AMERICAN JOURNAL OF PHARMTECH RESEARCH

Journal home page: http://www.ajptr.com/

Simultaneous Estimation of Telmisartan and Chlorthalidone in Tablet Dosage Form by Using Reversed Phase High Performance Liquid Chromatographic Method

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ABSTRACT

A simple, accurate, precise and stability-indicating RP-HPLC method has been developed and validated for the simultaneous estimation of Telmisartan and Chlorthalidone in fixed-dosage formulation. The separation was achieved on a octadecyl C-18 reversed phase column (Symmetry C-18, 250mm x 4.6mm , 5µ) using acetonitrile:phosphate buffer at pH 6.5 (70:30 v/v) as mobile phase at a flow rate of 1.0mL/min and temperature of 25°C. The UV detection was carried out at 270nm. The retention time of Chlorthalidone and Telmisartan was found to be 5.48 and 13.38 min. respectively. The method has been validated for Specificity, Linearity, Accuracy, Precision and Robustness. The calibration curve for Chlorthalidone and Telmisartan were linear from the range of 1.25-20.01 µg/mL and 8.0 to 128.4 µg/mL respectively. The mean recoveries obtained for Telmisartan and Chlorthalidone were 100.9% and 99.7% respectively. The developed method was found to be Specific, accurate, Precise, Robust and rapid for the simultaneous estimation of Telmisartan and Chlorthalidone in Telmisartan and Chlorthalidone Tablets 80mg/12.5mg.

Keywords: Telmisartan, Chlorthalidone, RP-HPLC, Simultaneous estimation, Method development and Validation.

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Received 27 July 2014, Accepted 13 August 2014

Please cite this article in press as: Mukunthakumar N *et al*., Simultaneous Estimation of Telmisartan and Chlorthalidone in Tablet Dosage Form by Using Reversed Phase High Performance Liquid Chromatographic Method . American Journal of PharmTech Research 2014.

INTRODUCTION

Telmisartan (TEL) is an Angiotensin II receptor antagonist used an Antihypertensive drug [1-7]. chemically it is 4′-[[4-methyl-6-(1-methyl-2- benzimidazolyl)-2-propyl-1-benzimidazolyl]methyl]-2- biphenylcarboxylic acid (Figure.1). It is official in Indian Pharmacopoeia (IP), British Pharmacopoeia (BP) and U.S. Pharmacopoeia (USP). It is estimated by Liquid Chromatography as per IP and Potentiometric titration as per BP and USP [5- 7]. Literature review reveals that HPLC [8-12], UV[13-15] spectrophotometric and HPTLC[16-22]methods has been reported for estimation of TEL in pharmaceutical dosage forms. Chlorthalidone (CHL) is chemically (RS)-2-chloro-5-(1-hydroxy-3oxoisoindolin-l-yl)benzenesulphonamide (Figure.2). It is a diuretic drug used to treat hypertension[1-7]. It is official in IP, BP and USP and estimated by potentiometric titration as per IP and Liquid Chromatography as per BP and USP[5-7]. Literature review also reveals that HPLC [23-26], UV [27] spectrophotometric methods has been reported for the estimation of CHL in pharmaceutical dosage forms. Literature survey reveals that HPTLC [28] and UV [29] methods have been reported for the simultaneous determination of TEL and CHL in pharmaceutical dosage forms However, so far, no method was reported for the simultaneous determination of TEL and CHL in Pharmaceutical dosage form. The present developed HPLC method is simple, precise and accurate for simultaneous determination of both drugs in their Pharmaceutical Dosage forms as per International Conference on Harmonization (ICH) guidelines [30].

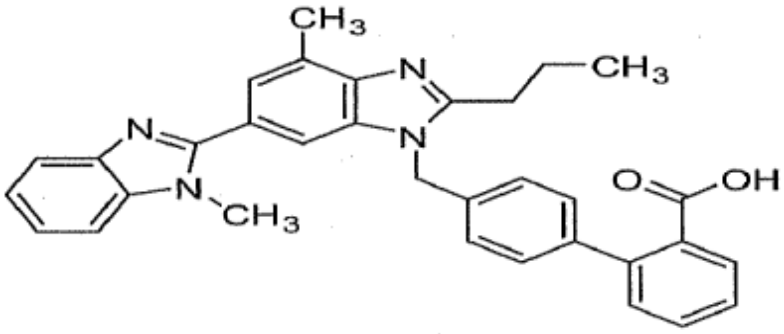

Figure. 1: Structure of Telmisartan (TEL)

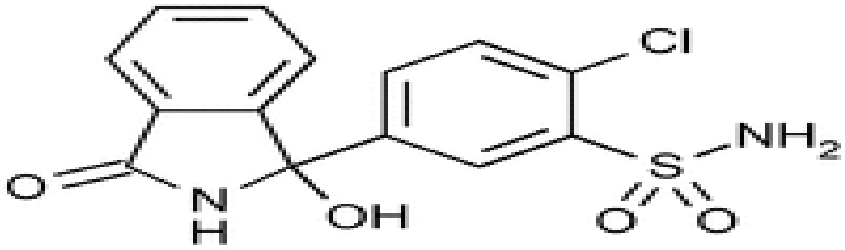

Figure. 2: Structure of Chlorthalidone (CHL)

MATERIALS AND METHODS

Chemicals and Reagents

Drug substances, working standards of Telmisartan, Chlorthalidone and Telmisartan and Chlorthalidone Tablets 80mg/12.5mg kindly sponsored by Aurobindo pharma limited, Hyderabad, India. All the chemicals and reagents sodium hydroxide, hydrochloric acid, disodium hydrogen orthophosphate dihydrate, hydrogen peroxide (30 %) and Orthophosphoric acid (88%) were used of Analytical grade. HPLC grade Methanol, Acetonitrile (Merck) was used. Milli-Q water was used in mobile phase and diluents preparation.

Instruments

Integrated HPLC system, Shimadzu Prominence with SPD-M20A PDA detector and LC Solution Software was used for method development and method validation. This system comprised of a quaternary gradient pump, auto sampler, column oven and a photodiode array detector. PC installed Chromeleon software was used to record and integrates the chromatograms. The analysis was carried out at ambient temperature. Photostability studies were performed in a photostability chamber, from Thermolab (India).

Method Development and Chromatographic Conditions

A variety of mobile phases were investigated in the development of a stability-indicating LC method for the analysis of Telmisartan and Chlorthalidone Tablets 80mg/12.5mg. The suitability of mobile phase was decided on the basis of selectivity and sensitivity of the assay, stability studies and separation among impurities formed during forced degradation studies. Chromatographic separations were achieved by using Symmetry C-18, 250mm x 4.6mm, 5µ analytical column. The mobile phase is consisting of a mixture of disodium hydrogen orthophosphate dihydrate buffer pH 6.5(pH adjusted by dilute orthophosphoric acid): acetonitrile in the ratio 30:70 *v/v*. The flow rate was maintained at 1.0 mL/min with injection volume of 10µl. The UV detection was made at 270 nm and all analyses were done at column temperature (25 ± 2°C) under isocratic conditions.

Preparation of Solutions

Preparation of Mobile Phase and Diluent

Disodium hydrogen orthophosphate dihydrate buffer was prepared by dissolving 1.78 gms of Na_2HPO_4buffer in 1000 ml of water and by adjusting the pH to 6.5 with dilute ortho phosphoric acid. For mobile phase, mix Buffer (pH6.5): Acetronitril (30 :70v/v) in this ratio and mixture of Water and methanol in 20:80 ratio were finalized as diluent.

Preparation of Standard Solution

Accurately 80mg of Telmisartan, 25 mg of Chlorthalidone standards were weighed and taken in 100 mL and 200 mL volumetric flask respectively. Dissolved by sonication in sufficient quantity of diluent and then diluted up to the mark. Further 5 mL of the above standard stock solution from both were taken in 50 mL volumetric flask and made up to mark with diluent to get a concentration of 80µg/mL and 12.5µg/mL for Telmisartan and Chlorthalidone respectively.

Preparation of sample solution

Weigh and finely powder not less than 10 tablets in a suitable mortar and pestle. Accurately weigh and transfer tablets powder equivalent to one tablet (equivalent 12.5 mg of Chlorthalidone and 80mg Telmisartan) into a 100 mL clean, dry volumetric flask, add about 75 mL of diluent and sonicate for about 30 minutes with intermittent shaking at room temperature. Allow the solution to cool to room temperature and dilute the volume with diluent and mix. Centrifuge a portion of the solution at 5000 rpm for about 5 minutes to get a clear solution. Then transfer 5 mL of clear, supernatant solution into a 50 mL volumetric flask, dilute to the volume with diluent and mix. Filter the solution through a suitable 0.45 µ membrane filter. Standard and sample solutions were injected five and two times respectively to get the chromatograms. Responses obtained were calculated with other important variables taken into consideration.

Analytical Method Validation

The optimized chromatographic conditions were validated for assay of Telmisartan and Chlorthalidone in Telmisartan and Chlorthalidone Tablets 80mg/12.5mg by evaluating specificity-Forced degradation, linearity, precision, accuracy, robustness and system suitability parameters in accordance with the ICH guideline Q2 (R1).

Specificity

Specificity-Blank and Placebo interference

To establish the interference of placebo, study was conducted. Assay was performed on placebo in duplicate equivalent to concentration of test preparation as per proposed method.

Specificity- Forced Degradation Study

Forced degradation studies were performed to provide an indication of the stability indicating property and specificity of the proposed method. Intentional degradation was attempted using acid, base, oxidation and light. Acid degradation studies were carried out by heating 5 mL stock solution of Sample solution containing 800 µg mL−1 of Telmisartan and 125 µg mL−1 of Chlorthalidone along with 1.0mL of 0.1N Hydrochloric acid at 85°C for 30 min. Base degradation studies were carried out by heating 5 mL stock solution of Sample solution containing 800 µg mL−1 of Telmisartan and 125 µg mL−1 of Chlorthalidone along with 1.0mL of 0.1N Sodium hydroxide at

85°C for 30 min. Oxidative degradation was carried out by heating 5 ml stock solution of Sample solution containing 800 µg mL−1 of Telmisartan and 125 µg mL−1 of Chlorthalidone along with 1.0mL of hydrogen peroxide (30%) for 30 min. Photolysis studies were carried out on their dosage form. The sample powder in a petri plate was spread as a thin layer (1 mm) and exposed to light in a photostability chamber. After completion of the degradation treatments, the samples were cooled to room temperature, neutralized (where required), diluted to 50mL with the diluent and injected into the chromatographic system. The degraded samples were analyzed against a control sample.

Linearity

Linearity was studied by plotting a graph of concentration versus response and determining the correlation coefficient, slope and Y-intercept. A series of solutions of Telmisartan and Chlorthalidone standard solutions were prepared in the concentration range of about 8.0µg/mL to 128.4 µg/ mL for Telmisartan and in the concentration range of about 1.25 µg/mL to 20.01 µg/ mL for Chlorthalidone.

Method Precision and Intermediate Precision

The precision of the proposed method was evaluated by carrying out six independent assays of test samples. %RSD of six assay values obtained was calculated. Intermediate precision was carried out by analyzing the samples by a different analyst on another instrument.

Accuracy

The recovery of Telmisartan and Chlorthalidone from spiked placebo was conducted at three different spike levels i.e. 50%, 100% and 150 %. Samples were prepared by mixing placebo with Telmisartan and Chlorthalidone drug substances equivalent to test concentration. Sample solutions were prepared in triplicate for each spike level and recovery (%); RSD (%) were calculated.

Solution Stability

Standard and Sample Solutions were prepared as per proposed method and analyzed initially and at different time intervals by keeping the solutions at Room Temperature (~ 25°C) for 24 hours. % Difference between the areas obtained for Telmisartan and Chlorthalidone at initial and different time interval should not be more than 2.0.

Robustness

The robustness was studied by evaluating the effect of small but deliberate variations in the chromatographic conditions. The conditions studied were flow rate (altered by ±0.1 mL min−1), wavelength (altered by ±5 nm), variation in mobile phase composition (±0.2% absolute), Column Oven temperature (±5°C) and pH of buffer in mobile phase (altered by ± 0.2), standard solution

was prepared and injected into HPLC system. The system suitability parameters were evaluated for each deliberate variation.

System suitability

System Suitability testing is an integral part of liquid chromatographic method validation performed to check and ensure on-going performance of a chromatographic system. The System Suitability was estimated by five replicate injections standard solution at 100% of test concentration. The column efficiency as determined from Telmisartan and Chlorthalidone peaks is not less than 2000 USP plate count; the USP Tailing for the same peaks is not more than 2.0. RSD for corresponding peak areas of five replicate injections of the standard solution should not be more than 2.0%.

RESULTS AND DISCUSSION

HPLC Method Development

The maximum absorption wavelength of the reference drug solutions and of the forcefully degraded drug solution was found to be 270 nm and selected as detection wavelength for LC analysis. The main objective of this chromatographic method was separation of degraded impurities from all both drugs. Forced degradation study revealed a critical separation of closely eluting impurity formed from the Telmisartan and Chlorthalidone peaks. Symmetry C-18, 250mm x 4.6mm, 5µ analytical column helped in resolving all peaks as the column had carbon loading approx 11% against conventional ODS. This effect was observed by using the mobile phase disodium hydrogen orthophosphate dihydrate buffer pH 6.5: acetonitrile in the ratio 30:70 *v/v*.

Analytical Method Validation

The assay test method is validated for Specificity, Linearity, Precision, Accuracy (Recovery), Stability of Analytical Solution and Robustness and was found to be meeting the predetermined acceptance criteria.

Specificity

Specificity-Blank and Placebo interference

From the chromatograms of Blank and Placebo solutions showed no peaks at the retention time of Telmisartan and Chlorthalidone peaks. This indicates that the excipients used in the formulation do not interfere in estimation of Telmisartan and Chlorthalidone in Telmisartan and Chlorthalidone Tablets. The chromatogram of blank, placebo, and standard using the proposed method is shown in Figure 3, Figure 4 and Figure 5.

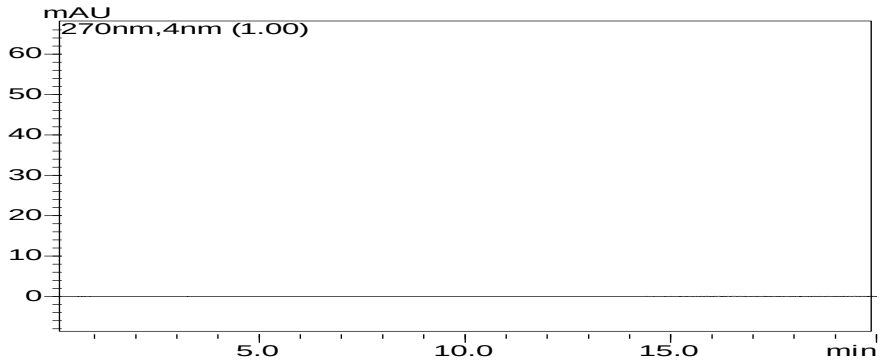

Figure 3: Blank Chromatogram

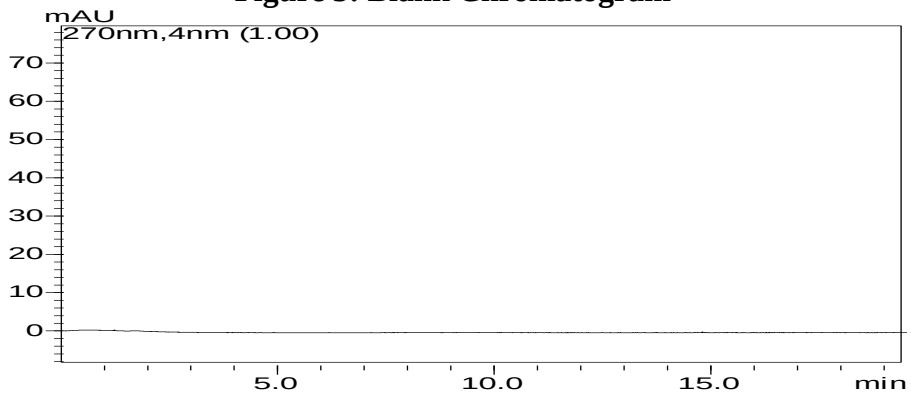

Figure 4: Placebo Chromatogram

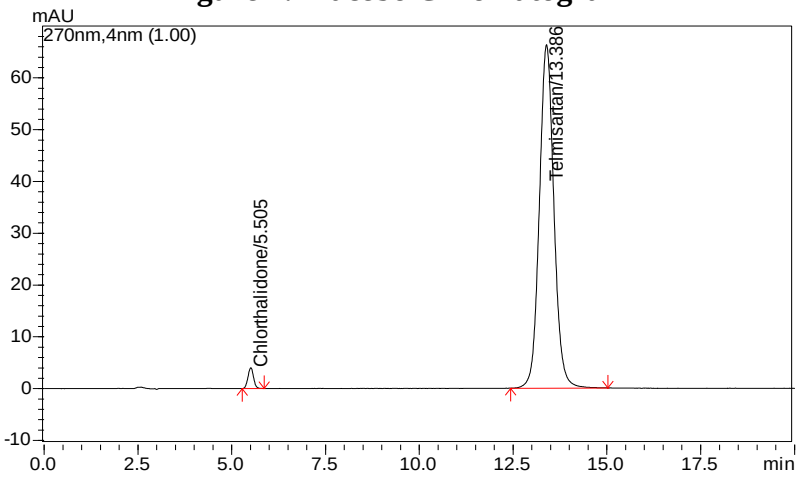

Figure 5: Standard Chromatogram

Specificity- Forced Degradation Study

From the results of various stress conditions employed to degrade Telmisartan and Chlorthalidone Tablets indicates that the drug product is susceptible to degradation under Acidic, Oxidative and Photolytic Conditions, while, it is found stable to Alkaline condition employed. The percent degradation shown by Telmisartan and Chlorthalidone at each stress condition given in Table 1. The chromatograms were extracted for Peak purity and demonstrated as in Figure. 6a, 6b, 6c, 6d and 6e

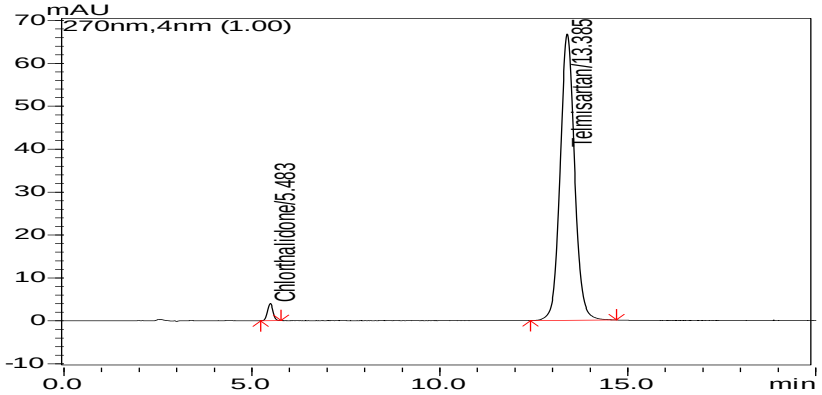

Figure 6a: Control Sample Chromatogram

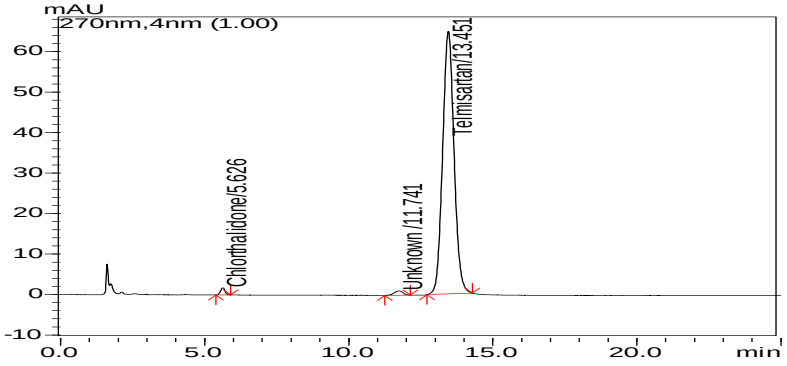

Figure 6b: Acid degradation Sample Chromatogram

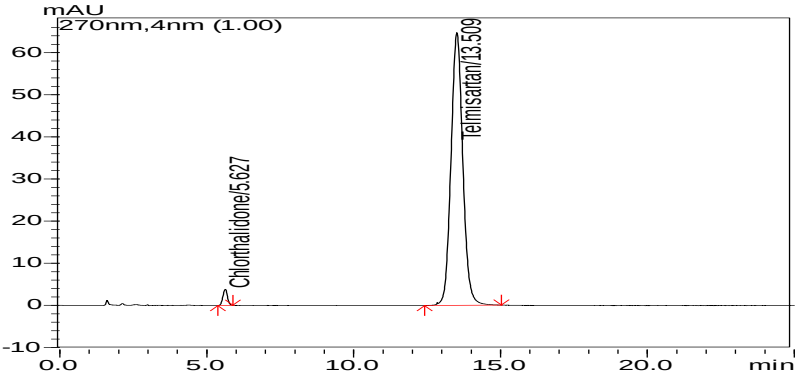

Figure 6c: Base degradation Sample Chromatogram

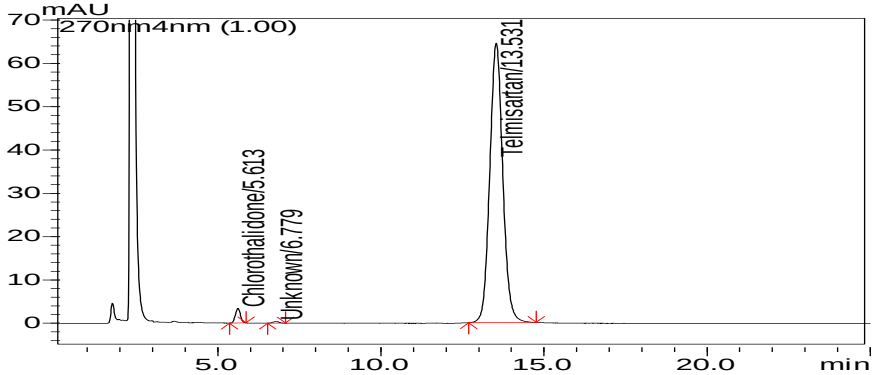

Figure 6d: Peroxide degradation Sample Chromatogram

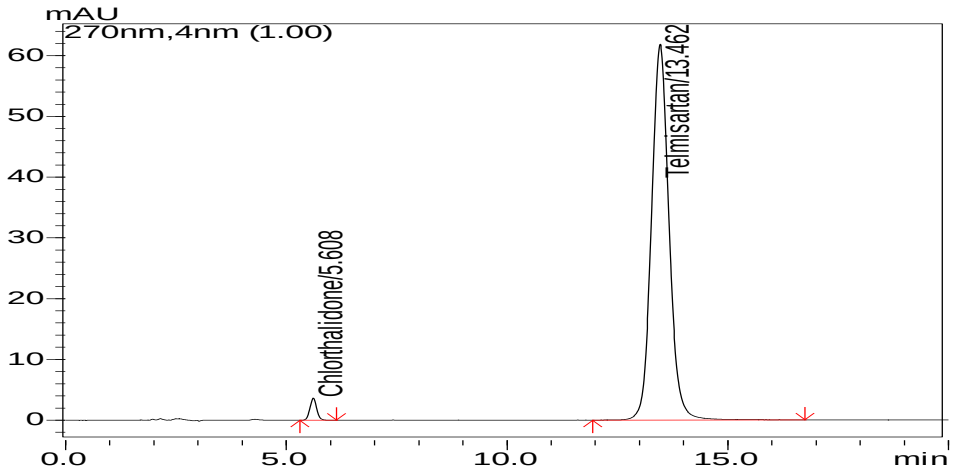

Figure 6e: Photolytic degradation Sample Chromatogram

Table 1. Summary of Forced degradation study

Degradation Mechanism	Content in mg/unit		% Labeled amount		% Degradation	
	Telmisartan	Chlorthalidone	Telmisartan	Chlorthalidone	Telmisartan	Chlorthalidone
Undegraded Sample	79.68	12.37	99.6	99.0	-	-
Acid degradation (0.1N HCl /85°C/30min)	79.79	5.69	99.7	45.5	Nil	54.0
Base degradation (0.1N NaOH /85°C/30min)	80.89	12.40	101.1	99.2	Nil	Nil
Peroxide degradation (30% H_2O_2/85°C/30min)	76.76	10.98	95.9	87.9	3.7	11.2
Photolytic degradation (10K Lux / 120 Hours)	76.42	12.00	95.5	96.0	4.1	3.0

Linearity

Calibration curve obtained by the least square regression analysis between peak area and concentration showed linear relationship with a correlation coefficient of greater than 0.999 over the calibration ranges tested for both the actives. The results show an excellent correlation obtained between peak area and concentration of Telmisartan and Chlorthalidone. Linearity results obtained are presented in Table 2 and Linearity graph of Telmisartan and Chlorthalidone and are shown in Figure 7 and Figure 8.

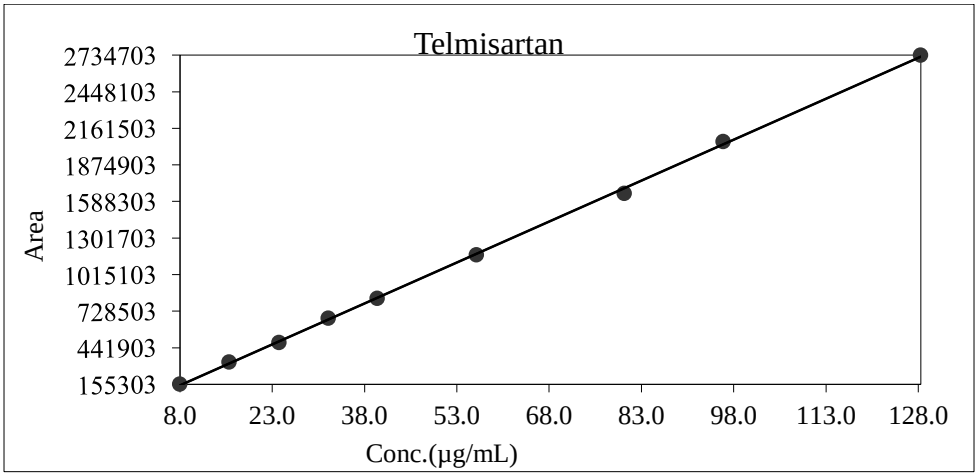

Figure 7: Linearity Graph of Telmisartan

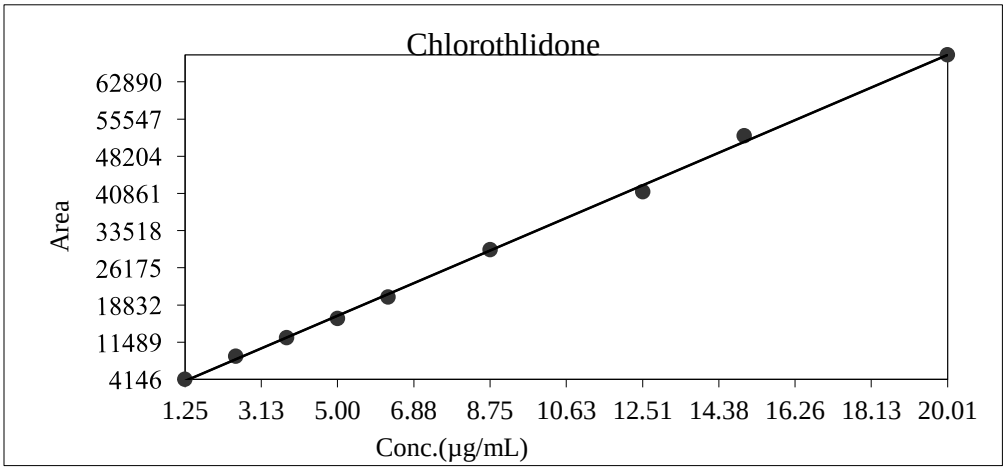

Figure 8: Linearity Graph of Chlorthalidone

Table 2. Linearity Results for Telmisartan and Chlorthalidone

% Level	Telmisartan		Chlorthalidone	
	Concentration (µg/mL)	Response	Concentration (µg/mL)	Response
10% Linearity Solution	8.0	155303	1.25	4146
20% Linearity Solution	16.0	330365	2.50	8730
30% Linearity Solution	24.1	482723	3.75	12372
40% Linearity Solution	32.1	673322	5.00	16159
50% Linearity Solution	40.1	828560	6.25	20430
70% Linearity Solution	56.2	1169749	8.76	29787
100% Linearity Solution	80.2	1650662	12.51	41187
120% Linearity Solution	96.3	2057094	15.01	52238
160% Linearity Solution	128.4	2735185	20.01	70233
Statistical Analysis				
Slope	21392		3433	
Intercept	-23879		-477	
%Y-Intercept	-1.4		-1.2	
Correlation Coefficient	0.9997		0.9994	

Method Precision and Intermediate Precision

The average % assays of Telmisartan and Chlorthalidone in tablets were found to be 99.4 and 99.6 respectively. The %RSD found to be 0.3 and 0.7 respectively. The average results between method precision and intermediate precision has also shown less than 1.0% RSD. The results were given in Table 3.

Table 3. Method Precision and Intermediate Precision Results for Telmisartan and Chlorthalidone

Sr. No	% Assay - Telmisartan		%Assay - Chlorthalidone	
	Method Precision	Intermediate Precision	Method Precision	Intermediate Precision
1	99.8	99.9	99.2	100.5
2	99.1	100.2	99.2	99.3
3	99.5	99.6	99.2	99.9
4	99.4	100.5	99.2	100.2
5	99.6	99.9	100.0	99.9
6	99.1	99.2	100.8	99.8
Statistical Analysis				
Mean	99.4	99.9	99.6	99.9
SD	0.28	0.45	0.67	0.40
%RSD	0.3	0.5	0.7	0.4
95% Confidence Interval (±)	0.3	0.5	0.7	0.4
Overall Statistical Analysis for Method Precision and Intermediate Precision				
Mean	99.7		99.8	
SD	0.43		0.55	
%RSD	0.4		0.6	
95% Confidence Interval (±)	0.3		0.3	

Accuracy

Accuracy was assessed at three different levels including 50%, 100% and 150% of the test concentration level for both components. The observed recovery results were found in the range between 98 to 102%. The recovery results indicated that the test method has an acceptable level of accuracy for the assay of Telmisartan and Chlorthalidone in Telmisartan and Chlorthalidone Tablets 80mg/12.5mg from 50% to 150% test concentration. The results were given in Table 4.

Solution Stability

No significant changes are observed in the area of Telmisartan and Chlorthalidone during solution stability experiment. From the results it can be concluded that the Standard and Sample Solutions are stable upto 24 hours at room temperature (~ 25°C). The results were given in Table 5.

Table 4: Recovery on Synthetic Mixture of Both Drug Substances

Concentration / Sample ID	Telmisartan			Chlorthalidone		
	Amount Added (mg)	Amount Found (mg)	% Recovery	Amount Added (mg)	Amount Found (mg)	% Recovery
50% Level Sample-1	40.0	40.4	101.0	6.25	6.25	100.0
50% Level Sample-2	40.1	40.5	101.0	6.25	6.28	100.5
50% Level Sample-3	40.2	40.5	100.7	6.25	6.20	99.2
100% Level Sample-1	80.1	80.9	101.0	12.50	12.46	99.7
100% Level Sample-2	79.8	80.8	101.3	12.60	12.39	98.3
100% Level Sample-3	80.3	80.9	100.7	12.50	12.50	100.0
150% Level Sample-1	120.4	121.5	100.9	18.60	18.67	100.4
150% Level Sample-2	120.0	121.1	100.9	18.70	18.51	99.0
150% Level Sample-3	120.2	121.4	101.0	18.60	18.62	100.1
Overall Mean			100.9	Overall Mean		99.7
Overall SD			0.18	Overall SD		0.72
Overall %RSD			0.2	Overall %RSD		0.7
95% Confidence Interval (±)			0.1	95% Confidence Interval (±)		0.4

Table 5: Results for Sample Solution Stability

Time	Telmisartan		Chlorthalidone	
	Area	% of Difference	Area	% of Difference
Initial	1895123	-	42536	-
After 1 hour	1889253	0.3	42356	0.4
After 5 hours	1892123	0.2	42458	0.2
After 10 hours	1893125	0.1	42745	0.7
After 15 hours	1896123	0.2	42652	0.2
After 20 hours	1897456	0.1	42556	0.2
After 24 hours	1894526	0.2	42356	0.5

Robustness

Based on the obtained results from the method robustness, in all the cases, the %RSD obtained was less than 1.0. From the above study the proposed method was found to be robust. The results were given in Table 6.

System suitability

The results of System Suitability test, USP Plate Count, USP Tailing and %RSD were found within the acceptable range indicating that the system was suitable for the intended analysis. The results were given in Table 7.

Table 6: Results for Robustness

Parameter	Variation	Telmisartan			Chlorthalidone		
		USP Plate Count	USP Tailing	%RSD	USP Plate Count	USP Tailing	%RSD
STP	-	4322	1.1	0.1	3889	1.1	0.2
Flow Rate	-10%	3793	1.2	0.3	4502	1.0	0.5
	+10%	4304	1.1	0.4	2802	1.2	0.6
Wavelength	-5 nm	4012	1.2	0.2	3785	1.3	0.5
	+5 nm	3985	1.3	0.3	3856	1.4	0.4
Organic in Mobile Phase	-2% absolute	2845	1.1	0.5	4030	1.0	0.6
	+2% absolute	10361	1.1	0.4	3804	1.2	0.7
Column Oven Temperature	-5°C	3944	1.1	0.6	3561	1.0	0.6
	+5°C	4095	1.1	0.5	3877	1.1	0.5
pH of Buffer	-0.2 units	3625	1.3	0.3	3045	1.3	0.4
	+0.2 units	3845	1.4	0.5	3215	1.2	0.3

Table 7: Results for System Suitability

Injection ID	Area	
	Telmisartan	Chlorthalidone
1	1887876	45269
2	1876302	45074
3	1890222	45717
4	1878696	45036
5	1883411	45327
Statistical Analysis		
Mean	1883301	45285
SD	5896	272
%RSD	0.3	0.6
USP Plate Count	4322	3889
USP Tailing	1.1	1.1

CONCLUSION

The stability indicating RP-HPLC assay method was developed and validated for simultaneous estimation of Telmisartan and Chlorthalidone in tablets dosage forms. The method was found to be simple, specific, Precise and Robust and can be applied for the routine and stability analysis for commercially available formulation.

ACKNOWLEDGEMENTS

The author wish to thank the management of Aurobindo Pharma Limited (A Division of APL Research centre, Bachupally, Hyderabad, India) for supporting this work and also thankful to

entire team of Vinayaka Missions University and Konde Abbulu for their encouragement and support during the work.

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