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Simultaneous Determination of Hydrochlorothiazide and Telmisartan by Using Reverse Phase HPLC Technique

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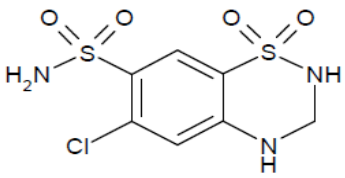
ABSTRACT

A rapid specific reverse-phase HPLC method has been developed for assaying Hydrochlorothiazide and Telmisartan by simultaneous method in pharmaceutical dosage forms. The method involves an isocratic elution of drug in a stationary phase of Phenomenex Prodigy, C18, 150 mm X 4.6 mm, 5 µm column using a mobile phase composition of methanol and 0.1 % orthophosphoric acid in the composition ratio 70:30 % (V/V) and with flow rate of 1.0 ml / min at 260nm of detection.The developed method is found to be linear in the range of 4.99 to 99.80 µg/ml for Telmisartan and 2.49 to 49.75 µg/ml for Hydrochlorothiazide respectively.The injection volume is 20µL.The method has been validated for specificity, linearity, range, precision, accuracy, limit of detection, limit of quantification, ruggedness and robustness. The % recovery of Telmisartan and Hydrochlorothiazide was found to be in the range of 99.00 % - 101.00 %. All the validation parameters are within the acceptance range.

Keywords: Reverse-phase HPLC, Isocratic, Hydrochlorothiazide, Telmisartan.

INTRODUCTION

Telmisartan is **(figure 1b)** 4 - [1,4 -dimethyl-2 - propyl- [2,6 -bi-1H-benzimidazole]-1 -yl)methyl] [1,1 - biphenyl]-2-carboxylic acid and hydrochlorothiazide is 6-chloro-3,4-dihydro-2H-1, 2, 4-benzothiadiazine-7-sulphonamide-1,1-dioxide **(figure-1a)**.Telmisartan is a new angiotension-II receptor antagonist for the treatment of essential hypertension usually given in combination with hydrochlorothiazide. The combination is useful in the treatment of mild to moderate hypertension, well tolerated with a lower incidence of cough than ACE inhibitors. The marketed tablet formulation contains telmisartan and hydrochlorothiazide in the ratio of 40:12.5 mg. Literature survey revealed linear sweep polarography [1], parallel catalytic hydrogen wave method [2], and HPLC [3] method for estimation of telmisartan alone in pharmaceutical preparations. Hydrochlorothiazide in combination with other drugs is reported to be estimated by spectrophotometric [4] [5], HPLC [6] [7] methods. The present work describes a validated reverse phase HPLC method for simultaneous determination of these drugs in tablets. The proposed method is validated as per ICH guidelines [8].



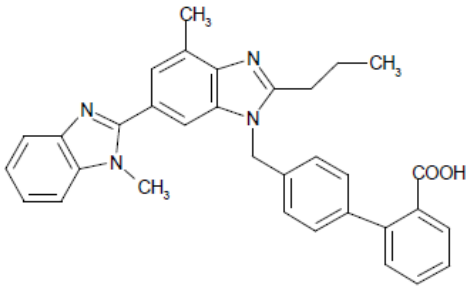


Fig-1a: Structure of Hydrochlorothiazide **Fig-1b**: Structure of Telmisartan

MATERIALS AND METHODS

Reagents and chemicals: Orthophosphoric acid (AR Grade, SD Fine Chem ltd), Methanol (HPLC grade, Merck ltd), Milli-Q water, Hydrochlorothiazide (99.8 % w/w is a gift sample from Unichem Laboratories Ltd) and Telmisartan (99.5 % w/w procured from SMS Pharmaceuticals, India). All other chemicals are of the highest grade commercially available unless otherwise specified.

Apparatus and chromatographic conditions: The Chromatographic system consisted of a Shimadzu Class VP Binary pump LC-10ATvp, SIL-10ADvp Auto sampler, CTO-10Avp Column Temperature Oven, SPD-10Avp UV-Visible Detector. All the components of the system are controlled using SCL-10Avp System Controller. Data acquisition was done using LC Solutions software. The mobile phase consisted of 70:30 % (v/v) of Methanol and 0.1% Orthophosphoric acid operated on isocratic mode. The flow rate is 1.0 ml/min. Chromatographic determination of Hydrochlorothiazide and Telmisartan was performed on Phenomenex® Prodigy C_{18} column (150 X 4.6 mm id, ODS 2, 5µm). The wavelength of detection is 260 nm. The injection volume is 20µL.

Preparation of standard solutions, Calibration Standards and Quality Control Samples: Stock solutions of Hydrochlorothiazide (1mg mL^{-1}), and Telmisartan (1mg mL^{-1}) were prepared separately in a volumetric flask using methanol and labeled accordingly. Suitable dilutions were then prepared using 50:50 %v/v methanol and milli-Q water as diluent solution. A linear calibration curve containing eight non-zero standards were prepared using diluent solution in the concentration range of 4.99–99.80 µg/mL for Telmisartan and 2.49 – 49.75 µg mL^{-1} for Hydrochlorothiazide. The calibration standard sample is then transferred into the auto sampler for analysis. Samples for specificity (Sample with Telmisartan alone, sample with Hydrochlorothiazide alone, Blank Sample and sample containing both the drugs) were also prepared accordingly. For the preparation of quality control samples, a separate stock containing approximately the same concentration of the Telmisartan and Hydrochlorothiazide were prepared and labeled as quality control stocks. From these stocks, quality control samples containing Telmisartan and Hydrochlorothiazide were prepared at three concentration levels namely LQC, MQC, HQC so as to obtain low, median and high concentration quality control samples. The performance of the linear calibration curve is then evaluated using quality control samples.

Assay: The assay of tablets containing Hydrochlorothiazide and Telmisartan is done using the procedure given in Indian Pharmacopoeia under tablets. The active ingredients in each of 10 dosage units is taken by random sampling and analyzed by the developed method. The tablets are said to be compliance if the each individual content is 90 – 110 % of the average content or labeled claim. For the current assay ten tablets were randomly taken and transferred separately into 100ml volumetric flasks and dissolved in 20 ml methanol. The solution was then ultrasonicated for 10min and then made up to volume. Required amount

of solution is then taken and filtered through 0.45µ nylon membrane and diluted with diluent solution so that the resultant concentrations are within the calibration range of the developed method. The samples are then analyzed by using the validated method. The sample is then injected in triplicate.

System Suitability: A sample containing mixture of Hydrochlorothiazide (approximate concentration of 25µg ml^{-1}) and Telmisartan (approximate concentration of 50µg ml^{-1}) was used as system suitability sample. System suitability was assessed by six replicate analysis. A percent coefficient of variation (% CV) less than 1 % for retention times for the drugs is taken as the acceptance criterion.

Detection and Quantitation Limits (Sensitivity): Limits of detection (LOD) and quantification (LOQ) (**Fig-2**) were estimated from both linearity calibration curve method and signal to noise ratio method. The detection limit was defined as the lowest concentration level resulting in a peak area of three times the baseline noise. The quantification limit was defined as the lowest concentration level that provided a peak area with signal to noise ratio higher than 5, with precision (%CV) and accuracy with (±) 20%.

Linearity (Calibration Curve): The calibration curve was constructed with eight non-zero standards ranging from 4.99 to 99.80 µg mL^{-1} for Telmisartan and 2.49 – 49.75 for Hydrochlorothiazide. The linearity was evaluated by linear regression analysis, which was calculated by least square method. It is depicted in (**Fig- 3**).

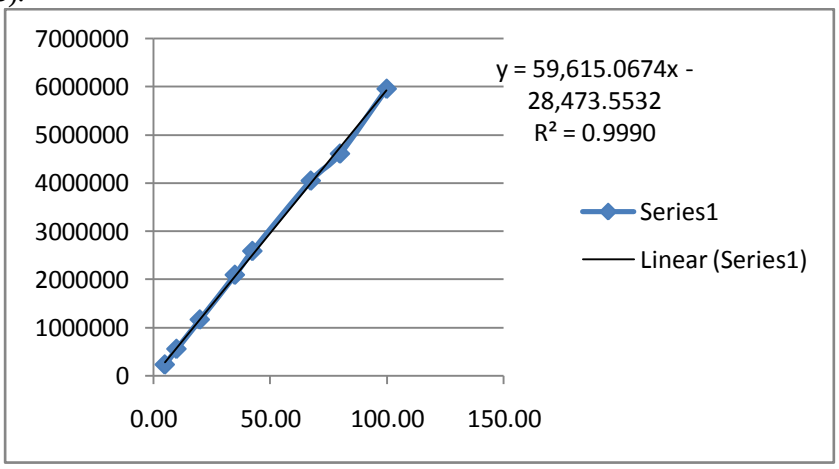


Fig-3: Linear calibration curve of Telmisartan.

Accuracy and Precision: Accuracy of assay method was determined for both intra-day and inter-day variations using triplicate analysis of the QC samples. Precision of the assay was determined by repeatability (intra-day) and intermediate precision (inter-day). Repeatability refers to the use of the analytical procedure within the laboratory over the shorter period of the time that was evaluated by assaying the QC samples during the same day. Intermediate precision was assessed by comparing the assays on different days (3 days).

Specificity: For demonstration of specificity, 4 samples namely blank sample, sample containing Telmisartan alone, sample containing Hydrochlorothiazide alone and sample containing the mixture of Hydrochlorothiazide and Telmisartan were prepared separately. Specificity of the method was determined by comparing results of all the samples (**fig-4**). The developed method is said to be specific if the % interference calculated as peak area (if any) at the retention time of each of the analytes in the blank sample is less than 20% of peak area at the corresponding retention times of each of the drugs in the lowest calibration standard. Sample Specificity is also observed in the degradation study of the drug. None of the degraded products must interfere with the quantification of the drug.

Stability: The stability of the drug is determined by placing the MQC samples for the short term stability at room temperature up to 12 hours and then comparing the obtained peak area with that of the similarly prepared fresh sample. Further, auto-sampler stability for up to 24 hrs was studied and established.
Stress Degradation Studies: For Stress Degradation Analysis, 1 mL aliquots (in duplicate) of samples containing MQC level concentration are treated separately with 100 µl of 0.1N HCl (Acid stress), 0.1N NaOH (Alkaline stress), 5% v/v Hydrogen Peroxide (Oxidative Stress), for 24 Hrs. Samples for Photolytic stress are placed in a transparent glass vial and placed in a UV chamber for 24 Hrs. Samples are then injected for analysis. The results of analysis are then compared with similarly prepared fresh samples. The analysis is performed in triplicate.

RESULTS AND DISCUSSION

Method Development and Validation: The HPLC procedure was optimized with a view to develop a stability indicating assay method. functional group analysis revealed the presence of acidic character to the molecules. Therefore evaluation of the chromatographic behavior at different pH values ranging from pH 3.0 to pH 6.5 using various columns like Hypersil-BDS-C18, Symmetry C18, Ymc-pack C18, Ymc-pack pro, Spherisorb C18, Phenomenex C18 have been tried with different buffer salts such ammonium Formate, orthophosphoric acid, di-potassium hydrogen orthophosphate, in combination with acetonitrile, methanol and tetrahydrofuran is done. However less tailing and high theoretical plates are obtained with Phenomenex Prodigy ODS2 column C18 150 X 4.6 cm 5µm column. The final mobile phase composition consisted of (70:30 v/v) of Methanol and 0.1% Orthophosphoric acid on isocratic mode. The flow rate of the method is 1.0 ml/min. Calibration standards were prepared in diluents solution containing 50:50 % v/v of Methanol and Milli-Q water. The wavelength of detection is 260nm. The column temperature is maintained at 25^{O}C.At the reported flow rate, peak shape was excellent; however increasing or decreasing the flow rate resulted in unacceptable tailing factor and poor peak shape. Hence 1.0 ml min^{-1} was optimized flow rate decreasing the consumption of the mobile phase, which in turn proves to be cost effective for long term routine quality control analysis. To evaluate the feasibility of the experiment under regular lab conditions, assessment of the stability of Telmisartan and Hydrochlorothiazide under room temperature and under normal light conditions is done.
System Suitability: The % RSD of the peak area for both drugs is within the acceptable criteria (**table-1**). The efficiency of the column was expressed as the number of theoretical plates for the six replicate injections was around 9242±57 for Telmisartan and 5546±65 for Hydrochlorthiazide. The USP tailing factor was 0.96 ± 0.02 for Telmisartan while that of Hydrochlorthiazide is 1.15 ± 0.02.
Determination and Quantification Limits (Sensitivity): Fig-2 represents the chromatogram of limit of detection and limit of quantification. The method is found to be sensitive which can be determined from the data obtained from the (**Table-2)**.

Table 1. System Suitability test for Telmisartan (above) and Hydrochlorothiazide

Telmisartan		
Sample ID	Peak Retention Time	Peak Area
1	4.23	2754943
2	4.19	2781206
3	4.2	2747095
4	4.19	2768197
5	4.2	2756896
6	4.2	2926051
MEAN	4.202	2789064.667
STDEV	0.0147	68151.3578
%CV	0.35	2.44

Hydrochlorothiazide		
Sample ID	Peak Retention Time	Peak Area
1	1.82	1157527
2	1.79	1171439
3	1.80	1155342
4	1.78	1164404
5	1.80	1160355
6	1.80	1218623
MEAN	1.798	1171281.667
STDEV	0.0133	23879.6347
%CV	0.74	2.04

Table 2. Sensitivity of Telmisartan and Hydrochlorothiazide by HPLC

TELMISARTAN

LOD

SR NO	DRUG	
	Retention Time	Peak Area
1	4.25	17225
2	4.25	18788
3	4.25	19823
MEAN	4.3	18612.000
ST DEV	0.00	1307.91
% CV	0.00	7.03

HYDROCHLORoHIAZIDE

LOD

SR NO	DRUG	
	Retention Time	Peak Area
1	1.85	6225
2	1.86	7222
3	1.86	6701
MEAN	1.9	6716.000
ST DEV	0.01	498.67
% CV	0.31	7.43

TELMISARTAN

LOQ

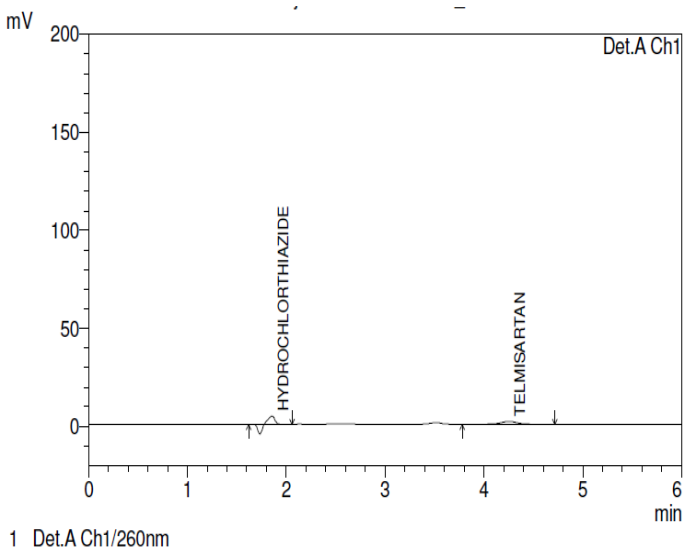
SR NO	DRUG	
	Retention Time	Peak Area
1	4.22	31214
2	4.23	31146
3	4.24	32819
MEAN	4.2	31726.333
ST DEV	0.01	946.89
% CV	0.24	2.98

HYDROCHLORoTHIAZIDE

LOQ

SR NO	DRUG	
	Retention Time	Peak Area
1	1.82	10698
2	1.85	10096
3	1.86	10774
MEAN	1.8	10522.667
ST DEV	0.02	371.45
% CV	1.13	3.53

Linearity: The linearity was demonstrated in triplicate. The results of the best fit line (y = mx + c) for the triplicate analysis is given in **table 3**. The accuracy of the calibration standards was evaluated from the back calculated concentrations **(table 4)**. All the standards were found to be within the range of 97 – 103 %.



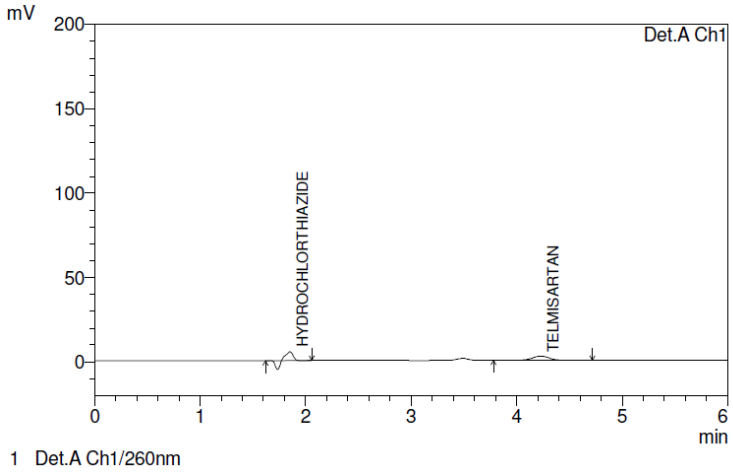


Fig-2: Chromatograms shown below indicate limit of Detection (LOD) above and Limit of Quantitation (LOQ) below.

Table 3. Results of best-fit line for triplicate analysis for Telmisartan (above) and Hydrochlorothiazide (below)

Telmisartan			
Curve	Slope	Intercept	r^2
1	59615.07	-28473.5	0.9990
2	61341.41	-56559.07	0.9991
3	59493.65	-4333.17	0.9982
Mean	60150.043	-29788.58	0.99877

Hydrochlorothiazide			
Curve	Slope	Intercept	r^2
1	47961.48	-12704.13	0.9997
2	49460.03	-29797.13	0.9999
3	49477.83	-26476.58	0.9996
Mean	48966.447	-22992.61	0.99973

Table 4. Linearity and Range for Telmisartan (above) and Hydrochlorothiazide (below) demonstrating accuracy, carryover effect and specificity of the method (Curve 1).

Concentration (Microgram/mL)	Retention Time	Peak Area	Back Calc Concentration	% Accuracy
Blank	NA	0	NA	NA
4.99	4.21	224920	4.25	85.18
9.98	4.20	549540	9.70	97.15
19.96	4.19	1159161	19.92	99.81
34.93	4.20	2086580	35.48	101.57
42.42	4.20	2580713	43.77	103.19
67.37	4.21	4040596	68.26	101.32
79.84	4.20	4601656	77.67	97.28
99.80	4.17	5947547	100.24	100.44
Blank	NA	0	NA	NA

- NA - Not applicable

Concentration (Microgram/mL)	Retention Time	Peak Area	Back Calc Concentration	% Accuracy
Blank	NA	0	NA	NA
2.49	1.81	97031	2.21	88.65
7.46	1.8	328101	6.85	91.78
14.93	1.79	711342	14.55	97.49
19.90	1.79	959325	19.53	98.16
27.36	1.79	1306758	26.52	96.91
32.34	1.81	1553887	31.48	97.35
44.78	1.79	2121219	42.88	95.77
49.75	1.77	2365039	47.78	96.05
Blank	NA	0	NA	NA

- NA - Not applicable

Accuracy and Precision: Accuracy and precision calculated for the QC samples during the intra- and inter –day run are given the (**table-5)**.The intra-day (day-1) and inter-day accuracy for Telmisartan ranged from 98.00 to 102.00 % while that of Hydrochlorthiazide ranged from 97.00 – 103.00 %. The results obtained from intermediate precision (inter-day) also indicated a good method precision. All the data were within the acceptance criteria.

Table 5a. Results of inter and intra-day accuracy and precision for Telmisartan by HPLC

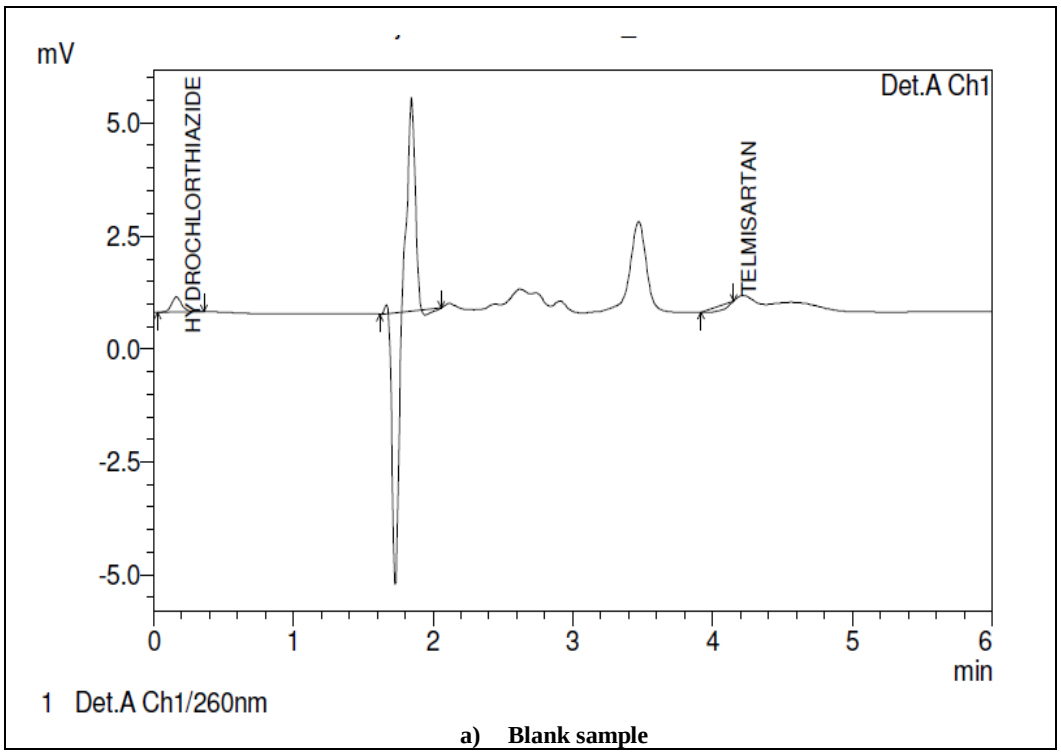
TELMISARTAN	Nominal Concentration (µg mL^{-1})		
	24.95 (LQC)	49.9 (MQC)	74.85 (HQC)
DAY 1			
MEAN (n=6) S.DSD	105.33	93.45	103.78
SD % CV	0.58	2.10	0.44
% CV	0.55	2.24	0.43
DAY 2			
MEAN (n=6)	101.24	99.85	99.58
SD	0.32	1.12	0.58
% CV	3.16	1.12	0.58
DAY 3			
MEAN (n=6)	99.96	100.67	101.24
SD	0.43	0.97	0.21
% CV	0.43	0.96	0.21

Table 5b. Results of inter and intra-day accuracy and precision for Hydrochlorthiazide by HPLC

HYDROCHLORTHIAZIDE	Nominal Concentration (µg mL^{-1})		
	12.44(LQC)	24.88 (MQC)	37.31(HQC)
DAY 1			
MEAN (n=6)	98.61	94.19	96.88
SD	0.34	1.98	0.44

% CV	0.35	2.10	0.45
DAY 2			
MEAN (n=6)	101.27	99.67	100.45
SD	0.25	0.65	0.32
% CV	0.24	0.65	0.32
DAY 3			
MEAN (n=6)	102.65	100.98	101.24
SD	0.51	0.21	0.33
% CV	0.50	0.21	0.33

Specificity: Specificity was determined by comparison of the Blank chromatogram with that of the Standard chromatogram (**fig-4**)



a) Blank sample

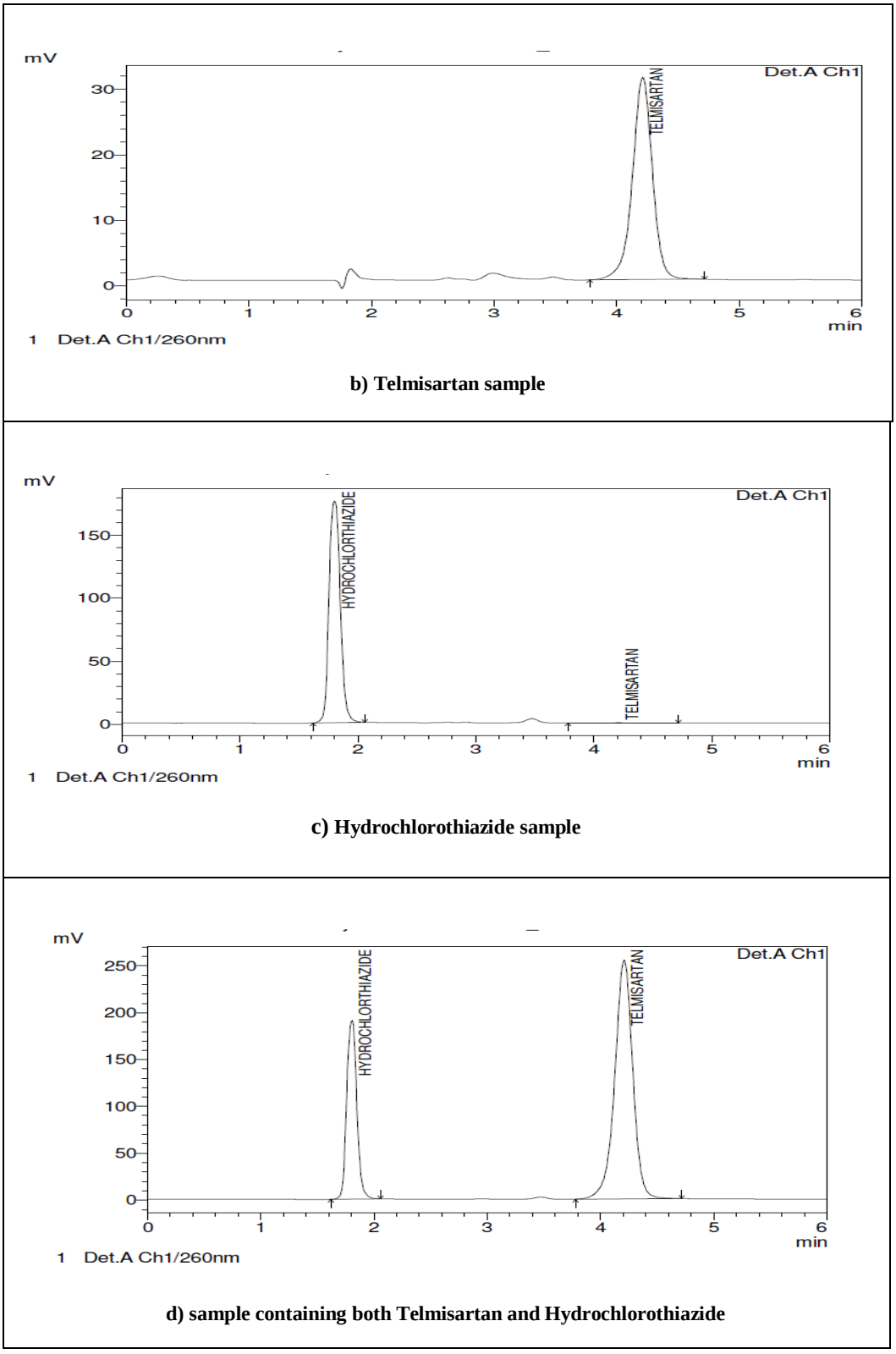


Fig-4: Comparison of (a)Blank Chromatogram, (b) Telmisartan alone (c) Hydrochlorothiazide alone and (d) sample containing both Hydrochlorothiazide and Telmisartan

Room Temperature Stability: Stability studies were done for short term stability up to 12 hrs on the bench top for the MQC levels conditions. Stability is calculated as the ratio of the mean peak area of the stability sample to the mean peak area of the fresh sample and expressed as the percentage (n=6). The room temperature stability was found to be 100.27 % for Telmisartan and 100.03 % for Hydrochlorthiazide. The results are tabulated in **table-6**.

Table 6a. Room Temperature Stability of Telmisartan (n = 6).

TELMISARTAN

STABILITY SAMPLE

SR NO	SAMPLE ID	DRUG	
		RETENTION TIME	PEAK AREA
1	STABILITY SAMPLE	4.22	2969279
2	STABILITY SAMPLE	4.24	2943580
3	STABILITY SAMPLE	4.23	2934281
4	STABILITY SAMPLE	4.23	2950842
5	STABILITY SAMPLE	4.25	2944208
6	STABILITY SAMPLE	4.21	2812370
MEAN		4.23	2925760.0
STDEV		0.014	56764.06
% CV		0.33	1.94

FRESH SAMPLE

SR NO	SAMPLE ID	DRUG	
		RETENTION TIME	PEAK AREA
1	FRESH SAMPLE	4.23	2957541
2	FRESH SAMPLE	4.19	2844513
3	FRESH SAMPLE	4.2	2926327
4	FRESH SAMPLE	4.25	2957611
5	FRESH SAMPLE	4.21	2871635
6	FRESH SAMPLE	4.2	2950230
MEAN		4.21	2917976.2
STDEV		0.023	48560.65
% CV		0.53	1.66

% Stability 100.27

Table 6b. Room Temperature Stability of Hydrochlorothiazide (n = 6).

Hydrochlorothiazide

STABILITY SAMPLE

SR NO	SAMPLE ID	DRUG	
		RETENTION TIME	PEAK AREA
1	STABILITY SAMPLE	1.81	1228801
2	STABILITY SAMPLE	1.83	1210714
3	STABILITY SAMPLE	1.82	1213214
4	STABILITY SAMPLE	1.82	1217347
5	STABILITY SAMPLE	1.84	1217681
6	STABILITY SAMPLE	1.8	1174510
MEAN		1.82	1210377.8
STDEV		0.014	18633.1796
% CV		0.78	1.54

FRESH SAMPLE

SR NO	SAMPLE ID	DRUG	
		RETENTION TIME	PEAK AREA
1	FRESH SAMPLE	1.82	1228612
2	FRESH SAMPLE	1.78	1188352
3	FRESH SAMPLE	1.79	1216963
4	FRESH SAMPLE	1.84	1219951
5	FRESH SAMPLE	1.8	1180349
6	FRESH SAMPLE	1.79	1225770
MEAN		1.80	1209999.5
STDEV		0.023	20447.12
% CV		1.25	1.69

% Stability 100.03

Stress Degradation: Stress studies revealed that Telmisartan is not susceptible to degradation under acid, light (UV) and oxidative stress conditions (**fig 5**). However, in alkaline conditions (0.1N NaOH), the drug was instable and the degradation peak eluted earlier accompanied with a drastic peak distortion and increased tailing. Except for alkaline conditions, the drug content was within 95 –105 % for all stress conditions indicating the stability and specificity of the analytical method to differentiate the degradation peaks. Stress studies on Hydrochlorothiazide indicated instability under alkaline and photolytic conditions. This has been clearly demonstrated by the help of overlap spectra of all the stress samples as compared with that of freshly prepared sample of similar concentration **(fig 5)**.

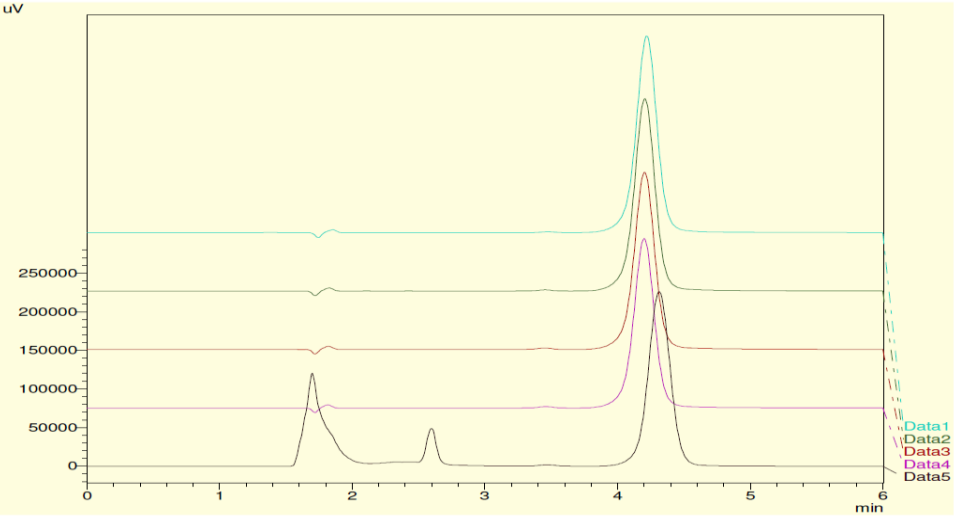


Fig-5a: Overlay Chromatogram showing the influence of various stress conditions on Telmisartan; Data 1-Acid Stress, Data 2 – Oxidative Stress; Data 3 – Photolytic Stress; Data 4 – Fresh sample Data 5 – Alkaline Stress. Data 5 clearly indicates the spectral degradation of Telmisartan due to alkaline instability.

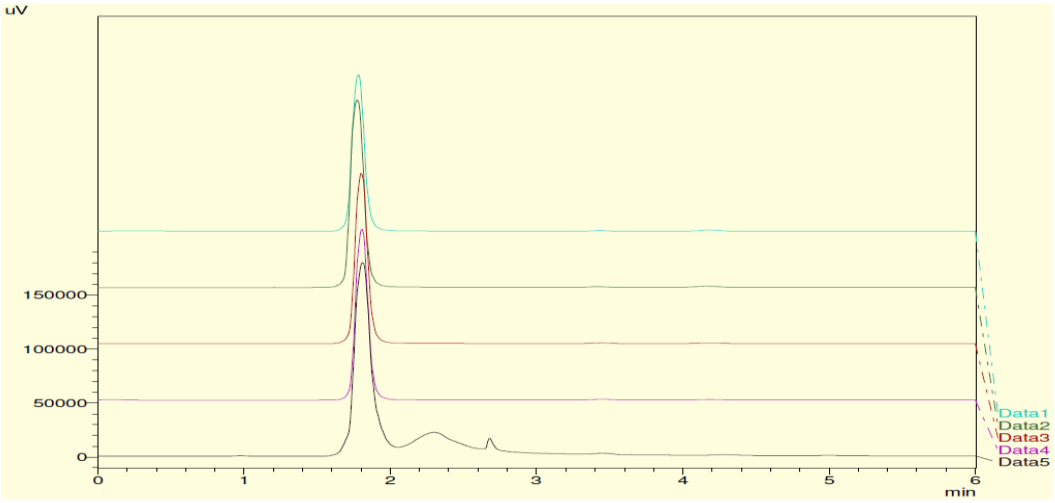


Fig-5b: Overlay Chromatogram showing the influence of various stress conditions on Hydrochlorothiazide; Data 1-Acid Stress, Data 2 – Oxidative Stress; Data 3 – Photolytic Stress; Data 4 – Fresh sample Data 5 – Alkaline Stress. Data 5 clearly indicates the spectral degradation of Hydrochlorothiazide due to alkaline instability

Robustness study: Robustness is the measure of method capacity to remain unaffected by deliberate small changes in the chromatographic conditions. The experimental conditions were deliberately altered to evaluate the robustness of the method. The impact of flow-rate (1.0 ± 0.1 ml min^{-1}), and effect of mobile-phase composition (± 5%) on chromatographic parameters such as retention time, theoretical plates, and tailing factor, were studied**.** At lower flow rate, the retention time of Telmisartan was 4.68 ± 0.03 minutes (n=6) while that of Hydrochlorothiazide was 1.79 ± 0.01 min. At lower flow rate, the tailing factor for Telmisartan is 0.96 ± 0.01 while that of Hydrochlorothiazide is 1.12 ± 0.02. At higher flow rate, tailing factor for both Hydrochlorothiazide and Telmisartan remained unchanged as compared to normal flow. At a lower flow rate of 0.9 ml/min, Telmisartan and Hydrochlorothiazide eluted at 4.69 ± 0.03 and 2.01 ± 0.02 minutes respectively. The retention time of Telmisartan and Hydrochlorothiazide were 3.82 ± 0.02 and 1.62 ± 0.01 minutes respectively (n=6) when the flow rate is 1.1 ml min^{-1}. At mobile phase composition of 65: 35 % v/v of Methanol and 0.1% v/v orthophosphoric acid the retention times of Telmisartan and Hydrochlorthiazide were 5.9 ± 0.01 and 1.832 ± 0.01 minutes (n=6). At mobile phase composition of 75: 25 % v/v of Methanol and 0.1% v/v orthophosphoric acid the retention times of Telmisartan and Hydrochlorothiazide were 3.31 ± 0.01 and 1.79 ± 0.01 min (n=6).

APPLICATIONS

Application of the method to dosage forms: The HPLC method developed is sensitive and specific for the quantitative determination of Telmisartan and Hydrochlorthiazide. Also the method is validated for different parameters; hence it has been applied for the simultaneous estimation in pharmaceutical dosage forms. The amount of Hydrochlorothiazide and Telmisartan in the commercial tablet dosage form is within the pharmacopoeial specifications. None of the tablets ingredients interfered with the analyte peak. The spectrum of Telmisartan and Hydrochlorothiazide in the extracted tablet was matching with that of standard compounds indicating the purity of the compounds in the tablets.

CONCLUSIONS

The method gave accurate and precise results in the concentration range of 4.99 to 99.80µg mL^{-1} for Telmisartan and 2.99 to 49.75 µg mL^{-1} for hydrochlorothiazide. The mobile phase composition consists of 70:30 % v/v of Methanol and 0.1 % orthophosphoric acid at the flow rate of 1.0 ml/min. The retention time of Telmisartan is 4.19 ± 0.05 minutes and that of Hydrochlorothiazide is 1.82 ± 0.03 min. The column is Phenomenex Prodigy ODS 2, 150 X 4.6mm, C18 column with the particle size of 5µm.A rapid sensitive and specific method for the simultaneous estimation of Telmisartan and Hydrochlorothiazide in the pharmaceutical tablet formulations has been developed and validated.

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