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Research

Development And Validation Of UV Spectrophotometric Method For The Determination Of Nintedanib In Pharmaceutical Dosage Form

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Abstract

A precise, simple, cost-effective, accurate Ultraviolet spectro-photometric method has been developed for the determination of Nintedanib in the Pharmaceutical dosage form. Nintedanib shows the highest λmax at 270nm. The Nintedanib follows linearity in the concentration range of 2.0-12.0 µg/mL with a superior correlation coefficient value of 0.9999. The precision of the method was studied in intra-day and inter-day studies. The % RSD value is < 2 which indicates that the method is precise. The % recovery was found to be in the range lies between 99.75-99.85 %. The percentage assay of Nintedanib obtained was 99.33 %. The Proposed Spectrophotometric method was validated as per the ICH Q2 (R1) guidelines. The developed UV method is accurate, precise, and reproducible. Hence this rapid method can be feasible for the quality control analysis of Nintedanib in the pharmaceutical dosage form.

Keywords: Nintedanib, Validation, Ultraviolet spectroscopy, Method development.

INTRODUCTION

The chemical name for Nintedanib is 1HIndole-6-carboxylic acid,2,3--dihydro-3-[[[4-[methyl[(4-methyl-1-piperazinyl) acetyl] amino] phenyl] amino] phenyl methylene]-2-oxo-, methyl ester. It has the molecular formula C31H33N5O4 and a molecular weightof 539.6248g/mol. 1H-Indole-6-carboxylic acid,2,3--dihydro-3-[[[4-[methyl[(4-methyl-1-piperazinyl) acetyl] amino] phenyl] amino] phenyl methylene]-2-oxo-, methyl ester. Nintedanib indolinone-derived inhibitor of Multiple Receptor Tyrosine kinases (RTKs)and Non- Receptor Tyrosine kinases (nRTKs) selectively binds to and inhibitsvascular endothelial growth factor receptor (VEGFR), fibroblast growth factor receptor(FGFR), platelet-derived growth factor receptor (PDGFR), and colony-stimulatingfactor 1 receptor (CSF1R) tyrosine kinases, which may result in the induction ofendothelial cell

apoptosis, the reduction in tumor vasculature, the inhibition of tumorcell proliferation and migration, and antifibrotic activity in pulmonary fibrosis.Nintedanib works by decreasing the blood supply to the cancer tumor to slow tumorgrowth. Nintedanib is used to treat Potential antiangiogenic, antifibrotic, andantineoplastic activities. Idiopathic Pulmonary Fibrosis (IPF). Literature Surveyshows that the Nintedanib has been determined by HPLC [1], HPTLC [2],UPLC [6], and LC-MS/MS [17], in biological fluids like human and rat plasma.However, no UV spectrophotometric method has been reported for the estimation ofNintedanib in bulk and pharmaceutical dosage forms hitherto. Hence the majorobjective of the present research is to develop and validate a simple, precise, sensitive UVspectrophotometric method for Nintedanib in Capsule dosage form as per InternationalConference on Harmonization (ICH) Q2 (R2) guidelines Figure 1, shows the chemicalstructure of Nintedanib.

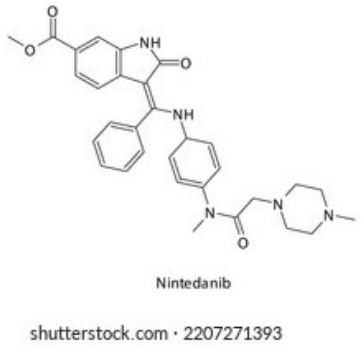

Fig 1: Chemical Structure of Nintedanib

MATERIALS AND METHODS

Instrument

A double beam PG instrument UV –Visible spectrophotometer containing two matchedquartz cells with a one cm light path was taken for measuring of absorbance ofNintedanib (0.1 mg sensitivity) balance was used for weighing. Ultra Sonicator bath Model no - 91250, PCI Ltd., Mumbai was used in this present study.

Chemicals and reagents

Nintedanib was procured from Hetero Drugs Ltd., Hyderabad, and Telangana, India. TheNintedanib capsules containing 100 mg labeled claim of Nintedanib tablets were used for thisstudy. Dimethylsulphoxide and sodium hydroxide were procured from Taranath scientific solutions., Hyderabad, India. Selection of solvent: Plentiful trials were executed to find out thesuitable solvent system for dissolving theNintedanib. The solvents such as, Dimethyl sulphoxide and sodium hydroxide and distilled water were triedbased on the solubility of the drug. Nintedanib is soluble in solvents such as Dimethyl sulphoxide and sodium hydroxide and distilled water. Thus, Dimethyl sulphoxide and sodium hydroxide and distilled water were selected.

Selection of detection wavelength

To determine the optimum λmax of Nintedanib, 10 µg/ml of the Nintedanib solution was prepared and scanned in the Ultra Violet wavelength range of 200 – 400 nm. It was observed that the drug showed maximum absorbance at 270.0 nm which was chosen as the detection wavelength for the estimation of Nintedanib.

Standard preparation solution

A stock solution of Nintedanib at 100 µg/ml is prepared in Dimethyl sulphoxide and sodium hydroxide (50:50) by sonication. Dilution in Dimethyl sulphoxide and sodium hydroxide (50:50) is made up at 2.0µg/ml-12.0 µg/ml concentrations.

Preparation of Calibration curve

From the above prepared Nintedanib stock solution, appropriate dilutions were preparedto get the ultimate concentrations of 2, 4, 6, 8,10 and 12.0 µg/ ml, and absorbance wastaken at λmax 270.0 nm. The average of such six sets of values was taken for the standardcalibration plot, and the calibration curve was plotted. The calibration curve was done byplotting Nintedanib concentration on the xaxis and their respective absorbances on they-axis.

Table 1: Calibration data of Nintedanib

S. No.	Concentration (µg/ml)	Absorbance
1	**2**	**0.065**
2	**4**	**0.133**
3	**6**	**0.209**
4	**8**	**0.274**
5	**10**	**0.339**
6	**12**	**0.407**

Table 2: Linear regression data

S. No.	Parameter	Results
1	Detection wavelength (λmax)	270nm
2	Regression equation (y= mx+ c)	y = 0.0341x+0.0008 r^2 = 0.9996
3	Slope (m) & Intercept (c)	0.0341&0.0008
4	Correlation coefficient (r2)	0.999

Linearity overlay for Nintedanib

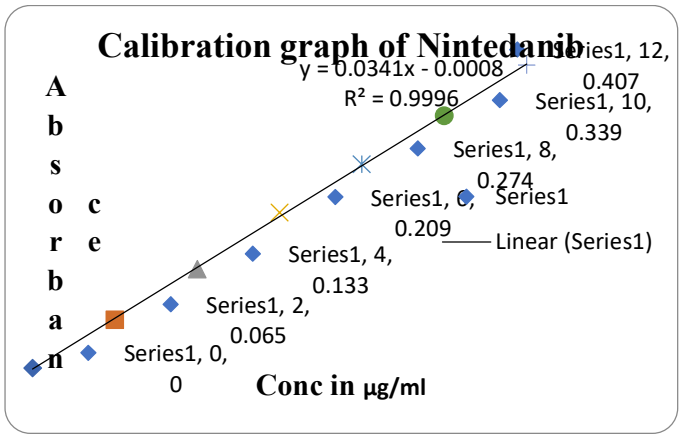

Fig 2: Calibration Curve for Nintedanib (2-12 µg/ml)

Table 3: Linearity Data of Nintedanib

Analyte	Concentration (µg/mL)	Absorbance	Linear regression Equation
Nintedanib	**2**	**0.065**	**y = 0.0341x+0.0008 r^2 = 0.9996**
	4	**0.133**	
	6	**0.209**	
	8	**0.274**	
	10	**0.339**	
	12	**0.407**	

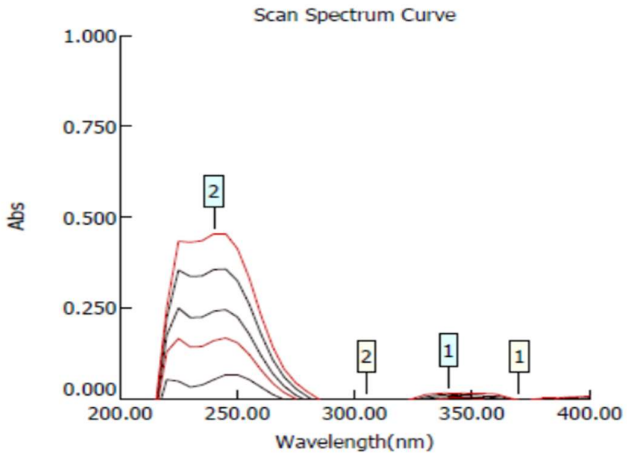

Fig 3: Ultraviolet Overlain Spectra of Nintedanib

Method development and validation

A lot of solvents were tested for solubility for Nintedanib, solvents such as Distilled water, Methanol, Acetonitrile, Dimethyl sulphaoxide and N-methyl pyrrolidine at 10 µg/ml concentrations. Nevertheless, Nintedanib was soluble and stable in the Dimethyl sulphaoxide and sodium hydroxide mixture for a minimum of 24 hours at room temperature. Hence DMSO-NaOH mixture was used for the detection of wavelength and preparation of standard and working concentration. To ensure the planned method for the pharmaceutical formulation, an assay of Nintedanib 100 mg capsules was utilized at working concentration. An assay for the working concentration of the sample at 270 nm was analyzed. UV spectrophotometric method is validated according to ICH Q2 (R1), guidelines for validation of analytical procedures. The method was validated for parameters such as specificity, linearity, range, accuracy, precision, LOD, LOQ, robustness, and system suitability testing.

Precision

System precision: In system precision 0.6µg/ml concentrations of six reproducible recordings of absorbance at 270.0nm were measured on the same day and corresponding responses were studied. The mean, SD, and % RSD were calculated.

Method precision

Method precision was estimated by conducting the assay of a sample under the test of repeatability (intraday precision) and intermediate precision was performed on three successive days three times. Eventually, the mean, SD, and % Relative standard deviation were determined.

Accuracy (recovery studies)

Recovery studies of Nintedanib were accomplished by applying the standard addition method. To a known amount of the pre-analyzed drug sample 50 %, 100 %, and 150 % of standard drug substance were added and suitably diluted. The absorbances of the resultant solutions were measured at 270.0nm. The amount recovered was determined by fitting the absorbance valuesin the calibration graph. At each level, 3analyses were performed. % Mean recovery was calculated as shown in Table 5. The accepted limits of recovery are 99.90% -99.99%. In fact, from the amount of Nintedanib was found and % recovery was estimated.

Ruggedness

Ruggedness is done by performing the proposed method on different instruments. In addition, this method is carried out by two different analysts and performing the method on different instruments to check the reproducibility (Table 6).

Analysis of marketed formulation

The validated method was applied to the estimation of Nintedanib. 20 capsules were assayed and the results are represented in table 7 which indicates that the amount of drug in the tablet sample was in good agreement with the label claim of the formulation as indicated by the percentagerecovery of 99.87% (Table 7.1).

Table 4: Results of system precision

S. No	Absorbance	
1	270	0.335
2	270	0.338
3	270	0.341
4	270	0.342
5	270	0.339
6	270	0.334
Mean	0.338	0.338
Standard deviation	0.003	0.003
% Relative Standard deviation	0.94	0.94

Table 5: Accuracy of results

Recovery level	Amount of standard drug added (µg/mL)	Amount of testadded (µg/mL)	Total amount recovered (µg/mL)	% Recovery
50%	0.170	100.09	0.002	1.47
100%	0.337	99.21	0.002	0.45
150%	0.505	99.11	0.003	0.60
Mean Recovery: 99.77				

Table 6: Results of ruggedness

S.NO.	Absorbance			
	Analyst-1	Analyst-2	Instrument-1	Instrument-2
1	0.334	0.338	0.336	0.338
2	0.339	0.334	0.339	0.338
3	0.337	0.34	0.334	0.337
Statistical validation data of Intraday precision				
SD	0.00251	0.00305	0.0025	0.00057
Mean	0.336	0.337	0.336	0.337
%RSD	0.81%	0.81%	0.80%	0.80%

$$\%\ Assay = \frac{Test\ absorbance}{Standard\ absorbance} * \frac{weight\ of\ standard}{dilution\ of\ standard} * \frac{Dilution\ of\ test}{wWeight\ of\ test} * \frac{Average\ weight}{Label\ claim} * \frac{\%\ Purity\ of\ drug}{100} * 100$$

$$\%\ Assay = \frac{0.426}{0.428} * \frac{100}{100} * \frac{10}{100} * \frac{10}{100} * \frac{100}{256} * \frac{100}{10} * \frac{100}{10} * \frac{640}{250} * \frac{99.8}{100} * 100 = 99.33$$

Table 7: Result of Assay of pharmaceutical formulation Nintedanib

	Nintedanib	
	Standard	Sample
Absorbance 1	0.429	0.424
Absorbance 2	0.426	0.428
Absorbance 3	0.428	0.427
Average	0.428	0.426
Standard deviation	0.002	0.002
% RSD	0.36	0.49

Table 7.1: Result of Assay of pharmaceutical formulation Nintedanib

S.NO	Formulation	Amount present (mg)	Amount obtained* (mg)	% Purity (% w/w)
1	CAPSULE	100	99.8	99.33

RESULTS AND DISCUSSIONS

The ultraviolet spectra of Nintedanib were scanned in the region between 200-400 nm. The overlay spectra of Nintedanib at different concentrations were absorbedmaximum at 270.0nm, which was selected asthe detection wavelength. The response ofthe Nintedanib was found to be linear in theconcentration range of 2.0-12.0 µg/ml with a good correlation coefficient of r2=0.999Figure 3 shows the Nintedanib linearitycalibration curve and Table 3 shows the calibration data of Nintedanib linear regression data of the proposed UVmethod. Figure 3 displays the over lay spectra of Nintedanib. The system precision of Nintedanib are tabulated in Tables 4 respectively. The % RSD was less than 2 inall precision results cases which indicatesthat the method was precise. In this recovery study accuracy was carried out by using a standard addition method at three different concentration levels (50%, 100%, and 150%). The mean percentage recovery at each level should be 99.66% - 99.77%. All the results are well within the acceptance criteria and results indicate that the method isaccurate. Results are excellent and displayed in Table 5. Ruggedness was performed to check the reproducibility which showed the % RSD less than 2 which indicates that the method was rugged (Table 6). The developed method was eventually applied for the quantification of Nintedanib in capsules. The mean % assay values were found to be 99.33 %. The amount of the drug in thecapsule sample was in good agreement with the label claim of the formulation. The assay results are shown in Table 7.1.

CONCLUSION

The UV method was developed for the determination of Nintedanib. In this study,the precision and accuracy were < 2 % RSD. This method provides reproducible resultswith high precision, and accuracy and was capable of analyzing Nintedanib in low concentrations. However, this UV method is simple, quick, and sensitive. The results proved that this method is successfully idealfor routine quality control testing of Nintedanib samples

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