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A stability-indicating and validated LC method for the quantitative estimation of Elafibranor in bulk drug and dosage forms

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Abstract
Elafibranor is a dual peroxisome proliferator-activated receptor (PPAR)-α/δ agonist known to improve insulin sensitivity, glucose homeostasis, lipid metabolism, and reduce inflammation. This study aimed to evaluate whether elafibranor could induce resolution of nonalcoholic steatohepatitis (NASH) without worsening liver fibrosis. In a randomized controlled trial, patients with NASH were assigned to receive either elafibranor 120 mg/day or placebo. The primary endpoint was the resolution of NASH without fibrosis progression, while secondary endpoints included changes in liver enzymes, lipid profiles, glucose metabolism, and inflammatory markers.
In post hoc analyses, 19% of patients receiving elafibranor achieved NASH resolution without worsening fibrosis, compared to 12% in the placebo group (odds ratio 2.31, 95% CI 1.02–5.24, p = 0.045). Among patients with a NAFLD activity score ≥4, NASH resolution rates were even higher in the elafibranor group (20% vs 11%; modified definition: 19% vs 9%), with odds ratios of 3.16 and 3.52, respectively. Patients who responded to treatment showed a mean reduction in fibrosis stage of 0.65 ± 0.61, whereas nonresponders experienced a mean increase of 0.10 ± 0.98 (p < 0.001). Additionally, elafibranor treatment led to significant improvements in liver function tests, lipid parameters, glucose levels, and systemic inflammatory markers compared to placebo.
The drug was generally well tolerated, with no significant weight gain or cardiac events observed. However, a mild but reversible increase in serum creatinine (~4.31 µmol/L) was noted (p < 0.001). Although elafibranor showed promising effects in resolving NASH without fibrosis progression and improving metabolic parameters, the study did not meet its predefined primary endpoint in the intention-to-treat population.

Keywords: Elafibranor, specificity, robustness, ruggedness and system suitability

Introduction

Quantitative chemical analysis is an important tool that assures the use of crude substances and the intermediates to meet the requisite stipulations [1].
Analytical techniques are generally employed for drug analysis are spectral methods, chromatographic methods, electro analytical techniques, biological method and microbiological methods, physical methods, radioactive methods and other techniques like conventional titrimetric method, gravimetric and polarimetric methods [2].
For qualitative analysis the separated compounds are treated with reagents that could be identified by colour, by their boiling point or melting points, their solubility in a series of solvents, their optical activities or their refractive indices. For quantitative analysis, the amount of analyte was determined by gravimetric or titrimetric measurements [3].
Elafibranor, sold under the brand name Iqirvo, is a medication used for the treatment of primary biliary cholangitis [4].
Elafibranor is a dual PPARα/δ agonist. Elafibranor and its main active metabolite GFT1007 are peroxisome proliferator-activated receptor (PPAR) agonists, both of which activate PPAR-alpha, PPAR-gamma, and PPAR-delta *in vitro*.
In June 2024, the US Food and Drug Administration (FDA) granted accelerated approval to elafibranor [5].

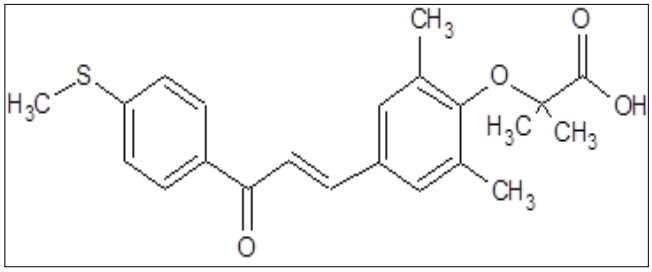

Fig 1: Molecular structure of Elafibranor

Mechanism of action

Peroxisome proliferator-activated receptors (PPARs) are nuclear receptors that regulate a variety of cellular processes, including lipid metabolism and inflammation [6]. Activation of PPARδ enhances fatty acid transport and oxidation, raises HDL cholesterol, and improves glucose homeostasis. Both PPARα and PPARδ also exert anti-inflammatory effects [7].

Literature Review

Few analytical methods are available for Idarubicin, mostly involving HPLC with other drugs [8]. A 2025 study on Elafibranor evaluated forced degradation under ICH conditions and identified novel products under basic and oxidative stress using UHPLC–MS, HRMS, and NMR, emphasizing the need for stability-indicating methods [9]. Research in 2023 showed that lipid-based formulations of Elafibranor (Ela) and Obeticholic Acid (OA) reduced hepatic fibrogenesis and improved lipid composition in hepatic stellate cells, indicating safer and more effective delivery [10].

Another 2023 investigation compared Elafibranor, Lanifibranor, and Seladelpar and revealed distinct PPARα/δ/γ binding and activation profiles, explaining variations in therapeutic outcomes [11]. Clinical findings from 2016 demonstrated that Elafibranor (120 mg) improved NASH resolution, fibrosis, and metabolic markers with good tolerability, despite not achieving all primary endpoints [12]. An experimental 2024 study showed that Elafibranor reduced hepatic steatosis, fibrosis, and inflammation in alcohol-associated liver disease (ALD) through PPARα/δ activation, enhancing autophagy and intestinal barrier integrity [13]. Preclinical work in 2021 using a NASH–HFpEF hamster model found that Elafibranor alleviated hepatic fibrosis and cardiac dysfunction, indicating combined hepatic-cardioprotective effects [14]. A 2019 comparative study showed that Elafibranor and Obeticholic Acid, alone and in combination, improved steatosis and inflammation in NASH mice, with additive metabolic and histological benefits supporting FXR–PPARα/δ dual therapy [15].

Aim and Objectives

The aim of this research is to develop and validate a stability-indicating HPLC method for the quantification of Elafibranor in single dosage formulations. The method will be designed to identify and estimate degradants formed during storage. Validation will follow ICH guidelines, covering parameters such as accuracy, precision, linearity, range, LOD, LOQ, selectivity, specificity, robustness, ruggedness, stability, and system suitability. Forced degradation studies will be conducted to ensure method reliability under stress conditions. The developed method aims to be simple, accurate, precise, rapid, and cost-effective, suitable for routine quality control of Elafibranor in both technical and formulated products.

Materials and Methods

Instrumentation

The lab has an HPLC system (LC–7000, PEAK HPLC, India) with LC-P7000 pump, Rheodyne injector (20 µL, Hamilton USA), UV detector, Autochro-3000 software, balance, UV-Vis spectrophotometer, pH meter, sonicator, filtration kit, and 0.2 µ membrane filter.

Chemicals and solvents

The working standard drug Elafibranor (99% purity) along with the formulation tabletdosage form (IQIRVO -80MG) were obtained fromIPSEN BIOPHARMACEUTICALS INC.HPLC grade Methanol, Water and Acetonitrile were purchased form Merk chemicals private limited, Mumbai.The buffer solutions used for the study were AR Grade and purchased from Merck Specialties Private Limited, Mumbai, India.

Preparation of standard drug solution

Dissolve the drug in the solvent and make up to the mark. Then it was filtered through0.45µ filter paper to remove un-dissolved particles or any solid substances. The solution was preserved safely and used when required.

Preparation of formulation solution

The tabletIQIRVO®brand containing 80mgof Elafibranor was utilized for the preparation of formulation solution in the study. Then an amount of tablet solution equivalent to 10 mg of Elafibranor was accurately measured and taken in a 10 mL volumetric flask containing 5 mL of methanol. The flask was sonicatorfor 5 min to dissolve the drug completely in solvent and filtered through 0.45 µ membrane filter. The flaks were made up to the mark using same diluent and then it was diluted while doing the formulation analysis.

Results and Discussion

To develop a precise, accurate and suitable RP- HPLC method for the simultaneous estimation of Elafibranor in different mobile phases were tried and the proposed chromatographic conditions were found to be appropriate for the quantitative determination. Proper selection of the stationary phase depends up on the nature of the sample, and molecule's physico- chemical properties.

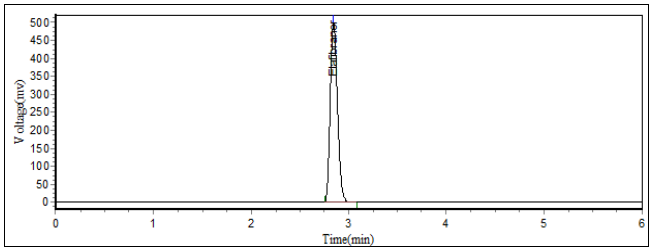

Fig 2: Chromatogram of Sample in the optimized conditions

Mixture ofMethanol: 0.01 % acetate bufferin the ratio of 75:25 (v/v) was selected as mobile phase and the effect of composition of mobile phase on the retention time of Elafibranor was thoroughly investigated. Proper selection of the stationary phase depends up on the nature of the sample, molecular weight and solubility. The drug Elafibranor is non - polar. Non-polar compounds preferably analyzed by reverse phase columns. Between C_8 and C_{18}, C_{18} column was selected. Non-polar compound is very attractive with reverse phase columns. So, the elution of the compound from the column was influenced by polar mobile phase. The system suitability results obtained for proposed method were within acceptable limits (capacity factor >2.0, tailing factor =2.0 and theoretical plates >2000), thus, the system meets suitable criteria.

The calibration curve for Elafibranor was obtained by plotting the peak area of Elafibranor versus concentration of Elafibranor over the range of 20-120µg/mL, and it was found to be linear with r= 0.9997. The regression equation for Elafibranor was found to be y = 4059.7x+10850(R^2 = 0.9997).

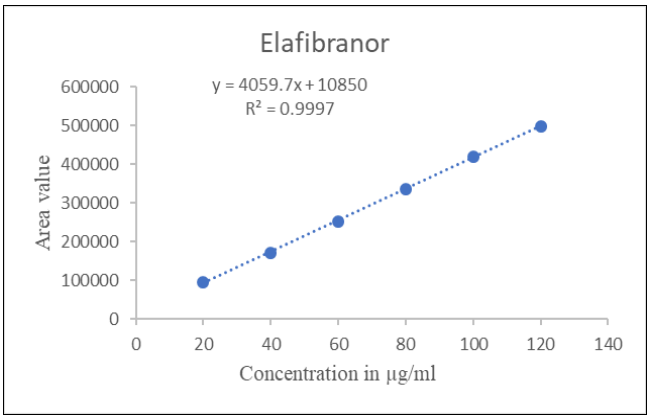

Fig 3: Linearity graph

Precision was evaluated by carrying out six independent sample preparation of a single lot of formulation. Percentage relative standard deviation (%RSD) was found to be less than 2% for within a day (Intra-1.00%), day to day (Inter-0.87%) variations and ruggedness (0.78%), which proves that method is precise.

Table 1: Precision results

S. No	Intraday Precision	Interday Precision
1	335482.1	335694.2
2	339641.7	331489.7
3	338524.7	335263.4
4	331254.9	334089.1
5	332548.6	330548.2
6	337526.9	338456.3
% RSD	1.00	0.87

Table 2: Ruggedness result

S. No	Peak area observed
1	337485.6
2	332486.3
3	332648.5
4	331593.7
5	334185.9
6	337586.4
RSD	0.78

To check the degree of accuracy of the method, recoverystudies were performed in triplicate by standard additionmethod at 50%, 100% and 150%. Results of recovery studies are shown range 99.45–101.30%. The mean recovery data obtained for each level as well as for all levels combined were within 2.0% of the label claim for the active substance with an R.S.D. < 2.0%, which satisfied the acceptance criteria set for the study.

To evaluate the robustness of the developed RP-HPLC method, small deliberate variations in the optimized method parameters were done. The effect of change in flow rate, pHand mobile phase ratio on the Area was studied. These parameters were found to change proportionally.

When stress conditions were applied to Elafibranor, the HPLC results showed that there was no interference between the tested drug and the degradation products. Peak purity results were also within the acceptable limit for all the degradation conditions studies confirms that the Elafibranor peak is homogeneous in all stress conditions. In all the stress degradation conditions, the standard drug Idarubicin was effectively separated, identified and quantified. The % assay of Elafibranor was found to be very high and the % degradation was found to be very less in the developed method. The degradation products were found to be 2, 1, 0, 0 and 0in acidic, base, peroxide, thermal and UV light conditions respectively.

Table 3: Forced degradation study results

S No	Condition studied	No of degradation compounds separated	% Assay	% Degradation
1	Acid	2	93.51	6.49
2	Base	1	95.75	4.25
3	Peroxide	0	96.37	3.63
4	Thermal	0	97.99	2.01
5	UV light	0	98.01	1.99

Among the degradation conditions studied, very high % degradation was observed in acid condition in which the % degradation was observed to be 6.49 % with 2 additional degradation products. Very less % degradation was observed in UV condition in which the % degradation of 1.99 % obtained confirms that the drug was more stable in thermal conditions. All the degradation products were effectively separated and there is no overlap of degradation compounds with the standard drug. Hence the developed method was found to be stability indicating.

The developed method was applied for the estimation of Elafibranor in its formulation solution prepared from IQIRVO®brand tablets of Elafibranor. The % assay in formulation analysis was found to be 99.01(tablet)for Elafibranor in the developed method. More than 98% assay was observed in the developed method. Hence the method was found to be suitable for the routine analysis of Elafibranor in bulk drug as well as formulations.

The sensitivity test results of Elafibranor indicated that the method was sensitive enough to detect a concentration of 0.06µg/mL and able to quantify at a concentration of above 0.20µg/ml. The proposed method uses a simple mobile phase composition which is easy to prepare. The rapid run time of 6 min and the relatively low flow rate allows the analysis of large number of samples with less mobile phase that proves to be cost-effective. Efficient UV detection at 247nm was found to be suitable without any interference from injectable solution excipients or solvents. The method was validated showing satisfactory data for all the method validation parameters tested. The developed methods can be conveniently used by quality control laboratories.

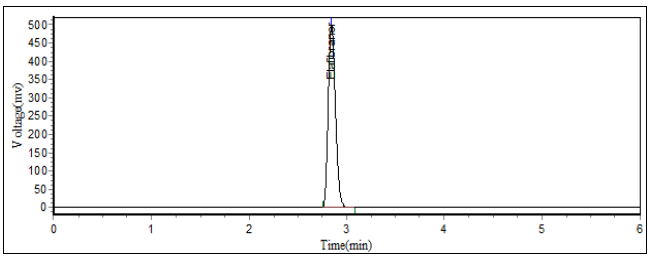

Fig 4: Formulation chromatogram for tablet IQIRVO®

The summary results observed method development, validation and application of the analytical method developed for the analysis of Elafibranor in formulations was given in table.

Table 4: Summary resultsachieved in the method developed for analysis of Elafibranor

Study	Parameter	Results
Method Developed	Elution	Isocratic
	Mobile Phase	Methanol: 0.01 % acetate bufferin the ratio of 70:25 (v/v)
	pH	5.3
	Column	Thermo Scientific Hypersil GOLD™ C18 (250 mm) column
	Wavelength	247nm
	Flow	6 mL/min
	Runtime	6 min
	Temperature	Ambient
Method validation	Retention Time	2.8min
	Theoretical Plates	6724
	Tailing Factor	1.01
	Resolution	--
	Linearity range	20 to 120 µg/mL
	Slope	4059.7
	Intercept:	10850
	r^2 (correlation coefficient)	0.9997
	Intraday Precision	1.00
	Interday Precision	0.87
	Ruggedness	0.78
	Recovery	99.45–101.30
	% Change in Robustness	0.06 to 0.70
	LOD	0.06µg/mL
	LOQ	0.20µg/mL
Method Application	% Degradation in Acidic Base Peroxide Thermal UV Light	6.49 4.25 3.63 2.01 1.99
	Formulation assay	99.01(Tablet)

Conclusion

A simple, highly sensitive, isocratic stability indicating reversed phase-high performance liquid chromatography (RP-HPLC) method with UV detection at 247nm was developed and validated for analysis of Elafibranor. Retention time of the Elafibranor was found to be 2.8 min. A mobile phase consisting of Methanol: 0.01 % acetate buffer in methanol in the ratio of 75:25 (v/v) at flow rate of l.0 mL/min was employed in this study. The calibration curves were linear in the concentration range of 20 to 120 µg/mL with regression coefficient (r^2) of 0.9997. The limits of detection (LOD) and the limits of quantification (LOQ) were found to be 0.06 and 0.20 µg/mL, respectively. The method was statistically validated in accordance with international conference on harmonization (ICH) guidelines. The method can effectively separate the stress degradation compounds formed during the stress study and the % drug content was observed to be very high in all the stress studies. Hence based on the statistical analysis of the data it has been unequivocally construed that the method is reproducible and selective for the routine analysis of Elafibranor in bulk drug and tablet dosage form.

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