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RP-HPLC Method Development and Validation of Telmisartan and Hydrochlorothiazide in Combination Dosage Form (Tablets)

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ABSTRACT

A simple, accurate, precise and fast reverse phase, gradient RP-HPLC method was developed for the separation of telmisartan and hydrochlorothiazide in combination dosage form of Tablets. The method was carried out by using Kromasil, C18, 4.6 x 150mm, 5 µm enhanced polar selectivity column and mobile phase comprised of potassium dihydrogen phosphate buffer pH adjusted to 3.2 ± 0.5 with orthophosphoric acid and acetonitrile, and degassed under ultrasonication. The flow rate was 1.5 mL/min and the effluent was monitored at 225nm. The retention time of hydrochlorothiazide and telmisartan were 2.7 ± 0.5 and 7.3 ± 0.5 respectively. The method was validated as per ICH guideline. The proposed method is suitable for simultaneous determination of telmisartan and hydrochlorothiazide in pharmaceutical dosage form.

Keywords: Telmisartan, Hydrochlorothiazide, RP-HPLC, Kromasil, ICH Guideline.

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INTRODUCTION

Telmisartan is a non peptide molecule, is chemically 4'-[(1,4-dimethyl-2'-propyl [2,6'-1H-benzimidazol]-1'-yl) methyl]-[1,1'-biphenyl]-2-carboxylic acid [Figure 1], and hydrochlorothiazide is chemically 6-Chloro-3, 4-dihydro-2H-1,2,4-benzothiadiazine-7sulfonamide1,1-dioxide [Figure 2]. Telmisartan is an angiotensin II receptor antagonist that is highly selective for type 1 angiotensin II receptor for the treatment of essential hypertension usually given in combination with hydrochlorothiazide. Angiotensin II is the principle pressor agent of the rennin angiotensin system, with effects that include vasoconstriction, stimulation of synthesis and release of aldosterone, cardiac stimulation, and renal reabsorbtion of sodium. Hydrochlorothiazide is a thiazide diuretic. Thiazide affects the renal tubular mechanisms of electrolytes reabsorbtion, directly increasing excretion of sodiumsalt and chloride in approximately equivalent amount. The combination is useful in the treatment of mild to moderate hypertension, well tolerated with a lower incidence of cough than ACE inhibitors.[1,2].

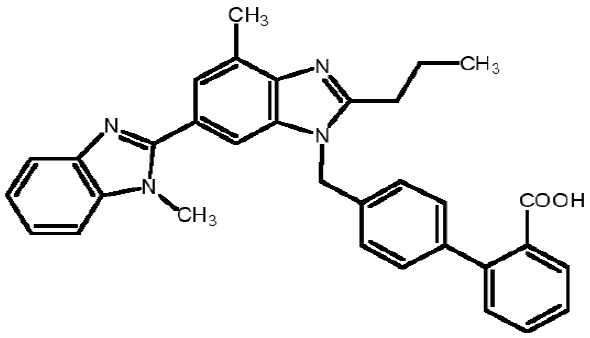

Figure-1: Telmisartan

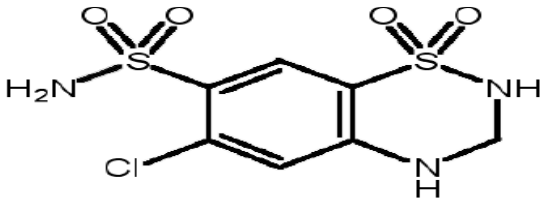

Figure-2: Hydrochlorothiazide

The literature survey reveals that several methods were reported for the individual estimation of telmisartan and hydrochlorothiazide. The methods for telmisartan in combination with other drugs in plasma, serum, and in tablets by high-performance liquid chromatography (HPLC) and is for the estimation of hydrochlorothiazide in combination with other drugs in plasma, serum, and in tablets by HPLC[3-16]. However, recently three methods were published for the simultaneous determination of the telmisartan and hydrochlorothiazide in combined pharmaceutical-dosage form by high-performance thin-layer chromatography (HPTLC) and HPLC[17-19].

In the present research study, attempts were made to develop a rapid, economical, precise, and accurate method for the simultaneous estimation of the active ingredients of combination dosage form. A good separation of the analytes was achieved by using a mobile phase containing

Potassium dihydrogen phosphate buffer and acetonitrile as mobile phase. The proposed method is rapid, less expensive, and is successfully applied for the simultaneous determination of telmisartan and hydrochlorothiazide in combined-dosage form (tablets) available in the commercial market. It can be used for the quality control of formulation products.

MATERIAL AND METHODS

Material

Telmisartan and hydrochlorothiazide standards were obtained from Ranbaxy laboratories Ltd. (Gurgaon, India); Phosphate buffer, and acetonitrile (HPLC grade) were obtained from Qualigens Fine Chemicals (Mumbai, India). The 0.45 µm nylon filter was obtained from Millipore India Pvt. Ltd. (Banglore, India). The (Telista) tablets of the combination of telmisartan and hydrochlorothiazide were purchased from Lupin pharmaceutical Ltd. (Mumbai, India). Double distilled water (Milli Q) was used throughout the experiment. Other chemicals used were analytical or HPLC grade. Water and Alliance 2690 series HPLC, Perkin and Elmer UV and mettler and Toledo analytical balance were used for this research work.

Methods

Chromatographic conditions

The Telmisartan and Hydrochlorothiazide soluble in organic solvents, hence, reversed phase or ion- pair chromatography method may be used.

Selection of Stationary Phase

On the basis of reversed phase HPLC mode and number of carbon present in molecule (analyte) C_{18} column of following configuration was selected for further study.

C18, 150 x 4.6 mm, particle size 5 µm.

Selection of Mobile Phase

Both the drugs are freely soluble in Phosphate buffer and Acetronitrile mixture. Hence buffer and acetonitrile in gradient profile was selected for initial separation.

Preparation of Buffer

Dissolve 3.5g of Potassium dihydrogen phosphate in 1000 ml water and adjust the optimum pH.

Experimental

Selection of Detector and Detection Wavelength

PDA detector was selected, as it is reliable and easy to set at the correct wavelength. From the UV scan of telmisartan and hydrochlorothiazide (Figure-3&4), spectrum 225nm was selected as a wavelength of measurement.

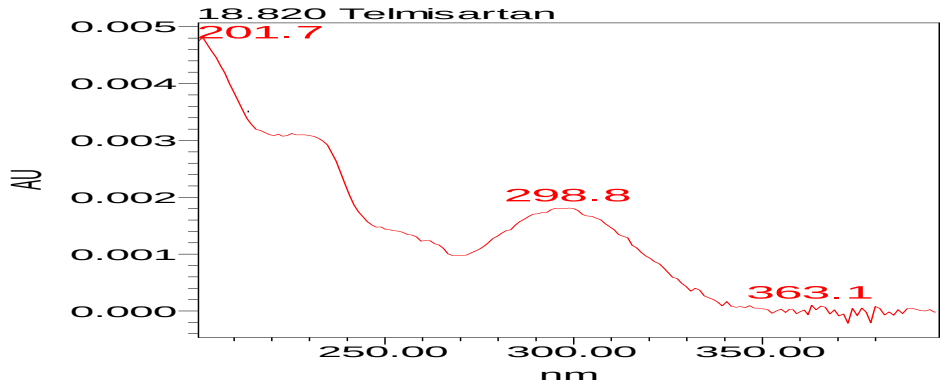

Figure-3: UV Spectra of Telmisartan

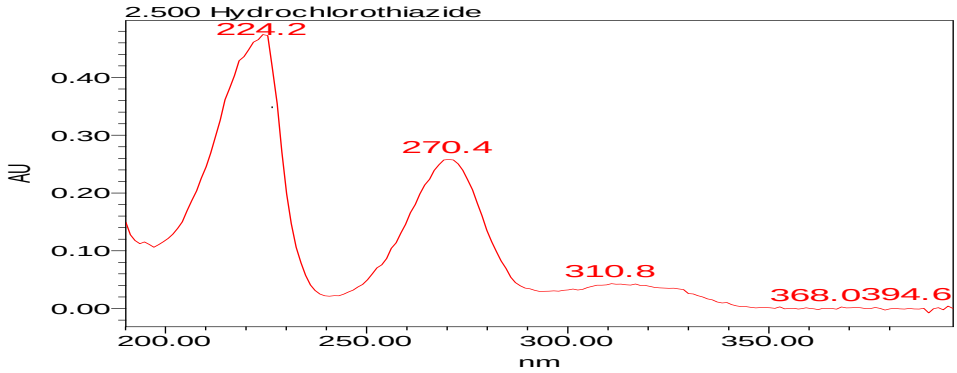

Figure-4: UV Spectra of Hydrochlorothiazide

Trials (For development)

Optimization of HPLC Parameters

Optimization in HPLC is the process of finding a set of conditions that adequately separate and enable the quantification of the analytes from the endogenous material with acceptable accuracy, precision, sensitivity, specificity, cost, ease and speed. Development was performed by the following chromatographic conditions:

Estimation of Best Chromatographic Condition:

S.No.	Mobile Phase Strength	pH	Column (C18, 150 mm × 4.6 mm,5µm)	Flow Rate (ml/min)	Wave Length (in nm)	R_t of Hydrochlorothiazide (in min.)	R_t of Telmisartan (in min.)
1	Gradient profile	3.2	ACE C18	1.5	225	2.5	8.7
2	Gradient profile	3.2	Hypersil-gold C18	1.5	225	2.9	11.3
3	Gradient profile	3.2	Kromasil C18	1.5	225	2.7	7.3

Mobile phase Gradient	Time (min)	Buffer pH 3.2 (%)	Acetonitrile (%)
	0	80	20

3	70	30
4	45	55
9	50	50
10	80	20
14	80	20

Trial-1

Optimization of Mobile Phase pH - Mobile Phase 0.025M Phosphate buffer (KH_2PO_4) pH adjusted to 3.2 with orthophosphoric Acid: Acetonitrile in the gradient profile. Chromatographic was set as per following parameters.

Mobile Phase Strength (Buffer : ACN)	pH	Column (C18, 150 mm ×4.6 mm, 5 µm)	Flow Rate (ml/min)	Wave Length (in	R_t of Hydrochlorothiazide (in min.)	R_t of Telmisartan (in min.)
Gradient profile	3.2	ACE-C18	1.5	225	2.585	8.764

Observation: Peak shape of Telmisartan was not proper [Figure-5]

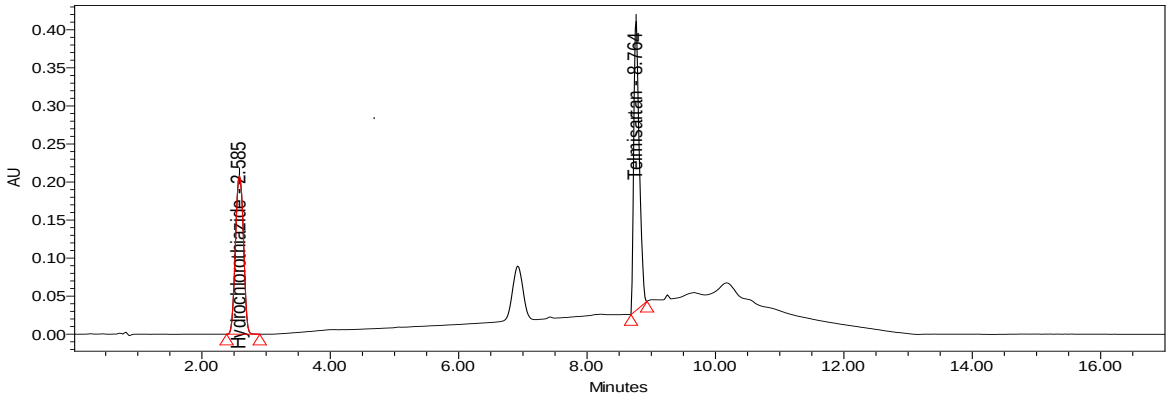

Figure-5: Chomatogram of Trial-1

Trial-2

Optimization of Mobile Phase pH - Mobile Phase 0.025M Phosphate buffer (KH_2PO_4) pH adjusted to 3.2 with Orthophosphoric Acid: Acetonitrile in the gradient profile. Chromatographic was set as per following parameters.

Mobile Phase Strength (Buffer:ACN)	pH	Column (C18, 150 mm ×4.6 mm, 5 µm)	Flow Rate (ml/min)	Wave Length (in nm)	R_t of Hydrochlorothiazide (in min.)	R_t of Telmisartan (in min.)
Gradient profile	3.2	Hypersil-gold C18	1.5	225	2.996	11.306

Observation: Retention time of Telmisartan was so long and fronting was observed. Peak shape of Telmisartan was also not proper [Figure-6]

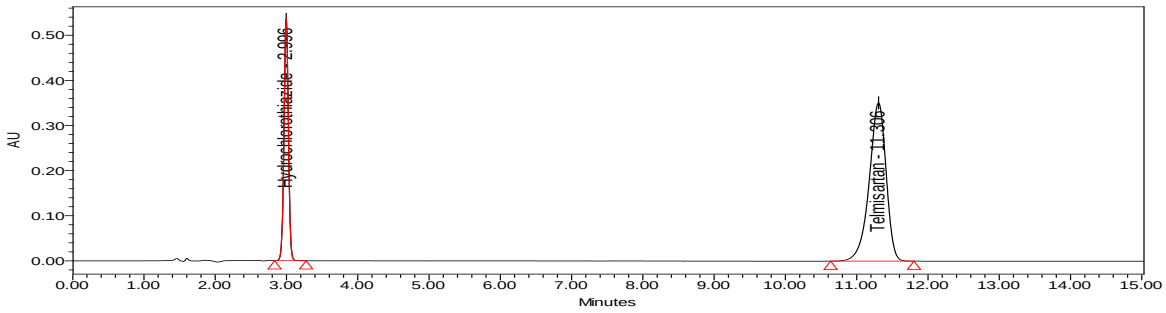

Figure-6: Chomatogram of Trial-2

Trial-3

Optimization of Mobile Phase pH - Mobile Phase 0.025M Phosphate buffer (KH_2PO_4) pH adjusted to 3.2 with 5% Orthophosphoric Acid: Acetonitrile in the gradient profile. . Chromatographic was set as per following parameters.

Mobile Phase Strength (Buffer : ACN)	**Buffer pH**	**Column (C18, 150 mm × 4.6 mm, 5 µm)**	**Flow Rate (ml/min)**	**Wave Length (in nm)**	**R_t of Hydrochlorothiazide (in min.)**	**R_t of Telmisartan (in min.)**
Gradient profile	3.2	Kromasil C-18	1.5	225	2.779	7.371

Observation: Peak shape and retention time was found satisfactory, resolution was also good. [Figure-7]

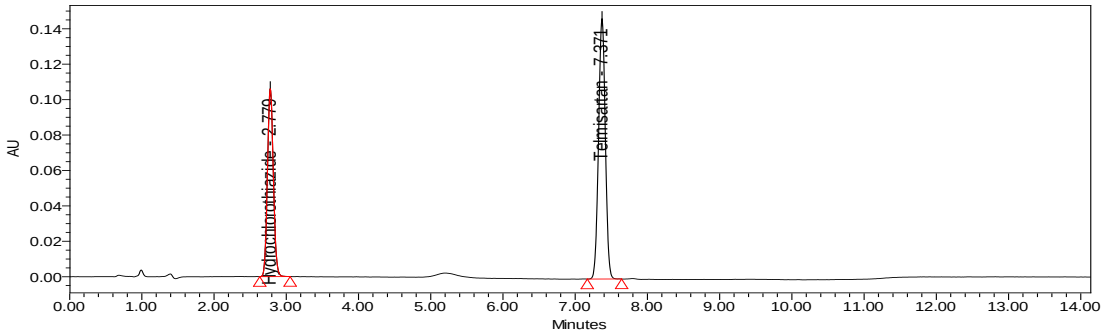

Figure-7: Chomatogram of Trial-3

Observation and conclusion from the trials for final chromatographic parameters for assay of telmisartan and hydrochlorothiazide in combined dosage form:

Selection of mobile phase

The mobile phase was selected from the method development for assay of Telmisartan and Hydrochlorothiazide Tablets. A filtered and degassed buffer (pH 3.2 buffer) and Acetonitrile in a Gradient Profile is used for final assay method. On this set area of peak, height of peak and peak shape are good. Separation and resolution are also good.

Preparation of buffer solution

Transfer about 3.5 g of Potassium dihydrogen phosphate to a 1000 ml volumetric flask, adjust pH to 3.2 ± 0.05 with ortho phosphoric acid solution.

Selection of column

Initially trials were taken on ACE C-18 and Hypersil GOLD, C18, 4.6 x 150mm, 5 µm but the peak shape was not proper, Finally Kromasil, C18, 4.6 x 150mm, 5 µm –column was used keeping all the other parameters same which gave satisfactory peak shape and theoretical plates results and good separation and resolution.

Selection of wavelength

The photodiode array detector was used in scan mode with a scan mode of 200-400nm. The peak homogeneity was expressed in terms of peak purity and was obtained directly from the spectral analysis report obtained using above mentioned software. According to the scan result, it was observed that Hydrochlorothiazide has maxima at 224 nm and Telmisartan at 227 nm. But decided final wavelength selection was 225 nm for good response at 225 nm for both Hydrochlorothiazide and Telmisartan.

Selection of diluent

The diluent selected was mixture of Water and Acetonitrile in the ratio of 50:50. Mix and degas.

Assay concentration

Response of Telmisartan and Hydrochlorothiazide standards preparation and sample preparation was found well within limit at 160 ppm and 25 ppm, respectively.

Final Method for Assay of Telmisartan and Hydrochlorothiazide Tablets

The test sample was analyzed for the contents of Hydrochlorothiazide and Telmisartan in the formulation in the HPLC using the following chromatographic condition.

Chromatographic parameters

Column	Kromasil C18, 150mm × 4.6mm, 5µm
Column temperature	30°C
Flow rate	1.5 ml/min
Wavelength	225 nm
Injection volume	10 µl
Sample compartment temperature	Ambient
Run time	14 minutes

Standard preparation

Standard solution 1:

Weigh accurately about 40 mg of Telmisartan working standard in 25 mL volumetric flask. Add 15 mL of Diluent and sonicated to dissolve completely. Dilute to volume with diluent and mix.

Standard solution 2:

Weigh accurately about 25 mg of Hydrochlorothiazide working standard in 100 mL volumetric flask. Add about 50 mL of Diluent and sonicate to dissolve completely. Dilute to volume with diluent and mix.

Final Standard Solution:

Dilute 5 mL of Telmisartan standard stock solution and 5 mL of Hydrochlorothiazide standard stock solution to 50 mL with diluent to obtain final concentration of Telmisartan equivalent to about 160 µg/mL and Hydrochlorothiazide equivalent to about 25 µg/mL. Filter through 0.45µm nylon filter with discarding first few mL.

Sample Preparation

Transfer 10 intact tablets in 1000 mL volumetric flask. Add about 700 mL of diluent. Sonicate the flask for about 25 min with intermittent shaking. (Tablets disintegrate completely within 10 min). Dilute to volume with diluent and mix. Allow to stand the solution for about 5 min to settle the excipents. Dilute 5 mL of supernant solution to 50 mL with diluent to obtain the concentration of Telmisartan equivalent to about 160 µg/mL and of Hydrochlorothiazide to about 25 µg/mL. and mix. Filter through 0.45µm nylon filter with discarding first few mL.

% Assay of Hydrochlorothiazide and Telmisartan tablets was found 99.27% for Hydrochlorothiazide and 99.91% for Telmisartan.

RESULTS AND DISCUSSION

Final methods were validated as per ICH guideline by the following parameters:

Specificity:

Specificity of the method was evaluated by injecting the blank, placebo and the sample solution prepared as per the proposed method and injected into HPLC system to check for the interference if any at the retention time of Hydrochlorothiazide and Telmisartan peak. There was no interference from the blank and from the placebo at the retention time of Hydrochlorothiazide and Telmisartan peak [Figure-8-11].

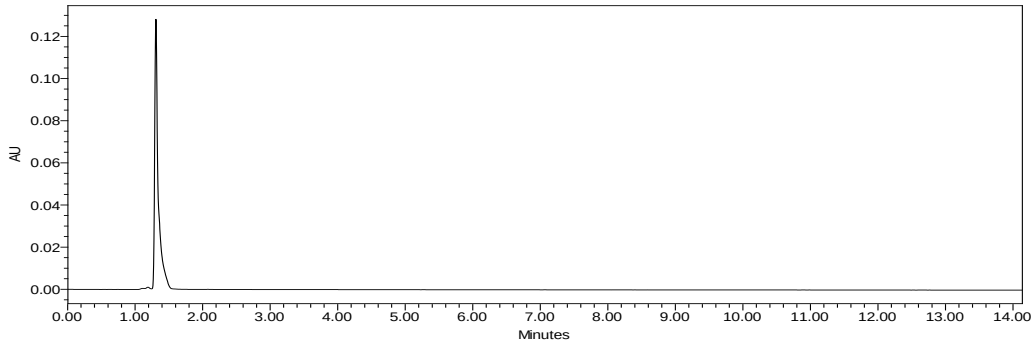

Figure-8: Chromatogram for Blank

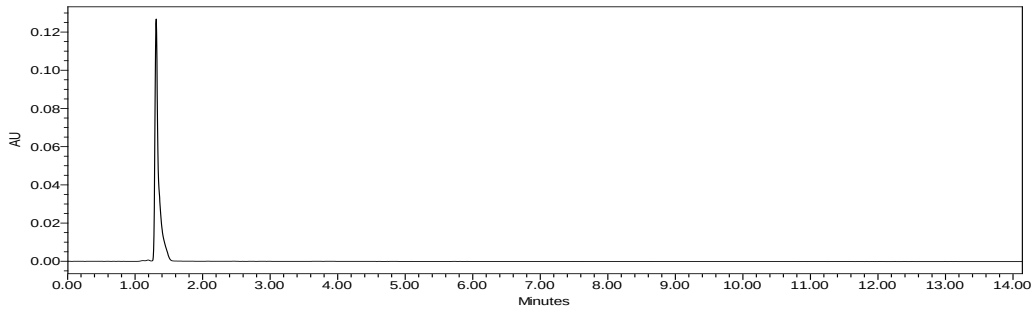

Figure-9: Chromatogram for Placebo

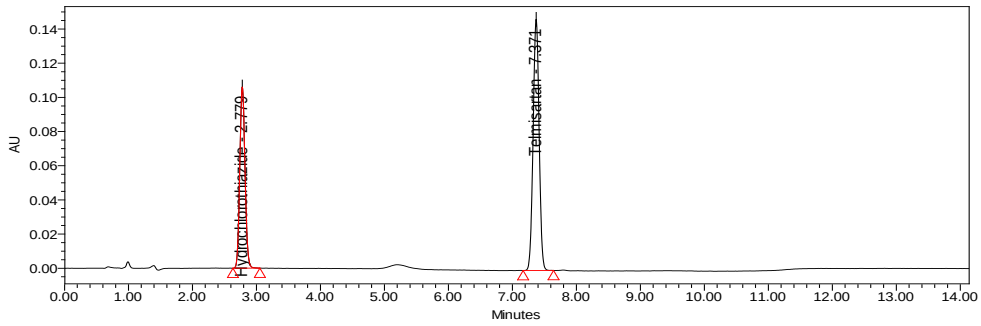

Figure-10: Hydrochlorothiazide and Telmisartan Standard

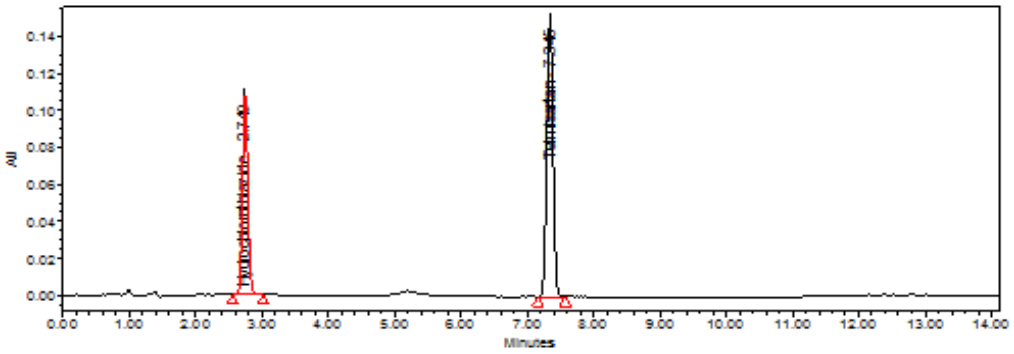

Figure-11: Hydrochlorothiazide and Telmisartan Sample

Acceptance criteria: No interference at the Retention time of Hydrochlorothiazide and Telmisartan.

Linearity

The linearity of response for Hydrochlorothiazide and Telmisartan was determined. The results shown in Table- 1 and its graphical representation in Figure-12 (Hydrochlorothiazide), & Figure-13 (Telmisartan) indicates that the response is linear over the specified range.

Table-1: Linearity of Response

S.No.	Conc. (%)	Area counts Of Hydrochlorothiazide	Area counts Of Telmisartan
1	40	247808	369951
2	60	373413	557927
3	80	496617	743903
4	100	622022	926879
5	120	757426	1105854
6	140	869430	1301830
Slope		12530	18531
Intercept		12256	18577
Correlation Coefficient(R^2)		0.999	0.999

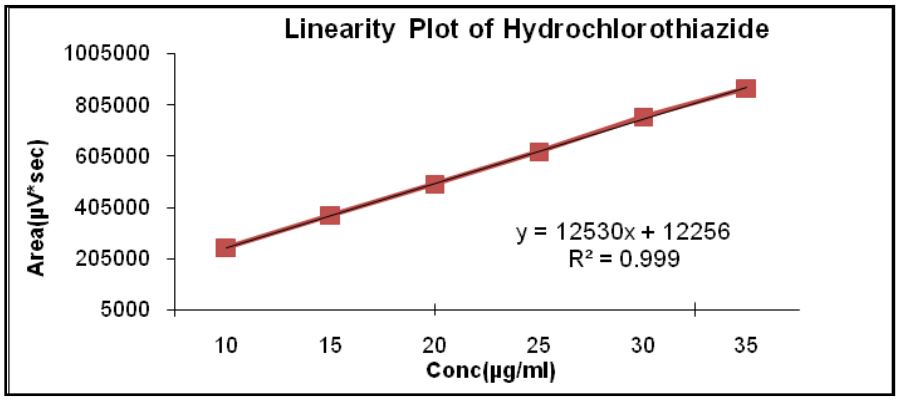

Figure-12: Linearity plot of Hydrochlorothiazide

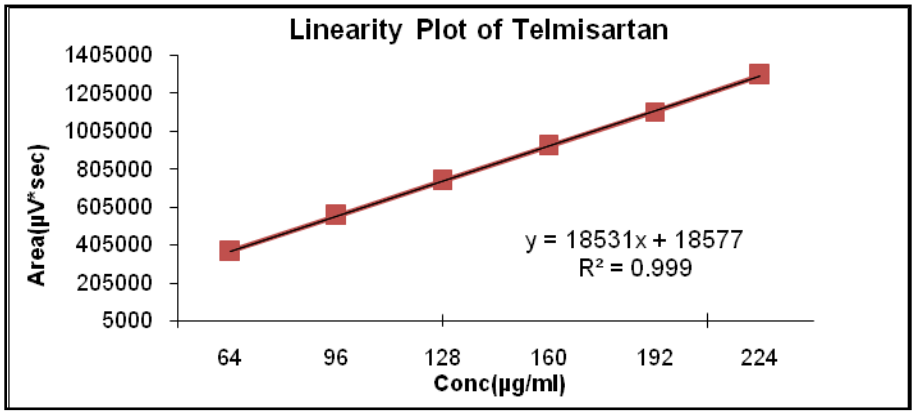

Figure-13: Linearity plot of Telmisartan

Acceptance Criteria: Correlation Coefficient should NLT 0.99.

Precision

System Precision

The system precision was evaluated by measuring the peak responses of Hydrochlorothiazide and Telmisartan for six replicate injections of standard solution, prepared as the proposed method [Table-3]

Acceptance criteria: % RSD NMT (Not more than) 2.0

Table-2: System Precision

S.No.	Area counts of Hydrochlorothiazide	Area counts of Telmisartan
1	624601	929880
2	623954	922183
3	622164	927709
4	622716	927701
5	621676	928362
6	621676	929167
Mean	622798	927500
SD	1226	2740
%RSD	0.20	0.30

Conclusion: The results shown in the Table-2 indicate that the precision of the system was within the limit.

Method Precision

The method precision was determined by preparing a sample solution of single batch Hydrochlorothiazide and Telmisartan Tablets six times and analyzing as per the proposed method.

Acceptance criteria: % RSD NMT (Not more than) 2.0

Table-3: Method Precision

S.No.	% Assay of Hydrochlorothiazide	% Assay of Telmisartan
1	98.54	100.09
2	99.18	100.45
3	98.64	100.02
4	98.78	99.99
5	99.13	100.17
6	98.24	99.43
Mean	98.75	100.03
SD	0.360	0.335
%RSD	0.36	0.33

Conclusion: The results are shown in Table- 3 indicate that the proposed method was precise.

Ruggedness

The ruggedness of the proposed method determined by analyzing the same batch of

Hydrochlorothiazide and Telmisartan Tablets by two different analysts using two different instruments, different columns on different days. The overall mean, standard deviation and % RSD of the assay values are shown in Table-4 and 5.

Acceptance criteria: Over all % RSD NMT 2.0

Table-4: Ruggedness for Hydrochlorothiazide

S.No.	% Assay of Hydrochlorothiazide	
	SET-1	**SET-2**
1	98.54	99.60
2	99.18	98.69
3	98.64	98.48
4	98.78	98.31
5	99.13	98.29
6	98.24	99.26
Mean	98.75	98.61
SD	0.360	0.701
%RSD	0.36	0.71
Over all Mean	98.68	
Over all SD	0.537	
Over all %RSD	0.54	

Table-5: Ruggedness For Telmisartan

S.No.	% Assay Of Telmisartan	
	SET-1	**SET-2**
1	100.09	99.01
2	100.45	100.90
3	100.02	99.83
4	99.99	99.21
5	100.17	100.88
6	99.43	100.87
Mean	100.03	100.12
SD	0.335	0.882
%RSD	0.33	0.88
Over all Mean	100.07	
Over all SD	0.638	
Over all %RSD	0.64	

Conclusion: The analytical method meets the pre established acceptance criteria i.e. 0.54 for Hydrochlorothiazide and 0.64 for Telmisartan, hence the method is precise.

Stability in Analytical Solution:

A sample solution of Hydrochlorothiazide and Telmisartan Tablets was prepared as per the proposed method and analyzed initially and also analyzed at different time intervals by keeping the solution at room temperature [Table-6 and 7]

Acceptance criteria: Cumulative % RSD NMT 2.0

Table-6: Stability in Analytical Solution (Hydrochlorothiazide)

Time (hours)	Area count of Hydrochlorothiazide	Cumulative % RSD
Initial	622015	--
6	622234	0.04
12	622345	0.05
18	622501	0.08
24	622600	0.09

Table-7: Stability in Analytical Solution [Telmisartan]

Time (hours)	Area count of Telmisartan	Cumulative % RSD
Initial	927548	-
6	928104	0.06
12	928890	0.14
18	929098	0.17
24	929290	0.19

Conclusion: The cumulative % RSD for the area counts of Hydrochlorothiazide and Telmisartan shown in Table-6 and 7 indicates that solution was stable up to at least 24 hours.

Accuracy (Recovery)

Known amounts of Hydrochlorothiazide and Telmisartan were spiked to placebo at 80%, 100% and 120% of specification in triplicate and analyzed as per the proposed method to determine the accuracy of the method. Percentage recovery was calculated from the amount found and amount added. The results are shown in Table-8 and 9. The percentage recovery is within the acceptance criterion, which indicates the accuracy of the method.

Acceptance criteria: % Recovery should be between 98 and 102.

Table-8: Recovery Study: Hydrochlorothiazide

Recovery Level	Amount of HCTZ Added in mg	Area.1	Area.2	Mean Area.	Amount of HCTZ Found in mg	% Recovery
80	100.25	500348	503977	502163	100.77	100.52
80	101.59	506180	506842	506511	101.64	100.05
80	100.07	498845	497676	498261	99.99	99.92
100	125.14	617824	624304	621064	124.63	99.59
100	125.21	624519	630693	627606	125.94	100.58
100	125.32	632331	625650	628991	126.22	100.72
120	150.46	759658	753284	756471	151.80	100.89
120	150.01	742932	745205	744069	149.31	99.53
120	150.05	754789	752478	753634	151.23	100.79

Table-9: Recovery Study: Telmisartan

Recovery Level	Amount of Telmisartan Added in mg	Area.1	Area.2	Mean Area.	Amount of Telmisartan Found in mg	% Recovery
80	320.84	742458	738974	740716	322.31	100.96
80	320.01	731458	732478	731968	318.50	100.03
80	321.42	733478	737894	735686	320.12	100.10
100	401.69	916458	917458	916958	399.00	99.83
100	400.68	914789	919758	917274	399.13	100.11
100	400.96	926478	924478	925478	402.70	100.94
120	481.88	1101454	1092454	1096954	477.32	99.55
120	481.35	1094879	1121454	1108167	482.20	100.68
120	481.22	1114785	1101454	1108120	482.18	100.70

Conclusion: The analytical method satisfy with the pre established acceptance criteria for Recovery study, hence the method was accurate.

Robustness

The robustness of the method was evaluated by deliberately varying the chromatographic conditions viz composition of organic phase in mobile phase by ± 2% absolute, flow rate by ± 0.1 ml, column oven temperature by ± 5 °C, and change in wavelength of detection by ± 2 nm. At these changed condition the standard and Test preparation were injected. The system suitability was evaluated in each varied condition. The amount of Hydrochlorothiazide and Telmisartan was calculated from Test preparation in each varied condition. The results were compared with the controlled data (Method Precision data). Results are tabulated in Table-10,11 and Table-12,13 indicates that the method is robust under varied conditions.

Acceptance criteria: Overall % RSD: NMT 2.0

Table-10: Robustness Data: Hydrochlorothiazide

Method Precision data		Set 1	Set 2	Set 3	Set 4	Set 5	Set 6	Set 7	Set 8	Set 9
98.54	99.18	98.55	101.23	101.97	102.56	100.40	100.42	101.10	99.87	99.69
98.64	98.78									
98.13	98.24									
Mean	98.75									
SD	0.360									
RSD %	0.36									
Overall Mean		98.72	99.11	99.21	99.30	98.99	98.99	99.09	98.91	98.89
Overall SD		0.337	0.993	1.260	1.476	0.704	0.711	0.946	0.535	0.483
Overall RSD %		0.34	1.00	1.27	1.49	0.71	0.72	0.95	0.54	0.49

Table-11: Robustness Data: Telmisartan

Method Precision data	**Set 1**	**Set 2**	**Set 3**	**Set 4**	**Set 5**	**Set 6**	**Set 7**	**Set 8**	**Set 9**
100.09 99.99	101.02	98.67	99.93	100.53	99.49	99.64	100.02	99.15	98.76
100.45 100.17									
100.02 99.43									
Mean 100.03									
SD 0.335									
RSD 0.33 %									
Overall Mean	100.17	99.83	100.01	100.10	99.95	99.97	100.02	99.90	99.84
Overall SD	0.484	0.598	0.308	0.360	0.367	0.339	0.306	0.450	0.567
Overall RSD %	0.48	0.60	0.31	0.36	0.37	0.34	0.31	0.45	0.57

Conclusion: The % RSD of a method by small deliberate variation in method parameters is within limit.

Table-12: Robustness Data: Hydrochlorothiazide

Varied conditions	**% RSD**	**Tailing factor**	**Theoretical Plates**
Method precision	0.36	0.9	6481
Set 1	0.34	1.0	6169
Set 2	1.00	1.0	6264
Set 3	1.27	1.1	5947
Set 4	1.49	0.9	6982
Set 5	0.71	1.0	6020
Set 6	0.72	1.0	6172
Set 7	0.95	1.1	5969
Set 8	0.54	1.0	6208
Set 9	0.49	1.2	12584.5

Table-13: Robustness Data: Telmisartan

Varied conditions	**% RSD**	**Tailing factor**	**Theoretical Plates**
Method precision	0.33	1.0	17684
Set 1	0.48	1.1	18614
Set 2	0.60	1.0	18841
Set 3	0.31	1.0	19484
Set 4	0.36	1.1	17531
Set 5	0.37	1.1	17581
Set 6	0.34	1.0	19305
Set 7	0.31	1.0	18928
Set 8	0.45	1.1	19442
Set 9	0.57	1.0	17735

Where,

Set 1) Change in flow rate by + 0.2 ml/ min

Set 2) Change in flow rate by - 0.2 ml/min

Set 3) Change in column temperature by + 5.0 units

Set 4) Change in column temperature by - 5.0 units

Set 5) Change in wavelength by - 2 nm

Set 6) Change in pH by + 0.2

Set 7) Change in pH by -0.2

Set 8) Change in organic composition by + 2%

Set 9) Change in Organic composition by - 2%

System Suitability

System suitability was verified by injecting standard preparation to verify the system suitability. % RSD, Tailing factor and Theoretical plates were verified from the replicate injections of standard preparation. Various system suitability data is given in Table-14 and 15.

Acceptance criteria:

- ✓ %RSD of Hydrochlorothiazide and Telmisartan (for six replicate injections): NMT 2.0%.
- ✓ Theoretical Plates for Hydrochlorothiazide and Telmisartan peak: NLT 2000 and 8000 respectively.
- ✓ Tailing Factor for Hydrochlorothiazide and Telmisartan peak: NMT 1.5%.

Table-14: System Suitability Data: Hydrochlorothiazide

Experiment	% RSD	Tailing Factor	Theoretical Plates
Method precision	0.36	1.1	6481
Ruggedness study	0.71	1.0	6100

Table-15: System Suitability Data: Telmisartan

Data Experiment	% RSD	Tailing Factor	Theoretical Plates
Method precision	0.33	1.1	17684
Ruggedness study	0.88	1.1	19702

CONCLUSION:

In the current study a new RP-HPLC method was successfully developed and validated as per ICH guideline for the separation of telmisartan and hydrochlorothiazide in combination dosage form of Tablets. The method was accurate, precise, linear, reliable, simple, economic and robust. The method has several advantages, including simple mobile phase, rapid analysis, simple sample preparation and improved selectivity as well as sensitivity. The method can be used for routine analysis of marketed products of telmisartan and hydrochlorothiazide in combined tablet formulation.

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