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A NEW STABILITY INDICATING RP-HPLC METHOD DEVELOPMENT AND VALIDATION FOR THE SIMULTANEOUS ESTIMATION OF BEMPEDOIC ACID ANDEZETIMIBE IN PHARMACEUTICAL DOSAGE FORM

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Abstract:

A reasonable, Exact, distinct technique was made for the synchronous assessment of the Bempedoic Disastrous and Ezetimibe inward breath assessments structure. Chromatogram was gone through Suitable RP C18 150 x 4.6 mm, 5mm. Adaptable stage containing 0.01N Ammonium acetic acid derivation: Acetonitrile engaged in the degree 50:50 was coordinated through portion at a stream speed of 1.0 ml/min. Temperature was remained mindful of at 30°C. Significant level repeat picked was 230nm. Support season of Bempedoic Horrendous and Ezetimibe were viewed as 2.231 min and 2.865. %RSD of the Bempedoic Horrendous and Ezetimibe were and viewed as0.4 and 0.3 autonomously. %Recovery was acquired as 99.90% and 100.189% for Bempedoic Horrendous and Ezetimibe autonomously. LOD, LOQ values developed fromlose the faith territories of Bempedoic Disastrous and Ezetimibe were 0.07, 0.20 and 0.01,0.03 autonomously. Fall away from the faith province of Bempedoic Disastrous is y = 22346x + 7034.5, y = 30936x + 304.5 of Ezetimibe. Upkeep times were moderated and that run time was moderated, so the technique made was immediate and reasonable that canister be taken on in common in Undertakings.

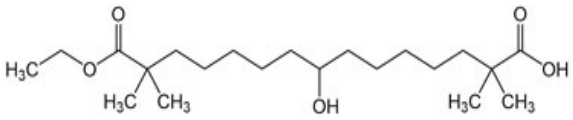
Key Words: Bempedoic Acid and Ezetimibe, RP-HPLC

Introduction

Bempedoic destructive is first-in-class adenosine triphosphate-citrate lyase (leg ligament) inhibitor included once each day for lessening LDL cholesterol levels in statin-difficult patients. Chemically called as 8-hydroxy-2,2,14,14-tetramethylpentadecanedioic acid. Ezetimibe is a lipid-cutting down compound that limits stomach related cholesterol and phytosterol maintenance. Ezetimibe IUPAC name as (3R,4S)-1-(4-fluorophenyl)-3-[(3S)-3-(4-fluorophenyl)-3-hydroxypropyl]-4-(4-hydroxyphenyl) azetidin-2-oneEzetimibe is used as an adjunctive treatment to a sound eating routine to cut down cholesterol levels in fundamental hyperlipidemia, mixed hyperlipidemia, homozygous familial hypercholesterolemia (HoFH), and homozygous sitosterolemia (phytosterolemia)]. Literature review reveals that very few analytical method has been reported for the determination of ETZ in biological fluid which includes UV,HPLC But recently very few methods has been developed for the simultaneous estimation of Bempedoic and Ezetimibe by HPLC using 0.01N Ammonium acidic derivation: Acetonitrile (50:50).The present study was aimed Cultivate a definite, precise, fragile, specific, reproducible and fast coherent strategy for simultaneous appraisal of Ezetimibe Bempedoic Destructive in mass bug tablet portion structure

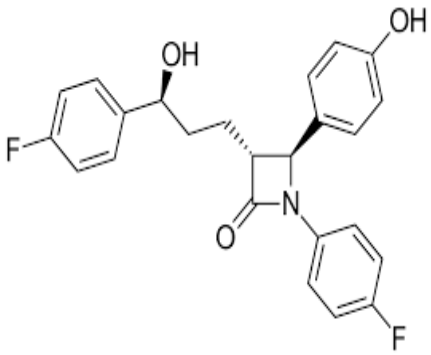
Drug Profile:

Structure of Bempedoic



IUPAC Name: 8-hydroxy-2,2,14,14-tetramethylpentadecanedioic acid
Chemical formula: C19H36O5
Molecular weight: 344.492
Solubility: 0.0211 mg/mL
Melting Point: 87-92
Pka: 4.44 (Strongest Acidic)
Category: ACL Inhibitors

Structure of Ezetimibe



IUPAC Name: (3R,4S)-1-(4-fluorophenyl)-3-[(3S)-3-(4-fluorophenyl)-3-hydroxypropyl]-4-(4-hydroxyphenyl) azetidin-2-one
Chemical formula: C24H21F2NO3
Molecular weight: 409.4252
Cas number: 163222-33-1
Pka: 9.48 (Strongest Acidic)
Melting Point: 163°C
Category: Selective Cholesterol- Absorption inhibitors

Material and Methods

Bempedoic Disastrous and Ezetimibe unadulterated medications (Programming point of association), Blend Bempedoic Damaging and Ezetimibe. Nexlizet (Ezetimibe 180mg, Bempedoic Disastrous 10mg.) got from range labs, water, Acetonitrile, Phosphate, Methanol, Potassium dihydrogen ortho phosphate, Ortho-phosphoric of AR grade, were purchased from obtained from local market.

Chromatographic condition:A mobile phase consisted of 0.01 N Ammonia acetic acid derivation : Acetonitrile (60;40) ration was pumped at a flow rate rate of 1 ml/min. The elution was monitored at 220 nm and the injection volume was 10 µL. The validation of the method was done following the ICH guidelines.

Instrumentation:

WATERS HPLC 2695 System outfitted with quaternary siphons, Photo Diode Bunch pointer and Auto sampler composed with Draw in 2 Programming. UV-Visible spectrophotometer PG Instruments T60, pH meter, Ultrasonicator, Syringe- Hamilton, HPLC column STD Denali C18 (4.6 x 150mm, 5µm) were used.

Preparation of Solutions:

Preparation of 0.01N Ammonium Acidic buffer

0.77gm of Ammonium Acidic was weighed and dissolved in 1000ml ofVolumetric cup add around 900ml of milli-Q water added and degas to sonicate finally make up the volume with water then, added 1ml of Triethylamine then PH changed by 3.8 with dil. Orthophosphoric.The buffer was filtered through 0.45µ filters to remove all fine particles and gases

Preparation of mobile phase.

A mixture of 0.01N Ammonium acetic acid derivation: Acetonitrile 60:40 (HPLC grade). The mobile phase was sonicated for 10min to remove gases**.**

Preparation of Stock solution of Bempedoic and Ezetimibe:

Standard stock solutions of Bempedoic and Ezetimibe (mg/ml) were prepared by dissolving weighed 45 mg of Bempedoic Unfortunate,2.5 mg of Ezetimibe and moved to 25ml volumetric holders and 3/4 th of diluents was added to these compartment and sonicated for 10 minutes. After that filtered the solution using 0.45- micron syringe filter and Sonicated for 5 min and dilute to 100 ml with mobile phase.1ml from each stock game plan was pipetted out and taken into a 10ml volumetric carafe and made up with diluent. (900µg/mlof Bempedoic Lamentable and 50µg/ml Ezetimibe)

Preparation of Sample solution of Bempedoic and Ezetimibe:

10 tablets were checked the standard heap of each and every as yet hanging out there, then, the weight unclear from 1 tablet was moved into a 100 ml volumetric cup, 50ml of diluents was added and sonicated for 25 min, further the volume wasmade up with diluent and isolated by HPLC filters. 0.5ml of segregated model stock arrangement was moved to 10ml volumetric cup and made up with diluent. (90µg/ml of Bempedoic Horrendous and 5µg/ml of Ezetimibe).

Selection of mobile phase for method Optimization and experimental condition:

Several trial has been taken for the proper optimization of RP HPLC method by changing different mobile phase with different ratio. And finally the mobile phase for Optimized condition was selected and given follows. And the Optimized parameters was for BEP and ETZ was given.

Chromatographic conditions:

Mobile phase	: 0.01N Ammonium acetic acid derivation: Acetonitrile
Ratio	: 60:40
Column	: STD Denali C18 (4.6 x 150mm, 5µm)
Wavelength	: 220
Temperature	: 30
Runtime	: 10min
Injection volume	: 10mL

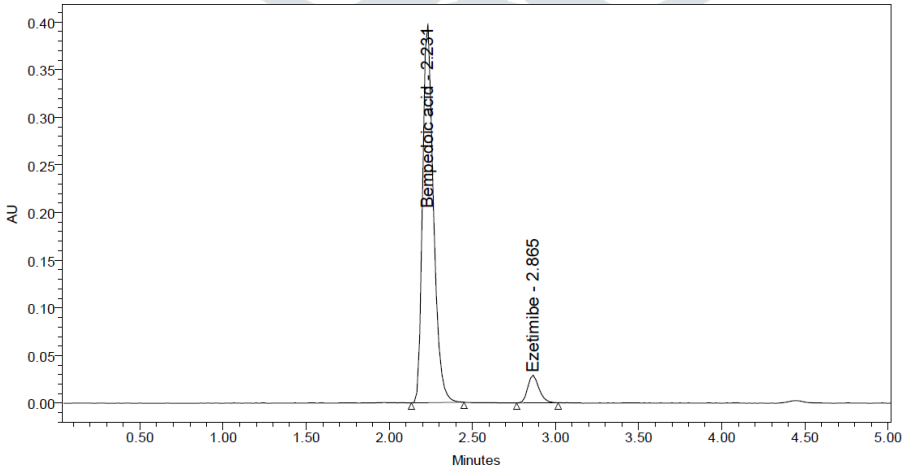


Figure 01: A typical Optimized chromatogram of BEP and EZT

Assay:

Assay of marketed tablet formulation containing Bempedoic acid 44 mg and Ezetimibe100 mg equivalent to 100 mg was performed by preparing the sample solutions as described earlier in the preparation of the sample. Six injections of above prepared sample and standard solutions were injected. The assay of the commercial sample was calculated by comparing the areas of standard and sample peaks. The assay of AVYCAZ marketed formulation found within limit. And the chromatogram was given as figure

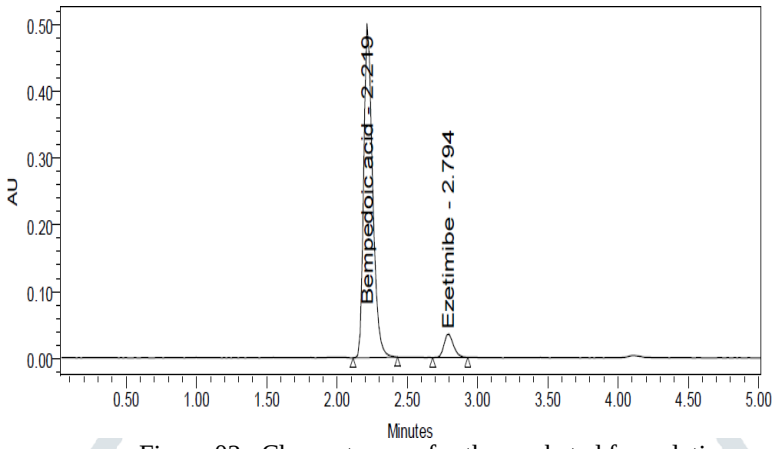


Figure 02: Chromatogram for the marketed formulation

This optimized method was validated in terms of linearity, accuracy, precision, specificity, limit of detection, limit of quantification and solution stability as per ICH guidelines.

Linearity:

Calibration curve was constructed by plotting concentrations of Bempedoic acid and Ezetimibe**.** vs. peak areas, and the regression equations were calculated. The linearity of this method was investigated by using the concentrations 0,22.5.45,67.5,90,112.5and 135 µg/ml for Bempedoic acid and 0,1.25,2.5,3.75,5,6.25 and 7.5 µg/ml for Ezetimibe. These concentrations were prepared by diluting appropriate volume of working standard with mobile phase.

Bempedoic Acid		**Ezetimibe**	
Conc (µg/mL)	**Peak area**	**Conc (µg/mL)**	**Peak region**
0	0	0	0
22.5	518517	1.25	40654
45	1000873	2.5	75110
67.5	1523734	3.75	116558
90	2032051	5	155755
112.5	2513541	6.25	194933
135	3018843	7.5	231181

Table No: 01 Data of Linearity

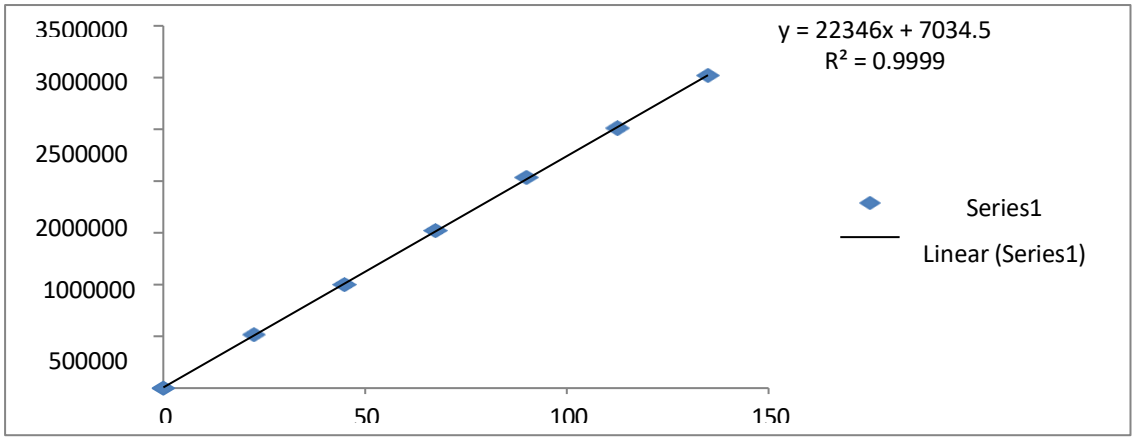


Fig No. 3 Calibration curve of Bempedoic Acid

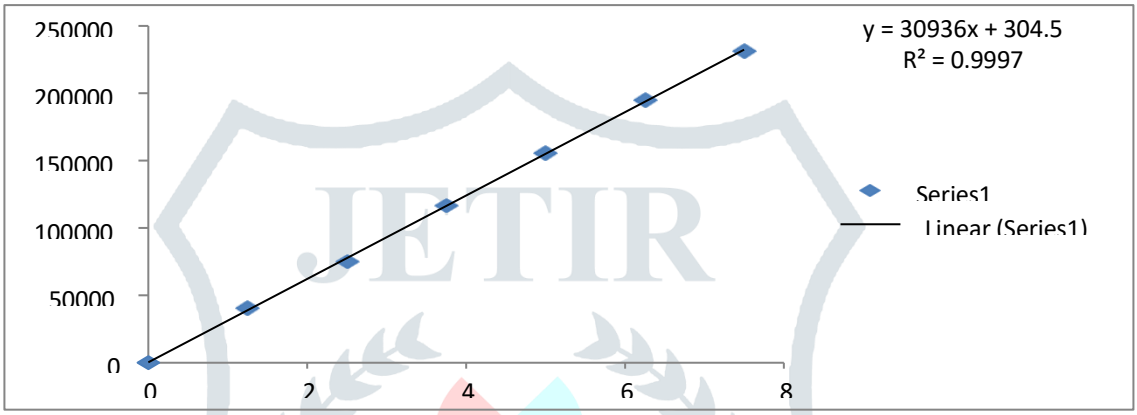


Fig No. 4 Calibration curve of Ezetimibe.

System suitability:

Standard solutions were prepared as per the test method and injected into the chromatographic system. The system suitability parameters like theoretical plates, resolution and asymmetric factor were evaluated

S. No	Area of Bempedoic Acid	Area of Ezetimibe
1.	1989021	152867
2.	1992900	153096
3.	2011184	152692
4.	1997966	153256
5.	1994888	154047
6.	2003378	153203
Mean	1998223	153194
S.D	7984.5	469.1
%RSD	0.4	0.3

Table 2: System precision table of Bempedoic Destructive and Ezetimibe

Results:

From a singular volumetric cup of working standard plan six implantations were given and the got locales were referred to beforehand. Ordinary locale, standard deviation and% not entirely settled for two drugs. % RSD got as 0.4% and 0.3% independently for Bempedoic Destructive and Ezetimibe. As the limitation of Exactness was under "2" the system precision was passed in this method.

Accuracy

Accuracy of the method was determined by Recovery studies. To the formulation (pre analyzed sample), the reference standards of the drugs were added at the level of 50%, 100%, 150%. The recovery studies were carried out three times and the percentage recovery and percentage mean recovery were calculated for drug is shown in table. To check the accuracy of the method, recovery studies were carried out by addition of standard drug solution to pre-analyzed sample solution at three different levels 50%, 100%, 150%.

% Level	Amount Spiked(µg/mL)	Amount recovered(µg/mL)	% Recovery	Mean %Recovery
50%	45	44.8	99.5	99.90%
	45	45.2	100.5	
	45	45.4	100.9	
100%	90	90.3	100.3	
	90	89.5	99.5	
	90	89.5	99.4	
150%	135	134.5	99.6	
	135	134.3	99.5	
	135	134.7	99.8	

Table 03 Accuracy table of Bempedoic Destructive

% Level	Amount Spiked(µg/mL)	Amount recovered(µg/mL)	% Recovery	Mean %Recovery
50%	2.5	2.52	100.81	99.96%
	2.5	2.50	100.04	
	2.5	2.54	101.49	
100%	5	4.98	99.55	
	5	4.95	99.07	
	5	4.99	99.78	
150%	7.5	7.48	99.77	
	7.5	7.42	98.94	
	7.5	7.51	100.17	

Table 04 Accuracy table of Ezetimibe Destructive

Results

Three levels of Accuracy tests were prepared by standard extension procedure. Three-overlap mixtures were given for every level of precision and mean %Recovery was gotten as 99.90% and 99.96% for Bempedoic Destructive and Ezetimibe independently.

Precision:

Intra-day precision was calculated from results obtained from six-fold replicate analysis of samples at three different concentrations of on the same day. Inter-day precision was calculated from results from the same samples analyzed on six consecutive days. Standard solution was prepared as per the test method and injected six times as per the test procedure. And Relative standard deviation was calculated.

S. No	Area of Bempedoic Acid	Area of Ezetimibe
1.	2015829	153945
2.	2006554	154363
3.	1989632	152459
4.	2022031	152392
5.	2011455	154345
6.	2003546	154248
Mean	2008175	153625
S.D	11218.1	941.6
%RSD	0.6	0.6

Table :05: precision table of Bempedoic Destructive and Ezetimibe

Results:

Different looking at from a model stock plan was done and six working model courses of action of same obsessions were prepared, each mixture from each working model course of action was given and gotten locales were referred to in the above table. Ordinary locale, standard deviation and % not entirely set in stone for two meds and procured as 0.6% and 0.6% independently for Bempedoic Destructive and Ezetimibe. As the limitation of Exactness was under "2" the structure precision was passed in this strategy.

Midway precision (Day_ Day Exactness):

S. No	Area of Bempedoic Acid	Area of Ezetimibe
1.	1916376	149384
2.	1897962	149499
3.	1905664	149682
4.	1912891	148898
5.	1935647	149701
6.	1911281	148578
Mean	1913304	149290
S.D	12701.6	455.1
%RSD	0.7	0.3

Table 06 Midway precision table of Ezetimibe and Bempedoic Destructive

Results:

Various looking at from a model stock course of action was done and six working model plans of same obsessions were prepared, each imbuement from each working model course of action was given on the next day of the model preparation and got areas were referred to in the above table. Typical area, standard deviation and % not entirely settled for two prescriptions and got as 0.7% and 0.3% independently for bempedoic destructive and Ezetimibe. As the limitation of Precision was under "2" the structure exactness was passed in this methodology.

Robustness:

Robustness of the method was demonstrated by deliberately changing the chromatographic conditions. The flow rate of the mobile phase was changed from 1.0 ml/min to 0.9 ml and 1.1 ml/min., temperature of column oven (±27C) and 33°C unit. The mobile phase composition also little changed

S.no	Condition	%RSD Bempedoic Acid	%RSD of Ezetimibe
	Flow rate (-) 0.9ml/min	1.1	1.4
2	Flow rate (+) 1.1ml/min	0.7	0.7
3	Mobile phase (-) 55B:45A	0.7	1.3
4	Mobile phase (+) 45B:55A	0.4	0.5
5	Temperature (-) 27°C	0.6	0.6
6	Temperature (+) 33°C	0.9	1.7

Table 07 Responsiveness table of Bempedoic Destructive and Ezetimibe

Results:

Strength conditions like Stream less (0.9ml/min), Stream not withstanding (1.1ml/min), compact stage short (55B:45A), flexible stage notwithstanding (45B:55A), temperature less (27°C) and temperature notwithstanding (33°C) was stayed aware of and tests were implanted in duplicate manner. Structure suitability limits next to no influenced and all of the were passed. % RSD was inside in the end.

LOD and LOQ:

Combine standard solution were prepared by sequential dilutions and injected on to the chromatograph, at a decreasing concentration in the range of 0.050 to 15µm/ml for BEP and 0.045 µm/ml to 10 µm/ml for EZT. The limit of detection was defining as the concentration for which a signal-to-noise ratio of 3 was obtained and for Quantitation limit, a signal-to-noise ratio of 10 was considered.

Molecule	LOD	LOQ
Bempedoic Acid	0.07	0.20
Ezetimibe	0.01	0.03

Table 08 Responsiveness table of Bempedoic Destructive and Ezetimibe

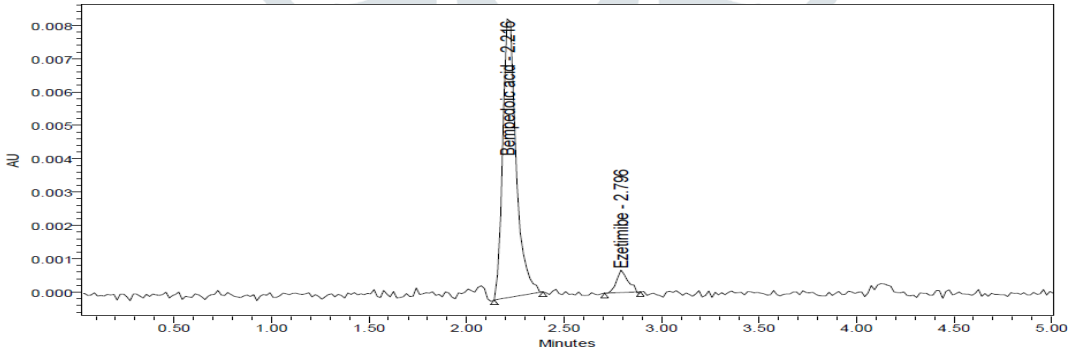


Fig. No. 13 LOD Chromatogram of Standard

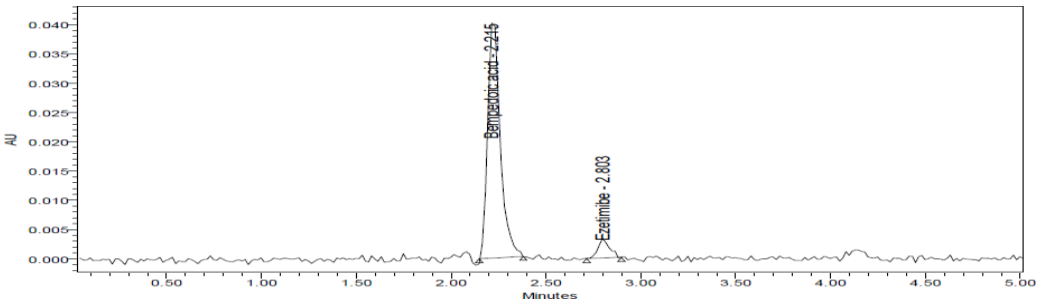


Fig. No. 14 LOQ Chromatogram of Sample

Assay:

Avycaz, bearing the name ensure Ezetimibe 100mg, Bempedoic Destructive 44mg. Look at was performed with the above plan. Typical % Look at for Bempedoic Destructive and Ezetimibe got was 100.40% and 100.18% exclusively.

S.no	Standard Area	Sample area	% Assay
1	1989021	2015829	100.78
2	1992900	2006554	100.32
3	2011184	1989632	99.47
4	1997966	2022031	101.09
5	1994888	2011455	100.56
6	2003378	2003546	100.17
Mean	1998223	2008175	100.40
SD	7984.5	11218.1	0.56
%RSD	0.4	0.6	0.6

Table 09 Assay Data of Bempedoic Acid

S.no	Standard Area	Sample area	% Assay
1	152867	153945	100.39
2	153096	154363	100.66
3	152692	152459	99.42
4	153256	152392	99.38
5	154047	154345	100.65
6	153203	154248	100.59
Mean	153194	153625	100.18
SD	469.1	941.6	0.61
%RSD	0.3	0.6	0.61

Table 10 Assay Data of Ezetimibe

DEGRADATION

Defilement Audit: Degradation survey were performed with the definition and the debased models were injected. Inspect of the imbued not set in stone and all of the models passed the limitations of debasement

S.NO	Condition	Area	% Recovery	% Degraded
1	Acid	1895683	94.77	5.23
2	Alkali	1914367	95.71	4.29

3	Oxidation	1921794	96.08	3.92
4	Thermal	1936098	96.79	3.21
5	UV	1954748	97.73	2.27
6	Water	1985439	99.26	0.74

Table 11 Degradation of Bempedoic Acid

S.NO	Condition	Area	% Recovery	% Drug Degraded
1	Acid	143979	93.89	6.11
2	Alkali	145752	95.05	4.95
3	Oxidation	146641	95.63	4.37
4	Thermal	147279	96.04	3.96
5	UV	148922	97.11	2.89
6	Water	152717	99.59	0.41

Table.12 Degradation Data of Ezetimibe

Discussion: with respect to the pH change in versatile stage for the destructive and base defilement studies have improvement in upkeep time of meds. However, as a result of killed destructive model through 2N Base game plan and base model with 2N Destructive plan in attendance will be no change of upkeep time.

DATA SUMMARY

Parameters		Bempedoic Acid	Ezetimibe	LIMIT
Linearity Range (µg/ml)		22.5-135 µg/ml	1.25-7.5µg/ml	R< 1
Regression coefficient		0.998	0.998	
Slope(m)		22346	30936	
Intercept(c)		7034.5	304.5	
Regression equation (Y=mx+c)		y = 22346x + 7034.5	y = 30936x + 304.5	
Assay(%mean assay)		100.40%	100.18%	90-110%
Specificity		Specific	Specific	No check of any zenith
System precision %RSD		0.4	0.3	NMT 2.0%
Technique accuracy %RSD		0.6	0.6	NMT 2.0%
Accuracy %recovery		99.90%	99.96%	98-102%
LOD		0.07	0.01	NMT 3
LOQ		0.20	0.03	NMT 10
Robustness	**FM**	1.1	1.4	
	FP	0.7	0.7	
	MM	0.7	1.3	
	MP	0.4	0.5	
	TM	0.6	0.6	
	TP	0.9	1.7	

CONCLUSION

An essential, Definite, exact strategy was delivered for the concurrent assessment of the Bempedoic Destructive and Ezetimibe in Tablet estimation structure. Support time of Bempedoic Destructive and Ezetimibe were seen as 2.219 min and 2.794. %RSD of the Bempedoic Destructive and Ezetimibe were and seen as 0.6 and 0.3 independently. % Recuperation was acquired as 99.90% and 99.91% for Bempedoic Destructive and Ezetimibe exclusively. LOD, LOQ values expanded from backslide states of Bempedoic Destructive and Ezetimibe were 0.07, 0.20 and 0.01, 0.03 exclusively. Backslide state of Bempedoic Destructive is y = 22346x + 7034.5, y = 30936x + 304.5 of Ezetimibe. Support times be situated lessened and that run time was reduced, so the system made was quick and reasonable that can be taken on in standard Quality control test in Attempts. Hence, proposed analytical method was simple, novel, economical, rapid, sensitive, reproducible and accurate for the Bempedoic and Ezetimibe. A method was set up for synchronous estimation of a Bempedoic and Ezetimibe by RP-HPLC system.

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