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Synchronized analysis of bempedoic acid and ezetimibe in pure binary mixture and their combined tablets by a new stability indicating RP-UPLC method

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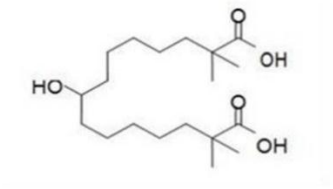
***Abstract*---**The primary purpose of the designed study was to develop and validate a commercial, insightful, precise and simple RP-UPLC approach with greater response for the synchronized investigation of Bempedoic acid and Ezetimibein pure form and their fixed-dose combination tablet form. A method with Phenyl XBD (100 x 2.1mm, 1.7mm) column, mobile (solvent) phase of 0.1% v/v TFA in water and acetonitrile in 60:40 v/v pumped with a flow of 0.4mL/min and a wavelength of 236nm were competently separate the BPA and EZM with excellent resolution and shorter RT about 0.43min and 0.86 min for BPA and EZM respectively.The R2 for a range of concentrations stated for the Bempedoic acid (20-120µg/mL) and Ezetimibe (1-6µg/mL) were 0.999 and 0.999 correspondingly. The LOD and LOQ values of Bempedoic acid (0.41µg/mL and 1.23µg/mL) and Ezetimibe (0.02 µg/mL and 0.07µg/mL) unveiled the sensitivity of the stated method. The method has been validated in compliance with ICH standards. Identification of degradants peaks accompanyingthe intended analyte peaks with acceptable resolution is ascertaining the stbilitiy –indicating feature of the proposed method. Hence, the proposed approach has significant acceptance in the pharmaceutical sector.

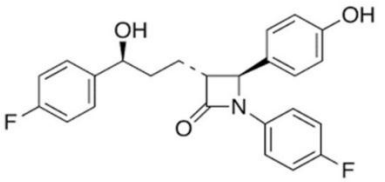
***Keywords*---**bempedoic acid, ezetimibe, pheny XBD column, ortho phosphoric acid, stability-indicating.

Introduction

In developed nations, cardiovascular diseases remain the key cause of illness and death. One of the key causative associated with a higher risk of atherosclerotic CVD (ASCVD) is hyperlipidemia, which is one of the seven key considerations used by the American Heart Association (AHA) to assess cardiovascular fitness in adults and children[1]. Despite the fact that statin medication is still the first-line treatment for hyperlipidemia, many patients do not attain ideal low-density lipoprotein-cholesterol (LDL-C) levels despite using moderate- to increased-intensity statins; As a result, non-statin medication is often required along with statin therapy.[1-2]Bempedoic acid (BPA) is a prodrug, the active form can decreases LDL-C levels in blood by the inhibiting the of adenosine triphosphate citrate lyase enzyme produced in the liver.[1-3]Ezetimibe(EZM) is a medication that blocks intestinal cholesterol absorption specifically by inhibiting the activity of Niemann-Pick C1 like 1 protein.[4-5] Early studies showed that taking EZM with a statin reduced LDL-C levels by an additional 12–19%.[5] A combined regimen with BPAand EZMwas licensed by US-FDA in 2020 for management of chronic hyperlipidemia in patients, who tolerated maximum with statins therapy and were highly affected by diabetes along with hyperlipidemia.[6-7] The IUPAC names andmolecular structures of BPA andEZM were mentioned in Figure-1.



Name: Bempedoic acid
Molecular formula: $C_{19}H_{36}O_5$
IUPAC: 8-hydroxy-2,2,14,14 -tetramethylpentadecanedioic acid



Name: Ezetimibe
Molecular formula: $C_{24}H_{21}F_2NO_3$
IUPAC: (3R,4S)-1-(4-fluorophenyl)-3-[(3S)-3-(4-fluorophenyl)-3-hydroxypropyl]-4-(4-hydroxyphenyl)azetidin-2-one

Figure 1. Molecular structures of BPA and EZM

The key requisite in the pharmaceutical manufacturing industry to have an efficient, precise and economical analytical procedure to identify and assess the amount of active drug in dosage form manufactured in batch wise before releasing into the market. A broad literature survey ensures that simple and reliable UV, HPLC and UPLC methods were observed for individual moieties of BPA and EZM[8-13]. As it is a recently approved combination no single analytical method were reported in any official pharmacopoeias. Only two HPLC methods with longer retention time and less sensitive methods were observed in reputed journals[14,15]. Only one UPLC method with complex solvent phase and longer RT for EZM was traced out by efficient literature review[16]. As UPLC method has

several advantages over UV and HPLC methods, research was focused to develop a new stability associated UPLC method with good sensitivity, simple and economical mobile phase, accurate and reliable precision.

Materials and Methods

Reagents and chemicals

The API's of BPA and EZM were attained from Fortune Lab, Hyderabad. The HPLC grade solvents have been procured from local supplier of Merck India. Analytical grade solvents and chemical were borrowedfrom Sigma Aldrich.

Instruments

UPLC (Waters, 2695) coupled with Photo Diode Array (PDA) Detector, Xbridge Phenyl (100 x 2.1mm, 1.7µm) column and auto sampling system was used to separate the compounds. Empower 2 module version opted to process and assimilate the obtained data from UPLC.

Method development

To accomplish the efficient separation of the both analytes, a standard solution (100% level)of 0.4µl was introduced into UPLC system. The trial and error procedure was adopted to trace out the appropriate chromatographic conditions for effective separation.Different columns include CHS C18, Hiber C8 and phenyl Xbridge were trialed with different compositions of solvent systems prepared by solvents like methanol, phosphate buffer, acetonitrile (ACN) and 0.1% TFA (Trifluoro Acetic acid) in various proportions. A method conditions include Phenyl XBD(100 x 2.1mm, 1.7µm) column, mobile phase of 0.1% v/v TFA in water and ACN in 60:40 v/v pumped with a flow of 0.4mL/min and a wavelength of 236nm were competently separate the BPA and EZM with good resolution and system suitability. The mobile (solvent) phase and all prepared solution were filtered all the way through the 0.45µm filters to confiscatepossible particulate matter.

Procedure to Prepare standard solution

4mg of EZM and 80mg of BPA and were properly weighed and dissolved with suitable diluent (Acetonitrile: Water (1:1)) to 100mL. 1mL of the above resultant solution was diluted further to 10mL to prepare a solution having 80µg/mL and 4µg/mL for BPA and EZM respectively.

Procedure to Prepare sample (tablet) solution

The tablet (Nexlizet) powder weight equal to 4mg of EZM and 80mg of BPA were properly weighed and dissolved with diluent to 100mL. 1mL of the above resultant solution was diluted once more to 10mL to attain a solution having 4µg/mL and 80µg/mL for EZM and BPA respectively. 0.45µm Nylon filters were aid to exclude potential particulate matter from sample solution.

Method Validation

Q2 provisions of ICH regulations were considered while validating the stated method[17].

System suitability

To verify the system suitability of the projected method, six subsequent injections of standard solution were introduced to the UPLC system. Parameters including tailing factor (T), resolution(R), plate count (N) and %RSD werecalculated for the peaks of the both analytes in the recorded chromatograms.

Linearity

The linearity of the produced responses ensures that they are precisely proportionate to the stated concentrations. The stated method's linearity was tested by injecting a sequence of working standards containing around20, 40, 60, 80, 100 and 120µg/mL for BPA and 1, 2, 3, 4, 5 and 6µg/mL for EZM. Finally, linearity graphs were plotted between concentrations (X-axis) and peak areas(Y-axis) for both analytes to determine the regression coefficient (R^2) value. The slope and y-intercept %RSD values were calculated three times using the same approach.

Sensitivity

The limit detection limit (LOD) and limit quantification limit (LOQ) were computed by following formulae

$$LOD=3\sigma/S$$

$$LOQ = 10\ \sigma/S$$

Where, σ -standard deviation (SD) of the y- intercepts of the 3 replicate linear plots

S –Average or mean slope of 3 replicate linear plots

Specificity

When the analyte under study is determined successfully by the approach in the existence of other substances without any interference, the method is shown to be specific. It was done by injecting 0.4µL of each separate solution of blank, standard preparation (100%level), sample preparation, and placebo spiked in standard solution in a sequential fashion. The recorded chromatograms were interpreted to identify the interferences from the RT of placebo and blank at the RT of both analytes. The method's specificity was strengthened further by comparing the chromatograms of the different degradation solutions with the standard solution chromatogram to rule out interferences between the RT of degradation products and both EZM and BPA.

Precision

When a close association is ascertained among the attained responses from the homogeneous sample on several applications under the same circumstances, the

approach is expressed to be precise. System precision of the anticipated method was accomplished by injecting standard concentration for 6 times subsequently, while method precision was performed by injecting sample solution for 6 times subsequently. The %RSD of the peak areas (System precision) and the % assay of peak areas (method precision) have been calculated.

Accuracy

The accuracy parameter was validated using the % recovery approach. In this approach, a certain quantity of sample was spiked to three distinct levels of standard preparation (50%, 100%, and 150%). Each spiked preparation was evaluated three times. The mean % recoveries of each analyte in spiked solutions were assessed.

Robustness

The capacity of a method to achieve the same result when the method circumstances are purposely changed to some extent is considered to be robustness. Minor alterations to the parameters including flow rate (±0.1 mL/min), mobile (solvent) phase ratio (± 1mL organic phase) and temperature (± 5^0C) were done to verify the robustness of the offered approach. For the recorded chromatograms, the system suitability parameters were determined.

Stability indicating studies

To confirm the method's stability representing feature, forced degradation procedures were done to a typical drug solution. Researchers can readily estimate the degradation routes and storage environment for pharmaceuticals using this study. Forced degradation investigations were carried out in harmony with ICH Q1A, QIB, and Q2B requirements.

Acid degradation

10mL stock solution of standard and 4mL of 2N HCl mixed properly and reflex for 2hr at 70^0C set aside for while, neutralize with 2N NaOH. 1mL of the above resultant solution was diluted further to 10mL to prepare a solution having 80µg/mL and 4µg/mL for BPA and EZM respectively. The resultant solution was evaluated for 24hr with an interval of 6hr.

Base degradation

10mL stock solutionof standard and 4mL of 2N NaOH mixed properly and reflex for 2hr at 70^0C set aside for while, neutralize with 2N HCl. 1mL of the above resultant solution was diluted further to 10mL to prepare a solution having 80µg/mL and 4µg/mL for BPA and EZM respectively. The resultant solution was evaluatedfor 24hr with an interval of 6hr.

Oxidative degradation

10mL stock solutionof standardand 4mL of 10% H_2O_2 mixed properly and reflex for 2hr at 70^0C set aside for while. 1mL of the above resultant solution was diluted further to 10mL to prepare a solution having 80µg/mL and 4µg/mL for BPA and EZM respectively. The resultant solution was evaluatedfor 24hr with an interval of 6hr.

Photo degradation

10mL stock solutionof standardwas placed in UV compartment at 254nm for 24 hrs. At each 6hr of interval 1ml of the above solutions was collected and diluted to achieve concentration of 4µg/mL and 80µg/mL for EZM in and BPA respectively. The resultant solution was injected to verify the extent of degradation occurred in the EZM and BPA.

Thermal degradation

10mL of stock solutionof standardwas placed in heating compartment at 105°C/75% RH for 24 hrs. At each 6hr of interval 1ml of the above solutions was collected and diluted to attain concentration of 4µg/mL and 80µg/mL for EZM in and BPA respectively. The resultant solution was examined to find out the extent of degradation occurred in the EZM and BPA.

Neutral degradation or hydrolysis

Equal portions of stock solution of standard and water (Milli-Q) were uniformly mixed and reflux for 2hr at 70^0C and cool the solution for a while. 1ml of the above solutions was collected and diluted to attain concentration of 4µg/mL and 80µg/mL for EZM and BPA respectively.

Assay of marketed tablets

The contemporary method was practiced to determine the % purity of the commercial tablets where, injecting successive injections of standard and sample preparations containing the same concentrations, The % purity of each drug was determined using the peak area responses of BPA and EZM in both solutions.

Results and Discussion

Optimized method conditions

A method with Phenyl XBD (100 x 2.1mm, 1.7µm) column, mobile or solvent phase of 0.1% v/v TFA in water and ACN in 60:40 v/v pumped with a flow of 0.4mL/min and a wavelength of 236nm were competently separate the BPA and EZM with excellent resolution and system suitability and shorter RT about 0.43min and 0.86 min for BPA and EZM respectively (Figure-2).

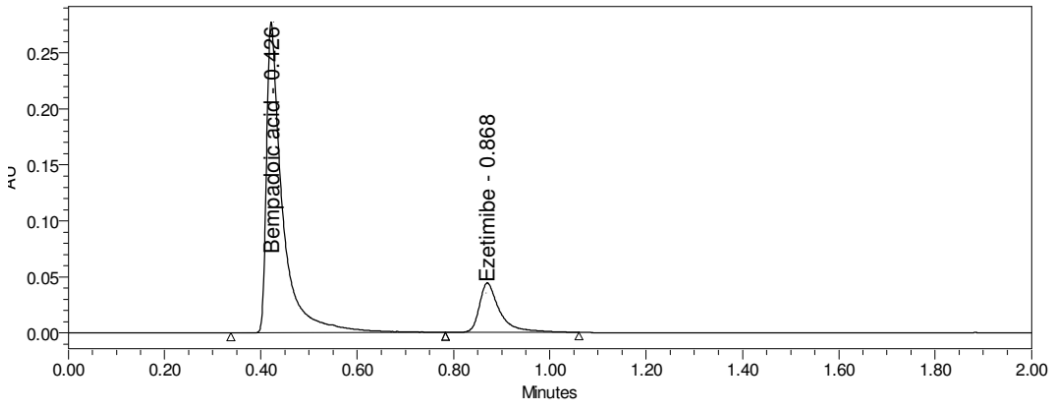


Figure 2. Optimized method chromatogram

Method validation
System suitability

The analytical statistics of the acquired from the 6 replicated injections of same standard preparation determined that almost all parameters including % RSD, T, R, and N would be within the ICH approved limits[17,18]. Table-1 summarizes the acquired findings and acceptability limits for system suitability parameters.

Table 1
System suitability results of standard solution (BPA (80 µg/mL) and EZM (4 µg/mL))

Drug name	Parameter	RT (min)	Peak area	Plate count	Tailing Factor	Resolution
BPA	Mean (n=6)	0.422	723835.2	3027	1.52	
	SD	0.0005	2571.1	14.48	0.03	-
	%RSD	0.12	0.35	0.48	1.94	-
EZM	Mean (n=6)	0.87	146678	2444.6	1.68	6.88
	SD	0.0009	635.0	29.4	0.028	0.07
	%RSD	0.102	0.43	1.20	1.66	1.09
Acceptance criteria: % RSD: ≤ 2, Tailing factor: ≤ 2, Plate count: > 2000 and Resolution: > 2						

Linearity

Mean (n=3) R^2 values derived by data analysis for a series of concentrations stated for the BPA (20-120µg/mL) and EZM (1-6µg/mL) were 0.999 and 0.999 correspondingly, illustrating the linearity of the procedure with significant results (Figure-3).

% Level	Bempedoic acid		Ezetimibe	
	Concentration (µg/mL)	Peak area	Concentration (µg/mL	Peak area
25	20	185188	1	39058
50	40	379746	2	76938.33
75	60	553820	3	118318.7
100	80	741619.3	4	150584.3
125	100	925328.7	5	185879
150	120	1093755	6	223703.3

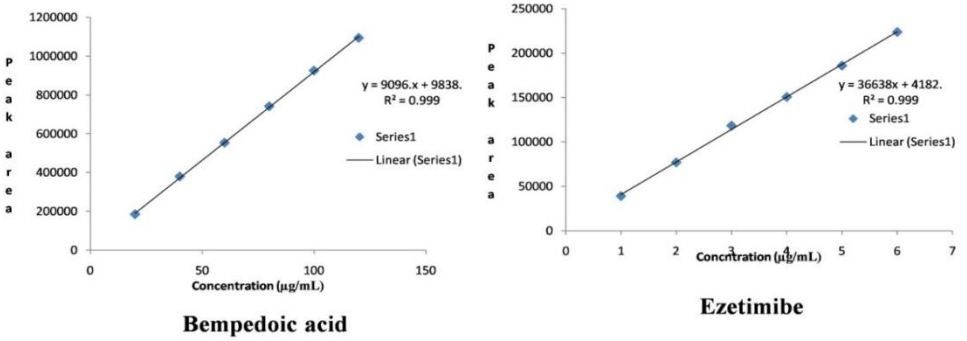


Figure 3. Linearity results of BPA and EZM

Sensitivity

The LOD and LOQ concentrations were assessed to be 0.41µg/mL and 1.23µg/mL for BPA and 0.02 µg/mL and 0.07µg/mL for EZM. Those values depict the sensitivity of the method as compared with already existed UPLC and HPLC procedures.

Specificity

The blank, degradation products, and placebo did not interact with the RT of BPA and EZM. These findings express that the approach has a high specificity for estimating BPA and EZM in both tablet and bulk forms (Figure-5).

Precision

In several injections of BPA and EZM, the % RSD of the peak area values of standard preparation (system precision) and assay of sample (method precision) was measured to be ≤ 2 (Table-2), which strongly indicates the methods precision.

Table 2
Precision results of 100% level standard solution

Precision	Parameter	BPA	EZM
		Peak area	% Assay
System	Mean (n=6)	735124.3	146704.8

precision	SD	2597.6	876.5034
	%RSD	0.35	0.59746
Method precision	Mean(n=6)	100.1	100.54
	SD	0.471	0.55
	%RSD	0.47	0.54

Accuracy

The average % recovery of the BPA and EZM in spiked solutions of various levels of standard solution was 100.4%-108% and 99.2% to 99.6% respectively (Table-3), indicating that the method was extremely accurate and in adherence with ICH standards.

Table 3
Percentage recovery studies of BPA and EZM in spiked solutions

Drug	% Level	Amount added (µg/mL)	Amount found (µg/mL)	Average % Recovery (n=3)	Limit
BPA	50	40	40.2	100.5	100±2%
	100	80	80.64	100.8	
	150	120	120.48	100.4	
EZM	50	2	1.99	99.6	
	100	4	3.968	99.2	
	150	6	5.97	99.6	

Robustness

Slight variations with intention were done for flow rate, temperature, and mobile (organic) phase ratio, did not confirm considerable deflections in parameters to be considered while verifying the system suitability (Table- 4), which notably represents the methods robustness.

Table 4
Robustness results of 100% standard solution at different conditions

Peak area	Flow rate (0.4±0.1 mL/min)		Mobile phase (Organic phase) (40± 1 mL)		Temperature (30 ±5^{0}C)	
	Plus	Minus	Plus	Minus	Plus	Minus
Mean (n=6)	164708.2	137951.3	150924.2	149405.7	147244.7	146805.8
SD	2849.49	856.92	1642.69	1553.08	1076.38	1560.52
% RSD	1.73	0.62	1.09	1.04	0.73	1.06

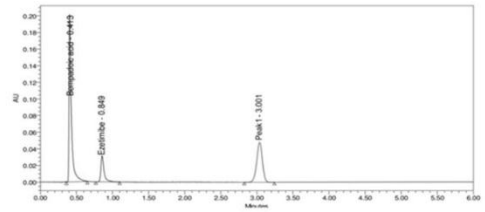
Stability indicating studies

In the majority of instances, 5 to 20 % degradation of the drug is deemed acceptable for stability demonstrating procedures[19-21]. The peak areas values

noticed in chromatograms of fresh solution had been compared with degradation solution to analyze the % degradation of BPA and EZM. The recorded chromatograms and computed results were represented in Table-5 and Figure-4. It was noticed that the purity threshold was greater than purity angle of all the produced peaks revealing the purity of drug substances and degradantsis indicating the stability indicating feature of the stated method.At given acidic pH conditions,both drugs were highly degraded indicating that BPA and EZM are highly sensitive to acidic environments. Based on obtained results it was observed that EZM was easily prone to oxidation as compared with BPA and both the analytes were highly stable at neutral conditions.

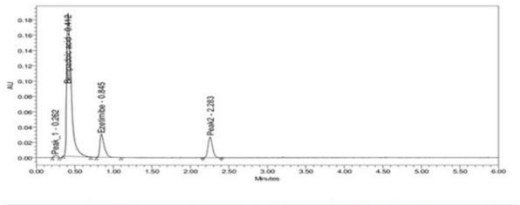
Table 5
%Degradation of BPA and EZM at various forced conditions

Kind of degradation	Degradation (%)	
	BPA	EZM
Acid degradation	17.5	12.0
Alkali degradation	9.0	4.4
peroxide degradation	3.2	11.9
Photo degradation	2.4	2.7
thermal degradation	1.01	0.9
Neutral Degradation	1.9	1.74



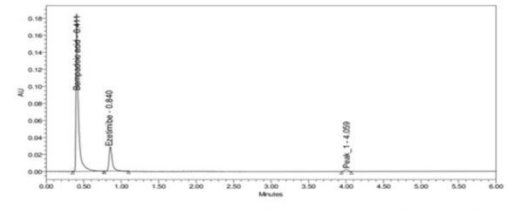
Peak Name	RT	Area	Purity1 Angle	Purity1 Threshold	USP Plate Count	USP Tailing	USP Resolution
Bempadoic acid	0.413	597462	1.52	1.96	3036	1.5	-
Ezetimibe	0.849	129231	0.69	1.38	2403	1.7	6.6
Peak1	3.001	111547	0.73	1.08	1112	1.3	9.91

Acid degradation



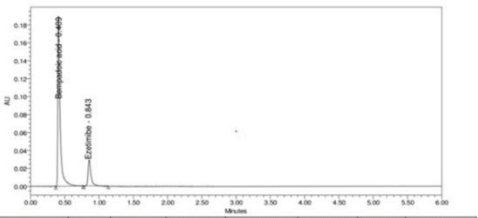
Peak Name	RT	Area	Purity1 Angle	Purity1 Threshold	USP Plate Count	USP Tailing	USP Resolution
Peak1	0.262	4540	0.65	1.01	562	2.3	
Bempadoic acid	0.413	658506	1.49	1.91	3027	1.4	2.4
Ezetimibe	0.849	140239	0.65	1.41	2413	1.6	6.45
Peak2	3.001	102450	0.73	1.28	1361	1.2	8.73

Base degradation



Peak Name	RT	Area	Purity1 Angle	Purity1 Threshold	USP Plate Count	USP Tailing	USP Resolution
Bempadoic acid	0.411	706781	1.57	2.01	3062	1.4	-
Ezetimibe	0.840	142692	0.91	1.37	2451	1.6	6.4
Peak1	4.059	3069	0.47	0.79	3456	1.5	13.8

Oxidative degradation



Peak Name	RT	Area	Purity1 Angle	Purity1 Threshold	USP Plate Count	USP Tailing	USP Resolution
Bempadoic acid	0.409	717033	1.83	2.24	3064	1.5	-
Ezetimibe	0.843	145261	0.94	1.71	2542	1.7	6.7

Photo degradation

Figure 4. Forced degradation data of the developed method

Assay of marketed tablets

The purity (%) of the BPA and EZM in marketed tablet were assessed as 100%±2 (Table-6), which assures that the % assay results of BPA and EZM were in obedience with the confines of the ICH.

Table 6
Assay results of marketed formulation

Drug	Peak Area	Label claim (mg)	Average weight of tablet	%Assay±SD
BPA	721378	180	523.5mg	98.6±0.32
EZM	145618	10		98.7±0.49

As of today only two HPLC procedures and UPLCmethod have been reported for the combined tablet of BPA and EZM. In reported methods, UPLC method has drawback of longer RT of 3.5min for EZM. Longer RT with less sensitivity was observed for the both drugs in HPLC procedures.The solvent system (mobile phase) of the reported method was complex for some extent, made of complex mixture of Methanol: ACN: Water. In the one of the reported work did not have stability indicating future. To get better from drawbacks and evadeambiguity in the available methods research was further proceeded to make an inexpensive, perceptive and easy RP-UPLC method. In the stated method elution of BPA and EZM were occurred at 0.43 min and 0.87 min correspondingly demonstrating the less RT. A ratio of 60:40 v/v of 0.1% TFA and Acetonitrile used as solvent system. The currently projected technique was cost-effective compared to already reported methods as it has RT and simple mobile phase. A quick investigation of improved number samples can be possible within the stipulated time.

Conclusion

A simple as well as economically effective RP-UPLC approach with reliable accuracy, high sensitivity and precise was developed to analyze BPA and EZM concurrently in blended mixture and their marketed combined tablets. Exploration of BPA and EZM under various forced conditions makes us very confident regarding the stability indicating nature of the stated approach. The approach was to adequately separate BPA, EZM and feasible degradants created by both respective agents with good resolution. Hence, the proposed approach has significant credit in the pharmaceutical sector.

List of Abbreviations

BPA: Bempedoic acid
EZM: Ezetimibe
RP- UPLC: Reverse Phase Ultra Performance Liquid Chromatography
LOD: Limit of Detection
LOQ: Limit of Quantification
ICH: International Conference on Harmonization
SD: Standard Deviation
RSD: Relative Standard Deviation

Conflict of Interest

The authors declare that there is no conflict of interest

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