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DEVELOPMENT OF STABILITY - INDICATING HPLC METHOD FOR SIMULTANEOUS DETERMINATION OF THIRTEEN RELATED IMPURITIES IN NINTEDANIB ESYLATE DRUG SUBSTANCE & ITS APPLICATION IN DRUG PRODUCT

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Keywords:

Nintedanib esylate, Degradant impurities, Stability-indicating method, RP-HPLC

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ABSTRACT: A stability indicating reverse phase high-performance liquid chromatography (RP-HPLC) method was developed and validated for the determination of thirteen related impurities in Nintedanib esylate, applicable to both bulk drug and finished product. Chromatographic separation was achieved on a Waters X-Bridge C18 column (250 mm × 4.6 mm i.d., 5 µm) under gradient elution. The mobile phase consisted of 0.01 M ammonium bicarbonate buffer (pH 8.0 ± 0.05, adjusted with sodium hydroxide) as phase A, and a mixture of methanol, acetonitrile, and buffer (45:45:10, v/v) as phase B. Detection was performed at 240 nm, ensuring baseline resolution of Nintedanib from its impurities, with peak resolution consistently greater than 2. Forced degradation studies under acidic, alkaline, aqueous hydrolysis, and oxidative conditions confirmed the method's ability to separate Nintedanib from its degradation products, including the major related substance (RS9). The method was validated in accordance with ICH guidelines for selectivity, linearity, accuracy, precision, and solution stability. This validated RP-HPLC method provides a robust and reliable approach for routine analysis of related impurities in Nintedanib esylate drug substance and drug product, supporting quality control and stability assessment in pharmaceutical development and manufacturing.

INTRODUCTION: Idiopathic pulmonary fibrosis (IPF) is a chronic, progressive fibrosing interstitial pneumonia of unknown origin that predominantly affects adults between 50 and 75 years of age. Globally, more than 100,000 patients have been reported with this condition, which is characterized by worsening dyspnea and a gradual decline in pulmonary function [1].

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The pathogenesis of IPF is linked to aberrant tissue remodeling and fibrotic proliferation, driven by dysregulated signaling pathways involving tyrosine kinases such as vascular endothelial growth factor (VEGF), fibroblast growth factor (FGF), and platelet derived growth factor (PDGF).

Nintedanib, a potent intracellular inhibitor of multiple tyrosine kinases, has been approved for the treatment of IPF. By targeting VEGF, FGF, and PDGF receptors, it effectively modulates fibrotic signalling [2, 3]. Chemically, Nintedanib esylate is 4-tert - butyl - N - [6 - (2 - hydroxyethoxy) - 5 - (2 - methoxyphenoxy) - 2 - (pyrimidin - 2 - yl) pyrimidin - 4 - yl] benzene - 1 - sulfonamide, with

a molecular weight of 649.76 g/mol and molecular formula $C_{33}H_{39}N_5O_7S$ [4]. It is a bright yellow, water-soluble powder, exhibiting greater solubility at lower pH and notable stability under solid-state conditions, being non-hygroscopic and insensitive to light.

Despite its therapeutic importance, Nintedanib esylate has not yet been included in major pharmacopeia's (USP, EP, JP, IP). Analytical studies reported in the literature primarily focus on quantification in biological matrices using LC-MS [5, 6] or assay methods [7]. However, detail information about related impurities (process/degradant) as well its stability-indicating HPLC nature for drug substance is represented in this manuscript. Also, Current regulatory guidelines were considered the need to monitor intermediates, raw materials, process impurities, and degradants in drug substances [8].

The present study addresses this gap by developing and validating a robust, stability-indicating RP-HPLC method for Nintedanib esylate. The method enables comprehensive impurity profiling in both drug substance and drug product, while remaining compatible with LC-MS for mass identification of impurities without buffer modification.

Experimental:

Materials and Reagents: Analytical grade ammonium bicarbonate (Merck, Mumbai, India), hydrochloric acid (Rankem), sodium hydroxide (Merck) and hydrogen peroxide (Merck) was used throughout the analysis.

Orthophosphoric acid (OPA) was obtained from spectrochem, Mumbai (India). The investigated samples of Nintedanib drug substance, crude samples and impurities were synthesized in API R&D, Unit1, Patalganga, Raigad, Maharashtra. The marketed formulation Ofev (soft gel. capsule) was purchased from market and used for analysis.

Apparatus and Conditions:

HPLC: The HPLC systems used in this study were Agilent 1200 HPLC and Agilent 1260 equipped with degasser & photodiode array (PDA) detector, UV detector with Chromeleon software. The HPLC column used in this study was X-Bridge C18, 250mm×4.6mm, 5µm (Waters corporation).

The analysis was conducted on X-Bridge C18, 250mm×4.6mm, 5µm column, thermostat at 25 °C. The solvent A was ammonium bicarbonate buffer (0.01M NH_4HCO_3, pH adjusted to 8.0 with sodium hydroxide) and solvent B was mixture of methanol, acetonitrile and solvent A. Solvent A was filtered through 0.45 µm membrane filter and degassed prior to pumping into the system along with solvent B. The mobile phase flow rate was 0.8 ml/min. The HPLC gradient program was time (min)/%B (v/v): 0/35, 2/35, 15/40, 25/52, 65/65, 77/85, 90/90, 91/35 and 100/35. The injection volume was ten µl. Sample cooler temperature was set to 5°C. The chromatograms were recorded at 240 nm using UV detector.

Analytical Procedure: Nintedanib working reference standard at 1.0 mg/ml and subsequent concentrations were prepared in diluent (methanol: acetonitrile with the ratio of 1:1) respectively. Solutions of all the impurities (0.15 mg/ml) were prepared by dissolving requisite amounts of the compounds initially in diluent and diluted up to the mark with the same diluent. These solutions were prepared freshly and diluted further quantitatively to study the validation attributes. The specification limit considered for validation studies was 0.15 % for known impurity. The known and unknown impurities were found against mean areas obtained from six replicate injections of standard solution and relevant impurity standard solution.

Procedure for Forced Degradation Study: To demonstrate stability indicating power of developed method for the determination of impurities in Nintedanib, solution-state forced degradation of Nintedanib was carried out by treating the 1.0 mg/ml solutions with 0.5NHCl, 0.1N NaOH and 3% H_2O_2 at 60°C for 1 hour respectively. Solid state forced degradation (thermal, photolytic and humidity) of the drug was conducted by exposing Nintedanib to (1) heating at 110°C for 24 h, (2) white fluorescent light (1.2 million lux hours) followed by UV light of 200 w-h/m^2 and all these solutions were analyzed by the presented method.

Method Validation: Validation of the chromatographic method was conducted about linearity, sensitivity (limit of detection and limit of quantification), precision, accuracy, and robustness.

Linearity, LOD and LOQ: The linearity of detector response to different concentrations was evaluated for Nintedanib and all the impurities (RS2, RS3, RS4, RS5, RS6, RS7, RS8, RS9, RS10, RS11, RS12, RS 13& RS14) using six levels ranging from LOQ, 50%, 80%, 100% & 150% with respect to sample concentration in the range of 0.30 to 1.50 µg/ml. The linear regression data for all the impurities evaluated were evaluated. The LOD and LOQ were found for Nintedanib and each of the impurities based on the precision and RSD of precision.

System Precision: The system precision for analytes in the present study was assessed by conducting repeatability experiments. The standard solution of Nintedanib and that of impurities was injected six times to evaluate the precision of the system.

Method Precision: The precision of the method was found by analyzing samples of Nintedanib spiked with all known impurities at 100% of the specification limit (Six replicate sample preparations).

Intermediate Precision (Ruggedness): The intermediate precision of the method was determined by evaluating the variability of the results obtained for related impurities with the analysis of Nintedanib sample spiked with impurities, six times at the specification limit by different analysts, different instruments, using different columns, and on different days.

Accuracy (Recovery): The accuracy of the method was found using three solutions having Nintedanib spiked with the impurities at four levels LOQ, 50%, 100% and 150% of the specification limit.

Robustness: The robustness of the method was evaluated through the studies of influence of small and premeditated alteration of analytical parameters. The parameters selected were flow rate (±10%), (pH of buffer ±0.2), column temperature (±5°C).

Stability of Analytical Solutions: To find the stability of sample solution, the sample solution of Nintedanib spiked with impurities at specified level was subjected to analysis immediately after preparation and at time interval up to 24 h and 48 h, while keeping the sample cooler temperature at 5°C.

Sample Preparation for Drug Substance & Drug Product: Three batches of Nintedanib esylate and marketed formulation (Ofev) were taken and prepared as per procedure and injected into HPLC system.

RESULTS AND DISCUSSION: After comprehensive investigation about manufacturing process of Nintedanib esylate, the potential impurities which include process as well as degradation impurities were considered for present study. It is shown in **Table 4**.

The structures of Nintedanib and its process impurities (RS1, RS2, RS3, RS4, RS5, RS6, RS7, RS8, RS9, RS10, RS11, RS12, RS13) are depicted in **Fig. 2.** The compounds RS1, RS5 are key starting materials and RS13, RS14 are process intermediates, while RS9, RS11 and RS12 are process impurities produced during the synthesis of Nintedanib.

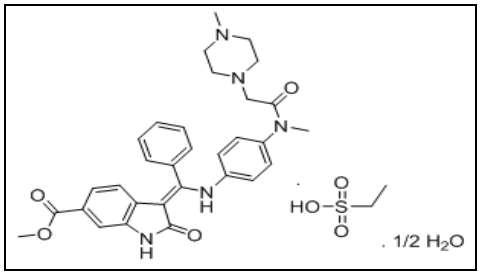
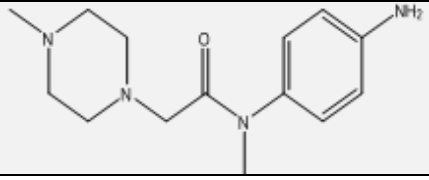
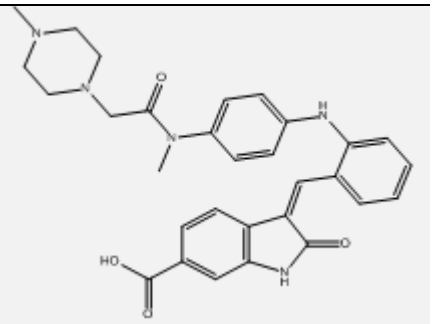
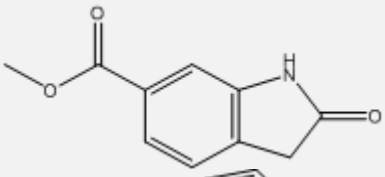
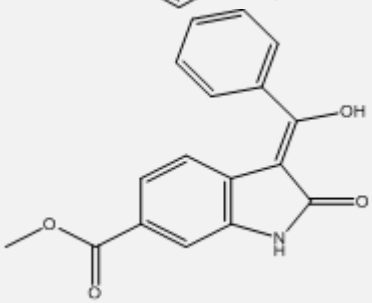
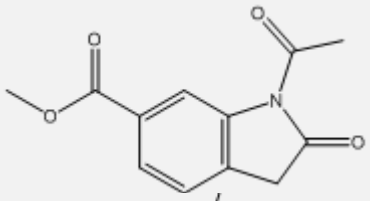
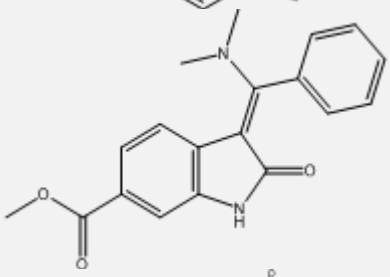
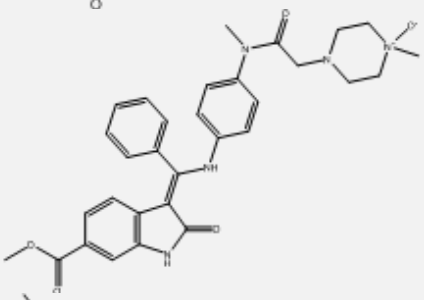
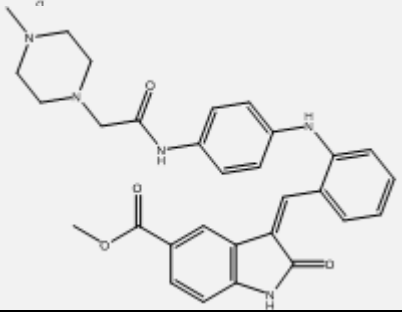
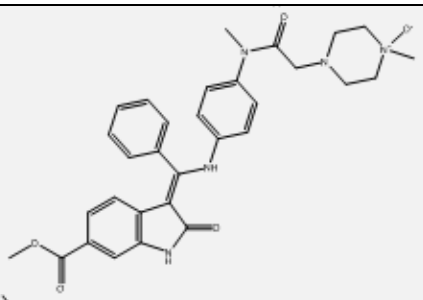
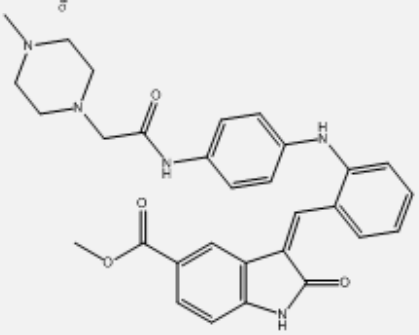
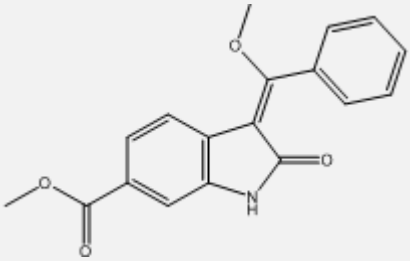
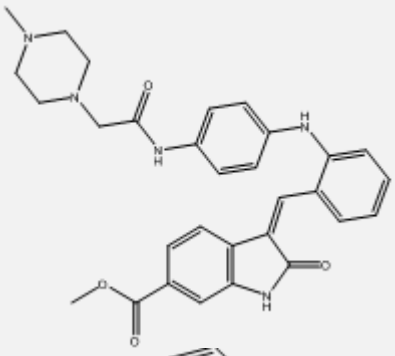
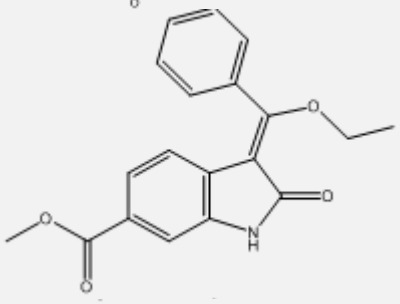
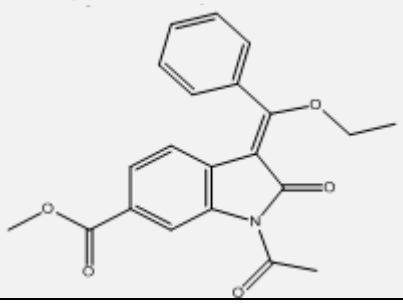


FIG. 1: THE STRUCTURE OF NINTEDANIB ESYLATE

TABLE 1: CHEMICAL NAMES AND STRUCTURES OF NINTEDANIB AND ITS RELATED PROCESS AND DEGRADANT IMPURITIES

Short Number	Name of the Impurity	Chemical Name	Structure
RS1	Nintedanib Acetamide	N-(4-aminophenyl)-N,4-dimethyl-1-piperazine acetamide	

RS2	Nintedanib carboxylic acid impurity	(Z)-3-(((4-(N-methyl-2-(4-methylpiperazin-1-yl) acetamido) phenyl) amino) (phenyl) methylene)-2-oxoindoline-6-carboxylic acid	
RS3	Nintedanib oxindole	Methyl 2-oxoindoline-6-carboxylate	
RS4	Nintedanib hydroxy enolindole	Methyl (Z)-3-(hydroxy(phenyl)methylene)-2-oxoindoline-6-carboxylate	
RS5	Nintedanib N-acyl oxindole	1-Acetyl-2,3-dihydro-2-oxo-1H-indole-6-carboxylic acid methyl ester	
RS6	Nintedanib N, N dimethyl amine	Methyl (E)-3-(dimethylamino) (phenyl)methylene)-2-oxoindoline-6-carboxylate	
RS7	Nintedanib N-methyl N-oxide impurity	(Z)-4-(2-(4-((6-(methoxycarbonyl)-2-oxoindolin-3-ylidene) (phenyl)methyl) amino) phenyl) (methyl)amino)-2-oxoethyl)-1-methylpiperazine 1-oxide	
RS8	5-carboxymethyl desmethyl acetamido Nintedanib	Methyl (Z)-3-(4-(2-(4-methylpiperazin-1-yl) acetamido) phenyl) amino) (phenyl) methylene)-2-oxoindoline-5-carboxylate	

RS9	Nintedanib Methoxy enolindole	(Z)-4-(2-(4-((6-(methoxycarbonyl)-2-oxoindolin-3-ylidene) (phenyl)methyl) amino) phenyl) (methyl)amino)-2-oxoethyl)-1-methylpiperazine 1-oxide	
RS10	Desmethyl acetamido Nintedanib	Methyl (Z)-3-(4-(2-(4-methylpiperazin-1-yl) acetamido) phenyl) amino) (phenyl) methylene)-2-oxoindoline-5-carboxylate	
RS11	Nintedanib Ethoxy enolindole	Methyl (E)-3-(methoxy(phenyl)methylene)-2-oxoindoline-6-carboxylate	
RS12	Nintedanib ethyl ester impurity	Methyl (Z)-3-(4-(2-(4-methylpiperazin-1-yl) acetamido) phenyl) amino) (phenyl) methylene)-2-oxoindoline-6-carboxylate	
RS13	N-Acyl Nintedanib base	(Z)- Methyl 3-(ethoxy(phenyl)methylene)-2-oxoindoline-6-carboxylate	
RS14	Nintedanib N-Acyl ethoxy enolindole	(Z)-methyl 1-acetyl-3-(ethoxy(phenyl)methylene)-2-oxoindoline-6-carboxylate	

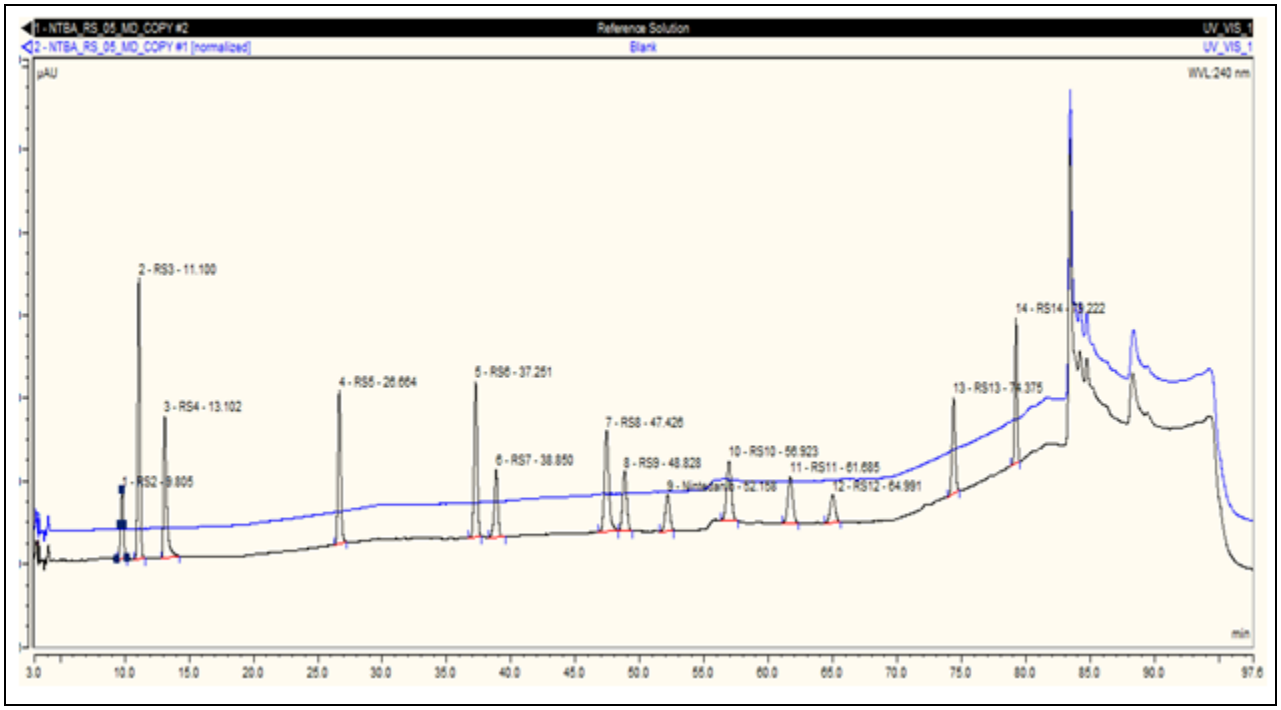


FIG. 2: REFERENCE CHROMATOGRAM OF BLANK AND STANDARD

Optimization of HPLC Conditions: The first step of method development for the quantification of process related and degradation impurities in Nintedanib esylate drug substance is the proper choice of wavelength to obtain good sensitivity with minimum noise. Hence the detector wavelength was kept as 240 nm throughout the analysis. The column selectivity for separation of all the related impurities was critical because of their similar chemical structures and polarities. Preliminary experiments were performed using different columns, like YMC pack pro C18(25 cm x 4.6 mm,5 µm), Zorbax Ecplise XDB C18 (150 mm x 4.6 mm,3.5 µm), Waters XBridge C18(25 cm x 4.6 mm,5 µm) and Inertsustain AQ C18 (25 cm x 4.6 mm,5 µm). It was seen that the studied compounds were well retained and separated as sharp peaks on Waters XBridge C18(25 cm x 4.6 mm, five µm). So, further optimization of chromatographic parameters was conducted on this column. Based on later trials and observations, ammonium bicarbonate buffer was selected as mobile phase A and Methanol-Acetonitrile-Mobile phase A in the ratio of 45:45:10 v/v was selected as mobile phase B. This mobile phase composition could offer significant improvement in resolution between Nintedanib and its related impurities. The pH of mobile phase was also a critical factor and played vital role considering the chromatographic behavior of API and all process impurities. Nintedanib esylate has pKa (Acid) 11.06, pKa (Basic) -0.92, considering pKa and LogD values of target analytes basic pH is selected for trials. Initial trials from pH 6 to 9.0 were taken. From the varied pH trials, it was seen that pH has significant impact on resolution of all impurities. At pH 8.0, all process and degradant impurities were well separated with baseline resolution more than 2.0. Therefore, considering baseline separation of all process impurities and degradants, the pH value of the mobile phase perfected to 8.0.

Results of Forced Degradation: When Nintedanib was subjected to different conditions (acid, alkaline and peroxide) the drug molecule degraded up to 12 % in alkali condition (0.1 M NaOH, 30 min. reflux) resulting in formation of Nintedanib carboxylic acid impurity. In acidic condition (0.1 M HCL, 1.5 h reflux), it resulted in the formation of Nintedanib acetamide impurity (4.73%), Nintedanib Hydroxyenolindole (5.84%), Nintedanib Oxindole (0.16%), whereas, in oxidation condition (using H_2O_2 reagent as 3% H_2O_2, 60 min reflux), it resulted in the formation of Nintedanib N-Methyl N-Oxide impurity (1.95%). Further, with water hydrolysis condition (5 ml of H_2O_2 reflux at 80°C for 30 min) it resulted in the formation of Nintedanib Hydroxyenolindole impurity (0.19%). Nintedanib was found to be stable under solid state forced degradations under UV and white,

fluorescent light. The peaks of unknown degradants produced in the forced degradation were well separated (Resolution > 2.0) from the peaks of Nintedanib and known impurities. All major degradation impurities produced under above mentioned conditions were isolated and characterized using various analytical techniques like IR, Mass, NMR, the data of which are compiled or presented in **Table 6** & **7**, respectively.

Method Validation:

Specificity: Separate solutions of process impurities and Nintedanib esylate were prepared at a concentration of 150 µg/ml each. All these solutions were analyzed using the PDA detector. The related impurities RS1, RS2, RS3, RS4, RS5, RS6, RS7, RS8, RS9, RS10, RS11, RS12 and RS13, RS 14 eluted at different retention times and were adequately resolved from each other and from the peak of Nintedanib esylate. The Reference chromatogram of Blank and standard has been shown in **Fig. 3**. Among the reported impurities, RS1 impurity, being highly polar, could not be analyzed with the present method and hence, a separate method was developed (or evolved) and validated for its analysis.

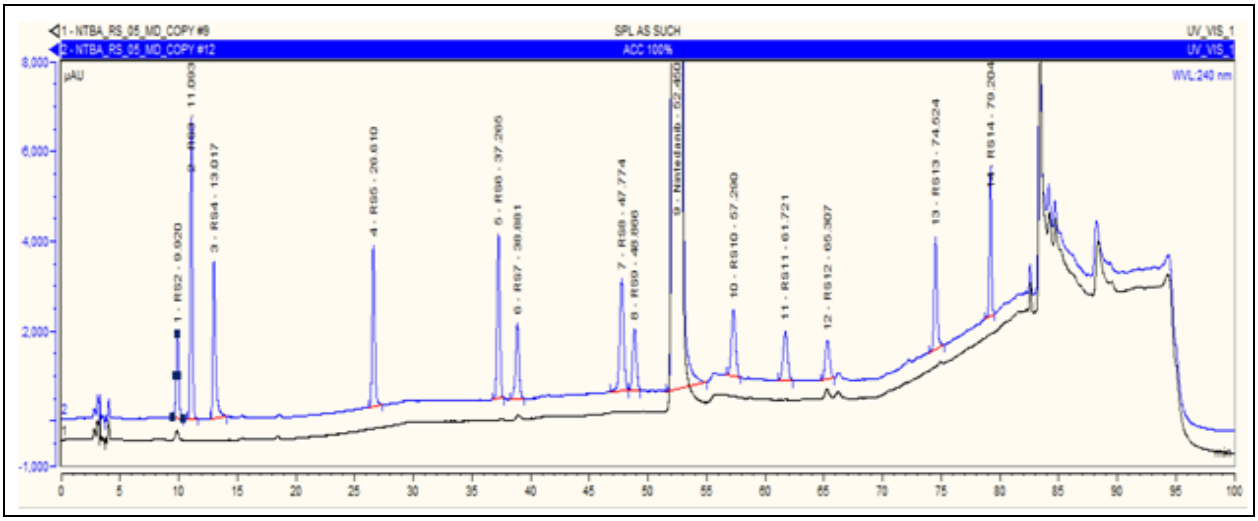


FIG. 3: REFERENCE CHROMATOGRAM OF SAMPLE AND 100 % SPIKED CONCENTRATION OF ALL KNOWN IMPURITIES

System Suitability Test: The solution of Nintedanib (1.0 mg/ml) spiked with 0.15 % w/w of impurities was analyzed during validation studies. It is found that the resolution value of more than 2.0 was achieved for all the compounds. It is shown in **Fig. 4.** RRTs and tailing factors of the compounds were found to be within acceptance criteria.

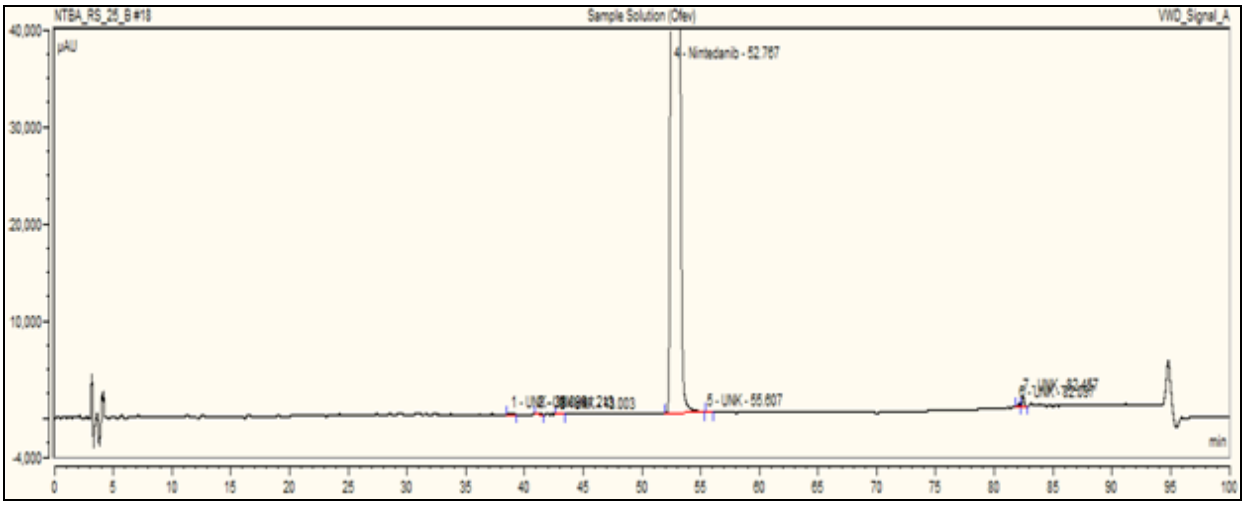


FIG. 4: REFERENCE CHROMATOGRAM OF MARKETED FORMULATION OF NINTEDANIB ESYLATE (OFEVCAPSULE)

The percentage relative standard deviation of peak of six replicate injections of standard solution was observed NMT 5.0%.

Linearity, LOD and LOQ: The linear regression results **Table 1** showed that the detector response at 240 nm was linear over the concentration range studied. The precision of LODs and LOQs were verified by analyzing solutions of Nintedanib and its impurities at these levels in six replicates and it was found to be below 5% RSD. The data is presented in **Table 1** & **2.**

TABLE 2: LIMIT OF DETECTION AND LIMIT OF QUANTIFICATION OF NINTEDANIB ESYLATE AND IMPURITIES

Component	LOD (% w.r.t concentration)	% RSD	LOQ (% w.r.t concentration)	% RSD
RS2	0.022	0.7	0.043	0.1
RS3	0.018	0.3	0.036	0.1
RS4	0.018	1.1	0.036	0.1
RS5	0.019	2.2	0.039	0.0
RS6	0.024	1.6	0.048	0.0
RS7	0.022	2.2	0.043	0.0
RS8	0.022	2.7	0.043	0.0
RS9	0.018	2.6	0.037	0.0
Nintedanib	0.012	1.5	0.024	0.1
RS10	0.022	4.9	0.043	0.1
RS11	0.019	0.9	0.038	0.1
RS12	0.022	1.3	0.043	0.1
RS13	0.021	0.6	0.043	0.0
RS14	0.018	0.8	0.037	0.0

TABLE 3: LINEARITY OF NINTEDANIB AND ITS IMPURITIES

Component	Range Covered	% Y-Intercept	R
RS2	LOQ to 150%	-0.7	1.000
RS3	LOQ to 150%	-0.7	0.999
RS4	LOQ to 150%	-1.9	0.999
RS5	LOQ to 150%	-0.6	0.999
RS6	LOQ to 150%	-0.6	0.999
RS7	LOQ to 150%	-1.3	0.999
RS8	LOQ to 150%	-1.0	0.999
RS9	LOQ to 150%	-0.1	0.999
Nintedanib	LOQ to 150%	-2.0	0.999
RS10	LOQ to 150%	-0.8	0.999
RS11	LOQ to 150%	1.8	0.999
RS12	LOQ to 150%	-1.0	0.999
RS13	LOQ to 150%	0.1	0.999
RS14	LOQ to 150%	1.1	0.999

TABLE 4: RECOVERY OF NINTEDANIB IMPURITIES AT LOQ, 50%, 100% AND 150%

Components	LOQ		50%		100%		150%	
	% Recovery	% RSD of Recovery	% Recovery	% RSD of Recovery	% Recovery	% RSD of Recovery	% Recovery	% RSD of Recovery
RS2	97 to 103	1.1	97 to 99	0.8	98 to 103	11.5	97 to 99	1.3
RS3	98 to 99	0.5	97 to 99	1.2	98 to 101	0.9	96 to 98	1.0
RS4	95 to 97	1.1	98 to100	1.1	100 to 102	0.9	101 to 108	3.4
RS5	90 to 94	2.1	99 to 103	1.8	97 to 101	1.7	98 to 102	1.9
RS6	104 to 106	0.7	101 to 102	0.5	100 to 102	0.8	98 to 101	1.7
RS7	100 to 101	0.7	98 to 99	0.6	97 to 99	0.8	95 to 103	4.1
RS8	99 to 104	2.5	96 to 99	1.5	97 to 98	0.8	96 to 102	3.7
RS9	92 to 95	2.2	99 to 100	0.8	96 to 99	1.3	98 to 99	0.2
RS10	95 to 97	1.4	105 to 108	1.3	102 to 106	1.0	106 to 108	0.8
RS11	102 to 106	1.8	106 to 107	0.4	102 to 106	1.3	99 to 101	0.8
RS12	92 to 99	1.8	102 to 106	2.1	99 to 104	1.6	103 to 106	1.5
RS13	97 to 99	1.0	103 to 106	1.4	103 to 105	0.9	100 to 101	0.9
RS14	88 to 89	0.7	97 to 100	1.4	101 to 104	1.0	97 to 98	0.4

TABLE 5: ORIGIN AND CLASSIFICATION OF IMPURITIES

Sr. no.	Impurity Name	Type of Impurity	Origin of impurity	Short numbering
1	Nintedanib Acetamide	Process impurity	API degradation	RS1
2	Nintedanib carboxylic acid impurity	Degradation	API degradation	RS2
3	Nintedanib oxindole	Degradation /Process	API degradation	RS3
4	Nintedanib hydroxy enolindole	Degradation	API degradation	RS4
5	Nintedanib N-acyl oxindole	Process	Starting material	RS5
6	Nintedanib N, N dimethyl amine	Degradation/process	Starting material/API degradation	RS6
7	NintedanibN-methylN-oxideimpurity	Degradation	API degradation	RS7
8	5-carboxymethyl desmethyl acetamido Nintedanib	Process	Starting material	RS8
9	Nintedanib Methoxy enolindole	Process	inprocess	RS9
10	Desmethyl acetamido Nintedanib	Process	Starting material	RS10
11	Nintedanib Ethoxy enolindole	Process	In-process	RS11
12	Nintedanib ethyl ester impurity	Process	In-process	RS12
13	N-Acyl Nintedanib base	Process	In-process	RS13
14	Nintedanib N-Acyl ethoxy enolindole	Process	In-process	RS14

TABLE 6: RESULTS OF ANALYSIS OF THREE VALIDATION BATCHES OF NINTEDANIB ESYLATE

Name of Impurity	Batch No.: I	Batch No.: II	Batch No.: III
		Impurity in % w/w	
RS2	ND	ND	ND
RS3	ND	ND	ND
RS4	ND	ND	ND
RS5	ND	ND	ND
RS6	ND	ND	ND
RS7	ND	ND	ND
RS8	ND	ND	ND
RS9	ND	ND	ND
RS10	ND	ND	ND
RS11	BDL	ND	ND
RS12	BDL	BLOQ	BDL
RS13	BLOQ	BLOQ	BLOQ
RS14	ND	ND	ND

*ND = Not detected, BDL = Below detection limit, BLOQ = Below quantification limit.

Precision (System precision, Method Precision, and Intermediate Precision): The system precision evaluated using 0.15% Nintedanib standard solution of was 1.5%.

Method precision study showed that the RSD values for Nintedanib and process impurities were in the range of 0.3–1.4% (n = 6) showing good repeatability. The intermediate precision of the method was found to be cumulative % RSD and % recovery in the range of 90.0 to 104.0%.

Accuracy: Recovery of each impurity was seen in the range of 96-106% and RSD for all impurities was found to be in the range of 0.5 to 1.7%. The data is shown in **Table 3.**

Robustness: Robustness study is done by doing deliberate changes in flow rate (±10%), (pH of buffer ±0.2), column temperature (±5°C).

The studies showed no effect on the determination of related impurities and selectivity and sufficiently robust to conduct the quantification of impurities in Nintedanib.

Stability of Analytical Solutions: The % difference in peak area of all the impurities from first to relevant time interval was calculated and found to be below 5.0. So, sample solution was declared to be stable for at least 48 h at room temperature.

Application of the Method for Drug Substance: Three Commercial batches of Nintedanib drug substance were analyzed using the proposed method.

The levels of impurities compared to Nintedanib were in the range of BDL–BLOQ. It is shown in **Table 5.**

Application of the Method for the Drug Product: Marketed formulation of Nintedanib esylate (Ofev) was analyzed in proposed method. The Chromatogram of drug product is shown in **Fig. 5.**

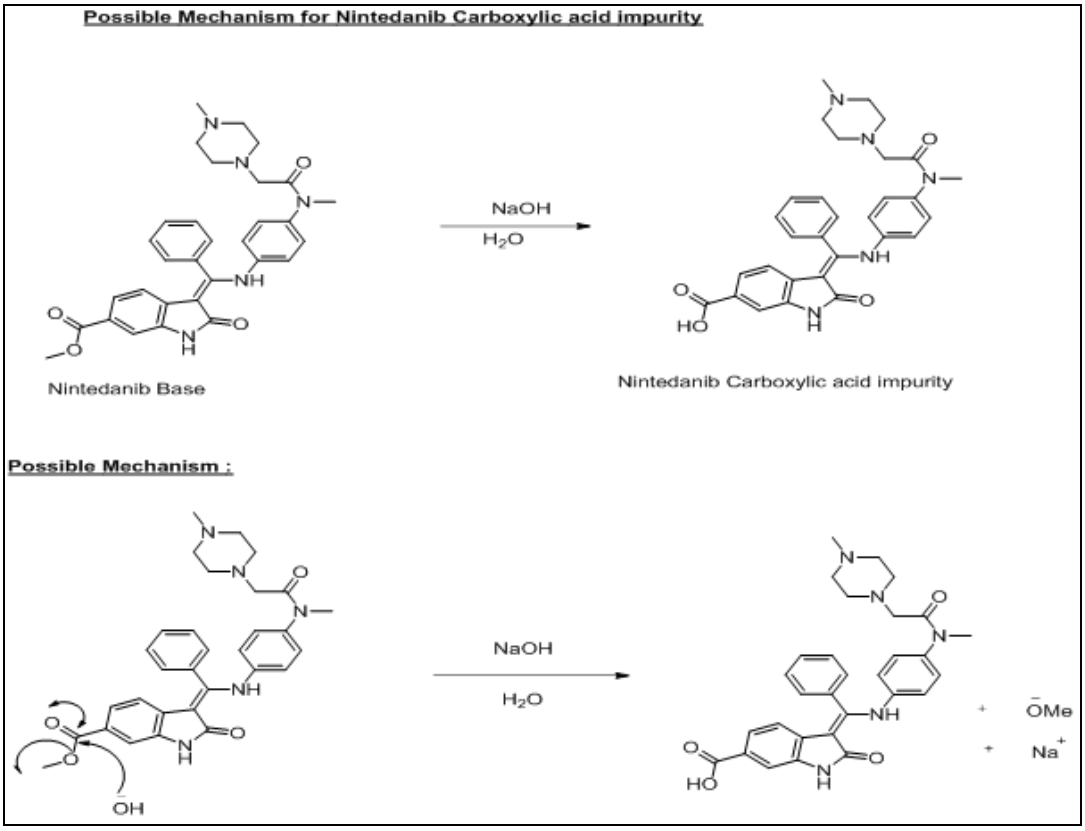


FIG. 5: REACTION MECHANISM OF DEGRADANT IMPURITY (NINTEDANIB CARBOXYLIC ACID)

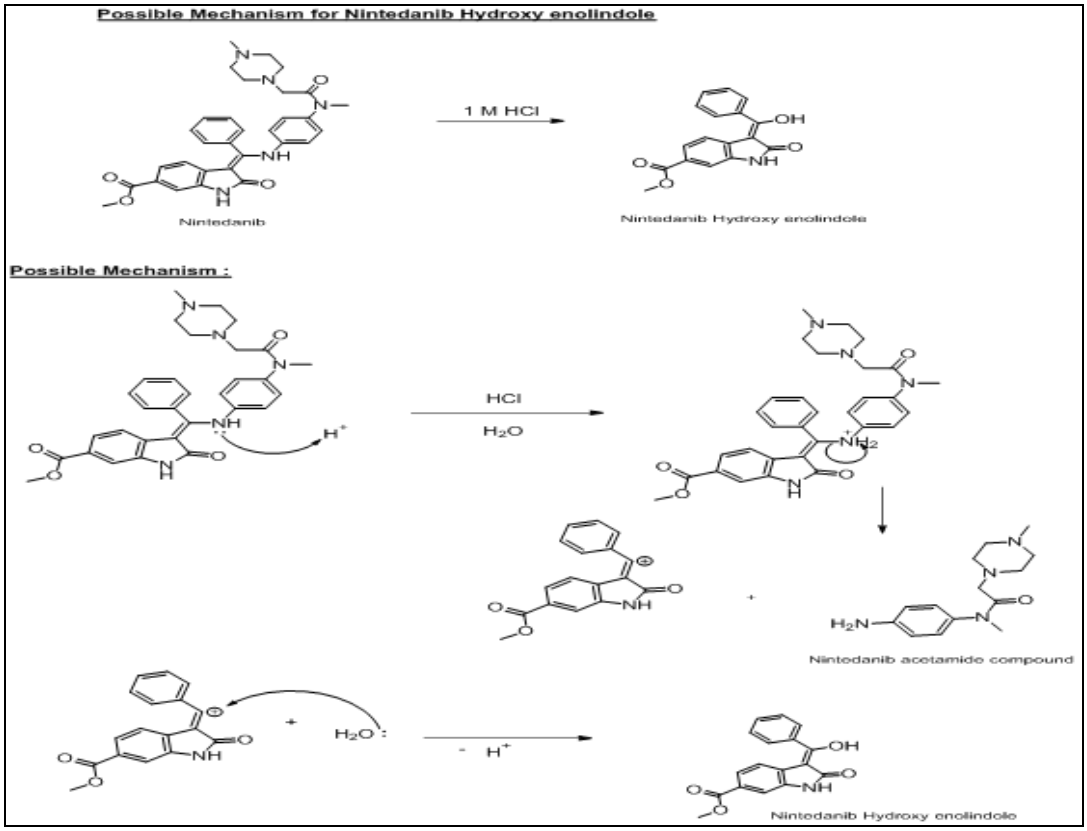


FIG. 6: REACTION MECHANISM OF DEGRADANT IMPURITY (NINTEDANIB HYDROXY INOLINDOLE)

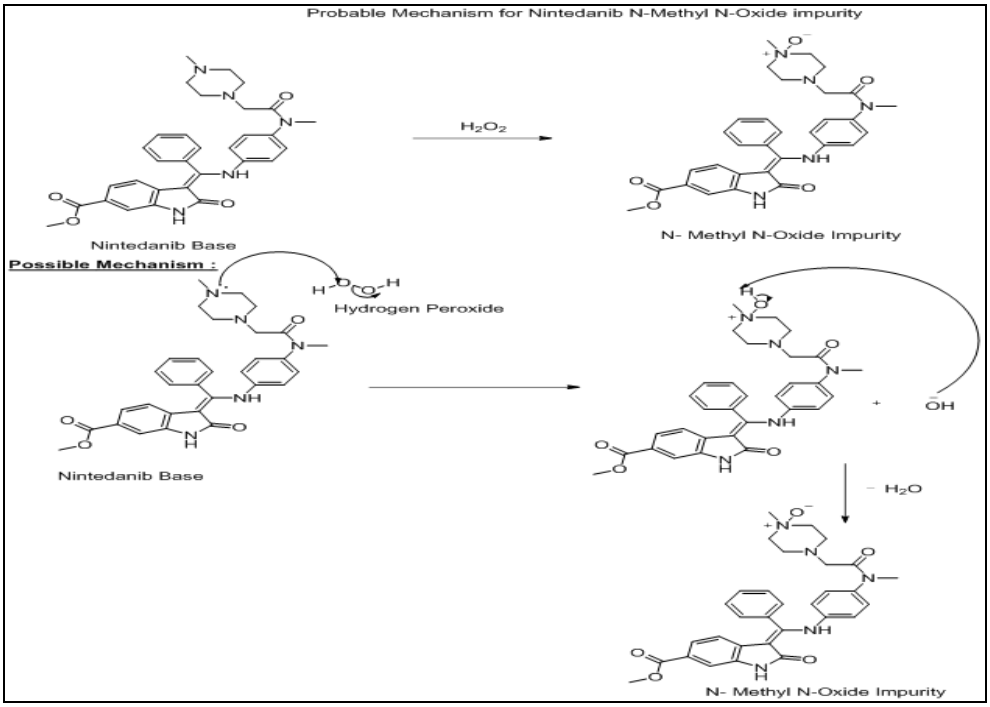


FIG. 7: REACTION MECHANISM OF DEGRADANT IMPURITY (NINTEDANIB N-METHYL N-OXIDE IMPURITY

CONCLUSIONS: A simple gradient RP-HPLC method was developed and validated for quantitative determination of impurities of Nintedanib drug substance. The method was developed considering current ICH Q11 guidelines which show control of starting materials with process & degradant impurities.

The method showed higher sensitivity towards the determination of impurities and was found to be specific, sensitive, precise, linear, accurate and robust. Totally Thirteen impurities in Nintedanib drug substance were found and isolated in the present work. Detailed characterization was conducted using various spectroscopic techniques. The reported method thus can be used for routine testing and stability analysis of Nintedanib drug substance as well as in drug product.

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CONFLICTS OF INTEREST: Nil

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