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Stability-indicating RP-HPLC method development and validation for simultaneous estimation of telmisartan and rosuvastatin calcium in bulk and in tablet dosage form

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Abstract

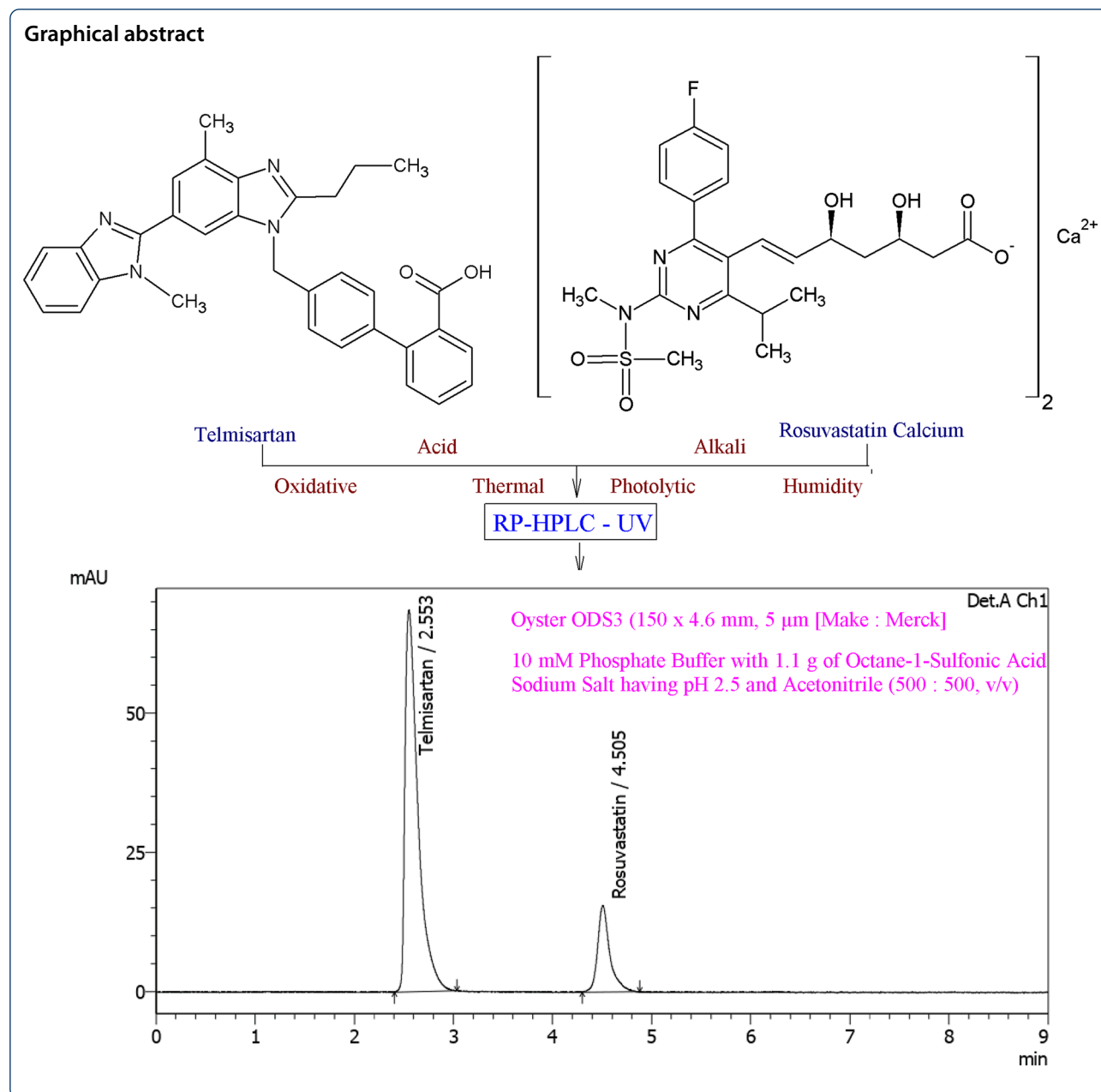
Background: The stability-indicating chromatographic method was developed and validated for simultaneous estimation of telmisartan and rosuvastatin calcium in bulk and in tablet dosage form. The RP-HPLC elution was carried out at 242.0 nm using column Oyster ODS3 (150 × 4.6 mm, 5 μm) isocratically, and a mobile phase containing 10 mM phosphate buffer with 1.1 g octane-1-sulfonic acid sodium salt having pH 2.5 (adjusted with 5% OPA) and acetonitrile, with a proportion of 500:500, v/v was pumped through the column maintained at ambient (about 25 °C) temperature with 1.0 mL/min flow rate. The proposed method was validated according to ICH Q2 (R1) guideline.

Results: Telmisartan and rosuvastatin were eluted at 2.553 min and 4.505 min, respectively. The method is linear from 99.9073 to 299.7218 μg/mL for telmisartan ($R^2 = 1.000$) and 23.6841 – 71.0522 μg/mL for rosuvastatin ($R^2 = 0.999$). The average recovery percentage was found 100.51, 99.76, and 99.14% for telmisartan and 99.68, 99.72, and 98.56% for rosuvastatin at three different levels. Results of method repeatability and intermediate precision were found within acceptable limits. Results of solution stability showed that mobile phase was stable for 2 days; standard and sample preparations are stable for 1 day at room temperature as well as in the refrigerator (2–8 °C). Also, forced degradation study results show that method is stability indicating as capable of distinguishing the active analytes peak from the degraded product.

Conclusion: The developed stability-indicating method is linear in studied concentration range as well as precise, accurate, specific, and robust. Hence, successfully this method can be used for routine analysis and stability study.

Keywords: Telmisartan, Rosuvastatin calcium, Forced degradation, Solution stability, Method validation, RP-HPLC

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Background

Telmisartan (TLS) is chemically 4'-[[4-Methyl-6-(1-methyl-1*H*-benzimidazole-2-yl)-2-propyl-1*H*-benzimidazole-1-yl]methyl][1,1'-biphenyl]-2-carboxylic acid (Fig. 1a) which is a white to slightly yellowish, crystalline powder and official in Indian Pharmacopoeia, United States Pharmacopoeia, and European Pharmacopoeia. It is categorized as an antihypertensive agent.

Rosuvastatin calcium (RST) is chemically calcium [(3*R*,5*S*,6*E*)-7-[4-(4-fluorophenyl)-2-(*N*-methanesulfonamido)-6-(propan-2-yl)pyrimidin-5-yl]-3,5-dihydroxyhept-6-enoate

which (Fig. 1b) is white or almost white, hygroscopic powder and official in Indian Pharmacopoeia, United States Pharmacopoeia, and European Pharmacopoeia. It is categorized as the anti-hyperlipidemic agent [1–3].

The two risk factors of cardiovascular diseases like hypertension and dyslipidemia are likely to present simultaneously. Earlier treatment of such multiple complications is given separately that may result poor compliance which leads to possible treatment failure. Hence, treatment with a fixed dose combination containing telmisartan and rosuvastatin drugs showed similar effectiveness

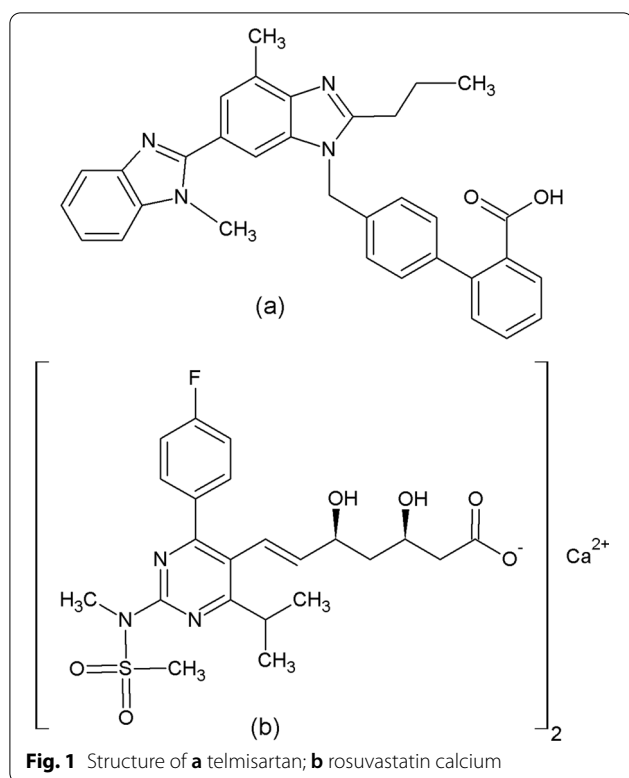


Fig. 1 Structure of **a** telmisartan; **b** rosuvastatin calcium

in lowering blood pressure and low-density lipoprotein—cholesterol levels without increase in adverse effects, compared with that of every single drug [4].

The stress testing is to be carried out to recognize the inherent stability characteristics of the active components [5]. The impurities from the manufacturing process and inappropriate storage or handling lead to produce degradants widely influenced the results relating to quality, safety, and efficacy. A good stability-indicating method is capable of distinguishing the active analytes peak from degraded product [6–9].

Nowadays, the HPLC technique is used in a variety of analytical studies to estimate the drugs in pure and in pharmaceutical formulations as well as in biological fluids and their competence for stability-indicating method development. It has the advantage of being efficient, accurate, easy to use, and the ability to provide best separation of analytes; hence, it is used widely [10–15].

A survey of the literature shows that for simultaneous estimation of TLS and RST, few HPLC methods are reported [16–20]. The existing methods have some limitations as complex procedure of test preparation, long run time, and low resolution. Validated stability-indicating data were available for one reported method, but stress studies were performed only on the drug substance, not on the drug product. Moreover, few robustness parameters and solution stability shall be required

to be performed. Hence, this proposed study is undertaking to develop and validate stability-indicating RP-HPLC method for simultaneous estimation of TLS and RST which is more rapid, simple, precise, accurate, linear, robust enough as compared to existing methods.

Methods

Chemicals and materials

Telmisartan (Batch no.: TLSCB19618, assay on as is basis: 99.43%) and rosuvastatin calcium (Batch No. 100077008, assay on as is basis: 94.03%) were obtained as a gift sample from Alembic Pharmaceutical Ltd., Alembic Research Centre, Vadodara, Gujarat—India. The study was performed by using the chemicals of HPLC or equivalent grade. Potassium dihydrogen phosphate (Batch no.: H14A/1514/1306/53) was procured from SD Fine Chem Ltd., Mumbai—India; orthophosphoric acid (Batch No. 2467211117) was procured from Research Lab Fine Chem Industries, Mumbai—India; acetonitrile (Batch no.: 1038350516) was procured from Fischer Scientific India Pvt. Ltd., Mumbai—India; sodium hydroxide (Batch no.: DH6D662478) and hydrochloric acid (Batch No. CK6C660816) were procured from Merck, Mumbai—India; 6% v/v hydrogen peroxide (Batch No. MCM-1171) procured from Molychem, Mumbai—India. Marketed formulation of telmisartan and rosuvastatin tablets 40/10 mg (Batch No. 2008001049, Make: Alembic Pharmaceuticals Ltd., Samardung Basti—Sikkim, India) with brand name TELLZY[®]-RS (each film-coated tablet contains 40 mg telmisartan and rosuvastatin calcium equivalent to 10 mg rosuvastatin) was purchased from the local pharmacy shop. Various kinds of filters were utilized in this study, nylon membrane filter [Cat No. HNNX0902XXXX104, (0.45 μm)], Syringe filter like Nylon [Cat No. SYNNO602MNXX104, (0.45 μm)], and PVDF [Cat No. SYVF0602MNXX104, (0.45 μm)] made by Advanced Microdevices Pvt. Ltd. and Whatman filter paper (Cat No. 1001-1250) made by GE Healthcare UK Ltd.

Instruments

Analytical weighing balance (CY204) made by Citi-zon was used for weighing of material. Ultrasonic bath (LMUC-3) made by Labman Scientific Instruments was used for sonication. The digital pH meter (LT-49) made by Labtronic Laboratory Instruments was used for solution pH checking. Stability chamber (GMP) made by Labline Stock Centre, Photostability chamber (SRL-PHSC-11-A) made by S R Lab Instruments India Pvt. Ltd., and hot air oven (BTI-29) made by Bio-Technics India were used during forced degradation study. A water purification system (WPS211) made by Analytical Technologies Ltd was used for collecting ultrapure

Table 1 Chromatographic conditions

Parameters	Results
Type of system	HPLC with UV detector or equivalent
Pump mode	Isocratic
Mobile phase	10 mM phosphate buffer with 1.1 g octane-1-sulfonic acid sodium salt having pH 2.5 (adjusted with 5% OPA) and Acetonitrile (500:500, v/v)
Column	Oyster ODS3 (5 μ m, 4.6 \times 150 mm) P/N: S670153 (Make: Merck & Co.)
Injection volume	20 μ L
Run time	9 min
Flow rate	1.0 mL/min
Detection	242.0 nm
Column temperature	Ambient (about 25 $^{\circ}$ C)
Blank	Diluent

water. To study the solution stability, LG refrigerator (GL-A282SPZL) was used. The Oyster ODS3 (5 μ m, 4.6 \times 150 mm) column of Merck & Co. was joined to a Shimadzu HPLC (SCL-10Avp) instrument, and injection volume of 20 μ L with UV detector was used for method development. The instrument control and chromatographic data processing were made by using software LCsolution version 1.25.

Chromatographic conditions

The study was performed by maintaining the conditions for chromatographic analysis as specified in Table 1.

Buffer pH 2.5

1.36 g KH_2PO_4 and 1.1 g of octane-1-sulfonic acid sodium salt (OSASS) were weighed and transferred into 1000 mL water and sonicated for 10 min to dissolve. The pH 2.5 was adjusted with 5% OPA and under vacuum filtration filtered through a nylon membrane filter (0.45 μ m).

Mobile phase

500 mL ACN was mixed with 500 mL buffer pH 2.5 and sonicated for 10 min to degas.

Phosphate buffer pH 2.5

1.36 g KH_2PO_4 was weighed and transferred into 1000 mL water and sonicated for 10 min to dissolve. The pH 2.5 was adjusted with 5% OPA and under vacuum filtration filtered through a nylon membrane filter (0.45 μ m).

Diluent

500 mL ACN was mixed with 500 mL 10 mM phosphate buffer pH 2.5 and sonicated for 10 min to degas.

Standard solution

40.0 mg telmisartan and 10.4 mg of rosuvastatin calcium (equivalent to 10 mg of rosuvastatin) were weighed and transferred into a 200-mL dry volumetric flask; 140 mL diluent was introduced to it and sonicated for 10 min with intermediate shaking to dissolve. Subsequently, the cooled solution was filled up to the mark by diluent and mixed thoroughly which gave the concentration of telmisartan (200 μ g/ml) and rosuvastatin (50 μ g/mL).

The standard solution suitability was established with two different preparations.

Sample solution

Twenty telmisartan and rosuvastatin tablets 40/10 mg (TELLZY[®]-RS) were weighed and crushed, and 278.2 mg powder (equivalent to 40 mg telmisartan and 10 mg rosuvastatin) was transferred into a 200-mL dry volumetric flask; 140 mL diluent was introduced to it and sonicated for 20 min with intermediate shaking to completely dissolve the content. Subsequently, the cooled solution was filled up to the mark by diluent and mixed thoroughly. Finally, it was filtered using Whatman filter paper by discarding the initial 5 mL filtrate, and then, the sample was analyzed with HPLC.

Method validation

The proposed method was validated as per the ICH guideline Q2(R1) [21].

System suitability and system repeatability

To ensure the adequate performance of a chromatographic system, system suitability and system repeatability parameters were checked by injecting standard 1st in replicates of five and standard 2nd in a replicate of one into a chromatographic system, and the % RSD for peak area of 1st standard and % RD between two standards were calculated. Also, retention time, tailing

factor, theoretical plates, and resolution among TLS and RST peak from 1st injection of the first standard were reported.

Specificity

The interference from blank was checked at the retention time of TLS and RST during the specificity. Besides, specificity was studied through forced degradation by extending elution time twice to observe any late eluting peaks because of the degraded product. Individually both drug(s) and their marketed product TELLZY[®]-RS were exposed to forced degradation with predetermined concentration in acid (5 N HCl/ 3 h/ RT), alkali (5 N NaOH/ 3 h/ RT), oxidative (6% v/v H₂O₂/3 h/ RT), thermal (105 °C/ 24 h/ hot air oven), photolytic (UV light/ 24 h/ photostability chamber), and humidity (75% RH/ 48 h/ stability chamber) stress conditions. Similarly, solutions of blank were exposed to stress conditions like acid, alkali, and oxidative to know any interference at TLS and RST retention time. However, the proposed RP-HPLC method was used for evaluating stressed samples against the standard; mass balance (% assay + % degradant) results were calculated for each stressed sample and compared with the unstressed sample.

Linearity

The standard stock solution containing telmisartan (1248.8408 µg/mL) and rosuvastatin (296.0508 µg/mL) was prepared to ascertain the method's linearity. The aliquots of linearity stock solution were diluted further to 5 different levels 50–150% of the nominal working concentration from 99.9073 to 299.7218 µg/mL for telmisartan and 23.6841 to 71.0522 µg/mL for rosuvastatin and injected each solution into the chromatographic system. The squared correlation coefficient (R^2) was calculated by constructing the linearity curve for concentration versus peak area.

DL and QL

As per the ICH guideline, the DL and QL for TLS and RST were established using the standard deviation of response (residual value) and the slope method and it was calculated by the following equations.

$$DL = \frac{3.3 \times \sigma}{S} \quad \text{and} \quad QL = \frac{10 \times \sigma}{S}$$

where σ = the standard deviation of the response; S = the slope of the calibration curve.

Accuracy

The samples containing telmisartan and rosuvastatin calcium with placebo mixture were analyzed at 50, 100, and 150% levels of the nominal working concentration in triplicate preparations at each level and injected all solutions into the chromatographic system, and determined the percentage recovery.

Precision

The six sample preparations of telmisartan and rosuvastatin tablets 40/10 mg (TELLZY[®]-RS) were analyzed during method repeatability; % RSD and 95% CI were calculated for observed results of the assay. Also, the results of system suitability and system repeatability were determined.

The six sample preparations of the same sample (i.e., batch, storage condition, etc.) of telmisartan and rosuvastatin tablets 40/10 mg (TELLZY[®]-RS) tested for method repeatability were analyzed on a different day for intermediate precision. % RSD and 95% CI were calculated for observed results of assay, and the average results observed during method repeatability and intermediate precision study were compared. Also, the results of system suitability and system repeatability were determined.

Robustness

Robustness was done for filter compatibility studies; variation in sample sonication time; and making deliberate changes in chromatographic conditions.

Three samples of telmisartan and rosuvastatin tablets 40/10 mg (TELLZY[®]-RS) were prepared to perform a filter compatibility study. Part of every sample solution was filtered using Nylon SF (0.45 µm), PVDF SF (0.45 µm), and Whatman filter paper (as per method) by throwing away the initial 5 mL filtrate, and all samples were injected into chromatographic system. Results for % assay and % relative difference were calculated.

The sonication effect on extraction efficiency was assessed by varying sample sonication time ± 5 min with three sample preparations of telmisartan and rosuvastatin tablets 40/10 mg (TELLZY[®]-RS) at each changed condition, and all samples in a chromatographic system were injected. Results for % assay and % relative difference were calculated.

Besides, robustness is performed by doing little variation in chromatographic conditions like flow rate (± 0.1 mL/min) and relating to the mobile phase, buffer phase ($\pm 10\%$); organic phase ($\pm 10\%$); buffer pH (± 0.2); quantity of KH₂PO₄ in buffer ($\pm 10\%$); quantity of OSASS in buffer ($\pm 10\%$), and their effect was evaluated based on the results of system suitability and system repeatability.

Table 2 System suitability and system repeatability results

Parameters	TLS	RST	Acceptance criteria
Retention time (min)	2.553	4.505	–
USP plate counts	2917	8288	> 2000
USP tailing factor	1.44	1.23	NMT 2.0
USP resolution	–	9.40	NLT 2.0
% RSD of five replicate injections of standard 1	1.67	1.52	≤ 2.0%
The % RD between two standards	0.75	0.51	≤ 2.0%

Solution stability

The duplicate standard solutions stored at room temperature and in the refrigerator (2–8 °C) were used to establish stability after day 1 and day 2. By comparing the results of stored standard solutions with the solution of freshly prepared standard, the % RD was calculated.

The triplicate sample solutions stored at room temperature and in the refrigerator (2–8 °C) were used to establish stability after day 1 and day 2. The stored sample solution results were compared with earlier results and the % assay was calculated with % RD.

To establish mobile phase stability, results for change in appearance, system suitability, and system repeatability were evaluated after day 1 and day 2 storage at bench top (RT).

Range

Linearity and accuracy of TLS and RST were verified in the range of 50–150% of the nominal working concentration. The range of method was demonstrated on basis of linearity, accuracy, and precision results.

Results

Chromatographic method development and optimization

Different proportions of 10 mM phosphate buffer with or without octane-1-sulfonic acid sodium salt at a varied pH level (2.5, 2.6, and 3.0) were tried with organic modifiers like MeOH and ACN to select a suitable mobile phase. Also, Thermo Scientific's ODS Hypersil (5 µm, 4.0 × 250 mm) and Merck's Oyster ODS3 (5 µm, 4.6 × 150 mm) stationary phases were used at ambient temperature (about 25 °C) for method development and optimization.

In the end, simultaneous estimation TLS and RST was performed on Oyster ODS3 (5 µm, 4.6 × 150 mm) column at 242.0 nm with a flow rate of 1.0 mL/min by using a mobile phase mixture of 10 mM phosphate buffer with 1.1 g of OSASS having pH 2.5 ± 0.05 and acetonitrile in the proportion of 500:500, v/v as it elutes both the peaks well in short time with good resolution, theoretical plate count, and tailing factor.

Method validation

System suitability and system repeatability

The chromatographic system reproducibility was checked using parameters of system suitability and system repeatability (Table 2) as it is an integral component of analytical method.

Specificity

The interference from blank absent at telmisartan and rosuvastatin peak shows the method is specific (Fig. 2).

The peaks due to degraded product generated during stress study did not interfere with TLS and RST peak. The mass balance data established for acid and photolytic-stressed RST show a decrease in response with the generation of major degradant at 8.955 min and 6.280 min, respectively. The mass balance data established for TLS and RST in the drug product sample show that the response of RST decreased in acid, thermal, and photolytic stressed conditions with the generation of major degradant at 8.687, 1.811, and 6.134 min, respectively. The mass balance data show that TLS is stable in all stressed conditions as no degradant is generated for it. As a product containing two active components TLS and RST, it is not possible to apply the more harsh stress condition to achieve the degradation of TLS because they may cause severe degradation as well as generation of secondary degradant of RST.

The stress study results signify that both drugs and their combined drug product are stable to alkali, oxidative, and humidity-stressed conditions, whereas they are unstable to acid, thermal, and photolytic-stressed conditions (Table 3). Hence, it is suggested that individual drugs and their combination drug product should be store protected from heat and light in a tightly closed container.

Stressed sample (acid, thermal, and photolytic) chromatograms are pointed up that the active analytes peak distinguishes from the degraded product, showing the method is specific (Fig. 3, 4, and 5).

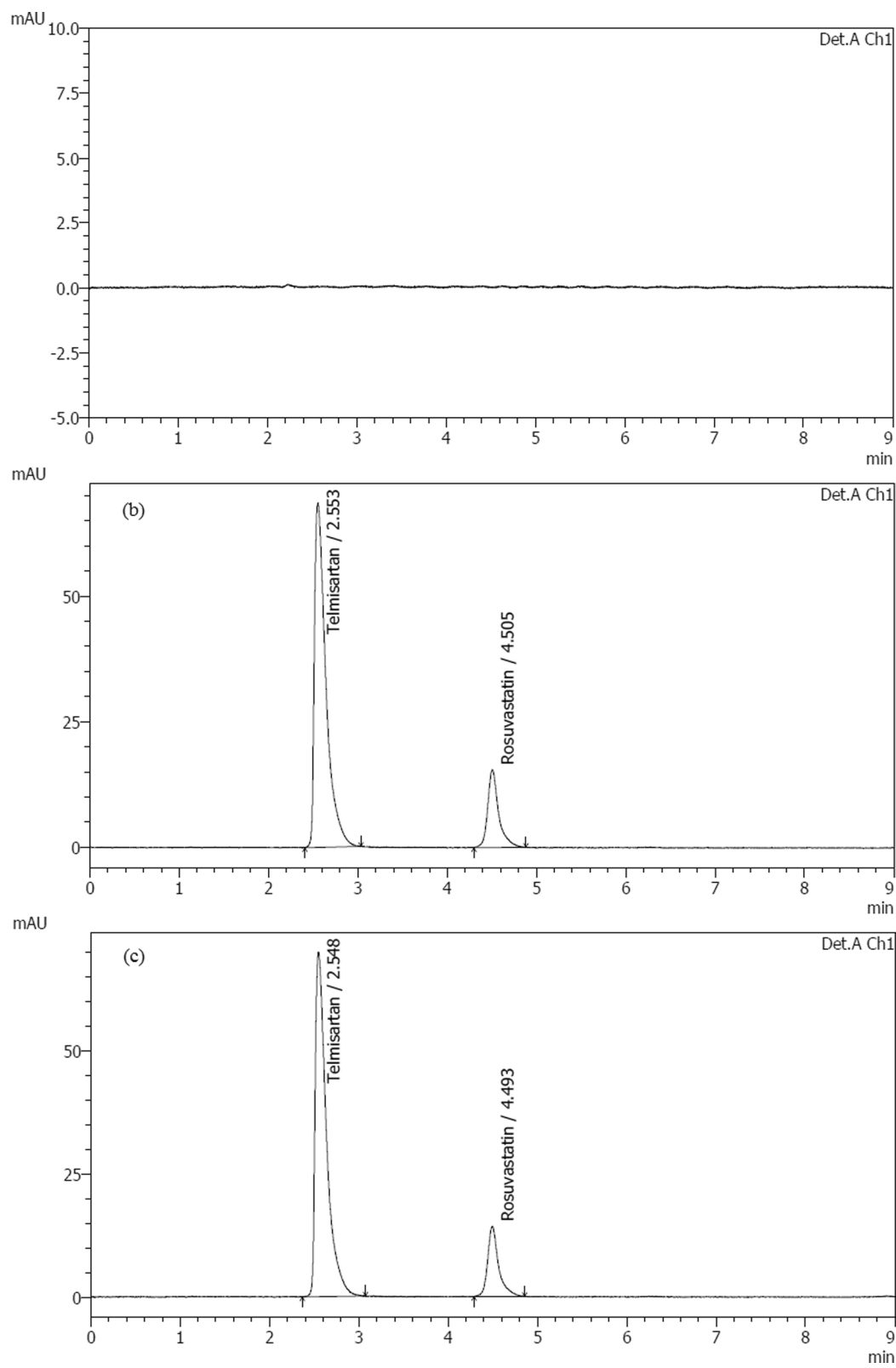


Fig. 2 Chromatograms of **a** blank; **b** standard; **c** sample

Table 3 Results of forced degradation study

Sample name/stress condition	Drug substance						Drug product					
	% Assay		% Total degradation		% Mass Balance		% Assay		% Total degradation		% Mass Balance	
	TLS	RST	TLS	RST	TLS	RST	TLS	RST	TLS	RST	TLS	RST
Unstressed (as per method)	99.74	98.70	ND	ND	99.74	98.70	98.14	98.74	ND	ND	98.14	98.74
Acid/5 N HCl/ 3 h/RT	98.72	81.82	ND	18.25	98.72	100.07	98.96	85.25	ND	15.80	98.96	101.04
Alkali/5 N NaOH/3 h/RT	99.82	98.23	ND	ND	99.82	98.23	100.44	101.15	ND	ND	100.44	101.15
Oxidative/6% H ₂ O ₂ /3 h/RT	99.16	99.87	ND	ND	99.16	99.87	99.52	99.15	ND	ND	99.52	99.15
Thermal/105 °C/24 h	98.94	98.19	ND	ND	98.94	98.19	98.25	62.72	ND	35.05	98.25	97.77
Photolytic/UV light/24 h	99.02	95.06	ND	2.62	99.02	97.68	98.37	85.52	ND	12.09	98.37	97.61
Humidity/75% RH/ 48 h	98.69	97.91	ND	ND	98.69	97.91	99.03	99.18	ND	ND	99.03	99.18

Linearity

The method was linear in concentration range 99.9073–299.7218 µg/mL for telmisartan ($R^2=1.000$) and 23.6841–71.0522 µg/mL for rosuvastatin ($R^2=0.999$), showing its fitness for analysis (Table 4). Linearity curves are represented in Fig. 6.

DL and QL

The DL was 1.1066 µg/mL for TLS and 0.6932 µg/mL for RST, respectively, indicating that even little amounts of TLS and RST can be detected.

The QL was 3.3532 µg/mL TLS and 2.1005 µg/mL for RST, respectively, indicating that even small amounts of TLS and RST can be quantified.

Accuracy

At each level of 50, 100, and 150%, the average results of % recovery were found to be 100.51, 99.76, and 99.14% for TLS and 99.68, 99.72, and 98.56% for RST, showing the method is accurate and free from excipients interference (Table 5).

Precision

The developed method is repeatable and precise, as the % RSD value for the assay was below 2.0 for both TLS and RST in method repeatability and intermediate precision (Table 6).

Robustness

Results of the sample filtered using Nylon SF (0.45 µm) and PVDF SF (0.45 µm) met the acceptance criteria (% RD = ≤ 3.0%) with results Whatman filter paper (as per method). Therefore, in addition to Whatman filter paper, the Nylon SF (0.45 µm) and PVDF SF (0.45 µm) are helpful in sample filtration.

The results for changed sample sonication time (± 5 min) met the acceptance criteria (% RD = ≤ 3.0%), without affecting on extraction efficiency.

The results of variation made in chromatographic method parameter met the acceptance criteria for the retention time change, system suitability, and system repeatability in all changed conditions, illustrating method robustness (Table 7).

Solution stability

The stability study results of standard (% RD = ≤ 2.0%) and sample solutions (% RD = ≤ 3.0%) met acceptance criteria after day 1 at room temperature and in refrigerator (2–8 °C). Results for day 2 at both storage conditions fail to meet the acceptance criteria mainly for RST, indicating solutions are unstable at this time point.

The appearance of the mobile phase was clear and free of visible particles, and results met acceptance criteria for system suitability and system repeatability at the time of stability study, signifying the mobile phase is stable up to 2 days at bench top (RT) storage.

Range

The results of linearity, accuracy, and precision show method range for TLS and RST is from 50 to 150% of the nominal working concentration.

Discussion

In this research work, an attempt has been made to develop a validated stability-indicating method for TLS and RST with adequate resolution from each other and from their degraded products. The peaks of telmisartan and rosuvastatin were eluted at 2.553 min and 4.505 min, respectively, with the resolution of 9.40 between them. During the system suitability and system repeatability testing, the parameters like retention time (min), theoretical plate count, tailing factor, resolution, % RSD,

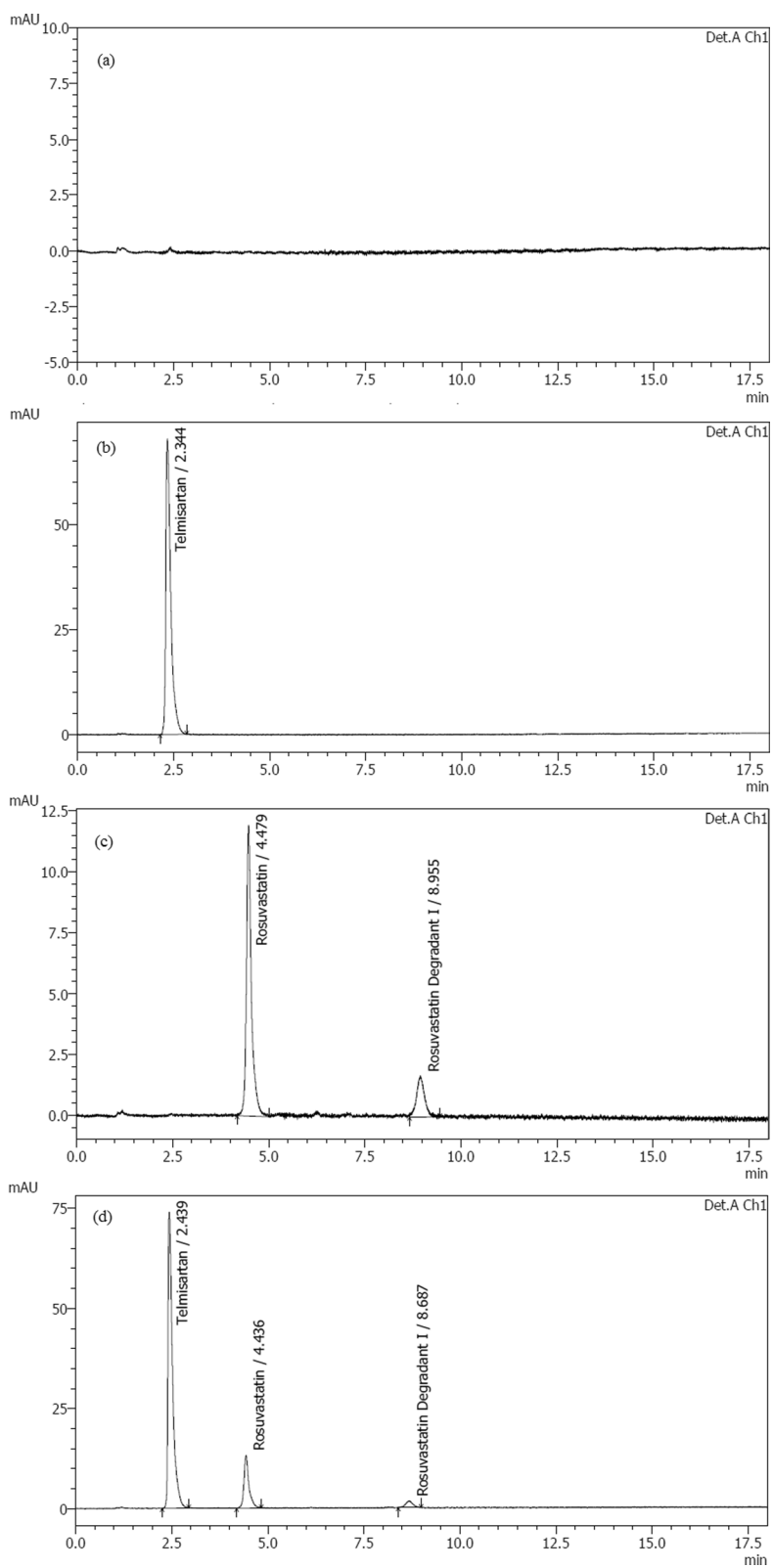


Fig. 3 Chromatogram of acid stressed **a** blank; **b** TLS; **c** RST; **d** sample

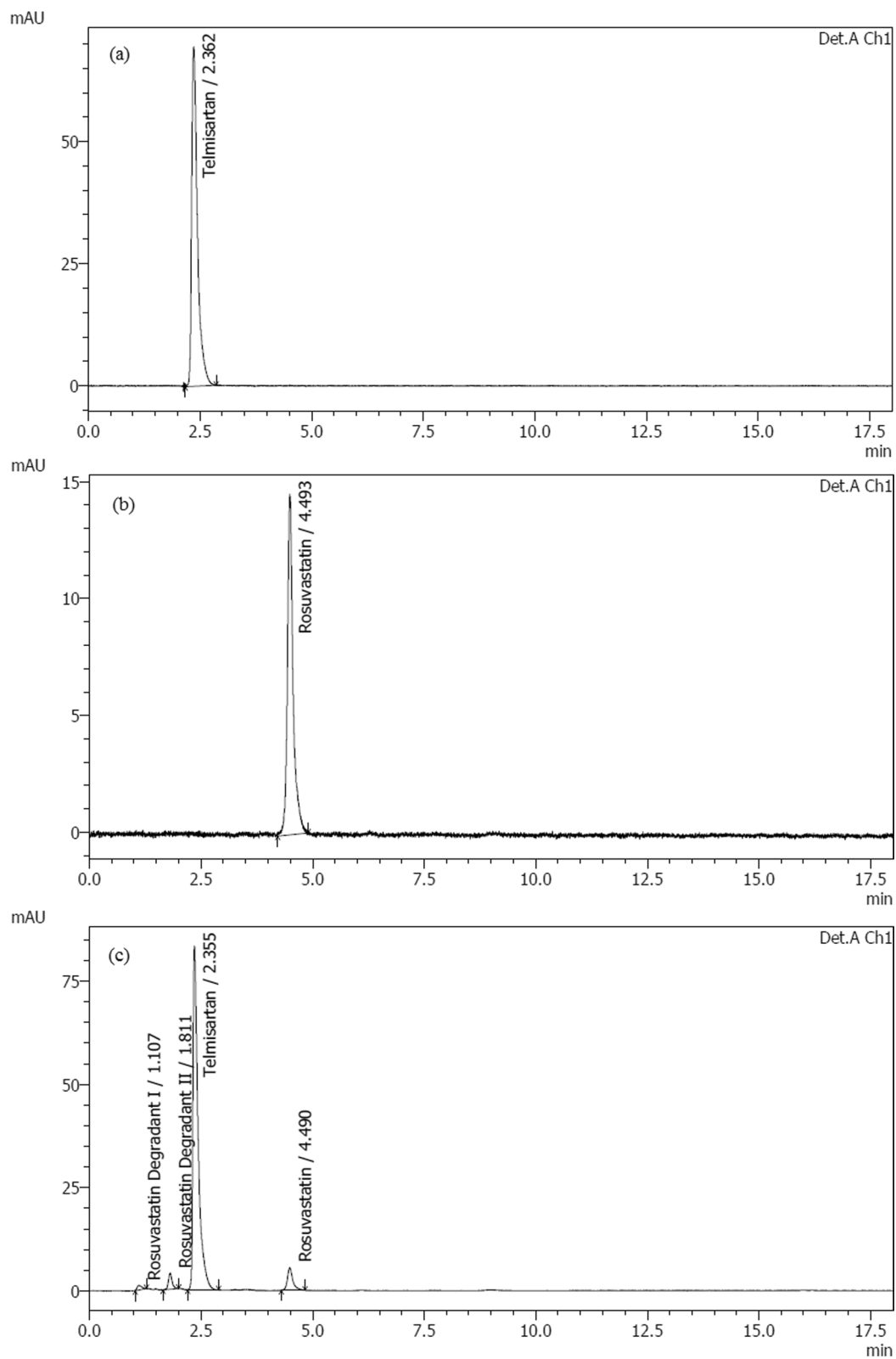


Fig. 4 Chromatogram of thermal stressed **a** TLS; **b** RST; **c** sample

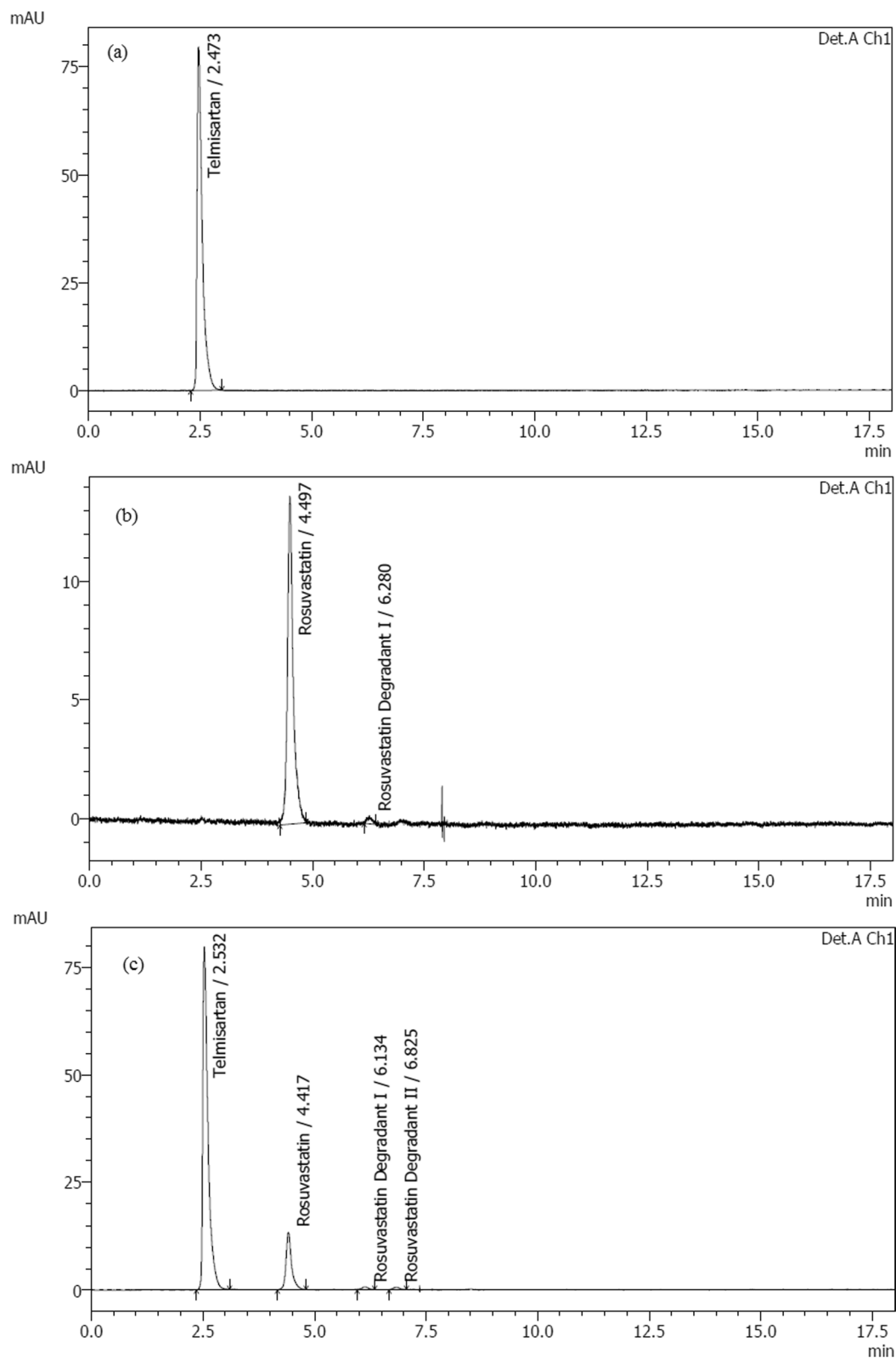


Fig. 5 Chromatogram of photolytic stressed **a** TLS; **b** RST; **c** sample

Table 4 Linearity study results

Linearity level (%)	Concentration (µg/mL)		Response (peak area)	
	TLS	RST	TLS	RST
50	99.9073	23.6841	316,671	61,762
75	149.8609	35.5261	477,572	92,815
100	199.8145	47.3681	635,827	124,256
125	249.7682	59.2102	793,079	157,100
150	299.7218	71.0522	954,313	189,386
Squared correlation coefficient (R^2); ≥ 0.995			1.000	0.999
(Y-intercept/response at 100% standard concentration) $\times 100$; $\leq 3.0\%$			0.13	2.21

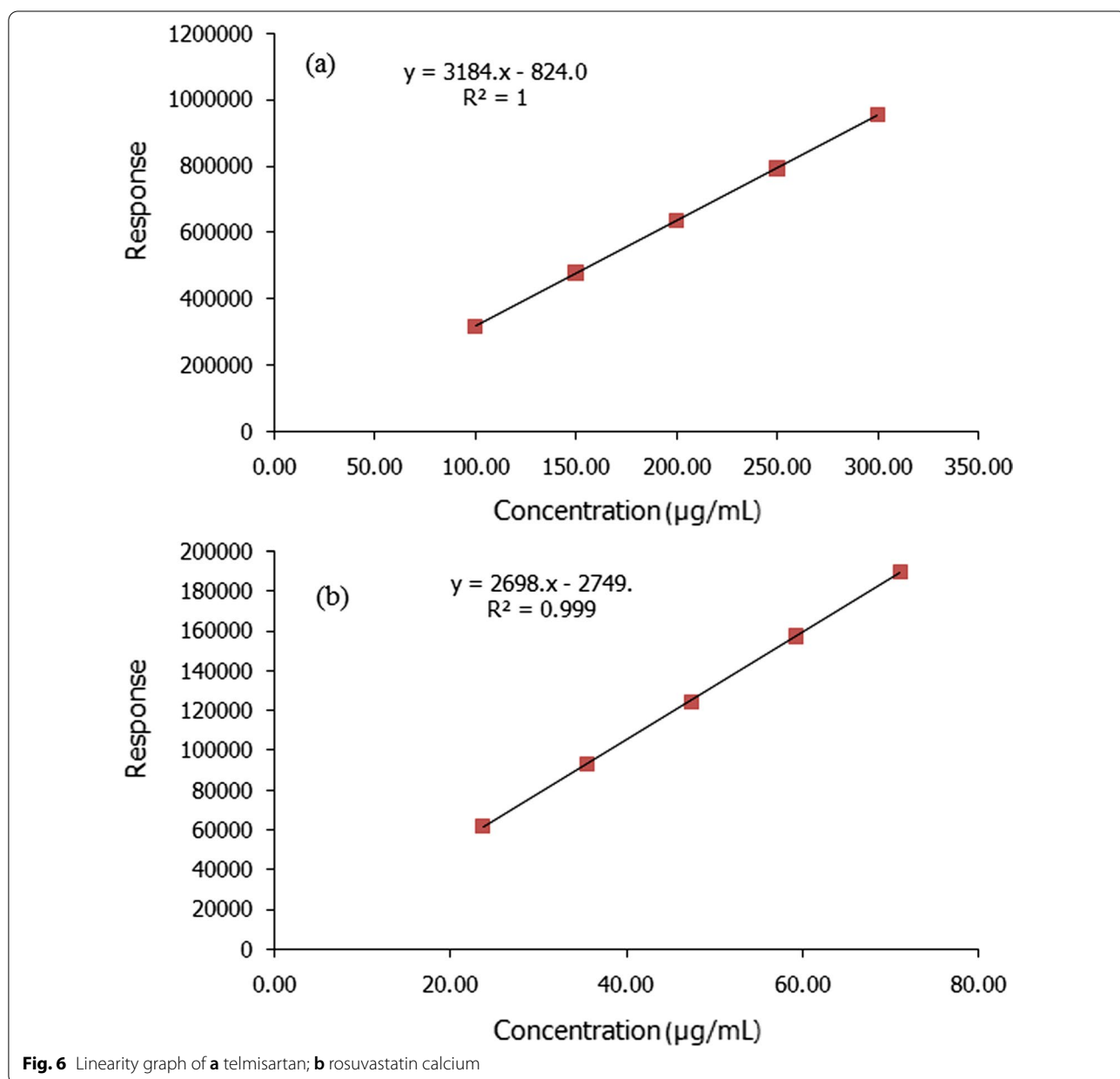


Table 5 Accuracy study results

Accuracy level (%)	Concentration ($\mu\text{g/mL}$)		% Recovery*		% RSD	
	TLS	RST	TLS	RST	TLS	RST
50	100	25	100.51	99.68	0.26	0.56
100	200	50	99.76	99.72	0.49	1.22
150	300	75	99.14	98.56	0.77	1.47

*Average of three replicates

Table 6 Precision study results

Sample no.	Method repeatability		Intermediate precision	
	TLS	RST	TLS	RST
1	98.20	99.23	99.67	99.44
2	99.54	100.81	100.40	100.13
3	101.44	99.78	99.62	100.27
4	99.36	101.09	99.06	99.92
5	100.41	98.61	99.41	100.70
6	100.95	99.50	99.84	101.63
Average	99.99	99.84	99.67	100.35
% RSD	1.18	0.95	0.45	0.75
% RD	–	–	0.32	0.52
95% CI	99.04–100.92	99.08–100.60	99.31–100.03	99.75–100.95

and % RD were checked to ensure reproducibility of the chromatographic system. The specificity of the method was established by verifying blank interference and in forced degradation study; the result shows the method is

stability indicating. The value of squared correlation coefficient (R^2) was found 1.000 for TLS and 0.999 for RST, indicating the method is linear and suitable to use in the studied concentration range. Recovery results show the method is accurate and with no interference from excipients. The method is repeatable and precise as the % RSD results below 2.0. The SS and SR parameters are used for establishing the robustness of change in chromatographic parameters; the results within the acceptance limits indicate its robustness. The standard and sample were found to be stable at room temperature and in the refrigerator for 1 day while the mobile phase was stable at room temperature for 2 days.

Furthermore, the results of the proposed method are compared with reported methods, and this method has more number of advantages for simultaneous estimation of TLS and RST which includes less analysis time, good resolution between peaks, simple solution preparations, and method is stability indicating as capable of distinguishing the active analytes peak from the degraded product. The stability was established

Table 7 Results of robustness for change in chromatographic parameters

Modification in chromatographic conditions	Retention time (min)		Plate count		Tailing factor		% RSD		Reso	Retention time from sample	
	TLS	RST	TLS	RST	TLS	RST	TLS	RST		TLS	RST
As per method	2.553	4.505	2917	8288	1.44	1.23	1.67	1.52	9.40	2.548	4.493
Flow rate – 0.1 mL/min	2.974	4.919	2804	8564	1.41	1.24	0.46	0.76	8.55	2.856	4.974
Flow rate + 0.1 mL/min	2.326	4.075	2746	7911	1.38	1.22	0.54	0.65	9.11	2.322	4.076
Organic phase – 10%	2.737	5.299	3226	8411	1.50	1.25	0.59	1.06	11.41	2.599	5.352
Organic phase + 10%	2.096	3.944	2986	6733	1.41	1.22	0.73	0.85	10.15	2.057	3.915
Buffer phase – 10%	2.095	4.047	2536	7191	1.48	1.22	0.51	0.58	10.93	2.108	4.000
Buffer phase + 10%	2.722	5.219	3070	9911	1.40	1.19	0.54	0.70	11.65	2.575	5.313
pH of buffer – 0.2	2.041	4.435	2762	8118	1.30	1.20	0.27	1.19	12.86	2.095	4.397
pH of buffer + 0.2	2.850	4.352	2630	7622	1.52	1.24	1.00	0.74	6.73	2.686	4.400
Quantity of PDP – 10%	2.376	4.632	2764	7875	1.53	1.22	0.32	0.66	11.16	2.340	4.593
Quantity of PDP + 10%	2.384	4.588	3038	6916	1.47	1.24	0.62	0.52	10.05	2.468	4.531
Quantity of OSASS – 10%	2.370	4.432	2961	7251	1.46	1.24	1.15	0.83	10.01	2.356	4.417
Quantity of OSASS + 10%	2.456	4.421	2879	7066	1.43	1.20	0.50	0.89	9.46	2.487	4.505
Acceptance criteria	–	–	> 2000		NMT 2.0		≤ 2.0		NLT 2.0	Similar to standard	

Reso. = USP resolution between telmisartan and rosuvastatin peak

for standard, sample, and mobile phase preparations. The study for filter compatibility and modification in sample sonication time was carried out being as part of robustness. In this method, the forced degradation performed on the individual drug(s) and their combination drug product as well as two standard preparations is used to check the reproducibility of the chromatographic system. Thus, the results of validation show the proposed method is more simple, rapid, precise, linear, accurate, specific, and robust enough in contrast with earlier reported methods.

Conclusions

The stability-indicating method was developed and validated according to the ICH guidelines for simultaneous estimation of TLS and RST in bulk and in tablet dosage form by RP-HPLC. Results of validation study show the proposed method is simple, specific, precise, accurate, and robust as well as linear in set concentration range. The stress study results (no hindrance from degradants) prove the method is specific and stability indicating. The standard, as well as sample preparation, was found stable for day 1 at room temperature and in the refrigerator and mobile phase stable for 2 days. Also, this method is cheaper as it requires less analysis time and simple solution preparations. Hence, the method can be applied successfully for regular analysis in quality control and stability studies of TLS and RST in bulk and in tablet formulation.

Abbreviations

RP-HPLC: Reverse-phase high-performance liquid chromatography; TLS: Telmisartan; RST: Rosuvastatin calcium; DS: Drug substance; DP: Drug product; FD: Forced degradation; RT: Room temperature; RF: Refrigerator; KH_2PO_4 /PDP: Potassium dihydrogen phosphate; OPA: Orthophosphoric acid; ACN: Acetonitrile; NaOH: Sodium hydroxide; HCl: Hydrochloric acid; H_2O_2 : Hydrogen peroxide; MeOH: Methanol; NMT: Not more than; NLT: Not less than; DL: Detection limit; QL: Quantitation limit; h: Hour(s); CI: Confidence interval; % RSD: Percentage relative standard deviation; % RD: Percentage relative difference; SF: Syringe filter; ND: Not detected; NA: Not applicable.

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Authors' contributions

Authors RG and SP designed the concept. RG performed experimental work, data analysis, and written the manuscript. Author SP supervised this research. Authors SP, SW, and TK contributed in data interpretation and editing of manuscript. All authors read and approved the final manuscript.

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Declarations

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Competing interests

The authors declare that they have no competing interests.

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