International Journal of Advances in Pharmaceutical Analysis
IJAPA Vol. 2 Issue 1 (2012) 01-05
Journal Home Page http://www.ssjournals.com/index.php/ijapa

STABILITY-INDICATING RP-HPLC METHOD FOR ANALYSIS OF TELMISARTAN IN THE DOSAGE FORM

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ABSTRACT

A simple, rapid, precise, rapid, sensitive and reproducible reverse phase high performance liquid chromatographic (RP-HPLC) method has been developed for quantitative analysis of Telmisartan (TELM) in pharmaceutical dosage forms. Chromatographic separation of TELM and its degradation products was achieved on a C_{18}, 250 × 4.6 mm, 5µ, Waters symmetry column. The flow rate was 1.0 ml/min, the column temperature 40^0C, and detection was by absorption at 230 nm using a photodiode array detector. The number of theoretical plates and tailing factor for TELM were 8,721 and 1.018, respectively. TELM was exposed to thermal, photolytic, hydrolytic (acidic and alkali), and oxidative stress, and the stressed samples were analyzed by use of the proposed method. Peak homogeneity data for TELM in the chromatograms from the stressed samples, obtained by use of the photodiode-array detector, demonstrated the specificity of the method for analysis of TELM in the presence of the degradation products. The linearity of the method was excellent over the range 10–50 µg/ml. The correlation coefficient was 0.999. Relative standard deviations of peak areas of all measurements were always less than 2%. The proposed method was found to be suitable and accurate for quantitative analysis of TELM and study of its stability.

***Keywords*:** Column liquid chromatography, Method validation, Telmisartan

1. Introduction:

Telmisartan (TELM) chemically described as 4[(1,4-dimethyl-2-propyl(2,6-bi-1H-benzimidazol]-1-yl)methyl][1,1-biphenyl]-2-carboxylic acid (fig. 1) is a potent, long-lasting, nonpeptide antagonist of the angiotensin II (AT1) receptor that is indicated for the treatment of essential hypertension. It selectively and insurmountably inhibits stimulation of the AT1 receptor by angiotensin II without affecting other receptor systems involved in cardiovascular regulation. In clinical studies, TELM shows comparable antihypertensive activity to other major antihypertensive classes, such as angiotensin converting enzyme (ACE) inhibitors, beta-blockers and calcium antagonists[1, 2].

Literature review revealed that there are various methods for determination of Telmisartan, individually and in combination with other drugs. A variety of analytical methods for estimation of Telmisartan are previously reported. The majority of methods reported are liquid chromatography coupled to UV, tendem mass spectrometry or mass spectrometry detection but some determinations were also performed by thin layer, ratio derivative spectrophotometry and spectrofluorimetry. Individually, Telmisartan is estimated by LC-MS [3], LC-tendem MS[4, 5]. The majority of methods reported are liquid chromatography in which Telmisartan was estimated simultaneously with hydrochlorthiazide [6, 7, 8], with ramipril [9, 10], with Amlodipine[11]. Some triple combinations are also reported along with telmisartan such as, Column Switching LC with fluorescence detection[12]. Some HPTLC methods are also reported for estimation of Telmisartan along with other drugs[13, 14, 15]. None of these analytical procedures has been described as a stability-indicating method for analysis of TELM in the presence of its degradation products.

2. Experimental:

a. Chemicals: Telmisartan (99.4%) was obtained from Cipla Pharmaceutical Ltd, Mumbai, India, as gift samples. Acetonitrile (HPLC Grade), Methanol (HPLC Grade), Potassium dihydrogen phosphate (AR Grade), ortho-phosphoric acid (AR Grade) were purchased from E. Merck (India) 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. Tablets were purchased from Indian

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market containing of Telmisartan 40 mg per tablet.

b. Instruments: Analysis was performed on a chromatographic system Agilent 1200 series separation module (Japan) equipped with an auto injector (G1329A), Diode array detector SL (G1315C), Quaternary pump (G1311A) and column thermostat (G1316A). Data acquisition was made with Chemstation software. The peak purity was evaluated with DAD detector.

c. Liquid chromatographic conditions: Chromatographic conditions were obtained using a stainless steel column (Waters symmetry C_{18} 250mm x 4.6mm 5µm), which was maintained at 40^0C. The analytical wavelength was set at 230 nm and samples of 60 µl were injected to HPLC system. The mobile phase was Potassium dihydrogen phosphate (10mM, pH 3.0 adjusted with ortho-phosphoric acid) and acetonitrile in ratio of 60:40 (v/v) to 70:30 (v/v) at a flow rate of 1ml/min. The mobile phase was filtered through 0.45µm filter and degassed for 10 minutes by sonication. For analysis of samples obtained by forced degradation, the photodiode-array detector was used in scan mode in the range 200–400 nm. Peak homogeneity was expressed as peak purity and was obtained directly from the spectral analysis report by use of the above-mentioned software[16,17].

d. Standard solutions:

1. **Stock standard solutions:** An accurately weighed quantity of 10 mg of Telmisartan was transferred into a 100 ml volumetric flask. Dissolved with 30 ml of methanol and diluted to required volume with mobile phase, having the concentration of 100 µg/ml of Telmisartan.
2. **Preparation of working standard:** From the standard stock solution 10 ml is pipette out into 100 ml volumetric flask and made up the volume with mobile phase, having the concentration of 10 µg/ml of Telmisartan[18].

e. Procedure for Forced Degradation Study: Stability testing is an important part of the process of drug product development. The purpose of stability testing is to provide evidence of how the quality of a drug substance or drug product varies with time under a variety of environmental conditions, for example temperature, humidity, and light, and enables recommendation of storage conditions, retest periods, and shelf life to be established. The two main aspects of drug product that play an important role in shelf-life determination are assay of the active drug and the degradation products generated during stability studies. The objective of this work was to develop an analytical LC procedure which would serve as a stability-indicating method for assay of TELM drug product. Forced degradation of the drug product was carried out under thermolytic, photolytic, acid/base hydrolytic, and oxidative stress conditions. Forced degradation of the drug products under acidic, basic, and oxidizing conditions was performed using centrifuged and filtered solution (as described in the section ‘‘Preparation of Sample Solution’’) containing 10 µg/ml TELM. For thermolytic and photolytic degradation, a quantity of powder equivalent to 10 mg TELM was exposed[19].

Acidic Degradation: Centrifuged sample stock solution (1 ml) was transferred to a 10 ml volumetric flask and 3 ml 1 M HCl was added. The mixture was left at 60 ^{0}C for 8 h in a water bath then left to equilibrate to ambient temperature, then diluted to 10 ml with diluent.

Alkaline Degradation: Centrifuged sample stock solution (1 ml) was transferred to a 10 ml volumetric flask and 3 ml 0.01 M NaOH was added. The mixture was left for 10 min at ambient temperature, then diluted to 10 ml with diluent.

Oxidative Degradation: Centrifuged sample stock solution (1 ml) was transferred to a 10 ml volumetric flask and 3 ml 30% H_2O_2 was added. The mixture was left for 2 h at ambient temperature then diluted to 10 ml with diluent.

Thermal Degradation: Approximately 250 mg drug product powder was left at 30^0C, 40^0C, 50^0C for 1 month. The sample was then treated to obtain solution containing 10 µg/ ml TELM.

UV Degradation: Approximately 250 mg drug product powder was exposed to short-wavelength UV light for 24 h. The sample was then treated to obtain solution containing 10 µg/ ml TELM[20,21,22].

3. Results and Discussion:

Optimization of the chromatographic conditions

Column : Waters symmetry, ODS C_{18}; 4.6 x 150 mm, 5microns
Mobile Phase : 10 mM pot. Di hydrogen phosphate: Acetonitrile (60:40) gradient method.
pH : 3.0 ±0.01
Flow rate : 1 ml/min
Detector : UV

Injection volume : 60µl
Column temperature : Ambient
Wavelength : 230 nm
Run time : 70 minutes.

Chromatographic separation of TELM from its degradation products was achieved on Waters symmetry, ODS C_{18}; 4.6 x 150 mm, 5microns. Development studies revealed that pot. Di hydrogen phosphate: Acetonitrile (60:40) was used which vary to (70:30 v/v) (gradient method) at a flow rate of 1.0 ml/min and a column temperature of 40^0C were suitable conditions for a stability-indicating method for study of the degradation of TELM. TELM peak shape was good, with little tailing, and TELM was well resolved from its degradation products. The retention time of TELM was, typically, approximately 28.82 min and chromatographic analysis time was than 70 min. Under the optimized conditions TELM and its degradation products were well separated.

Although the conditions used for forced degradation were attenuated to achieve degradation in the range 10–30%, this could not be achieved for thermal and photolytic degradation even after prolonged exposure. During the initial forced degradation experiments it was observed that alkaline hydrolysis of TELM was a rapid reaction the drug was extensively degraded by alkali hydrolysis, thermal and oxidative condition. Table 1 indicates the extent of degradation, and assay of TELM under the various stress conditions. Chromatograms obtained from TELM tablet solution, and solutions after acidic and alkaline hydrolysis and oxidative degradation of the drug product are shown in Fig. 2 &3, respectively.

Conclusion:

In this study, a selective and validated stability-indicating HPLC assay method for Telmisartan was developed, which could separate the drug and its degradation products formed under a variety of stress conditions.

Acknowledgements:

We are thankful to Head, Department of Pharmaceutical Chemistry, NRI Institute of Pharmacy, RGPV, Bhopal, India for providing laboratory facilities. Authors are also thankful to Cipla Ltd., Mumbai, India, for providing standards.

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Figures :

Fig. 1 Structure of Telmisartan

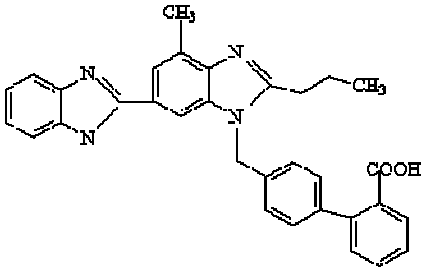


Fig. 2 Thermal degradation of tab sample at 40 °C temp.

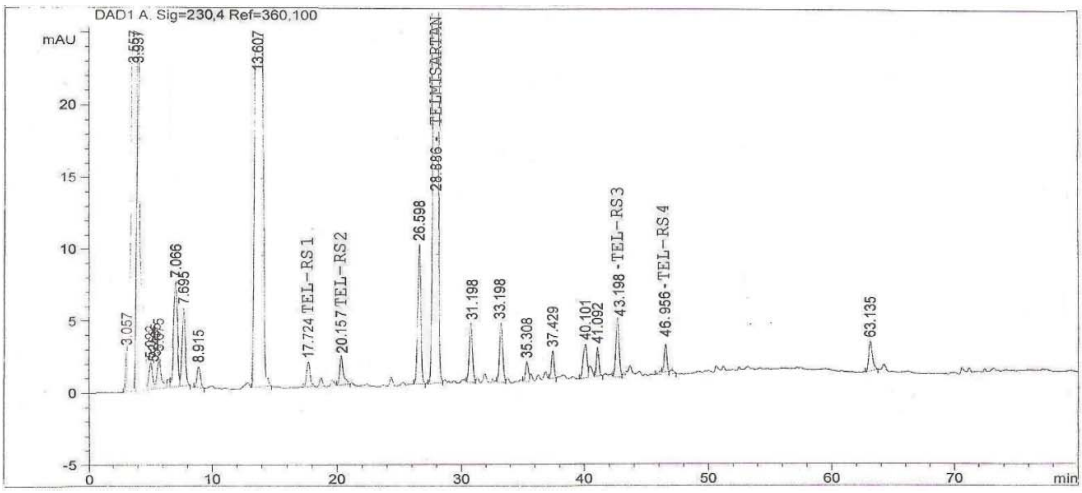
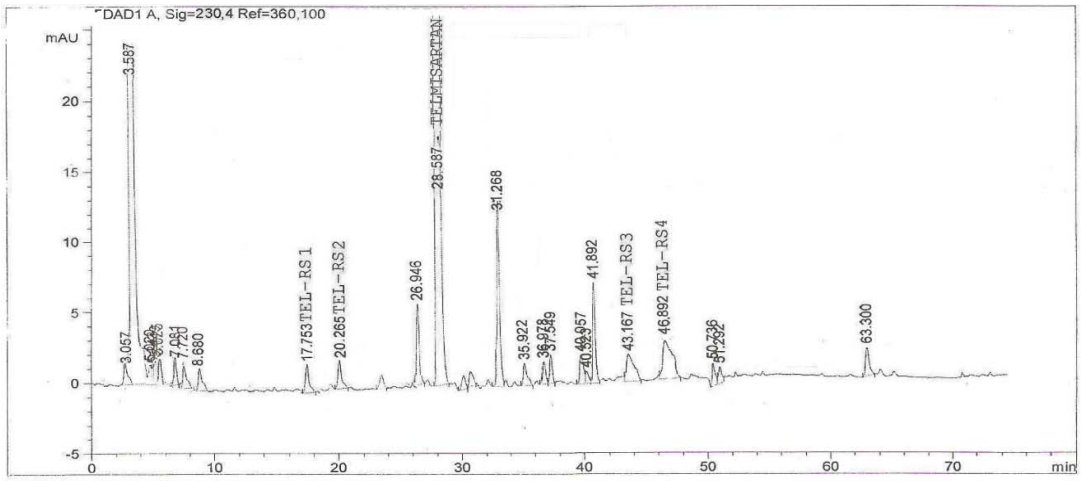


Fig. 3 Thermal degradation of tab sample at 50 °C temp.



TABLES

Table 1 Results of forced degradation study

Stress condition		Degradation % of TELM	% Assay
Thermal Stress	30 ^{0}C	3.16	96.84
	40 ^{0}C	7.88	92.12
	50 ^{0}C	18.64	81.36
Alkaline stress	0.1 N NaOH, 8h	8.8	91.20
	1 N NaOH, 12h	27.84	72.16
	2 N NaOH, 24h	38.29	61.71
Oxidative stress	3 %, 6 h	No Degradation	99.28
	3 %, 24 h	No Degradation	99.18
	10 %, 24 h	3.18	96.88
Acidic stress	0.1 N HCl / 8 h	No Degradation	99.28
	1 N HCl / 12 h	No Degradation	99.25
	2 N HCl / 24 h	No Degradation	99.25
	5 N HCl / 24 h	No Degradation	99.19
UV stress	1.2×10^6 Lux hours	No Degradation	99.18
	6×10^6 Lux hours	No Degradation	99.19