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STABILITY INDICATING ASSAY OF TELMISARTAN IN TABLETS

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Keywords:

RP-HPLC, Telmisartan, Validation, ICH guidelines, Stability indicating assay

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ABSTRACT: An accurate, simple, precise, rapid stability-indicating assay method was developed and subsequently validated for the estimation of Telmisartan in API and Tablets. The best separation of the drug was achieved on Kromasil C18 (4.6 × 150 mm, 5 µm) with the mobile phase consisted of mixture of 0.01 M Phosphate buffer (pH: 3) and Acetonitrile in ratio of (40:60%) at flow rate of 2 ml/min, with detection at 226 nm using PDA detector. The retention time was found to be 2.728 min. The method was found to be linear in the range of 10-60 µg/ml with a correlation coefficient (r^2) of 0.999. The LOD and LOQ of the method were calculated to be 0.256 and 0.776 µg/ml, respectively. The Precision was estimated by employing repeatability; intra-day and inter-day studies and the results were calculated as %RSD values and were found to be within the acceptable limits. Recovery of the drug was found to be in the range of 97-102%, which establishes the accuracy of the method. Forced degradation studies were conducted under a variety of conditions like acidic, alkali, thermal and oxidative. The stressed samples were analyzed by the developed analytical method, and the degradations in all stressed conditions was ≤ 30 % and within the acceptable limits. The proposed HPLC method is validated on the basis of ICH guidelines.

INTRODUCTION: Hypertension is the most prevalent disease worldwide and requires constant monitoring. The trend in cardiovascular drug research has been to develop new compounds acting on very specific targets. Telmisartan $C_{33}H_{30}N_4O_2$, (2-[4-[[4-methyl-2-propyl-6-[1(trideuteriomethyl) benzimidazol -2-yl] benzimidazol-1-yl] methyl]phenyl] benzoic acid) is abenzimidazole derivative, It blocks the vasoconstrictor and aldosterone-secreting effects of angiotensin II by selectively blocking the binding of angiotensin II to the AT1 receptor.

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It is safe with excellent therapeutic effect, having very few side-effects1, and is contraindicated during pregnancy. The half-life is 24 h. The chemical structure of the drug is shown in the below **Fig. 1**. UV Spectrophotometric 2-9 HPLC and HPTLC 10-17 methods are reported for estimation in Combination formulations and biological fluid.

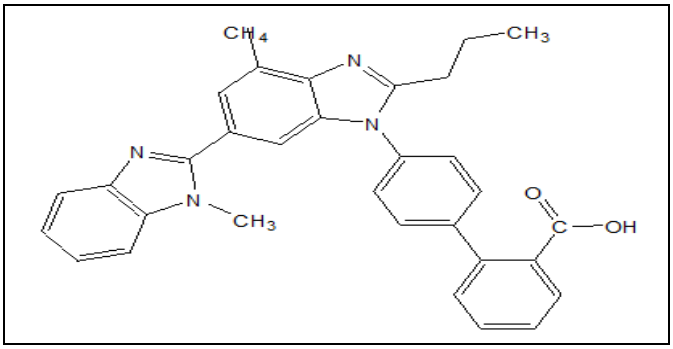

FIG. 1: THE CHEMICAL STRUCTURE OF TELMISARTAN

MATERIALS AND METHODS:

Instruments: The chromatography was performed on a Waters 2695 HPLC system, equipped with an autosampler, PDA detector, and Empower two software. Analysis was carried out at 226 nm with Kromasil C18 (4.6 × 150mm, 5 µm) dimensions at ambient temperature.

Chemicals and Reagents: Telmisartan Reference Standard, Methanol HPLC Grade, Ortho Phosphoric Acid Qualigens Fine Chemicals (Mumbai, India), Disodium Hydrogen Phosphate (Qualigens Fine, Chemicals, Mumbai, India), Acetonitrile HPLC (Qualigens Fine Chemicals, Mumbai, India) were procured from the local market.

Preparation of Buffer: 2.84 gram of Disodium hydrogen phosphate was accurately weighed and dissolved in 1000 ml HPLC grade water and sonicated for 3 min. The pH was adjusted to 3.0 with Ortho Phosphoric Acid.

Preparation of Mobile Phase: It was prepared by mixing of above buffer 400 ml (40%) and 600 ml of Acetonitrile HPLC grade (60%) and then it was sonicated for 5 min and filtered through 0.45µ filter membrane under vacuum filtration.

Diluent Preparation: Mobile phase was used as diluents.

Determination of λ_{max} of Analyte (Telmisartan): The λ_{max} of the Telmisartan standard solution (30µg/ml) was found with the help of UV-Visible Spectrophotometer mode of the instrument. The wavelength having maximum absorbance λ_{max} was found to be 226 nm.

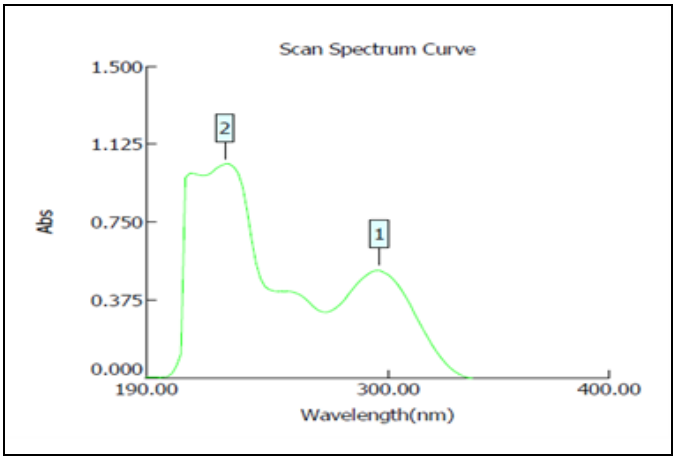

FIG. 2: UV SPECTRUM OF TELMISARTAN

Standard Stock Solution Preparation: Accurately weighed quantity of 10 mg of Telmisartan was transferred to 100ml volumetric flask containing 70 ml of diluents and sonicated for 3minutes to dissolve it completely and made up to the mark with diluents to obtain 100µg/ml.

Method Validation: The developed method was validated for linearity, accuracy, precision, and limit of detection, the limit of quantitation, robustness, and system suitability parameters as described in ICH guidelines [18].

Linearity: The concentration of the drug was prepared as given in **Table 1**.The linearity curve was constructed by taking concentration on the X-axis and Area on the Y-axis. The linear regression equation was found to be Y = 88278.08 X + 99607.46 and Co-relation coefficient (r2) = 0.999.The linearity data is given in **Table 1**. The calibration curve is given in **Fig. 1**. The representative chromatogram of the pure drug is shown in the below **Fig. 2**.

TABLE 1: LINEARITY DATA OF TELMISARTAN

S. no.	Concentration (µg/ml)	Area
1	10	1094214
2	20	1932452
3	30	2745378
4	40	3578254
5	50	4395563
6	60	5489787

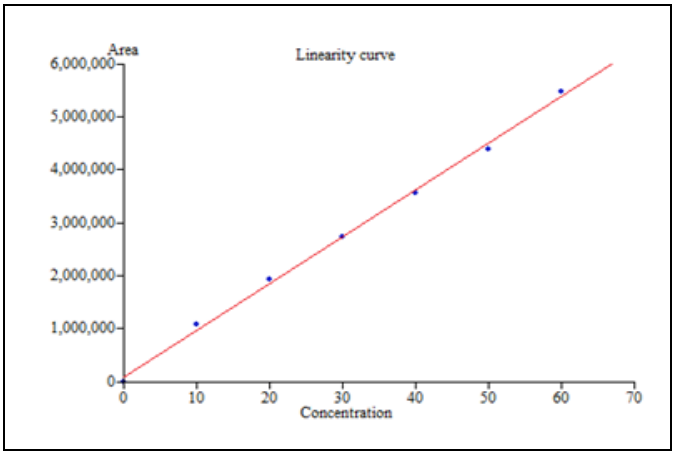

FIG. 3: THE CALIBRATION CURVE OF TELMISARTAN

Assay of Tablets: Accurately weighed 10 mg of tablet sample (Telmisartan) equivalent powder sample was taken into a 100 ml clean dry volumetric flask which was dissolved with diluent and sonicated and made volume up to the mark with the diluent. 2 ml of Telmisartan of the above

stock solution was taken into a 10 ml volumetric flask and made up to the mark with the diluents. The results of tablet analysis are given in **Table 2**.

The chromatograms of the tablet sample are shown in the below **Fig. 4**.

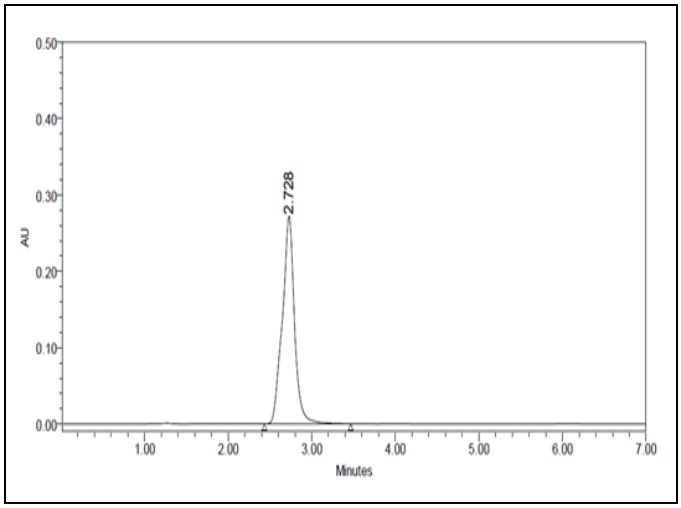

FIG. 4: REPRESENTATIVE CHROMATOGRAM OF TELMISARTAN (30 µG/ML)

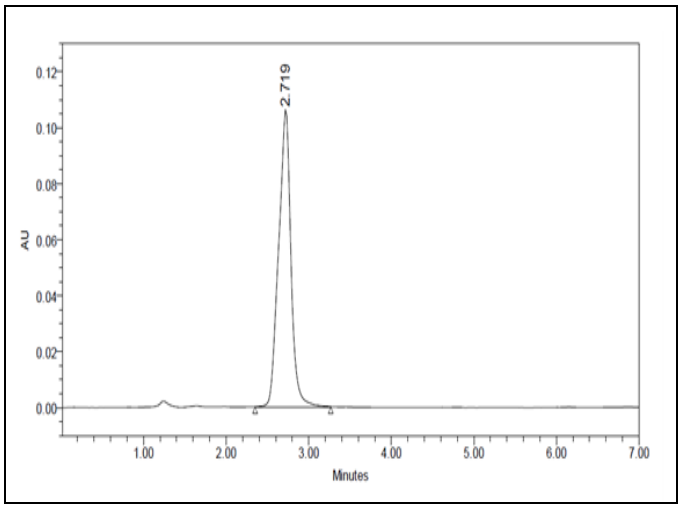

FIG. 5: REPRESENTATIVE CHROMATOGRAM OF TELMISARTAN TABLET SAMPLE SOLUTION

TABLE 2: RESULTS OF TABLET ANALYSIS (TELMISAT®)

Formulation Conc. (µg/ml)	Area	Found Conc. (µg/ml)	Label Claim (mg/tab)	% Assay	% RSD
20	1922417	20.734	20	103.673	
20	1920527	20.712	20	103.562	0.344
20	1932722	20.853	20	104.267	
20	1931517	20.839	20	104.196	

Precision: The precision of the method was evaluated by carrying repeatability in the same day (intra-day) and inter-day precision studies. The percentage relative standard deviation (% RSD) of each study was calculated and was found to be less than 1 % showing the method was precise.

TABLE 3: RESULTS OF SYSTEM SUITABILITY PARAMETER

Parameter	Results of Telmisartan
Retention time (minutes)	2.728
USP Plate count	1764.63
Tailing factor	1.03
Repeatability (% RSD)	0.47

System Suitability: It was carried out on a freshly prepared standard stock solution of Telmisartan (30 µg/ml), and the results of parameters were obtained by five replicate injections. The system suitability results are shown in **Table 3**.

Specificity: The peak purity of Telmisartan was assessed by comparing the retention time (Rt) of standard Telmisartan. A good correlation was also found between the retention time of standard and sample of Telmisartan.

Accuracy: It was found out by recovery study using standard addition method. Known amounts of standard Telmisartan were added to pre-analyzed samples at a level from 80 % upto 120% and then subjected to the proposed HPLC method. Results of recovery studies are shown in **Table 4**.

TABLE 4: RECOVERY DATA OF TELMISARTAN

% Level of recovery	Formulation (µg/ml)	Amount of drug added (µg/ml)	Amount of drug found (µg/ml)	C.I.	%RSD	SE	t
80	20	16	35.95	99.687±2.66	1.676	0.835	0.373
100	20	20	39.87	99.30±2.85	1.808	0.898	0.779
120	20	24	44.247	101.03+2.32	1.445	0.73	1.412

SD: Standard deviation, SE: standard error, C.I.: Confidence Interval within which true value may be found at 95% confidence level = R ± ts/√n, R: Mean percent result of analysis of Recovery study (n = 4). Theoretical 't' determined with respect to LOD and LOQ. The LOD and LOQ were separately determined based values at 95% confidence level for n-1 degrees of freedom t (0.05, 3) = 3.182

Sensitivity: The sensitivity of the method was on the standard calibration curve. The lower limit of detection and limit of quantitation were found to be 0.256 and 0.776 µg/ml, respectively.

Forced Degradation Studies:

Acid Degradation Sample: Twenty tablets were accurately weighed and finely powdered. An accurately weighed portion of tablet sample powder equivalent to 10 mg of Telmisartan was transferred into a 100 ml volumetric flask containing 50 ml of the 0.1 N HCl. The content of the flask was sonicated for 10mins and kept for 1hours at 40 °C, then cooled to room temperature, neutralized with 0.1N base (Sodium hydroxide), and diluted to volume with diluent. 5 ml of the above tablet sample solution was filtered through 0.45 µ membrane filter paper and transferred into a 10 ml volumetric flask, and then it was diluted with the diluents. Representative acid degradation chromatogram of Telmisartan is shown in the below **Fig. 6**.

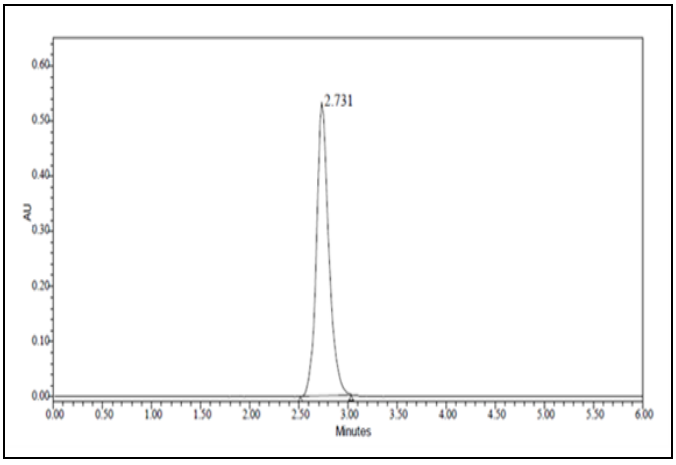

FIG. 6: REPRESENTATIVE ACID DEGRADATION CHROMATOGRAM OF TABLET SAMPLE

Base Degradation Sample: Twenty tablets were accurately weighed and finely powdered. An accurately weighed portion of tablet sample powder equivalent to 10 mg of Telmisartan was transferred into a 100 ml volumetric flask containing 50 ml of the 0.1 N NaOH. The content of the flask was sonicated for 10mins and kept for 1 h at 40 °C, then cooled to room temperature, neutralized with 0.1N HCl, and diluted to volume with diluent. 5 ml of the above tablet sample solution was filtered through 0.45 µ membrane filter paper and transferred into a 10ml volumetric flask, and then it was diluted with the diluents. The representative base degradation chromatogram of Telmisartan is shown in the below **Fig. 7**.

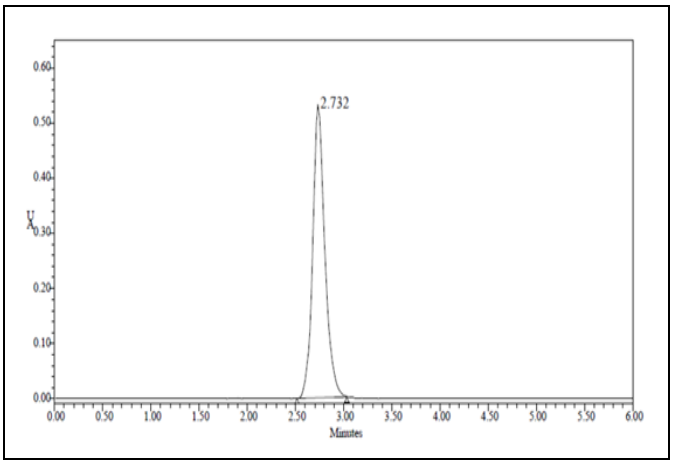

FIG 7: REPRESENTATIVE BASE DEGRADATION CHROMATOGRAM OF TELMISARTAN

Oxidative Degradation: Twenty tablets were accurately weighed and finely powdered. An accurately weighed portion of tablet sample powder equivalent to 10 mg of Telmisartan was transferred into a 100 ml volumetric flask containing 50 ml of the 3% H_2O_2.

The content of the flask was sonicated for 10mins and kept for 1 h at 4 0 °C, then cooled to room temperature and diluted to volume with 3% H_2O_2. 5 ml of the above tablet sample solution was filtered through 0.45 µ membrane filter paper and transferred into a 10 ml volumetric flask, and then it was diluted with the diluents. Representative oxidative degradation chromatogram of Telmisartan is shown in the below **Fig. 8**. The results of the forced degradation studies results are shown in **Table 5**.

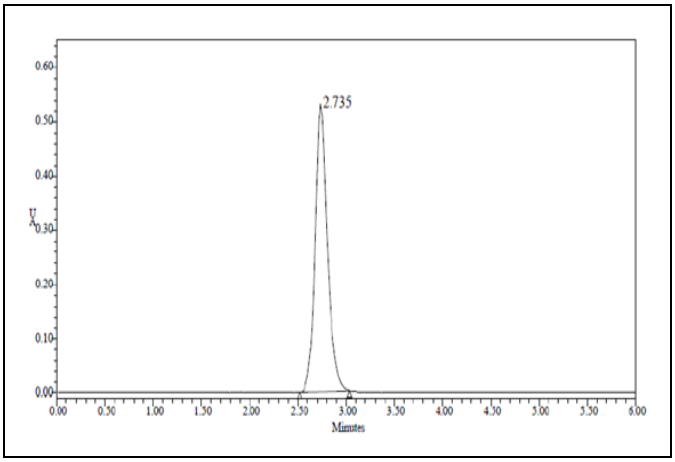

FIG. 8: REPRESENTATIVE OXIDATIVE DEGRADATION CHROMATOGRAM OF TELMISARTAN

Thermal Degradation: Twenty tablets were accurately weighed and finely powdered. An accurately weighed portion of tablet sample powder equivalent to 10 mg of Telmisartan was transferred into a 100 ml volumetric flask containing 50 ml of the diluent. The content of the flask was sonicated for 10 min and kept for 2 h at 80 °C, then cooled to room temperature and diluted to volume with diluent. 5ml of the above tablet sample solution was filtered through 0.45 µ membrane filter paper and transferred into a 10 ml volumetric flask, and then it was diluted with the diluents. Representative thermal degradation chromatogram of Telmisartan is shown in the below **Fig. 9**. The results of the forced degradation studies results are shown in the **Table 6**.

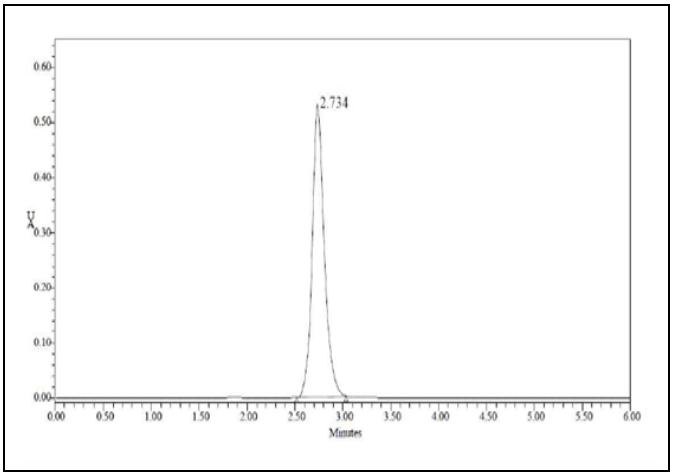

FIG. 9: REPRESENTATIVE THERMAL DEGRADATION CHROMATOGRAM OF THE SAMPLE

TABLE 5: RESULTS OF THE FORCED DEGRADATION STUDIES OF TABLET SAMPLE

Stress conditions	Degradation (Time) (Hr)	Telmisartan	
		% Assay	% Degradation
Control	1	99.94	-------
Acid	1	96.87	3.13
Base	1	90.78	9.22
Hydrogen Peroxide	1	82.88	17.12
Thermal	2	86.84	13.16

RESULTS AND DISCUSSION: The method was tried by utilizing different types of mobile phase compositions and different ratios of buffer and acetonitrile *i.e.* 70+30, 30+70, 50+50, and 60+40. The buffer and acetonitrile ratio was having 40% and 60% given the best chromatographic peak having Rt 2.728 min. The modalities adopted in experimentation were successfully validated as per analytical procedures laid down in routine.

The proposed method was validated by preliminary analysis of the standard sample and by recovery studies. The percentage of average recoveries was obtained in the range of 97.65 to 102.13. The results of average recoveries obtained in each instance were compared with the theoretical value of 100 percent by means of Student's t test. As the calculated't' values are less than theoretical 't' values in **Table 5**, it is concluded that the results of recoveries obtained in agreement with 100 percent for each analyte are accurate.

The absence of additional peaks in the chromatogram indicates a non-interference of the common excipients used in the tablets. The lower limit of detection and limit of quantitation were found to be 0.2563 and 0.7767 µg/ml, respectively.

Percentage relative standard deviation (%RSD) was found to be less than 2 % for all the parameters in the robustness study, which proves that method is robustness. Stress studies were performed by exposing the drug to 0.1 N HCl, 0.1 N NaOH, 3% H_2O_2, and thermal condition, and it was found that the drug was reasonably degraded (≤ 30 %) in acidic, basic, thermal, and oxidative medium, which is acceptable as per ICH guidelines.

CONCLUSION: The developed stability-indicating assay method is new, simple, linear, accurate, sensitive, precise, robust, and reproducible. Thus, the developed method can be easily used for the routine quality control of bulk and tablet dosage form.

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CONFLICTS OF INTERESTS: The authors declare that they have no conflict of interest.

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