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Optimized and Validated Stability Indicating RP-HPLC Method for the Determination of Telmisartan in Bulk and Pharmaceutical Formulations

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Abstract
A reverse phase high performance liquid chromatographic method (RP-HPLC) was developed for the determination of the amount of Telmisartan present in bulk and pharmaceutical formulations. Waters- Alliance High Performance Liquid Chromatographic system equipped with Auto Sampler, PDA detector and Hypersil BDS C18(4.6 × 50 mm, 3 µm) column were used for the method development. Separation of the components were carried out by using composition Ammonium dihydrogen phosphate and Methanol in the ratio 45:55 v/v was allowed as mobile phase at a flow rate of 1.0 mL per minute and the detection of the components was carried out at a wavelength of 298 nm. System suitability parameters such as retention time, tailing factor and USP theoretical plate count of the developed method were found to be 5 minute, 1.1 and 6500 respectively. The linearity between area of the peak and concentration of the drug was found to be 25-300%. The %recovery of Telmisartan were found to be 98.9(50%),98.9(100%) and 99.2(150%) respectively. From the study of forced degradation, the percent of recovery of the drug was found to be 97.2, 95.1, 99.8 and 96.5 under different degradation conditions such as acid (0.2N HCl), alkali (0.2N NaOH), peroxide (30%H_2O_2) and thermal. The developed method was found to be simple, fast, repeatable, reproducible, robust, rugged and economic hence it can be used as a new analytical method for the analysis of pharmaceutical formulations in any pharmaceutical industries.

Keywords
Telmisartan, RP-HPLC, Repeatability, Accuracy, Precision and Reproducibility and Linearity.

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INTRODUCTION
Telmisartan is a medication used to treat high blood pressure, heart failure, and diabetic kidney disease. It is a reasonable initial treatment for high blood pressure. It is a angiotensin II receptor antagonist and works by blocking the effects of angiotensin II. Telmisartan is contraindicated during pregnancy. Like other drugs affecting the renin–angiotensin

system (RAS), telmisartan can cause birth defects, stillbirths, and neonatal deaths. Telmisartan is an angiotensin II receptor blocker that shows high affinity for the angiotensin II receptor type 1 (AT1), with a binding affinity 3000 times greater for AT1 than AT2.In addition to blocking the 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 is chemically known as 2-[4-[[4-methyl-6-(1-methylbenzimidazol-2-yl)-2-propylbenzimidazol-1-yl]methyl]phenyl]benzoic acid. Chemical formula C33H30N4O2, molecular weight 514.629g/mol. V.P Kurade et.al[1] developed RP-HPLC Estimation of Ramipril and Telmisartan in Tablets. M. Lakshmi Surekha2 et.al developed, Development and Validation of RP - HPLC method for the estimation of Telmisartan in bulk and tablet dosage Form. Pravin y. khandagale3 et.al developed RP-HPLC method development and validation for simultaneous estimation of Clinidipine and Telmisartan in combined pharmaceutical dosage form. J.V.L.N. Seshagiri Rao4 et.al developed A Validated RP-HPLC Method for the Estimation of Telmisartan in Tablet Dosage forms. Biswa Ranjan patra5et.al developed stability indicating RP-UHPLC method for determination of Telmisartan in drug substance and marketed formulation.V.Bhavani6ety.al developed Stability indicating UPLC Method for the Estimation of Telmisartan Related Substances in Tablets Formulation. Yan T, Li H7et al developed Liquid chromatographic-tandem Mass spectrometric method for the simultaneous quantitation of telmisartan and hydrochlorothiazide in human plasma. Muthu AK8 et.al developed development and Validation of a Reversed Phase HPLC Method for Simultaneous Determination of Amlodipine and Telmisartan in Pharmaceutical Dosage Form. Bankey S9et.al developed Simultaneous determination of ramipril, hydrochlorothiazide and telmisartan by spectrophotometry. Komal Patel10et.al developed Stress degradation studies on telmisartan and development of a validated method by UV spectrophotometry in bulk and pharmaceutical dosage forms. Chitra Prabhu11et.al developed Determination of telmisartan by HPTLC- A stability indicating assay. Jayesh panchal G12et.al developed Development and validation of reversed-Phase LC method for simultaneous determination of telmisartan, amlodipine and their degradation products in fixed dose combination tablets. Psrchnp varma D13et.al developed a Stability indicating RP-HPLC method for simultaneous determination of telmisartan and hydrochlorothiazide in pharmaceutical dosage form. Rama mohana reddy M14et.al developed a Stability-indicating HPLC method for simultaneous estimation of low-level impurities of telmisartan and hydrochlorothiazide in tablet dosage forms. Dhanalakshmi K15et.al developed a analytical method development and validation of telmisartan and hydrochlorothiazide in dissolution by RP-HPLC.The aim of the present study was to develop and validate rapid, simple, and selective liquid chromatography method for Telmisartan quality control in tablets.

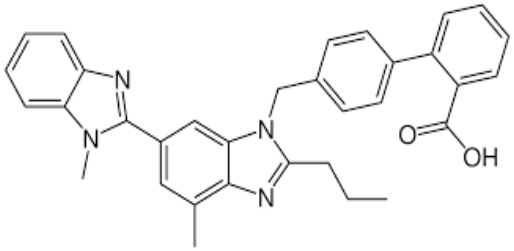

Figure 1: Molecular structure of Telmisartan

MATERIALS AND METHODS

Equipment

Waters-Alliance HPLC system equipped with auto sampler, binary gradient pump, and PDA detector was used for the separation. An analytical column; Hypersil BDS C18 (250mm x 4.6mm, 3 µm) was used in the analysis. Chromatographic software Empower -3 was used for data collection and processing. Double beam, 1cm length quartz coated optics and wavelength range190-400nm UV-Visible Spectrophotometer is used for measuring absorption spectrum.

Materials

Telmisartan pure drug was gifted Sample. The commercially available formulations of Telmisartan were purchased from the local market. The HPLC grade water was prepared by double glass distillation and filtration through 0.45 mm filters. Methanol of HPLC grade was obtained from E.Merck. (India) Ltd., Mumbai. Ammonium dihydrogen phosphate and

sodium hydroxide analytical grade are purchased from Qualigens Fine Chemicals Ltd., Mumbai. The mobile phase was prepared by mixing thoroughly 500ml of 0.02M Disodium hydrogen phosphate buffer pH 3.5 500ml of Acetonitrile in a 1000ml volumetric flask. Mobile phase was prepared and degassed for 10 minutes by sonication.

Preparation of standards

Stock solution (0.86 mg/mL) of the Telmisartan was prepared by dissolving accurately weighed 43mg of Telmisartan standard in 50mL of diluent in a volumetric flask, sonicated and made up to the mark. Further working standard (103µg/mL) was prepared by transferring 3mL of the stock solution into 25mL volumetric flask and diluted up to the mark with diluent, sonicated and filter through 0.45µm filter. A series dilute solution ranging from 25-150% were prepared by taking different aliquots (3–4mL) of the stock solution and diluted in different as explained under Linearity manner.

Preparation of test solution

Ten tablets of Telmisartan were accurately weighed and finely powdered in a mortar. An amount of tablet mass equivalent to 110mg was transferred to a 250mL volumetric flask and dissolved in 50 mL of water and then the flask was placed in sonicator for 5 min. The resulting solution was diluted to 130ml with diluent-1 and then sonicated for 15 minutes. Further sample diluted up to the mark with diluent 2, sonicated and filter through 0.45µm filter. An aliquot of 5 mL was transferred to a 20 mL volumetric flask and diluted upto the mark with diluent 2.

Developing optimum chromatographic conditions

Absorption spectrum of Telmisartan working standard was scanned from 200nm to 400nm range of wavelength with 2nm variation. From the absorbance spectrum it was found that 298 nm was the wavelength of maximum absorbance. The chromatographic separation was carried out under the isocratic conditions. The mobile phase was allowed to flow through the column at a flow rate of 1.0mL/min for 2 minutes to equilibrate the column at ambient temperature. Chromatographic separation was achieved by injecting a volume of 5 µl of standard into Hypersil BDS C18 (250mm x 4.6mm, 3 µm) column, the mobile phase of composition Ammo nium dihydrogen phosphate and Methanol in the ratio 45:55 v/v was allowed to flow through the column. Detection of the component was carried out at a wavelength of 298 nm. After some different trails with varying chromatographic parameters such as column, flow rate and injection volume were tested for obtaining best system suitability parameters such as peak shape, minimum run time and less tailing factor. The set of chromatographic conditions and the suitability parameters in four different trails were presented in Table-I and Table-II respectively.

RESULTS AND DISCUSSION

System suitability parameters

To evaluate system suitability parameters, a volume of 5 µl of Telmisartan working standard solution was injected into the analytical column, mobile phase was allowed to flow at a rate 1.0mL/min. for 2.0minutes and the components were detected at 298nm using PDA detector. System suitability parameters such as retention time, tailing factor and USP theoretical plate count of the developed method were found to be 5 minute, 1.1 and 6500 respectively. Typical chromatograms for blank, standard and test were shown in Figure 2, Figure 3 and Figure 4 respectively.

Intraday and inter day precision

Intraday precision of a method was the study of repeatability of the results. The repeatability was determined by injecting working standard (103µg/mL) solution of Telmisartan six times, chromatograms were obtained, and the % RSD of the area of six replicates was calculated and found to be 0.2%. The intermediate precision of the method was the study of reproducibility of the results in different days and was determined on six replicates from same lot by spiking. The %RSD of the area of five chromatograms was evaluated and found to be 0.2%. The results thus obtained were shown in Table-III and present within the acceptance criterion of NMT 2% RSD.

Linearity

To determine the linearity of the proposed method, a series of five different concentrated solutions of the standard Telmisartan were prepared and about 5µL of each solution was injected in duplicate into the HPLC system, chromatograms were recorded under the optimum chromatographic conditions. A plot between mean peak area and concentration was found to be linear in the range of concentration 25-300% and it was presented in Figure 5. Slope and correlation coefficient were calculated by least square regression method and were presented in Table-IV.

Accuracy

Accuracy of the proposed method was determined by analyzing Telmisartan sample spiked at three different concentration levels in triplicate. To find out the accuracy a known amount of standard drug was added to the fixed amount of pre-analyzed sample solution at three different concentration levels in triplicate. Percent recovery of the drug was

calculated by comparing the area before and after the addition of the standard drug. The mean recovery of the drug was found to be 98.9(50%),98.9(100%) & 99.2(300%) and shown in Table -V.

Robustness

The study of robustness was performed by slight modification in chromatographic conditions such as flow rate, wavelength and column temperature. The working standard solution of Telmisartan was analyzed under these new set of experimental conditions. Only one parameter was changed while the others were kept unaltered. The system suitability parameters were evaluated as per the test method in all the cases and found to be within limits shown in Table-VI.

Forced Degradation Studies

The percent of drug that was degraded in the presence of different stressed conditions like acid, base, peroxide, photolytic and thermal were studied. The drug standard was exposed to 0.2N HCl solution, 0.2N NaOH and 30% peroxide solutions for 24 hours at 80°C. In each case a working standard (103µg/mL) solution was prepared, injected into the system and the chromatograms were recorded. The amount of drug degraded was calculated by comparing the area of the standard with that of the area of the degraded sample. The results are presented in Table-VII.

Assay

The Developed method was functionalized for the tablet of Telmisartan and the mean % assay was found to be 99.62%. The results of % assay was shown in Table-VIII.

CONCLUSIONS

The system suitability parameters such as tailing factor and number of theoretical plates are found to be within the limits and the retention time of the component was found to be 5min. The intra-day precision and inter-day precision of a method was expressed in terms of %RSD found to be less than 2.0. The percentage recovery (accuracy) of the drug at three different concentration levels and the mean percent of recovery were found to be within the specified limits. The proposed method was linear in the range of concentration 25-300% with good correlation coefficient. Degradation of the drug under different stressed conditions was found to be negligible. Hence the proposed method was found to be simple, fast, precise, accurate, rugged, robust and economic; therefore, the method can be used for routine analysis in quality control.

Table-I: Optimization of the proposed HPLC method

Chromatographic conditions in different trails					
Trail Number	**Column**	**Flow Rate mL/min**	**Wavelength nm**	**Column Temp °C**	**Run Time min**
1	Hypersil BDS C18 (4.6 × 50 mm, 3 µm)	1.0	298	40	10
2	Hypersil BDS C18 (4.6 × 50 mm, 3 µm)	1.2	298	35	15
3	Hypersil BDS C18 (4.6 × 50 mm, 3 µm)	1.5	298	45	10
4	Hypersil BDS C18 (4.6 × 50 mm, 3 µm)	1.0	298	40	10

Optimized experimental conditions are achieved in Trail-4

Table-II: Chromatographic parameters obtained in various trails

Trail Number	Retention Time min	Peak area	Height	Plate count	Tailing factor	Remarks
1	4.00	2195810	16233	2747	1.64	Peak appears to be sharp having high tailing factor and an additional unknown peak was appeared
2	3.00	1137446	18025	3509	1.61	Peak shape was broad and diffused
3	5.00	1428920	43261	4578	1.96	Peak shape was not symmetric
4	5.00	1565409	33914	6500	1.1	Peak was symmetric having high area, height, plate count, valid tailing factor and comparable retention time relative to other chromatograms

Table-III: Intra –Day and Inter-Day Precision of the proposed method

Injection	Area	Area
	Intraday precision	Inter day precision
Injection-1	1567402	1562047
Injection-2	1563342	1567024
Injection-3	1566498	1563367
Injection-4	1561204	1566341
Injection-5	1564984	1561657
Injection-6	1569024	1561242
Average	1565409	1563613
Standard Deviation	2841.2	2491.5
%RSD	0.2	0.2

Table-IV: Linearity of the peak area against amount of the drug

Level No	Concentration µg/mL	Area
L1-25%	25.8	388706
L2-50%	51.6	781427
L3-100%	103.2	1564999
L4-150%	172.0	2574124
L5-300%	309.6	4662731
Slope		38447
Correlation Coefficient		0.998

Table -V: Accuracy of the proposed method

%Concentration	Amount Added	Amount Found	% Recovery	Mean Recovery
50%	0.05036	0.04977	98.9%	
100%	0.10042	0.09926	98.9%	99%
150%	0.30041	0.29787	99.2%	

Table- VI Study of Robustness of the proposed HPLC method

S.No.	Parameter	Retention time	Plate count	Tailing factor
1	Mobile phase 0.9mL/min	4.82	6251	1.0
	Mobile phase 1.0mL/min	4.41	5956	1.1
	Mobile phase 1.1mL/min	4.14	6104	1.2
2	Column Temp 23ºC	4.54	6152	1.0
	Column Temp 25ºC	4.41	5956	1.1
	Column Temp 27ºC	4.57	6041	1.2
3	wavelength 283nm	4.41	6177	1.2
	wavelength 285nm	4.41	5956	1.1
	wavelength 287nm	4.42	6114	1.2

Table -VII: Study of degradation of the drug

Degradation Parameter	%Assay	%Degradation	Purity Angle	Purity Threshold
Acid	97.2	3.8	0.51	0.60
Base	95.1	4.9	0.38	0.45
Peroxide	99.8	0.2	0.39	0.51
Thermal	96.5	3.4	0.35	0.44

Table -VIII: Assay data of Telmisartan Tablets

Tablet	Label Claim(mg)	Amount Found(mg/tablet)	% Label claim*± S.D	%Recovery
Telmisartan (Arbitel)	40	39.85	99.62±0.05	99.62

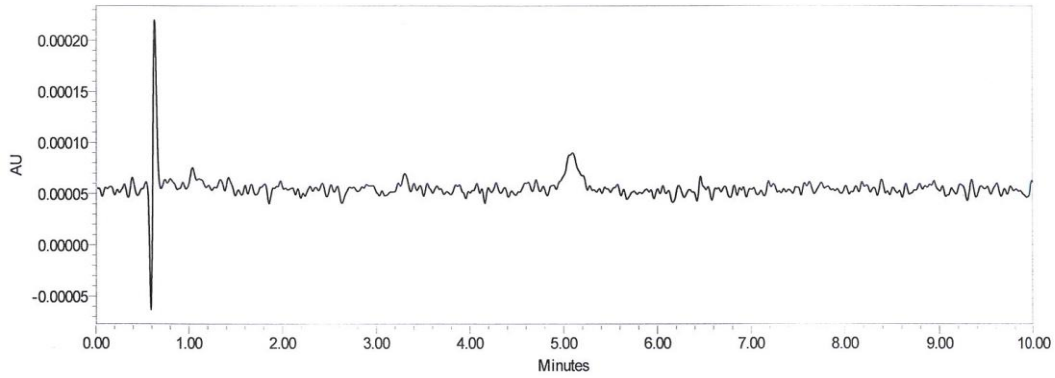

Figure 2: A typical chromatogram of Blank

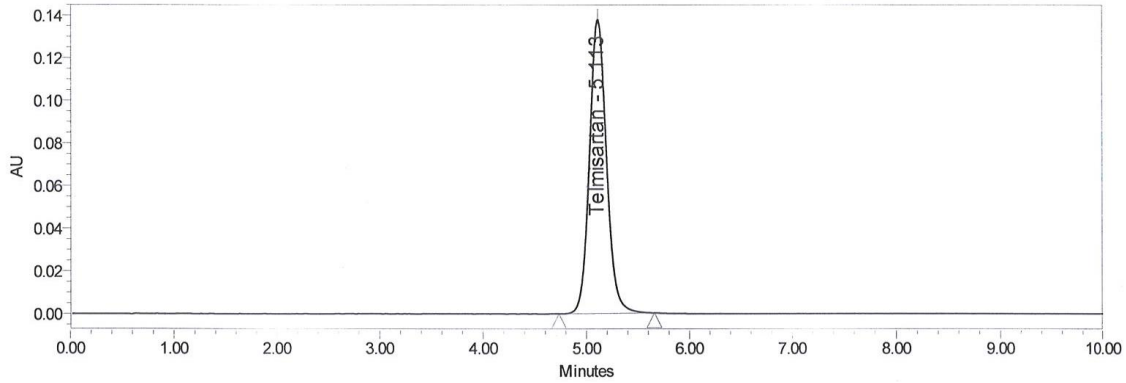

Figure 3: A typical chromatogram of Telmisartan standard

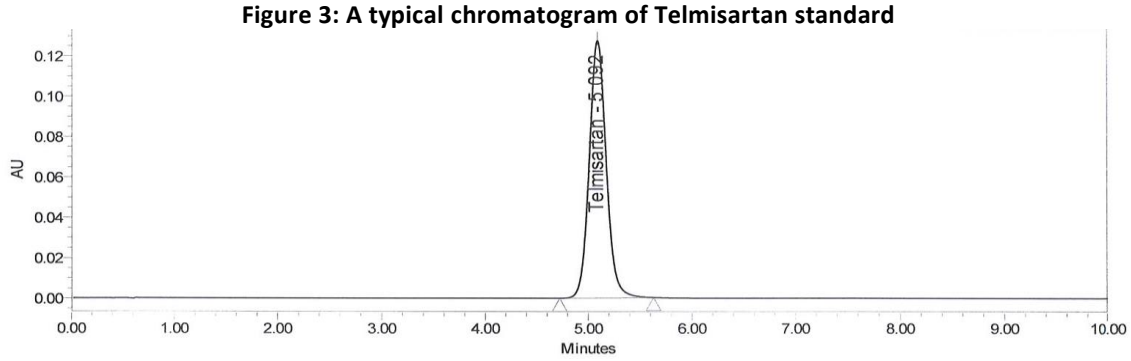

Figure 4: A typical chromatogram of Telmisartan sample

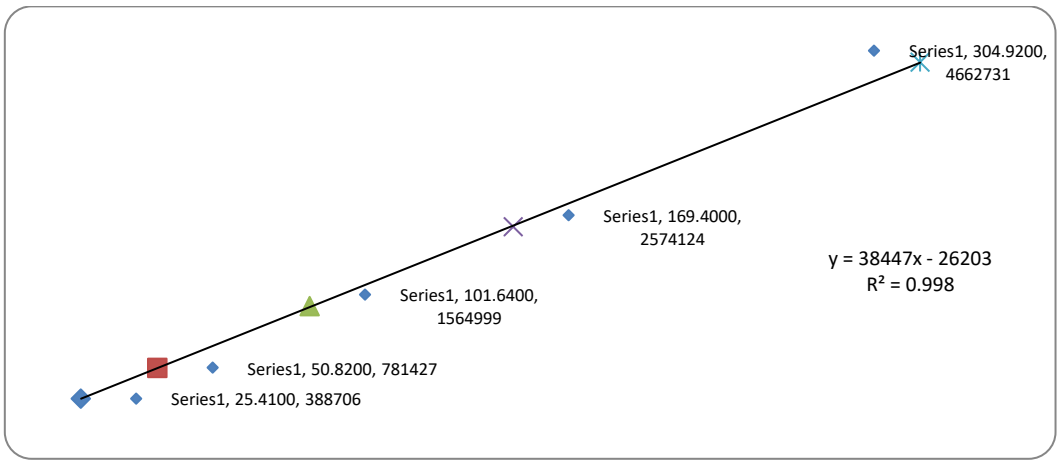

Figure 5: Linearity plot of peak area against to amount of Telmisartan

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