

## RESEARCH ARTICLE

# Stability Indicating Force Degradation Study of Nintedanib in Bulk and Pharmaceutical Dosage Form

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## ABSTRACT

Assay of the nintedanib drug substance can be determined using a newly designed and verified reverse-phase high-performance liquid chromatography (RP-HPLC) method, even when degradation products from forced degradation experiments are present. By using gradient elution, the mobile phase was a mixture of 70% acetonitrile and 30% water by volume. Acid, base, peroxide, thermal, and photolytic degradation were among the stress conditions that the product was subjected to. During the thermal and photolytic breakdown processes, no extra contaminants were detected. Using validation criteria such as specificity, linearity, limit of quantitation (LoQ), accuracy, precision, robustness, and ruggedness, the developed technique was validated in accordance with International Council for Harmonization (ICH) recommendations. At a concentration of 12.4 ng/mL, the LoQ value was attained. The results showed good linearity ( $r^2 > 1.00$ ) across doses ranging from 2 to 10  $\mu\text{g/mL}$ . Verification of recovery was done by adding concentrated solutions of 5, 10, and 15  $\mu\text{g/mL}$ . So, newly developed RP-HPLC technology can separate Nintedanib from its main degradation products, and it can also estimate the drug substance's concentration.

**Keywords:** Nintedanib, Chromatography, Degradation, Stability.

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**Conflict of interest:** None

## INTRODUCTION

Some forms of malignancy are being treated with nintedanib. The small chemical tyrosine-kinase inhibitor nintedanib targets three different receptors: Fibroblast growth factor receptor (FGFR), vascular endothelial growth factor receptor (VEGFR), and platelet-derived growth factor receptor (PDGFR). One of these receptors is VEGFR. Boehringer Ingelheim created nintedanib (BIBF 1120) and sold it under the OFEV and VARGATEF brands. Stable nintedanibesylate salt (mol. wt. 649.76) is accessible, with a molecular weight of 539.62.<sup>1</sup>

No one has documented the process of creating and validating an appropriate analytical technique for determining the assay of nintedanib (Figure 1). Therefore, this study set out to do three things: (i) Investigate how nintedanib breaks down in the body; (ii) Create a chromatographic stability indicator for the nintedanib drug substance assay; and (iii) Validate an analytical technique for the quantitative determination of drug.<sup>2</sup>

## MATERIAL AND METHODS

Nintedanib was obtained as a gift sample from Gift sample from Glenmark, Mohol. Methanol, methanol, acetonitrile, water (HPLC grade), and p-nitrophenol were procured from Shree Sadguru Hitech Pvt Ltd, Pune. Nintedanib (Nintedanib) capsules 150 mg were purchased from Market.

### Chromatographic Equipment and Conditions

A Thermo 2080 system, P4000 Quaternary pump, UV 6000 PDA detector, Ultrasonic cleaner power six sonic 420, UV spectrophotometer (UV 3092, Lab India, Mumbai), and vacuum

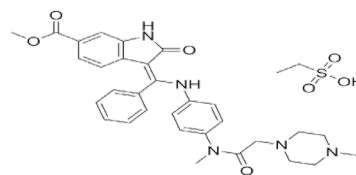


Figure 1: Chemical structure of nintedanib esylate

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oven were the components of the liquid chromatography (LC) system that was utilized for the development and validation of the methods.

#### Preparation of Standard Solution

After adding 10 mg of nintedanib to a 100 mL solvent, the diluent was sonicated and adjusted.<sup>3</sup>

#### Preparation of Sample Solution

Glass mortar was used to grind ten nintedanib capsules. In a 500 mL clean, dry volumetric flask, the amount of powder that is equal to ten capsules' worth of active ingredient was transferred. Then, 350 mL of diluent was mixed and the mixture was shaken with a mechanical stirrer and subjected to sonication for approximately 30 minutes, with 5-minute shaking intervals between. After allowing the residue to settle, a portion was taken out for further dilution, serving as a stock solution. Before injecting it into the high-performance liquid chromatography (HPLC) system, the sample was filtered through a 0.45 mcg/mL filter.<sup>4</sup>

#### Analytical Method Validation

The established reverse-phase high-performance liquid chromatography (RP-HPLC) method was checked for accuracy, precision, sensitivity, linearity, and stability of analytical solutions, among other metrics. The standards defined by the International Council for Harmonisation (ICH) were followed during the validation process.<sup>5</sup>

#### HPLC Method Validation

##### *Linearity, limit of detection, and limit of quantitation*

Required concentrations of 2, 4, 6, 8, and 10 µg/mL for nintedanib was achieved by diluting an appropriate proportion of the stock solution. The results are displayed in the Figure after the chromatogram was recorded. The concentration versus number of theoretical plates graph should be plotted for each concentration.<sup>6</sup>

##### *Precision*

- *Repeatability*

Precisely measure out 10 mg of nintedanib, then transfer the contents to a 100 mL flask. Mix 70 mL of diluent, sonicate to dissolve, then adjust the remaining volume with the same solvent. After that, 1.0 mL of nintedanib from solution A was transferred to a 10 mL volumetric flask using a pipette and then diluted with diluent until it reached the mark. The area was determined using HPLC after each of five injections of the standard solution.

- *Intermediate precision (Analyst to Analyst Variability)*

Using separate columns, we tested the method's intermediate precision on various days.<sup>7</sup>

##### *Accuracy*

The HPLC system was injected with standard solutions, as well as solutions with different levels of accuracy (50, 100, and 150%). Also computed were the amounts discovered and added for nintedanib's individual and average values.<sup>8</sup>

#### *Robustness*

Results were found to be within the defined limits of an assay, even though parameters may have differed.

- *Effect of variation of flow rate*

The impact of changing the flow rate was the subject of an investigation. From 0.8 to 1.2 mL/min, flow rate was adjusted.

- *Effect of variation of mobile phase composition*

Researchers set out to quantify the impact of mobile phase ratio fluctuation by manipulating the mobile phase ratio. The mobile phase's organic makeup ranged from ±2% v/v. An analysis was conducted using a standard solution containing 12 µg/mL of nintedanib and 50 µg/mL of, with the use of both the actual mobile phase composition and a range of mobile phase compositions. The HPLC system was flushed with a pre-made standard solution. The chromatograms are recorded.<sup>9</sup>

#### *Specificity*

Following the test protocol, samples were prepared and introduced into HPLC apparatus. Figure at findings and discussion shows the recorded chromatograms.<sup>10</sup>

#### *System suitability*

The nintedanib sample solution was introduced into the HPLC system three times in accordance with the test protocol. By computing statistical values, parameters were assessed from the standard chromatograms that were obtained.<sup>11</sup>

#### **Assay**

##### *Preparation of sample solution*

After grinding 10 to 150 mg nintedanib capsules, the powdered substance corresponding to 500 mg of the drug was moved to a 500 mL volumetric flask. Afterward, using the mobile phase, the volume was increased to a specified level and filtered using 0.45 µ filter paper. Squeeze off 5 mL of the aforementioned solution and dilute it to 50 mL using the mobile phase. It was determined how much Nintedanib was in each capsule.<sup>12</sup>

##### *Forced degradation studies*

The purpose of this forced degradation research is to identify the analytical technique for stability study in the formulation of nintedanib under different stressful situations.

##### *Control sample*

The nintedanib dosage form was ground from 10 capsules. A 500 mL clean and dry volumetric flask was used to dilute the powder in 10 capsules. Afterward mixing 350 mL of diluent, the system was shaken with a mechanical stirrer and subjected to sonication for approximately 30 minutes, with 5-minute shaking intervals between each. The mixture was then topped off with more diluent. After allowing the residue to settle, an aliquot was taken for further dilution. Using a 0.45 mcg/mL filter, 1-mL of the top clear solution was diluted with diluent until it reached the mark, then transferred to a 10 mL volumetric flask for injection into the HPLC system.

- *Acidic condition*

Two dozen pills were measured and ground into a powder. Put 90 mg of nintedanib powder into a 100 mL volumetric flask as a sample. About 75 mL of diluent was sonicated until dissolved and then diluted to volume. Add 35 mL of diluent and 3 mL of 5N HCl to 5 mL of this solution in a 50 mL volumetric flask, heated in a water bath at 70°C for 3 hours. Cooling at room temperature was allowed once the flask was taken out of the water bath. After the solution has cooled to room temperature, add 3 mL of 5 sodium hydroxide to neutralize it. Dilute it to volume with diluent and mix well.

- *Alkaline condition*

Two dozen pills were measured and ground into a powder. Put 90 mg of nintedanib powder into a 100 mL volumetric flask as a sample; sonicate and dilute it to volume. In a 50 mL volumetric flask, add 5 mL of the solution and dilute it with 35 mL of diluent. Then, add 2 mL of 5N NaOH. Heat system on a water bath at 70°C for 3 hours. Cooling at room temperature was allowed once the flask was taken out of the water bath. After it cooled to room temperature, dilute it to volume with diluent. After mixing, the sample was tested according to the test technique.

- *Oxidative condition*

Two dozen pills were measured and ground into a powder. Put 90 mg of nintedanib powder into a 100 mL volumetric flask as a sample. It was sonicated with about 75 mL of diluent until it dissolved and then diluted it to volume. Add 35 mL of diluent and 4 mL of 30% H<sub>2</sub>O<sub>2</sub> to 5 mL of this solution in a 50 mL volumetric flask, heated on a water bath at 70°C for 3 hours. Then, fill up to volume with diluent, mix, and then test according to the protocol.

- *Thermal condition*

Two dozen pills were measured and ground into a powder. Put 90 mg of nintedanib powder into a 100 mL volumetric flask as a sample. Sonicated 75 mL of diluent until it dissolved, and then diluted it to volume. Add 35 mL of diluent to 5 mL of this solution in a 50 mL volumetric flask. For at least 8 hours, the sample was left exposed to 80°C. Furthermore, diluted with diluent until it reaches the desired volume. Following the protocol, the exposed sample was examined.

- *Photolytic condition*

Two dozen pills were measured and ground into a powder. Fill a 100 mL volumetric flask with the sample powder that is equal to 90 mg of nintedanib. Sonicated 75 mL of diluent until it dissolved, and then diluted it to volume. Dissolve 5 mL of the solution in 50 mL of water. The sample was then exposed to 1.2 million lux hours of light with 35 cc of diluent. Tests were performed on the exposed sample.<sup>13,14</sup>

## RESULTS AND DISCUSSION

### Method Development and Optimization

The optimized method for nintedanib estimation showed a chromatogram with a sharp peak at a resolution time

5.612 minutes and had 4865 theoretical plates (N) (Table 1, and Figure 2).

### Linearity

With a R<sup>2</sup> value of 0.999, the linearity graph of nintedanib displayed the following equation:  $y = 25.45x + 4648$  (2–10 µg/mL) can be determined by this linear approach (Figure 3 and Table 2).

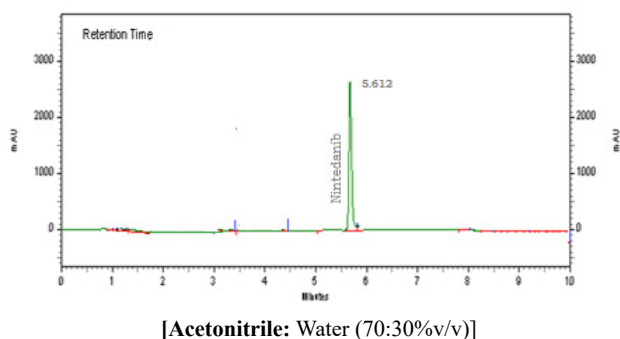
### Accuracy (%Recovery)

The conventional addition procedure was used to conduct the recovery experiment. Studies were conducted to determine accuracy at concentrations of 50, 100, and 150%. Below, you can see the chromatogram and recovery findings that were obtained for 5, 10, and 15 µg/mL.

The mean recoveries were found to be  $99.38 \pm 0.24$ . The recovery result indicates the accuracy of the method (Figure 4, and Table 3).

### Method Precision (Repeatability)

After injecting the standard solution five times, the area was measured by HPLC. We discovered that RSD values of nintedanib were 0.074% (Table 4). Results from five independent injections showed that the %RSD for the area was within the allowed range. Reproducible results are indicated by low values.



**Figure 2:** Standard chromatogram of nintedanib by optimized method

**Table 1:** Chromatographic details

Name of drug	Retention time (min)	Theoretical plates (N)	USP resolution	USP tailing
Nintedanib	5.612	4865	5.1	1.3

**Table 2:** Linearity results for nintedanib by HPLC

Concentration (µg/mL)	Theoretical plates (N)
2	4701
4	4752
6	4803
8	4855
10	4902
R <sup>2</sup> = 0.999	

**Table 3:** Accuracy results for nintedanib by HPLC

Spike level (%)	Concentration (µg/mL)	Replicate number	Theoretical plates (N)	%Recovery	Mean %Recovery
50	5	1	4817	99.7	99.66
		2	4495	99.8	
		3	4503	99.5	
100	10	1	4954	99.2	99.26
		2	4950	99.5	
		3	4953	99.1	
150	15	1	4996	99.0	99.23
		2	4875	99.3	
		3	4981	99.4	
SD					0.24
%RSD					0.00242

**Table 4:** RSD values of nintedanib by HPLC

Injection number	Retention time (minutes)	Theoretical plates (N)
1	5.670	4953
2	5.665	4958
3	5.616	4955
4	5.648	4948
5	5.652	4954
Mean		4953.6
S.D.		3.64
%RSD		0.074

**Table 5:** Intermediate precision results for nintedanib by HPLC

Parameter	%Assay
Mean*	99.56
SD	0.230
%RSD*	0.00231

**Intermediate Precision: (Reproducibility)**

We used high-performance liquid chromatography to measure the regions after injecting the standard solution five times. Based on the test procedure, the investigation was carried out by two analysts.

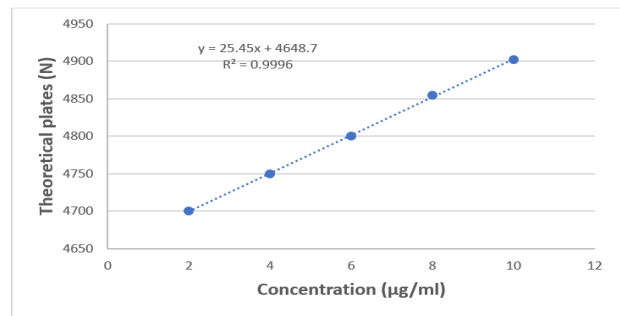
The RSD values of nintedanib are not more than 2.0 and %assay values were found within 98 to 102%, which reveals that the method is precise (Table 5).

**Robustness**

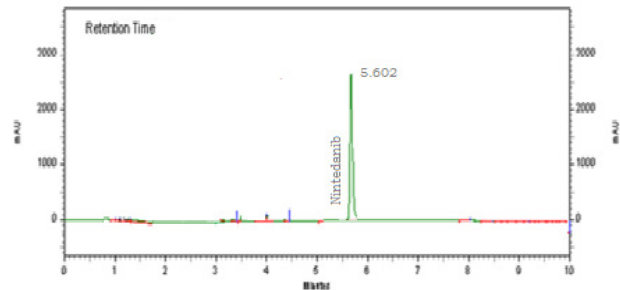
*Effect of variation in flow rate*

The impact of changing flow rate was the subject of an investigation. The flow rate was adjusted (Table 6).

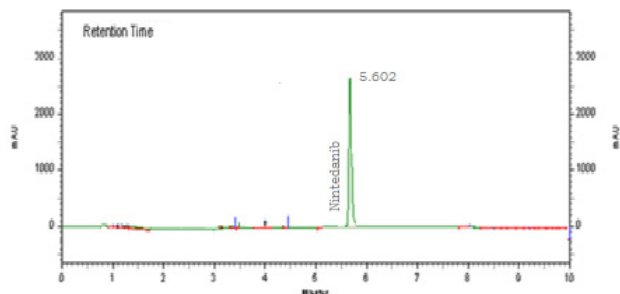
We measured the impact of different flow rates. Since the asymmetry and percentage RSD of retention time was within the range of allowable flow variations. Accordingly, 0.8 to 1.2 mL is the permissible flow rate.



**Figure 3:** Linearity graph for nintedanib



**Figure 4:** Standard chromatogram for accuracy



**Figure 5:** Standard chromatogram for nintedanib

*Effect of variation of mobile phase composition*

Researchers set out to quantify the impact of mobile phase ratio fluctuation by manipulating the mobile phase ratio.

We measured the impact of different flow rates because there was room for modification based on the percentage RSD of retention time and asymmetry (Table 7).

**Specificity**

With almost the same retention duration, the sample and standard chromatograms are indistinguishable. Since the retention duration of the analyte was unaffected by the placebo, we may conclude that the procedure was indeed specific.

Blank and placebo chromatograms do not exhibit a peak at a retention time of analyte peak. The retention time of the analyte is unaffected by the blank or placebo. Because of this, the approach is unique (Table 8 and Figure 5).

**Limit of Detection and Limit of Quantification**

It was determined that 3.96 ng/mL was LoD for nintedanib, S/N ratio of 3 or greater. Results showed that 12.4 ng/mL was the minimum detectable concentration. The chromatographic

**Table 6:** Robustness results for nintedanib by HPLC (variation in flow rate)

Flow rate (mL/min)	Theoretical plates (N)	Robustness results
		USP tailing
0.8	9948	1.4
1.0	4905	1.4
1.2	4977	1.3
SD		0.0577
%RSD		0.0422

**Table 7:** Robustness results for nintedanib by HPLC (variation in mobile phase composition)

Mobile phase composition (v/v)	Theoretical plates (N)	Robustness results
		USP tailing
+2%	4968	1.3
-2%	4948	1.4
SD		0.070
%RSD		0.54

**Table 8:** Specificity details of nintedanib chromatogram

Drug	Retention Time (minutes)	Theoretical plates (N)	USP resolution	USP tailing
Nintedanib	5.602	4856	5.1	1.4

**Table 9 :** Chromatographic details for LoD

Drug	Retention Time (minutes)	Theoretical plates (N)	USP resolution	USP tailing
Nintedanib	5.623	4109	5.1	1.4

**Table 10:** Chromatographic details for LoQ

Drug	Retention time (minutes)	Theoretical plates (N)	USP resolution	USP tailing
Nintedanib	5.621	4156	5.1	1.4

details for LoD and LoQ are given in Tables 9 and 10, respectively. Figure 6 represents LoD, and Figure 7 represents LoQ.

**System Suitability**

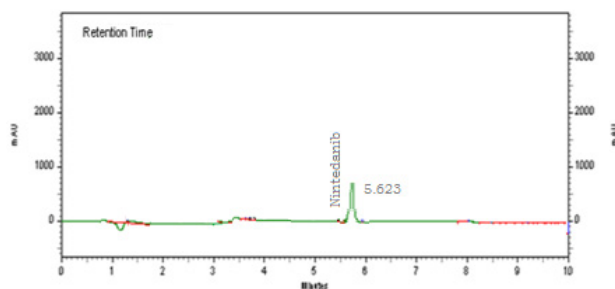
The nintedanib sample solution was introduced into HPLC system three times in accordance with test protocol (Table 11).

Assay for the drug can be performed with the selected system conditions.

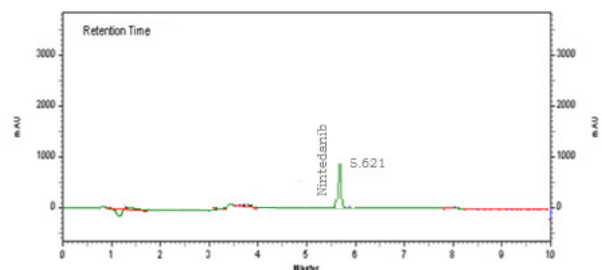
**Forced Degradation Studies**

*Acid induced degradation*

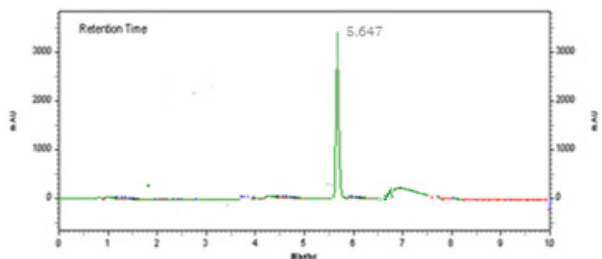
Peak area of nintedanib was not changed significantly and any additional peak was not observed in the chromatograph after refluxing in 5N HCl at 70°C for 3 hours. The chromatogram of nintedanib after degradation is displayed in Figure 8 and



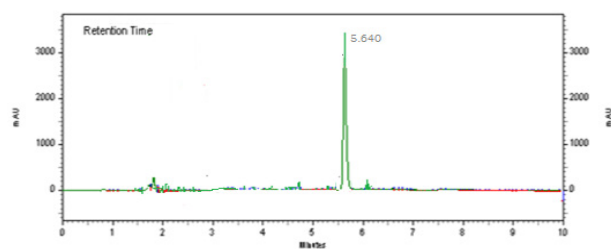
**Figure 6:** LoD for nintedanib



**Figure 7:** LoQ for nintedanib



**Figure 8:** Chromatogram for acid (5 N HCl) induced degradation of nintedanib (3 hours)



**Figure 9:** Chromatogram for alkali (5 N NaOH) induced degradation of nintedanib (3 hours)

chromatographic details are given in Table 12. The peak purity of the nintedanib after acid-induced degradation is 1.000, which shows the studied drug was stable in acid-induced stress conditions.

*Alkaline degradation*

The peak area of nintedanib was not changed significantly and any additional peak was not observed in the chromatograph after refluxing in 5 N NaOH at 70°C for 3 hours. The peak purity of the nintedanib after base-induced degradation is 1.000, which shows the purity of the nintedanib peak. The chromatogram of nintedanib after degradation with 5 N NaOH at 70°C for 3 hours is displayed in Figure 9 and Table 13.

**Table 11:** System suitability results for nintedanib by HPLC

Injection number	Concentration (µg/mL)	Theoretical plates (N)	Robustness results	
			USP resolution	USP tailing
1	10	4952	5.2	1.3
2	10	4956	5.2	1.4
3	10	4950	5.2	1.4
SD				0.0057
%RSD				0.042

**Table 12:** Chromatographic details (Acid degradation)

Name of drug	Retention time (minutes)	Theoretical plates (N)	USP resolution	USP tailing
Nintedanib	5.647	4978	5.2	1.4

**Table 13:** Chromatographic details (Alkaline Degradation)

Name of drug	Retention time (minutes)	Theoretical plates (N)	USP resolution	USP tailing
Nintedanib	5.640	4994	5.2	1.4

**Table 14:** Chromatographic details (Oxidative Degradation)

Name of drug	Retention time (minutes)	Theoretical plates (N)	USP resolution	USP tailing
Nintedanib	5.671	4982	5.16	1.4

**Table 15:** Chromatographic details (Thermal Degradation)

Name of drug	Retention Time (minutes)	Theoretical Plates (N)	USP resolution	USP tailing
Nintedanib	5.620	4974	5.2	1.4

**Table 16 :** Chromatographic details (Photolytic Degradation)

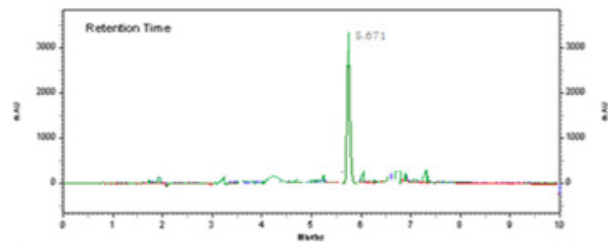
Name of drug	Retention time (minutes)	Theoretical Plates (N)	USP resolution	USP tailing
Nintedanib	5.634	4932	5.2	1.4

**Oxidative degradation**

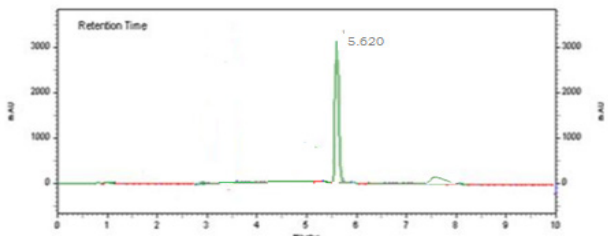
Peak area of nintedanib was not changed significantly and any additional peak was not observed in the chromatograph after refluxing in 30% H<sub>2</sub>O<sub>2</sub> at 70°C for 3 hours. The peak purity of nintedanib peak after oxidative degradation is 1.000. A chromatogram of nintedanib after degradation with 30% H<sub>2</sub>O<sub>2</sub> at 70°C for 3 hours is displayed in Figure 10 and Table 14. Hydrogen peroxide retention time is 2.9 minutes, which was confirmed by a chromatogram of 30% hydrogen peroxide.

**Thermal degradation**

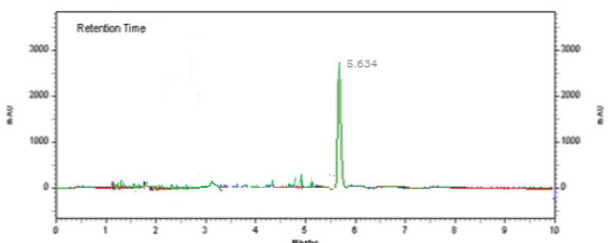
The peak area of nintedanib was not changed significantly and any additional peak was not observed in the chromatograph after exposure at 80°C for at least 8 hours. The peak purity of nintedanib peak is 1.000. Chromatogram of nintedanib after thermal degradation is displayed in Figure 11, Table 15.



**Figure 10:** Chromatogram for hydrogen peroxide (30% H<sub>2</sub>O<sub>2</sub>) degradation of nintedanib (3 hrs)



**Figure 11:** Chromatogram of thermal degradation of nintedanib (80°C)



**Figure 12:** Chromatogram of photolytic degradation of nintedanib

**Photolytic degradation**

The peak area of nintedanib was not changed significantly and any additional peak was not observed in the chromatograph after exposing at sample to 1.2 million lux hours of light. The peak purity of nintedanib peak is 1.000. A chromatogram of nintedanib after photolytic degradation under controlled conditions is displayed in Figure 12, Table 16.

The suggested approach was deemed stable based on the findings obtained from the forced degradation trials.<sup>15,16</sup> The study found that the RP-HPLC method was easy to use, quick, precise, sensitive, and selective. As a result, quality control laboratories can employ this technology for further work.<sup>17,18</sup>

**CONCLUSION**

The devised RP-HPLC method for estimating nintedanib in bulk and its formulations was obtained quickly, accurately, precisely, sensitive and easy to use. A novel approach to RP-HPLC for nintedanib was devised and subsequently validated. We validated the analytical process according to ICH requirements. Economic analytical procedure nintedanib is exemplified by this method. This approach works well for the regular, accurate analysis of big sample sizes. The thorough validation that was carried out led to the conclusion that the approach is stable and can be utilized for the duration of the

drug's shelf life. The suggested approach was deemed stable based on the findings obtained from the forced degradation trials. The study found that the RP-HPLC method was easy to use, quick, precise, sensitive, and selective. As a result, quality control laboratories can employ this technology for further analysis.

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