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Quantification of Telmisartan and Azelnidipine Combination in Using Liquid Chromatography: Stability studies

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ABSTRACT

A stability-indicating RP-HPLC method for the development of Telmisartan (TTN) and Azelnidipine (ADN) is analyzed in tablet dosage form. The quantification of TTN and ADN combination is done by Supel cosil C18 column (250 mm, 4.6 mm, & 5 µm). Isocratic mobile phase had mobile phase consists of 0.10M Na_2SO_4(pH 3.6) and acetonitrile (pH 3.6) as 55:45v/v. For this analysis flow rate is measured as 1.00 mL/minute. Wavelength is identified as 258nm to examine TTN and ADN. Stability for both these drugs under distinctive environments were performed. Injected volume is 10 µL. Run time is 8 minute. Retention time is 2.8 and 3.7 respectively. The responses were linear in the concentrate range as 37.4-110.3 for TTN and 2.24-10.51 µg/mL for ADN respectively. Percent comparative standard deviance to precision is 0.193% for TTN, 0.195% for ADN. Percent assay to accuracy for both these drugs are 98.76% and 99.04% respectively. LOD values for TTN and ADN were 0.020 µg/mL and 0.065 µg/mL and LOQ values for TTN and ADN were 0.009 µg/mL and 0.031 µg/mL. Robustness studies revealed that this method is robust by percent comparative standard deviance. This stability-indicating RP-HPLC procedure to both TTN, ADN analysis is more simple, highly sensitive, more precise, highly specific and robust, making it appropriate to the assessment of TTN and ADN in formulation.

Keywords: Telmisartan, Azelnidipine, Formulation, Stability indicating, Analysis, Tailing factor, Formulation.

INTRODUCTION

Telmisartan is chemically approved and the molecular formula is $C_{33}H_{30}N_4O_2$ and the molecular weight is 514.62. TTN is acting as receptor inhibitor for angiotensin II[1,2]. It consists of very broad area of dissemination which is matured to its very strong property as

lipophilicity along with a final eradication half-life as one day[1,2]. This also maintains very good blood pressure after one missing dosage. TTN by hydrochlorothiazide mixture provides in larger minimization in final 720 seconds average systolic and diastolic blood pressure[3,4]. The dosage of this drug is usually taken with the help of mouth.[5] This TTN is available in different versions includes telmisartan/hydrochlorothiazide, telmisartan/cilnidipine[6] and telmisartan/amlodipine.[5] Molecular formulae for Azelnidipine(ADN) is $C_{33}H_{34}N_4O_6$ and molar mass is 582.657 g•mol^{-1}. This drug is a decrease in blood pressure by comparable potency with various dihydropyridines, includes amlodipine, without pulse rate increasing[7]. Azelnidipine (ADN) is a dihydropyridine-kind calcium antagonist that may be newly developed to treat hypertension[8,9]. S. Yuvasri[10] *et al.,* proposed total two methods. Wavelengths are 324nm for TEL and 220nm to AZEL are identified. In the second method various derivatives are noted as 220nm to TEL as well as 244nm to AZEL. Linearity is 16-80 µg/mL to TEL, 3.2-16 µg/mL for AZEL. Parikh MB[11] *et al.,* separated by using ODS C18 (250*4.6mm) and Buffer as 0.05M KH_2PO_4 buffer with pH-4.0 methanol as 60v/v, 40v/v as mobile phase, rate of flow as 1.00 mL/minute. 215nm is wavelength. RT values are 3.440 min and 5.693 minutes. Linearity is 20-60 µg/mL and 40-120 µg/mL. M. S. Kalshetti[12] *et al.,* developed method to Metoprolol succinate, Telmisartan, as well as Clinidipine using Phenomenex Luna C18 (150mm×4.6mm, 5 µm) as stationary phase. Acetonitrile, methanol and phosphate buffer are used in the ratio of 45:30:25v/v/v maintained at pH range as 7.5. Flow rate is maintained at 1.00 mL/minute. Wave length is 229nm. Total drugs were eluted at 2.0 min, 2.8 min and 6.8 minute. Linearity range is 10-80 µg/mL, 6.25-50 µg/mL and 2.5-20.00 µg/mL by coefficients of regression 0.997, 0.995 and 0.999 to telmisartan, metoprolol succinate as well as clinidipine. Jayvadan K Patel[13] *et al.,* used Hypersil GOLD C18 (150mm×4.6mm with internal diameter, as well as size of the particle as 5 µm). Mobile phase is methanol 40v/v, acetonitrile 40v/v, and water 20v/v. The rate of flow is 0.50 mL/minute. 260nm is the wave length. RT values are 8.56, 3.04 minute. Curves of calibration are 2–48 µg/mL to AZL and 2.5–60 µg/mL to OLM by correlation coefficients value more than to 0.990. Other researchers[14,15] are developed different methods for the determination of various drugs. By using literature reviews authors are carried out this method for the development of telmisartan and azelnidipine.

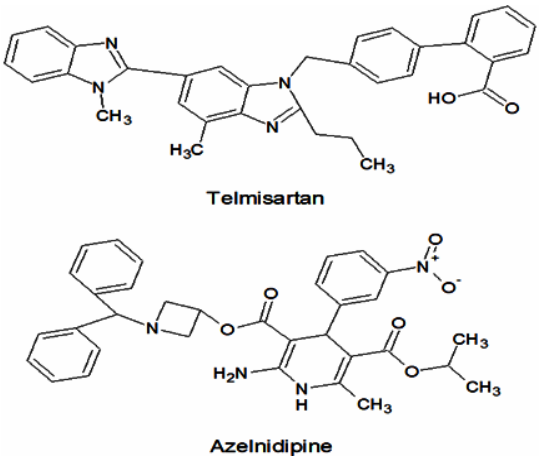

Fig. 1. Structures of Telmisartan and Azelnidipine (https://en.wikipedia.org/wiki/Telmisartan and https://en.wikipedia.org/wiki/Azelnidipine)

MATERIAL AND METHODS

Telmisartan and Azelnidipine were procured from local market, Hyderabad, India, as a gift sample. 0.10M Na_2SO_4, acetonitrile of HPLC Grade, 1N KOH (AR Grade), Buffer (AR Grade) were purchased from E. Merck (India) Ltd. Mili-Q water was used throughout the experiment. For analysis, drug product substance named Uniaz T40 solution comprising 40 g/mL TTN and 8 g/mL ADN was produced.

EXPERIMENTAL

A "Waters" HPLC system (model-2695) fitted out with a PDA (model-2998) detector was exploited for analysing TTN & ADN in Tablet of brand Uniaz T40. TTN and ADN were separated chromatographically with the help of a Supelcosil C18 column (250mm, 4.6mm, & 5 µm). At stream rate as 1.00 mL, mobile phase was constituted of 0.10M Na_2SO_4 having a pH of 3.6 and acetonitrile (55:45, vol/vol ratio). The volume of TTN & ADN solution injection was 10 µL. The temperatures of the column and also the autosampler tray remained maintained at 27°C all through the experiments. Weighed accurately 14.2 g of Na_2SO_4 taken into a beaker and then

added 1000 mL Milli-Q water along with dissolved it then altered pH 3.6 by using 1 N KOH solution and then filtered buffer solution over 0.22 µm filter paper. Mixed volumes of 550 mL Buffer solution and 450 mL acetonitrile into a 1 litre bottle and then degassed the mobile phase by using sonication.

Preparation of solutions

By dissolving TTN & ADN in mobile phase, the standard TTN & ADN stock solution was afresh made at concentrations of 400 µg/mL (TTN) and 80 µg/mL (ADN). Stock TTN & ADN solution (400 µg/mL-TTN and 80 µg/mL-ADN) was diluted utilizing mobile phase to working TTN & ADN solutions with serial concentrations (TTN–20 µg/mL to 60 µg/mL and ADN-4 µg/mL to 12 µg/mL) for calibration curves for TTN & ADN and working validation samples (40 µg/mL-TTN and 8 µg/mL-ADN). For analysis, a powdered Uniaz T40 solution comprising 40 g/mL TTN and 8 g/mL ADN was produced. Stock Uniaz T40 solution (400 µg/mL-TTN and 80 µg/mL-ADN) was diluted adopting mobile phase to working Uniaz T40 solutions with 40 g/mL TTN and 8 g/mL ADN for analysis. The Uniaz T40 formulations were evaluated and chromatograms were generated under appropriate TTN & ADN assay chromatographic conditions.

Method development

For 10ppm solution of TTN as well as ADN by using UV spectrophotometer the spectrum in Acetonitrile was recorded separately. Peak of maximum absorbance wavelength was measured at 258nm absorbance indicated the spectra of TTN as well as ADN. By using Supelcosil C18 column column required separation along with peak shapes were measured. In this method mobile phase was constituted of 0.1 M Na_2SO_4 having a pH of 3.6 as 55v/v and acetonitrile as 45v/v. Finally, noted from experiment is 1.00 mL/min flow rate is most suitable in order to elute analyte. The obtained chromatograms are denoted in Figure 2.

RESULTS AND DISCUSSION

System suitability

This parameter is inspected with working solution of TTN as 20 µg/mL as well as ADN as 10 µg/mL. Mean, SD along with %RSD to resolution, area to peak, period of retention, symmetry for peak along with theoretical plate number are measured and the results were denoted in the Table 1 & 2 to both TTN as well as ADN peaks conferring to ICH indorsed criteria. The obtained chromatograms are denoted in Figure 3.

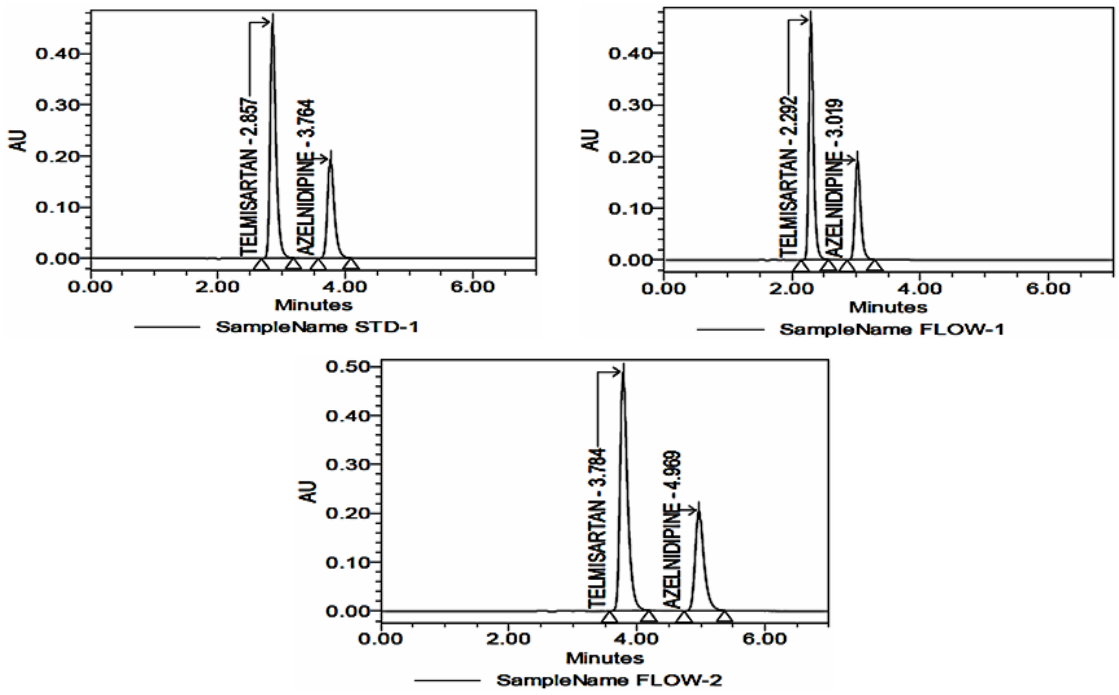

Fig. 2. Different Flow rate chromatograms

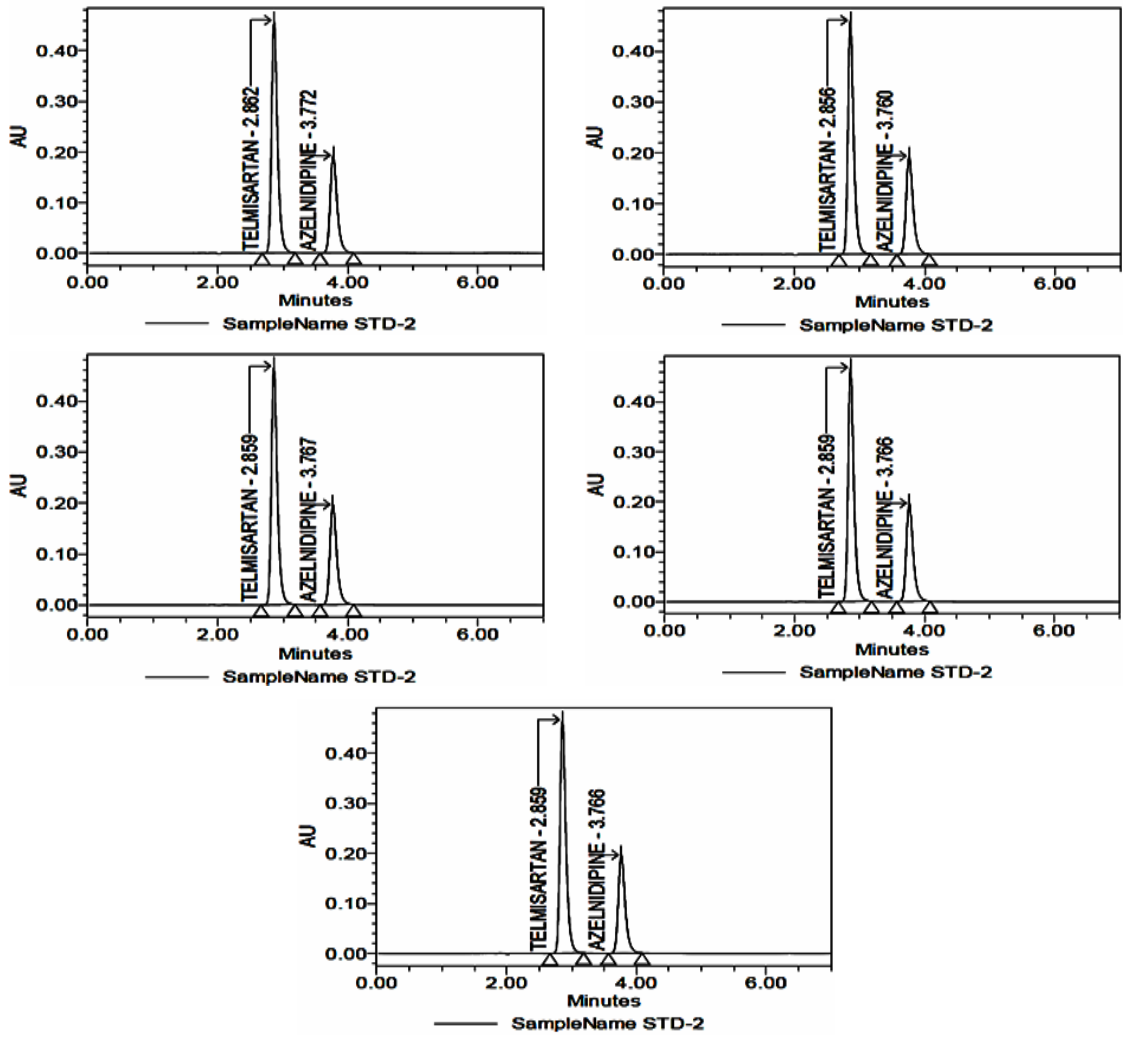

Fig. 3. Repeatability of standard injections

Table 1: TTN system suitability measures

Injection	TTN Retention time	TTN Area	TTN peak plate count	TTN peak tailing
I	2.862	2931157	5048	1.37
II	2.856	2952252	5157	1.37
III	2.859	2931529	5067	1.37
IV	2.859	2931681	5097	1.38
V	2.859	2946265	5001	1.37
Median value		2938577		
R.S.D value		0.3		

Table 2: ADN system suitability measures

Injection	ADN Retention time	ADN Area	ADN peak plate count	ADN peak tailing	Resolution
I	3.772	1466280	6081	1.31	4.97
II	3.760	1463687	6055	1.30	4.97
III	3.767	1476511	6123	1.31	4.98
IV	3.766	1474786	6150	1.31	4.99
V	3.766	1471510	6138	1.31	4.96
Median value	3.766	1470555	6109	1.31	4.97
R.S.D value		0.4			

Specificity

Examined and determined parameter to this proposed process after injecting Diluent as blank, construction of placebo, solution for system suitability, standard solution-diluted, sample construction as well as disparate Impurity's includes A, B, C, D, E as well as construction of spiked sample into the system of chromatography latter retention times are reported. From the values obtained finally it is noticed that there is no possibility for the presence of other interference by Diluent-blank, construction of placebo, solution of system suitability, standard solution-diluted, sample construction and divergent Impurity's like A, B, C, D, E at Rt of TTN and ADN peak together with each other. The final values were noted in the Table 3.

Table 3: Specificity results of TTN and ADN

S. No	Sample Weight	Sample Area-1	Sample Area-2	% Assay	% Assay
ACID	136.00	2651627	1336580	89.60	90.62
BASE	136.00	2715246	1368217	91.75	92.76
PEROXIDE	136.00	2805917	1407760	94.82	95.44
HEAT	136.00	2632042	1320568	88.94	89.53
SUNLIGHT	136.00	2741739	1394600	92.65	94.55
	136.00	2920684	1466587	98.70	99.43

Forced Degradation study

Base (0.1N NaOH) hydrolysis on TTN & ADN formulation solution disclosed 8.25% degradation of TTN and 7.24% degradation of ADN with products of degradation peaks at RT of 1.484 min, 1.892 min, 4.982 min and 6.079 minute. Acid (0.1N HCl) hydrolysis on TTN & ADN formulation solution disclosed 10.40% degradation of TTN and 9.38% degradation of ADN with products of degradation peaks at RT of 1.908 min, 5.569 min, 5.835 min and 6.422 minute. Oxidation (30% peroxide) hydrolysis on TTN & ADN formulation solution disclosed 5.18% degradation of TTN and 4.56% degradation of ADN with products of degradation peaks at RT of 1.192 min, 2.058 min, and 5.601 minute. Thermal (60°C) hydrolysis on TTN & ADN formulation solution disclosed 11.06 %degradation of TTN and 10.47% degradation of ADN with products of degradation peaks at RT of 1.183 min, 1.789 min, 4.747 min and 6.100 minute. Photo (sun light) hydrolysis on TTN & ADN formulation solution disclosed 7.35% degradation of TTN and 5.45% degradation of ADN with products of degradation peaks at RT of 1.261 min, 2.303 min and 6.610 minute. The stability indicating property for HPLC TTN & ADN assay was revealed by a well resolved peak of drugs (TTN & ADN) as well as degradation products at various RT. TTN and ADN degradation associated chromatograms are represented in the Figure 4.

Among diverse C18 columns (Kromasil, Develosil, Sunsil and Supelco) investigated, better resolution of TTN and ADN peaks, as well as peak symmetry for TTN and ADN were obtained with Supelco. TTN and ADN have the maximum sensitivity at 258nm, with the least amount of observed noise. TTN and ADN peaks were not eluted adequately with 0.1% phosphoric acid and 0.1M NaH_2PO_4 and provided an unsatisfactory baseline. As a consequence, 0.1M Na_2SO_4 having pH 3.6 was chosen since it produced a superior outcome. The resolution of TTN and ADN peaks, as well as peak symmetry for TTN and ADN, were markedly enhanced while acetonitrile was added in a 45% volume ratio to mobile phase. Chromatogram of TTN and ADN with optimized conditions is made known by the Figure 5.

Linearity

Carried out linearity with both TTN as well as ADN to 300% of impurity specification limit. Parameter like precision is measured at maximum level. Correlation coefficient and R square value is minimum to 0.995. The %intercept is below to 5.0 of response at 100% specification area. Precision for maximum levels of %RSD is NMT 5.0. Calibration curve is acquired to both TTN as well as ADN by injection as 10 µL volume of calibration BLS range as 10.00 µg/mL–30.00 µg/mL along with MTL range as 5 µg/mL–15.00 µg/mL solutions. TTN as well as ADN area below their peaks was marked selected against corresponding TTN as well as ADN strengths are indicated in the Fig. 81 & 82. Linear relationships for TTN as well as ADN were obtained around

concentration ranges 20–60 µg/mL (TTN) and 4–12 µg/mL (ADN) by reliable regression as 0.9998 for TTN and 0.9999 for ADN coefficients. The calibration factors demonstrated are 29431 and 181619 slope values and -24712 and 4475.2 intercept values for TTN and ADN, respectively. The linearity curves are represented in Fig. 6 & 7 and chromatograms are represented in Figure 8.

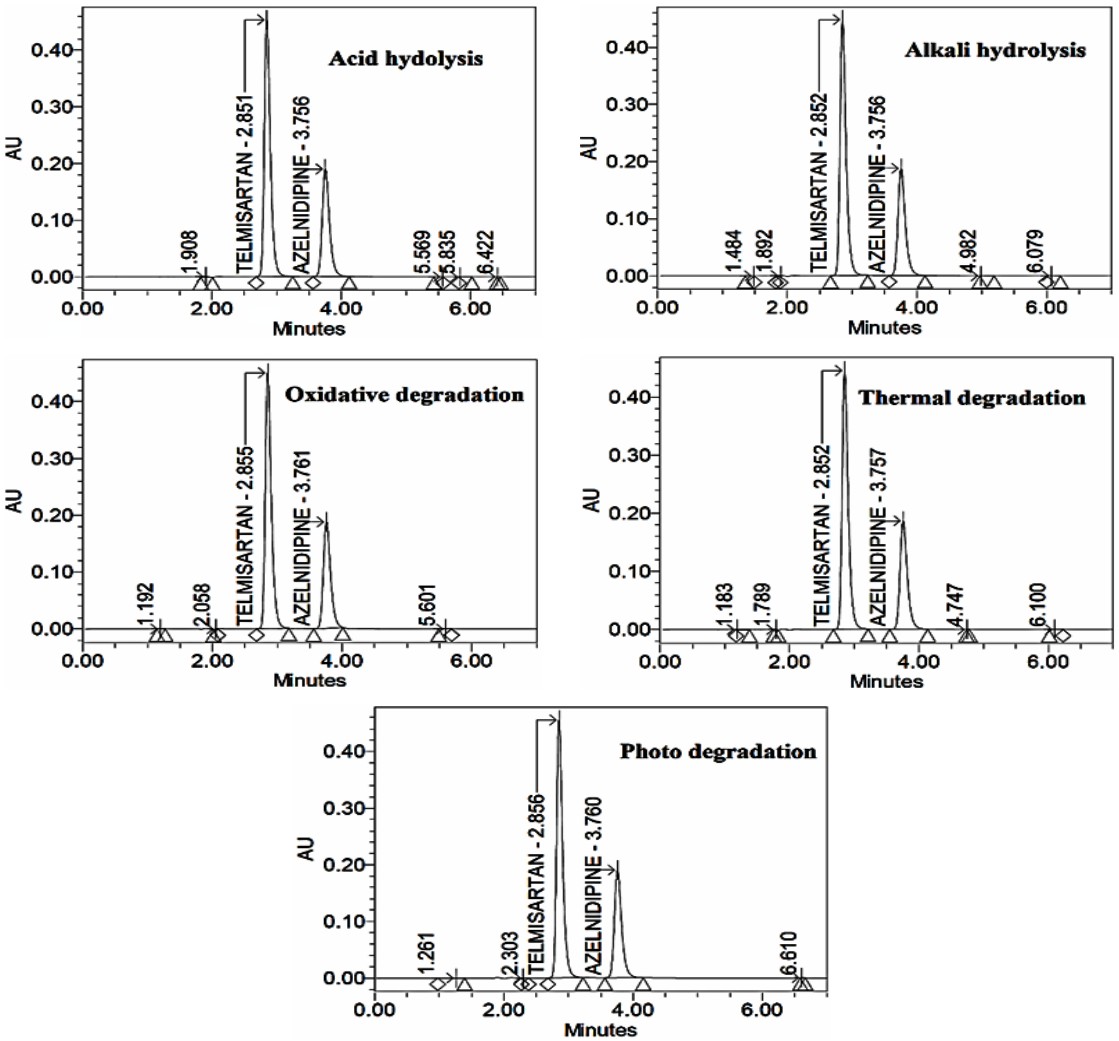

Fig. 4. TTN and ADN degradation associated chromatograms

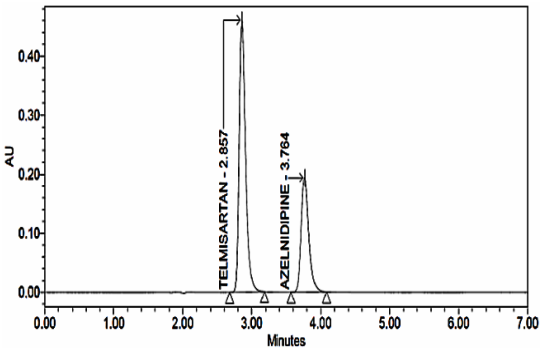

Fig. 5. Chromatogram of TTN and ADN by optimized circumstances

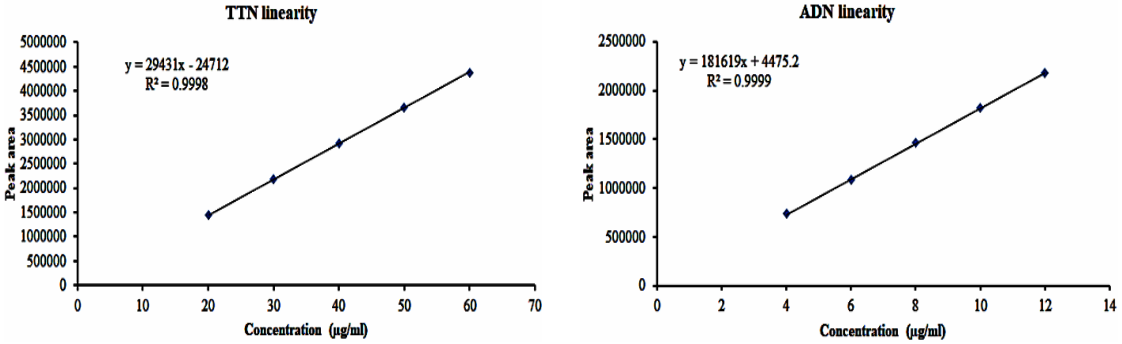

Fig. 6 & 7. TTN & ADN linearity curves

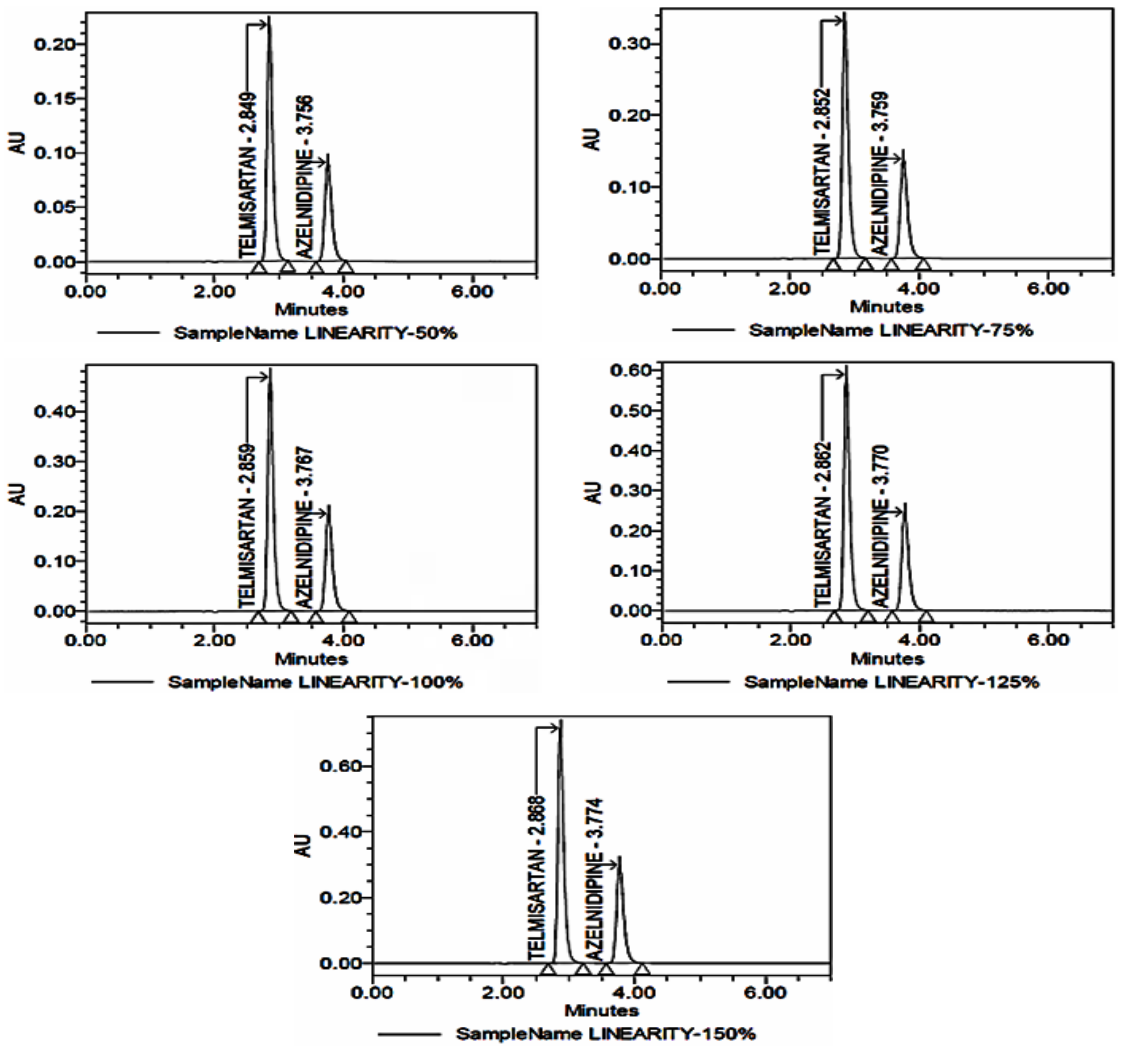

Fig. 8. Linearity chromatograms

Limit of detection & quantitation

With the help of intercept, slope along with residual regular deviation computed LOD and LOQ. Values to LOD as well as LOQ for both TTN along with ADN are profient which is dependent over area response standard deviation as well as calibration graph slope. Values to LOD for both TTN as well as ADNare 0.0180 µg/mL and

0.0240 µg/mL, respectively. The values to LOQ for both TTN as well as ADNwere 0.0590 µg/mL and 0.0810 µg/mL, respectively. The results are tabulated in the Table 4. The evaluates of the LOD and LOQ are 0.0200 µg/mL and 0.0650 µg/mL for TTN. The evaluates of the LOD and LOQ are 0.0090 µg/mL and 0.0310 µg/mL for ADN. These evaluates of TTN & ADN confirming the sensitivity. The results are shown in the Table 4.

Table 4: Peak results tables of LOD & LOQ

S. No	Sample name	Peak name	RT	Area(µV*Sec)	s/n
1	LOD	ADN	3.747	36.75	3.3
2	LOQ	ADN	3.748	97781	10.2
3	LOD	TTN	2.839	72930	3.4
4	LOQ	TTN	2.842	194720	10.7

Precision

The precision examination includes estimating TTN as 40 µg/mL & AND as 8 µg/mL drug solutions six times on relatively similar day. The peak areas for TTN & ADN from developed chromatograms were ascertained, and data variation was measured as a function of %RSD. These evaluates of %RSD for TTN & ADN confirming the precision. Results are shown in the Table 5 and 6.

Table 5: TTN & ADN-precision

Injection	TTN RT	TTN Area	TTN % Assay	ADN RT	ADN Area	ADN % Assay
I	2.863	2921726	98.73	3.769	1461001	99.05
II	2.858	2924535	98.83	3.763	1458797	98.90
III	2.857	2925550	98.86	3.762	1457448	98.81
IV	2.858	2918158	98.61	3.764	1465516	99.36
V	2.843	2919465	98.65	3.743	1460065	98.99
VI	2.843	2925565	98.86	3.745	1462141	99.13
Mean value		2922500	98.76		1460828	99.04
S.D value		3209.399	0.110		2823.571	0.193
R.S.D value		0.110	0.111		0.193	0.195

Accuracy

The accuracy for TTN & ADN from developed chromatograms were ascertained, and measured as a function of %TTN & ADN assay. These evaluates of %TTN & ADN assay confirming the accuracy. The obtained graphs are represented in the Figure 9.

Recovery

Recovery investigations were taken to ensure accuracy. A measured quantity of TTN & ADN was spiked into a pre-quantified Uniaz T40 formulation (40 µg/mL-TTN and 8 µg/mL-ADN) at different potencies (50%, 100%, and 150%) level. The Uniaz T40 formulations spiked were diluted and chromatograms were generated under appropriate TTN & ADN assay chromatographic conditions. The peak areas for TTN & ADN were observed, and using a regression models or calibration curves, the amount of TTN & ADN were calculated. These evaluates of %recoveries of TTN & ADN assay confirming the selectivity. The recovery results are denoted in Table 6.

Robustness

Total known impurities may be separated from each other latter to both TTN as well as ADN peak in sample that is spiked by impurities. Factors endorsed to evaluate robustness are: abnormality in wavelength as +2nm and –2nm, flow rate as +0.10 mL/min and –0.10 mL/min, methanol proportion as +5% volume and -5% volume, pH as +0.10 unit and -0.10 unit and column temperature as $+2^0$C and -2^0C. Robustness is authorized by working TTN as 20.00 µg/mL along with ADN as 10.00 µg/mL solution. Outcome of altered factors over analysis

of TTN as well as ADN is evaluated in relations of Mean, SD and %RSD for TTN as well as ADN peak areas captured along with the results shown in the Table 7.

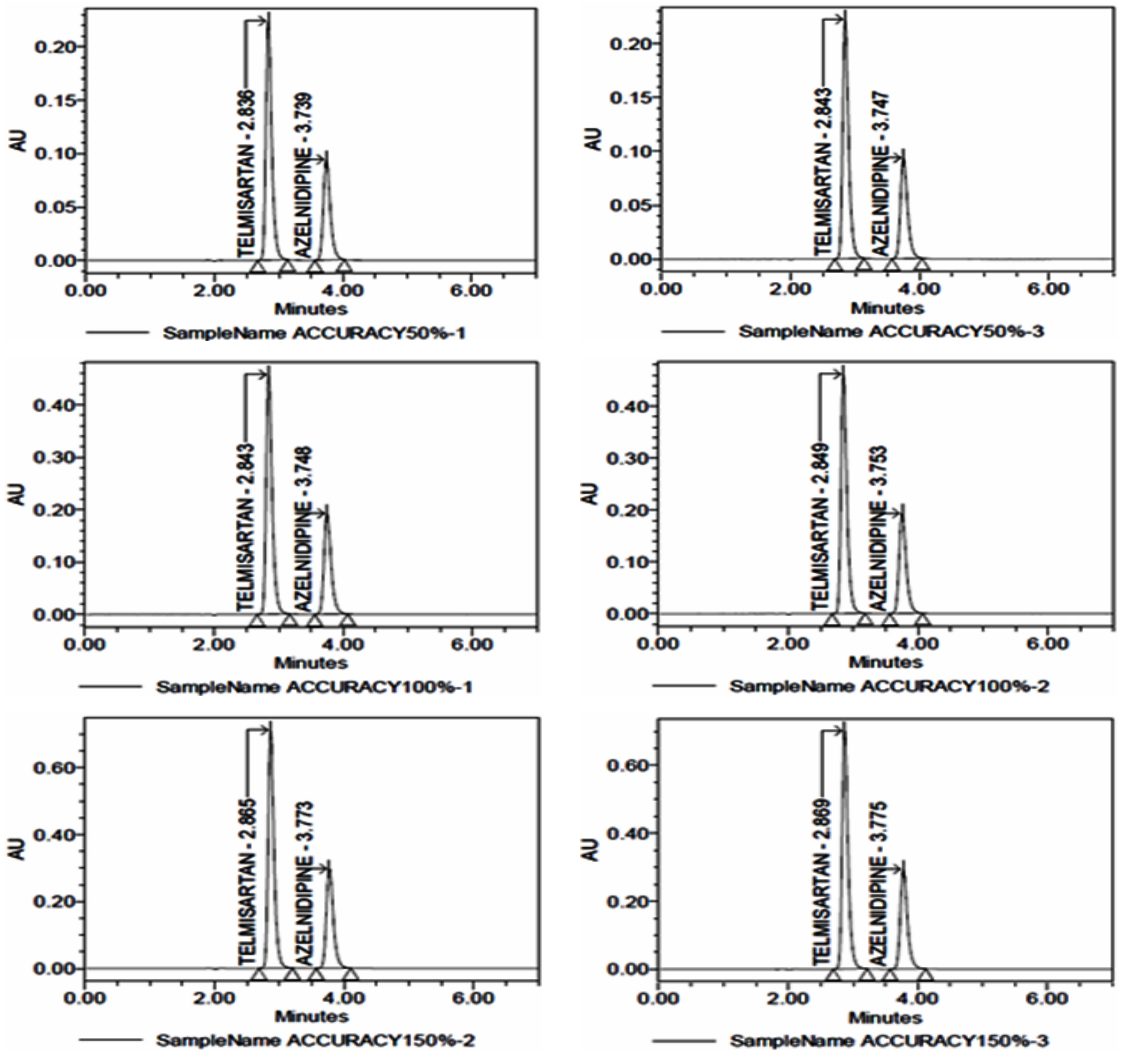

Fig. 9: Accuracy at 50%, 100%and 150% chromatograms

Table 6: TTN and ADN recovery results table

Added Level	µg/mL TTN added	µg/mL TTN found	%TTN Recovery	Mean value	S.D value	R.S.D value	µg/mL TTN added	µg/mL TTN found	% TTN Recovery	Mean value	S.D value	R.S.D value
			TTN						ADN			
50%	19.800	19.71	99.55	99.23	0.401	0.404	3.960	3.98	100.56	100.55	0.040	0.040
	19.800	19.56	98.78				3.960	3.98	100.51			
	19.800	19.67	99.36				3.960	3.98	100.59			
100%	39.600	39.39	99.47	99.64	0.154	0.155	7.920	7.92	99.95	100.14	0.162	0.162
	39.600	39.51	99.77				7.920	7.94	100.22			
	39.600	39.47	99.68				7.920	7.94	100.24			
150%	59.400	59.26	99.76	99.89	0.163	0.163	11.880	11.83	99.57	99.84	0.260	0.261
	59.400	59.44	100.07				11.880	11.86	99.85			
	59.400	59.30	99.83				11.880	11.89	100.09			

Table 7: TTN and ADN assay robustness

Parameter	Diverse value	Analyte	Counts of plate	Resolution	Tailing factor
Acetonitrile	40%	TTN	5011	-	1.40
		ADN	6107	5.00	1.34
	50%	TTN	4885	-	1.39
		ADN	5908	4.88	1.31
Temperature	23 ˚C	TTN	4965	-	1.39
		ADN	5890	4.82	1.31
	27 ˚C	TTN	4891	-	1.40
		ADN	6009	4.87	1.33
Flow rate	0.9 ml/min	TTN	4897	-	1.35
		ADN	6224	4.88	1.29
	1.1 ml/min	TTN	5027	-	1.39
		ADN	6044	5.00	1.35
pH	3.4 units	TTN	5051	-	1.37
		ADN	6168	4.97	1.31
	3.8 units	TTN	5025	-	1.37
		ADN	6091	4.95	1.30
Wavelength	256	TTN	4970	-	1.37
		ADN	6046	4.94	1.31
	260	TTN	5051	-	1.37
		ADN	6082	4.97	1.31

RESULTS AND DISCUSSION

Here in investigation, we designed an HPLC approach for detecting and analysing TTN and ADN in bulk & tablet doses. This HPLC approach was sensitive, having a quantification level of slightly below 0.1 µg/mL. This HPLC TTN and ADN assay technique can be incorporated in a few of the very precise, accurate, selective & sensitive procedure listed for TTN and ADN analysis, according to observed findings of validation criteria. These characteristics recommended that the presented technique be utilized in analytical quality assurance (QA) procedures that are frequently performed by regulatory bodies and QA laboratories, without the influence of some frequently used dosage additives. Herein investigation, we designed an HPLC approach for detecting and analysing Telmisartan (TTN) and Azelnidipine (ADN) in bulk & tablet doses. TTN and ADN were separated chromatographically using a Supelcosil C18 column and mobile phase was constituted of 0.10M Na_2SO_4 having pH 3.6 and acetonitrile (55:45, vol/vol ratio).

Linear relationships for these drugs obtained around concentration ranges 20–60 µg/mL and 4–12 µg/mL. The calibration factors demonstrated are 29431 and 181619 slope values and -24712 and 4475.2 intercept values for TTN and ADN, respectively. Evaluated %RSD for TTN as 0.110% & ADN as 0.193% confirmed the precision. The evaluates of %TTN as 98.78% and for ADN as 99.13% assay confirmed the accuracy. Forced degradation assessments were carried out on TTN & ADN as per ICH directives. The stability indicating property was revealed by a well-resolved TTN, ADN peaks N as well as degradation products at various elution periods. The precision examination includes estimating TTN as 40 µg/mL & AND as 8 µg/mL drug solutions six times on relatively similar day. The Uniaz T40 formulations spiked were diluted and chromatograms were generated under appropriate TTN & ADN assay chromatographic conditions. The peak areas for TTN & ADN were observed, and using a regression models or calibration curves, the amount of TTN & ADN were calculated.

Factors endorsed to evaluate robustness are: abnormality in wavelength as +2nm and –2nm, flow rate as +0.10 mL/min and –0.10 mL/min, methanol proportion as +5% volume and -5% volume, pH as +0.10 unit and -0.10 unit and column temperature as $+2^0$C and -2^0C. Robustness is authorized by working TTN as 20.00 µg/mL along with ADN as 10.00 µg/mL solution. Outcome of altered factors over analysis of TTN as well as ADN is evaluated in relations of Mean, SD and %RSD for TTN as well as ADN peak areas captured. The

presented technique be utilized in analytical quality assurance procedures that are frequently performed by regulatory bodies and quality assurance laboratories.

CONCLUSION

According to ICH guidelines, this HPLC method for the associated compounds in drug product of TTN & ADN is verified. The proposed procedure has been determined to be specific. The approach is also shown by stressful circumstances.

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Conflicts of Interest

There are no conflicts of interest among the authors.

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