International Journal of Drug Development & Research
| October-December 2011 | Vol. 3 | Issue 4 | ISSN 0975-9344 |
Available online http://www.ijddr.in
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RP-HPLC Method for the Simultaneous Estimation of Telmisartan and Hydrochlorothiazide in Pharmaceutical Dosage Form

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Abstract

A new simple, rapid, sensitive RP-HPLC method for the simultaneous determination of telmisartan and hydrochlorothiazide in pharmaceutical dosage forms was developed. Telmisartan has absorption maxima at 296 nm and hydrochlorothiazide has absorption maxima at 280 nm. For the simultaneous estimation of telmisartan and hydrochlorothiazide the detection wavelength was taken as 271 nm. Linearity for detector response was observed in the concentration range of 50 to 150 % of test concentration. Correlation coefficient (r) for calibration curve was found to be 1.0. Retention times were found to be 5.79 min and 2.85 min for telmisartan and hydrochlorothiazide respectively. Percent recovery was found to be with in the range of 98.0 % to 102.0%. The percent RSD for the analyzed tablet and recovery studied was less than 2. The results of recovery studies were found to be linear in the range 50 % to 150 % of test concentration. Results of the analysis were validated statistically and by recovery studies. The developed method was found to be precise, selective and rapid for the simultaneous determination of telmisartan and hydrochlorothiazide in bulk and in pharmaceutical dosage form.

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***Key words*:**
Telmisartan, Hydrochlorothiazide, Estimation, Validation.

***How to Cite this Paper*:**
T. Gopala Swamy, K. Nagaraju and A. Lakshmana Rao* "RP-HPLC Method for the Simultaneous Estimation of Telmisartan and Hydrochlorothiazide in Pharmaceutical Dosage Form", Int. J. Drug Dev. & Res., Oct-Dec 2011, 3(4): 362-368

Article History:----------
Date of Submission: 28-08-2011
Date of Acceptance: 25-10-2011
Conflict of Interest: NIL
Source of Support: NONE

INTRODUCTION

Telmisartan is chemically 2-(4-{[4-methyl-6-(1-methyl-1*H*-1,3-benzodiazol-2-yl)-2-propyl-1*H*-1,3-

benzodiazol-1-yl]methyl}phenyl)benzoic acid. It is an angiotensin receptor blocker (ARB) that shows high affinity for the angiotensin II type 1 (AT1) receptors, has a long duration of action, and has the longest half-life of any ARB [1]. In addition to blocking the renin-angiotensin system (RAS), telmisartan acts as a selective modulator of peroxisome proliferator-activated receptor gamma (PPAR-γ), a central regulator of insulin and glucose metabolism. It is believed that telmisartan's dual mode of action may provide protective benefits against the vascular and renal damage caused by diabetes and cardiovascular disease (CVD). Telmisartan has binding affinity 3000 times with AT-2 receptor than AT-1 receptor. Telmisartan is also having maximum half-life in sartans - 24 hrs.

Hydrochlorothiazide is chemically 6-chloro-1,1-dioxo-3,4-dihydro-2*H*-1,2,4-benzothiadiazine-7-sulfonamide. It belongs to the thiazide class of diuretics and acts on kidneys to reduce sodium reabsorption in the distal convoluted tubule [2]. This increases the osmolarity in the lumen causing less water to be reabsorbed from the collecting ducts, finally increasing urinary output. It is often used in the treatment of hypertension, congestive heart failure, symptomatic edema and the prevention of kidney stones. It is effective for nephrogenic diabetes insipidus and is also sometimes used for hypercalciuria, Dent's disease. Thiazides are also used in the treatment of osteoporosis. Thiazides decrease mineral bone loss by promoting calcium retention in the kidney and by directly stimulating osteoblast differentiation and bone mineral formation. Various HPLC estimations have been reported in the literature for the determination of telmisartan present in pharmaceutical dosage forms [3,4]. Only few methods were reported for the simultaneous estimation of telmisartan and hydrochlorothiazide by spectrophotometry [5,6], capillary electrophoresis [7], HPLC [8,9], HPTLC [10] and LC-MS [11]. Hence we had made an attempt to develop a simple, accurate and precise RP-HPLC method for the simultaneous estimation of telmisartan and hydrochlorothiazide in bulk and in tablet dosage forms.

EXPERIMENTAL

Materials

Telmisartan and Hydrochlorothiazide (Nivon Specialities (India), Vashi, Maharashtra; CTX Life Sciences Pvt. Ltd, Surat, Gujarat), Ortho phosphoric acid, acetonitrile (S.D. Fine Chemicals Ltd., Mumbai, Maharashtra) were used for the study.

Selection of wavelength

The detection wavelength was selected as 271 nm and hence this λ_{max} was selected for further studies.

Buffer preparation

Weighed 6.8 gm of potassium dihydrogen ortho phosphate and dissolve it in 1000 ml of Milli-Q water. Adjust the pH to 3.0 with ortho phosphoric acid and filter through 0.45 µ filter and degas.

Mobile phase preparation

Buffer solution and acetonitrile were mixed in the ratio of 40:60 % and degassed.

Standard stock solution

20 mg and 13 mg of telmisartan and hydrochlorothiazide was weighed and transferred into 50 ml volumetric flask and make up the volume with methanol and it is labeled as solution 1 and solution 2 respectively.

Standard preparation

2 ml of solution 1 and 1 ml of solution 2 were transferred into 100 ml volumetric flask and the volume was made up with mobile phase.

Sample preparation

Tablet powder equivalent to average weight of tablet was weighed and transferred into 100 ml flask. 50 ml methanol was added and sonicated for 20 min and the solution was made up with mobile phase. The solution then filtered through 0.45 µ filter and

diluted with 1 ml of the solution and made up to 50 ml with mobile phase.

Linearity

Linearity of detector response of assay method was found by injecting seven standard solutions with concentration ranging from 50 % to 150 % of the test concentration and a graph was plotted for concentration versus peak area. The results were shown in Table-1,2.

Precision

Repeatability

The precision of test method was determined by preparing six test preparations using the product blend and by mixing the active ingredient with excipients as per manufacturing formula. And the relative standard deviation of assay results was calculated. The results were shown in Table-3.

Accuracy

Telmisartan and hydrochlorothiazide tablets content were taken at various concentrations ranging from 50 % to 150 % (50 %, 75 %, 100 %, 125 %, and 150 %) to accurately quantify and to validate the accuracy. The assay was performed in triplicate. The results were shown in Table-4,5.

Ruggedness

System to system variability

System to system variability on two HPLC systems was carried out to get the ruggedness of assay method. The result was shown in Table-6.

HPLC column to column variability

Column to column variability on two HPLC systems was carried out to get the ruggedness of assay method. The result was shown in Table-7.

Robustness

Effect of variation in flow rate

System suitability parameters were checked by injecting system suitability preparation into HPLC system with 0.8 ml/min and 1.2 ml/min to get the robustness of the assay method. The results were shown in Table-8.

Effect of variation in column temperature

System suitability parameters were checked by injecting system suitability preparation into HPLC system at 20^{o}C and 30^{o}C to get the robustness of the assay method. The results were shown in Table-9.

HPLC filter to filter variability

HPLC filter to filter validation was checked by using two different filters to get the robustness of assay method. Different portions of test preparation was filtered and injected into HPLC system along with unfiltered standard. Similarity factor for test solution against unfiltered standard were calculated and tabulated. The results were shown in Table-10

RESULTS AND DISCUSSION

The proposed method for the simultaneous determination of telmisartan and hydrochlorothiazide in pharmaceutical dosage form was found to be precise, selective, rapid and economical. The present study describes RP-HPLC method development and validation for the simultaneous estimation of telmisartan and hydrochlorothiazide in tablets. All the drugs in the dosage form were analysed by Inertsil ODS-C18 (250mmX4.6mm) using phosphate buffer of pH 3.0 and acetonitrile in a isocratic programme with flow rate 1.0 ml/min and UV detection was performed at 271 nm. The retention times observed were 5.79 min and 2.85 min for telmisartan and hydrochlorothiazide respectively. The linearity for detector response was observed in the concentration range of 50 to 150% of test concentration and the correlation coefficient (r) for calibration curve was found to be 1.0. Percent recovery was found to be with in the range of 98.0 % to 102.0% indicating accuracy of the method. The percent RSD for the tablet analysis and recovery studied is less than 2 which is indicating high degree of precision. The results of recovery studies were found to be linear in

50 % to 150 % of final assay concentration range indicating linearity and range of proposed method. The results of robustness study indicates that the method is robust and is unaffected by small variations in the chromatographic conditions. The results of ruggedness study indicates that the method is unaffected by variations in analyst, column and system. Hence, it can be concluded that the developed RP-HPLC method is accurate, precise, rapid and selective and can be employed successfully for the estimation of telmisartan and hydrochlorothiazide in bulk and pharmaceutical dosage forms.

ACKNOWLEDGEMENTS

The authors are grateful to Nivon Specialities (India), Vashi, Maharashtra; CTX Life Sciences Pvt. Ltd, Surat, Gujarat for providing authentic sample of telmisartan and hydrochlorothiazide.

Table 1: Linearity of Telmisartan

S. No.	Concentration (µg/ml)	Area
1	4.00	68167
2	4.80	81844
3	6.40	109292
4	8.00	136683
5	9.60	164388
6	11.20	192136
7	12.00	205645

Table 2: Linearity of Hydrochlorothiazide

S. No.	Concentration (µg/ml)	Area
1	1.30	49991
2	1.56	59731
3	2.08	79694
4	2.60	99302
5	3.12	119381
6	3.64	139123
7	3.90	149098

Table 3: Precision of Telmisartan and Hydrochlorothiazide

S. No.	Assay % of Telmisartan	Assay % of Hydrochlorothiazide
1	99.7	99.5
2	100.0	100.2
3	98.7	99.2
4	99.2	99.3
5	99.2	99.5
6	98.8	99.2
Average	99.3	99.5
% RSD	0.501	0.37

Table 4: Accuracy for Telmisartan

S. No.	Spike level	µg/ml added	µg/ml found	% recovery	Mean % recovery
1	50%	4.01	3.99	99.4	99.5
2	50%	4.01	3.99	99.3	
3	50%	4.01	4.00	99.7	
1	75%	6.02	6.00	99.7	99.7
2	75%	6.02	5.99	99.6	
3	75%	6.02	6.01	99.9	
1	100%	8.03	8.00	99.7	99.8
2	100%	8.03	8.02	99.9	
3	100%	8.03	8.01	99.7	
1	125%	10.03	10.04	100.0	100.1
2	125%	10.03	10.05	100.2	
3	125%	10.03	10.03	100.0	
1	150%	12.04	12.08	100.3	100.3
2	150%	12.04	12.08	100.3	
3	150%	12.04	12.08	100.3	

Table 5: Accuracy for Hydrochlorothiazide

S. No.	Spike level	µg/ml added	µg/ml found	% recovery	Mean % recovery
1	50%	1.29	1.29	99.9	100.0
2	50%	1.29	1.29	99.8	
3	50%	1.29	1.30	100.3	
1	75%	1.94	1.94	99.9	100.0
2	75%	1.94	1.94	99.9	
3	75%	1.94	1.94	100.1	
1	100%	2.59	2.59	100.1	100.1
2	100%	2.59	2.59	100.1	
3	100%	2.59	2.58	100.0	
1	125%	3.23	3.23	100.1	100.2
2	125%	3.23	3.24	100.2	
3	125%	3.23	3.24	100.3	
1	150%	3.88	3.89	100.3	100.3
2	150%	3.88	3.89	100.3	
3	150%	3.88	3.89	100.2	

Table 6: System to system variability for Telmisartan and Hydrochlorothiazide

S. No.	System-1		System-2	
	Assay % of Telmisartan	Assay % of Hydrochlorothiazide	Assay % of Telmisartan	Assay % of Hydrochlorothiazide
1	99.7	99.5	99.8	100.4
2	100.0	100.2	99.8	100.4
3	98.7	99.2	98.7	99.5
4	99.2	99.3	100.1	100.5
5	99.2	99.5	100.0	100.6
6	98.8	99.2	99.0	99.9
Average	99.3	99.5	99.6	100.2
% RSD	0.501	0.37	0.57	0.44

Table 7: Column to Column variability for Telmisartan and Hydrochlorothiazide

S. No.	Column-1		Column-2	
	Assay % of Telmisartan	Assay % of Hydrochlorothiazide	Assay % of Telmisartan	Assay % of Hydrochlorothiazide
1	99.7	99.5	99.6	100.3
2	100.0	100.2	99.6	99.7
3	98.7	99.2	98.7	99.2
4	99.2	99.3	100.0	100.5
5	99.2	99.5	99.7	100.1
6	98.8	99.2	99.0	99.4
Average	99.3	99.5	99.4	99.9
% RSD	0.50	0.37	0.50	0.51

Table 8: Flow rate variability for Telmisartan and Hydrochlorothiazide

System Suitability Parameters	Observed value with flow rate			Acceptance criteria
	0.8ml/min	1.0ml/min	1.2ml/min	
RSD for replicate injections of 1. Telmisartan 2. Hydrochlorthiazide	 0.07 % 0.20 %	 0.10 % 0.04 %	 0.16 % 0.16 %	 NMT 2.0 % NMT 2.0 %

Table 9: Column temperature variability for Telmisartan and Hydrochlorothiazide

System Suitability Parameters	Observed value at column temperature			Acceptance criteria
	20°C	25°C	30°C	
RSD for replicate injections of 1. Telmisartan 2. Hydrochlorthiazide	 0.22 % 0.13 %	 0.12 % 0.16 %	 0.18 % 0.06 %	 NMT 2.0 % NMT 2.0 %

Table 10: Results for Filter variability of Telmisartan and Hydrochlorothiazide

S.No.	% Assay					
	0.45 µm MDI		0.45 µm Nylon		Difference	
	Telmisartan	Hydrochloro thiazide	Telmisartan	Hydrochloro thiazide	Telmisartan	Hydrochloro thiazide
1	99.7	100.5	99.9	100.4	0.2	0.1
2	99.7	100.4	100.0	100.7	0.3	0.3
3	99.0	100.0	99.0	99.9	0	0.1

Figure 1: Linearity of Telmisartan

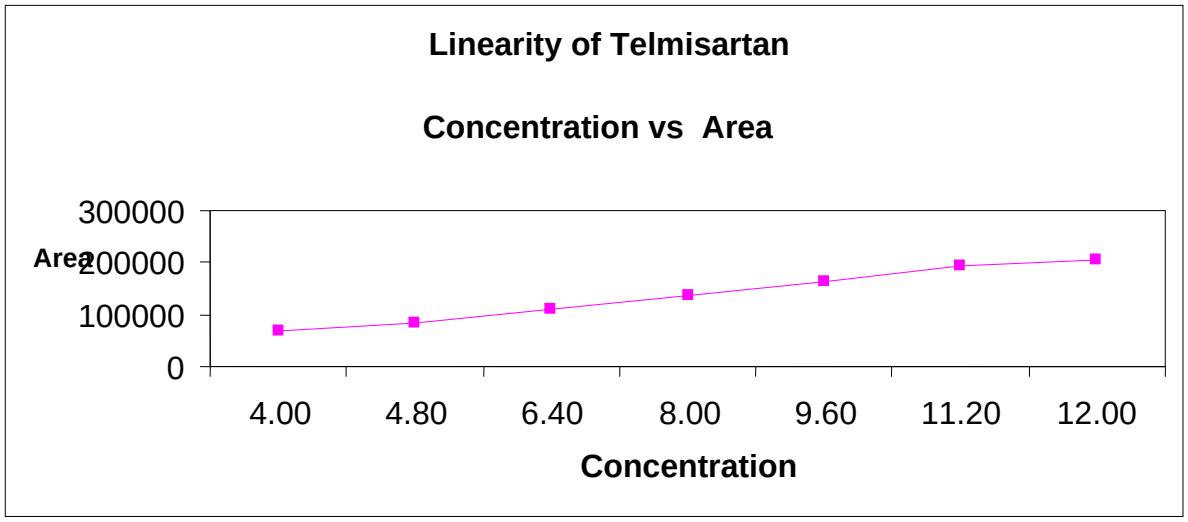


Figure 2: Linearity of Hydrochlorothiazide

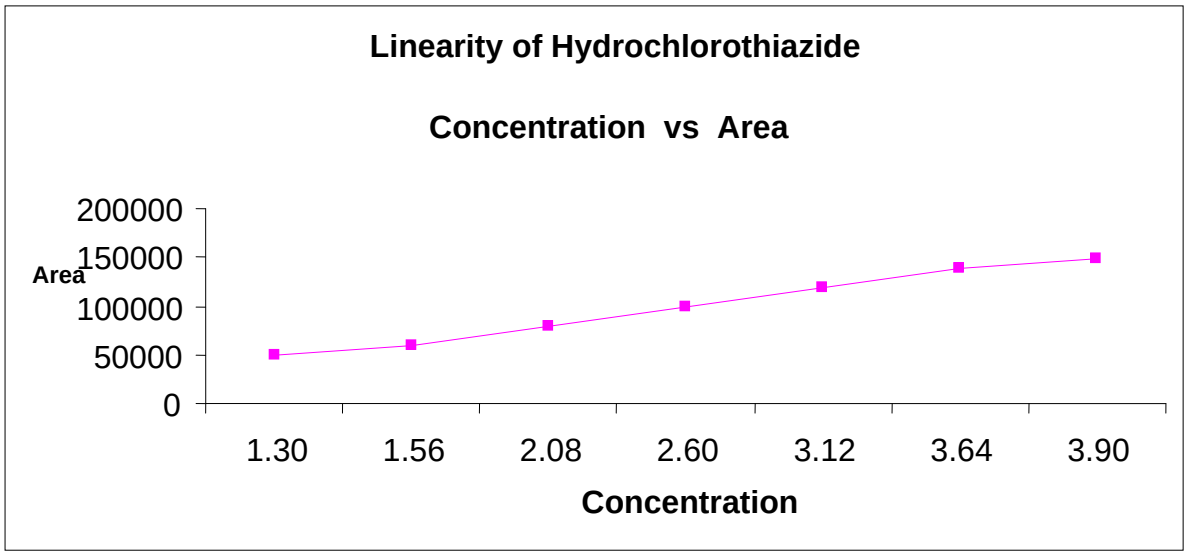
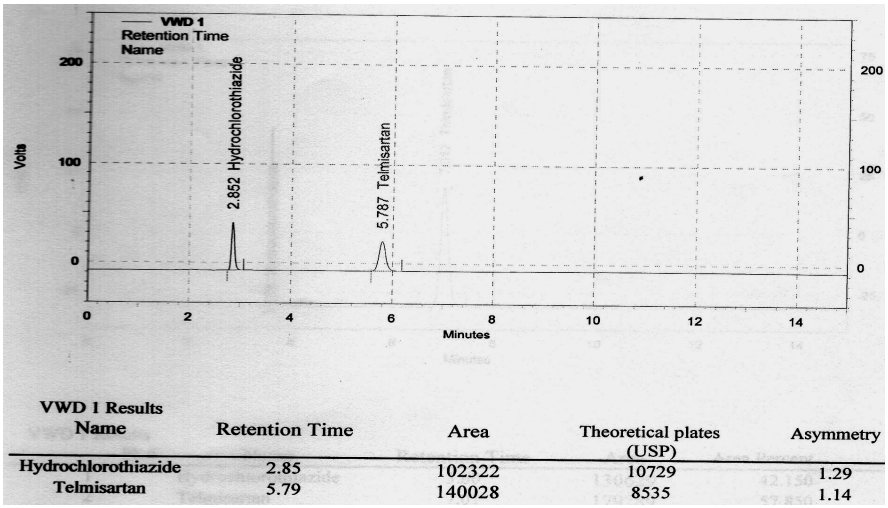


Figure 3: Typical chromatogram of Telmisartan and Hydrochlorothiazide



VWD 1 Results

Name	Retention Time	Area	Theoretical plates (USP)	Asymmetry
Hydrochlorothiazide	2.85	102322	10729	1.29
Telmisartan	5.79	140028	8535	1.14

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