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RELATED SUBSTANCES BY HPLC METHOD FOR THE DETECTION AND EVALUATION OF IMPURITIES IN EZETIMIBE DRUG MATERIAL

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ABSTRACT: The gradient HPLC method was developed to detect and quantify four related substances (FIP, FHO-2, STG-01, and desfluoro) in ezetimibe drug material. The efficient separation was carried out on Water X-Select CSH C18 column (4.6 mm × 100 mm, 2.5 µm). The impurities were separated in gradient mode of elution with 0.1% trifluoroacetic acid in water (mobile phase A) and 0.1% trifluoroacetic acid in acetonitrile (mobile phase B) at a flow rate of 1.0 ml /min. The effluents were detected at 254 nm. The method has been validated in compliance with the regulatory standards suggested by the International Conference on Harmonization. The parameters validated included precision, linearity, detection limit, quantification limit, specificity, accuracy, and robustness. The method showed good linearity from 0.03 µg/ml to 1.5 µg/ml for FIP, FHO-2, STG-01, and desfluoro. The developed method was applied to determine the studied impurities in three different batches of ezetimibe drug material. The method proposed in this work could be employed in quality control of ezetimibe bulk drug.

INTRODUCTION: Ezetimibe is a lipid-reducing agent which prevents the absorption of cholesterol and associated phytosterol in intestine [1, 2]. Ezetimibe is approved as an adjunctive nutritional treatment to reduce cholesterol levels in mixed hyperlipidemia, primary hyperlipidemia sitosterol-emia, and familial hypercholesterolemia [3, 4]. Ezetimibe shows its cholesterol-lowering effect inthe blood without disturbing the absorption of other nutrients and fat-soluble vitamins in the intestine.

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Chemically, ezetimibe is referred as (3 R, 4 S) – 1 - (4 - fluorophenyl) - 3 - [(3 S) - 3 - (4 -fluorophenyl) - 3 - hydroxypropyl] - 4 - (4 -hydroxyphenyl) azetidin - 2 - one **Fig. 1A**. Regulatory bodies such as the U.S. Food and Drug Administration (FDA) and International Conference on Harmonization (ICH) emphasize the requirements for purity and impurity identification in active pharmaceutical ingredient and formulation product [5-7].

Impurities in pharmaceutical products are from reagents, catalysts, heavy metals, catalysts, charcoal, filter aids, degraded end products obtained during or after bulk drug production, enantiomeric impurity, *etc.* [8] As indicated by ICH Impurity Standards for new drug or drug products, the detection of impurities below 0.1% is not considered necessary unless impurities are predicted to be extremely potent or toxic. The

overall acceptable daily dose level to be considered is 0.1%. A number of reports on the identification, development and characterization of ezetimibe-related impurities and their degradants were published [9-15]. Four process-related impurities 4-((4-fluorophenylimino)methyl)phenol (impurity-FIP), 3 - [5 - (4 - fluorophenyl) - 1, 5dioxaopentyl)] - 4 – phenyl (4S) - 2 - oxolidinone (impurity-FHO-2), 3 R, 4 S) – 3 - ((S) - 3 - (4 - fluorophenyl) - 3 – hydroxypropyl) - 4 - (4 - hydroxyphenyl) - 1 - phenylazetidin - 2 - one (impurity-desfluoro) and S) - 3- ((S) - 5 - (4 - fluorophenyl) - 5 - hydroxypentanoyl) - 4 - phenyloxazolidin-2-one (impurity - STG - 01) were identified during the manufacturing of ezetimibe drug substance. The structures of these impurities are given in **Fig. 1B, 1C, 1D,** and **1E**.

No method has been published for quantification of the impurities FIP, FHO-2, desfluoro, and STG-01 in ezetimibe drug material. In this report, a sensitive and reliable gradient HPLC method has been developed and validated to monitor and quantify FIP, FHO-2, desfluoro, and STG-01 simultaneously in the ezetimibe drug material.

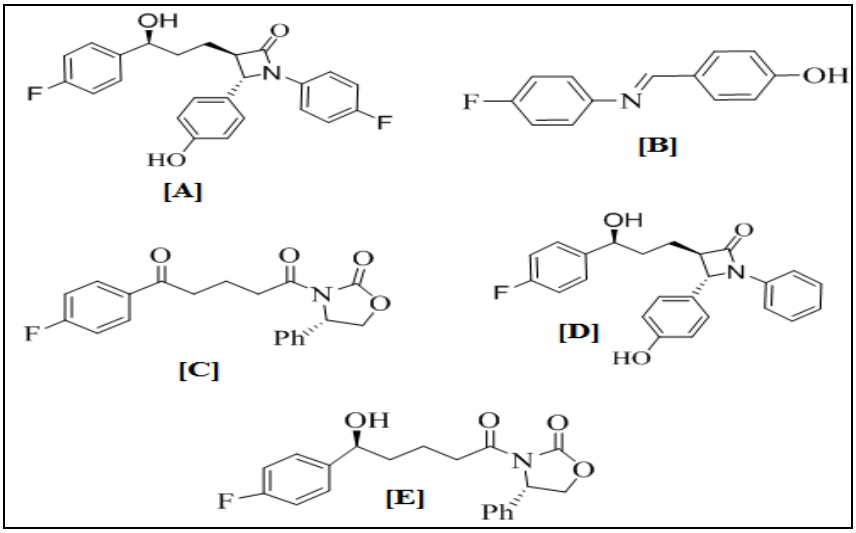

FIG. 1: STRUCTURE OF [A] EZETIMIBE [B] FIP [C] FHO-2 [D] DESFLUORO [E] STG - 01

MATERIALS AND METHODS:

Impurities, Drug and Chemicals and Solvents: GVK Biosciences Private Limited (Hyderabad, India) provided the gift reference samples of FIP, FHO-2, desfluoro, and STG-01 and ezetimibe. Trifluoro acetic acid and acetonitrile were purchased from Merck (Mumbai, India). Milli Q water produced from the Milli Qpurification system was used.

Apparatus and Conditions for Chromato-graphy: Waters Acquity Arc HPLC System and Water X-Select CSH C18 column (4.6 mm i.d. × 100 mm, 2.5 µm) were used in this current investigation. Chromatographic separation of FIP, FHO-2, desfluoro, and STG-01 was carried out at 40 ^{o}C temperature. The impurities and ezetimibe were separated in gradient mode of elution with 0.1% trifluoroacetic acid in water (mobile phase A) and 0.1% trifluoroacetic acid in acetonitrile (mobile phase B) at a flow rate of 1.0 ml /min with the sample injection volume of 10 µl. The effluents were detected at 254 nm wavelength. The mobile phase A and B gradient programme was set as shown in **Table 1**.

TABLE 1: GRADIENT PROGRAMME FOLLOWED IN THIS INVESTIGATION

Time (min)	Percentage of mobile phase (% volume)	
	A	B
0.01	80	20
25.0	20	80
30.0	20	80
30.1	80	20
35.0	80	20

Standard Solutions: The primary stock solution (1 mg/ml) was prepared in a 20 ml volumetric flask by accurately weighing 20 mg each of FIP, FHO-2, STG-01, and desfluoro, dissolved in 10 ml diluent (acetonitrile) and diluted to volume using dilent. The secondary stock solution (20 µg/ml) was prepared by diluting 2 ml of primary stock to 10 ml with diluent.

Procedure for Calibration Curves: The secondary stock solution (20 µ/ml) was diluting appropriately with diluent to get calibration solutions with concentrations ranging from 0.03 µ/ml to 0.15 µ/ml for FIP, FHO-2, STG-01, and desfluoro.

For each concentration, 10.0 µl injections are made and chromatographer under the above-mentioned conditions. In order to produce the calibration graph, the peak area obtained at each concentration was plotted against the corresponding concentration. The data from peak area and concentration were then applied to determine the regression equation.

Procedure for Monitoring Impurities in Test Sample (Ezetimibe Drug Material): Accurately weighed 50 mg of the test sample was transferred to a volumetric flask of 50 ml capacity, dissolved in 10 ml of diluent and diluted with diluent to mark. 10.0 µl injections are made and chromatographed under the above-mentioned conditions. The peak areas of FIP, FHO-2, STG-01, and desfluoro obtained were then used to quantify the content of impurities in the ezetimibe drug-using corresponding regression equation or calibration graph.

RESULTS AND DISCUSSION:

Method Optimization: The HPLC method was developed with an aim to make available a specific procedure for the simultaneous analysis of FIP, FHO-2, STG-01, and desfluoro impurities in ezetimibe drug material. A different range of analytical columns, isocratic, and gradient mobile phase systems with different flow rates have been tried in order to find the best HPLC conditions for the separation and analysis of examined impurities. Good separation was achieved using a Water X-Select CSH C18 column (4.6 mm × 100 mm, 2.5 µm). Gradient elution mode provided better results than isocratic elution mode. Therefore, gradient elution was chosen. The mobile phase composition was 0.1% trifluoroacetic acid in water (mobile phase A) and 0.1% trifluoroacetic acid in acetonitrile (mobile phase B) at a flow rate of 1.0 ml /min. The FIP, FHO-2, desfluoro, STG-01 were detected and quantified at 254 nm where the sensitivity is good **Fig. 2**.

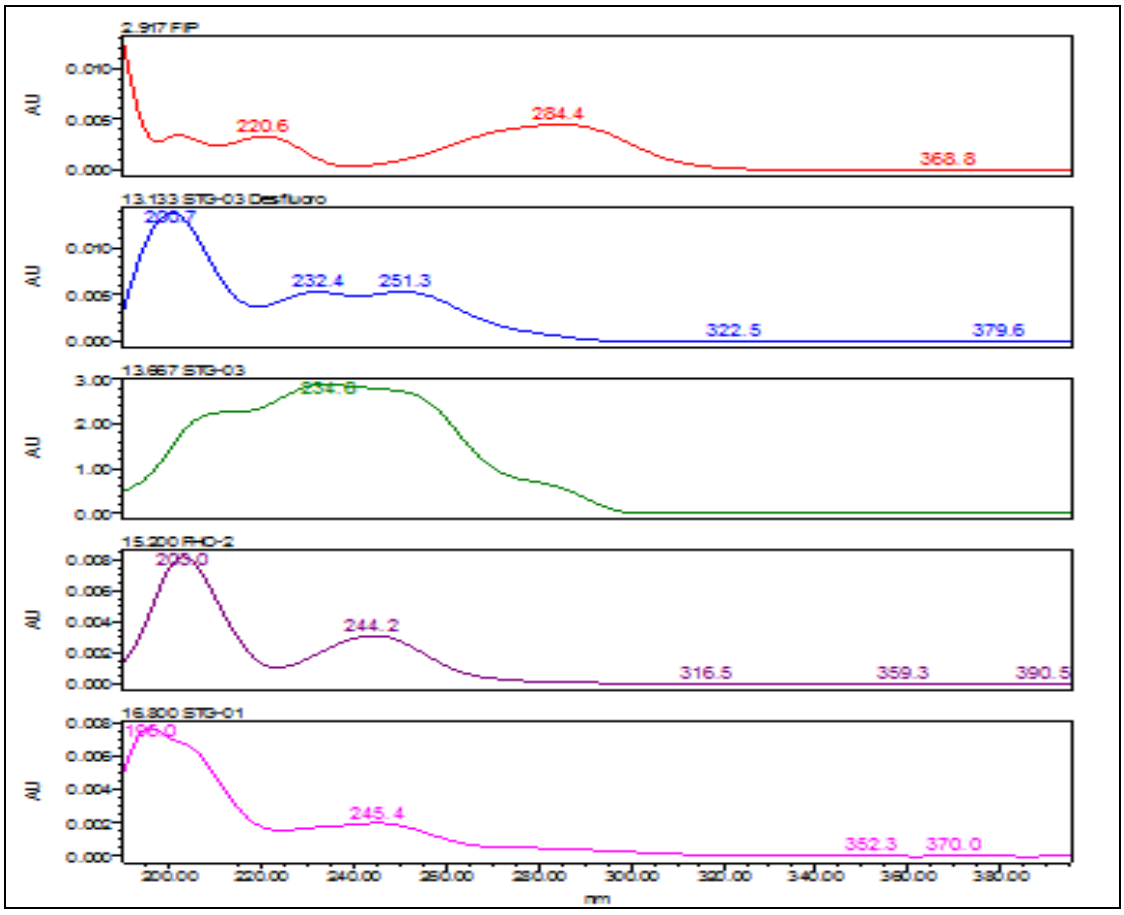

FIG. 2: UV SPECTRUM OF EZETIMIBE AND RELATED SUBSTANCES

The FIP, desfluoro, ezetimibe, FHO-2, STG-01, and their corresponding peaks were separated at the Rt 2.578 min, 12.51 min, 13.032 min, 14.446 min, and 16.163 min, respectively under the mentioned HPLC conditions optimized **Fig. 3**.

Validation: The optimized procedure was validated in agreement with ICH guidelines [16].

Specificity: The specificity was evaluated by injecting blank diluent (acetonitrile), standard solution (FIP-0.1 µg/ml, FHO-2 - 0.1 µg/ml, desfluoro - 0.1 µg/ml, STG-01- 0.1 µg/ml) and ezetimibe drug sample solution spiked with impurities (FIP-0.1 µg/ml, FHO-2 - 0.1 µg/ml, desfluoro - 0.1 µg/ml, STG-01- 0.1 µg/ml) and recorded the chromatograms **Fig. 4A, 4B** and **4C**. Interferences by acetonitrile and ezetimibe were not observed at the Rt of FIP, FHO-2, STG-01, and desfluoro impurities and thus proved the specificity of the method.

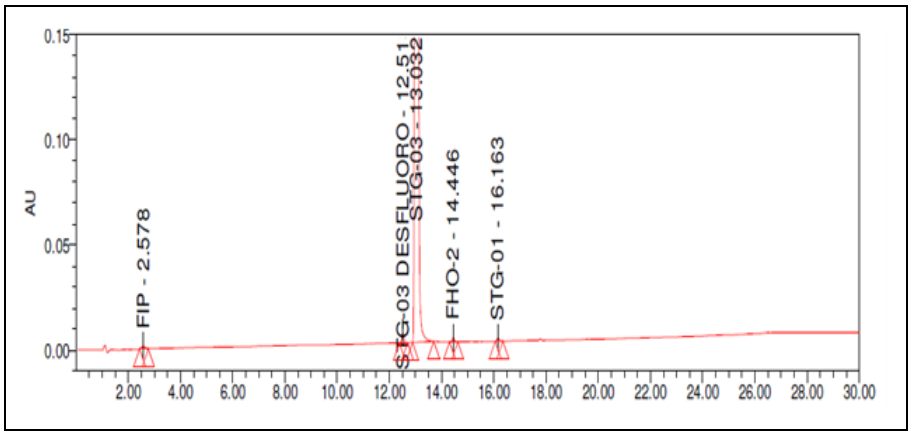

FIG. 3: CHROMATOGRAM OF FIP, DESFLUORO, EZETIMIBE, FHO-2, STG-01 OBTAINED AFTER METHOD OPTIMIZATION

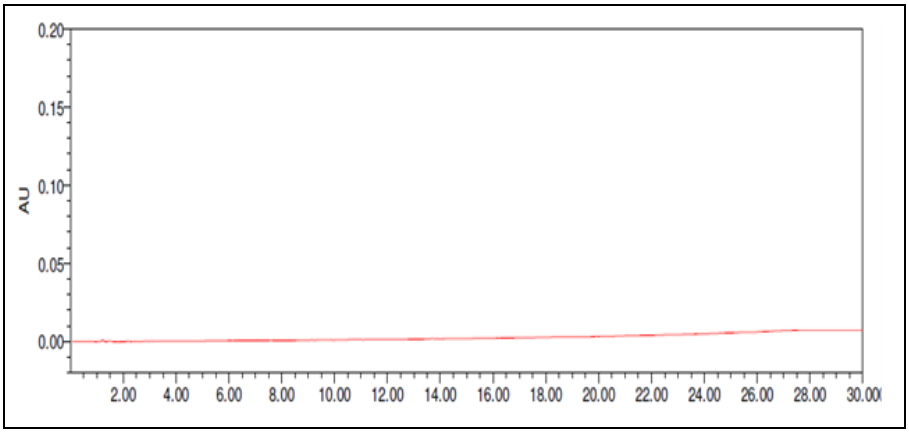

FIG. 4A: CHROMATOGRAM OF DILUENT BLANK

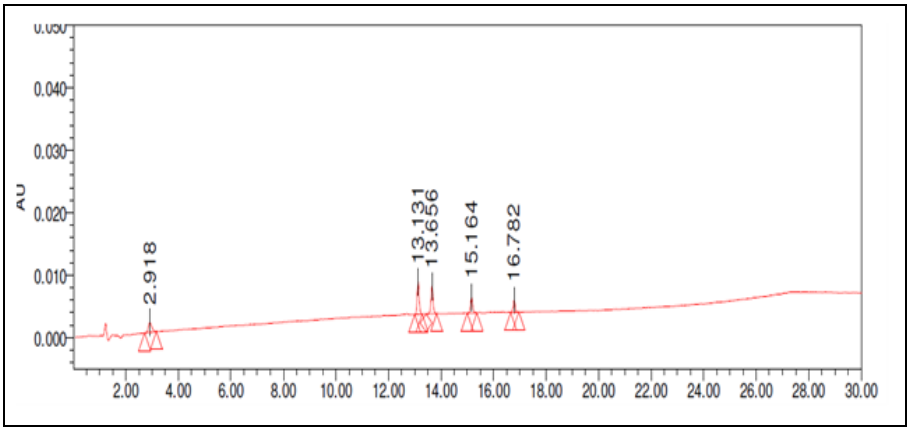

FIG. 4B: CHROMATOGRAM OF IMPURITIES STANDARD SOLUTION (FIP - 2.918 MIN, DESFLUORO - 13.131 MIN, EZETIMIBE - 13.656 MIN, FHO -2- 15.164 MIN, STG-01- 16.782 MIN)

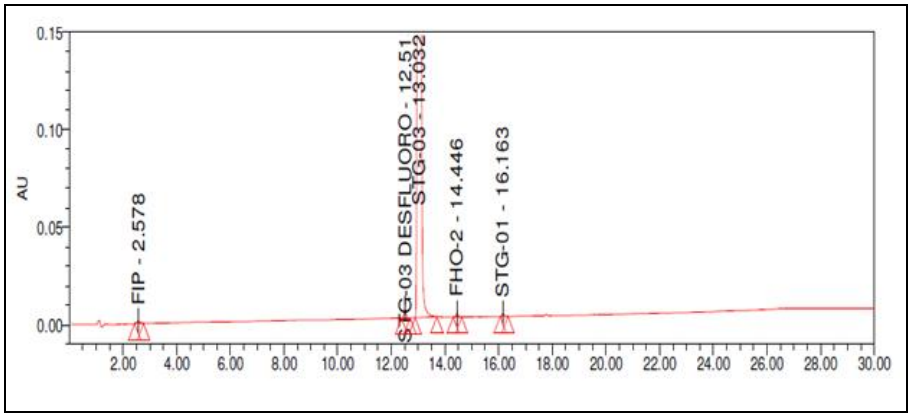

FIG. 4C: CHROMATOGRAM OF EZETIMIBE (13.032 MIN) DRUG SAMPLE SPIKED WITH IMPURITIES (FIP – 2.578 MIN, DESFLUORO – 12.51 MIN, FHO -2- 14.446 MIN, STG-01- 16.163 MIN)

Specificity was further assessed by determining the peak purity of ezetimibe, FIP, FHO-2, STG-01, and desfluoro. **Table 2** contains a summary of peak purity results. The low values for the purity angle of ezetimibe peak and impurities peaks than purity threshold values in standard solution and ezetimibe drug sample with impurities indicated the method specificity.

Limit of Detection and Limit of Quantification: The limit of detection (LD) and limit of quantification (LQ) were measured as the concentrations of impurities with a signal-to-noise ratio of ≥3 and ≥10, respectively.

Table 3 contains the LD and LQ results of FIP, FHO-2, STG-01, and desfluoro. LQ values of FIP, FHO-2, STG-01, and desfluoro were further confirmed through analysis of standard solution at LQ concentration level six times.

The relative standard deviation values for the peak areas of impurities were checked in **Table 4**. The relative standard deviation for the peak areas of FIP, FHO-2, STG-01, and desfluoro at LQ concentration was less than 10.0% indicated the preciseness of the method at LQ concentration level.

The chromatograms at LQ and LD concentration levels are shown in **Fig. 5A** and **5B**.

Linearity: Linearity was assessed from LQ to 150% of the specification level with respect to test concentration (0.1 µg/ml). The method showed good linearity from 0.03 µg/ml to 1.5 µg/ml for FIP, FHO-2, STG-01, and desfluoro. The details of the linearity study are shown in **Table 5**. The correlation coefficient values for FIP, FHO-2, STG-01, and desfluoro are greater than 0.99, indicating the good linearity of the proposed method.

TABLE 2: PEAK PURITY DATA FOR EZETIMIBE AND IMPURITIES STUDIED

Peak Purity in Standard Solution			
Name	**Purity angle**	**Purity threshold**	**Peak purity**
FIP	1.899	2.434	Pass
Desfluoro	2.465	3.254	
Ezetimibe	1.711	2.917	
FHO-2	4.721	7.047	
STG-01	6.118	9.081	
Peak Purity in Ezetimibe Drug Sample Spiked with Impurities			
FIP	1.601	2.267	Pass
Desfluoro	1.543	2.418	
Ezetimibe	1.665	5.158	
FHO-2	3.344	4.842	
STG-01	5.110	6.775	

TABLE 3: LD AND LQ DATA FOR IMPURITIES STUDIED

Name	Level	Conc. (mg/ml)	Percent W.r.t Test Conc.	S/N	Area	% Area
FIP	LQ	0.0003	0.03	14	4093	13.46
	LD	0.0001	0.01	4	1799	16.29
Desfluoro	LQ	0.0003	0.03	50	9008	29.60
	LD	0.0001	0.01	14	3183	28.82
FHO-2	LQ	0.0003	0.03	24	4566	15.00
	LD	0.0001	0.01	6	1491	13.50
STG-01	LQ	0.0003	0.03	18	3374	11.08
	LD	0.0001	0.01	5	1092	9.89

Concentration; W.r.t - with respect to; S/N - signal to noise ratio; LD - limit of detection; LQ - limit of quantification

TABLE 4: CONFIRMATION AT LIMIT OF QUALIFICATION LEVEL

Preparation	Peak areas of			
	FIP	Desfluoro	FHO-2	STG-01
1	4096	9008	4566	3374
2	4751	9388	4752	3142
3	4138	8611	4852	3303
4	4438	9633	4721	3402
5	4392	9006	4586	3053
6	4549	9476	4873	3229
Avg	4394	9187	4725	3250.5
Std Dev	248.094	379.319	129.135	135.795
RSD	5.646	4.128	2.733	4.177

Avg - average; STD Dev - standard deviation; RSD - relative standard deviation

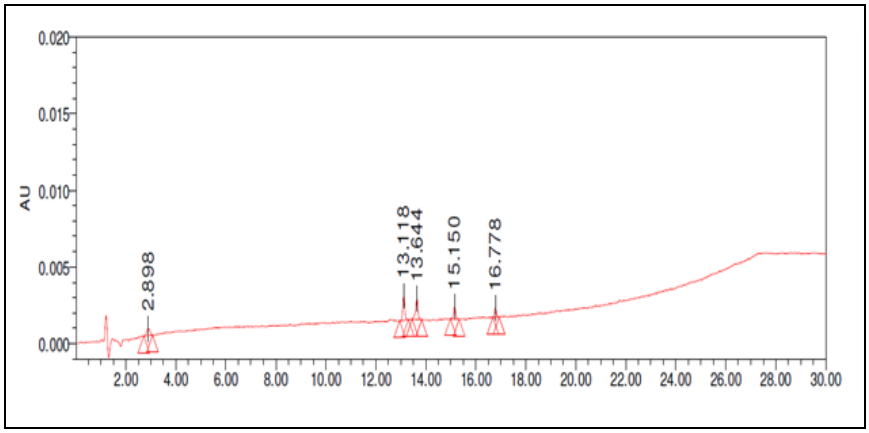

FIG. 5A: CHROMATOGRAMAT LQ CONCENTRATION LEVEL (FIP - 2.898 MIN, DESFLUORO - 13.118 MIN, EZETIMIBE - 13.644 MIN, FHO -2- 15.150 MIN, STG-01- 16.778 MIN)

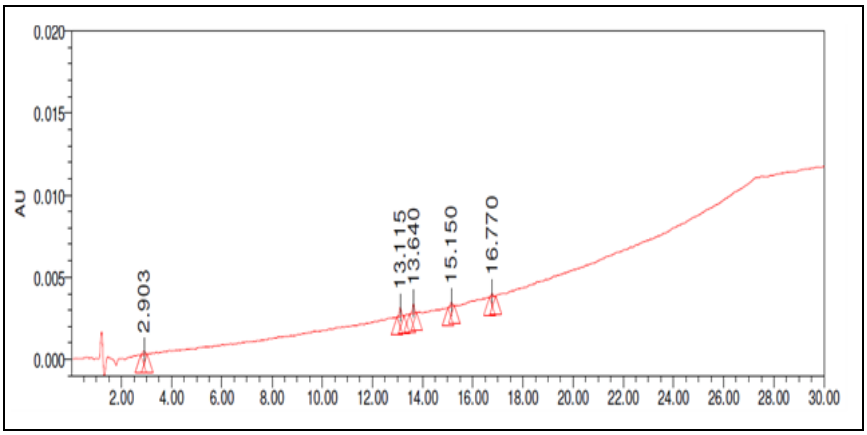

FIG. 5B: CHROMATOGRAMAT LQ CONCENTRATION LEVEL (FIP - 2.903 MIN, DESFLUORO - 13.115 MIN, EZETIMIBE - 13.640 MIN, FHO -2- 15.150 MIN, STG-01- 16.770 MIN)

TABLE 5: LINEARITY AND REGRESSION DATA FOR IMPURITIES STUDIED

Specification level (%)	FIP	DESFLUORO	FHO-2	STG-01	Concentration (0.1 µg/ml)
	Peak areas				
LQ	4096	9008	4566	3374	0.03
50	7070	14501	7997	5323	0.05
80	11123	22007	11202	8135	0.075
100	14018	28261	15197	10250	0.10
120	17014	34655	17389	12610	0.12
150	21742	43006	22401	15773	0.15
RRF	0.63	1.25	0.64	0.71	
Correlation coefficient	0.9991	0.9997	0.9988	0.9994	
Slope	144918.4	283413.2666	145452.816	102974.4681	
Y-intercept	-169.86	441.0058	398.2119	233.9007	

RRF - relative retention factor

Precision: The precision of the method has been established by the analysis of six replicates of the test sample (ezetimibe drug material) spiked with FIP, FHO-2, STG-01, and desfluoro at 0.1 µg/ml concentration level. The percentage relative standard deviation values for peak areas of FIP, FHO-2, STG-01, and desfluoro were calculated in **Table 6**. Relative standard deviation was less than 10.0%, indicated the preciseness of the method.

Accuracy: The accuracy was determined by analyzing test sample (ezetimibe drug material) spiked with studied impurities at LQ level, 50%, 100%, 150% of specification level concentration (0.1 µg/ml) in three replicates. As response difference was observed, the relative retention factor values for FIP, FHO-2, STG-01, and desfluoro was established and applied in recovery calculation. The recovery percentage of FIP, FHO-2, STG-01 and desfluoro obtained at each level was given in **Table 7**. The percentage recoveries for studied impurities at each level ranged from 70% to 130% (approved limit). The percentage recoveries indicated the method's accuracy. **Robustness:** In order to test the effect of slight and deliberate change in column temperature and flow rate on the analysis, a robustness study conducted on the test sample (ezetimibe drug material) spiked with FIP, FHO-2, STG-01 and desfluoro at a concentration of 0.1 µg/ml. The percent difference in relative retention time of FIP, FHO-2, STG-01, and desfluoro were determined **Table 8**. The difference value was less than 15% (acceptable limit). This study showed that the method is reasonably insensitive to variations in the conditions studied.

Batch analysis: The method developed was applied in three different batches of ezetimibe drug material to evaluate the content of FIP, FHO-2, STG-01, and desfluoro. The impurities were below the detection limit (0.03 µg/ml) in all three successive plant batches.

TABLE 6: PRECISION DATA FOR IMPURITIES STUDIED

Preparation	Peak areas of			
	FIP	DESFLUORO	FHO-2	STG-01
1	12852	30432	12961	8861
2	12342	30694	13371	9230
3	12106	30534	12281	9122
4	12453	29716	12745	9260
5	12792	29301	13045	9000
6	12427	30163	13428	8752
Avg	12495.33	30140	12972	9037.5
Std Dev	281.700	535.096	424.600	203.848
RSD	2.254	1.775	3.274	2.255

Avg - average; Std Dev - standard deviation; RSD – relative standard deviation

TABLE 7: ACCURACY DATA FOR IMPURITIES STUDIED

Level spiked (%)	Impurity	Corrected Amount Obtained (µg/ml)	Amount Added (µg/ml)	% Recovery (After RRF Value Correction)
LQ	FIP	0.02	0.03	105.8
	Desfluoro	0.07	0.03	106.7
	FHO-2	0.02	0.03	105.0
	STG-01	0.02	0.03	94.2
50	FIP	0.03	0.05	94.8
	Desfluoro	0.09	0.05	96.4
	FHO-2	0.04	0.05	126.0
	STG-01	0.03	0.05	84.8
100	FIP	0.07	0.10	110.6
	Desfluoro	0.19	0.10	128.5
	FHO-2	0.07	0.10	110.2
	STG-01	0.05	0.10	70.6
150	FIP	0.1	0.15	105.4
	Desfluoro	0.27	0.15	128.5
	FHO-2	0.1	0.15	105.0
	STG-01	0.08	0.15	75.3

RRF – relative retention after

TABLE 8: ROBUSTNESS DATA FOR IMPURITIES STUDIED

Condition	Impurity	RRT in Optimized Procedure	RRT in Altered Condition	Difference(%)
High flow rate - 1.1 ml/min	FIP	0.21	0.20	-4.8
	Desfluoro	0.96	0.96	0
	FHO-2	1.11	1.11	0
	STG-01	1.23	1.24	0.8
Low flow rate - 0.9 ml/min	FIP	0.21	0.24	14.3
	Desfluoro	0.96	0.96	0
	FHO-2	1.11	1.11	0
	STG-01	1.23	1.22	-0.81
Less column temperature – 35^{o}C	FIP	0.21	0.22	4.8
	Desfluoro	0.96	0.96	0
	FHO-2	1.11	1.12	0.9
	STG-01	1.23	1.23	0
High column temperature – 45^{o}C	FIP	0.21	0.21	0
	Desfluoro	0.96	0.96	0
	FHO-2	1.11	1.11	0
	STG-01	1.23	1.23	0

RRT - relative retention time

TABLE 9: BATCH ANALYSIS OF EZETIMIBE FOR FIP, FHO-2, STG-01 AND DESFLUORO

Batch details	FIP (µg/ml)	FHO-2 (µg/ml)	Desfluoro (µg/ml)	STG-01 (µg/ml)
ETM/A900/STG-03/06/129	≤0.012	≤0.012	≤0.012	≤0.012
ETM/A894/STG-3/06/173	≤0.012	≤0.012	≤0.012	≤0.012
ETM/A900/STG-03/08/161	≤0.012	≤0.012	≤0.012	≤0.012

CONCLUSION: The gradient HPLC method was developed to detect and evaluate FIP, FHO-2, STG-01, and desfluoro in ezetimibe drug material. The estimation of FIP, FHO-2, STG-01, and desfluoro in ezetimibe was found to be specific, precise, robust, and accurate. Applying the method to three successive batches of ezetimibe showed that these impurities were well below the specification limit (0.03%). Hence, these impurities (FIP, FHO-2, STG-01, and desfluoro) are omitted from the regular analysis of ezetimibe.

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CONFLICTS OF INTEREST: Nil

REFERENCES:

1. Omeed S and Raja T: Ezetimibe. Stat Pearls Internet, Treasure Island (FL) Stat Pearls Publishing 2019. Available at: https:// www. ncbi.nlm.nih. gov/books/ NBK532879/.
2. Cannon CP, Blazing MA, Giugliano RP, McCagg A, White JA, Theroux P, Darius H, Lewis BS, Ophuis TO, Jukema JW, De Ferrari GM, Ruzyllo W, De Lucca P, Im K, Bohula EA, Reist C, Wiviott SD, Tershakovec AM, Musliner TA, Braunwald E, Califf RM and IMPROVE-IT Investigators: Ezetimibe added to statin therapy after acute coronary syndromes. New England Journal of Medicine 2015; 372(25): 2387-97.
3. Hammersley D and Signy M: Ezetimibe: an update on its clinical usefulness in specific patient groups. Therapeutic Advances in Chronic Disease 2017; 8(1): 4-11.
4. NICE (2016) Ezetimibe for treating primary heterozygous-familial and non-familial hypercholesterolaemia. Guideline TA385. Available at: https:// www.nice. org.uk/guidance/ta385/resources/ezetimibe-for-treating-primary – heterozygousfamilial and nonfamilial – hypercholesterolaemia - 82602851386309 (accessed 19 october 2019).
5. Guidance for industry Q3A (R2), Impurities in new drug substances, in: International Conference on Harmonization, 2006.
6. Guidance for industry Q3B (R2), Impurities in new drug products, in: International Conference on Harmonization, 2006.
7. U.S. Department of Health and Human Services, Food and Drug Administration (FDA). Genotoxic and Carcinogenic Impurities in Drug Substances and Products. Rockville, MD, 2008.
8. Pilaniya K, Chandrawanshi HK, Pilaniya U, Manchandani P, Jain P and Singh N: Recent trends in the impurity profile of pharmaceuticals. J of Advanced Pharmaceutical Technology & Research 2010; 1(3): 302-10.
9. Filip K, Bankowski K and Sidoryk K: Physicochemical characterization of ezetimibe and its impurities. Journal of Molecular Structure 2011; 991(1-3): 162–70.
10. Ren Y, Li RJ and Deng Y: First synthesis and characterization of SRR/RSS-ezetimibe. Tetrahedron Letters 2013; 54 (48): 6443-46.
11. Raman B, Sharma BA and Butala R: Structural elucidation of a process-related impurity in ezetimibe by LC/MS/MS and NMR. Journal of PharmaceuticalandBiomedical Analysis 2010; 52 (1): 73-78.
12. Santa Z, Koti J and Szoke K: Structure of the major degradant of ezetimibe. Journal of Pharmaceutical and Biomedical Analysis 2012; 58: 125-29.

13. Guntupalli S, Ray UK and Murali N: Identification, isolation and characterization of process related impurities in ezetimibe. J of Pharm and Biom Anal 2014; 88: 385-90.
14. Ren Y, Duan YJ and Li RJ: First synthesis and characterization of key stereoisomers related to ezetimibe. Chinese Chemical Letters 2014; 25(8): 1157-60.
15. Bellur AE and Karlığa B: Identification, synthesis and characterization of process related desfluoro impurity of ezetimibe and HPLC method validations. Journal of Pharmaceutical Analysis 2015; 5(6): 356-70.
16. ICH Expert Working Group. Validation of Analytical Procedures: Text and Methodology, Q2 (R1), 2005.

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