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Simultaneous Determination of Rosuvastatin and Ezetimibe in pharmaceutical formulations by Stability Indicating Liquid Chromatographic Method

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Abstract

Rosuvastatin and Ezetimibe are used for the treatment of hyperlipidemia. A stability-indicating RP-HPLC method was developed and validated for the simultaneous determination of Rosuvastatin and Ezetimibe in tablet dosage forms using C 18 column with mobile phase consisting of tetra butyl ammonium hydrogen sulphate-acetonitrile (32:68, v/v) with a flow rate of 1.0 ml/min (UV detection 254 nm). Linearity was observed over the concentration range 0.1-200 µg/ml for both Rosuvastatin (r^2=0.9998) and Ezetimibe (r^2=0.9998). The LOD and LOQ were found to be 0.0282 µg/ml and 0.0853 µg/m for Rosuvastatin and the LOD and LOQ for Ezetimibe were 0.0297 µg/ml and 0.0901 µg/ml respectively. Rosuvastatin and Ezetimibe were subjected to stress conditions of degradation in aqueous solutions including acidic, alkaline, oxidation, photolysis and thermal degradation. Ezetimibe is highly sensitive towards alkaline conditions. The method was validated as per ICH guidelines. The percentage RSD for intra-day precision was found to be 0.41-0.94 and 0.31-0.59 for Rosuvastatin and Ezetimibe respectively whereas the inter-day precision was found to be 0.68-0.95 and 0.68-1.02 for Rosuvastatin and Ezetimibe respectively. The method is simple, specific, precise, robust and accurate for the simultaneous determination of Rosuvastatin and Ezetimibe in pharmaceutical dosage forms (Tablets).

Keywords: Rosuvastatin; Ezetimibe; RP-HPLC; Stability-indicating; ICH

Introduction

Ezetimibe (EZT) chemically [1] designated as (3R, 4S) - 1 - (4 - fluorophenyl) - 3 - [(3S) - 3 - (4 - fluorophenyl) - 3 - hydroxypropyl] - 4 - (4 - hydroxyphenyl) azetidin - 2 - one (Figure 1A). It is a selective cholesterol absorption inhibitor, used for the treatment of hyperlipidemia, which potentially inhibits the absorption of biliary and dietary cholesterol. Ezetimibe prevents intestinal absorption of cholesterol without affecting absorption of triglycerides, fatty acids, bile acids and fat-soluble vitamins [2-4].

Rosuvastatin (RST) (Figure 1B) is a selective and competitive inhibitor of hydroxylmethylglutaryl coenzyme A (HMG CoA) reductase, the rate- limiting enzyme that converts 3-hydroxyl-3-methylglutaryl coenzyme A to mevalonate, a precursor of cholesterol. Rosuvastatin is a member of the class 'statins' and chemically designated as (3R, 5S, 6E) - 7 - [4 - (4 - fluorophenyl) - 2 - (N - methylmethanesulfonamido) - 6 - (propan - 2 - yl) pyrimidin - 5 - yl] - 3, 5 - dihydroxyhept - 6 - enoic acid [1]. It is used for the treatment of Hyperlipidemia. It reduces levels of low-density lipoprotein, apolipoprotein B and triglycerides in the blood, while increasing levels of high-density lipoprotein in the management of hyper lipidaemias [5]. Various analytical techniques such as micellar liquid chromatography [6], HPLC [7-13], HPTLC [14,15], densitometric TLC [16], spectrophotometry [17-19] and spectrofluorimetry [20] have been developed for the simultaneous determination of Rosuvastatin and Ezetimibe in pharmaceutical formulations. In the present study the authors have developed a validated stability indicating liquid chromatographic method for the simultaneous determination of Rosuvastatin and Ezetimibe in pharmaceutical formulations [21]. As no suitable stability indicating method was reported before, a simple, rapid, precise, accurate and robust stability indicating liquid chromatographic method has been developed for the simultaneous determination of Rosuvastatin and Ezetimibe in tablets and validated as per ICH guidelines [22].

Experimental

Reagents and solutions

Reference standards of Rosuvastatin (purity 99%) and Ezetimibe (purity 99.5%) were obtained from Glenmark Pharmaceuticals Ltd., India. The combination of Rosuvastatin and Ezetimibe is available as film-coated tablets (10 mg of Rosuvastatin and 10 mg of Ezetimibe) with brand names RAZEL-EZ® (Glenmark Pharmaceuticals Ltd., India) and ROSUVAS-EZ® (Ranbaxy Laboratories Ltd., India) and were procured from the local pharmacy store. Acetonitrile (HPLC grade), tetra butyl ammonium hydrogen sulphate (TBAHS) sodium hydroxide and hydrochloric acid and hydrogen peroxide were purchased from Merck (India).

Tetra butyl ammonium hydrogen sulphate buffer (pH 3.4) solution

The mobile phase was prepared by accurately transferring 3.3954 g of TBAHS in to a 1000 mL volumetric flask and dissolved with HPLC grade water.

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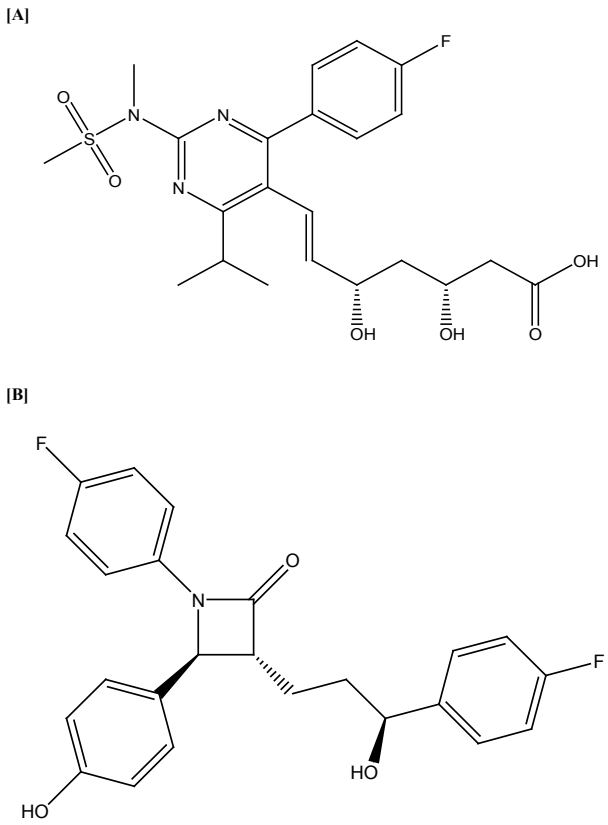

Figure 1: Chemical structures of Rosuvastatin [A] and Ezetimibe [B].

Preparation of rosuvastatin and ezetimibe stock solutions (1 mg/ml)

Stock solutions of Rosuvastatin (1000 µg/ml) and Ezetimibe (1000 µg/ml) were prepared by accurately transferring 25 mg of Rosuvastatin and Ezetimibe separately in two 25 ml volumetric flasks and the volume was made up to volume with mobile phase. Working solutions for HPLC injections were prepared on a daily basis from the stock solution with mobile phase containing tetra butyl ammonium hydrogen sulphate and acetonitrile (32:68, v/v). Solutions were filtered through a 0.45 µm membrane filter prior to injection.

HPLC instrumentation and conditions

Chromatographic separation was achieved by using a Shimadzu Model CBM-20A/20 Alite HPLC system, equipped with SPD M20A prominence photodiode array detector (250 mm × 4.6 mm, 5 µm particle size) maintained at 25°C. Isocratic elution was performed using tetra butyl ammonium hydrogen sulphate-acetonitrile (32:68, v/v) with a flow rate of 1.0 ml/min (UV detection 254 nm). 20 µl of sample was injected into the HPLC system and all chromatographic conditions were performed at room temperature (25°C ± 2°C).

Method validation

The method was validated for the following parameters: linearity, precision, accuracy, selectivity, robustness, limit of quantitation (LOQ), limit of detection (LOD) and system suitability [21].

Linearity

Linearity test solutions for the assay method were prepared from a stock solution at different concentration levels and 20 µL of each solution was injected in to the HPLC system and the peak area of the chromatogram obtained was noted.

The solutions extracted from the marketed formulations were also injected into the HPLC system and the peak area of the chromatograms was noted. A calibration curve was plotted by taking concentration of the drug solution on the x-axis and the corresponding peak area on the y-axis.

Precision

The intra-day precision of the assay method was evaluated at three concentration levels (10, 50 and 100 µg/ml) (n=3) against a qualified reference standard. The inter-day precision study was performed on three different days i.e. day 1, day 2 and day 3 at three different concentration levels (10, 50 and 100 µg/ml) (n=3). The %RSD of the obtained assay values at three different concentration levels was calculated.

Accuracy

The method accuracy was proved by the recovery test. The accuracy of the assay method was evaluated in triplicate at three concentration levels (80, 100 and 120%), and the percentage recoveries were calculated. A known amount of Rosuvastatin and Ezetimibe standards (10 µg/ml) were added to aliquots of sample solutions and then diluted to yield the total concentrations of 18, 20 and 22 µg/ml.

LOQ and LOD

The LOQ and LOD were based on the standard deviation of the response and the slope of the constructed calibration curve (n=3), as described in International Conference on Harmonization guidelines Q2 (R1) [21].

Robustness

The robustness of the assay method was established by introducing small changes in the HPLC conditions which included wavelength (252 and 256 nm), percentage of acetonitirile in the mobile phase (34 and 30) and flow rate (0.9 and 1.1 ml/min). Robustness of the method was studied using six replicates at a concentration level of 100 µg/ml of Rosuvastatin and Ezetimibe.

Forced degradation studies/Specificity

Stress studies were performed to evaluate the specificity of the method [22]. All samples were diluted with mobile phase to give a final concentration 100 µg/ml and filtered through 0.45 µm nylon filter before injection.

Acidic conditions: Acidic degradation was performed by treating the drug solution mixture (containing each of 1 mg/ml Rosuvastatin and Ezetimibe) with 0.1 N hydrochloric acid for 30 min in a thermostat maintained at 60°C. The drug solution mixture was cooled, neutralized with 0.1 N sodium hydroxide and then diluted with mobile phase as per the requirement and 20 µL of the solution was injected in to the HPLC system.

Alkaline conditions: Alkaline degradation was performed by treating the drug solution mixture (containing each of 1 mg/ml Rosuvastatin and Ezetimibe) with 0.1 N sodium hydroxide for 30 min in a thermostat maintained at 60°C. The drug solution mixture was cooled, neutralized with 0.1 N hydrochloric acid and then diluted with mobile phase as per the requirement and 20 µL of the solution was injected in to the HPLC system.

Oxidation conditions: Oxidation degradation was performed by treating the drug solution mixture (containing each of 1 mg/ml Rosuvastatin and Ezetimibe) with 30% H_2O_2 for 30 min in a thermostat maintained at 60°C. The drug solution mixture was cooled and then diluted with mobile phase as per the requirement and 20 µL of the solution was injected in to the HPLC system.

Photolytic conditions: The drug solution mixture (containing each of 1 mg/ml Rosuvastatin and Ezetimibe) was exposed to UV light (365 nm) for 3 hours, diluted with mobile phase as per the requirement and 20 µL of the solution was injected in to the HPLC system.

Thermal conditions: The drug solution mixture (containing each of 1 mg/ml Rosuvastatin and Ezetimibe) was in a thermostat maintained at 60°C for 8 hours, cooled and 20 µL of the solution was injected in to the HPLC system after necessary dilution with mobile phase.

Solution stability and mobile phase stability

The solution stability of Rosuvastatin and Ezetimibe in the assay method was carried out by leaving both the sample and reference standard solutions in tightly capped volumetric flasks at room temperature for 48 h. The same sample solutions were assayed at 12 h intervals over the study period. The mobile phase stability was also assessed by assaying the freshly prepared sample solutions against freshly prepared reference standard solutions at 12 h intervals up to 48 h. The prepared mobile phase remained constant during the study period. The % RSD of the Rosuvastatin and Ezetimibe assay was calculated for the mobile phase and solution stability experiments. An additional study was carried out using the stock solution by storing it in a tightly capped volumetric flask at 4°C.

Analysis of tablet formulation

Twenty tablets from each brand (RAZEL-EZ® and ROSUVAS-EZ®) were procured, weighed and crushed to a fine powder. Powder equivalent to 25 mg 25 mg of Rosuvastatin and Ezetimibe was accurately weighed into a 25 mL volumetric flask and made up to volume with mobile phase. The contents of the volumetric flask were sonicated for 30 min to enable complete dissolution of both the drugs. The solution was filtered and diluted with mobile phase as per the requirement. 20 µL of these solutions were injected into the system after filtering through 0.45 µm membrane and the peak area was recorded from the respective chromatogram.

Results and Discussion

HPLC method development and optimization

Initially the stressed samples were analyzed using a mobile phase consisting of TBAHS: acetonitrile (30:70, v/v) at a flow rate of 1.2 ml/min. Under these conditions, the resolution was not satisfactory. Therefore the mobile phase composition was changed to 32: 68, v/v with a flow rate 1.0 ml/min under which the resolution was good. Therefore mobile phase consisting of TBAHS: acetonitrile (32:68, v/v) with a flow rate of 1.0 ml/min was chosen as the best chromatographic response for the simultaneous determination of Rosuvastatin and Ezetimibe. UV detection was carried out at 254 nm (PDA detector). The present proposed method was compared with the previously published HPLC methods in the literature and discussed in Table 1.

Method validation

Linearity: The combination of Rosuvastatin and Ezetimibe shows linearity over a concentration range of 0.1-200 µg/ml (Table 2) and the linear regression equations were found to be y = 34716x + 3830.3 (r^2=0.9998) and y = 44508x + 25845 (r^2=0.9998) for Rosuvastatin and Ezetimibe respectively. The chromatograms of the mobile phase (blank) and that of the combination of Rosuvastatin and Ezetimibe were shown in Figure 2A-B respectively.

Accuracy: The accuracy study was repeated over three consecutive days and the resultant % RSD was found to be 0.10-0.14 and 0.10-0.63 for Rosuvastatin and Ezetimibe indicating that the method is precise. The recovery of for Rosuvastatin and Ezetimibe was found to be 99.38-99.95 % and 98.97-99.80 % respectively (Table 3).

Precision: The % RSD for intra-day precision was found to be 0.41-0.94 and 0.31-0.59 for Rosuvastatin and Ezetimibe respectively whereas the inter-day precision was found to be 0.68-0.95 and 0.68-1.02 for Rosuvastatin and Ezetimibe respectively (Table 4).

Sensitivity/ Limit of quantification (LOQ) and limit of detection (LOD)

The LOD and LOQ were found to be 0.0282 µg/ml and 0.0853 µg/ml for Rosuvastatin and the LOD and LOQ for Ezetimibe were 0.0297 µg/ml and 0.0901 µg/ml respectively.

Robustness: Usually a slight change in flow rate, mobile phase composition etc. affects the chromatographic response such as retention time, tailing factor and theoretical plates etc. During this study the theoretical plates were found to be more than 2000 for both the drugs and at the same time the % RSD was found to be < 2.0% (0.52-0.95 % and 0.71-1.38 % for Rosuvastatin and Ezetimibe respectively) indicating that the proposed method is robust. The results were shown in Table 5.

Solution stability and mobile phase stability: The % RSD for the solution stability was found to be 0.0149 and 0.0153 and for mobile

Method/Reagent	λ (nm)	Linearity (µg/ml)	Remarks	Ref.
Methanol: acetonitrile: phosphate buffer (60:20:20, v/v) (pH 3.5)	279	5-10 × 10^3	Micellar liquid chromtography	[7]
Acetonitrile: methanol: K_2HPO_4 (pH 3.0) (34.27: 20: 45.73, v/v/v)	239	0.5–1.0	Not stability indicating	[8]
Ammonium buffer: acetonitrile (55:45, v/v) (pH 6.5)	230	98.19 - 294.56 (RSV) 99.12 - 297.36 (EZT)	Low linearity range	[9]
Phosphate buffer: methanol (45:55, v/v) (pH 2.5)	242	5-80	Low linearity range	[10]
Ortho phosphoric acid : acetonitrile (63 : 37, v/v) (pH 3.5)	245	0.5-10	Not stability indicating	[11]
Ammonium acetate buffer: methanol: acetonitrile (30: 40: 30, v/v/v) (pH 7.2)	239	0.5-5 × 10^3	Not stability indicating	[12]
Acetonitrile: methanol: sod. di hydrogen phosphate (30:20:50, v/v)	263	10-60	Not stability indicating	[13]
Tetra butyl ammonium hydrogen sulphate: acetonitrile (32:68, v/v) (pH 3.4)	254	0.5-200	Stability indicating & wide linearity range	Present work

Table 1: Comparison of Performance Characteristics of the Present Method with the Previously Published HPLC Methods.

Conc. (µg/ml)	*Mean peak area ± SD	*%RSD
Rosuvastatin		
0.1	3387 ± 7.11	0.21
1	34320 ± 126.98	0.37
5	163427 ± 179.77	0.11
10	348814 ± 976.68	0.28
20	702587 ± 632.33	0.09
50	1729365 ± 3112.86	0.18
100	3562713 ± 7837.97	0.22
150	5146587 ± 18013.05	0.35
200	6954369 ± 39639.90	0.57
Ezetimibe		
0.1	4137 ± 22.34	0.54
1	40994 ± 147.58	0.36
5	216687 ± 238.36	0.11
10	412443 ± 1484.79	0.36
20	803747 ± 3456.11	0.43
50	2247531 ± 4719.82	0.21
100	4355771 ± 3920.19	0.09
150	6619726 ± 29126.79	0.44
200	8927091 ± 45528.16	0.51

Table 2: Linearity of Rosuvastatin and Ezetimibe.

phase stability was 0.0875 and 0.0843 (< 2 %) for Rosuvastatin and Ezetimibe respectively indicating that the mobile phase as well as the sample solutions used during the assays were stable up to 48 h at room temperature (Table 6).

Analysis of commercial formulations: The proposed method was applied for the determination of Rosuvastatin and Ezetimibe in marketed formulations available (RAZEL-EZ® and ROSUVAS-EZ®). The % recovery was found to be 98.57-98.71 and 96.02-96.19 for Rosuvastatin and Ezetimibe respectively (Table 7). The resultant chromatograms obtained from the extraction of marketed formulations were shown in Figure 2C-D.

Forced degradation studies: Rosuvastatin is highly resistant towards acidic, alkaline, oxidation, thermal and photolytic degradations as the percentage of degradation was found to be less than 10%. Ezetimibe has extensively undergone alkaline degradation (94.73%) and the phenolic hydroxyl group present in the chemical structure may be responsible for this. The resolution was found to be 6.272 and 5.123 (degradation product, R_t 5.950 min) which is greater than 2. During the oxidation an extra peak was observed at 2.502 min. and the resolution was found to be 7.261. The resultant chromatograms obtained during the forced degradation studies were shown in Figure 3A-E. The system suitability parameters for all the degradation studies were shown in Table 8.

Discussion

The present proposed method can be successfully applicable to perform long-term and accelerate stability studies of Rosuvastatin and Ezetimibe formulations. The complete separation of the analytes was accomplished in less than 10 min. In literature no suitable robust and validated stability indicating methods are available with wide linearity range and instead a mixture of solvents were employed as mobile phase.

The system suitability parameters such as the number of theoretical plates (N) is used to determine the performance and effectiveness of the column. The efficiency of a column can be measured by the number of theoretical plates per meter. It is a measure of band spreading of a peak. Smaller the band spread, higher is the number of theoretical plates, indicating good column and system performance. Columns with N ranging from 5,000 to 100,000 plates / meter are ideal for a good system. In the present method during all the stress studies, the

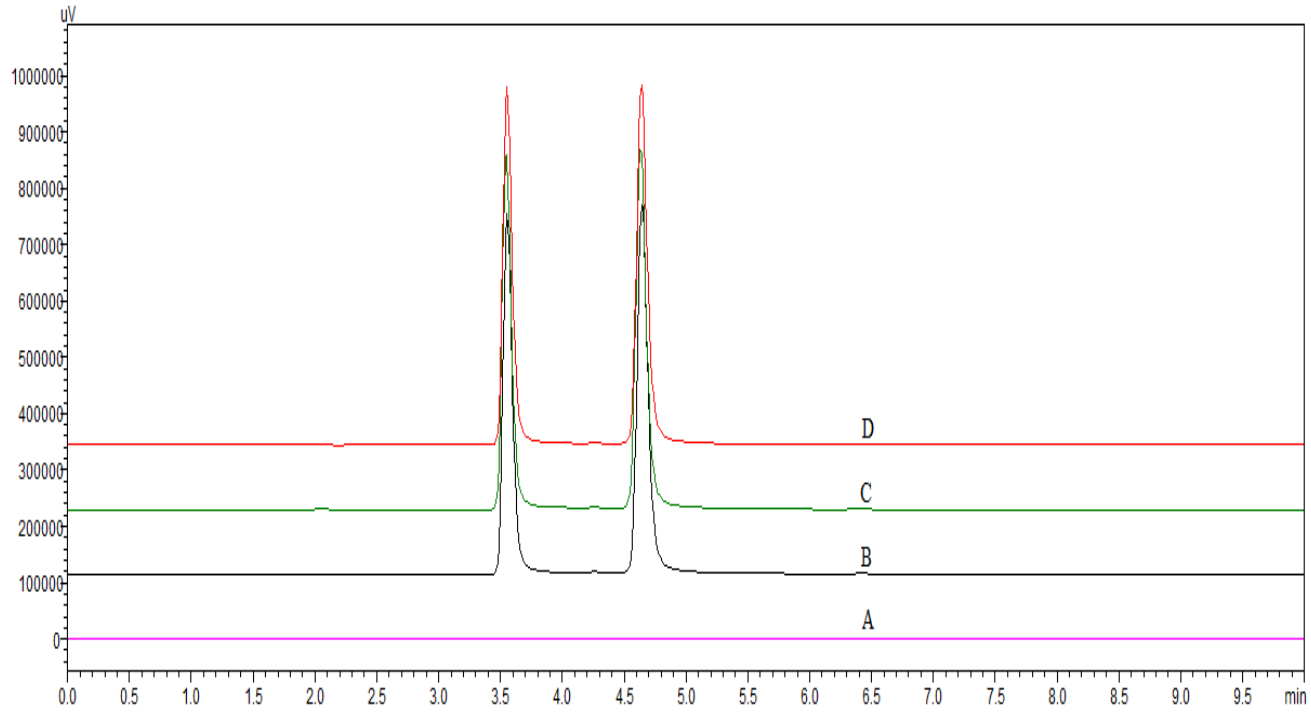

Figure 2: Typical chromatograms of blank [A], RSV and EZT [B], RAZEL-EZ® [C] and ROSUVAS-EZ® [D].

Drugs	Conc. (µg/ml)			*Mean peak area ± SD (% RSD)	Drug found (µg/ml)	% Recovery
	Formulation	Pure drug	Total			
Rosuvastatin	10	8	11	628394.67 ± 653.53 (0.10)	17.99	99.95
	10	10	20	696770.33 ± 952.04 (0.14)	19.96	99.80
	10	12	22	762850.00 ± 881.30 (0. 12)	21.86	99.38
Ezetimibe	10	8	18	820472.67 ± 3162.31 (0.39)	17.85	99.19
	10	10	20	914191.67 ± 947.12 (0.10)	19.96	99.80
	10	12	22	994905.00 ± 6310.08 (0.63)	21.77	98.97

Table 3: Accuracy Studies of Rosuvastatin and Ezetimibe.

Drugs	Conc. (µg/ml)	Intra-day precision	Inter-day precision
		Mean peak area ± SD (% RSD)	Mean peak area ± SD (% RSD)
Rosuvastatin	10	348863.33 ± 1047.48 (0.30)	346293.00 ± 2281.26 (0.66)
	50	1733410.33 ± 3549.39 (0.20)	1716940.00 ± 10770.65 (0.63)
	100	3600587.67 ± 21498.47 (0.60)	3544987.67 ± 15370.90 (0.43)
Ezetimibe	10	413280.33 ± 764.78 (0.19)	408913.00 ± 3086.61 (0.75)
	50	2242036.00 ± 6922.85 (0.31)	2224092.00 ± 21013.66 (0.95)
	100	4366382.67 ± 13599.62 (0.31)	4326490.33 ± 26479.69 (0.61)

Table 4: Precision Studies of Rosuvastatin and Ezetimibe.

Parameter	Condition	Mean peak area ± SD (% RSD)	% Assay	Theoretical plates
Rosuvastatin				
Flow rate (ml/min)	0.9	3557208.67 ± 8898.09 (0.25)	99.85	8134
	1.0			
	1.1			
Detection wavelength (nm)	252	3551673.00 ± 16076 (0.45)	99.69	8530
	254			
	256			
Mobile phase composition (v/v)	34:66	3532385.67 ± 26472.49 (0.75)	99.15	8457
	32:68			
	30:70			
pH	3.3	3551673.67 ± 38794 (1.09)	99.69	8265
	3.4			
	3.5			
Ezetimibe				
Flow rate (ml/min)	0.9	4346140.00 ± 8730.76 (0.20)	99.78	10986
	1.0			
	1.1			
Detection wavelength (nm)	252	4359196.67 ± 11949.63 (0.27)	100.08	10859
	254			
	256			
Mobile phase composition (v/v)	34:66	4318080.67 ± 36416.96 (0.84)	99.13	10945
	32:68			
	30:70			
pH	3.3	4325117.33 ± 30964.03 (0.72)	99.30	10674
	3.4			
	3.5			

Table 5: Robustness Studies of Rosuvastatin and Ezetimibe.

theoretical plates were found to be more than 2000 and the tailing factor was less than <1.5–2 or <2 indicating that the method is more selective and specific.

The specificity of the developed method can be determined from the stress studies and the percentage drug recovery was calculated from the peak area of the resultant chromatograms. During the stress studies it was observed that ezetimibe is highly sensitive towards alkaline degradation. The phenolic hydroxyl group present in its structure may be responsible for the major degradation during alkaline stress conditions.

Conclusion

The proposed method for the simultaneous determination of Rosuvastatin and Ezetimibe validated as per the ICH guidelines and it is simple, specific and robust and can be applied for the long term stability studies as well as for the kinetic studies of the pharmaceutical formulations.

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Solution stability				Mobile phase stability		
Time (hours)	*Assay (%)		Mean ± SD (% RSD)	Retention time (min)		Mean ± SD (% RSD)
	RST	EZT		RST	EZT	
Initial	98.71	96.19	**Rosuvastatin** 98.70 ± 0.0147 (0.0149)	3.542	4.628	**Rosuvastatin** 3.542 ± 0.0031 (0.0875)
6	98.72	96.17		3.540	4.624	
12	98.69	96.20		3.543	4.625	
18	98.70	96.18	**Ezetimibe** 96.19 ± 0.0147 (0.0153)	3.538	4.618	**Ezetimibe** 4.624 ± 0.0039 (0.0843)
24	98.71	96.18		3.541	4.627	
48	98.68	96.21		3.547	4.620	

*Mean of three replicates

Table 6: Analysis of Solution Stability and Mobile Phase Stability of Rosuvastatin and Ezetimibe.

Formulation	Labelled claim (mg)		Amount found* (mg)		Recovery* (%)	
	RST	EZT	RST	EZT	RST	EZT
RAZEL-EZ®	10	10	9.871	9.619	98.71	96.19
ROSUVAS-EZ®	10	10	9.857	9.602	98.57	96.02

* Mean of three replicates

Table 7: Analysis of Rosuvastatin and Ezetimibe in commercial formulation (Tablets).

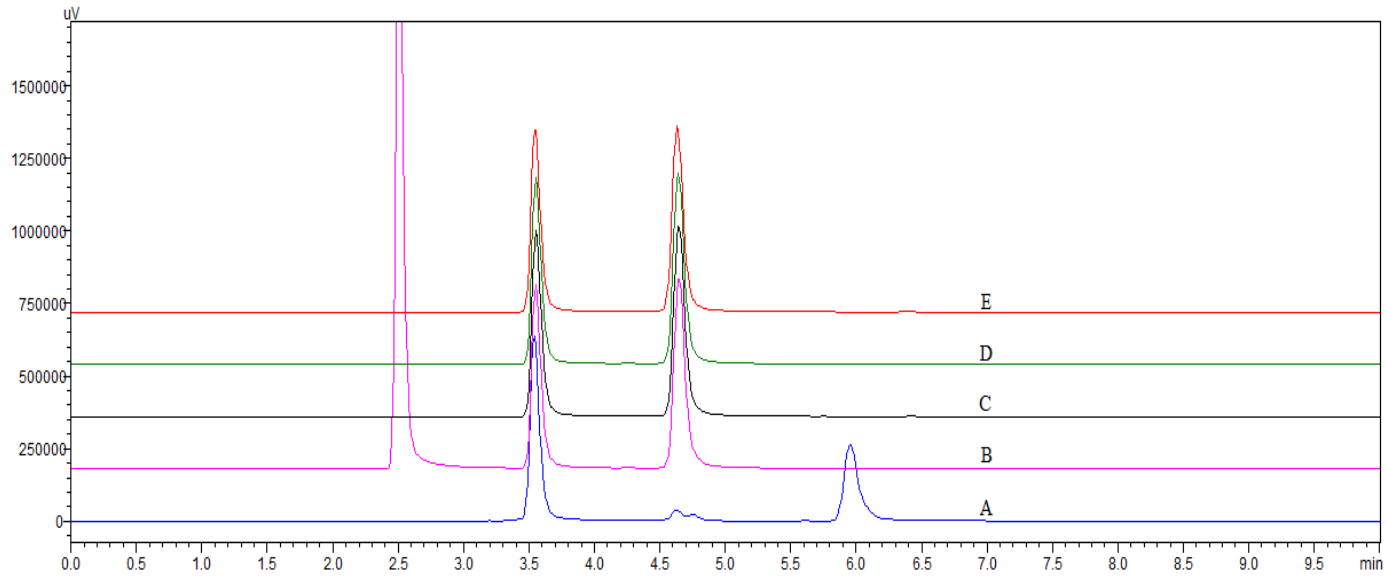

Figure 3: Typical Chromatograms for alkali [A], oxidation [B], acidic [C], thermal [D] and photolytic [E] degradations.

Stress conditions	% Drug recovered	% Drug decomposed	Theoretical plates	Tailing factor
Rosuvastatin				
Standard drug	100	0	8052.207	1.407
Acidic degradation	93.61	6.39	8410.217	1.429
Alkaline degradation	98.40	1.60	8352.050	1.436
Oxidative degradation	94.34	5.66	8480.252	1.430
Thermal degradation	92.74	7.26	8087.685	1.406
Photolytic degradation	91.85	8.15	8456.438	1.428
Ezetimibe				
Standard drug	100	0	10793.731	1.392
Acidic degradation	97.39	2.61	10966.786	1.413
Alkaline degradation	5.27	94.73	9279.186	1.476
Oxidative degradation	99.42	0.58	10824.863	1.469
Thermal degradation	96.77	3.23	10667.446	1.390
Photolytic degradation	93.70	6.30	10777.534	1.380

Table 8: Forced degradation studies of Rosuvastatin and Ezetimibe.

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