Journal of Neonatal Surgery
ISSN(Online): 2226-0439
Vol. 14, Issue 32s (2025)
https://www.jneonatalsurg.com

OPEN ACCESS

Development and Characterization of a Nint-Loaded Nanoparticulate Matrix Tablet for Enhanced Solubility and Sustained Release

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Cite this paper as: Mr.Vaibhav L.Narwade, Dr.Mahesh Thakare, Dr.Pranav Parekh, Ms. Mamta Pavale, Ms. Minakshi Londhe, Ms.Dhanshree Chivte, Ms.Priyanka Punde, Mr.Pritam Suresh Waghmode (2025) Development and Characterization of a Nint-Loaded Nanoparticulate Matrix Tablet for Enhanced Solubility and Sustained Release. *Journal of Neonatal Surgery*, 14 (32s), 8461-8466.

ABSTRACT

Nintedanib, a tyrosine kinase inhibitor, is a critical treatment for idiopathic pulmonary fibrosis but suffers from poor aqueous solubility and low oral bioavailability of approximately 4.7% due to extensive first-pass metabolism. These limitations hinder its therapeutic efficacy and necessitate frequent dosing. To overcome these challenges, a novel nanoparticulate matrix tablet was developed. Nintedanib-loaded nanoparticles were formulated using the polymer PLGA via a solvent evaporation technique and were subsequently compressed into matrix tablets by direct compression using polymers like HPMC K4M and Microcrystalline Cellulose. The prepared nanoparticles were characterized for entrapment efficiency, morphology (SEM), and physical state (XRD). The matrix tablets underwent evaluation for pre- and post-compression parameters, I understand you'd like a downloadable Word file. However, as an AI, I cannot generate files for download..

Keywords: *Nintedanib, Nanoparticles, Matrix Tablet, PLGA, Sustained Release, Bioavailability, Direct Compression.*

1. INTRODUCTION

Oral drug delivery remains the most preferred route of administration due to its convenience, cost-effectiveness, and high patient compliance. However, many potent drug molecules exhibit poor oral bioavailability, often due to low aqueous solubility and significant first-pass metabolism. Nintedanib, a triple angiokinase inhibitor used for idiopathic pulmonary fibrosis (IPF) and other interstitial lung diseases, is a prime example of such a drug. Despite its clinical importance, its therapeutic potential is limited by its poor water solubility and an extremely low oral bioavailability of around 4.7%, which necessitates a robust formulation strategy to ensure consistent therapeutic outcomes.

Novel Drug Delivery Systems (NDDS) offer innovative solutions to overcome these biopharmaceutical challenges. Nanotechnology, particularly the use of polymeric nanoparticles, has emerged as a powerful tool for enhancing the solubility and dissolution rate of poorly soluble drugs. Poly(lactic-co-glycolic acid) (PLGA), a biodegradable and biocompatible polymer, is widely used to encapsulate drugs, increasing their surface area and improving their interaction with physiological fluids.

While nanoparticles can improve drug dissolution, controlling their release over an extended period is crucial for reducing dosing frequency, minimizing side effects, and improving patient adherence. Matrix tablets are a well-established platform for achieving sustained drug release. In this system, the drug is homogeneously dispersed within a polymer matrix that

controls the rate of drug release through mechanisms of diffusion, erosion, or swelling. Hydrophilic polymers like Hydroxypropyl Methylcellulose (HPMC) are frequently used to form a gel layer upon hydration, which regulates drug diffusion from the tablet core.

This study aims to combine the benefits of these two platforms by developing a nanoparticulate matrix tablet of Nintedanib. The primary objective is to first enhance the drug's solubility by formulating it into PLGA nanoparticles and then incorporate these nanoparticles into a

hydrophilic matrix tablet to achieve sustained release. This dual-approach formulation is designed to improve the overall bioavailability and therapeutic profile of Nintedanib, offering a more effective and patient-friendly oral dosage form

2. MATERIALS AND METHODS

Materials

Nintedanib was received as a gift sample from Cure Medicines, Pune. PLGA, Microcrystalline Cellulose, HPMC K4M, Magnesium Stearate, Talc, and PVA were procured from Shree Sadguru Hightech Pvt Ltd, Pune. All other chemicals and reagents were of analytical grade.

Preformulation and Compatibility Studies

The compatibility between Nintedanib and the selected polymers (PLGA, HPMC) was assessed using Fourier Transform Infrared (FTIR) spectroscopy. The physical mixture of the drug and excipients was scanned over a range of 4000 to 400 cm^{-1} and compared against the individual spectra of the pure drug and polymers to detect any potential chemical interactions.

Formulation of Nintedanib Nanoparticles

Nintedanib-loaded nanoparticles were prepared using the solvent evaporation method.

Organic Phase: A specified amount of Nintedanib (400 mg) and PLGA (in varying concentrations from 10 mg to 80 mg for formulations F1-F8) were dissolved in 10 mL of ethanol.

Aqueous Phase: 50 mg of PVA was dissolved in 10 mL of water to act as a stabilizer.

Emulsification: The aqueous phase was added to the organic phase and homogenized using a vortex mixer for 1 minute, followed by sonication to reduce droplet size.

Solvent Removal: The organic solvent was evaporated using a flash evaporator to allow the formation and collection of solid nanoparticles.

The formulation with the highest drug entrapment efficiency was selected for further development.

Characterization of Nanoparticles

Drug Entrapment Efficiency (%EE): The amount of free, unentrapped drug in the supernatant after centrifugation was measured using a UV spectrophotometer at 390 nm. The %EE was calculated using the formula:

%EE = [(Total Drug - Free Drug) / Total Drug] × 100.

Surface Morphology and Structure: The shape and surface characteristics of the nanoparticles were observed using Scanning Electron Microscopy (SEM). The crystalline nature of the encapsulated drug was analyzed using X-Ray Diffraction (XRD).

In Vitro Drug Release: The release profile of the optimized nanoparticle formulation (F8) was studied for 24 hours using a dialysis membrane method in pH 7.4 phosphate buffer.

Formulation of Nanoparticulate Matrix Tablets Matrix tablets were prepared by the

direct compression method. The optimized Nintedanib-loaded nanoparticles (equivalent to 480 mg) were blended with varying concentrations of polymers (Microcrystalline Cellulose or HPMC K4M), Magnesium Stearate (lubricant), and Talc (glidant). The final powder blend was compressed into tablets using a multi- tablet punching machine.

Evaluation of Matrix Tablets

Pre-compression Evaluation: The powder blend was evaluated for flow properties, including bulk density, tapped density, Carr's compressibility index, Hausner's ratio, and angle of repose.

Post-compression Evaluation: The compressed tablets were characterized for thickness, hardness (Monsanto tester), friability (Roche friabilator), weight variation, and drug content uniformity.

In Vitro Dissolution Study: Drug release from the matrix tablets was studied using a USP Type-II (Paddle) apparatus at 50 rpm. The dissolution medium was 0.1 N HCl for the first 2 hours, followed by pH 6.8 phosphate buffer for the next 10 hours, maintained at 37±0.5°C.

Drug Release Kinetics: The release data was fitted into kinetic models (Zero- order, First-order, Higuchi, and Korsmeyer-Peppas) to determine the mechanism of drug release.

Stability Studies: The optimized tablet formulation was subjected to accelerated stability testing at 40°C / 75% RH for 3 months as per ICH guidelines

3. RESULTS AND DISCUSSION

Drug-Excipient Compatibility

The FTIR spectra of the physical mixture of Nintedanib and PLGA were compared with the spectra of the individual components. No significant shifts or disappearance of characteristic peaks were observed, confirming the absence of chemical interactions between the drug and the polymer. This indicates that PLGA is a suitable carrier for Nintedanib.

Nanoparticle Characterization

Entrapment Efficiency: The %EE for formulations F1 to F8 ranged from 61% to 97%. The efficiency increased with the concentration of PLGA, as a higher polymer amount provided a more extensive matrix to encapsulate the drug. Formulation

F8, containing 80 mg of PLGA, showed the highest %EE of 97 ± 0.06% and was therefore selected as the optimized batch for tablet formulation.

Table 1: Entrapment Efficiency of Nintedanib Nanoparticles | Formulation Code | PLGA (mg) | Entrapment Efficiency (%) | | :--- | :--- | :--- | | F1 | 10 | 61 ± 0.13 | | F2 | 20 | 68 ± 0.08 | | F3 | 30 | 69 ± 0.19 | | F4 | 40 | 79 ± 0.14 | | F5 | 50 | 84 ± 0.17 | | F6 | 60

| 88 ± 0.09 | | F7 | 70 | 96 ± 0.09 | | F8 (Optimized) | 80 | 97 ± 0.06 |

Morphology and Structure: SEM images revealed that the prepared nanoparticles were fluffy with clear particle observation. XRD analysis confirmed the successful formation of nanoparticles and the presence of Nintedanib within the polymer matrix.

In Vitro Drug Release (Nanoparticles): The optimized formulation F8 exhibited a sustained release pattern, releasing 98.59% of the drug over 24 hours. This controlled release from the nanoparticle core itself is beneficial for maintaining therapeutic drug levels.

Evaluation of Powder Blend for Tableting

The pre-compression parameters of the powder blends for all tablet formulations (F1- F6) indicated good to excellent flowability. The angle of repose was in the range of 22.59°–28.68°, and the Carr's index was between 8.26%–9.49%. These results

confirmed that the blend was suitable for the direct compression method, ensuring uniform die filling and consistent tablet weight.

Physicochemical Evaluation of Matrix Tablets

All formulated tablets met the required pharmacopeial standards for post-compression parameters. The hardness ranged from 4.7 to 5.6 kg/cm², and friability was below 1%, indicating good mechanical strength. The drug content was uniform across all batches, ranging from 97.7% to 99.8%.

Table 2: Post-Compression Evaluation of Matrix Tablets | Formulation |

Formulation	Thickness (mm)± SD	Hardness (kg/cm^2)	Weight Variation (mg)	Friability %	Content Uniformity (%)
F1	3.89±0.12	5.2± 0.06	504.14±1.33	0.83 ± 0.04	97.8 ± 0.09
F2	3.86±0.13	5.5 ± 0.05	503.2±1.34	0.62 ± 0.03	98.7 ± 0.06
F3	3.85±0.12	5.4 ± 0.07	502.6±1.32	0.49 ± 0.02	99.5 ± 0.05
F4	3.92±0.14	5.6 ± 0.08	501.2±1.35	0.45 ± 0.01	97.7 ± 0.03

F5	3.97±0.11	4.9± 0.05	500.4±1.36	0.39 ± 0.04	99.8 ± 0.04
F6	3.88±0.15	4.7 ± 0.04	501.16±1.31	0.48 ± 0.05	98.6 ± 0.04

***In Vitro* Drug Release from Matrix Tablets**

The dissolution studies showed that all formulations provided sustained drug release over 12 hours. Formulations F1, F2, and F3, containing MCC, released the drug faster than formulations F4, F5, and F6, which contained the release-retarding polymer HPMC K4M. Formulation

F5 was identified as the optimized batch, as it released 99% of the drug in a controlled manner over 12 hours, which is ideal for a once-daily or twice-daily dosing regimen

Drug Release Kinetics

The drug release data were fitted into various kinetic models. The regression coefficient (R^2) values indicated that the drug release from all formulations, especially F5, best followed

Zero-Order kinetics ($R^2 = 0.9936$), suggesting that the drug was released at a constant rate, independent of its concentration. The Korsmeyer-Peppas model showed that the release exponent 'n' for F5 was 0.4743, which indicates an

anomalous (Non-Fickian) transport mechanism. This suggests that drug release is controlled by a combination of diffusion through the swollen polymer matrix and erosion of the matrix itself, a mechanism characteristic of HPMC-based systems

Stability Studies

The optimized formulation (F5) was found to be stable after 3 months of storage at accelerated conditions (40°C / 75% RH). No significant changes were observed in the physical appearance, hardness, friability, drug content, or

in vitro release profile, confirming the robustness of the formulation.

4. CONCLUSION

The present study successfully demonstrated the development of a Nintedanib nanoparticulate matrix tablet as a promising oral drug delivery system. The formulation strategy effectively combined the solubility-enhancing benefits of PLGA nanoparticles with the sustained-release properties of an HPMC-based matrix tablet.

Key achievements include:

Successful preparation of Nintedanib-loaded PLGA nanoparticles using a simple solvent evaporation method, with the optimized formulation (F8) achieving a high drug entrapment of 97%.

Effective formulation of matrix tablets via direct compression, a cost-effective and straightforward manufacturing process.

The optimized matrix tablet (F5) exhibited excellent physicochemical properties and delivered a sustained drug release of 99% over 12 hours, aligning with the goals for a reduced-dosing-frequency regimen.

The drug release mechanism was found to follow a predictable zero-order kinetic model, governed by non-Fickian diffusion, which is ideal for maintaining consistent therapeutic drug levels.

In conclusion, the developed nanoparticulate matrix tablet is a viable and innovative platform for the oral administration of poorly soluble drugs like Nintedanib. This system has the potential to enhance bioavailability, reduce dose-related side effects, and improve patient compliance, marking a significant advancement in the formulation of Nintedanib for the treatment of idiopathic pulmonary fibrosis. Further *in vivo* studies are warranted to confirm these promising *in vitro* results.

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