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

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**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.*

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## 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.

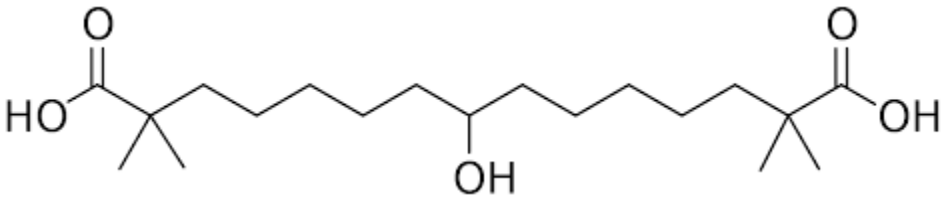


**Figure 1: Structure of Bempedoic acid**

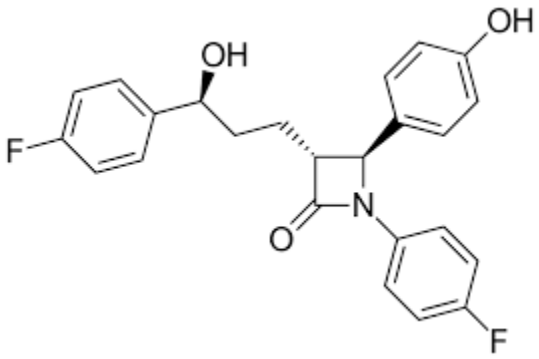


**Figure 2: Structure of Ezetimibe**

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) | Label amount (mg) | Stdpurity | Amount found (µg/ml) | % assay |
|---|---|---|---|---|---|---|---|---|
| NEXLIZET | Bempedoic Acid | 4618965 | 180 | 248 | 180 | 99.8 | 179.27 | 99.6 |
| | Ezetimibe | 232365 | 10 | 248 | 10 | 99.9 | 10.02 | 100.2 |

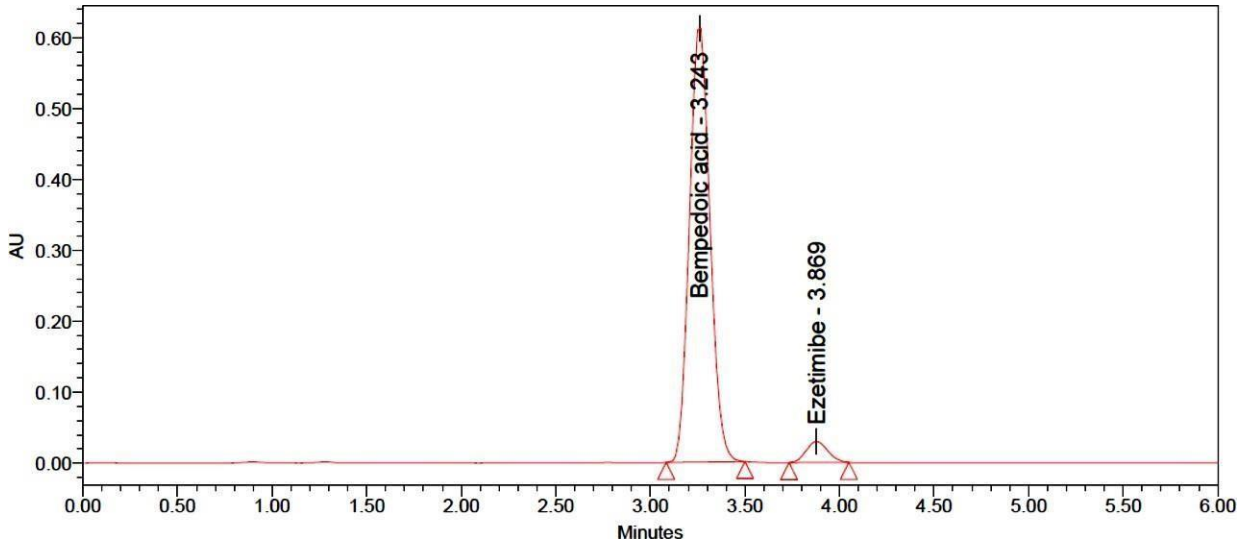


**Figure 3: Standard chromatogram**

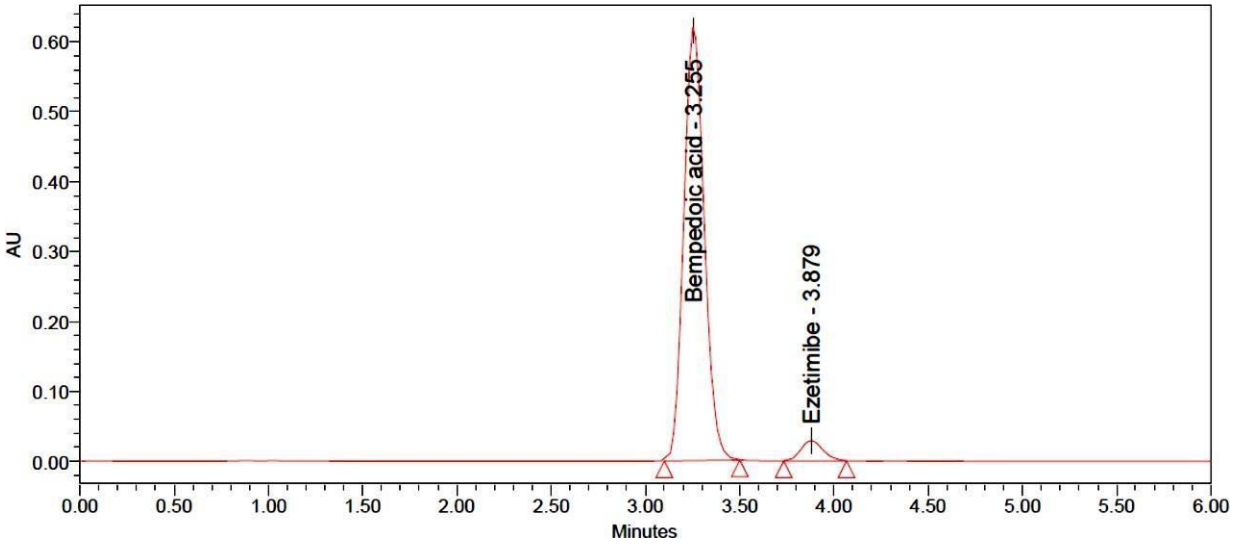


**Figure 4: Sample chromatogram**

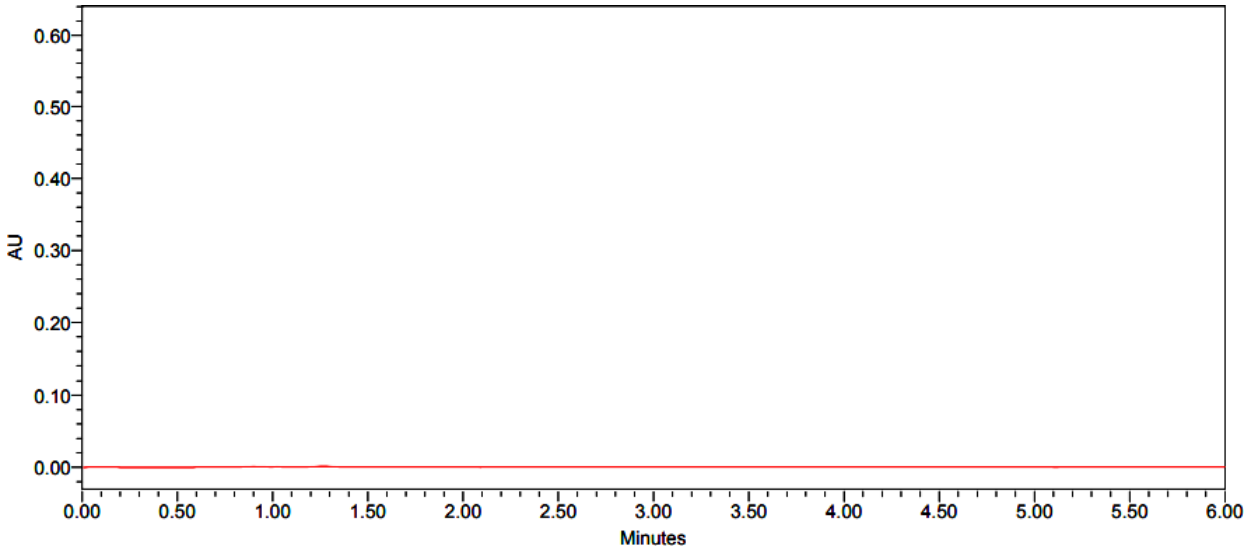


**Figure 5: Blank chromatogram**

**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 |
| **egression equation** | 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 | |

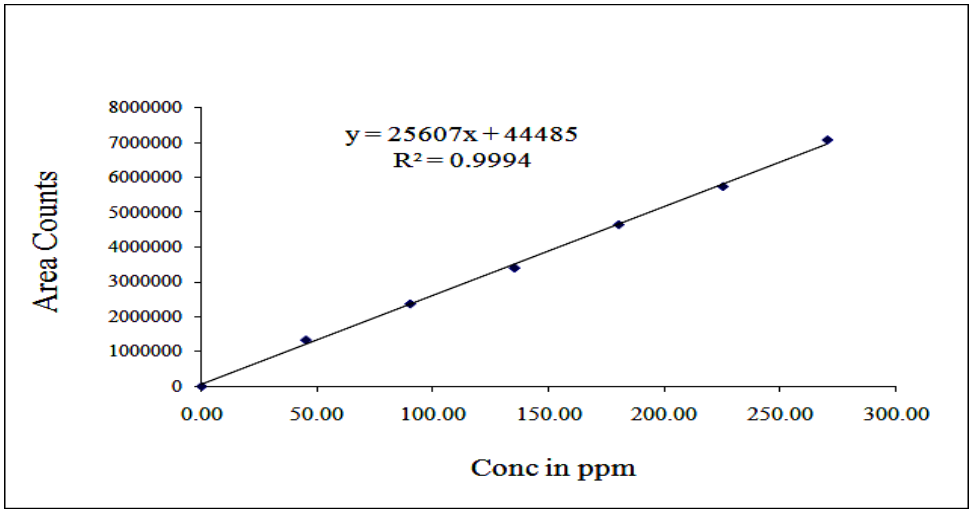


**Figure 6: Linearity graph for Bempedoic acid**

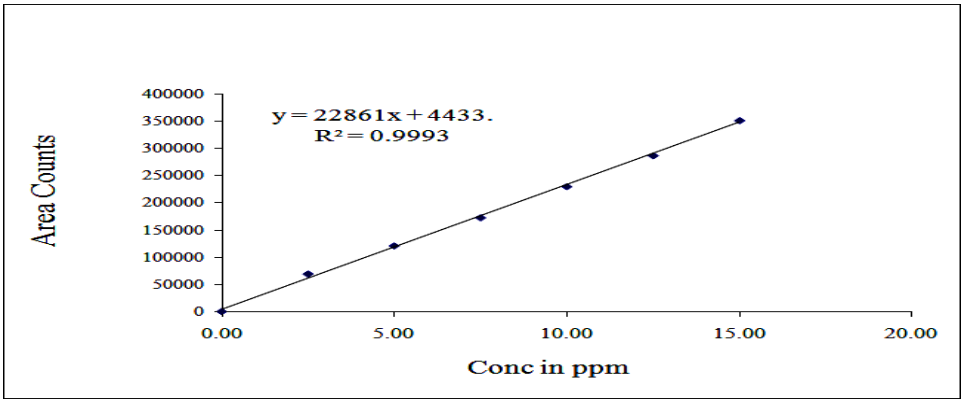


**Figure 6: Linearity graph for Ezetimibe**

**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 | Amount Added (mg) | Amount Found (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 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 | Retention time(min) | Peak area | Resolution | Tailing | Platecount |
| Flow rateChange (mL/min) | ess flow(0.8ml) | 3.897 | 5291586 | | 1.16 | 4138 |
| | Actual (1ml) | 3.246 | 4648402 | | 1.11 | 4112 |
| | lore flow(1.2ml) | 2.806 | 4086390 | | 1.08 | 4103 |
| anic 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.

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