ejpmr, 2024, 11(3), 109-116

SJIF Impact Factor 7.065

EUROPEAN JOURNAL OF PHARMACEUTICAL AND MEDICAL RESEARCH

www.ejpmr.com

Research Article

ISSN 2394-3211

EJPMR

DEVELOPMENT AND VALIDATION OF A RP - HPLC METHOD FOR THE SIMULTANEOUS DETERMINATION OF BEMPEDOIC ACID & EZETIMIBE IN PURE AND PHARMACEUTICAL DOSAGE FORM

***P. Bala Krishnaiah, Y. Sowmya, Bairam Ravindar and Manjunath S. Y.**

Srikrupa Institute of Pharmaceutical Sciences Velikatta V, Kondapak M. Siddipet Dist. Telangana 502277.

***Corresponding Author: P. Bala Krishnaiah**

Srikrupa Institute of Pharmaceutical Sciences Velikatta V, Kondapak M. Siddipet Dist. Telangana 502277.

Article Received on 05/01/2024 **Article Revised on 25/01/2024** **Article Accepted on 15/02/2024**

ABSTRACT

Analytical Method Development and Validation for Bempedoic acid and Ezetimibe in bulk and Combined Dosage Form by RP-HPLC. Include Stability Indicating RP-HPLC Method Development and Validation for Simultaneous Estimation of Bempedoic acid and Ezetimibe in Bulk and their Pharmaceutical dosage form. Using Waters alliance HPLC system, Quaternary gradient pump of e2695 series equipped with an auto sampler injector with 10µl is injected eluted with the mobile phase containing HSA and Acetonitrile in the ratio of 30:70 v/v which is pumped at a flow rate of 1ml/min and detected by UV detector at 225nm. The peak of Bempedoic acid and Ezetimibe was eluted at retention times of 3.246 min and 3.865 min respectively. In this proposed HPLC method for the selected drugs showed good linearity. Resultsfor the recoveries of selected drugs were found to be within limits (98 – 102 %). These indicate that the proposed method was accurate for the analysis.

KEYWORDS: Bempedoic acid and Ezetimibe, Method Development, Validation, Accuracy, Precision.

INTRODUCTION

Bempedoic acid is indicated as an adjunct to diet and maximally tolerated statin therapy for adults with heterozygous familial hypercholesterolemia or existing atherosclerotic cardiovascular disease that warrants additional lowering of LDL-C. The combination of bempedoic and ezetimibe is also indicated with diet management and maximally tolerated statin therapy to treat elevated LDL-C levels in adults with heterozygous familial hypercholesterolemia or existing atherosclerotic cardiovascular disease who require further lowering of LDL-C.[1-2] IUPAC name is 8-hydroxy-2,2,14,14-tetramethylpentadecanedioic acid. Molecular Formula is $C_{19}H_{36}O_5$. Molecular weight is 344.4. Bempedoic acid is sparingly soluble in aqueous buffers. For maximum solubility in aqueous buffers, Bempedoic acid should first be dissolved in DMSO and then diluted with the aqueous buffer of choice. Bempedoic acid has a solubility of approximately 0.25 mg/ml in a 1:3 solution of DMSO: PBS (pH 7.2) using this method.

Ezetimibe is indicated to reduce elevated total-C, LDL-C, Apo B, and non-HDL-C in patients with primary hyperlipidemia, alone or in combination with an HMG-CoA reductase inhibitor (statin). It is also indicated to reduce elevated total-C, LDL-C, Apo B, and non-HDL-C in patients with mixed hyperlipidemia in combination with fenofibrate, and to reduce elevated total-C and LDL-C in patients with homozygous familial hypercholesterolemia (HoFH), in combination with atorvastatin or simvastatin.[3] IUPAC name is (3R,4S)-1-(4-fluorophenyl)-3-[(3S)-3-(4-fluorophenyl)-3-hydroxypropyl]-4-(4 hydroxyphenyl)azetidin-2-one. Molecular Formula is $C_{24}H_{21}F_2NO_3$. Molecular weight is 409.4. It dissolves very well in all kinds of organic solvents, e.g., ethanol, DMSO, DMF, but it is practically insoluble in water.

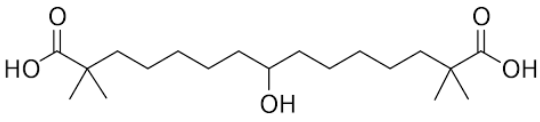

Figure 1: Structure of Bempedoic acid.

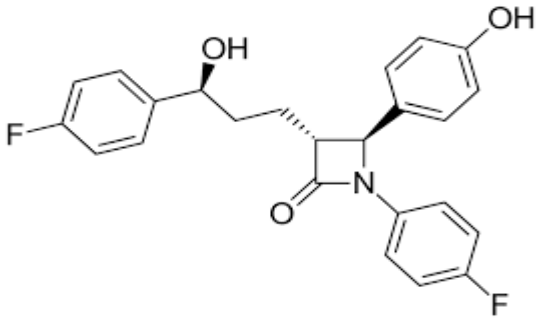

Figure 2: Structure of Ezetimibe.

A literature survey conveyed that, limited methods are available for simultaneous estimation of Bempedoic acid and Ezetimibe. A few articles reported spectrophotometric techniques for estimation of Ezetimibe alone and with other drugs.[4,5,6,7,8,9,10,11,12,13,14,15] Few HPLC methods were reported for the determination of Ezetimibe alone and in combination with other drugs.[16,17,18,19,20] One RP-HPLC method was reported for simultaneous estimation of Bempedoic acid Ezetimibe.[21] Few LC–MS methods were reported for determination of Ezetimibe alone and in combination with other drugs.[22,23,24,25] One LC–MS method was reported for estimation of Bempedoic acid in human plasma and urine.[26] In view of the demand for an appropriate, cost-effective RP-HPLC method for routine analysis of Bempedoic acid and Ezetimibe synchronized evaluation of in pharmaceutical dose type. Attempts were made to establish easy, precise, accurate as well as cost-efficient logical method for the estimate of Bempedoic acid and Ezetimibe. The recommended approach will be validated according to ICH guidelines. The objective of the recommended work is to establish a brand-new, simple, delicate, exact and economical logical method as well as recognition for the Synchronized evaluation of Bempedoic acid and Ezetimibe in pharmaceutical dose kind by utilizing RP-HPLC. To verify the established method based on ICH standards for the desired analytical application.

MATERIALS AND METHODS

Chemicals and Reagents: Bempedoic acid and Ezetimibe were Purchased from Honour Lab. NaH_2PO_4 was analytical grade supplied by Finerchem limited, Orthophosphoric acid (Merck), and Water and Methanol for HPLC (Lichrosolv (Merck).

Preparation of Mobile Phase: Mobile phase was prepared by mixing HSA and ACN taken in the ratio 30:70. It was filtered through a 0.45µ membrane filter to remove the impurities which may interfere in the final chromatogram.

Determination of Working Wavelength (λmax)

In simultaneous estimation of two drugs isobestic wavelength was used. Isobestic point is the wavelength where the molar absorptivity is the same for two substances that are inter convertible. So, this wavelength was used in simultaneous estimation to estimate two drugs accurately. The wavelength of maximum absorption of the solution of the drugs in mixture of Acetonitrile and HSA (70:30) were scanned using PDA Detector within the wavelength region of 200–400 nm against Acetonitrile and HSA (70:30) as blank. The absorption curve shows isobestic point at 225nm. Thus 225 nm was selected as detector wavelength for the HPLC chromatographic method.

Chromatographic conditions

During the selection of chromatographic conditions, numbers of trails were carried out and the best trail was selected for optimized method.

Preparation of standard stock solution

Accurately weigh and transfer 180 mg of Bempedoic acid, 10 mg of Ezetimibe working standard into a 100 ml clean dry volumetric flask add Diluent and sonicate to dissolve it completely and make volume up to the mark with the same solvent. (Stock solution).

Further pipette 5 ml of the above stock solutions into a 50 ml volumetric flask and dilute up to the mark with diluent. (18ppm of Bempedoic acid, 10ppm of Ezetimibe).

Sample Solution Preparation

Accurately weighed and transfer 248mg of Bempedoic acid and Ezetimibe sample into a 100mL clean dry volumetric flask add Diluent and sonicate it up to 30 mins to dissolve, and centrifuge for 30min. to dissolve it completely and make volume up to the mark with the same solvent. Then it is filtered through 0.45-micron Injection filter. (Stock solution). Further pipette 5 ml of the above stock solutions into a 50ml volumetric flask and dilute up to the mark with diluents. (180ppm of Bempedoic acid, 10ppm of Ezetimibe).

Procedure

Inject the samples by changing the chromatographic conditions and record the chromatograms, note the conditions of proper peak elution for performing validation parameters as per ICH guidelines.

RESULTS AND DISCUSSION

Method

The developed chromatographic method was validated for system suitability, linearity accuracy, precision, ruggedness and robustness as per ICH guidelines.

System suitability parameters: To evaluate system suitability parameters such as retention time, tailing factor and USP theoretical plate count, the mobile phase was allowed to flow through the column at a flow rate of 1.0 ml/min to equilibrate the column at ambient temperature. Chromatographic separation was achieved by injecting a volume of 10 µL of standard into Inertsil ODS (150x4.6 mm, 3.5 µ), the mobile phase of composition Acetonitrile: HSA (70:30) was allowed to flow through the column at a flow rate of 1.0 ml per minute. Retention time, tailing factor and USP theoretical plate count of the developed method are shown in table 1.

Table 1: System suitability parameters.

S.no	Parameter	Bempedoic acid	Ezetimibe
1	Retention time	3.248	3.865
2	Plate count	4112	5004
3	Tailing factor	1.11	1.10
4	Resolution	----	2.92
5	%RSD	0.30	0.63

Assay of pharmaceutical formulation: The proposed validated method was successfully applied to determine Bempedoic acid and Ezetimibe in their pharmaceutical dosage form. The result obtained for was comparable with the corresponding labeled amounts and they were shown in Table-2.

Table 2: Assay results for Bempedoic acid and Ezetimibe.

Brand	Drug	Avg sample area(n=5)	Std. wt (µg/ml)	Samplewt. (µg/ml)	Labelamount (mg)	Stdpurity	Amount found(µg/ml)	% assay
NEXL IZET	Bempedoic Acid	4618965	180	248	180	99.8	179.27	99.6
	Ezetimibe	232365	10	248	10	99.9	10.02	100.2

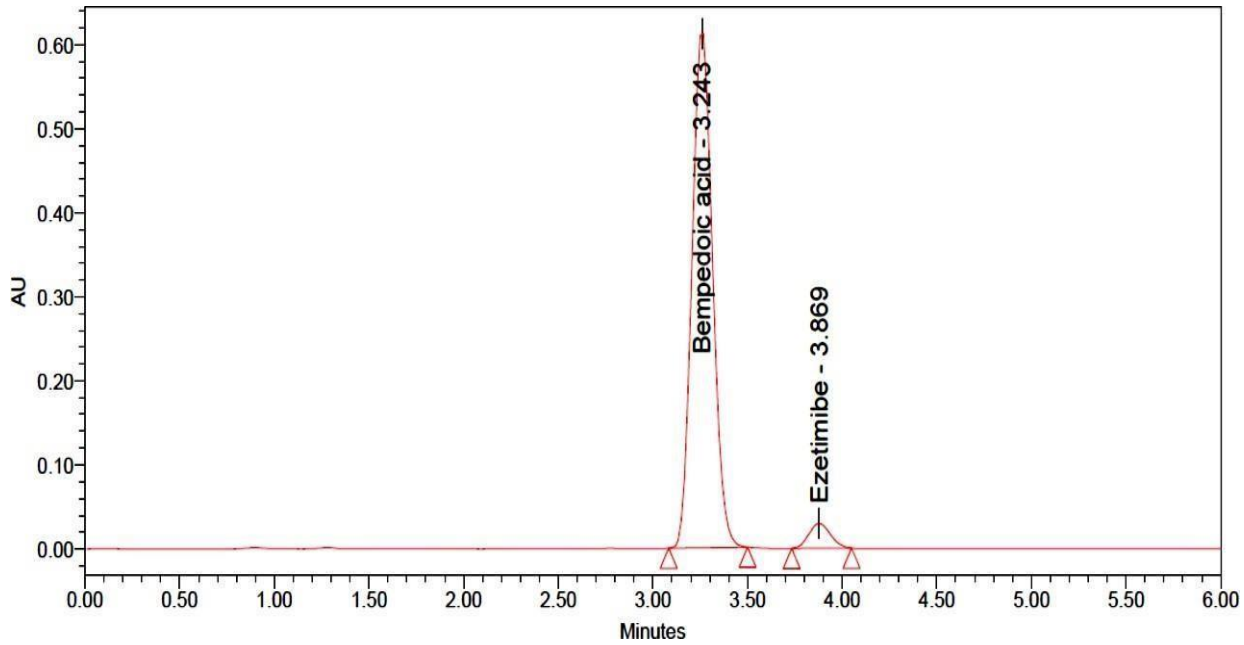

Figure 3: Standard chromatogram.

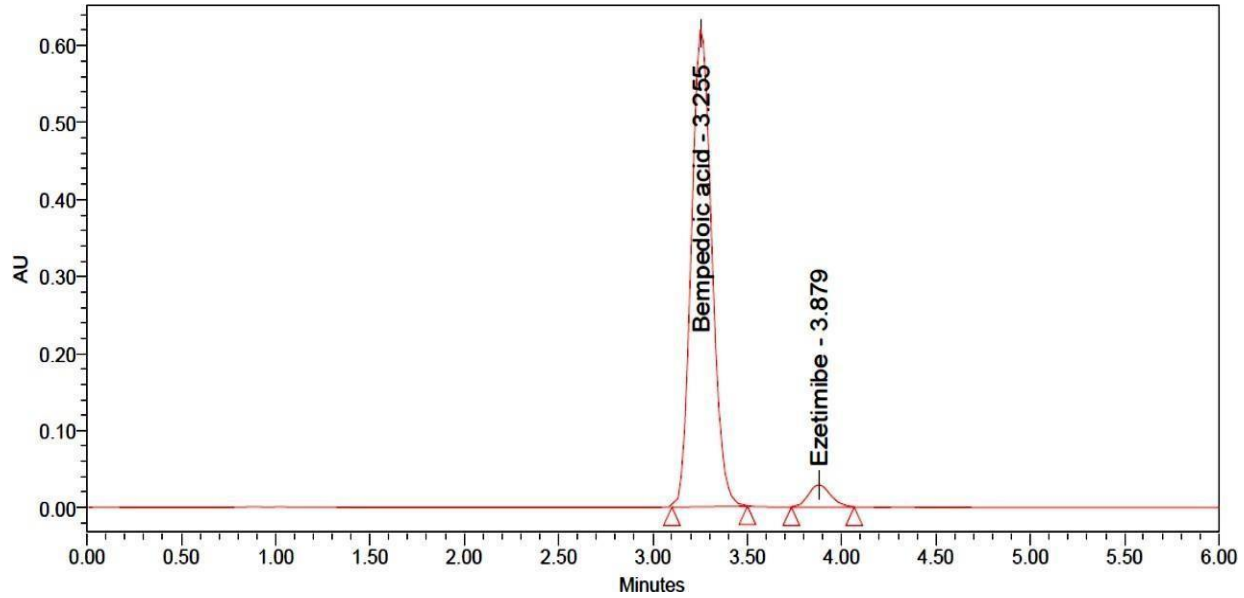

Figure 4: Sample chromatogram.

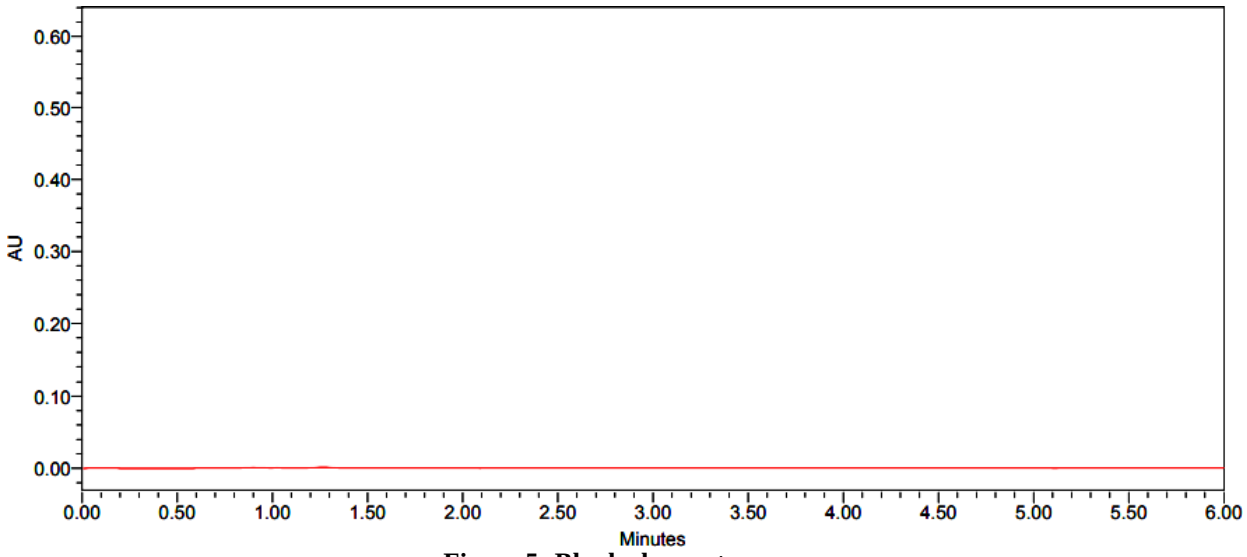

Figure 5: Blank chromatogram.

Validation of Analytical method

Linearity: The linearity study was performed for the concentration of 45 **µg/ml** to 270 **µg/ml** and 2.5 **µg/ml** to 15 **µg/ml** level. Each level was injected into chromatographic system. The area of each level was used for calculation of correlation coefficient. Inject each level into the chromatographic system and measure the peak area. Plot a graph of peak area versus concentration (on X-axis concentration and on Y-axis Peak area) and calculate the correlation coefficient. The results are shown in table 3.

Table 3: Results of linearity for Bempedoic acid & Ezetimibe.

S.NO	Bempedoic acid		Ezetimibe	
	Conc.(µg/ml)	Peakarea	Conc.(µg/ml)	Peak area
1	45.00	1329639	2.50	69046
2	90.00	2359735	5.00	120773
3	135.00	3394721	7.50	172648
4	180.00	4632381	10.00	230091
5	225.00	5729283	12.50	286974
6	270.00	7064333	15.00	351696
Regressionequation	y = 25607.09x +44484.61		y =22860.89x + 4433.07	
Slope	25607.09		22860.89	
Intercept	44484.61		4433.07	
R^2	0.9994		0.9993	

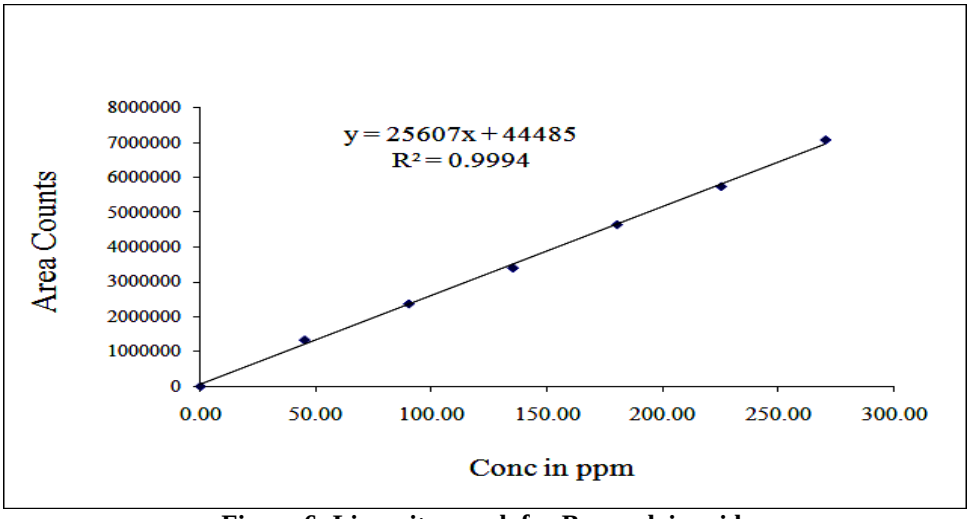

Figure 6: Linearity graph for Bempedoic acid.

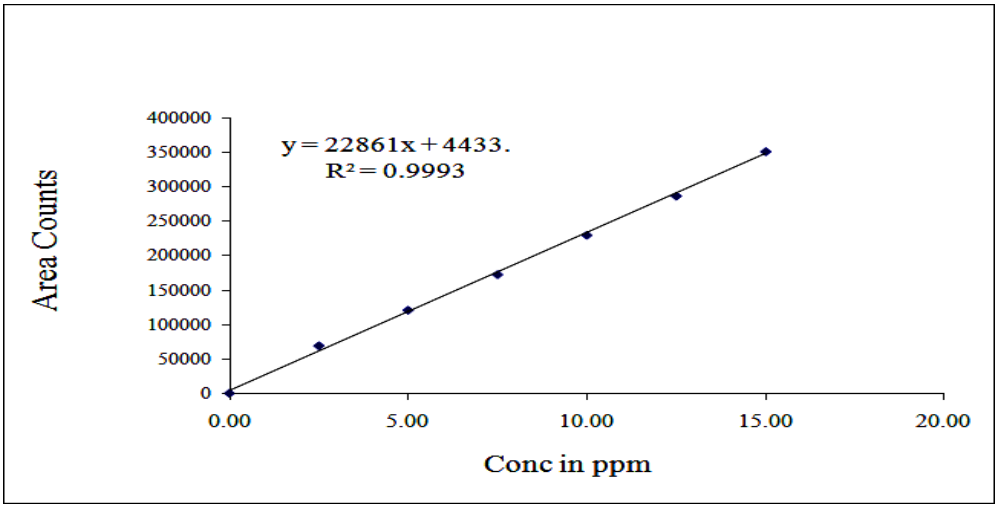

Figure 6: Linearity graph for Ezetimibe.

Accuracy studies: The accuracy was determined by help of recovery study. The recovery method carried out at three level 50%, 100%, 150% and 50%, 100%, 150% Inject the standard solutions into chromatographic system. Calculate the Amount found and Amount added for Bempedoic acid and Ezetimibe and calculate the individual recovery and mean recovery values. The results are shown in table 4,5.

Table 4: Showing accuracy results for Bempedoic acid.

%Concentration(at specificationLevel)	Area	AmountAdded (mg)	AmountFound (mg)	% Recovery	Mean Recovery
50%	2309857	90	89.65	99.6	100.4
100%	4671441	180	181.31	100.7	
150%	7010608	270	272.10	100.8	

Table 5: Showing accuracy results for Ezetimibe.

%Concentration (at specificationLevel)	Area	Amount Added(mg)	Amount Found(mg)	% Recovery	Mean Recovery
50%	117176	5	5.05	101.0	101.2
100%	236167	10	10.18	101.8	
150%	350163	15	15.1	100.7	

Precision Studies: precision was calculated from Coefficient of variance for six replicate injections of the standard. The standard solution was injected for six times and measured the area for all six Injections in HPLC. The %RSD for the area of six replicate injections was found. The results are shown in table 6.

Table 6: Precision results for Bempedoic acid and Ezetimibe.

S. No	Concentration Bempedoic acid(µg/ml)	Area of Bempedoic acid	Concentration of Ezetimibe (µg/ml)	Area of Ezetimibe
1.	180	4648402	10	230043
2.	180	4629073	10	233617
3.	180	4635956	10	230667
4.	180	4659647	10	231479
5.	180	4631617	10	233308
6.	180	4621456	10	232627
Mean	4637692		231957	
S. D	13960.95		1455.04	
%RSD	0.30		0.63	

Ruggedness: To evaluate the intermediate precision of the method, Precision was performed on different day. The standard solution was injected for six times and measured the area for all six injections in HPLC. The %RSD for the area of six replicate injections was found. The results are shown in table 7.

Table 7: Ruggedness results of Bempedoic acid and Ezetimibe.

S. No.	Area for Bempedoic acid		Area for Ezetimibe	
	Day-1	Day-2	Day-1	Day-2
1	4652261	4634652	234388	232686
2	4699950	4640724	232178	235978
3	4591334	4656481	234878	234629
4	4606891	4671708	232064	231547
5	4618068	4664553	235394	233265
6	4706522	4628639	234768	235903
Average	4645837	4649459	233945	234001
Standard Deviation	48807.047	17327.292	1449.422	1800.753
%RSD	1.05	0.37	0.62	0.77

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. The flow rate was varied at 0.8 ml/min to 1.2 ml/min. The results are shown in table 8,9.

Table 8: Robustness results of Bempedoic acid by RP-HPLC.

Parameter	Bempedoic acid					
	Condition	Retentiontime(min)	Peak area	Resolution	Tailing	Platecount
Flow rateChange (mL/min)	Less flow(0.8ml)	3.897	5291586		1.16	4138
	Actual (1ml)	3.246	4648402		1.11	4112
	More flow(1.2ml)	2.806	4086390		1.08	4103
Organic Phasechange	Less Org(63:37)	4.269	4809598		1.14	4166
	Actual (70:30)	3.245	4629073		1.10	4120
	More Org(77:23)	2.613	4367453		1.06	4102

Table 9: Robustness results of Ezetimibe by RP-HPLC.

Parameter	Ezetimibe					
	Condition	Retentiontime(min)	Peak area	Resolution	Tailing	Platecount
Flow rate	Less flow	4.647	278468	3.34	1.13	5163
Change (mL/min)	(0.8ml)					
	Actual (1ml)	3.865	230043	2.90	1.10	5004
	More flow(1.2ml)	3.340	206116	2.67	1.06	4989
Organic Phase change	Less Org(63:37)	5.006	251565	3.15	1.14	5058
	Actual(70:30)	3.863	233617	2.93	1.09	5007
	More Org(77:23)	3.131	213043	2.68	1.04	4986

LOD and LOQ: The sensitivity of RP-HPLC was determined from LOD and LOQ. Which were calculated from the calibration curve using the following equations as per ICH guidelines. The results are shown in table 10.

LOD = 3.3σ/S and

LOQ = 10 σ/S, where

σ= Standard deviation of y intercept of regression line,

S = Slope of the calibration curve

Table 10: LOD, LOQ of Bempedoic acid and Ezetimibe.

Name of drug	LOD(µg/ml)	LOQ(µg/ml)
Bempedoic acid	5.4	18
Ezetimibe	0.3	1

DEGRADATION STUDIES

Preparation of stock: Accurately weigh and transfer 180mg of Bempedoic acid, 10mg of Ezetimibe working standard into a 100 ml clean dry volumetric flask add Diluent and sonicate to dissolve it completely and make volume up to the mark with the same solvent. (Stock solution).

Acid degradation: Pipette 5 ml of above solution into a 50ml volumetric flask and 3 ml of 1N Hcl was added. Then, the volumetric flask was kept at 60ºC for 6 hours and then neutralized with 1 N NaOH and make up to 50ml with diluent. Filter the solution with 0.22 microns syringe filters and place in vials.

Alkali degradation: Pipette 5 ml of above solution into a 50ml volumetric flask and add 3ml of 1N NaOH was added. Then, the volumetric flask was kept at 60ºC for 6 hours and then neutralized with 1N Hcl and make up to 50ml with diluent. Filter the solution with 0.22 microns syringe filters and place in vials.

Peroxide degradation: Pipette 5 ml above stock solution into a 50ml volumetric flask, 1 ml of 3% w/v of hydrogen peroxide added in 50 ml of volumetric

flask and the volume was made up to the mark with diluent. The volumetric flask was then kept at room temperature for 15 min. Filter the solution with 0.45 microns syringe filters and place in vials.

Reduction degradation: Pipette 5ml of Stock solution transferred into 50ml volumetric flask to this add 1ml of 10% Sodium Bisulphate and kept on bench top for 10min then the remaining procedure is same as the test preparation.

Thermal induced degradation: Bempedoic acid and Ezetimibe samples were taken in Petridish and kept in Hot air oven at 1100 C for 24 hours. Then the sample was taken and diluted with diluents and injected into HPLC and analysed.

Table 14: Forced Degradation results for Bempedoic acid and Ezetimibe.

Results: % Degradationresults	Bempedoic acid		Ezetimibe	
	Area	% Degradation	Area	% Degradation
Control	4639135	0	231891	0
Acid	3957265	14.7	201097	13.3
Alkali	3939838	15.1	196199	15.4
Peroxide	4074515	12.2	206507	10.9
Reduction	4149295	10.6	202407	12.7
Thermal	3997236	13.9	205271	11.5

CONCLUSION

The Developed HPLC method was validated and it was found to be simple, precise, accurate and sensitive for the simultaneous estimation of Bempedoic acid and Ezetimibe in its pure and pharmaceutical dosage form. Hence, this method can easily and conveniently adopt for routine quality control analysis of Ezetimibe and Bempedoic acid in its pure and pharmaceutical dosage form.

REFERENCES

1. Saeed A, Ballantyne CM: Bempedoic Acid (ETC-1002): A Current Review. Cardiol Clin, 2018 May; 36(2): 257-264. doi: 10.1016/j.ccl.2017.12.007. Epub, 2018 Feb 21.
2. Bilen O, Ballantyne CM: Bempedoic Acid (ETC-1002): an Investigational Inhibitor of ATP Citrate Lyase. Curr Atheroscler Rep, 2016 Oct; 18(10): 61. doi: 10.1007/s11883-016-0611-4.
3. Zagelbaum NK, Yandrapalli S, Nabors C, Frishman WH: Bempedoic Acid (ETC-1002): ATP Citrate Lyase Inhibitor: Review of a First-in-Class Medication with Potential Benefit in Statin-Refractory Cases. Cardiol Rev., 2019 Jan/Feb; 27(1): 49-56. doi: 10.1097/CRD.000 0000000000218.
4. Khemchand G, Indrajeet, Development of UV spectrophotometric method for the estimation of ezetimibe from tablet formulation. Int J Chem Sci., 2015; 13: 1051–1056.
5. Metreyi S, Deepali VM, Mahadik M, Kadam SS, Dhaneshwar SR UV and three derivative spectrophotometric methods for determination of ezetimibe in tablet formulation. Indian J Pharm Sci., 2008; 70: 258–260. https:// doi.org/10.4103/0250-474X.41471.
6. Narasimharaju BC, Devalarao G, Ramanjaneyulu S. Spectrophotometric method for the determination of ezetimibe in pharmaceutical formulations. Biomed Pharmacol J., 2008; 1: 413–416.
7. Kabra RP, Kadam SC, Mane VB, Kadam SS, Mamde CG Simple novel UV-spectroscopic method for estimation of ezetimibe in tablet dosage form. Am. J Pharm Health Res., 2014; 2(9).
8. Rajput SJ, Raj HA Simultaneous spectroscopic estimation of ezetimibe and simvastatin in tablet dosage forms. Indian J Pharm Sci., 2007; 69: 759–762. https://doi.org/10.4103/0250-474X.39429.
9. Namratha S, Uma Rajeswari B, Swathi B, Arunk S, Ratnakar N UV spectrophotometric method development and validation of ezetimibe and simvastatin in bulk and pharmaceutical dosage form. Int J Pharma Chem Res, 2017; 3: 581–585.
10. Varsha BM, Surekha B, Nita K. Development of UV spectrophotometric method for the simultaneous estimation of simvastatin and ezetimibe in tablet dosage form by simultaneous equation and absorbance ratio method. Int J Pharm Tech Res, 2011; 3: 1459–1466.
11. Seema MD, Manjusha PY First derivative UV-spectrophotometric method for simultaneous determination of simvastatin and ezetimibe in tablet dosage form. Pharm Lett., 2015; 7: 124–128.
12. Anuradha G, Vishal SD Simultaneous UV-spectrophotometric estimation of rosuvastatin and ezetimibe in their combined dosage forms. Int J Pharm Pharm Sci., 2010; 2: 131–138.
13. Rajput SJ, Raj HA Simultaneous estimation of ezetimibe and rosuvastatin in drug mixture by frst derivative spectroscopic method. Int J Chem Sci., 2009; 7: 2354–2362.
14. Sonawane SS, Shirkhedkar AA, Fursule RA, Surana SJ Simultaneous spectrophotometric estimation of atorvastatin calcium and ezetimibe in tablets. Indian J Pharm Sci., 2007; 69: 683–684. https://doi.org/10.4103/0250- 474X.38477.
15. Manish K, Khandare MM, Kamble KG, Kamble KG UV Spectrophotometric estimation of ezetimibe and fenofbrate in bulk drug and dosage form using simultaneous equation method. Int J Chem Technol Res., 2011; 3: 749–754.

16. Sistla R, Tata VSSK, Kashyap YV, Chandrasekar D, Diwan PV Development and validation of a reversed-phase HPLC method for the determination of ezetimibe in pharmaceutical dosage forms. J Pharm Biomed Anal, 2005; 39: 517–522.
17. Akmar SK, Lata K, Asha T, Sumitra J, Deshpande AD Reverse phase high performance liquid chromatography method for estimation of ezetimibe in bulk and pharmaceutical formulations. Indian J Pharm Sci., 2007; 69: 695–697. https://doi.org/10.4103/0250-474X.38482.
18. Saroj KR, Atna Bhaskar A, Jhansi D RP-HPLC method development and validation for the simultaneous estimation of atorvastatin and ezetimibe in pharmaceutical dosage form. Asian J Pharm Clin Res, 2015; 8: 178–181.
19. Mohammed IB, Vanitha PK, Krishna MG RP-HPLC method for simultaneous estimation of rosuvastatin and ezetimibe from their combination tablet dosage form. Int J Chem Anal Sci, 2013; 4: 205–209.
20. Siva Kumar R, Santhanakrishnan MR, Kumar PN, Venkatanarayanan R Simultaneous RP-HPLC method for estimation of ezetimibe and eimvastatin in bulk and dosage forms. Res J Pharm and Tech, 2008; 1: 211–214.
21. Fatima HB, Ayesha BK A new validated RP-HPLC method for the analysis of bempedoic acid and ezetimibe in bulk drug samples. Int J of Pharmacy Anal Res, 2020; 9: 248–252.
22. Hossein D, Mehrdad H A rapid and sensitive LC–MS method for determination of ezetimibe concentration in human plasma: application to a bioequivalence study. Chromatographia, 2013; 76: 1667–1675.
23. Jung-Woo B, Chang-Ik C, Sang-Hun P, Choon-Gon J, Seok-Yong L. Analytical LC-MS/MS method for ezetimibe and its application for pharmacokinetic study. J Liq Chromatogr Relat Technol, 2012; 35: 141–152. https:// doi.org/10.1080/10826076. 2011.597065.
24. El-Bagary RI, Ehab FE, Zeinab AES, Ahmed MK LC-MS-MS simultaneous determination of atorvastatin and ezetimibe in human plasma. J Chromatogr Sci., 2014; 52: 773–780. https://doi.org/10.1093/chromsci/bmt109
25. Abhaysingh B, Mallika S, Priyanka AS, Pranav SS Simultaneous quantitation of rosuvastatin and ezetimibe in human plasma by LC-MS/ MS: pharmacokinetic study of fxed-dose formulation and separate tablets. Biomed Chromatogr, 2018; 32: e4291. https://doi.org/10.1002/bmc.4291
26. Brian JE, Karen P, Cameron B, Clay TC, Ronald S Measurement of bempedoic acid and its keto metabolite in human plasma and urine using solid phase extraction and electrospray LC-MS/MS. J Chromatogr B Analyt Technol Biomed Life Sci, 2020; 1154: 122291. https://doi.org/10.1016/j. jchromb.2020.122291.