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The Analytical Method for the Simultaneous Estimation of Rosuvastatin and Bempedoic Acid by RP-HPLC Method

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***Nayyar MD, Faheemuddin MOHD, Ashwini karankot, Afshan jabeen, Sai varsha Kavali, Yasaswini Gampala, Sareesh. K, Dr. Sunil kumar Chaitanya .P**

Department of Pharmaceutical Analysis, St. Paul's College of Pharmacy, Turkayamjal – 510510, Telangana, India.

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ABSTRACT

A new, simple, fast, rapid, accurate, efficient, and reproducible RP-HPLC method and spectroscopic method for the simultaneous analysis of Rosuvastatin and Bempedoic acid was developed. The developed method was validated according to ICH guidelines. A High-Performance Liquid Chromatography WATERS, software: Empower, 2695 separation module, UV Detector with Inertsil ODS (4.6*250mm, 5µ) column, with mobile phase 70% buffer 30% ACN was used. The flow rate of 1.0 ml/min and effluent was detected at 240 nm. The retention time of Favipiravir was 10 minutes. Linearity was observed over the concentration range of 8-40 µg/ml. The Limit of detection values are 2.97 µg/ml & 2.98 µg/ml and limit of quantification was found to be 9.98 µg/ml and 9.97 µg/ml respectively. The accuracy of the proposed method was determined by recovery studies and found to be 98% to 102%. Then a method was validated in terms of linearity, accuracy, precision, (repeatability, intermediate precision) specificity (by assay), robustness and system suitability. Thus, the validated method is can be successfully applied to routine analysis for regulate the quality. It also should be used for analytical research purpose.

INTRODUCTION

Rosuvastatin is an antilipemic agent that competitively inhibits hydroxymethylglutaryl-coenzyme A (HMG-CoA) reductase. HMG-CoA reductase catalyzes the conversion of HMG-CoA to mevalonic acid, the rate-limiting step in cholesterol biosynthesis. Rosuvastatin belongs to a class of medications called statins and is used to reduce plasma cholesterol levels and prevent cardiovascular disease.

Structure:

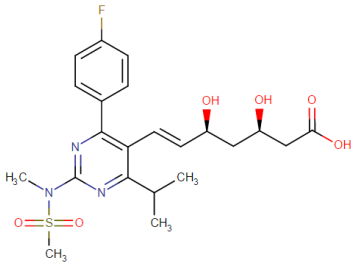

FIG 1: Structure of rosuvastatin

IUPAC Name: (3R,5S,6E)-7-[4-(4-fluorophenyl)-2-(N-methylmethanesulfonamido)-6-(propan-2-yl) pyrimidin-5-yl]-3,5-dihydroxyhept-6-enoic acid

Chemical Formula: C22H28FN3O6S
Melting point: >1510C

Molecular weight: 500.57g/mol

Solubility: DMSO (Slightly), Methanol (Slightly)

Half-life:19hours

Rosuvastatin is a competitive inhibitor of HMG-CoA reductase. HMG-CoA reductase catalyzes the conversion of HMG-CoA to mevalonate, an early rate-limiting step in cholesterol biosynthesis. Rosuvastatin acts primarily in the liver. Decreased hepatic cholesterol concentrations stimulate the upregulation of hepatic low-density lipoprotein (LDL) receptors which increases hepatic uptake of LDL. Rosuvastatin also inhibits hepatic synthesis of very low-density lipoprotein (VLDL). The overall effect is a decrease in plasma LDL and VLDL. In vitro and in vivo animal studies also demonstrate that rosuvastatin exerts vasculoprotective effects independent of its lipid-lowering properties. Rosuvastatin exerts an

anti-inflammatory effect on rat mesenteric microvascular endothelium by attenuating leukocyte rolling, adherence, and transmigration (PMID: 11375257). The drug also modulates nitric oxide synthase (NOS) expression and reduces ischemic-reperfusion injuries in rat hearts (PMID: 15914111). Rosuvastatin increases the bioavailability of nitric oxide (PMID: 11375257, 12031849, 15914111) by upregulating NOS (PMID: 12354446) and by increasing the stability of NOS through post-transcriptional polyadenylation (PMID: 17916773). It is unclear as to how rosuvastatin brings about these effects though they may be due to decreased concentrations of mevalonic acid.

Bempedoic acid is a drug used in conjunction with lifestyle modification and/or other agents for the treatment of refractory hypercholesterolemia.

Structure:

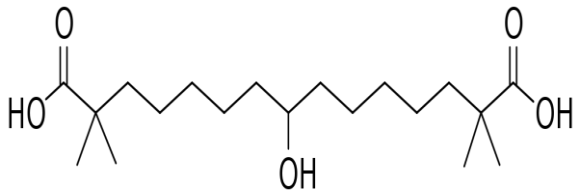

FIG 2: Structure of bempedoic acid

IUPAC name: 8-hydroxy-2,2,14,14-tetramethylpentadecanedioic acid.

Solubility: 0.0211 mg/mL

Formula: $C_{19}H_{36}O_5$

Molecular weight: 344.492/mol

Melting point: 87-92^{0}C

MATERIALS AND METHODS

Table: 1 INSTRUMENTS USED

SL. No	Instrument	Model
1	HPLC	WATERS, software: Empower, 2695 separation module, UV detector.
2	UV/VIS spectrophotometer	LABINDIA UV 3000^{+}
3	pH meter	Adwa – AD 1020
4	Weighing machine	Afcoset ER-200A
5	Pipettes and Burettes	Borosil
6	Beakers	Borosil

Table 2: CHEMICALS USED

SL. No	Chemical	Company Name
1	Rosuvastatin	Glenmark
2	Bempedoic acid	Glenmark
3	KH_2PO_4	FINER chemical LTD
4	Water and Methanol for HPLC	LICHROSOLV (MERCK)
5	Acetonitrile for HPLC	MOLYCHEM
6	Orthophosphoric Acid	MERCK

HPLC METHOD DEVELOPMENT:

Standard Solution Preparation:

Accurately weigh and transfer 90 mg of Bempedoic acid and 20 mg of Rosuvastatin working standard into a 25 ml clean dry volumetric flask add about 7 mL of Diluent and sonicate to dissolve it completely and make volume up to the mark with the same solvent. (Stock solution).

Further pipette 0.3 ml of the above stock solutions into a 10 ml volumetric flask and dilute up to the mark with diluent.

Sample Solution Preparation:

Accurately weigh and transfer equivalent tablet powder of 90 mg of Bempedoic acid and 20 mg of Rosuvastatin (330 mg) into a 25 ml clean dry volumetric flask add about 7 mL of Diluent and sonicate to dissolve it completely and make volume up to the mark with the same solvent. (Stock solution).

Further pipette 0.3 ml of the above stock solutions into a 10 ml volumetric flask and dilute up to the mark with diluent.

Mobile Phase Optimization:

Initially the mobile phase tried was methanol: Ortho phosphoric acid buffer and Methanol: phosphate buffer, Acetonitrile: methanol with various combinations of pH as well as varying proportions. Finally, the mobile phase was optimized to Phosphate buffer (pH 3.0) and acetonitrile in proportion 70: 30 v/v respectively.

Wavelength selection:

UV spectrum of 10 µg/ml Telmisartan and 10 µg/ml Azelnidipine in diluents (mobile phase composition) was recorded by scanning in the range of 200nm to 400nm. From the UV spectrum wavelength selected as 240 nm. At this wavelength both the drugs show good absorbance.

Optimization of Column:

The method was performed with various columns like C18 column Phenomenex column, YMC, and Inertsil ODS column. Inertsil ODS (4.6 x 250mm, 5µm) was found to be ideal as it gave good peak shape and resolution at 1.0 ml/min flow. The peak results of Bempedoic acid and Rosuvastatin are recorded in the table 3.

METHOD VALIDATION

SYSTEM SUITABILITY:

Tailing factor for the peaks due to Bempedoic acid and Rosuvastatin in Standard solution should not be more than 2.0Theoretical plates for the Bempedoic acid and Rosuvastatin peaks in Standard solution should not be less than 2000.

Acceptance criteria: Resolution for the bempedoic acid and Rosuvastatin peaks in standard solution should not be less than 2.

ASSAY: Calculation: (For bempedoic acid)

$$\%\,Assay = \frac{AT}{AS} * \frac{WS}{DS} * \frac{DT}{WT} * \frac{Average\ weight}{Label\ Claim} * \frac{P}{100} * 100$$

Where:

AT = average area counts of sample preparation.

AS = average area counts of standard preparation.

WS = Weight of working standard taken in mg.

P = Percentage purity of working standard

LC = Label Claim mg/ml.

PRECISION:

The standard solution was injected six times and the area for all six. Injections in HPLC. The %RSD for the area of six replicate injections was found to be within the specified limits. The precision results of Bempedoic acid and Rosuvastatin are recorded in table 4.

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

INTERMEDIATE PRECISION/RUGGEDNESS:

To evaluate the intermediate precision (also known as Ruggedness) of the method, Precision was performed on different day.

The standard solutions prepared in the precision was injected on the other day, for six times and measured the area for all six injections in HPLC. The %RSD for the area of six replicate injections was found to be within the specified limits. The ID precision results of Bempedoic acid and Rosuvastatin are recorded in table 5.

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

ACCURACY:

Inject the standard solution, Accuracy -50%, Accuracy -100% and Accuracy -150% solutions. Calculate the Amount found and Amount added for Bempedoic acid and rosuvastatin and calculate the individual recovery and mean recovery values. The accuracy results of Bempedoic acid and Rosuvastatin are recorded in the table 6 and 7 respectively.

LINEARITY:

Preparation of stock solution:

Accurately weigh and transfer 90 mg of Bempedoic acid and 20 mg of Rosuvastatin working standard into a 25 ml clean dry volumetric flask add about 7 mL of Diluent and sonicate to dissolve it completely and make volume up to the mark with the same solvent. (Stock solution). Prepare 5 levels of dilutions from the above stock solution. Inject each level into the chromatographic system and measure the peak area. Plot a graph of peak area versus concentration (on the X-axis concentration and on Y-axis Peak area) and calculate the correlation coefficient. The linearity results of Bempedoic acid and Rosuvastatin are recorded in the table 8 & 9 respectively.

DETECTION LIMIT

Limit of Detection: (for bempedoic acid)

The LOD of 1500µg/ml and 16.006 µg/ml solution was prepared and injected, for three times and measured the area for all three injections in HPLC. The %RSD for the area of six replicate injections was found to be within the specified limits.

Limit of Detection: (for Rosuvastatin)

The LOD of 15µg/ml and 2.527 µg/ml solutions was prepared injected, for three times and measured the area for all three injections in HPLC. The %RSD for the area of six replicate injections was found to be within the specified limits.

Acceptance Criteria:

S/N Ratio value shall be 3 for the LOD solution.

LIMIT OF QUANTIFICATION:

Limit of Quantification: (for Bempedoic acid)

The LOQ of 1500µg/ml and 52.974 µg/ml solution was prepared and injected, for three times and measured the area for all three injections in HPLC. The %RSD for the area of six replicate injections was found to be within the specified limits.

Limit of Detection: (for Rosuvastatin)

The LOQ of 15µg/ml and 8.824 µg/ml solutions was prepared injected, for three times and measured the area for all three injections in HPLC. The %RSD for the area of six replicate injections was found to be within the specified limits.

Acceptance Criteria:

The S/N Ratio value shall be 10 for LOQ solution.

ROBUSTNESS:

As part of the Robustness, deliberate change in the Flow rate, Mobile Phase composition, Temperature Variation was made to evaluate the impact on the method.

A. The flow rate was varied at 0.9 ml/min to 1.1ml/min.

Standard solution 108 ppm of Bempedoic acid & 24 ppm of Rosuvastatin were prepared and analysed using the varied flow rates along with method flow rate. On evaluation of the above results, it can be concluded that the variation in flow rate affected the method significantly. Hence it indicates that the method is robust even by a change in the flow rate ±10%.

B. The Organic composition in the Mobile phase was varied from 50% to 50%.

Standard solution 108 ppm of Bempedoic acid & 24 ppm of Rosuvastatin were prepared and analysed using the varied Mobile phase composition along with the actual mobile phase composition in the method. On evaluation of the above results, it can be concluded that the variation in 10%.

Organic composition in the mobile phase affected the method significantly. Hence it indicates that the method is robust even by change in the Mobile phase ±10. The results of

robustness Bempedoic acid and Rosuvastatin are recorded in the table 10, 11, 12 and 13 respectively.

RESULTS AND DISCUSSION

METHOD DEVELOPMENT:

OPTIMIZED CHROMATOGRAPHIC CONDITIONS:

Equipment	:	High performance liquid chromatography equipped with Auto Sampler and PDA detector
Column	:	Inertsil ODS (4.6*250mm, 5µ)
Buffer	:	Phosphate buffer
pH	:	3.0
Mobile phase	:	70% buffer 30% ACN
Flow rate	:	1.0 ml per min
Wavelength	:	240 nm
Injection volume	:	20 µl
Run time	:	10 min.

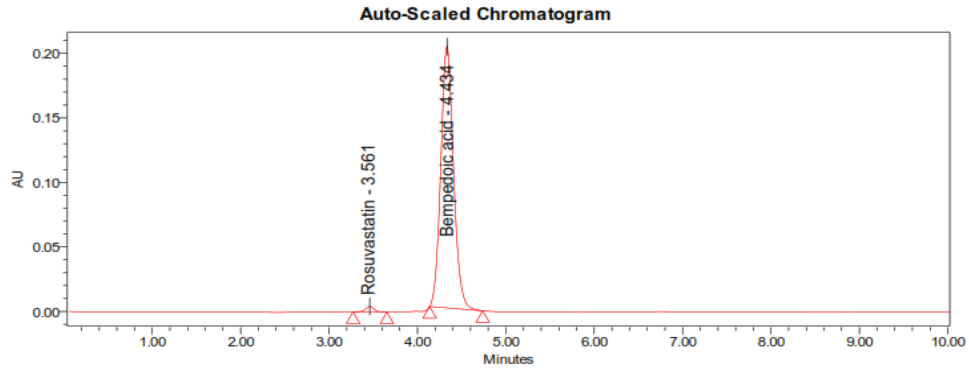

FIG 3: Optimized Chromatogram (Standard)

Table 3: Peak results of Rosuvastatin

Peak Name	Retention time	Area	Height	Resolution	USP Plate count	USP Tailing
Rosuvastatin	**3.561**	**27012**	**15839**		**4736**	**1.06**
Bempedoic acid	**4.434**	**217829**	**201931**	**3.29**	**5219**	**1.2**

Specificity:

Assay Results: (bempedoic acid)

$$\frac{194317}{194265} * \frac{20}{25} * \frac{0.3}{10} * \frac{25}{330} * \frac{10}{0.3} * \frac{660}{40} * \frac{99.8}{100} * 100 = 100.57\%$$

Assay Results: (For Rosuvastatin)

$$\frac{100673}{100648} * \frac{90}{25} * \frac{0.3}{10} * \frac{25}{330} * \frac{10}{0.3} * \frac{660}{180} * \frac{99.8}{100} * 100 = 100.15\%$$

Precision:

Table 4: The results are summarized for Rosuvastatin and Bembodoic acid

Injection	Area for Bembodoic acid	Area for Rosuvastatin
1	191361	107337
2	191229	107228
3	191667	107167
4	191987	107387
5	192879	107016
6	194692	107086
Average	192301.0	107200.8
Std.Dev.	1303.9	147.2
%RSD	0.7	0.1

ID precision:

Table: 5 The results are summarized for Rosuvastatin and Bembodoic acid:

Injection	Area for Bembodoic acid	Area for Rosuvastatin
1	192337	104529
2	192442	104228
3	192969	104527
4	192891	104389
5	192879	104014
6	192341	104684
Average	192645.2	104401.1
Standard Deviation	304.6	242.4
%RSD	0.2	0.2

Accuracy:

Table 6: The Accuracy Results for Bempedoic Acid

%Concentration (at specification Level)	Area	Amount Added (mg)	Amount Found(mg)	% Recovery	Mean Recovery
50%	95505	45	44.85	99.67	99.59
100%	191399	90	89.91	99.87	
150%	285309	135	134.45	99.25	

Table 7: The Accuracy Results for Rosuvastatin

%Concentration (at specification Level)	Area	Amount Added (mg)	Amount Found (mg)	% Recovery	Mean Recovery
50%	53846	10	10.06	100.23	100.01
100%	107344	20	20.09	99.90	
150%	159676	30	29.45	99.89	

Acceptance Criteria:

The % Recovery for each level should be between 98.0 to 102.0%**.**

Linearity:

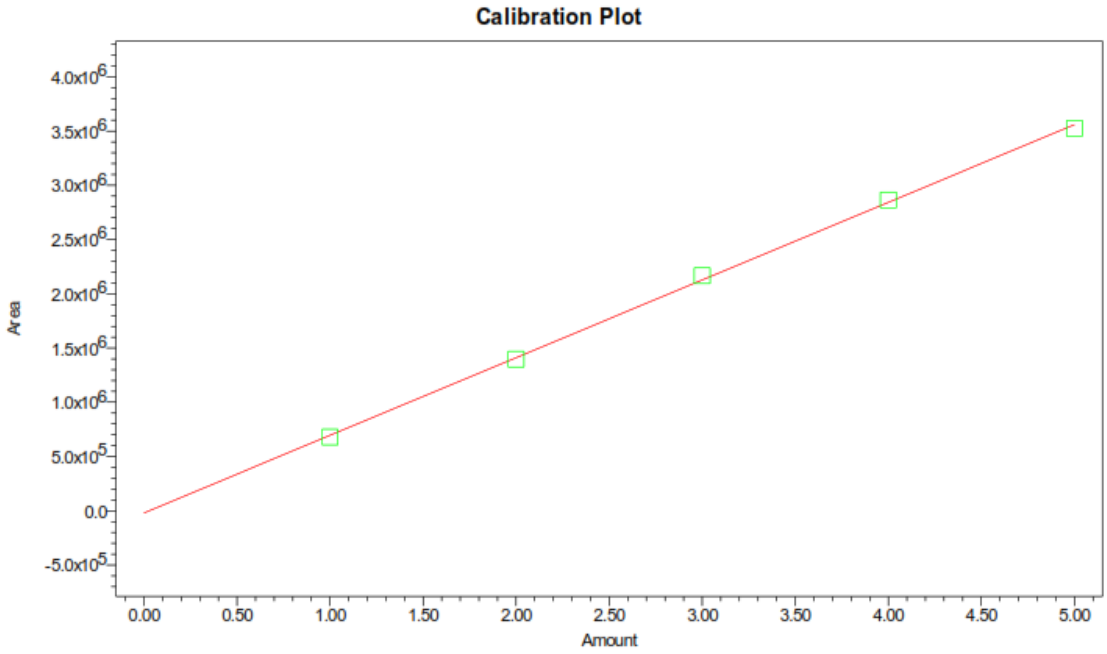

Fig 4: Linearity graph of Bembodoic acid

Table 8: linearity results of Bempedoic acid

	Level	Conc.(µg/ml)	Area
	1	36	65779
	2	72	131778
	3	108	194310
	4	144	256238
	5	180	317741
R^2			0.999

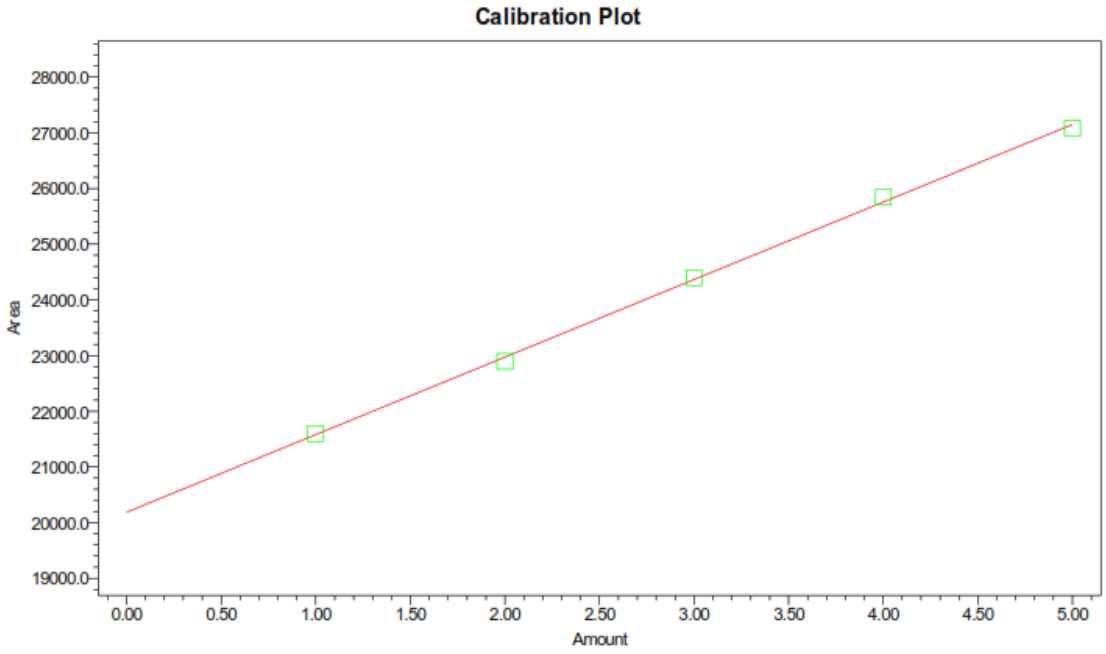

Fig 5: Linearity graph of Rosuvastatin

Table 9: linearity results of Rosuvastatin

	Level	Conc.(µg/ml)	Area
	1	8	32443
	2	16	67723
	3	24	100632
	4	32	134445
	5	40	172467
Corr. coeff			0.999

Limit of detection:

Bembodoic acid:

Calculation of S/N Ratio:

Avg Base line Noise from Blank : 58 µV

Signal from LOD solution : 173 µV

S/N = 173/58 = 2.98

Rosuvastatin:

Calcn. of S/N Ratio:

Avg Base line noise Blank : 58 µV

Signal from LOD solution : 172 µV

S/N = 172/58 = 2.97

Limit of quantification:

Bembodoic acid:

Calcn of S/N Ratio:

Avg Base line Noise Blank : 58 µV

Signal from LOQ solution : 578µV

S/N = 578/58 = 9.97

Rosuvastatin:

S/N Ratio:

Avg base line Noise Blank : 58 µV

Signal from LOQ solution : 579µV

S/N = 579/58 = 9.98

Robustness:

Table 10: System suitability results for Bempedoic acid with change in flow rate

Sr. No	Flow Rate (ml/min)	System Suitability Results	
		USP Plate Count	USP Tailing
1	0.9	3828.18	1.21
2	1	3417.62	1.14
3	1.1	3328.18	1.11

Table 11: System suitability results for Rosuvastatin with change in flow rate

Sr. No	Flow Rate (ml/min)	System Suitability Results		
		USP Plate Count	USP Tailing	USP Resolution
1	0.9	3213.92	1.23	4.96
2	1	2381.56	1.11	4.42
3	1.1	3415.92	1.21	4.96

Table 12: System suitability results for Bempedoic acid with change in mobile phase

Sr. No	Change in Organic Composition in the Mobile Phase	System Suitability Results	
		USP Plate Count	USP Tailing
1	10% less	3726.18	1.21
2	*Actual	3417.62	1.14
3	10% more	3343.64	1.34

Table 13: System suitability results for Rosuvastatin witch change in mobile phase

Sr. No	Change in Organic Composition in the Mobile Phase	System Suitability Results		
		USP Plate Count	USP Tailing	USP Resolution
1	10% less	3175.92	1.31	4.96
2	*Actual	2381.56	1.11	4.42
3	10% more	34445.92	1.23	4.96

***** Results for actual Mobile phase composition (50:50 Buffer: ACN) have been considered.

SUMMARY AND CONCLUSION:

A new method was established for simultaneous estimation of Rosuvastatin and Bempedoic acid by RP-HPLC methods. The chromatographic conditions were successfully developed for the separation of Rosuvastatin and Bempedoic acid by using Inertsil ODS C18 column (4.6×250mm)5µ, flow rate was 1ml/min, mobile phase ratio was (70:30 v/v) ACN: KH2PO4 pH 3, detection wavelength was 225nm. The instrument used for HPLC, WATERS HPLC Auto Sampler, Separation module 2695, photo diode array detector 996, Empower-software version-2. The retention times were found to be 3.598 mins and 4.487 mins. The % purity of Rosuvastatin and Bempedoic acid was found to be 100.15% and 100.57% respectively. The system suitability parameters for Rosuvastatin and Bempedoic acid such as theoretical plates and tailing factor were found to be 4260, 1.2 and 5085 and 1.2, the resolution was found to be 3.67. The analytical method was validated according to ICH guidelines (ICH, Q2 (R1)). The linearity study of Rosuvastatin and Bempedoic acid was found in concentration range of 8µg-40µg and 36µg-180µg and correlation coefficient (r^2) was found to be 0.999 and 0.999, % recovery was found to be 98.56% and 99.96%, %RSD for repeatability was 1.2, % RSD for intermediate precision was 1.9. The precision study was precision, robustness and repeatability. LOD value was 3.72 and 0.0242 and LOQ value was 7.40 and 0.0202 respectively.

Hence the suggested RP-HPLC can be used for routine analysis of Rosuvastatin and Bempedoic acid in API and Pharmaceutical dosage form.

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