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Method development and validation for simultaneous estimation of telmisartan and amlodipine by RP-HPLC

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ABSTRACT

A novel, precise, accurate, rapid and effective isocratic RP-HPLC method was developed, optimized and validated for the estimation of Telimsartan (TEL) and Amlodipine (AML) in pharmaceutical dosage forms (tablet). The drugs were estimated using Symmetry C18 (250 x 4.6 mm, 5 µm) column. A mobile phase composed of phosphate buffer of pH 6 and acetonitrile in the ratio of 40:60, v/v), at a flow rate of 0.8 ml/min was used for the separation. Detection was carried out at 243 nm. The linearity range obtained was 16-48 µg/ml for TEL and 2-6 µg/ml for AML with retention times ($_R$t) of 3.209 min and 5.351 min for TEL and AML respectively. The correlation coefficient values were found to be 0.999. Precession studies showed % RSD values less than 2 % for both the drugs in all the selected concentrations. The percentage recoveries of TEL and AML were in the range of 98.01-101.62% and 99.30-101.40% respectively. The assay results of TEL and AML were 99.60% and 99.75% respectively. The method was validated as per the International Conference on Harmonization (ICH) guidelines. The developed validated method was successfully used for the quantitative analysis of commercially available dosage form.

Keywords: Telmisartan, Amlodipine, RP- HPLC, Symmetry C18 Column, Validation.

INTRODUCTION

Telmisartan (**fig 1**) is chemically 2-(4-{[4-methyl-6-(1-methyl-1H-1,3-benzodiazol-2-yl)-2-propyl-1H-1,3-benzodiazol-1-yl]methyl}phenyl)benzoic acid. It interferes with the binding of angiotensin II to the angiotensin II AT_1-receptor by binding reversibly and selectively to the receptors in vascular smooth muscle and the adrenal gland. As angiotensin II is a vasoconstrictor, which also stimulates the synthesis and release of aldosterone, blockage of its effects results in decreases in systemic vascular resistance [1]. Amlodipine (**fig 2**) is chemically 3-ethyl 5-methyl 2-[(2-aminoethoxy) methyl]-4-(2-chlorophenyl)-6-methyl-1,4-dihydropyridine-3,5-dicarboxylate. It decreases arterial smooth muscle contractility and subsequent vasoconstriction by inhibiting the influx of calcium ions through L-type calcium channels [2]. Literature survey reveals good number of analytical methods are available like UV [3-9], Spectroflourimetry [10], HPTLC [11], HPLC[12-16] and LC-MS [17-19] for their estimation individually or in combination with other drugs in pharmaceutical formulations and in biological samples. Few analytical methods like UV [20,21], HPTLC[22], HPLC[23-27] are available for the simultaneous estimation of Telmisartan (TEL) and Amlodipine (AML) in pharmaceutical dosage forms. We tried to develop a simple and alternative method for the estimation of TEL and AML by RP-HPLC in pharmaceutical dosage forms. The proposed method was optimized and validated as per the International Conference on Harmonization (ICH) guidelines [28].

MATERIALS AND METHODS

Instrumentation: To develop a high pressure liquid chromatographic method for simultanous estimation of Telmisartan and Amlodipine using Waters HPLC system. Symmetry C18 column (250 mm x 4.6 mm, 5µ) was used. The instrument is equipped with PDA detector 2487. A 20µL rheodyne injector port was used for injecting the samples. Data was analyzed by using Empower 2 software.

Chemicals and solvents: The working standard of Telmisartan and Amlodipine was obtained as gift

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samples from Dr.Reddy's Laboratories Ltd, Hyderabad, India. The market formulation Telma AM tablets (Telmisartan (40mg) and Amlodipine (5mg)) were procured from local market. HPLC grade water was purchased from Quiligens, Ortho Phosphoric acid (A.R.Grade) from E.Merck (India) Ltd, Mumbai, India.

Optimized chromatographic conditions:

Instrument used	Waters HPLC equipped with PDA detector
Temperature	Ambient
Column	Symmetry C18 (4.6 x 250mm, 5µm, Make: Waters)
Buffer	7.0 grams of potassium dihydrogen ortho phosphate in 1000 ml water pH adjusted with Sodium Hydroxide.
pH	6.0
Mobile phase	40% buffer, 60% acetonitrile
Flow rate	0.8 ml per min
Wavelength	243 nm
Injection volume	20 µl
Run time	7 min
Diluent	Mobile phase

Chromatographic conditions:
Preparation of buffer and mobile phase:

Preparation of Phosphate buffer: Accurately weighed 7.0 grams of KH_2PO_4 was taken in a 1000ml volumetric flask, dissolved and diluted to 1000ml with HPLC water and the volume was adjusted to pH 6.0 with Sodium hydroxide.

Preparation of mobile phase: Accurately measured 400 ml (40%) of above buffer and 600 ml of Acetonitrile HPLC (60%) were mixed and degassed in an ultrasonic water bath for 10 minutes and then filtered through 0.45µ filter under vacuum filtration.

Diluent Preparation: The Mobile phase is used as the diluent.

The buffer and mobile phase were filtered through a 0.45-µ (MILLIPORE, Germany) membrane filter prior to use. Prior to injection of the solutions, column was equilibrated for least 30min with mobile phase flowing through the system.

Standard Amlodipine besylate, and Telmisartan solution:

Preparation of Standard Solution: Accurately weighed 10mg equivalent amounts of Amlodipine and Telmisartan were taken into two separate 10ml cleaned and dried volumetric flasks. Then they are diluted with diluent and were sonicated. Then 1ml is pipetted out from both the stock solutions and volume was made to 10ml with the same solvent. This was labelled as Stock solution (100µg/ml). Further, an amount of 0.4ml Amlodipine and 1.6ml of Telmisartan each were pipetted from the above stock solutions into two 10ml volumetric flasks and diluted up to the mark with diluents to get 4µg/ml of Amlodipine and 32µg/ml of Telmisartan. The optimized chromatogram was given in **fig 7**.

Sample Amlodipine besylate, Telmisartan solution:

Sample Preparation (Assay): Accurately weighed 5mg equivalent amounts of Amlodipine and Telmisartan were taken into two separate 50ml cleaned and dried volumetric flasks. Then they are diluted with 40ml of diluent and were sonicated. The volume was made up to 50ml with the same solvent. This was marked and labeled as Stock solution(100µg/ml). Further, an amount of 0.4ml Amlodipine and 3.2 ml of Telmisartan each were pipetted from the above stock solutions into two 10ml volumetric flasks and diluted up to the mark with diluents to get 4µg/ml of Amlodipine and 32µg/ml of Telmisartan. The standard and sample solutions of 32µg/ml of Telmisartan and 4µg/ml of Amlodipine were injected for five times and the peak areas were recorded.

Injection of Standards and Samples into the Chromatographic system: 20µL of each standard and sample solution were injected into the chromatographic system and measured the areas of Telmisartan and Amlodipine peaks.

The assay results, expressed as % of the label claim, are in **table 1** .This indicates that the amount of each drug in the product meets the requirements.

Method Validation

System Suitability: System Performance parameters of developed HPLC method were determined by injecting standard solutions. Parameters such as number of theoretical plates (N), tailing factor, resolution(R), retention time (RT) were determined. The results are shown in **table 2**, it indicates good performance.

Specificity: Specificity is the ability of a method to discriminate between the analyte(s) of interest

and other components that are present in the sample. Studies are designed to evaluate the degree of interference, if any, which can be attributed to other analyte, impurities, degradation products, reagent "blanks" and excipients. This provides the analyst with a degree of certainty that the response observed is due to the single analyte of interest. The degree of specificity testing varies depending on the method type and the stage of validation. Specificity should be evaluated continually through the drug development process.

Placebo interference: A study of placebo interference from excipients was conducted. Equivalent weight of placebo taken as per the test method and placebo interference was conducted in duplicate.

The chromatograms were shown in **Fig.3&4**.The data is shown in **table 3**

Acceptance criteria: Placebo chromatogram should not show any peak at the retention times of TEL and AML.

Linearity: The linearity of the analytical procedure is its ability (within a given range) to obtain the test results which are directly proportional to the concentration (amount) of analyte in the sample.

Preparation of sample stock solution: Accurately weighed 5mg equivalent amounts of Amlodipine and Telmisartan were taken into two separate 50ml cleaned and dried volumetric flasks. Then they are diluted with 40ml of diluent and was sonicated. The volume was made up to 50ml with the same solvent. This was marked and labelled as Stock solution (100µg/ml).

Preparation of Level – I (2µg/ml of Amlodipine &16µg/ml of Telmisartan): 0.2ml of Amlodipine and 1.6ml of Telmisartan stock solutions are taken into two 10ml of volumetric flasks respectively and diluted up to the mark with diluent.

Preparation of Level – II (3µg/ml of Amlodipine & 24µg/ml of Telmisartan): 0.3ml of Amlodipine and 2.4ml of Telmisartan stock solutions are taken into two 10ml volumetric flasks respectively and diluted up to the mark with diluent.

Preparation of Level – III (4µg/ml of Amlodipine & 32µg/ml of Telmisartan): 0.4ml of Amlodipine and 3.2ml of Telmisartan stock solutions are taken into two 10ml of volumetric flasks and diluted up to the mark with diluent.

Preparation of Level – IV (5µg/ml of Amlodipine & 40µg/ml of Telmisartan): 0.5ml of Amlodipine and 4ml of Telmisartan stock solutions are taken into two 10ml of volumetric flasks and diluted up to the mark with diluent.

Preparation of Level – V (6µg/ml of Amlodipine & 48µg/ml of Telmisartan): 0.6ml of Amlodipine and 4.8ml of Telmisartan stock solutions are taken into two 10ml of volumetric flasks and diluted up to the mark with diluent.

Injecting the Solutions to the Chromatographic System: Each level of solution was injected to the chromatographic system and the peak area was measured. The calibration curves **(fig.5&6)** were constructed by plotting absorbance versus concentration and the regression equations were calculated**.** The results are shown in **tables 4**.

Acceptance Criteria: The Correlation coefficient should be not less than 0.99

Precision: Precision is the degree of agreement among individual test results when the method is applied repeatedly to multiple samplings of a homogenous sample. Precision of an analytical method is usually expressed as the standard deviation or relative standard deviation (coefficient of variation) of a series of measurements.

Precision may be measure of either the degree of reproducibility or of repeatability of the Analytical method under normal operating conditions.

Intermediate or method precision

4µg/ml of Amlodipine and 32µg/ml of Telmisartan of the above sample solution were injected for five times in five different days and peak areas were recorded. The results are given in **table 5 & 6.**

Acceptance Criteria: The %RSD for the area of five standard injections results should not be more than 2%.

Accuracy: The accuracy of an analytical procedure expresses the closeness of agreement between the value which is accepted either as a conventional true value or an accepted reference value and value found.

For accuracy determination, three different concentrations were prepared separately i.e. 50%, 100% and 150% for the analyte and chromatograms are recorded for the same. The results are given in **table 7.**

Preparation Sample solutions:

Preparation of 50% solution (2µg/ml of Amlodipine and 16µg/ml of Telmisartan): 0.2ml of Amlodipine and 1.6ml of Telmisartan stock solutions are diluted to 10ml in two separate volumetric flasks to get 2µg/ml of Amlodipine and 16µg/ml of Telmisartan.

Preparation of 100% solution (4µg/ml of Amlodipine and 32µg/ml of Telmisartan): 0.4ml of Amlodipine and 3.2ml of Telmisartan stock solutions are diluted to 10ml in two separate volumetric flasks to get 4µg/ml of Amlodipine and 32µg/ml of Telmisartan

Preparation of 150% solution (6µg/ml of Amlodipine and 48µg/ml of Telmisartan): 0.6ml of Amlodipine and 4.8ml of Telmisartan stock solutions are diluted to 10ml in two separate volumetric flasks to get 6µg/ml of Amlodipine and 48µg/ml of Telmisartan

These solutions were filtered through 0.45µ membrane and then each concentration; three replicate injections were made under the optimized conditions.

Acceptance Criteria: The % Recovery for each level should be between 98.0 to 102.0%.

Robustness: The analysis was performed in different conditions to find the variability of test results. The following conditions are checked for variation of results. From the above 100µg/ml stock solutions of Amlodipine and Telmisartan 0.4 ml and 3.2ml were pipetted respectively into two 10ml volumetric flasks and diluted up to the mark with diluents to get 4µg/ml of Amlodipine and 32µg/ml of Telmisartan. The results are given in **table 8.**

Effect of Variation of flow: The sample was analyzed at 0.7ml/min and 0.9ml/min flow rate instead of 0.8ml/min flow rate remaining conditions are same. 20µl of the above sample was injected thrice and chromatograms were recorded.

Effect of Variation of mobile phase organic composition: The sample was analyzed by variation of mobile phase i.e. phosphate buffer: acetonitrile was taken in the ratio 35:65 and 45:55 instead of 40:60, remaining conditions are same. 20µl of the above sample was injected thrice and chromatograms were recorded.

Ruggedness: The ruggedness of an analytical method is determined by analysis of aliquots from homogenous lots by different analysts using operational and environmental conditions that may differ but are still within the specified parameters of the assay. The assay was performed in different condition, different analyst, and different dates. The results are given in **table 9**.

Limit of Detection (LOD): The limit of detection (LOD) is the smallest concentration that can be detected but not necessarily quantified as an exact value.

(for Telmisartan):

Preparation of 1µg/ml solution: From 100µg/ml of above stock solution of Telmisartan prepare serial dilutions by taking 1ml from each stock and diluting it to 10ml until we get 0.1µg/ml of final stock solution.

Preparation of Telmisartan solution at Specification level (0.02µg/ml solution): From the above 0.1µg/ml stock solution take 0.2ml and dilute it to 10ml to get 0.02µg/ml of Telmisartan.

Limit of Quantitation (LOQ): The limit of quantitation is the lowest amount of analyte in the sample that can be quantitatively determined with precision and accuracy.

LOD,LOQ are shown in the **table10.**

for Amlodipine):

Preparation of 1µg/ml solution: From 100µg/ml of above stock solution of Amlodipine prepare serial dilutions by taking 1ml from each stock and diluting it to 10ml until we get 0.1µg/ml of final stock solution.

Preparation of 4.25% solution at Specification level (0.17µg/ml solution): From the above 0.1µg/ml stock solution take 1.7ml and dilute it to 10ml to get 0.17µg/ml of Amlodipine.

(for Telmisartan):

Preparation of 1µg/ml solution: From 100µg/ml of above stock solution of Telmisartan prepare serial dilutions by taking 1ml from each stock and diluting it to 10ml until we get 0.1µg/ml of final stock solution.

Preparation of 1.75% solution at Specification level (0.07µg/ml solution): From the above 0.1µg/ml stock solution take 0.7ml and dilute it to 10ml to get 0.07µg/ml of TEL.

RESULTS AND DISCUSSION

The objective of the proposed work was to develop method for the determination of TEL and AML and to validate the method according to ICH guidelines and applying the same for its estimation in pharmaceutical formulations. Initially, various mobile phase compositions were tried to elute title ingredients. Potassium dihydrogen ortho phosphate buffer was optimised at pH 6.0 by using sodium hydroxide. The mobile phase consists of Acetonitrile: phosphate buffer mixed in the ratio of 60:40 v/v. A Symmetry C18 column (4.6 x 250mm, 5µm) chemically bonded to porous silica particles was used as stationary phase. The detection was carried out using PDA detector at 243nm. The solutions were chromatographed at a constant flow rate of 0.8ml/min. The linearity range of AML and TEL were found to be from 2-6 µg/ml and 16-48 µg/ml respectively. Linear regression coefficient was more than 0.99. The values of %RSD are less than 2% indicating accuracy and precision of the method. The percentage recovery varies from 98-102% for AML and TEL. LOD and LOQ on the lower side indicates the sensitivity of the method. The results of robustness study also indicates that the method is robust and is unaffected by small variation in chromatographic condition. It was observed that excipient present in formulation did not interfere with peaks of TEL and AML. The summary of validation results are given in **table 11**.

CONCLUSION

From all results it was concluded that the developed RP-HPLC method is simple, sensitive, accurate, precise, and selective. Percentage

recovery shows that the method is free from interference of excipients used in the formulation. The results obtained on the validation parameters have been met with ICH guidelines and requirements. The method was found to have suitable application in routine laboratory analysis.

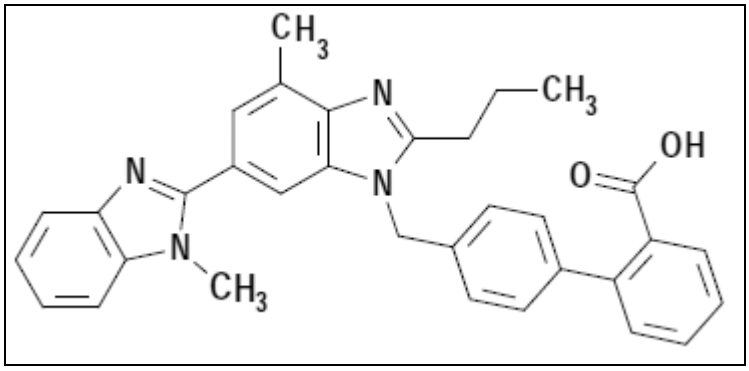

FIG. 1: STRUCTURE OF TELMISARTAN

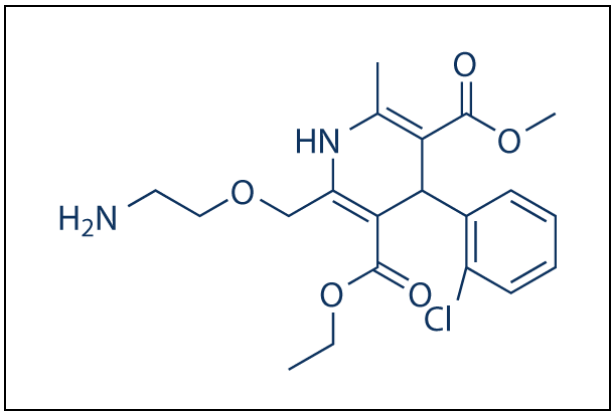

FIG. 2: STRUCTURE OF AMLODIPINE

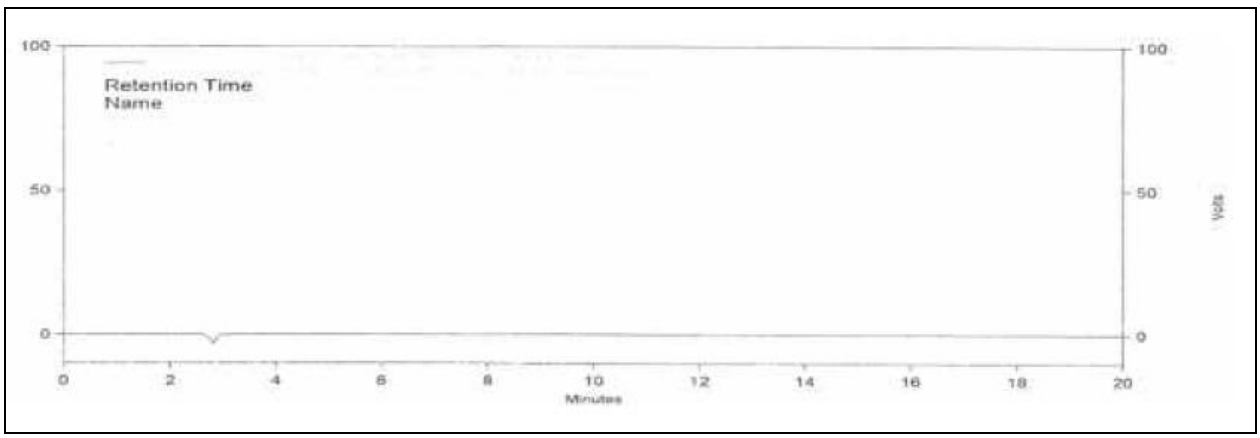

FIGURE 3: BLANK CHROMATOGRAM

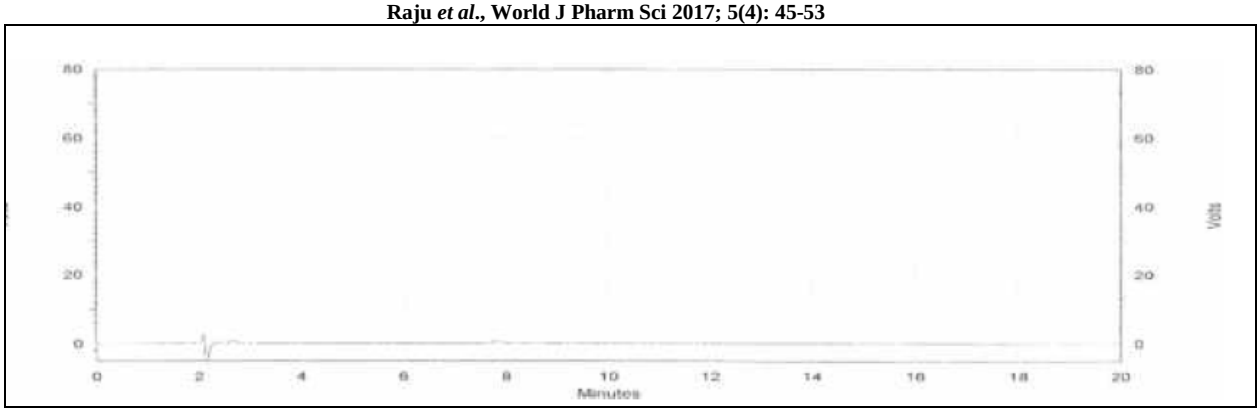

FIGURE 4: PLACEBO INTERFERENCE

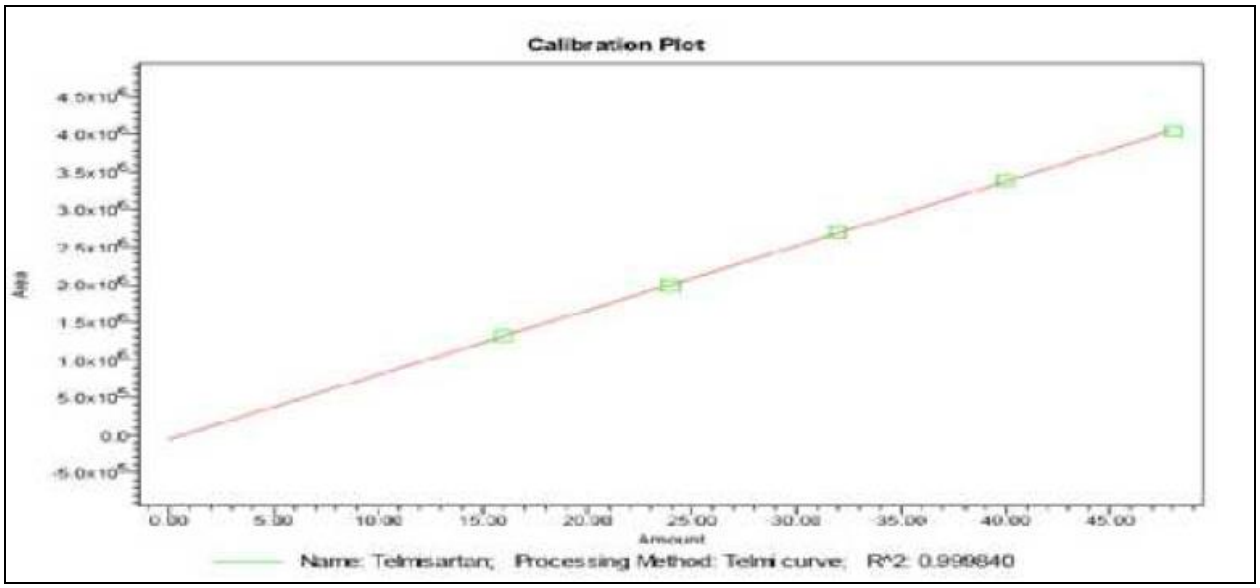

FIG. 5: LINEARITY CURVE FOR TELMISARTAN

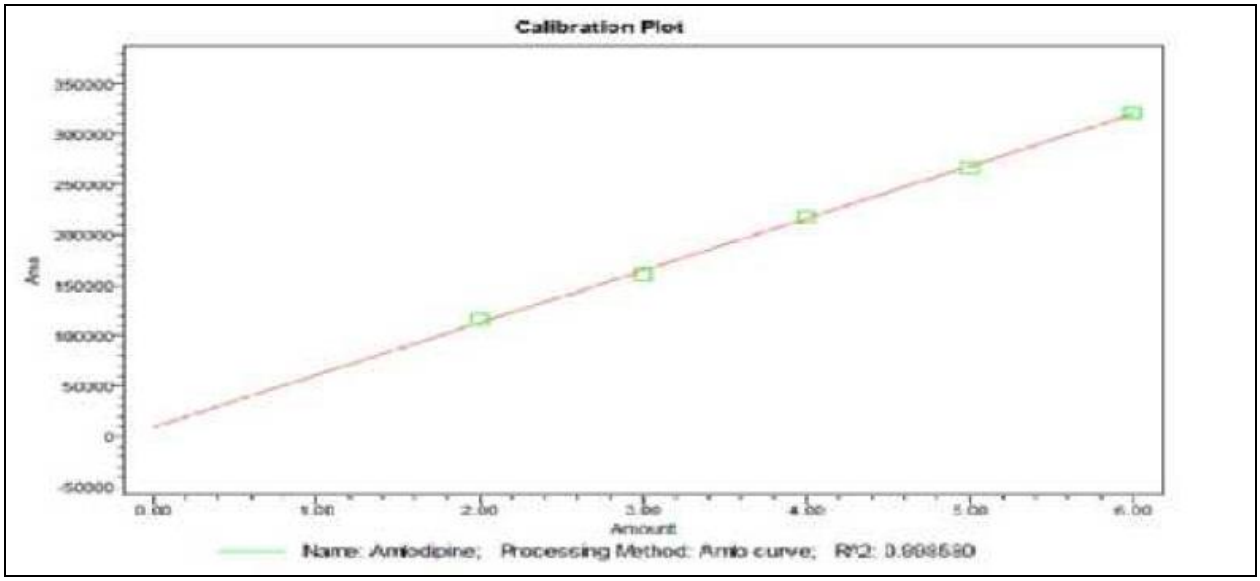

FIG. 6: LINEARITY CURVE FOR AMLODIPINE

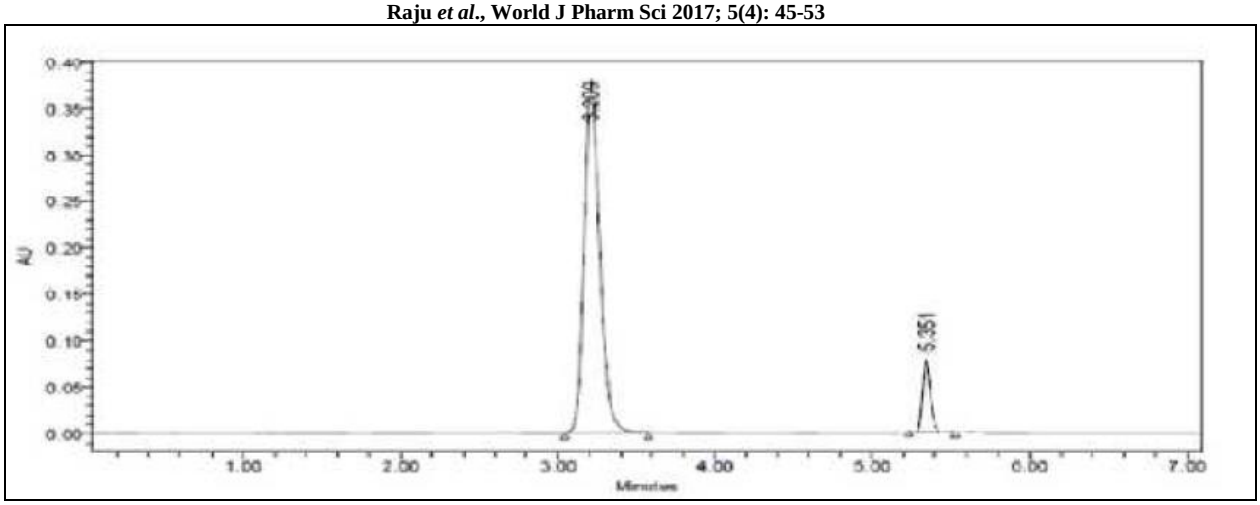

FIG. 7 THE CHROMATOGRAM REPRESENTING THE WELLRESOLVED PEAKS OF TEL & AML

TABLE 1: ASSAY OF TEL AND AML

Drug % Assay Amount in mg	Label recovered in mg	Amount Found	Assay %
Telmisartan	40 mg	39.97 mg	99.92%
Amlodipine	5 mg	4.98 mg	99.60%

TABLE 2: SYSTEM SUITABILITY PARAMETERS OF TEL AND AML

Drug	Theoretical plates	Tailing factor	Retention time	Resolution
Telmisartan	6087	1.201	3.212	10.012
Amlodipine	5471	1.210	5.508	

TABLE NO: 3 INTERFERENCE OF BLANK AND PLACEBO

Name	Interference	Retention time (minutes)
Blank	Nil	Nil
Placebo	Nil	Nil

TABLE 4: LINEARITY OF TEL AND AML BY RP-HPLC

S .No	Conc. Taken in µg/ml (TEL)	Conc. Taken in µg/ml (AML)	Peak area of TEL	Peak area of AML
1	16	2	1319889	115953
2	24	3	1983641	160213
3	32	4	2695378	218697
4	40	5	3385089	267002
5	48	6	4043725	321658

TABLE 5: SYSTEM PRECISION OF TEL AND AML

	Telmisartan		**Amlodipine**	
S NO	Rt	Area	Rt	Area
1	3.208	2694635	5.518	218236
2	3.224	2700238	5.521	219089
3	3.213	2701826	5.511	219096
4	3.308	2712297	5.551	219982
5	3.219	2718896	5.532	220774
AVG	3.234	270577.6	5.522	219434.9
STDEV	0.415	9807.71	0.155	971.21
% RSD	1.28	0.40	0.282	0.42

TABLE 6: METHOD PRECISION OF TEL AND AML

	Telmisartan		**Amlodipine**	
S NO	Rt	Area	Rt	Area
1	3.319	2722993	5.521	219902
2	3.321	2727423	5.510	220445
3	3.362	2734174	5.531	220528
4	3.299	2739277	5.521	221176
5	3.322	2742199	5.502	221602
AVG	3.324	2733213.3	5.517	220730.7
STDEV	0.022	8006.5	0.11	664.72
%RSD	0.69	0.32	0.203	0.38

TABLE 7: ACCURACY AND % RECOVERY OF EACH ANALYTE

Accuracy Level %	**Mean recovery of Telmisartan (%)**	**Mean recovery of Amlodipine (%)**
50	98.01	101.40
100	100.52	99.32
150	99.61	99.91

TABLE 8: ROBUSTNESS PARAMETERS OF TELMISARTAN AND AMLODIPINE

S No	**Parameter**	**Telmisartan**			**Amlodipine**		
		Rt	**Area**	**Tailing Factor**	**Rt**	**Area**	**Tailing Factor**
1	Initial Sample	3.213	2705126	1.202	4.439	218963	1.211
2	Flow (+0.2ml/min)	3.017	2427635	1.196	4.123	195919	1.195
3	Flow (-0.2ml/min)	3.721	3113051	1.212	4.721	201411	1.166
4	Temp Change 10 % more	3.282	2757335	1.188	4.452	217786	1.186
5	Temp Change 10 % less	3.241	2718476	1.199	4.448	207644	1.211

TABLE 9: RUGGEDNESS OF TELMISARTAN AND AMLODIPINE

S No	**Drug**	**Analyst-1(area)**	**Analyst-2(area)**	**SD**	**%RSD (Limit NMT 2.0%)**
1	Telmisartan	2712031	2824931	8862.21	0.39
2	Amlodipine	209861	213546	930.21	0.54

TABLE 10: LOD & LOQ OF TELMISARTAN AND AMLODIPINE

Drug	**LOD**	**LOQ**
Telmisartan (µg/mL)	0.02	0.07
Amlodipine (µg/mL)	0.05	0.17

TABLE 11: SUMMARY OF SYSTEM SUITABILITY AND VALIDATION PARAMETERS OF TEL AND AML

Parameter	Results	
	TEL	AML
Linearity range (µg/mL)	16-48	2-6
Correlation coefficient	0.999	0.999
Theoretical plates (N)	6087	5471
Tailing factor	1.201	1.210
LOD (µg/mL)	0.02	0.07
LOQ (µg/mL)	0.05	0.17

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