Research Article

Stability-Indicating RP-HPLC Method and its Validation for Analysis of Telmisartan and Rosuvastatin in Bulk and Pharmaceutical Dosage Form

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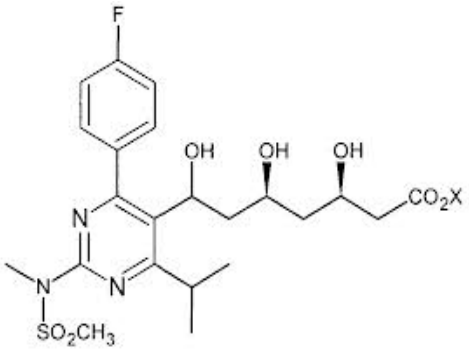
ABSTRACT

A simple, rapid, precise, sensitive and reproducible reverse phase high performance liquid chromatographic (RP-HPLC) method has been developed for quantitative analysis of Telmisartan & Rosuvastatin (TELROSE) in pharmaceutical dosage forms. Chromatographic separation of TELMI and ROSUVA was achieved on: Zodiac C18, 150mm x 4.6mm, 5µm. Waters symmetry column. The flow rate was 1.5 ml/min, the column temperature 50C, and detection was carried out by absorption at 241nm using a photodiode array detector. The number of theoretical plates and tailing factor for TELMI & ROSUVA were NLT 3000 and should be more than 2 respectively. TELROSE was exposed to thermal, photolytic, hydrolytic acid, alkali, and oxidative stress, and the stressed samples were analyzed by use of the proposed method & chromatograms from the stressed samples, obtained by use of the photodiode-array detector. The linearity of the method was excellent over the range 2-60 µg/ml and 8-240 µg/ml for ROSUVA & TELMI respectively. The correlation coefficient was 0.999. Relative standard deviations of peak areas of all measurements were always less than 2.0%. The proposed method was found to be suitable and accurate for quantitative analysis of TELROSE and study of its stability.

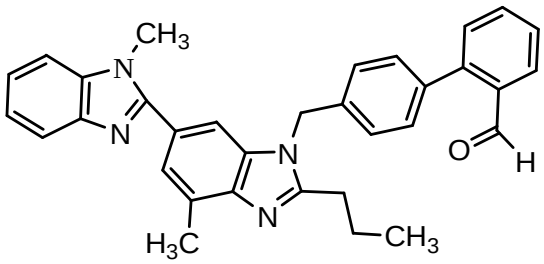
Keywords: High performance liquid chromatography, Telmisartan, Rosuvastatin.

INTRODUCTION

ROS calcium {(3R, 5S, 6E)-7-[4-(4-fluorophenyl)-2-(N-methyl methane sulfonamide)-6-(propan-2-yl) pyrimidin-5-yl]-3, 5-dihydroxyhept-6-enoic acid} , is used as lipid lowering agent. Its mode of action is competitive inhibitor of HMG CO-A reductase 1, 2. It acts by catalyses the reduction of 3hydroxyl -3-methyl glutaryl coenzyme to mevalonate which is a rate limiting step in hepatic cholesterol synthesis. **TEL** {2-(4-{[4-methyl-6-(1-methyl1H-1, 3-benzodiazol-2-yl)-2-propyl-1H-1, 3-benzodiazol-1-yl] methyl} phenyl) benzoic acid} is used as anti hypertensive agent. Its mode of action is interferes with binding of angiotensin II to angiotensin II AT1receptor by binding reversibly and selectively to the receptors in vascular smooth muscle and adrenal gland 3, 4. It does not inhibit the angiotensin work is aimed at development of a rapid, reliable, economic, sensitive and validated HPLC-PDA method for the simultaneous estimation of ROS and TEL in bulk and pharmaceutical dosage forms for routine and quality control tests. The method was validated in compliance with ICH guidelines.



Rosuvastatin calcium



Telmisartan

MATERIALS AND METHODS

Rosuvastatin and Telmisartan were obtained as gift samples from Dr. Reddy's laboratories, Hyderabad, India. Distilled, 0.45 µm filtered water used for HPLC analysis and preparation of buffer. Buffers, Acetonitrile and all other chemicals were analytical grade. The HPLC system consisted of a Waters model LC-20AD dual pump, a Waters model DGU-20A degasser, Waters model SPD-M20A photo diode array (PDA) detector and a Waters model SIL-20A HT auto injector. It was operated byEmpower2 software. The Zodiac-RP aqueous (C18) (250×4.6mm, 5µm) column was used and mixture of acetonitrile and buffer (pH 2.5 adjusted with ortho phosphoric acid) in the proportion of 40:60 v/v was used as mobile phase at a flow rate of 1.5 mL/min. The column was maintained at 50c temperature. Detector was programmed at 241 nm for detection of ROS and TEL.

Reagents required

1. Triethylamine (HPLC grade)
2. Ortho Phosphoric Acid (HPLC grade)
3. Acetonitrile (HPLC grade)
4. Methanol (HPLC grade)
5. HPLC grade Water (Milli Q or equivalent)

Preparation of Buffer

Pipette out 1ml of Triethylamine is dissolved into 1lt Water and adjust the pH-2.5 with Ortho Phosphoric acid.

Mobile phase

Prepare a mixture of Buffer and Acetonitrile in the ratio of (60:40% V/V). Filter and degas.

Chromatographic condition

Use suitable High Performance Liquid Chromatogram equipped with UV-visible detector.

Column : Zodiac C18, 150mm x 4.6mm, 5µm.
Wavelength : 241 nm
Injection Volume : 10µL
Column Temperature : 50°C
Flow rate : 1.5 mL/min
Retention time of Telmisartan is about 3.0 min and Rosuvastatin is about 5.4 min.

Preparation of Diluent

Prepare mixture of Acetonitrile, Methanol and Water in the ratio of 50+40+10. Used as a Diluent.

Preparation of standard solution

Weigh accurately about 160 mg of Telmisartan working standard and 40mg of Rosuvastatin Calcium.

Preparation of Sample solution

Weigh 10tablets and crush the tablets weigh powder then take 8 tablets equalent of sample into a 100 mL volumetric flask. Add 70 mL of diluent, sonicate to dissolve and dilute to volume diluent. Further dilute 5 mL to 100 mL with the diluent. Filter through 0.45µ Nylon syringe filter.

Procedure

Inject 10µL of Standard preparation five times and Sample preparation in the Chromatograph. Record the chromatograms and measure the peak responses for Telmisartan & Rosuvastatin. The System suitability parameters should be met. From the peak responses, calculate the content of Telmisartan & Rosuvastatin in the sample.

Evaluation of system suitability

1. Relative Standard Deviation of five replicate injections of Standard preparation for Telmisartan & Rosuvastatin peaks should not be more than 2.0%.
2. The tailing factor for Telmisartan & Rosuvastatin peaks should be more than 2.0 and plate count will be not less than 3000.

Forced Degradation studies

Forced degradation study was carried out by treating the sample under the following conditions. Sample Stock solution is from **Method Precision** sample flask.

a) Acid degradation

5 ml of the above stock solution was transferred into 100ml volumetric flask and added 60ml of diluent, treated with 5.0ml of 5N hydrochloric acid and heated at 60°c for 10 minutes, and cooled, neutralized with 5ml of 5N sodium hydroxide and diluted to volume with diluent and was analyzed as per the test method.

b) Alkali degradation

5 ml of the above stock solution was transferred into 100ml volumetric flask and added 60ml of diluent, treated with 5.0ml of 5N sodium hydroxide and heated at 60°c for 10 minutes, and cooled, neutralized with 5ml of 5N hydrochloric acid and diluted to volume with diluent and was analyzed as per the test method.

c) Peroxide degradation
5 ml of the above stock solution was transferred into 100ml volumetric flask and added with 60ml diluent was treated with 5 ml of 30% v/v solution of hydrogen peroxide and heated at 60°c for 10 minutes, cooled and diluted to volume with diluent and was analyzed as per the test method.

d) Reduction
5 ml of the above stock solution was transferred into 100ml volumetric flask and added with 60ml diluent was treated with 5 ml of 1N solution of sodium bisulphate and heated at 60°c for 10 minutes, and cooled, diluted to volume with diluent and was analyzed as per the test method.

e) Photolytic degradation
Sample was exposed to 1.2 Million lux hours of light and analyzed the exposed sample as per test procedure.

f) Thermal degradation
Sample was kept in hot air oven at 60°C for 1 hour. Treated sample was analyzed as per the test method.

RESULT AND DISCUSSION
Literature review reveals only individual methods for estimation of Rosuvastatin Calcium and Telmisartan but no methods were reported for simultaneous estimation of Rosuvastatin Calcium and Telmisartan. So method was developed method more superior than previously published methods of individual estimation of both drugs.. The composition of mobile phase is adjusted to maintain highly accurate and specific results. The detection wavelength of 241nm was chosen in order to achieve a good sensitivity for quantitative determination of Rosuvastatin Calcium and Telmisartan in solid dosage form. The chromatographic separation of Rosuvastatin and Telmisartan in the present combination is shown in figure and separation of active ingredients. The compounds eluted in the order of Rosuvastatin Calcium and Telmisartan with retention time of 3.0 min and 5.4min respectively. The isocratic program throughout HPLC method was adopted to analyze two components in a single run.

Method validation
This method described above had been validated as per the ICH guidelines for the parameters like accuracy, linearity, precision, detection limit, quantitation limit and robustness. And the results were summarized below.

Linearity
The linearity responses in the concentration range of 2-60 µg/mL for ROS and 8-240 µg/mL for TEL was determined. And the co-relation coefficient was NLT 0.99.

Precision
Precision was measured in terms of repeatability of application and measurement. Study was carried out by injecting six replicates of the standard at a concentration of 40µg/mL for ROS and 160µg/mL for TEL. And the RSD calculated from replicates of assay values NMT 2.0%

Accuracy
Accuracy (Recovery) of the method was determined by spiking 50, 100 and 150% of working standard at a concentration of 40µg/mL for ROS and 160µg/mL for TEL. Samples were injected in triplicate across its range according to the assay procedure. The RSD calculated from replicates of assay values NMT 2.0% and the percentage recovery was in between 98% to 102%

Detection and quantitation limits
The LOD and LOQ values were determined by the formulae LOD = 3.3 s/ m and LOQ = 10 s/m (Where, s is the standard deviation of the responses and m is mean of the slopes of the calibration curves).

System suitability
The system suitability was assessed using five replicate analyses of drugs at concentration of 40µg/mL for ROS and 160µg/mL for TEL by increasing the injection volumes 10-50µL.

Specificity
Specificity studies were carried for both pure drug and drug product by comparing the plots with blank and placebo. Peak purity tests were also carried out to show that the analyte chromatographic peak is not attributable to more than one component as the impurities are not available by purity index data.

Robustness
Robustness of the method was determined by making slight changes in the chromatographic conditions, such as flow rate (1±0.1 mL/min), wavelength (±1nm),organic phase(± 10%) and pH (±0.2).

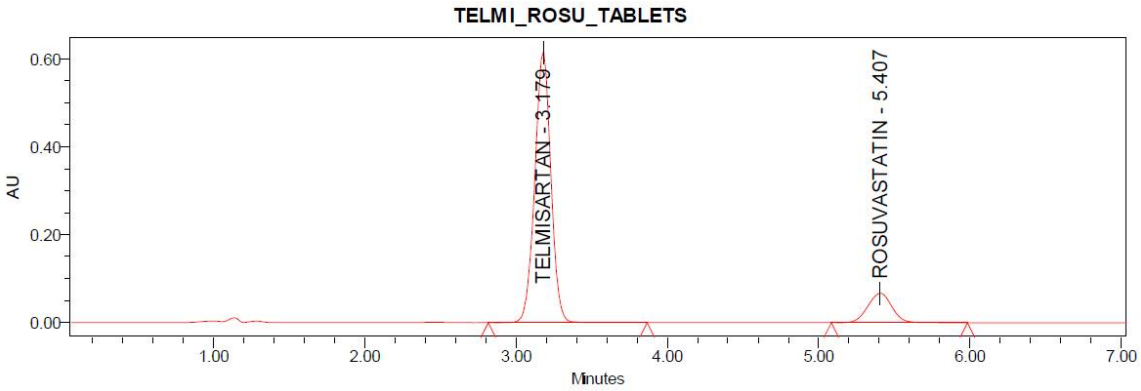


Fig. 1: Control peak

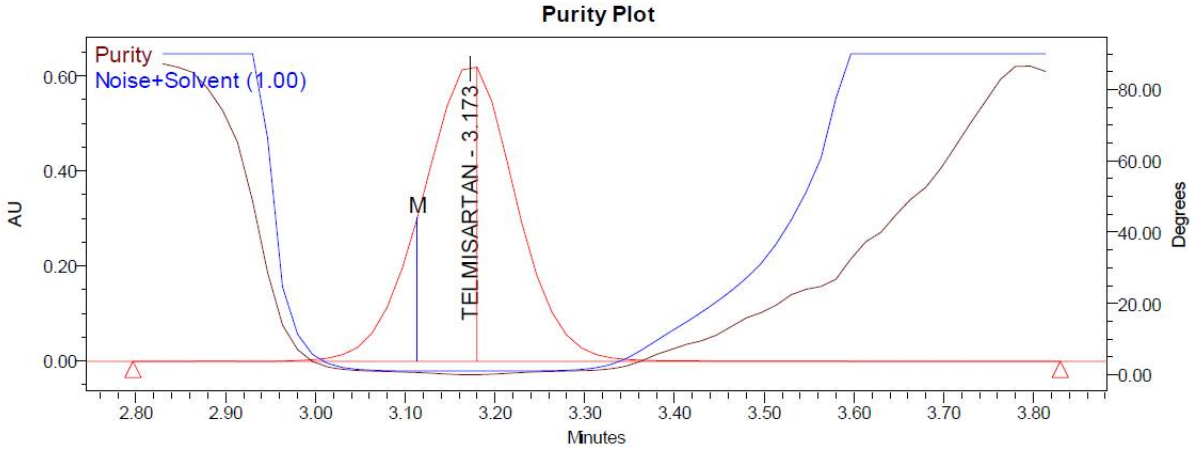


Fig. 2: Purity plot for Telmisartan

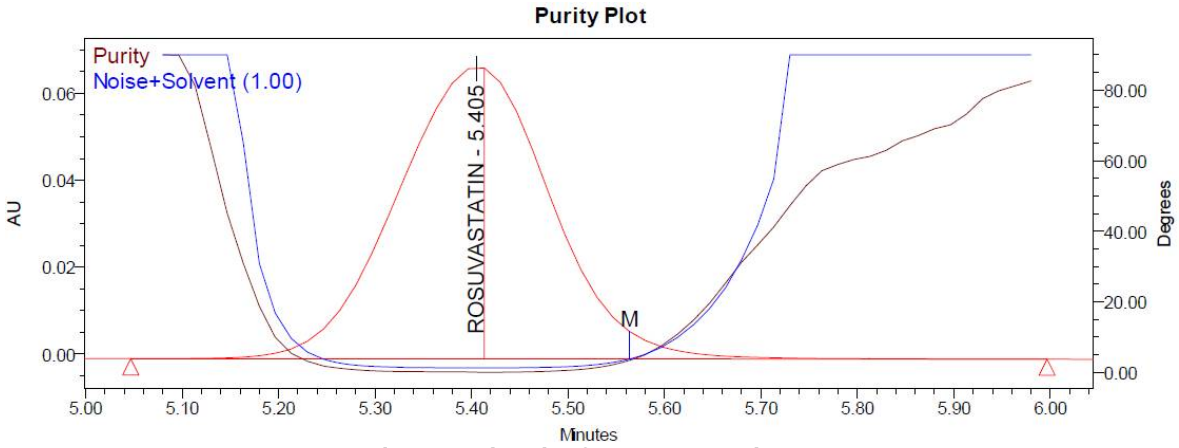


Fig. 3: Purity plot for Rosuvastatin

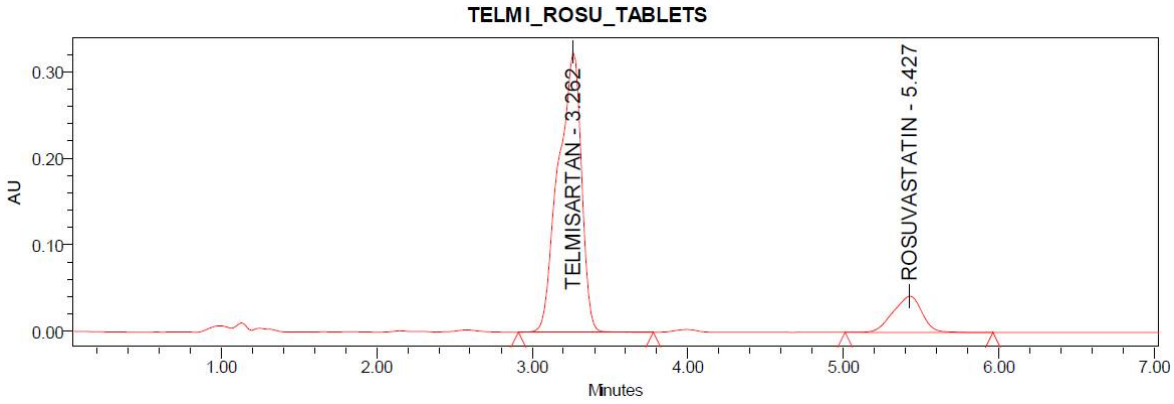


Fig. 4: Acid degradation

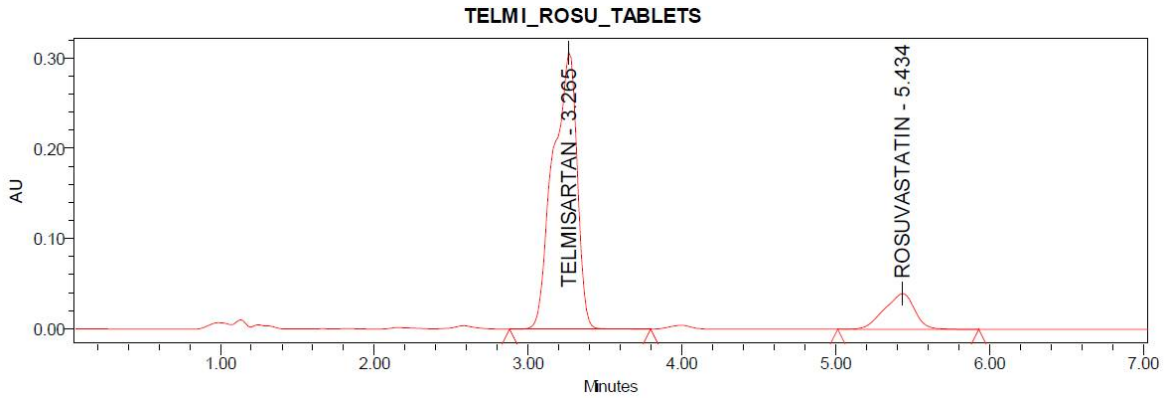


Fig. 5: Alkali degradation

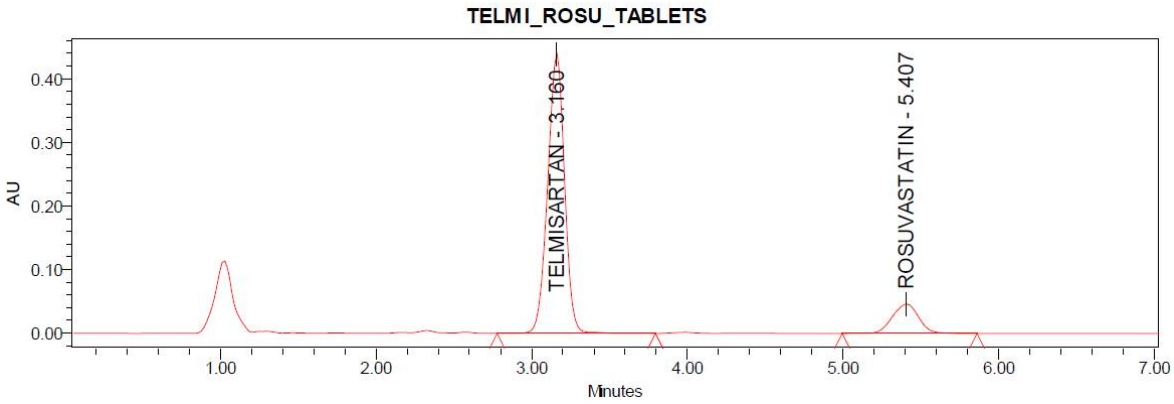


Fig. 6: Peroxide degradation

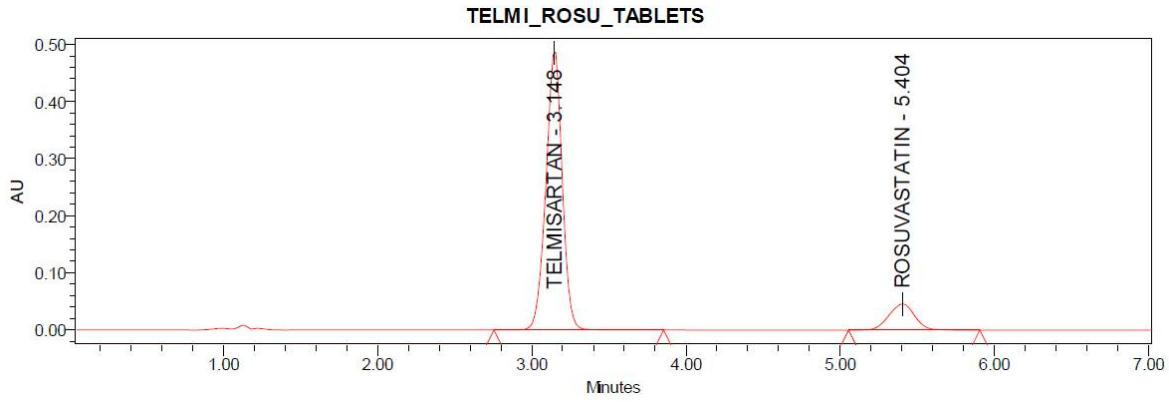


Fig. 7: Reduction degradation

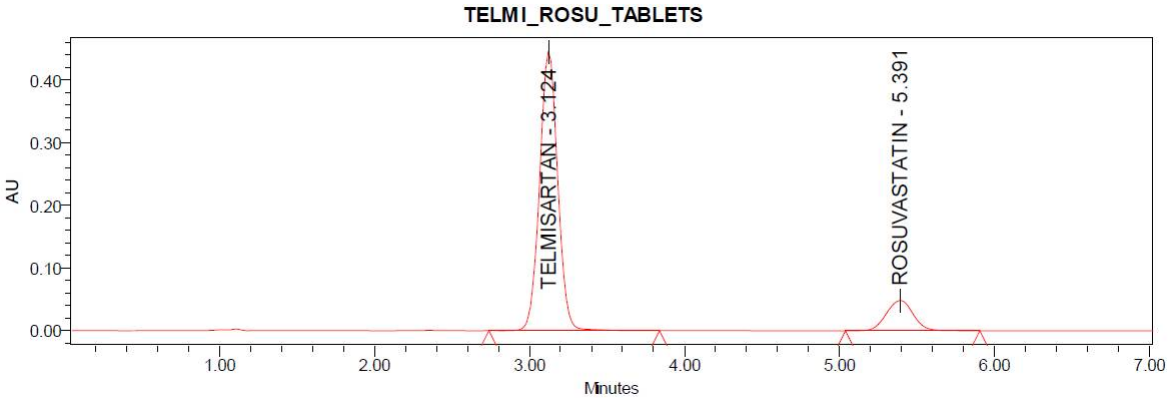


Fig. 8: Thermal degradation

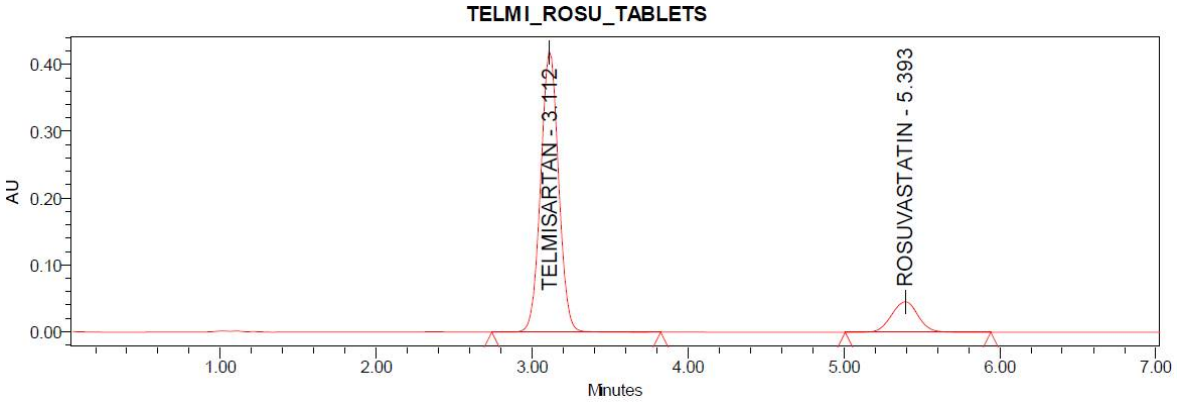


Fig. 9: Photolytic degradation

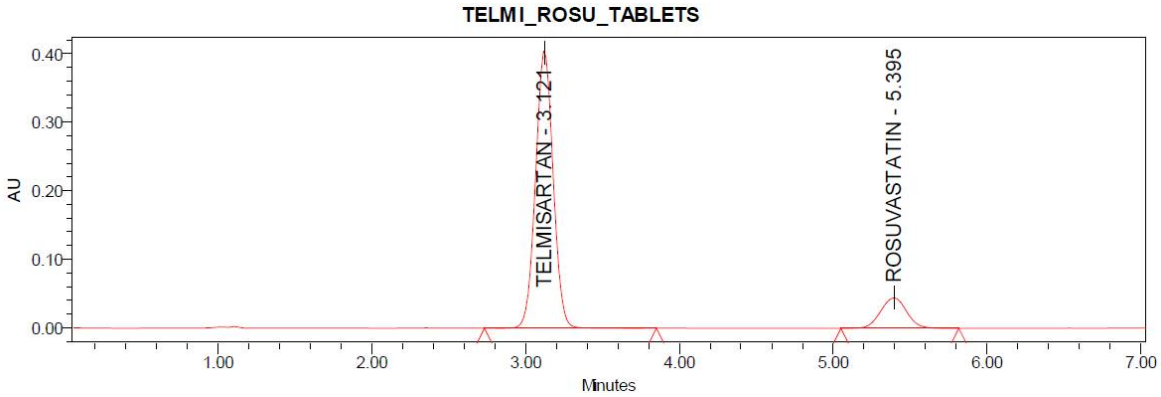


Fig. 10: Hydrolysis degradation

ASSAY

Table 1:

Peak Results
Name: ROSUVASTATIN

	Name	Injection	RT	Area	USP Plate Count	USP Tailing
1	ROSUVASTATIN	1	5.398	770522	9200	1.066
2	ROSUVASTATIN	2	5.400	774186	9185	1.058
3	ROSUVASTATIN	3	5.402	774829	9154	1.069
4	ROSUVASTATIN	4	5.404	777581	9151	1.063
5	ROSUVASTATIN	5	5.404	781677	9187	1.066
6	ROSUVASTATIN	6	5.406	781720	9150	1.074
7	ROSUVASTATIN	1	5.398	779973	9189	1.076
Mean				777213		

Table 2:

Peak Results
Name: TELMISARTAN

	Name	Injection	RT	Area	USP Plate Count	USP Tailing
1	TELMISARTAN	1	3.093	4502987	6281	1.088
2	TELMISARTAN	2	3.093	4517885	6306	1.095
3	TELMISARTAN	3	3.095	4523565	6311	1.089
4	TELMISARTAN	4	3.094	4529793	6317	1.089
5	TELMISARTAN	5	3.092	4562682	6349	1.096
6	TELMISARTAN	6	3.086	4554642	6242	1.096
7	TELMISARTAN	1	3.081	4578301	6300	1.087
Mean				4538551		
% RSD				0.598		

Table 3: Linearity

Peak Results
Name: ROSUVASTATIN

	Vial	Injection	Sample Name	Name	RT	Area	USP Resolution	USP Tailing	USP Plate Count
1	3	1	LINEARITY-1	ROSUVASTATIN	5.936	36846	16.1941	0.9961	7151
2	3	2	LINEARITY-1	ROSUVASTATIN	5.956	36911	16.4803	0.9816	7414
3	4	1	LINEARITY-2	ROSUVASTATIN	5.883	60381	16.3736	0.9901	7133
4	4	2	LINEARITY-2	ROSUVASTATIN	5.842	60416	16.1021	0.9965	6950
5	5	1	LINEARITY-3	ROSUVASTATIN	5.838	156816	16.1147	0.9936	6882
6	5	2	LINEARITY-3	ROSUVASTATIN	5.852	156959	16.2180	0.9977	7145
7	6	1	LINEARITY-4	ROSUVASTATIN	5.857	330094	16.0920	0.9974	7063
8	6	2	LINEARITY-4	ROSUVASTATIN	5.866	328047	16.1080	0.9970	6870
9	7	1	LINEARITY-5	ROSUVASTATIN	5.873	473538	16.2058	1.0028	7017
10	7	2	LINEARITY-5	ROSUVASTATIN	5.873	475497	16.1016	1.0056	6970
11	8	1	LINEARITY-6	ROSUVASTATIN	5.864	620154	16.1486	1.0070	6899
12	8	2	LINEARITY-6	ROSUVASTATIN	5.866	622684	16.0643	1.0077	6847
13	9	1	LINEARITY-7	ROSUVASTATIN	5.862	780049	16.3192	1.0019	7041
14	9	2	LINEARITY-7	ROSUVASTATIN	5.810	765451	16.1677	1.0097	7038
15	10	1	LINEARITY-8	ROSUVASTATIN	5.805	948741	15.9261	1.0101	7025
16	10	2	LINEARITY-8	ROSUVASTATIN	5.793	950338	15.9532	1.0101	7033
Mean						425183			
% RSD						0.634			

Table 4:

Peak Results
Name: TELMISARTAN

	Vial	Injection	SampleName	Name	RT	Area	USP Resolution	USP Tailing	USP Plate Count
1	3	1	LINEARITY-1	TELMISARTAN	2.425	210413		1.0755	4714
2	3	2	LINEARITY-1	TELMISARTAN	2.427	213703		1.0479	4793
3	4	1	LINEARITY-2	TELMISARTAN	2.404	341926		1.0618	4696
4	4	2	LINEARITY-2	TELMISARTAN	2.384	342581		1.0610	4353
5	5	1	LINEARITY-3	TELMISARTAN	2.370	892635		1.0853	4468
6	5	2	LINEARITY-3	TELMISARTAN	2.395	892314		1.0654	4665
7	6	1	LINEARITY-4	TELMISARTAN	2.402	1803679		1.0991	4470
8	6	2	LINEARITY-4	TELMISARTAN	2.383	1793228		1.0763	4333
9	7	1	LINEARITY-5	TELMISARTAN	2.371	2554084		1.1065	4440
10	7	2	LINEARITY-5	TELMISARTAN	2.373	2564974		1.1059	4492
11	8	1	LINEARITY-6	TELMISARTAN	2.362	3292549		1.0883	4471
12	8	2	LINEARITY-6	TELMISARTAN	2.357	3304727		1.1118	4444
13	9	1	LINEARITY-7	TELMISARTAN	2.353	4108246		1.1225	4289
14	9	2	LINEARITY-7	TELMISARTAN	2.367	4027963		1.1216	4254
15	10	1	LINEARITY-8	TELMISARTAN	2.373	4968574		1.1275	4476
16	10	2	LINEARITY-8	TELMISARTAN	2.381	4977924		1.1136	4353
Mean						2268095			
% RSD						0.923			

Table 5: ACCURACY

Peak Results
Name: ROSUVASTATIN

	Vial	Injection	SampleName	Name	RT	Area	USP Resolution	USP Tailing	USP Plate Count
1	11	1	ACCURACY-50%-1	ROSUVASTATIN	5.789	292234	16.0065	1.0041	7241
2	11	2	ACCURACY-50%-1	ROSUVASTATIN	5.789	292591	16.0217	1.0061	7255
3	12	1	ACCURACY-50%-2	ROSUVASTATIN	5.786	300345	16.0788	0.9982	7106
4	12	2	ACCURACY-50%-2	ROSUVASTATIN	5.782	293449	15.9921	1.0063	7023
5	13	1	ACCURACY-50%-3	ROSUVASTATIN	5.786	327602	16.2935	0.9992	7444
6	13	2	ACCURACY-50%-3	ROSUVASTATIN	5.795	331510	16.1322	1.0039	7191
7	14	1	ACCURACY-100%-1	ROSUVASTATIN	5.790	620349	15.9631	1.0167	7273
8	14	2	ACCURACY-100%-1	ROSUVASTATIN	5.789	619979	15.9116	1.0174	7226
9	15	1	ACCURACY-100%-2	ROSUVASTATIN	5.783	628048	16.1297	1.0140	7093
10	15	2	ACCURACY-100%-2	ROSUVASTATIN	5.789	627965	16.0090	1.0183	7152
11	16	1	ACCURACY-100%-3	ROSUVASTATIN	5.792	626440	16.1407	1.0165	7181
12	16	2	ACCURACY-100%-3	ROSUVASTATIN	5.783	625419	16.1020	1.0173	7054
13	17	1	ACCURACY-150%-1	ROSUVASTATIN	5.777	985657	16.0370	1.0214	7095
14	17	2	ACCURACY-150%-1	ROSUVASTATIN	5.763	973176	16.2641	1.0218	7324
15	18	1	ACCURACY-150%-2	ROSUVASTATIN	5.646	964278	16.0250	1.0221	7061
16	18	2	ACCURACY-150%-2	ROSUVASTATIN	5.671	964241	16.0503	1.0175	7212
17	19	1	ACCURACY-150%-3	ROSUVASTATIN	5.672	903347	16.0089	1.0236	7221
18	19	2	ACCURACY-150%-3	ROSUVASTATIN	5.666	904561	16.1215	1.0208	7158
Mean						626733			
% RSD						0.042			

Table 6:

Peak Results
Name: TELMISARTAN

	Vial	Injection	SampleName	Name	RT	Area	USP Resolution	USP Tailing	USP Plate Count
1	11	1	ACCURACY-50%-1	TELMISARTAN	2.394	1613907		1.0835	4724
2	11	2	ACCURACY-50%-1	TELMISARTAN	2.389	1620893		1.1036	4656
3	12	1	ACCURACY-50%-2	TELMISARTAN	2.388	1666258		1.1033	4662
4	12	2	ACCURACY-50%-2	TELMISARTAN	2.390	1632967		1.1050	4676
5	13	1	ACCURACY-50%-3	TELMISARTAN	2.387	1802776		1.1023	4675
6	13	2	ACCURACY-50%-3	TELMISARTAN	2.395	1821833		1.0834	4734
7	14	1	ACCURACY-100%-1	TELMISARTAN	2.391	3340777		1.1181	4643
8	14	2	ACCURACY-100%-1	TELMISARTAN	2.391	3354597		1.1180	4618
9	15	1	ACCURACY-100%-2	TELMISARTAN	2.387	3413978		1.1174	4550
10	15	2	ACCURACY-100%-2	TELMISARTAN	2.388	3401714		1.1173	4610
11	16	1	ACCURACY-100%-3	TELMISARTAN	2.386	3396539		1.1163	4522
12	16	2	ACCURACY-100%-3	TELMISARTAN	2.386	3400080		1.1165	4518
13	17	1	ACCURACY-150%-1	TELMISARTAN	2.381	5228888		1.1104	4472
14	17	2	ACCURACY-150%-1	TELMISARTAN	2.381	5258246		1.1109	4453
15	18	1	ACCURACY-150%-2	TELMISARTAN	2.334	5076385		1.1181	4298
16	18	2	ACCURACY-150%-2	TELMISARTAN	2.333	5081762		1.1052	4329
17	19	1	ACCURACY-150%-3	TELMISARTAN	2.337	4784871		1.1220	4493
18	19	2	ACCURACY-150%-3	TELMISARTAN	2.335	4793888		1.1195	4382
Mean						3371686			
% RSD						0.292			

Table 7: METHOD PRECISION

	Name	Injection	RT	Area	USP Plate Count	USP Tailing
1	ROSUVASTATIN	1	5.399	766804	9213	1.072
2	ROSUVASTATIN	2	5.398	766534	9171	1.066
3	ROSUVASTATIN	1	5.378	757696	9155	1.068
4	ROSUVASTATIN	2	5.395	756300	9172	1.074
5	ROSUVASTATIN	1	5.393	757194	9159	1.073
6	ROSUVASTATIN	2	5.395	754072	9170	1.068
7	ROSUVASTATIN	1	5.398	753993	9172	1.075
8	ROSUVASTATIN	2	5.405	739161	9246	1.078

Table 8:

Peak Results
Name: TELMISARTAN

	Name	Injection	RT	Area	USP Plate Count	USP Tailing
1	TELMISARTAN	1	3.091	4534283	6330	1.086
2	TELMISARTAN	2	3.087	4538244	6307	1.092
3	TELMISARTAN	1	3.070	4461581	6359	1.086
4	TELMISARTAN	2	3.081	4472034	6377	1.102
5	TELMISARTAN	1	3.083	4470808	6305	1.085
6	TELMISARTAN	2	3.082	4473123	6323	1.085
7	TELMISARTAN	1	3.081	4456230	6435	1.095
8	TELMISARTAN	2	3.085	4371974	6330	1.086
9	TELMISARTAN	1	3.093	4369156	6314	1.090
10	TELMISARTAN	2	3.092	4464907	6347	1.086
11	TELMISARTAN	1	3.087	4536334	6320	1.087
12	TELMISARTAN	2	3.086	4548296	6299	1.086
Mean				4474747		
% RSD				1.333		

CONCLUSION

In this study, a selective and validated stability-indicating HPLC assay method for Telmisartan & Rosuvastatin was developed, which could separate the drug and its degradation products formed under a variety of stress conditions. %Assay was found to be between 98 to 102% indicating good compliance with the label claim for both compounds. None of the tablet ingredients interfered with the analysis of both the drugs. In the proposed study, rapid RP-HPLC method was developed for the simultaneous estimation of ROS and TEL was validated as per ICH guidelines. Statistical analysis proved that method was accurate, precise, and repeatable. The developed method was found to be simple, sensitive and selective for analysis of ROS and TEL in combination without any interference from the excipients.

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