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VALIDATED STABILITY-INDICATING HPLC METHOD FOR THE SIMULTANEOUS DETERMINATION OF EZETIMIBE, ROSUVASTATIN, AND SIMVASTATIN IN COMBINED TABLET DOSAGE FORMS

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ABSTRACT

Rugged and robust HPLC method was developed for assay determination of Ezetimibe, Rosuvastatin, and Simvastatin in tablet dosage form. These three drugs used to treat the human body bad and good cholesterol management in blood. Ezetimibe and rosuvastatin are available in the market in tablets dosage form; Ezetimibe and simvastatin combinations also available in the market. 0.05 M KH_2PO_4 buffer was used as mobile phase A and acetonitrile is used as mobile phase B. Gradient program was used as eluent, 30% of mobile phase B at 0 min; 30 % at 5 min; 42% at 8 min; 40 % at 12 min; and 30 % at 16 min and 30 % at 20 min. Agilent make Zorbax SB C18 150*4.6 mm, 5 µ HPLC column was used. 20 µL injection volume, 20 min runtime,1.0 ml/min flow rate, 230 nm and 50°C column oven temperature were applied for analysis. Mobile phase A and B were mixed in the ratio of 50:50 v/v and used as diluent. All three analytes were eluted with high resolution and the retention time of ezetimibe 15.3 min, rosuvastatin 9.0 min and simvastatin 17.1 min. method validation was performed as per ICH quality guidance. Results were achieved with accuracy and precision. Hence, the developed and validated method was applicable for routine drug product manufacturing quality evaluation.

KEYWORDS: Ezetimibe, Rosuvastatin, Simvastatin, HPLC, Method development, Method validation.

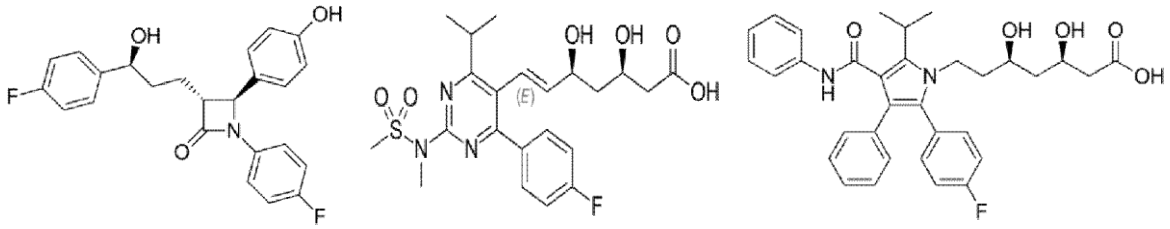
INTRODUCTION

Ezetimibe controls the absorption of cholesterol and decreasing the release of intestinal cholesterol to the liver. Ezetimibe (EZE) is [(3R,4S)-1-(4-fluorophenyl)-3-[(3S)-3-(4- fluorophenyl)-3- hydroxypropyl]-4-(4-hydroxyphenyl)- 2-azetidinone]. It manages the cholesterol absorption (primary hypercholesterolemia). It inhibits the absorption of biliary and dietary cholesterol from small intestine without influencing absorption of fat soluble vitamins, triglycerides and bile acids.[1-2] After oral administration, Ezetimibe is metabolized into its glucuronide in the liver and small intestine, which is also active in prevention of absorption of cholesterol. Ezetimibe does not have significant pharmacokinetic interactions with other lipid lowering drugs.[3-4]

Simvastatin is used to treat anti-hyperlipidemic (lipid lowering) class of drug which reduces the amount of fatty or lipid substances such as cholesterol and triglycerides from the body. Chemical name of simvastatin is 7-[2-(4-fluorophenyl)-3-phenyl-4-(phenylcarbamoyl)-5-(propan-2-yl)- 1H- pyrrol-1-yl]-3,5-dihydroxyheptanoate**,** calcium salt (2:1) trihydrate**.** Figure-1 represented the chemical structures of ezetimibe, Simvastatin, rosuvastatin.

Rosuvastatin calcium is chemically, bis[(E)-7[4-(4-fluorophenyl)-6-isopropyl-2-[methyl (methyl-sulphonyl)amino]pyrimidin-5-yl](3R,5S)-3,5-dihydroxyhept-6-enoic acid] calcium salt). It belongs to a statins family, which are employed to lower

hypercholesterolemia and related conditions and to prevent cardiovascular diseases. It increases the number of hepatic low density lipoprotein receptors involved in the catabolism of LDL and also inhibits hepatic synthesis of very low density lipoprotein.[5-8]



Ezetimibe **Rosuvastatin** **Simvastatin**

Figure 1: Chemical structure of Ezetimibe, Simvastatin and Rosuvastatin.

Literature survey was performed for these three analytes determination for single HPLC method but there is no single method was reported. Few methods were reported for ezetimibe and rosuvastatin determination by using HPLC, UV spectrophotometric methods.[9-11] Ezetimibe and simvastatin combination product also have very few reported methods.[12-17]

The main objective of this research work was to develop an single, accurate and rugged HPLC method to determine ezetimibe, rosuvastatin and simvastatin in pharmaceutical drug products.

MATERIALS AND METHOD

Chemicals and reagents

HPLC standard acetonitrile and methanol were purchased from Qualigens fine chemicals, Mumbai, India. Distilled, 0.45 µm filtered water used for HPLC analysis. Sd. fine chem analytical grade KH_2PO_4 salt was purchased and used for the preparation of mobile phase. Milli- Q water was used for the analysis.

Chromatographic conditions

Agilent make HPLC systems and carry win UV spectrophotometer were used for this research work. Zorbax SB C18, 150×4.6 mm, 5 µm HPLC column was used (agilent make). 1.0 ml/min flow rate, 420 µL injection volume and 50°C column oven temperature were applied. UV absorbance was measure at 230 nm.

Mobile phase A

6.8 g of KH_2PO_4 buffer salt was weighed accurately and transferred in to 1000 ml beaker, mixed well. Sonication was performed to dissolve the contents. Resulting solution was degassed with and filtered through 0.45µm Millipore membrane filter and sonicated.

Mobile phase B

HPLC grade acetonitrile was used as mobile phase B, degassed through 0.45µm. Millipore membrane filter and sonicated for few minutes.

Diluent

Mobile phase A and B were mixed in the ratio of 50:50 v/v and degassed through 0.45µ filter.

Standard Solution

40 mg of each standard material such as rosuvastatin, ezetimibe and Simvastatin was weighed accurately and transferred in to a 100 mL volumetric flask and dissolved in 50mL of diluent and sonicated to dissolve the contents. Further, volume was filled with diluent solution. From the above stock solution 5 mL aliquot was pipetted in to a 50mL volumetric flask and dissolved in the solvent and made up to the mark with the diluent.

Ezetimibe and Simvastatin test sample solution

The contents of twenty ezetimibe and Simvastatin tablets were taken and finely powdered. A mass equivalent to 56mg of each ezetimibe and Simvastatin was transferred to a 100mL volumetric flask and dissolved in 50mL of the diluent. The solution was kept for sonication for 15min. The solution was made up to the mark with the diluent and filtered through a 0.45µ membrane filter. 5mL aliquot of the above solution was transferred to a 50mL volumetric flask and diluted to the mark with diluent.

Ezetimibe and rosuvastatin test sample solution

The contents of twenty ezetimibe and rosuvastatin tablets were taken and finely powdered. A mass equivalent to 56mg of each ezetimibe and rosuvastatin was transferred to a 100mL volumetric flask and dissolved in 50mL of the diluent. The solution was kept for sonication for 15min. The solution was made up to the mark with the diluent and filtered through a 0.45µ membrane filter. 5mL aliquot of the above solution was transferred to a 50mL volumetric flask and diluted to the mark with diluent.

Assay Calculation

% of Assay=

$$\frac{Ta \times Tw \times 5 \times 100 \times 50 \times Tweight \times Spotency}{Sa \times 100 \times 50 \times Sw \times 5 \times Label\ claim \times 100} \times 100$$

Ta= Peak area in test solution

Sa= Peak area in standard solution

Tw= Sample weight used for test solution preparation

Sw= Standard weight used for standard solution preparation Tweight= Tablets average weight

Label claim= drug content in one tablet Spotency= Standard material potency

RESULTS AND DISCUSSION

Method Optimization

Ezetimibe, Simvastatin, rosuvastatin standard materials are available in solid stable form and can be stored at room temperature. Solubility of three ingredients was evaluated with different solvents like different pH value buffers, acetonitrile and methanol. Solubility study results shown that, all the three components have solubility with mixture of buffer, methanol and acetonitrile. Further UV spectral studies were performed by using Agilent makes carry 60 UV/ Visible spectrophotometer. Three ingredients were prepared with 2 ppm concentration to perform the UV spectral analysis. UV spectrum was scanned from 200 to 400 nm. Figure-2 to 4 represented the UV spectrum of ezetimibe, Simvastatin and rosuvastatin. Based on the UV spectrum results we have selected 230 nm to measure the analytes.

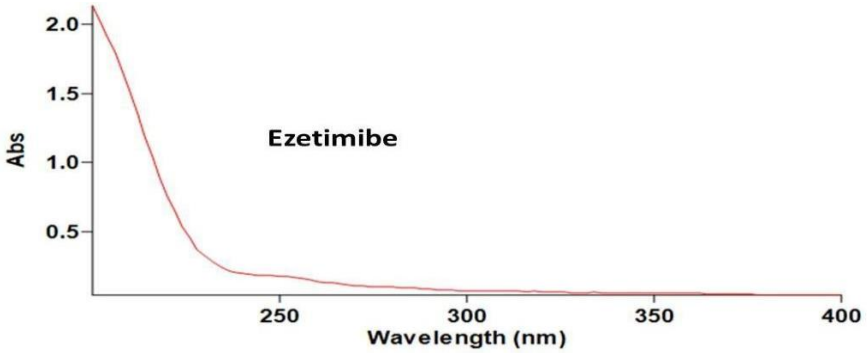


Figure 2: Ezetimibe UV spectrum.

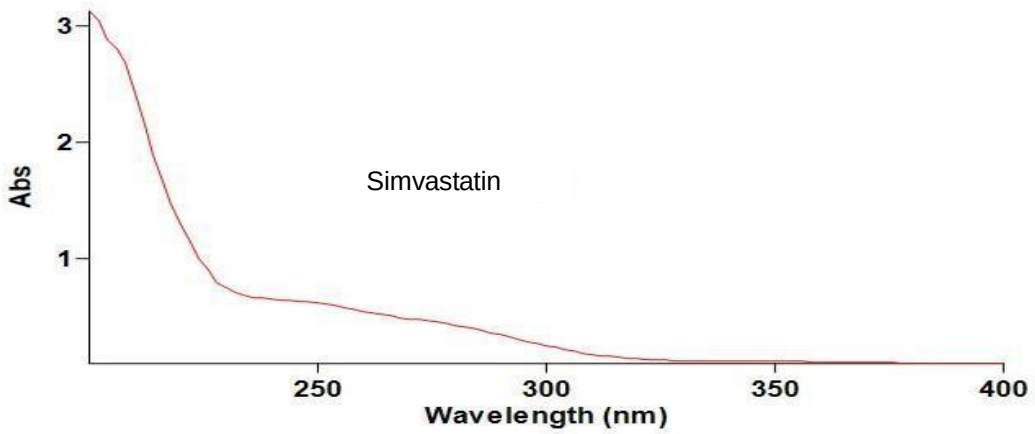


Figure 3: Simvastatin UV spectrum.

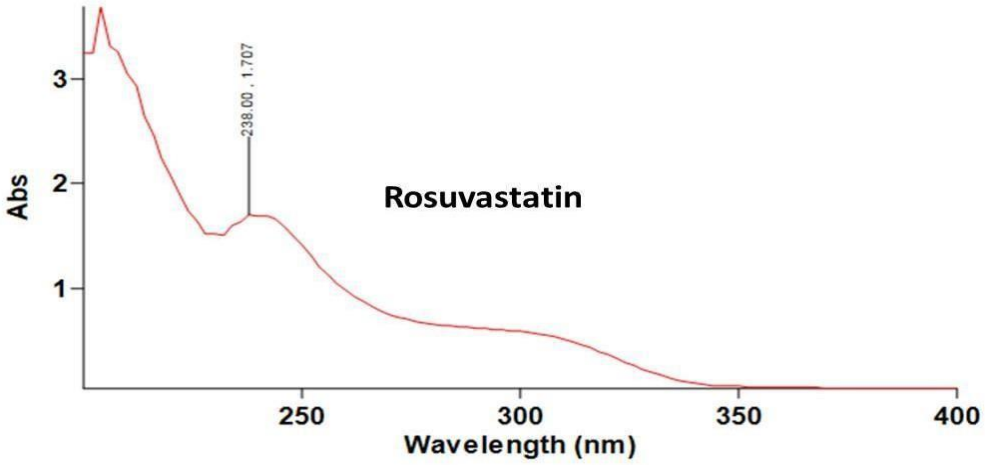


Figure-4: Rosuvastatin UV spectrum Method development experiment-1.

Conditions

Buffer: 0.5 ml orthophosphoric acid and 0.5 ml tri-ethyl amine transferred in to 1000 mL of water and mixed well to dissolve. Adjusted the pH value to 3.5 with tri-ethyl amine and filtered the solution through 0.45µm membrane filter and degassed. Mobile Phase A: Buffer;

Mobile Phase B: Analytical grade acetonitrile. Isocratic elution: Mobile phase A: Mobile phase B 55:45 v/v, Column: Intertsil C8, 250 x 4.6 mm, 5µm; Flow rate: 1.0 mL/min Column Temperature: Ambient; Volume of Injection: 20µL; Wave Length: 230 nm; Run Time: 35 min. Diluent: Mixed 500 mL of water and 500 mL of Acetonitrile in the ratio of 50:50% v/v and degassed. Preparation of Standard Solution: Individual sample solutions were prepared with 250 ppm concentration with diluent solution.

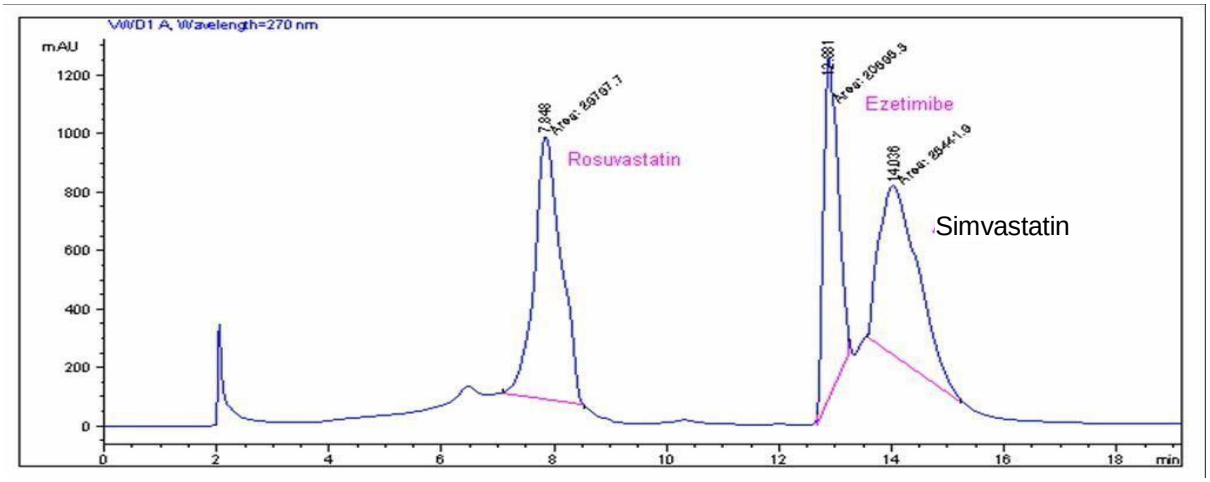


Figure-5: Method development trial-1 chromatogram.

Observation: Three standard materials were eluted (rosuvastatin 7.8 min; ezetimibe 12 min and simvastatin 14min) at but Simvastatin and ezetimibe were eluted closely. Further experiments shall be carried out with salt buffer to optimize retention time and peak shape. Figure-5 represented the method development trail chromatogram.

Method development experiment-2

Conditions

Buffer: 0.7 g of ammonium acetate salt was weighed accurately and transferred in to one liter milli-Q water and mixed well to dissolve. Adjusted the pH value to 3.0 with acetic acid and filtered the solution through 0.45µm membrane filter and degassed. Mobile Phase A: Buffer; Mobile Phase B: Analytical grade acetonitrile; elution: Mobile phase A: Mobile phase B 60:40 v/v; Column: Intertsil C8, 250 x 4.6 mm, 5µm; Flow rate: 1.0 mL/min; Column Temperature: Ambient; Volume of Injection: 20µL; Wave Length: 230 nm; Run Time: 35 min; Preparation of diluent: 500 mL of water and 500 mL of Acetonitrile were mixed and degassed. Standard Solution: Individual sample solutions were prepared with 250 ppm concentration with diluent solution.

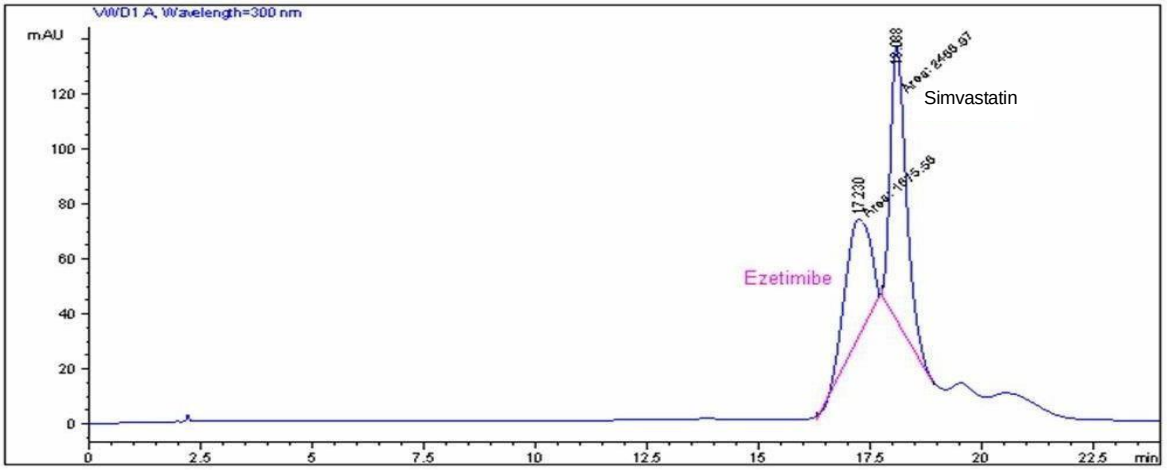


Figure 6: Method development trial-2 chromatogram.

Observation: ezetimibe and simvastatin were co-eluted. Further experiments shall be carried out by changing the buffer salt to achieve good peak shape and different retention time for each analyte. Figure-6 represented the method development trial chromatogram.

Method development experiment-3

Buffer solution: 3.4 g of KH_2PO_4 salt was weighed accurately and transferred in to 1000 mL of water and mixed well to dissolve. Filtered the solution through 0.45µm membrane filter and degassed. Mobile Phase A: Buffer; Mobile Phase B: Analytical grade acetonitrile.

Gradient program was applied to separate the ezetimibe and simvastatin.

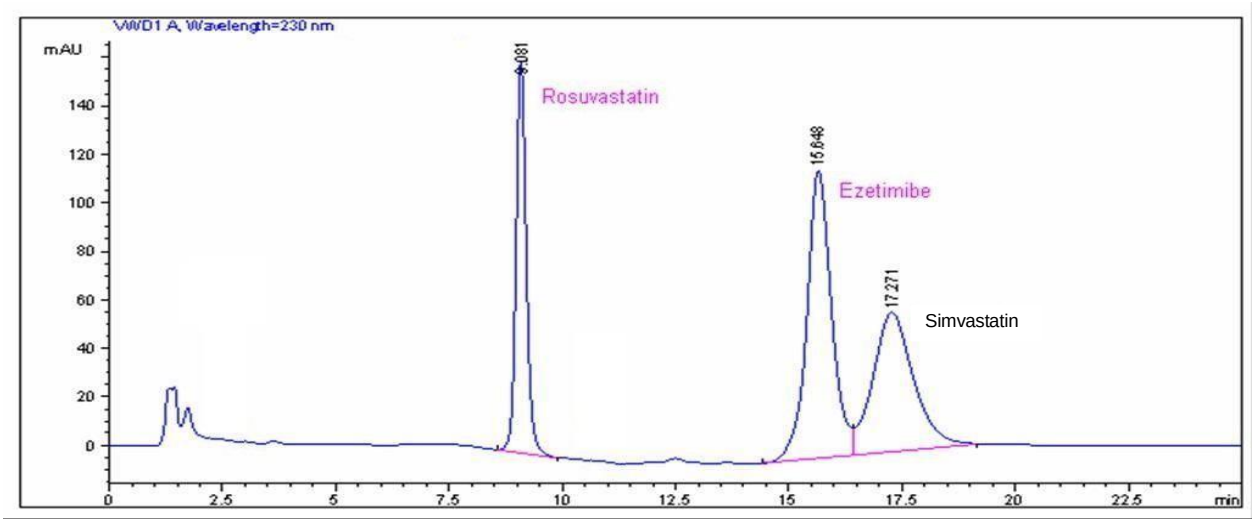


Figure-7: Method development trial-3 chromatogram.

Observation: Three standard materials were eluted but resolution between ezetimibe and simvastatin was low. Figure-7 represented the method development trial chromatogram.

Method development experiment-4

Buffer solution: 6.8 g of KH_2PO_4 salt was weighed accurately and transferred in to 1000 mL of water and mixed well to dissolve. Filtered the solution through 0.45µm membrane filter and degassed. Mobile Phase A: Buffer and B: acetonitrile; Gradient elution: mobile phase B 27% at 0 min; 32% at 4 min; 45% at 8 min; 58% at 12 min; 27% at 16 min and 27% at 20 min. other chromatographic conditions were applied as like development trial 3.

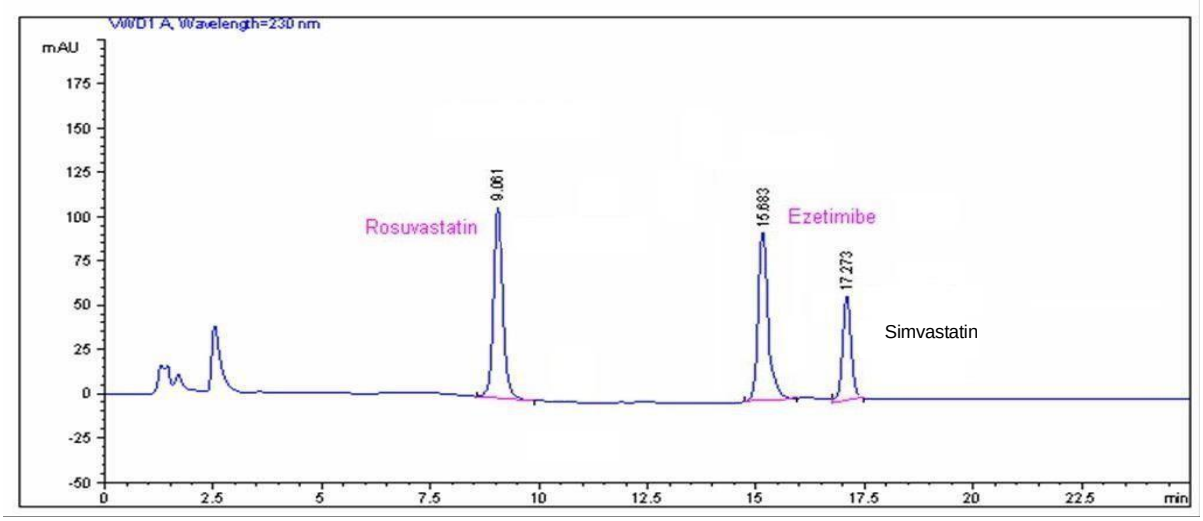


Figure-8: Method development trial-4 chromatogram.

Observation: Three analytes were eluted with good peak shape. Hence, this optimized method has been considered as final method. Further, method validation can be performed. Figure-8 represented the mixed sample chromatogram.

Method validation

Method validation was performed as per ICH (international council for harmonization of technical requirements for pharmaceutical for human use), USFDA guidance. All parameters such as precision, linearity, specificity, accuracy, ruggedness, robustness were performed. Method validation results are meeting the acceptable limits which are specified in the guidance documents.

Specificity

Specificity was performed to check the interference from the diluent, placebo and stress study conditions. Acidic, base, peroxide, thermal, photolytic and water stress

conditions were applied on drug product. Ezetimibe and rosuvastatin test samples and ezetimibe and simvastatin samples were stressed separately. Freshly prepared stress samples were injected into the HPLC. Stress studies results were tabulated in table 1 and 2. Figure 9 to 20 were represented the force degradation studies chromatograms. Stress study conditions were listed below,

Ezetimibe and Rosuvastatin tablets Stress study conditions

- Acid Hydrolysis : 0.5 N HCl at 55°C for 10 hours
- Base Hydrolysis : 1N NaOH at 55°C for 15 hours
- Oxidation (10% H_2O_2): at 30 °C for 6 hours
- Photolytic : UV-light (200 watts hr / m^2)
- Heat : at 55°C for 18 hours
- Water Hydrolysis : at 55°C for 10 hours

Ezetimibe and Simvastatin tablets Stress study conditions:

- Acid Hydrolysis : 0.5N HCl at 55°C for 12 hours
- Base Hydrolysis : 1N NaOH at 55°C for 6 hours
- Oxidation (10% H_2O_2): at 30 °C for 12 hours
- Photolytic : UV-light (200 watts hr / m^2)
- Heat : at 55°C for 12 hours
- Water Hydrolysis: at 55°C for 10 hours

Table 1: Stress study results.

Active Name	1. Force degradation % assay results					
	Acid	Base	Peroxide	UV	Thermal	Water
Ezetimibe and rosuvastatin tablets						
Ezetimibe	91.8	92.9	93.6	92.8	91.8	94.8
Rosuvastatin	92.6	92.1	92.8	92.1	93.0	93.8
Ezetimibe and simvastatin tablets						
Ezetimibe	90.2	92.6	92.3	95.1	92.0	94.0
Simvastatin	91.1	93.5	93.9	92.6	93.4	94.9

Table 2: Stress study unknown peaks data.

RT	2. Force degradation % area					
	Acid	Base	Peroxide	UV	Thermal	Water
Ezetimibe and rosuvastatin tablets						
2.9	2.1	2.4	ND	ND	1.9	2.9
6.7	2.0	1.9	2.3	2.7	2.1	2.1
21.0	ND	ND	1.5	1.6	1.6	1.4
Ezetimibe and simvastatin tablets						
2.9	2.9	2.1	ND	ND	ND	ND
6.7	1.2	1.0	2.4	1.4	ND	ND
21.0	1.2	ND	1.6	0.9	1.1	1.0

*ND= Not Detected

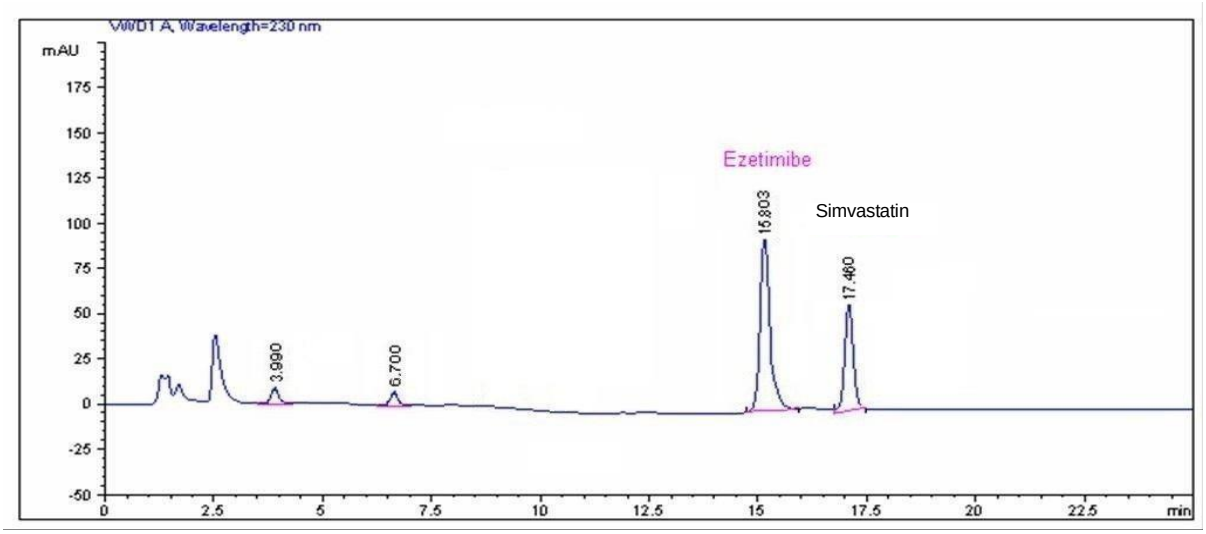


Figure 9: Ezetimibe and Simvastatin acid degradation chromatogram.

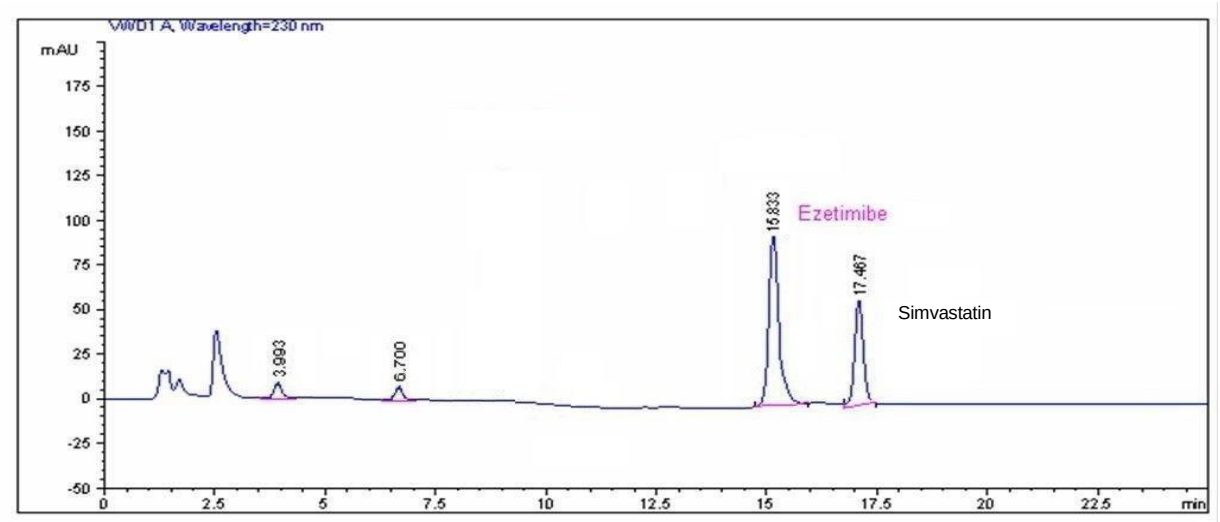


Figure 10: Ezetimibe and Simvastatin base degradation chromatogram.

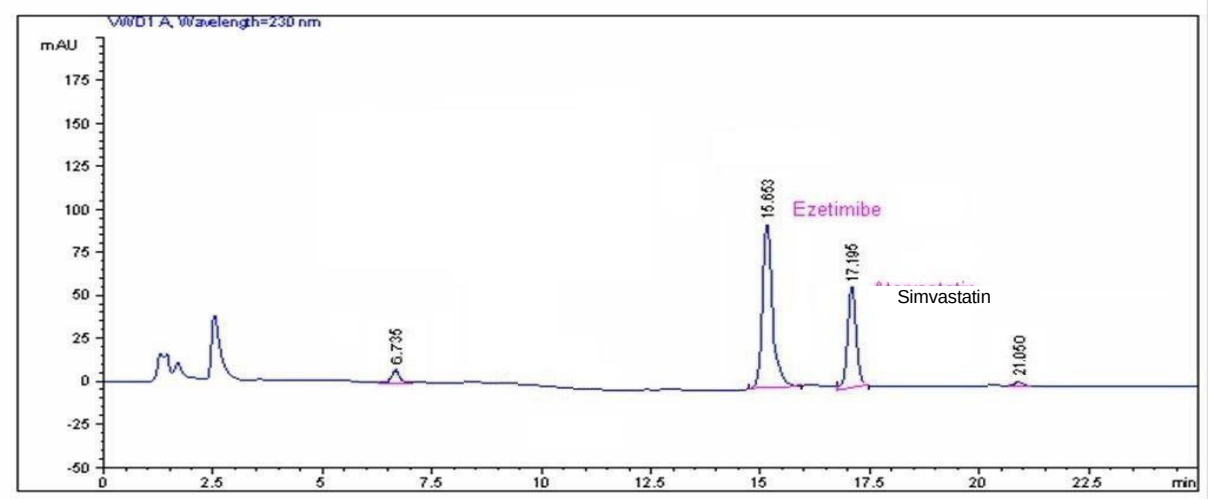


Figure 11: Ezetimibe and Simvastatin peroxide degradation chromatogram.

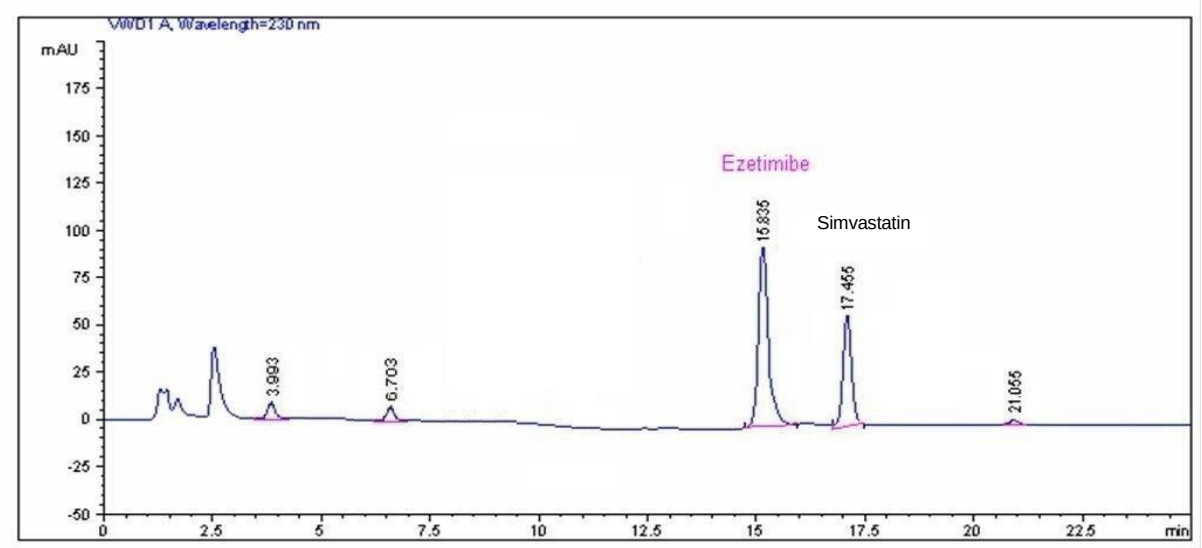


Figure-12: Ezetimibe and Simvastatin thermal degradation chromatogram.

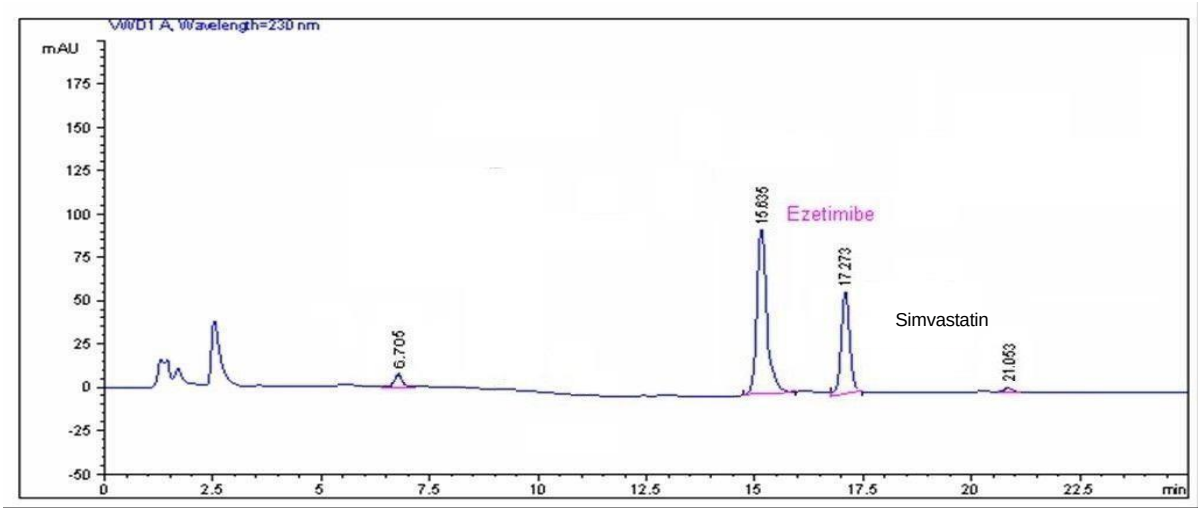


Figure-13: Ezetimibe and Simvastatin UV degradation chromatogram.

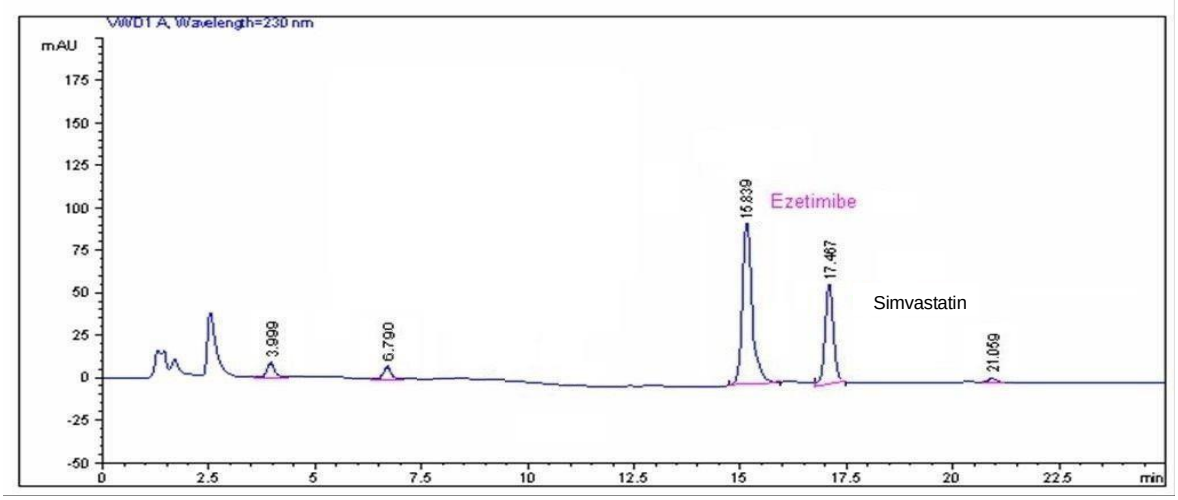


Figure-14: Ezetimibe and Simvastatin water degradation chromatogram.

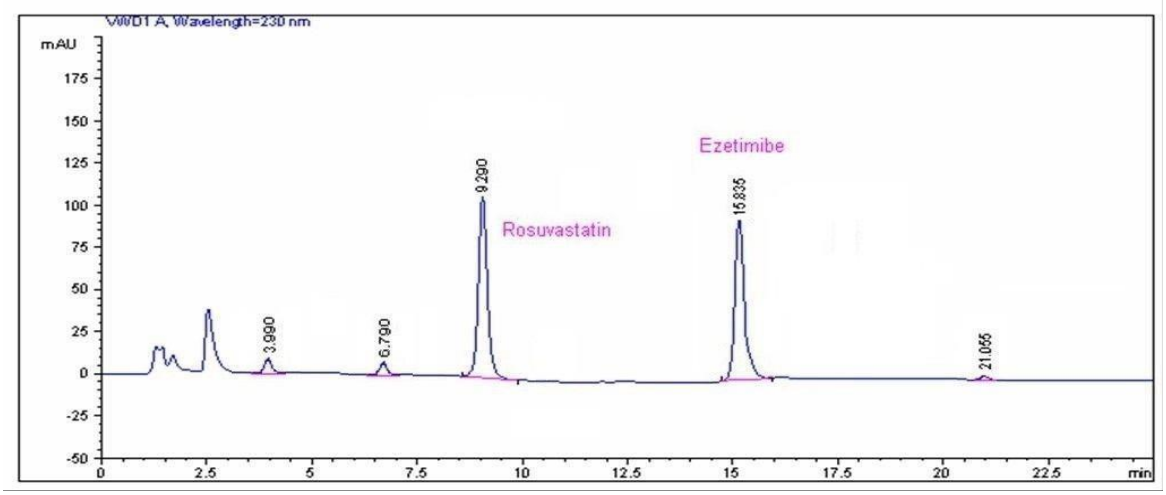


Figure 15: Ezetimibe and Rosuvastatin acid degradation chromatogram.

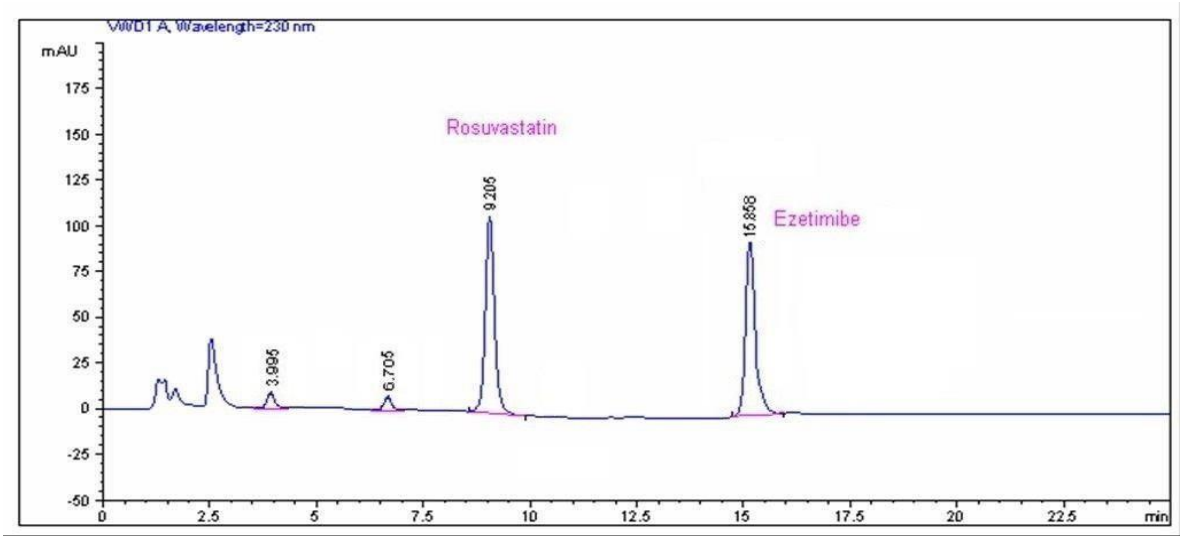


Figure-16: Ezetimibe and Rosuvastatin base degradation chromatogram.

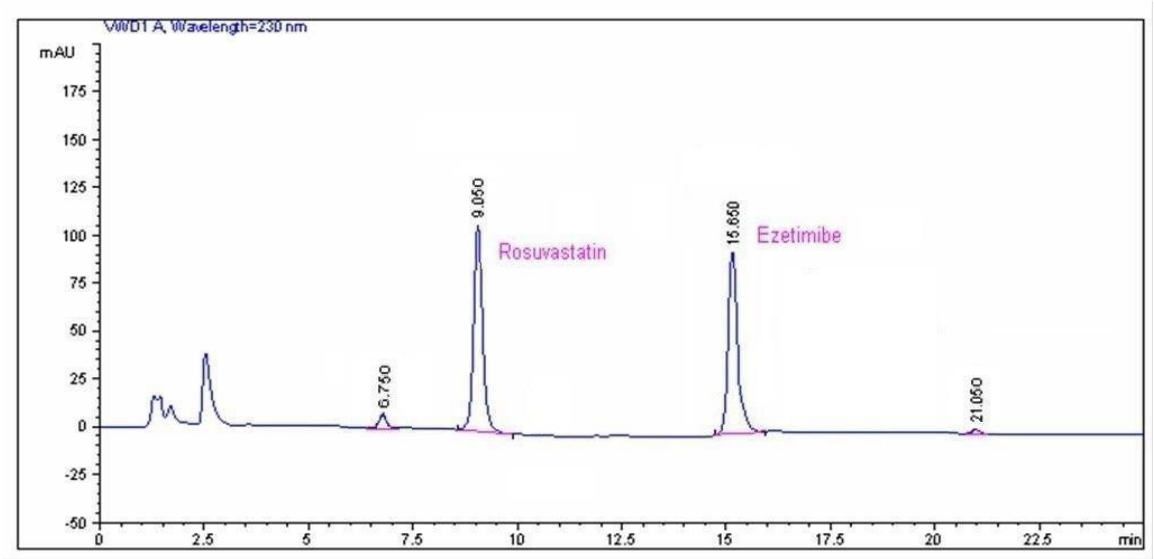


Figure-17: Ezetimibe and Rosuvastatin peroxide degradation chromatogram.

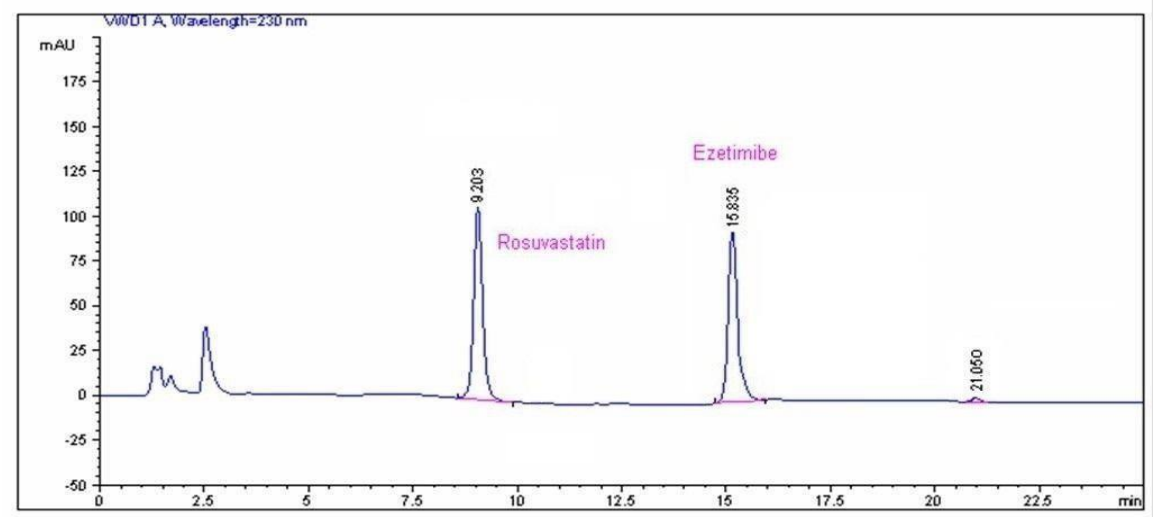


Figure-18: Ezetimibe and Rosuvastatin thermal degradation chromatogram.

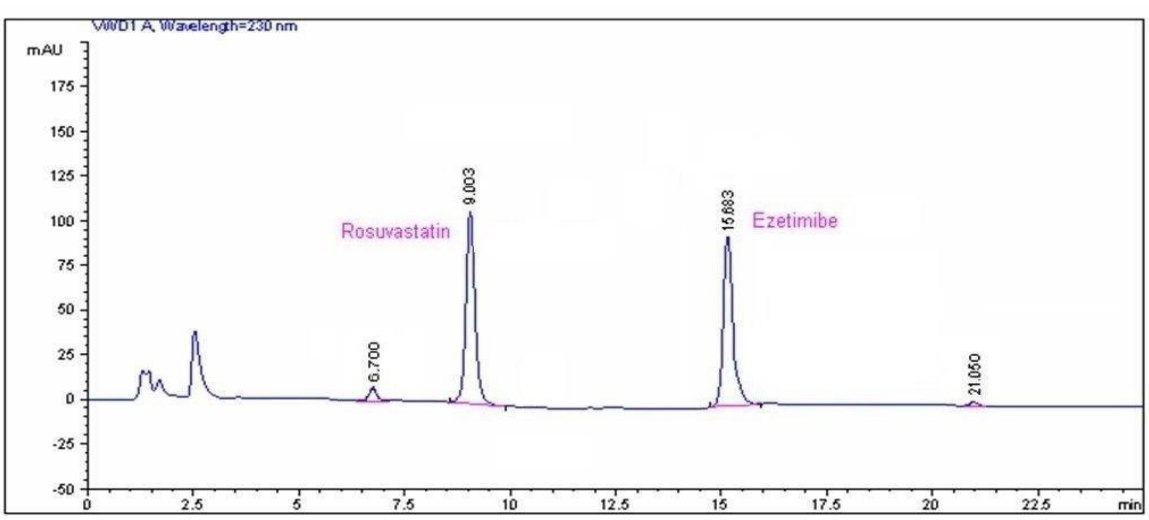


Figure-19: Ezetimibe and Rosuvastatin UV degradation chromatogram.

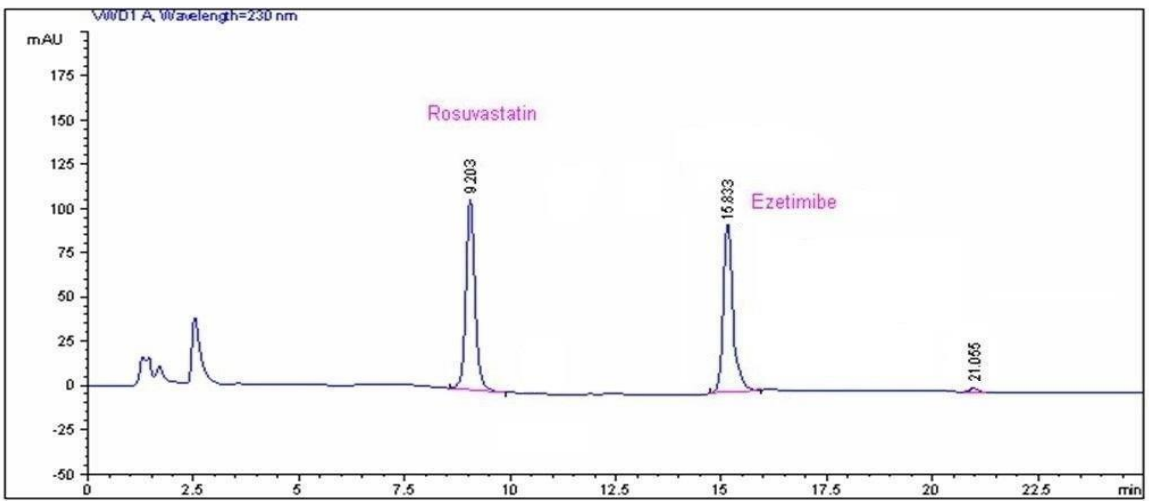


Figure-20: Ezetimibe and Rosuvastatin water degradation chromatogram.

Precision

Precision was performed for system precision with 5 replicate standard injections and method precision with 6 replicate sample preparations. Ezetimibe and rosuvastatin tablets were used to prepare the ezetimibe, rosuvastatin sample solution. Ezetimibe and Simvastatin tablets were used to prepare ezetimibe, Simvastatin sample solution. Figure-21 to 27 represented the blank, placebo sample, standard solution and test sample chromatograms. Table 3 and 4 summarized the system suitability and precision results.

Table 3: System suitability Results.

System Suitability parameter (five replicate injections)	Observations		
	Rosuvastatin	Ezetimibe	Simvastatin
Retention time (min)	9.0	15.5	17.2
Tailing factor (avg.)	1.09	1.3	1.01
%RSD (5 replicates)	1.22	1.11	1.16

Table-4: Method Precision Results.

Active Name	Precision sample preparation (% content)						%RSD
	1	2	3	4	5	6	
Rosuvastatin	100.16	99.86	99.68	100.58	100.61	101.25	0.57
Ezetimibe	99.18	100.25	99.76	101.21	100.56	101.31	0.82
Ezetimibe	101.25	101.29	100.98	100.36	100.28	100.64	0.44
Simvastatin	100.29	100.28	100.25	101.29	101.21	101.52	0.59

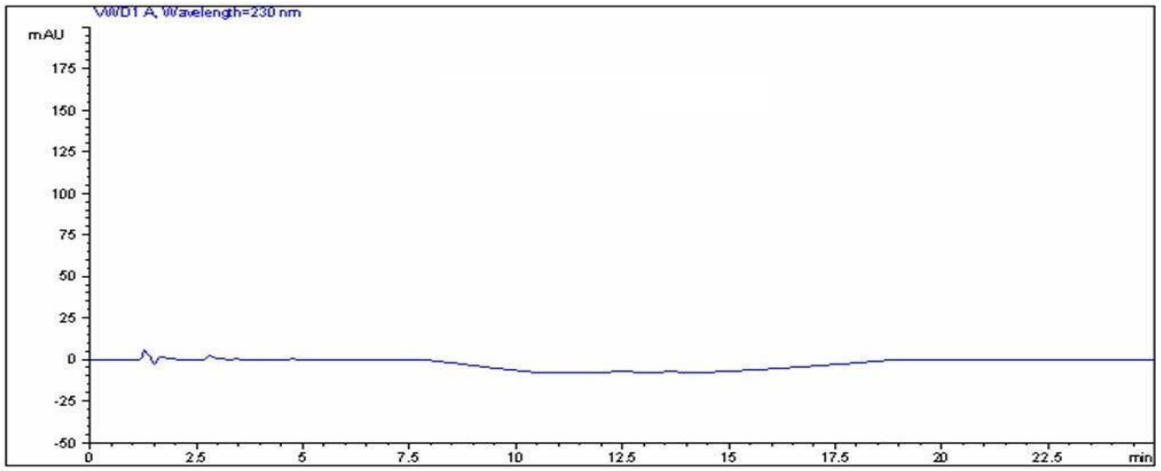


Figure 21: Blank Chromatogram.

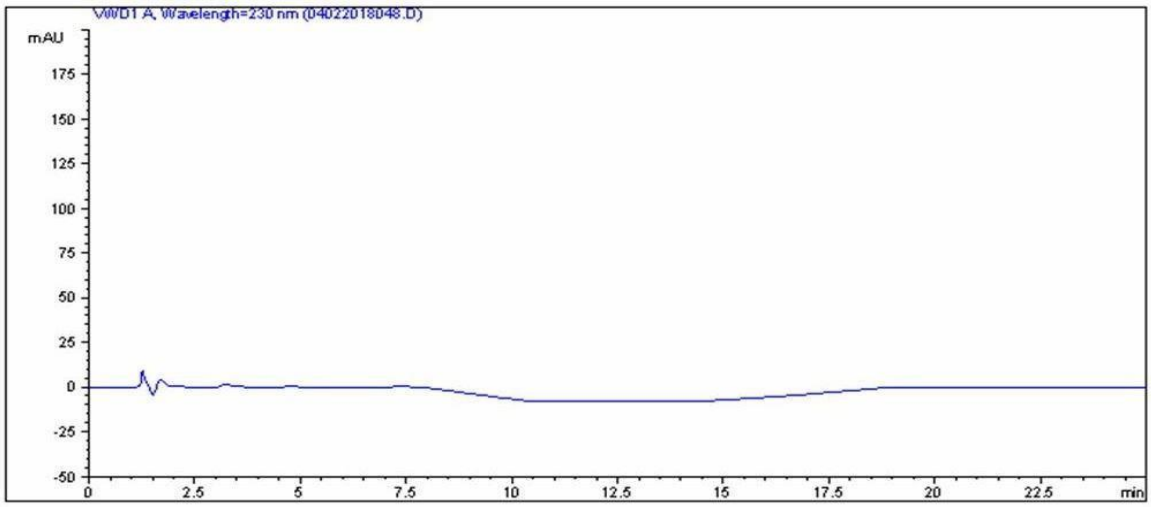


Figure 22: Placebo Chromatogram.

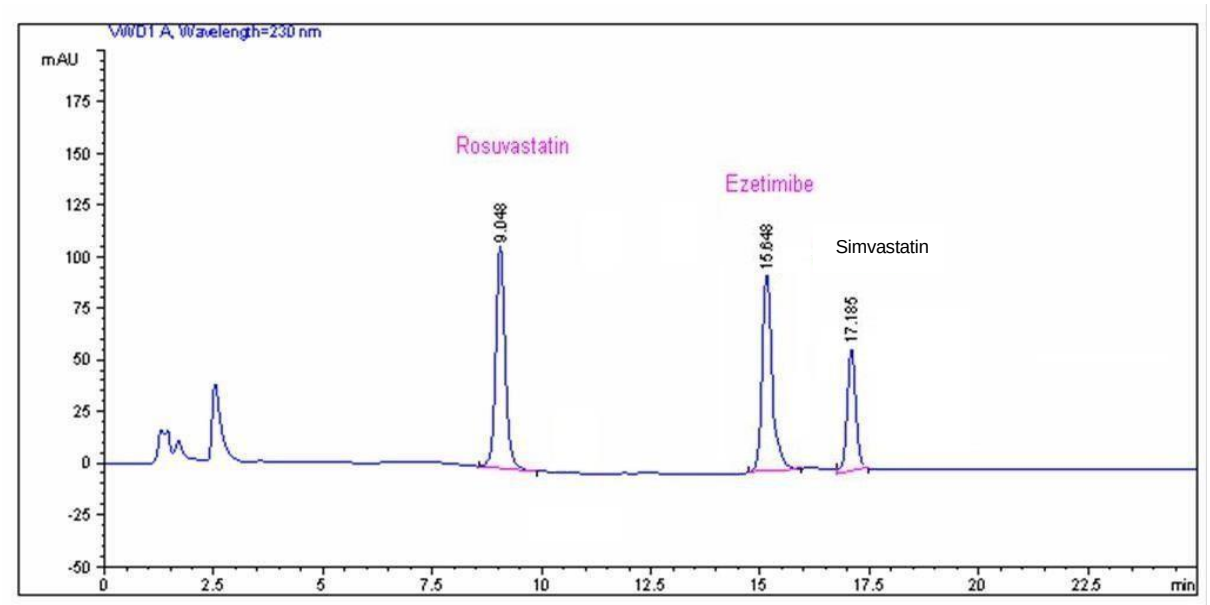


Figure 23: Standard-1 Chromatogram.

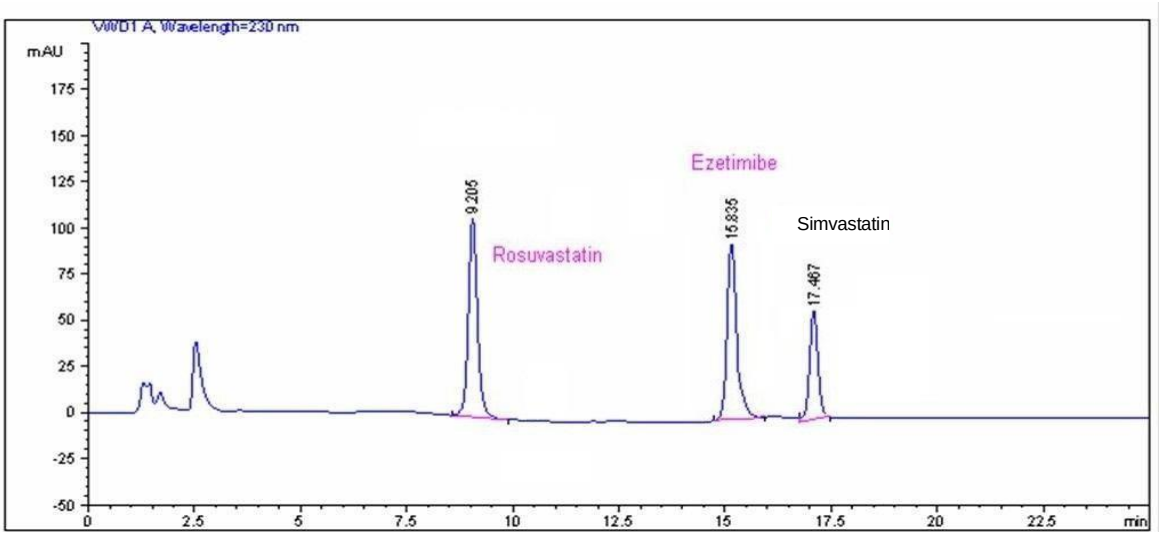


Figure 24: Standard-2 Chromatogram.

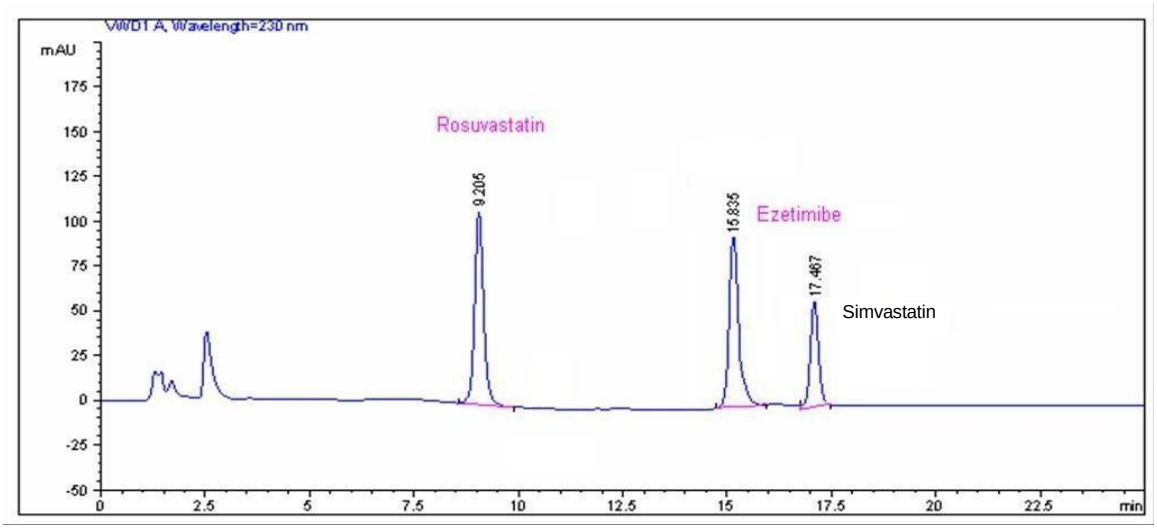


Figure 25: Standard-3 Chromatogram.

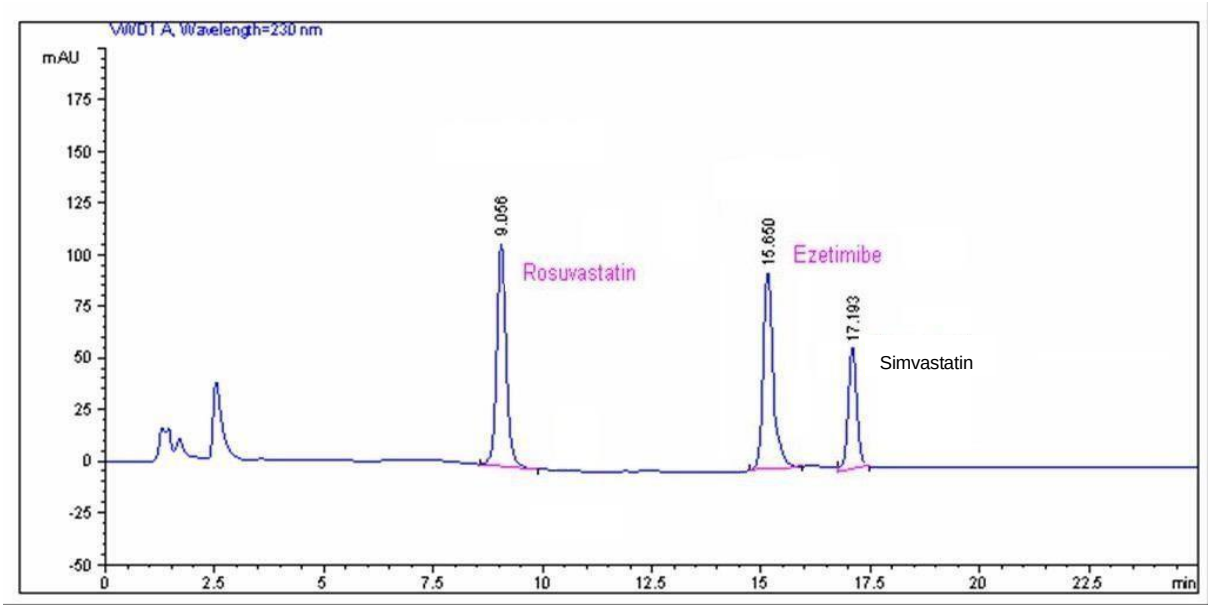


Figure 26: Standard-4 Chromatogram.

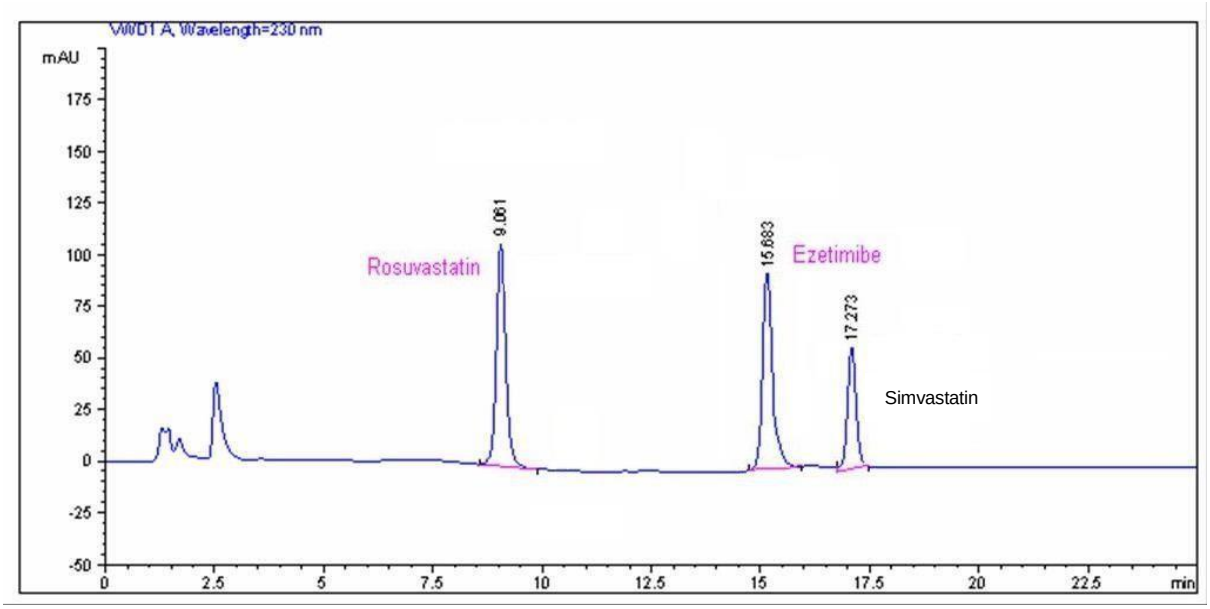


Figure 27: Standard-5 Chromatogram.

Linearity

Linearity was performed with five different concentration levels. Linearity solutions were prepared 50%, 75%, 100 %, 125% and 150% of solutions. These samples were prepared as per the finalized method. Linearity chromatograms were repsented in figure-28. Table-5 represented the linearity results. Figure-29 to 31 shown the linearity graph for rosuvastatin, ezetimibe and simvastatin.

Table 5: Linearity Results.

Linearity Level	Rosuvastatin		Ezetimibe		Simvastatin	
50%	28	753	28	1342	28	2811
75%	42	1173	42	1965	42	4460
100%	56	1600	56	2653	56	5950
125%	70	1933	70	3223	70	7405
150%	84	2379	84	3928	84	8775
Correlation Coefficient	0.9991		0.9995		0.9994	

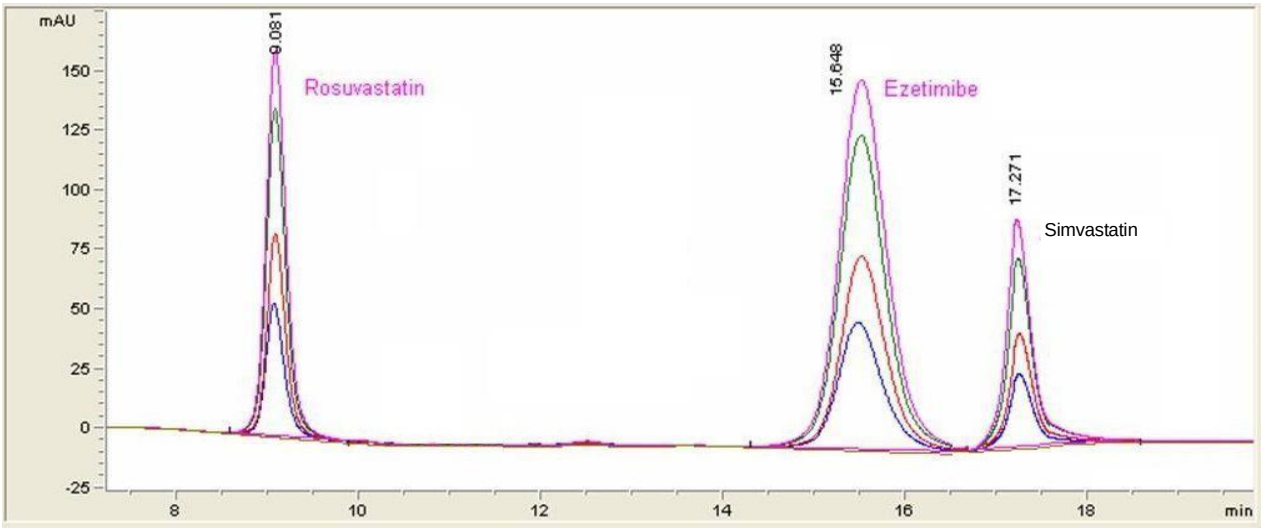


Figure-28: Linearity solutions overlay chromatogram.

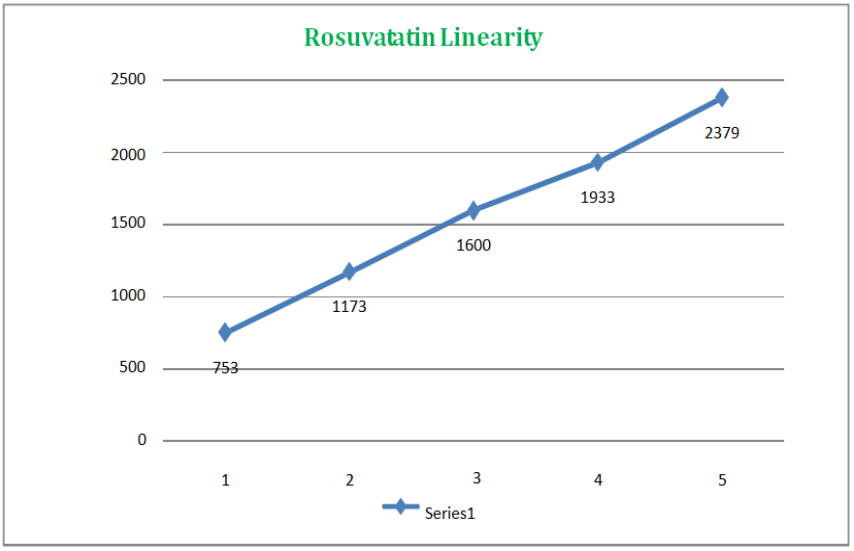


Figure 29: Rosuvastatin Linearity graph.

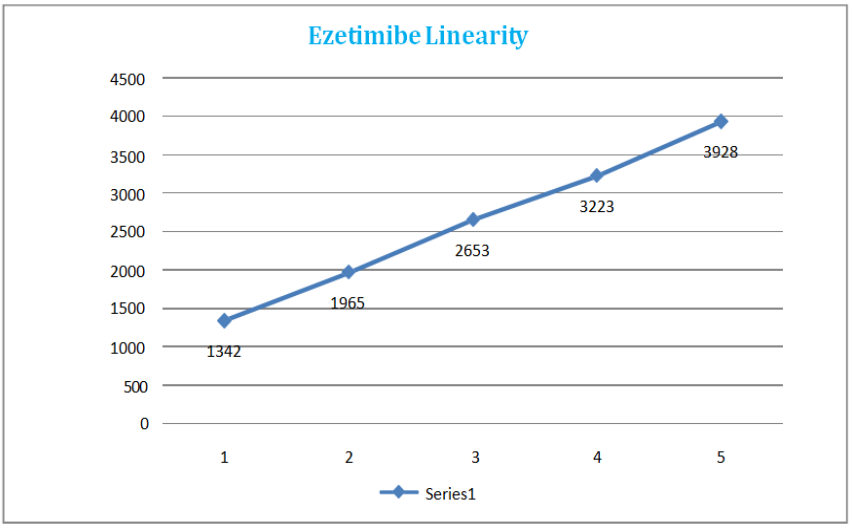


Figure 30: Ezetimibe linearity graph.

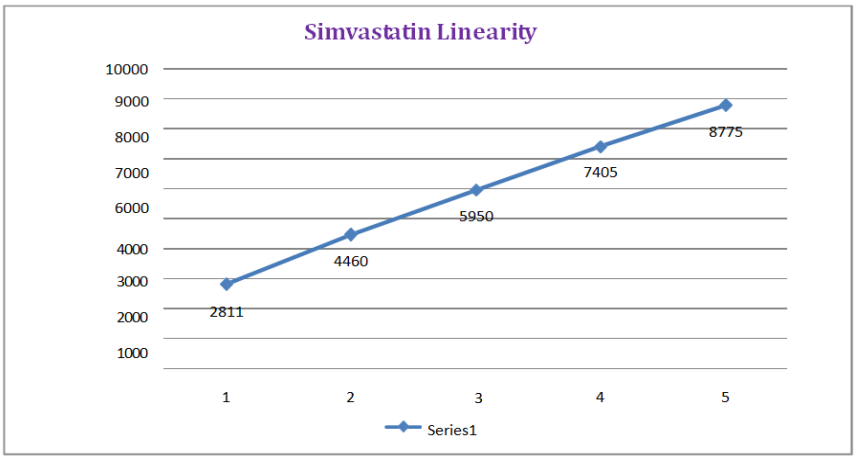


Figure 31: Simvastatin Linearity Graph.

Accuracy

Accuracy of the method was determined on three concentration levels by recovery experiments. The recovery studies were carried out by spiked placebo recovery method and the percentage recoveries with standard deviations were calculated. Accuracy results were tabulated in table 6. Method was found to be accurate.

Table 6: Accuracy results.

(a) Accuracy results			
Level		***Rosuvastatin***	
50%	28.01	27.19	97.07
	28.04	27.87	99.39
	28.07	28.13	100.21
100%	56.15	55.87	99.50
	56.17	56.25	100.14
	55.89	56.21	100.57
150%	84.18	84.81	100.75
	83.89	86.12	102.66
	84.52	84.56	100.05
Ezetimibe			
50%	27.89	27.71	99.35
	28.14	28.14	100.00
	28.65	28.53	99.58
100	56.17	56.54	100.66
%	56.52	56.58	100.11
	56.24	56.17	99.88
150%	84.87	84.36	99.40
	84.56	84.57	100.01
	84.31	84.39	100.09
Simvastatin			
50%	28.14	28.18	100.14
	28.61	27.81	97.20
	28.15	28.65	101.78
100%	56.54	56.18	99.36
	56.27	56.80	100.94
	56.19	56.94	101.33
150%	84.81	84.37	99.48
	84.26	84.15	99.87
	84.57	84.60	100.04

Ruggedness

Freshly prepared samples were analysed as part of precision parameter. The same samples were stored at room temperature for three days and analysed at day 1 and day-3. Ruggedness was performed with day-1 sample and day 3 sample. Both time intervals results are complying with the specified limits (not more than 2.0% of assay). Table-7 presented the ruggedness results.

Table 7: Solution stability of Assay samples.

Duration	Sample solution-1		Sample solution-2	
	Actual	% variation	Actual	% variation
Rosuvastatin				
Initial	101.54	NA	100.56	NA
Day-1	100.92	0.6	100.32	0.2
Day-3	100.26	1.3	100.34	0.2
Ezetimibe				
Initial	100.68	NA	99.98	NA
Day-1	99.89	0.79	101.00	1.02
Day-3	101.60	0.92	100.06	0.08
Simvastatin				
Initial	100.14	NA	100.65	NA
Day-1	99.98	0.16	100.31	0.34
Day-3	101.00	0.86	99.87	0.78

Robustness

Robustness parameter was performed with flow variation, column oven temperature variation and filter validation. Flow rate was checked with 0.8ml/min and 1.2ml/min; column oven temperature evaluated at 45°C and 55°C and filter validation was performed with centrifuged and PVDF filter paper. Results were listed in table 8 and 9.

Table 8: Robustness results.

S.No.	Parameter		Rosuvastatin		Ezetimibe		Simvastatin	
			Tailing factor	%RSD (5inj.)	Tailing factor	%RSD (5inj.)	Tailing factor	%RSD (5 inj.)
1	Flow rate (mL/min)	0.8	1.0	0.63	1.1	0.45	1.1	0.61
2		1.2	0.9	0.59	1.0	0.16	1.0	0.54
3	Temp.(°C)	45	1.1	0.14	1.2	0.61	0.9	0.16
4		55	1.0	1.0	0.9	0.56	1.1	1.13

Table 9: Effect of 0.45 µm PVDF filters on standard solution.

S. No.	Standard solution	Rosuvastatin		Ezetimibe		Simvastatin	
		% Assay(w/w)	% of difference	% Assay(w/w)	% of difference	% Assay(w/w)	% of difference
1	Centrifuged	100.90	NA	104.16	NA	100.77	NA
1	0.45 µm PVDF filter	100.63	0.27	101.16	3.00	100.17	0.60

CONCLUSION

Simple, high resolution and accurate cost effective RP-HPLC method has been developed for estimation of ezetimibe, Rosuvastatin and Simvastatin in tablet dosage forms. Optimized method was evaluated with all validation parameters such as precision, accuracy, linearity, specificity, ruggedness and robustness. Method has no interference with placebo and diluent. Six replicate test samples assay value %RSD values were 2.0%, linearity correlation coefficient value was below 0.999 and accuracy recovery %RSD was 97% to 103%. The proposed method is simple, fast, accurate and precise for the simultaneous quantification three ingredients in tablets dosage form. The proposed method can be used for the routine analysis.

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