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Nintedanib : A Review on Analytical Method Development and Validation for Quantification in Bulk and Pharmaceutical Dosage Form and Characterization of Degradation Products by Various Analytical Techniques

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ABSTRACT

A potent tyrosine kinase inhibitor (TKI), nintedanib has recently been identified as a promising therapeutic agent for the management of fibrotic and neoplastic diseases. The development, validation, and optimization of analytical methods for analysis of Nintedanib in bulk and its formulations, and characterization under various conditions of degradation are the themes of this review. Multiple studies have been conducted to develop stability, efficacy, and safety of Nintedanib by using techniques such as RP-HPLC, UV spectrophotometry, UPLC-MS/MS and HPTLC. These methods were validated in compliance with ICH guidelines for precision, linearity, specificity, and accuracy. This was done by conducting comprehensive stress degradation studies that provided insights into Nintedanib stability profile and degradation pathways, relevant to developing stability indicating methods for Quality Control and regulatory compliance. This review provides a detail about the development of methods to optimize the monitoring of therapeutic efficiency of Nintedanib and its clinical use.

Keywords: Nintedanib, Idiopathic pulmonary fibrosis, Method development, validation.

INTRODUCTION

Over the last few years, Nintedanib, a new tyrosine kinase inhibitor (TKI), has attracted much interest because of its capability to effectively treat fibrotic and neoplastic diseases. Initially developed as an angiogenesis inhibitor, it has in vitro specificity for blockade of vascular endothelial growth factor receptor (VEGFR), platelet derived growth factor receptor (PDGFR), and fibroblast growth factor receptor (FGFR). This is an interference with fibrosis and tumor progression signaling pathways that binds to a huge spectrum of molecules.[1]

In 2014, Nintedanib was the first and only fibrosis fibrosis therapy approved in the treatment of idiopathic pulmonary fibrosis (IPF), providing a new novel therapeutic option to slow disease progression. Later, its indications expanded to include systemic sclerosis associated interstitial lung disease (SSc-ILD) and some advanced cancer, including non-small cell lung cancer (NSCLC) in combination with docetaxel. As a dual anti–fibrotic and anti–angiogenic agent, nintedanib boasts unique properties and is a potential therapy for a broad spectrum of pathological conditions in which dysregulated cell signaling and extracellular matrix remodeling are both key.[2]

Inhibiting key pathways regulating fibroblast proliferation, differentiation, and migration, nintedanib successfully ameliorates the fibrotic processes that are critical to IPF and other fibrotic diseases. Its utility in long term management is in part due to its tolerability profile and manageable side effects such as gastrointestinal disturbances. Still ongoing research will be necessary to optimize its application and reveal new therapeutic potentials.[3]

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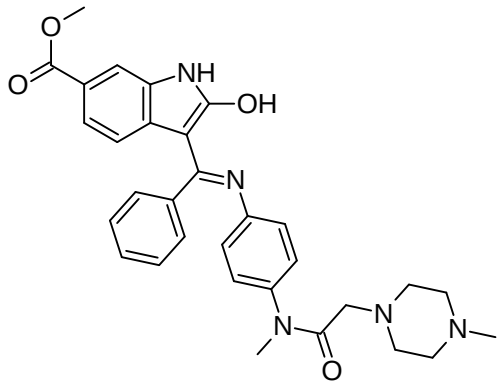

Figure No-1 Structure of Nintedanib

The efficacy of nintedanib in slowing progress of lung diseases and marked by landmark trials such as INPULSIS and SENSCIS have been validated by key studies. These trials revealed its disease modifying role in diseases that have traditionally been associated with poor prognosis and limited treatment options.[4]

Mechanism of action:

The precise mechanism of action of Nintedanib in IPF is unclear, although it is known to inhibit the receptor tyrosine kinases of platelet-derived growth factor (PDGF), fibroblast growth factor (FGF), and vascular endothelial growth factor (VEGF). In preclinical studies using nintedanib, it was surmised that the mechanism of action for its antifibrotic effects is through the inhibition of one or more of these receptor tyrosine kinases. However, it was acknowledged that nonreceptor tyrosine kinases and yet unidentified targets and/or cellular processes might play a role in exerting in vivo antifibrotic effects.[5]

Nintedanib work by binding to the ATP binding pocket FGF, PDGF and VEGF receptors resulting in blockade of the autophosphorylation of these receptors and subsequent downstream signalling pathways. This approach blocks pro-fibrotic and proliferative pathways downstream of the receptors stimulation.[6]

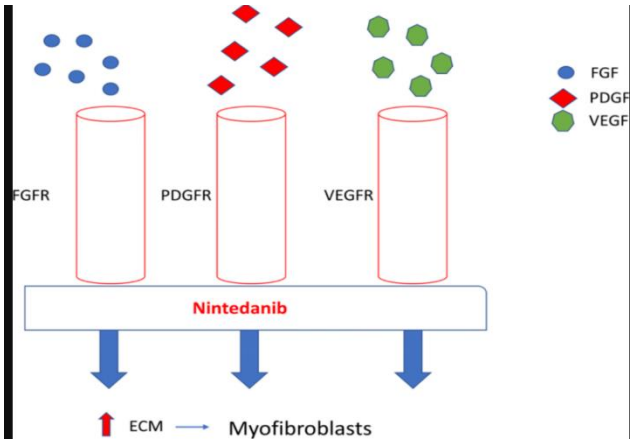

Figure No-2 Mechanism of Action of Nintedanib

Analytical Methods Reported for Quantification of Nintedanib:

Chaitanya M et al (2024) proposed a simple, selective, isocratic RP-HPLC method for the quantitative determination of Nintedanib and carried out validation of the method. The chromatographic strategy utilized Symmetry ODS (C18) RP Column, 250 mm x 4.6 mm, 5µm, using isocratic elution with a mobile phase of Phosphate Buffer (0.02M) and Acetonitrile were consisting of 48:52% v/v (pH-2.80). A flow rate of 1.0 ml/min and a detector wavelength of 248 nm utilizing the UV detector were given in the instrumental settings. Validation of the proposed method was carried out according to an international conference on harmonization (ICH) guidelines.[7]

Kadam S et al (2024) designed and verified reverse-phase high-performance liquid chromatography (RP-HPLC) method for nintedanib 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 (r2 > 1.00) across doses ranging from 2 to 10 µg/mL. Verification of recovery was done by adding concentrated solutions of 5, 10, and 15 µg/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.[8]

Divya et al (2023) developed and validated a simple, reliable, sensitive, precise, rapid, and reproducible RP-HPLC method for the determination of Nintedanib in the pharmaceutical dosage form. Separation was achieved under optimized chromatographic conditions on a Poroshell C18 isocratic column, (4.5 mm i.d. X 150 mm, 3.5 µm particle size maintained at ambient temperature). The mobile phase consisted of methanol, and acetonitrile in the ratio 50:50 v/v, isocratic elution at a flow rate of 1 mL/ min at ambient temperature, and using a PDA detector to monitor the elute at 379.5 nm. The retention time of Nintedanib was found to be 1.239 min and the calibration curve was a linear function of the drug in the concentration range of 2-10 ppm (r2 = 0.9999). The limit of detection and the limit of quantitation was found to be 0.039911843 µg/mL and 0.120944979 µg/mL respectively. The recovery (accuracy) studies were performed and the percentage recovery was found to be 98.06 - 99.32 % w/w. The proposed method was validated as per ICH guidelines. Thus, the developed reversed-phase HPLC method was found to be feasible for the determination of Nintedanib in pharmaceutical formulation.[9]

Nagendra G et al (2023) developed a precise, simple, cost-effective, accurate Ultraviolet spectrophotometric method for the determination of Nintedanib in the Pharmaceutical dosage form. Nintedanib shows the highest λmax at 379.5 nm. The Nintedanib follows linearity in the concentration range of 0.2-1.0 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 99.93 %. 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.[10]

Velagacherla et al (2023) developed a method for Nintedanib which is simple, precise, reproducible, stable, and accurate. The inherent stability of NTB was evaluated using the proposed analytical method approach and force degradation studies were carried out. NTB was separated chromatographically on the Shimadzu C_{18} column as stationary phase (250 ×4.6 mm, 5 µm) using an isocratic elution method with 0.1% v/v triethyl amine (TEA) in HPLC grade water and acetonitrile (ACN) in the ratio 35:65% v/v. The mobile phase was pumped at a constant flow rate of 1.0 ml/min, and the eluent was detected at 390 nm wavelength.[11]

Yendra P et al (2023) discussed how a related substance method can be developed for Nintedanib esylate. The best possible separation between the critical peak pairs was achieved using an X-Select charged surface hybrid Phenyl Hexyl (150 × 4.6) mm, 3.5 µm column. A mixture of water, acetonitrile, and methanol in mobile phase-A (70:20:10) and mobile phase-B (20:70:10), with 0.1% trifluoroacetic acid and 0.05% formic acid in both eluents. The set flow rate, wavelength, and injection volumes were 1.0 ml/min, 285 nm, and 5 µl, respectively, with gradient elution. The method conditions were validated as per regulatory requirements and United States Pharmacopeia general chapter < 1225 >. The correlation coefficient for all impurities from the linearity experiment was found to be > 0.999. The % relative standard deviation from the precision experiments ranged from 0.4 to 3.6. The mean %recovery from the accuracy study ranged from 92.5 to 106.5. Demonstrated the power of the stability-indicating method through degradation studies; the active drug component is more vulnerable to oxidation than other conditions. Final method conditions were further evaluated using a full-factorial design. The robust method conditions were identified using the graphical optimization from the design space.[12]

Sole PP et al (2022) developed the new sensitive and rapid RP-HPLC method for determination of Nintedanib in bulk and pharmaceutical dosage forms; it was validated according to ICH and FDA guidelines. The RPHPLC analysis was performed on the Thermo 2080 system equipped with a Scientific ARP-C18 (250 mm X 4.6 mm), 5µ column, with a mixture Acetonitrile: water (80:20 % v/v) as the mobile phase, at the flow rate of 1.0 mL/min. Detection was performed at the wavelength (λ) of 210 nm, and the retention time of Nintedanib was found to be 4.42 min. The total run time was 10 min. The calibration plot gave linear relationship over the concentration range of 20-100 µg/ml. The LOD and LOQ were 4 and 12.5ng/ml, respectively. The accuracy of the proposed method was determined by recovery studies and was found to be 99.93%. Repeatability testing for both standard and sample solutions showed that the method is precise within the acceptable limits.[13]

Dhiman V et al (2021) studied degradation chemistry under various stress conditions recommended in ICH guidelines Q1A R(2) for ninetedanib. The drug was subjected to hydrolytic, photolytic, thermal, and oxidative (H_2O_2, AIBN, $FeCl_3$ and $FeSO_4$) stress conditions. The degradation products formed in stressed solutions were successfully separated on an ACQUITY UPLC CSH C18 (2.1 × 100 mm, 1.7 µm) column, using a gradient UPLC-PDA method, developed with acetonitrile: methanol (90:10) and 0.1 % formic acid (pH 3.0) as the mobile phase. The drug proved to be labile to acidic, neutral, and alkaline hydrolytic, and H_2O_2/AIBN oxidative conditions. It was stable to photolytic and thermal stress conditions, and even in oxidative reaction solutions containing $FeCl_3$ or $FeSO_4$. Additionally, the drug exhibited instability when its powder with added sodium bicarbonate was stored at 40 °C/75 % RH for 3 months. In total, nine degradation products (DPs 1–9) were formed. To characterize them, a comprehensive mass fragmentation pathway of the drug was first established using UHPLC-Q-TOF/MS/MS data. Similarly, the mass studies were then carried out on the stressed samples using the developed UPLC method. All the degradation products were primarily characterized through comparison of their mass fragmentation profiles with that of the drug. To confirm the structure in one case (DP 3), additional nuclear magnetic resonance (NMR) studies were carried out on the isolated product.[14]

Waghmare SA et al (2021) developed and validated a simple, robust, and accurate Reverse- Phase High-Performance Liquid Chromatography method for estimation of Nintedanib Esylate in bulk, Pharmaceutical Dosage form, and Human Plasma. Full 3 Level Factorial design was employed for optimizing columns C_8 and C_{18}. The optimized chromatographic conditions are column C_{18}, Ammonium format buffer: Acetonitrile (28.19:71.81 v/v) and pH of buffer (3). Furthermore, acetonitrile was used as a precipitating agent to extract Nintedanib in human plasma. After centrifuging at 2000 rpm, the supernatant was then injected and observed that the peak from blank plasma does not interfere with the peak of Nintedanib by using *p*-nitrophenol as an internal standard. Linearity was observed in the concentration range of 10 µg to 50 µg/mL (r^2=0.9988). The accuracy range was 99.87 to 100.08 %. Intra-day and Inter-day precision was found to be 0.5432 & 0.5242 (% RSD). The bioanalytical method was validated as per ICH guideline M10 and results were found to be r^2 (0.9988), Recovery (99.91 %), Specificity (99.94 %), Precision (Less than 0.543 % RSD), and Robustness (less than 0.500 % RSD. The proposed method was useful for the best analysis of Nintedanib Esylate in Bulk, pharmaceutical dosage forms and was successfully applied to a pharmacokinetic study.[15]

Jayagopal B et al (2020) developed and validated a UHPLC method for estimating degradation products using QbD approach. Five degradation impurities were separated and well characterized. Further, the degradation pathway of the anticancer drug nintedanib (NIN) was explored for the first time in the soft gel formulation using tandem quadrupole MS abetted mass identification, and ESI/MS/MS aided structure elucidation was performed. By carefully demonstrating the step-by-step procedure for QbD-based optimization, parameters such as the analytical target profile (ATP) and critical quality attributes (CQAs) were assessed. The risk assessment was performed using failure mode effect analysis (FMEA). Critical method attributes and critical method parameters were identified based on the magnitude of the calculated risk priority number (RPN) value. Designed experiments using 4-factor two-level factorial design monitored three critical quality attributes to arrive at a method operable design space (MODS). The effect of individual method attributes was also analysed using half-normal and Pareto charts. Control strategies design and RPN values were recalculated based on the DOE output. This RPN value is eventually identified to be significantly smaller and satisfactory within the allowable limit.[16]

Kumar R et al (2020) developed an optimized Reverse Phase High Performance Liquid Chromatographic (RP-HPLC) method to quantify Nintedanib in pharmaceutical formulations using Inertsil sustain (C18, 250 mm × 4.6 mm id, 5µ) column. The mobile phase consisted of 0.1% (v/v) Trifluoroacetic acid in water and Acetonitrile in the ratio of 60: 40 (v/v) pumped at a flow rate of 1.0 ml/min, in an isocratic mode with an injection volume of 20 µl. Nintedanib was detected at 265nm having a retention time of about 5.3 mins with no interference of commonly used excipients. The method was linear over the concentration range of 1-30 µg/ml (R2 =1). The proposed method is rapid, accurate, economical, and validated as per ICH guidelines and may be used in case routine analysis of Nintedanib in pharmaceutical formulations due to its sensitivity and reproducibility.[17]

Paquini B et al (2020) presented a liquid chromatography-tandem mass spectrometry method for the simultaneous determination of NIN and its seven potential impurities. The risk-based approach of Analytical Quality by Design was applied in method development. The critical method parameters (CMPs) were the type of organic solvent in the mobile phase, formic acid percentage, column flow rate, oven temperature, gradient slope of organic eluent. The critical method attributes (CMAs) were selected as analysis time and selectivity between the main compound NIN and the adjacent peaks. Design of Experiments methodology was effectively employed for establishing the relationship between the CMPs and the CMAs. In the scouting step, a Restek Ultra AQ C18 (100 × 2.1 mm, 2.7 µm) core-shell column was selected, and then the effects of different levels of the five CMPs on the CMAs were evaluated by means of a 3^5//16 symmetric screening matrix. A Box-Behnken Design made it possible to obtain detailed maps of predicted CMAs throughout the investigated experimental domain, pointing out the presence of interaction and quadratic effects. The probability of meeting the specifications for the CMAs was calculated by Monte-Carlo simulations, performing a risk analysis, and drawing risk of failure maps, which were used to visualize and define the method operable design region (MODR) with a probability $\pi \geq 90\%$. The final working conditions (enclosing the MODR interval) were as follows: methanol as organic solvent; formic acid percentage, 0.15% v/v; flow rate, 0.40 mL min^{-1} (0.37–0.43 mL min^{-1}); oven temperature, 40 °C (38–40°C); gradient

slope of organic eluent, 14.00% eluent B min^{-1} (12.85–15.15% eluent B min^{-1}). The resulting analysis time was about 10 min. Validation was carried out according to International Council for Harmonisation guidelines and the optimized method was applied to the analysis of NIN soft capsules for quality control purposes.[18]

Parmar et al (2020) developed and validated an accurate, sensitive, and rapid gradient reverse phase high performance liquid chromatography (RP-HPLC) method for related substances of Nintedanib Esylate. HPLC analysis was performed on YMC Triart, C18 (250 x 4.6) mm, 3µm. Column temperature maintained at 35°C conditions. Chromatographic separation was achieved with mobile phase gradient program at flow rate of 1.0mL/min. The injection volume was 10µl. The UV detection wavelength was 245nm. The method suitability was checked and validated according to the ICH guidelines Q2 (R1) for specificity, linearity, accuracy, precision, limit of quantification, limit of detection. Limit of detection of each impurity was found to be less than 0.031% w/w indicating that the developed method is highly sensitive. The calibration curve of each impurity was found to be linear within the concentration range of about 0.10µg/ml to 2.0µg /ml. The regression data for calibration curve shows good linear relationship. Correl coefficient (r2) of each impurity was found to be greater than 0.998. The Recovery was found to be accurate for each impurity within the spike concentration range of about 0.10µg/ml to 1.5µg /ml. The Recovery of each impurity was found to be between 80% to 120%.[19]

Shukla SK et al (2020) developed a high throughput ultra-performance liquid chromatography (UPLC)-ultraviolet method for quantification of nintedanib in rat and human plasma which was optimized using chemometrical approach. Design of experiment and multivariate statistical approach was used for definition of optimized method. Final separation was performed using protein precipitation method on ACQUITY HSS T3 C18 column in isocratic mode using potassium phosphate buffer (pH 7.5): acetonitrile. Method was validated as per US-FDA guidelines linearly from 15–750 ng/ml. All quality control samples showed <15% relative standard deviation for precision and 85–115% accuracy along with >98% extraction recovery. The developed method is easily applicable in determining pharmacokinetic parameters in preclinical subjects along with successful implementation for quantification in human plasma samples.[20]

Dutta D et al (2019) developed a simple and rapid stability-indicating method for determination of nintedanib (NTB) in bulk drug using HPTLC and LC-MSn. Stress degradation studies were carried out by hydrolysis, oxidation, thermal and photolytic. Drug was found to be stable in thermal whereas one degradant was found in acid hydrolysis, three in basic hydrolysis, five in oxidative and two in photolytic stress. The probable structures of the degradation products were predicted & the degradation pathway was also established. Chromatography was carried out using silica gel 60 F254 TLC plate and mobile phase of Chloroform: Methanol in the ratio 7:3 v/v. The densitometric determination was done at 386 nm. The degradants were not detectable when stressed as per ICH recommended conditions but on increasing the strength of acid, base and peroxide, the degradants were very much prominent and were easily detectable in HPTLC. The LC system consisted of a Zorbax Bonus C18 (150 mm×4.6 mm, 3.5 µ). A gradient mobile phase consisting of mobile phase A: 10mM Ammonium formate (0.05% formic acid): ACN (pH 3.9) (90:10) and mobile phase B: 10mM Ammonium formate (0.05% formic acid): ACN (pH 3.9) (10:90) with a flow rate of 0.7mL/min was used to separate the degradants up to a total retention time of 15 min. Mass spectrometric detection was performed using Thermo Scientific LCQ fleet Ion Trap LC/MSn.[21]

Dutta D et al (2018) developed a simple, rapid, precise, and accurate High-Performance Thin Layer Chromatography (HPTLC) method and validated for the estimation of Nintedanib, a novel tyrosine kinase inhibitor used in idiopathic pulmonary fibrosis, in bulk drug. Chromatography was carried out using silica gel 60 F254 Thin Layer Chromatography (TLC) plate and mobile phase Chloroform: Methanol in the ratio 7:3 v/v. The densitometric determination was done at 386 nm. Regression analysis data for the calibration plot were indicative of a good linear relationship between response and concentration over the range of 800–3200 ng/band. The variance (r) was found to be 0.999. The Limit of Detection (LOD) and Limit of Quantitation (LOQ) were found to be 83.357 ng/band and 252.599 ng/band respectively. The method was validated according to the International Council for Harmonisation of Technical Requirements for Pharmaceuticals for Human Use [ICH Q2(R1)] guideline. The method was precise and accurate with %RSD 0.5323 (intraday) and 0.6939 (interday) respectively and percentage recoveries in the range 99.65–101.43%.[22]

Darwish HW et al (2016) developed and validated a fast, sensitive, and simple liquid chromatographic method coupled with tandem mass spectrometry for the determination of the potent tyrosine kinase inhibitor, ninetedanib (NTB) in plasma, utilizing cyclobenzaprine (CBP) as internal standard (IS). Separation of the two components (NTB and CBP) was performed on a pentafluorophenyl (PFP) reversed phase column (50 × 2 mm, 3µm) at ambient temperature using isocratic elution with acetonitrile-water (60:40, v/v) containing 0.01 M ammonium formate buffer (pH 4.2) at a flow rate of 0.4 mL/min. NTB and CBP were monitored by a triple quadrupole tandem mass spectrometer with electrospray ionization source in the positive ion mode. The method was validated following the European Medicines Agency (EMA) guideline. The proposed method allowed rapid and specific quantification of NTB in the calibration range of 2 - 150 ng/mL and determination coefficient of ≥ 0.999. Intra- and inter-day

accuracy and precision were < 4 % in all cases. The developed procedure is rapid, specific, reliable, and validated for quantification of NTB in human plasma, and thus can be applied efficiently for the analysis of clinical samples containing NTB.[23]

Purnachand D et al (2015) developed a novel stability indicating Reverse Phase-Liquid Chromatography (RP-HPLC) method and validated for the determination of Assay of Nintedanib Drug Substance in the presence of degradation products generated from forced degradation studies. Chromatographic separation was achieved on YMC Pack ODS-AQ (C18) column (Size: 250 x 4.6 mm; 5 µm particle size) at flow rate 1.0 mL/min. with 210 nm detection. The mobile phase was Water: Acetonitrile (pH of water was adjusted to 3.0 with Orthophosphoric acid) through gradient elution. Product was subjected to stress conditions like acid, base, peroxide, thermal and photolytic degradation. No new impurities were observed during thermal and Photolytic degradation. Developed method was validated as per ICH guidelines using validation parameters like specificity, linearity, LOQ, accuracy, precision, robustness, and ruggedness. LOQ value was achieved at 2 µg/mL concentration. Good linearity (r2 > 1.00) was obtained ranging from 25 µg/mL to 150 µg/mL concentrations. Recovery was verified by spiking 40 µg/mL, 50 µg/mL, and 60 µg/mL concentrated solutions to 50 µg/mL concentrated solution. Hence newly developed RP-HPLC method is capable for estimating assay of Nintedanib Drug Substance and the present method is effectively separated the Nintedanib from its major degradation products.[24]

Xu D et al (2015) developed a sensitive and rapid ultra-performance liquid chromatography tandem mass spectrometry (UPLC-MS/MS) method to determine nintedanib in mice plasma using diazepam as the internal standard (IS). Sample preparation was accomplished through a protein precipitation procedure using acetonitrile. The analyte and IS were separated on an ACQUITY UPLC BEH C18 column (2.1 mm × 50 mm, 1.7 µm) with the mobile phase of acetonitrile and 0.1% formic acid in water with gradient elution at a flow rate of 0.40 mL min^{-1}. The detection was performed on a triple quadrupole tandem mass spectrometer equipped with positive-ion electrospray ionization (ESI) by multiple reaction monitoring (MRM) of the transitions at *m/z* 540.3 → 113.0 for nintedanib and *m/z* 285.2 → 193.1 for IS. The linearity of this method was found to be within the concentration range of 0.1–500 ng mL^{-1} with a lower limit of quantification of 0.1 ng mL^{-1}. Only 3.0 min was needed for an analytical run.[25]

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Conflicts of Interest

The author declares there is no conflict of interest.

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