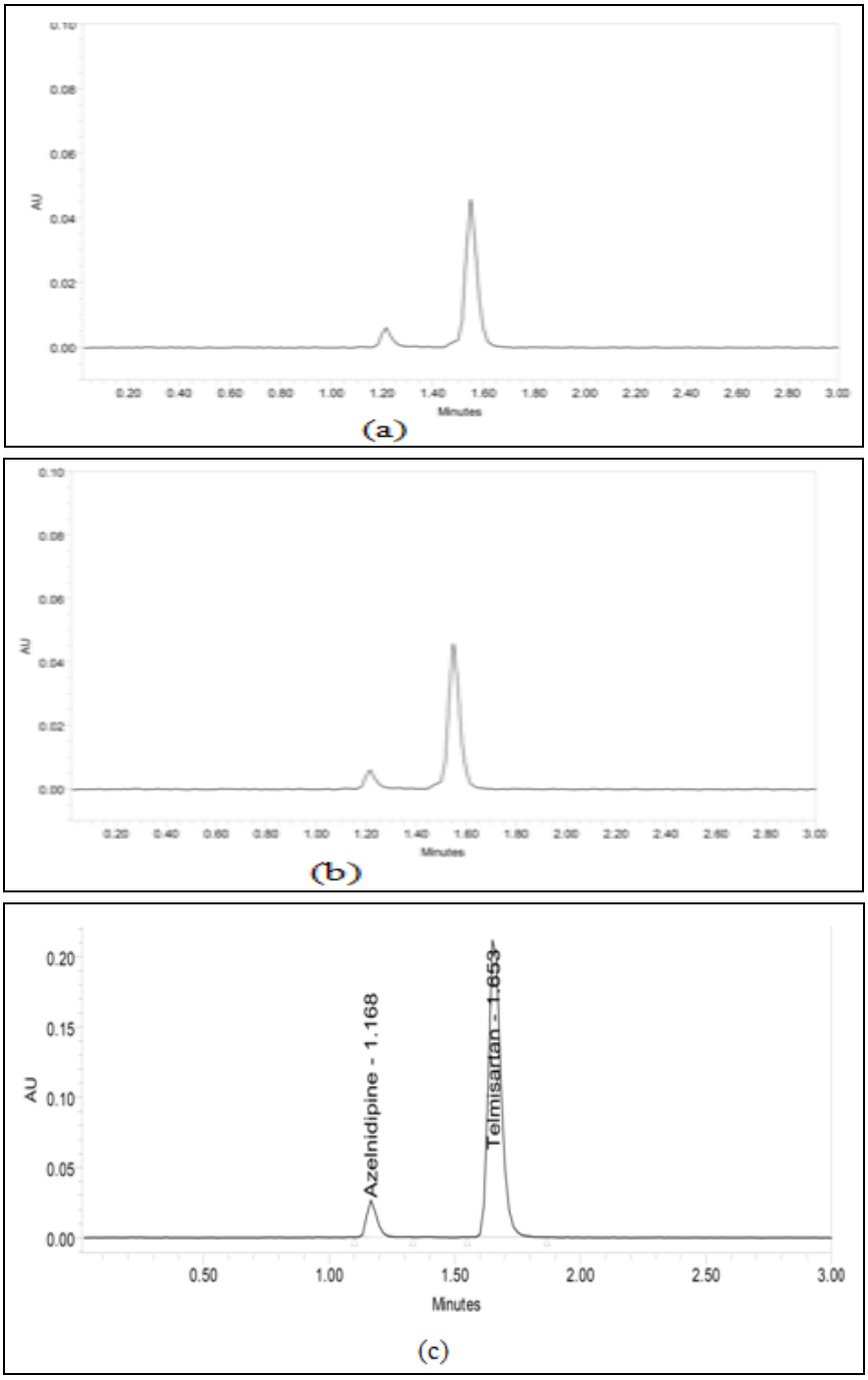

FIG. 3: CHROMATOGRAM OF TELMISARTAN AND AZELNIDIPINE (A. BLANK, B. PLACEBO AND C. STANDARD)

TABLE 2: SYSTEM SUITABILITY PARAMETERS FORTELMISARTAN AND AZELNIDIPINE

S. no.	Azelnidipine			Telmisartan			
Injection	RT (min.)	USP Plate Count	Tailing factor	RT (min.)	USP Plate Count	Tailing factor	RS
1	1.153	4404	1.26	1.636	5706	1.20	5.6
2	1.153	4445	1.28	1.639	5706	1.21	5.5
3	1.156	4420	1.28	1.640	5713	1.22	5.5
4	1.157	4458	1.30	1.646	5686	1.15	5.8
5	1.171	4459	1.22	1.655	5787	1.21	5.5

TABLE 3: LINEARITY TABLE FOR TELMISARTAN AND AZELNIDIPINE

Telmisartan		Azelnidipine	
Conc. (µg/mL)	*Peak area ± SD	Conc. (µg/mL)	*Peak area ± SD
20	315609± 3822.15	2	34167.67 ± 307.15
40	658182± 5157.96	4	67501 ± 212.03
60	962397 ± 1862.28	6	101550 ± 351.52
80	1271981± 3442.88	8	135026.67 ± 752.04
100	1586749 ± 5491.36	10	170264 ± 193.20
120	1882115 ± 13325.72	12	199632 ± 1142.71

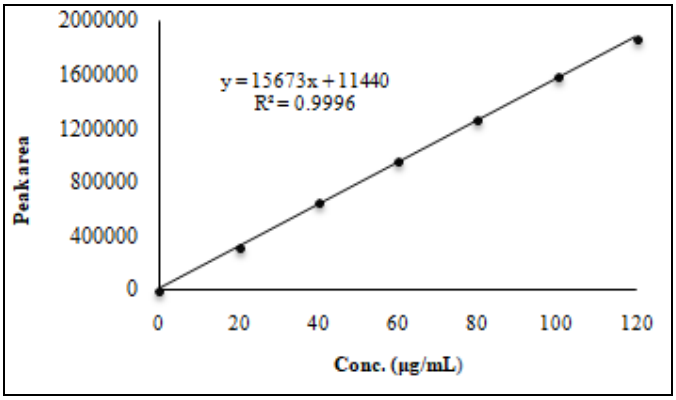

FIG. 4: CALIBRATION CURVE OF TELMISARTAN

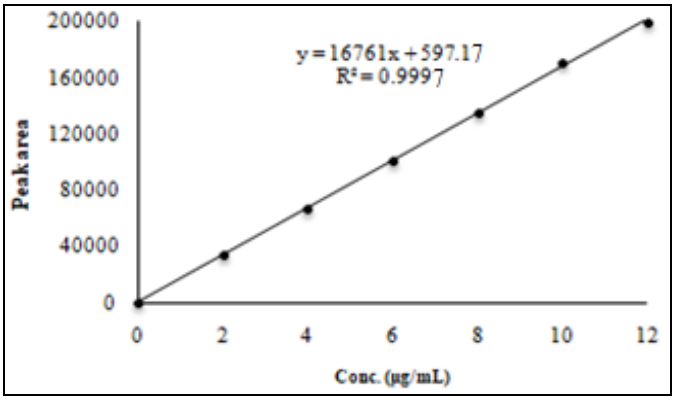

FIG. 5: CALIBRATION CURVE OF AZELNIDIPINE

TABLE 4: ACCURACY TABLE OF TELMISARTAN AND AZELNIDIPINE

Level	Sample conc. (µg/mL)		Std. drug added (µg/mL)		*%Recovery ± SD (%RSD)	
(%)	Telmisartan	Azelnidipine	Telmisartan	Azelnidipine	Telmisartan	Azelnidipine
50	80	8	40	4	100.40 ± 0.79 (0.79)	99.53 ± 0.43(0.43)
100	80	8	80	8	100.92 ± 0.60(0.60)	99.83 ± 1.04 (1.04)
150	80	8	120	12	101.16 ± 0.59(0.58)	100.18 ± 0.41 (0.41)

*Mean of three replicates

TABLE 5: PRECISION TABLE OF TELMISARTAN AND AZELNIDIPINE

Telmisartan				
Conc. (µg/mL)	Repeatability	*Assay (%w/w) ± SD, % RSD	Intermediate	*Assay (%w/w) ± SD, % RSD
80	101.14	100.15 ± 0.89	99.49	
80	100.64	(0.89)	99.99	99.89 ± 0.33
80	99.47		100.27	(0.33)
80	99.28		99.53	
80	99.33		99.92	
80	101.08		100.18	
Azelnidipine				
Conc. (µg/mL)	Repeatability	*Assay (%w/w) ± SD, % RSD	Intermediate	*Assay (%w/w) ± SD, % RSD
8	99.58		100.36	
8	100.82	100.21 ± 0.53	100.55	99.90 ± 0.58
8	99.52	(0.50)	99.3	(0.59)
8	100.48		99.75	
8	100.38		99.15	
8	100.49		100.3	

*Mean of six replicates

TABLE 6: LOD AND LOQ DATA

Analyte	LOD (µg/mL)	LOQ (µg/mL)
Telmisartan	0.55	1.66
Azelnidipine	0.07	0.21

TABLE 7: ROBUSTNESS DATA FOR TELMISARTAN AND AZELNIDIPINE

Drugs	Parameters	Condition	*Peak Area	Tailing Factor	Theoretical plates	*Assay (% w/w) ± SD (% RSD)
Telmisartan	Flow rate (± 0.1 mL/min.)	0.2	1253078	1.19	5012.00	99.75 ± 1.11 (1.12)
		0.3	1271768	1.21	4348.00	
		0.4	1280878	1.19	5508.67	
	Mobile phase composition (± 5 % v/v)	65:25	1246913	1.20	5107.00	99.67 ± 1.49 (1.50)
		70:30	1271768	1.21	4348.00	
		75:35	1284200	1.19	4894.67	
	Temperature (± 5 °C)	25	1269683	1.18	5111.67	100.28 ± 0.63 (0.63)
		30	1271768	1.21	4348.00	
		35	1284489	1.18	4892.67	
Azelnidipine	Flow rate (± 0.1 mL/min.)	0.2	132848	1.23	3170.33	99.68 ± 1.17 (1.18)
		0.3	135027	1.19	3166.00	
		0.4	135925	1.19	4255.33	
	Mobile phase composition (± 5 % v/v)	65:25	132867	1.24	3673.33	99.49 ± 0.94 (0.94)
		70:30	135027	1.19	3166.00	
		75:35	135101	1.38	3738.00	
	Temperature (± 5° C)	25	133799	1.25	3646.00	100.21 ± 1.24 (1.23)
		30	135027	1.19	3166.00	
		35	137102	1.72	3807.00	

*Mean of three replicates

TABLE 8: ASSAY DATA

Brand	Label claim (mg)		*Amount found (mg)	*Assay (% w/w) ± SD
Telma_Az	Telmisartan	80	79.95	99.94 ± 0.04
	Azelnidipine	8	7.91	98.96 ± 0.26

*Mean of three replicates

TABLE 9: DEGRADATION DATA OF TELMISARTAN AND AZELNIDIPINE

Degradation condition	Peak area	Tailing factor	USP plate count	Resolution	% Degradation
Telmisartan					
Acidic	1219939	1.2	5500	4.2	2.22
Alkali	1207347	1.2	5543	4.8	3.23
Oxidation	1208209	1.2	5505	2.8	3.16
Thermal	1219012	1.2	4953	5.5	2.30
UV	1218427	1.2	4926	5.4	2.35
Water	1239180	1.1	4977	5.6	0.68
Azelnidipine					
Acidic	121577	1.2	2158	-	4.60
Alkali	124174	1.3	2469	-	2.56
Oxidation	122241	1.3	2470	-	4.07
Thermal	125707	1.2	3035	-	1.35
UV	125124	1.2	3378	-	1.81
Water	126336	1.3	3524	-	0.86

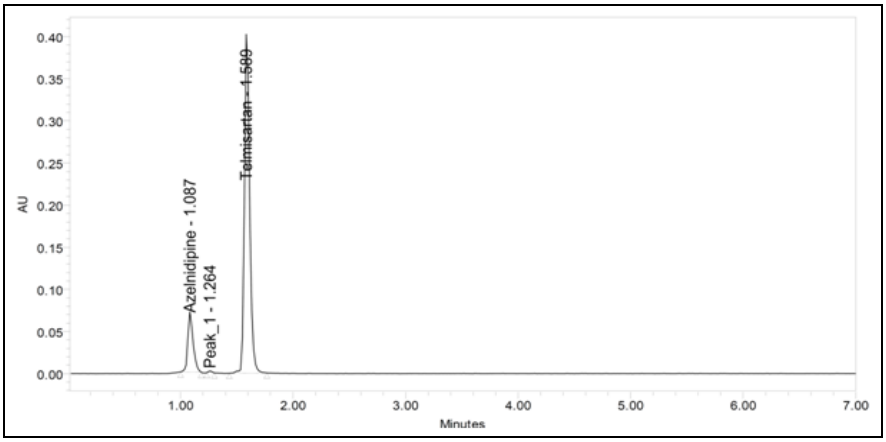

FIG. 6: FORCED DEGRADATION CHROMATOGRAM OF TELMISARTAN AND AZELNIDIPINE (ACIDIC)

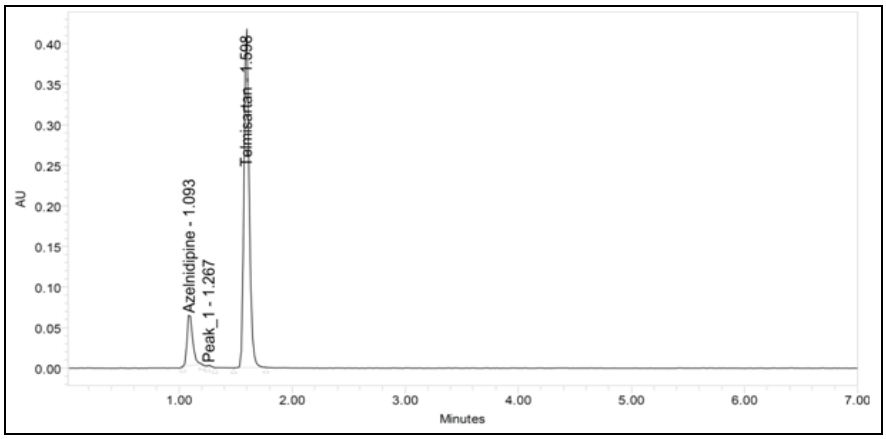

FIG. 7: FORCED DEGRADATION CHROMATOGRAM OF TELMISARTAN AND AZELNIDIPINE (BASIC)

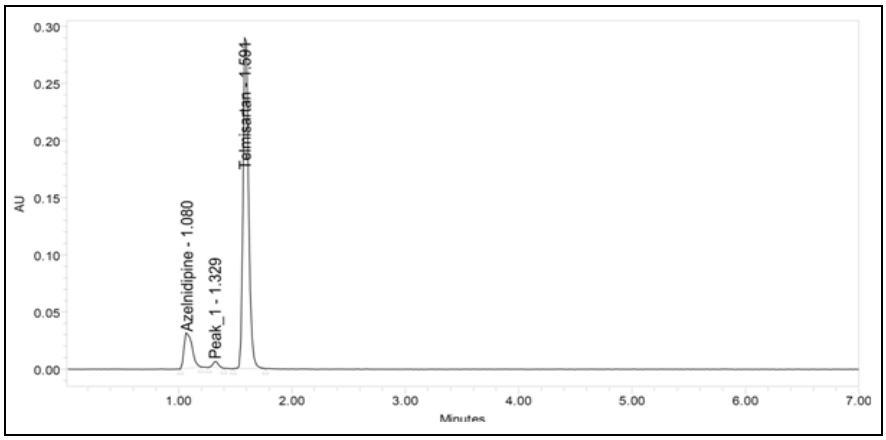

FIG. 8: FORCED DEGRADATION CHROMATOGRAM OF TELMISARTAN AND AZELNIDIPINE (PEROXIDE)

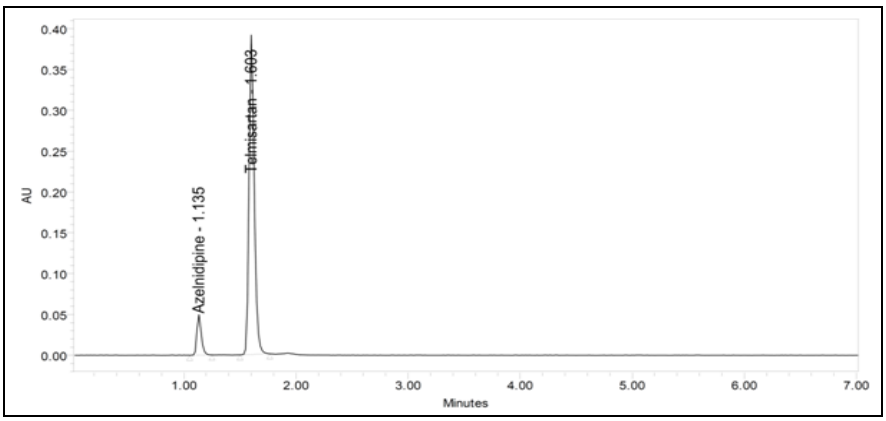

FIG. 9: FORCED DEGRADATION CHROMATOGRAM OF TELMISARTAN AND AZELNIDIPINE (THERMAL)

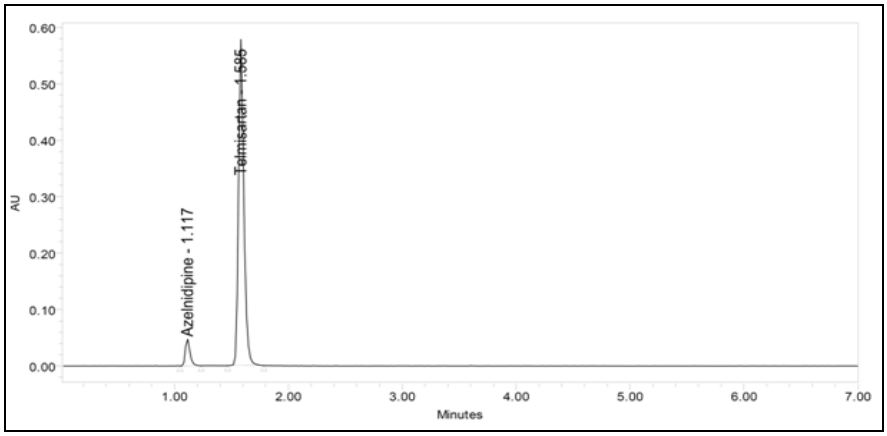

FIG. 10: FORCED DEGRADATION CHROMATOGRAM OF TELMISARTAN AND AZELNIDIPINE (PHOTOLYTIC)

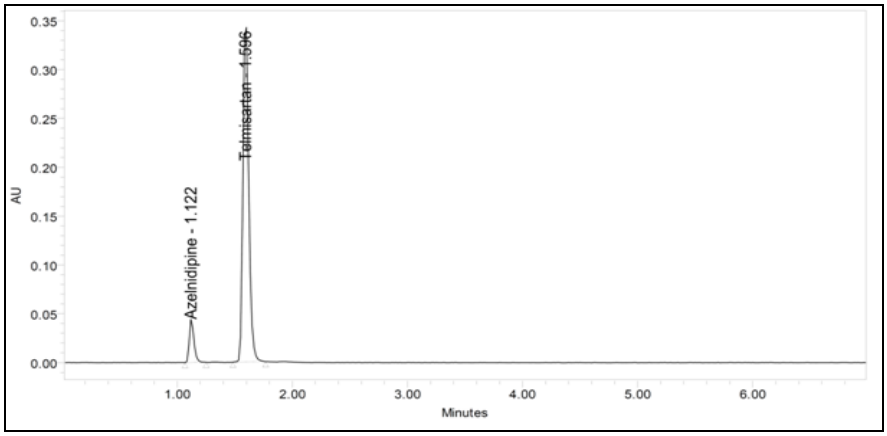

FIG. 11: FORCED DEGRADATION CHROMATOGRAM OF TELMISARTAN AND AZELNIDIPINE (WATER)

CONCLUSION: A simple RP-UPLC method was developed and validated (as per the ICH) for the simultaneous quantification of Telmisartan and Azelnidipine in the dosage form. The developed method was rapid as the run time was 3.0 min and the retention time for Telmisartan and Azelnidipine was 1.636 min. and 1.153 min, respectively. The method was sensitive as assessed under signals to noise ratio with accepted precision and accuracy.

The method also indicated stability, with good separation of Telmisartan and Azelnidipine among the other degraded peaks because of forced degradation studies. Hence the present developed method can be considered a rapid and reliable liquid chromatographic method which could be appropriate for the routine quality control analysis of the Telmisartan and Azelnidipine in the bulk and tablet dosage form.

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CONFLICTS OF INTEREST: The authors have no conflict of interest to declare.

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