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DEVELOPMENT AND VALIDATION OF TELMISARTAN IN TABLET DOSAGE FORM BY RP-HPLC ASSAY TECHNOLOGY

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ABSTRACT

A simple, selective, rapid, precise and economical reverse phase high-pressure liquid chromatographic method has been developed as per ICH nomination for Development and Validation of Telmisartan in Tablet Dosage form By RP-HPLC Assay Method. The assay method was carried out by using a mobile phase consisting of Buffer Solution and Solution A ((Methanol and Acetonitrile (1:1)) in the gradient ratio. The detection was carried out by using HPLC Shimadzu LC with UV-Visible PDA at 298nm.The column was Hypersil BDS C-8 (12.5 cm X 4.0 mm, 5 µ). The flow rate was selected as 1.2ml/min. The retention time of Telmisartan was found to be 8.3 min respectively. The developed method was validated in terms of specificity, accuracy, precision, linearity and system suitability. The optimized proposed method easy to handle and commercially used for the routine quality control checking of Telmisartan pharmaceutical combine tablets dosage form.

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INTRODUCTION

Telmisartan is an ACE II receptor antagonist with actions similar to those of losartan. It is used in the management of hypertension[1]. The patients who have no ability of taking ACE inhibitors could be affected by this drug. It acts through interfering with the binding of angiotensin II to the angiotensin II AT1- receptor by binding reversibly and selectively to the receptors in vascular smooth muscle and the adrenal gland. Angiotensin II is the principle pressor agent of the rennin-angiotensin system, with effects that shows stimulation of synthesis, vasoconstriction and release of aldosterone, cardiac stimulation, and renal reabsorption of sodium. Micardis (Telmisartan) was approved for use by U.S. FDA in November 10, 1998[2]. It has the structural formula and given in Fig.-1.

The literature reveals that there are some of the methods have been reported for development and validation of Telmisartan by RP-HPLC. Most of the literatures are the development and validation of Telmisartan by UV spectrophotometry[3-5], HPTLC and HPLC[6, 7] for Telmisartan development and validation of UV spectrophotometry[8], HPTLC[9], and HPLC[10] method for the development and validation of Telmisartan. An attempt was made to develop and report a simple, sensitive, validated and economic method for the development and validation determination of Telmisartan by RP- HPLC.[11]

EXPERIMENTAL

Materials

Telmisartan was obtained from Macleods Pharmaceuticals Ltd. in Baddi, India, as gift samples. Acetonitrile (HPLC Grade) and Methanol (HPLC Grade) were purchased from Central Drug House (P) Ltd., India. While Ammonium di hydrogen phosphate (AR Grade) from S.D. fine chemicals, India; Ortho-phosphoric acid (AR Grade) from Central

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Drug House (p) Ltd. The 0.45- μm nylon filters were purchased from Advanced Micro Devices Pvt. Ltd. Chandigarh, India. Mili-Q water was used throughout the experiment. The pharmaceutical formulation TELMED – AH 40 (containing 40 mg TEL, 12.5 mg HCTZ and 5 mg Amlodipine) tablets were purchased from local pharmacy shops.

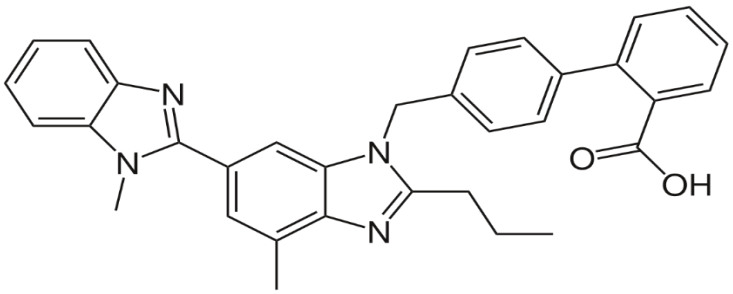

Fig.-1: Chemical Structure of Telmisartan

Liquid Chromatographic Conditions

Chromatographic condition were obtained using a stainless steel column (Hypersil BDS C-8 12.5 cm X 4.00 mm, 5μ), which was maintained at 40°C. The analytical wavelength was set at 298 nm and samples of 20 μl were injected to HPLC system. The mobile phase was Ammonium Dihydrogen Phosphate (pH 3.0 adjust with Ortho phosphoric Acid) and Solution A ((Methanol and Acetonitrile (1:1)) in the gradient ratio at a flow rate of 1.2 ml/min. The mobile phase was filtered through 0.45 μm nylon filter and degassed for 10 min by sonication.

Buffer Preparation

Weigh accurately about 2 gm of Ammonium Dihydrogen Phosphate, transferred it in 1000 ml of HPLC water. Then continuous string to dissolve it. After complete dissolved the buffer solution adjust the pH 3.0 with drop wise added Phosphoric Acid. Filter through 0.45 μ nylon filter. Then sonicated it for 10 minutes to free from air bubbles.

Preparation of 0.1N Sodium Hydroxide

Weigh accurately about 4 gm of Sodium Hydroxide, transferred it into a 1000 ml volumetric flask, then Added 700 ml HPLC water and sonicated to dissolved properly. After that diluted to volume with water.

Diluent Preparation

Weigh accurately about 0.2 gm of Sodium Hydroxide, transferred it into a 1000 ml volumetric flask, then Added 700 ml Methanol and dissolved properly. After that diluted to volume with methanol (0.005 M Methanolic solution).

Solution A: Methanol and Acetonitrile (1:1) ratio was prepared. It was mixed well and degas for 10 minutes to free from air bubbles.

Solution B: Buffer and Solution A (1:1) ratio was prepared. It was mixed well and degas for 10 minutes to free from air bubbles.

Blank Solution

Solution B was considered as blank solution. Buffer: Solution A (1:1) ratio was prepared. It was mixed well and degas for 10 minutes to free from air bubbles. The solution was loaded in HPLC and the chromatogram was recorded.

Reference Stock Solution

Weigh accurately about 40.0 mg of Telmisartan Working Standard, transferred it in to 25 ml volumetric flask, then Added 10 ml diluent (0.005 M Methanolic solution) and Sonicate to dissolved and then diluted to volume with diluent (Conc.: 1600 ppm).

Reference Solution
Take 2 ml from reference stock solution to a 10 ml volumetric flask. Then diluted to volume with Solution B (1:1 solution of Buffer and solution A), (Conc.: 320 ppm). The reference solution was loaded in HPLC and six injections ware taken from the same vial. The chromatogram was recorded, and the amount of the drug was calculated.

Test Stock Solution
Weigh accurately 20 tablets and calculated average weight. Then weigh and transferred 5 intact tablets into a 250ml of volumetric flask. Added 12.5 ml of 0.1 N Sodium Hydroxide solution into the sample and shake until the tablets had completely disintegrated. Then added 140 ml of methanol and sonicated for 10 min at 25°C. Then the test solution was stir vigorously for 30 min at 300 rpm by the mechanical shaker. After that it allowed to cool to room temperature. Then diluted to volume with methanol and mixed the solution properly. The test solution was centrifuge at 4000 rpm for 10 min. (Conc.: 800 ppm).

Test Solution
Take 4 ml from test stock solution to a 10 ml volumetric flask. Then diluted to volume with Solution B (1:1 solution of Buffer and solution A), (Conc.: 320 ppm). The test solution was loaded in HPLC and two injections ware taken from the same vial. The chromatogram was recorded, and the amount of the drug was calculated.

Injection Procedure
1. Gradient Blank for two times.
2. Blank Solution (Solution-B).
3. Reference Solution for six times.
4. Test Solution for two times.
5. Reference solution after every six injections of test solution and at the end of the sequence.

Evaluation
Integrate the Telmisartan peak.
Calculated the tailing factor of Telmisartan peak from reference solution.
Calculated % RSD for the area of Telmisartan peak from the reference solution.

System Suitability
In the chromatograms obtained with reference solution ensure whether the following requirements are met:

1. The tailing factor for the Telmisartan peak should not be more than 2.0
2. The relative standard deviation of the areas from each peak of Telmisartan of first six injections must not be greater than 2.0%.
3. The relative standard deviation of the areas from each peak of Telmisartan for all reference solution injections must not be greater than 2.0%.

If the above conditions are not met, the HPLC system needs to be checked.

Assay Method
With the optimized chromatographic condition, a steady baseline was recorded, the reference solution was injected and the chromatogram was recorded. The retention time of Telmisartan was found to be 8.3 min. This procedure was repeated for the test solution obtained from the formulation.

RESULTS AND DISCUSSION

A chromatogram obtained from reference substances solution is presented in Fig.-2. The six Telmisartan reference substance areas are given below in Table-1. A chromatogram obtained from test substances solution is presented in Fig.-3. The two Telmisartan test substance areas are given below in Table 2.

Method Validation

Specificity

The excipients in the tablets used in this study. The chromatograms obtained from the drug with the most commonly used interfering materials were compared with those obtained from the blank solution and placebo solution to determine the specificity of the method. The chromatogram observed in the study run time indicates the absence of interfering material peaks near the drug peak. This indicates the specificity of the proposed method. The interference result of this proposed method does not show any interference peak (Table-3) (Fig.-3).

Table-1: Areas of Telmisartan (Reference)

S. No.	Standard Area
1.	8114110
2.	8113311
3.	8131879
4.	8110588
5.	8124481
6.	8111033
Mean	8117567
Std. Dev.	8649.86
RSD	0.11

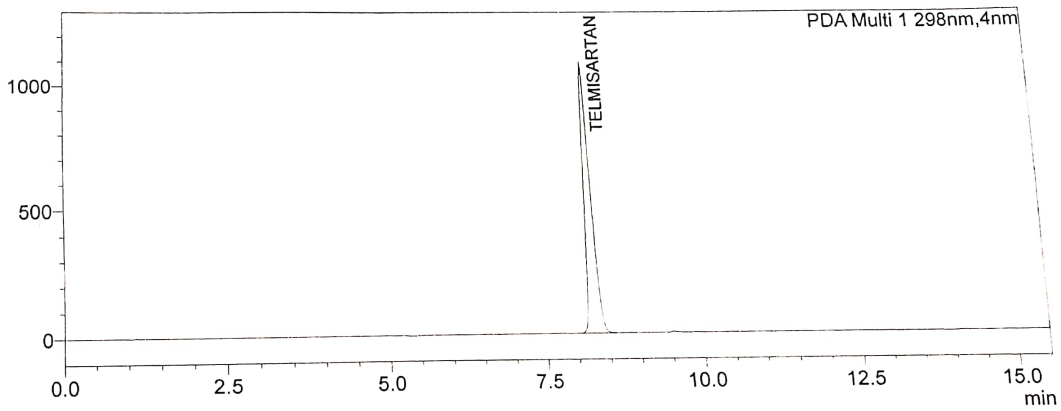

Fig.-2: Chromatogram of Telmisartan Reference Substance Solution

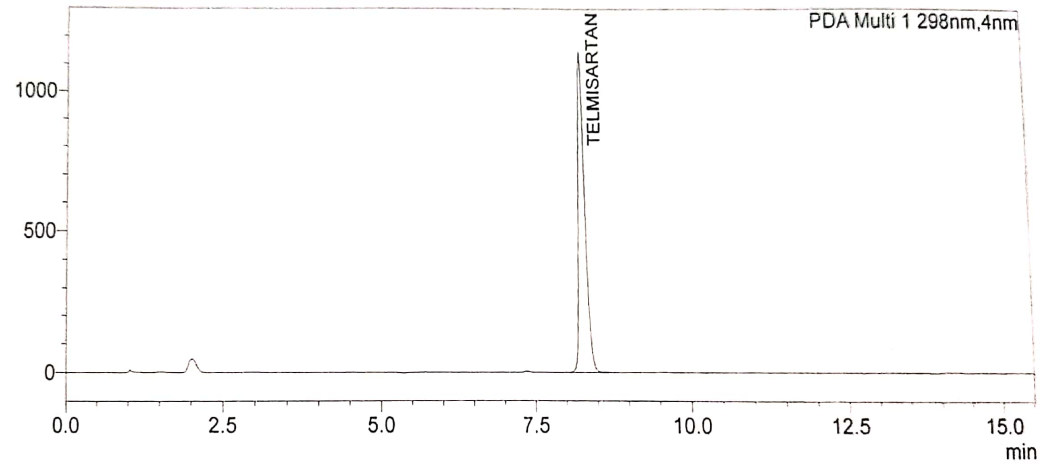

Fig.-3: Chromatogram of Telmisartan in Test Solution

Table-2: Areas of Telmisartan in Test Solution

Area- 1	Area- 2	Mean Area	% Assay of Telmisartan
8541308	8533220	8537264	105.8

Table-3: Interference Details of Specificity Test

Solution Name	Retention Time of The Peak(min.)	Peak Observed Due to Telmisartan	Interference at Telmisartan RT(Yes/No)	Purity Match (NLT 990)
Blank Solution	ND	ND	No	NA
Placebo Solution	ND	ND	No	1000
Reference Solution	8.26	Peak Due to Telmisartan	No	1000
Test Solution	8.28	Peak Due to Telmisartan	No	1000

Method Precision

The intraday precision was performed at multiple samplings with proposed same conditions. And the intraday precision was no more difference. The result shows that the propose method are more reproducible. The precision results as represent as (Table-1 and 4). The percentage of relative standard deviation was calculated.

Table-4: Intraday method precision result of propose assay method (Telmisartan)

S. No.	Telmisartan Area 1	Telmisartan Area 2	Telmisartan Mean Area	% Assay
Method Precision 1	8487484	8491747	8489616	104.60
Method Precision 2	8497970	8480838	8489404	104.60
Method Precision 3	8507426	8519979	8513703	104.88
Method Precision 4	8561120	8551789	8556455	105.40
Method Precision 5	8488970	852027	8504623	104.76
Method Precision 6	8541007	8557554	8549281	105.31
			AVG.	104.9
			STDEV	0.3507
			%RSD	0.33

Accuracy

According to the ICH guidelines[12], the % recovery of drug was performed to the addition of known quantity of drug at proposed assay conditions. 50%, 100%, 150% level was performed and every level has three determinations. The percentage recovery result represent as (Table- 5).

Table-5: Percentage Recovery Result of Telmisartan

% w.r.t. Reference Concentration	API Added (mg)	% Recovery of Telmisartan	AVG.	% RSD	Confidence Interval
50 %	100.25	98.58	99	0.12	0.14
	100.25	98.81			
	100.32	98.76			
100 %	200.03	98.86	99	0.19	0.22
	200.13	99.09			
	200.07	99.23			
150 %	300.10	101.26	101	0.12	0.14
	300.00	101.27			
	300.07	101.05			
	Mean	99.66			
	STD Dev	1.1710			
	RSD	1.17			

Linearity

The concentration range of drug (Telmed-AH 40) was 5-15µg/ml. the linearity equation of Telmisartan was $y = 26308.8085_X - 377340.0683$. There value of the drug was 0.9989 of Telmisartan. The %RSD value of the drug was less than 2%. The HPLC of linearity of the drug show to (Fig.-4). The absorbance versus concentration plotted data of drug is given in Table- 6.

Table-6: Assay Study of Linearity Result of Telmisartan

% w.r.t. Reference Concentration	Concentration in µg/ml (Telmisartan)	Area	%RSD
50	160.0000	3906154	0.13
80	256.0000	6316059	0.20
100	320.0000	7945331	0.00
120	384.0000	9558770	0.09
150	480.0000	12379256	0.13

CONCLUSION

A simple, specific, precise and linear and accurate RP- HPLC method has been developed and validated for quantitative determination of Telmisartan in new tablet formulation. The method is very straightforward and all the parameters and results were found within the acceptance limit. And specific peak was well isolated from its others excipient peaks and which complete in total runtime of 15.5 min, makes the developed its suitable for routine quality control analysis work.

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