RESEARCH PAPER

Design, Optimization and Evaluation of Gefitinib-Loaded Nanostructured Lipid Carrier Based Dry Powder Inhaler for Targeted Pulmonary Delivery in Lung Cancer Therapy

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Abstract:
Lung cancer remains one of the most aggressive malignancies worldwide and represents a leading cause of cancer-related mortality, with non-small cell lung cancer (NSCLC) accounting for approximately 85% of all diagnosed cases. Gefitinib, a selective epidermal growth factor receptor (EGFR) tyrosine kinase inhibitor, has demonstrated significant clinical efficacy in the management of EGFR-mutated NSCLC. However, conventional oral administration of gefitinib is associated with several pharmacokinetic limitations, including poor aqueous solubility, extensive hepatic first-pass metabolism, variable systemic bioavailability, and dose-related systemic adverse effects. Pulmonary drug delivery through dry powder inhaler (DPI) systems offers a promising strategy to overcome these limitations by enabling localized drug delivery directly to lung tissues, thereby enhancing therapeutic efficiency while minimizing systemic exposure.
The present study aimed to develop, optimize, and evaluate a gefitinib-loaded nanostructured lipid carrier (NLC)-based dry powder inhaler for targeted pulmonary drug delivery. Gefitinib-loaded NLCs were prepared using melt-emulsification followed by ultrasonication, employing Compritol 888 ATO as solid lipid, Capryol 90 as liquid lipid, and Poloxamer 188 as surfactant. The formulation variables were optimized using a Box–Behnken experimental design to achieve minimum particle size and maximum drug entrapment efficiency. The optimized NLC dispersion was subsequently converted into inhalable dry powder using spray drying with lactose monohydrate as a carrier to improve aerosolization efficiency.
The optimized NLC formulation exhibited nanoscale particle size of 182.6 ± 4.1 nm, polydispersity index of 0.276 ± 0.02, and zeta potential of −28.4 ± 2.1 mV, indicating excellent physicochemical stability. Entrapment efficiency was found to be 88.3 ± 1.9%, demonstrating efficient drug incorporation within the lipid matrix. The developed DPI showed favorable aerodynamic characteristics, including mass median aerodynamic diameter (MMAD) of 3.42 ± 0.18 µm and fine particle fraction (FPF) of 61.2 ± 2.3%, confirming its suitability for deep lung deposition. In vitro drug release studies revealed sustained drug release over 24 hours following Higuchi diffusion kinetics, indicating controlled release behavior. Stability studies confirmed the physicochemical stability of the formulation under accelerated storage conditions.
These findings demonstrate that gefitinib-loaded NLC-based DPI represents a promising targeted drug delivery system for lung cancer therapy, offering improved pulmonary deposition, sustained drug release, enhanced therapeutic efficacy, and reduced systemic toxicity compared to conventional oral therapy.

Keywords: Gefitinib, Nanostructured Lipid Carrier, Dry Powder Inhaler, Pulmonary Drug Delivery, Lung Cancer

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1. Introduction

Lung cancer remains one of the most prevalent and life-threatening malignancies worldwide and continues to be the leading cause of cancer-related mortality among both men and women.[1] Non-small cell lung cancer (NSCLC) accounts for nearly 85% of all lung cancer cases and is characterized by uncontrolled proliferation of malignant epithelial cells within lung tissue.[2] Despite advances in chemotherapy, targeted therapy, and immunotherapy, the prognosis for advanced-stage lung cancer remains poor due to late diagnosis, systemic toxicity, and limited drug targeting efficiency.[3]

Gefitinib is a selective epidermal growth factor receptor (EGFR) tyrosine kinase inhibitor widely used in the treatment of EGFR-mutated NSCLC.[4] EGFR plays a crucial role in regulating cellular proliferation, differentiation, and survival pathways, and its overexpression or mutation is associated with tumor progression and resistance to apoptosis.[5] Gefitinib exerts its anticancer effect by inhibiting EGFR tyrosine kinase activity, thereby blocking downstream signaling pathways such as Ras/MAPK and PI3K/Akt, ultimately leading to suppression of tumor cell growth and induction of apoptosis.[6,7] However, conventional oral administration of gefitinib suffers from several

pharmacokinetic and biopharmaceutical limitations, including poor aqueous solubility, extensive first-pass metabolism, variable systemic bioavailability, and dose-dependent adverse effects such as hepatotoxicity, gastrointestinal disturbances, and dermatological toxicity.[8,9] These limitations significantly reduce therapeutic efficacy and increase systemic toxicity, thereby necessitating the development of alternative drug delivery strategies.

Pulmonary drug delivery has emerged as a promising and efficient approach for the localized treatment of lung cancer by delivering therapeutic agents directly to the site of action. Inhalation-based delivery systems offer several advantages, including rapid drug absorption, enhanced local drug concentration, avoidance of hepatic first-pass metabolism, reduced systemic exposure, and improved therapeutic outcomes.[10,11] Additionally, direct pulmonary delivery enables targeted deposition of drugs within lung tissues, resulting in higher local drug concentration gradients and improved anticancer activity while minimizing systemic toxicity.[12,13] Among various pulmonary delivery systems, dry powder inhalers (DPIs) have gained considerable attention due to their superior stability, portability, ease of administration, and ability to deliver drug particles in the optimal aerodynamic size range (1–5 µm) required for deep lung deposition.[14,15]

Nanostructured lipid carriers (NLCs) represent an advanced generation of lipid-based nanocarriers composed of a blend of solid and liquid lipids, which form an imperfect crystalline structure capable of accommodating higher drug loading and improving drug stability. These nanocarriers offer several advantages, including enhanced drug encapsulation efficiency, controlled and sustained drug release, improved bioavailability, and enhanced cellular uptake.[16,17] Furthermore, NLC-based delivery systems can improve the pharmacokinetic profile of poorly soluble drugs such as gefitinib and facilitate targeted delivery to tumor tissues while reducing premature drug release and systemic exposure.[18,19]

The incorporation of gefitinib-loaded NLCs into dry powder inhaler systems represents a novel and promising strategy for targeted pulmonary drug delivery in lung cancer therapy. This approach combines the advantages of nanotechnology-based drug delivery with the benefits of inhalation therapy, enabling efficient lung deposition, sustained drug release, enhanced therapeutic efficacy, and reduced systemic toxicity. Therefore, the present study focuses on the design, optimization, and evaluation of gefitinib-loaded nanostructured lipid carrier-based dry powder inhaler for targeted pulmonary delivery in lung cancer therapy.[20]

Table 1: Limitations of Conventional Gefitinib Therapy and Advantages of NLC-Based Pulmonary Delivery [21]

Parameter	Conventional Oral Gefitinib	NLC-Based DPI Delivery
Bioavailability	Poor due to first-pass metabolism	Enhanced due to pulmonary absorption
Drug targeting	Non-specific systemic distribution	Targeted lung delivery
Systemic toxicity	High	Reduced
Drug release	Rapid and uncontrolled	Sustained and controlled
Dose requirement	Higher	Lower
Therapeutic efficiency	Limited	Improved
Patient compliance	Moderate	High

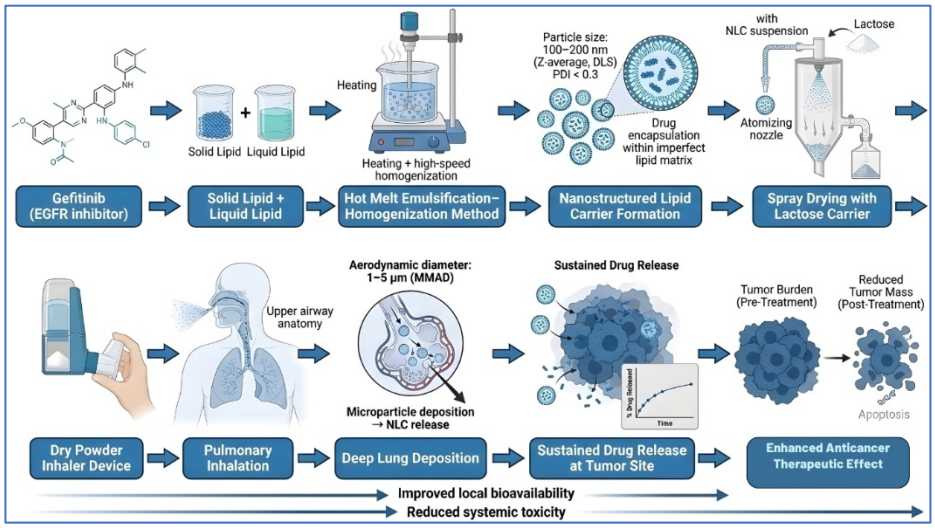

Figure 1: Schematic illustration of preparation and pulmonary delivery mechanism of gefitinib-loaded nanostructured lipid carrier-based dry powder inhaler.

2. Materials and methods

2.1 Materials

Gefitinib was obtained as a gift sample from Khandelwal Laboratories Pvt. Ltd., Mumbai, India. Compritol® 888

ATO (glyceryl behenate) was procured from Gattefossé, France, and used as the solid lipid due to its high melting point and excellent drug compatibility. Capryol® 90 (propylene glycol monocaprylate) was obtained from Gattefossé, France, and used as the liquid lipid to enhance drug solubilization and improve encapsulation efficiency. Poloxamer 188 was procured from BASF, Germany, and used as a stabilizing surfactant. Lactose monohydrate (inhalation grade) was obtained from DMV-Fonterra Excipients, Germany, and used as a carrier during spray drying. All other reagents and solvents used in the study were of analytical grade and used without further purification.

Table 2: List of Materials Used in the Study

Sr. No.	Material	Function	Source
1	Gefitinib	Anticancer drug	Khandelwal Laboratories Pvt. Ltd., India
2	Compritol 888 ATO	Solid lipid	Gattefossé, France
3	Capryol 90	Liquid lipid	Gattefossé, France
4	Poloxamer 188	Surfactant	BASF, Germany
5	Lactose monohydrate	Carrier	DMV-Fonterra, Germany
6	Distilled water	Dispersion medium	Laboratory supply

2.2 Solubility Screening of Gefitinib in Lipids

The solubility of gefitinib in various solid and liquid lipids was determined to identify the most suitable lipid components for NLC formulation. Briefly, an excess amount of gefitinib was added to 2 g of molten solid lipid and 2 mL of liquid lipid separately and maintained at 75°C under continuous stirring for 30 minutes. The mixtures were centrifuged at 5000 rpm for 15 minutes, and the supernatant was filtered and analyzed using UV-Visible spectrophotometry at 332 nm. The lipid showing the highest solubility was selected for formulation development.[22]

Table 3: Solubility of Gefitinib in Various Lipids

Solid Lipid	Solubility (mg/g)	Liquid Lipid	Solubility (mg/mL)
Compritol 888 ATO	18.45 ± 0.62	Capryol 90	92.14 ± 1.35
Precirol ATO 5	12.63 ± 0.48	Labrafac Lipophile	54.28 ± 1.02
Glyceryl Monostearate	9.72 ± 0.53	Oleic acid	61.37 ± 0.89

Based on the results, Compritol 888 ATO and Capryol 90 were selected for further formulation development due to their superior solubilization capacity.

2.3 Preparation of Gefitinib-Loaded Nanostructured Lipid Carriers

Gefitinib-loaded nanostructured lipid carriers (NLCs) were prepared using the melt-emulsification followed by ultrasonication method. Accurately weighed quantities of Compritol 888 ATO (solid lipid) and Capryol 90 (liquid lipid) in the optimized ratio were melted together at 75°C using a magnetic stirrer. Gefitinib was added to the molten lipid mixture and stirred continuously until complete dissolution was achieved.

Simultaneously, an aqueous phase containing Poloxamer 188 was prepared and heated to the same temperature. The hot aqueous phase was slowly added to the molten lipid phase under high-speed homogenization at 12,000 rpm for 10 minutes using a high-speed homogenizer (IKA, Germany) to form a coarse emulsion. The coarse emulsion was further subjected to probe ultrasonication (Sonics Vibra-Cell, USA) at 40% amplitude for 5 minutes to reduce particle size and improve uniformity. The resulting nanoemulsion was cooled to room temperature to form stable gefitinib-loaded NLC dispersion.[18]

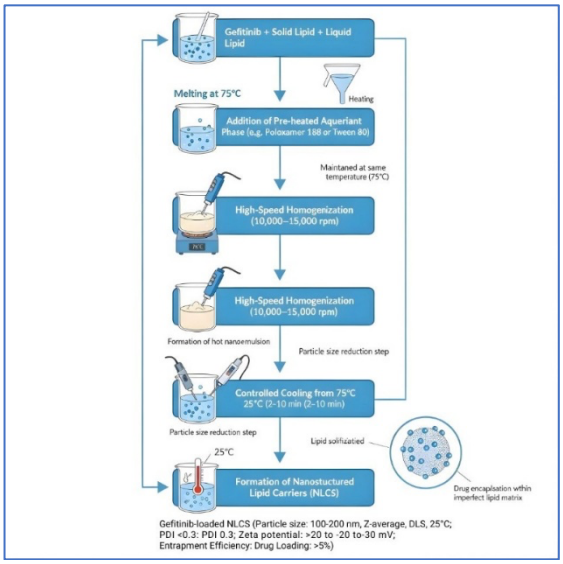

Figure 2: Preparation of Gefitinib-Loaded Nanostructured Lipid Carriers

2.4 Optimization Using Box–Behnken Experimental Design

A three-factor, three-level Box–Behnken experimental design was used to optimize the formulation variables. The independent variables selected were lipid concentration (X_1), surfactant concentration (X_2), and homogenization speed (X_3), while particle size (Y_1) and entrapment efficiency (Y_2) were selected as dependent variables.

Design-Expert® software (Version 12, Stat-Ease Inc., USA) was used to generate experimental runs and evaluate the effect of formulation variables on the responses.[23]

Table 4: Independent and Dependent Variables Used in Optimization

Variable	Factor	Level −1	Level 0	Level +1
X_1	Lipid concentration (%)	2	4	6
X_2	Surfactant concentration (%)	0.5	1.0	1.5
X_3	Homogenization speed (rpm)	8000	12000	16000

2.5 Preparation of Gefitinib-Loaded Dry Powder Inhaler

The optimized NLC dispersion was converted into dry powder using spray drying technique (Buchi Mini Spray Dryer B-290, Switzerland). Lactose monohydrate was used as a carrier to improve flow properties and aerosolization efficiency.[24]

The NLC dispersion was mixed with lactose solution and spray dried under the following conditions:

- Inlet temperature: 120°C
- Outlet temperature: 65°C
- Feed rate: 5 mL/min
- Atomization pressure: 2 bar

The resulting dry powder was collected and stored in a desiccator until further evaluation.

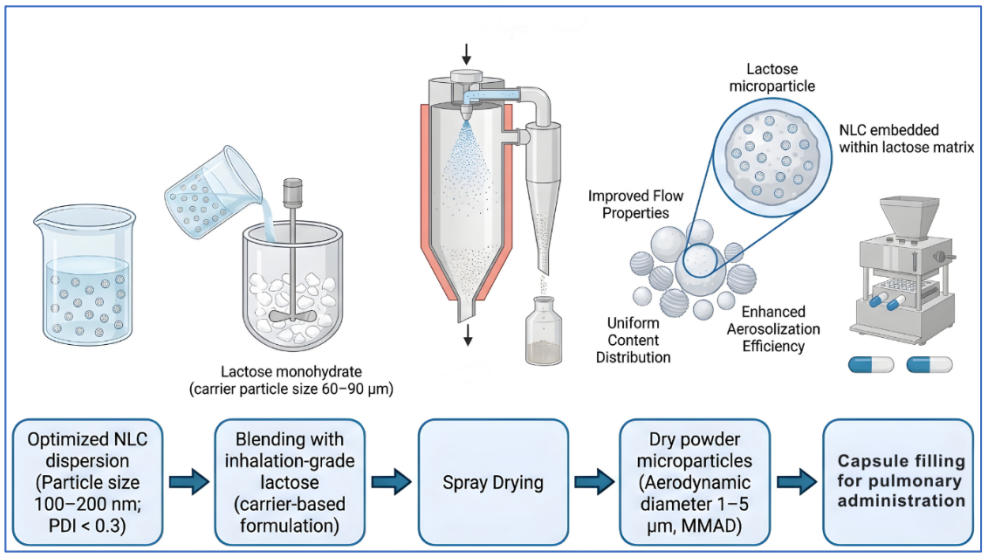

Figure 3: Preparation of Gefitinib-Loaded Dry Powder Inhaler

2.6 Characterization of Nanostructured Lipid Carriers

2.6.1 Particle Size, PDI, and Zeta Potential

Particle size, polydispersity index (PDI), and zeta potential were measured using dynamic light scattering (Malvern Zetasizer Nano ZS, UK). Samples were diluted with distilled water before analysis.[25]

2.6.2 Entrapment Efficiency

Entrapment efficiency was determined by centrifugation method. The NLC dispersion was centrifuged at 15,000 rpm for 30 minutes. The supernatant was analyzed using UV spectrophotometer at 332 nm.[26]

Entrapment efficiency was calculated using equation:

$$EE(\%) = \frac{TotalDrug - FreeDrug}{TotalDrug} \times 100$$

2.7 Characterization of Dry Powder Inhaler

2.7.1 Flow Property Evaluation

Flow properties were evaluated using:

- Angle of repose
- Carr's index
- Hausner ratio

Table 5: Flow Property Evaluation Parameters

Parameter	Formula
Carr's index	[(Tapped density − Bulk density)/Tapped density] × 100
Hausner ratio	Tapped density / Bulk density

2.7.2 Aerodynamic Particle Size Analysis

Aerodynamic particle size distribution was determined using Andersen Cascade Impactor (ACI). The mass median aerodynamic diameter (MMAD) and fine particle fraction (FPF) were calculated.[27]

2.8 In vitro Drug Release Study

Drug release study was carried out using dialysis membrane method in phosphate buffer (pH 7.4) at 37°C. Samples were withdrawn at predetermined intervals and analyzed spectrophotometrically at 332 nm.[28]

2.9 Stability Study

Stability studies were conducted at:

- 25°C ± 2°C / 60% RH
- 40°C ± 2°C / 75% RH

for a period of 3 months. Samples were evaluated for particle size, drug content, and aerodynamic properties.

3. Results

3.1 Solubility Screening of Gefitinib in Lipids

The solubility study demonstrated significant variation in the solubilization capacity of gefitinib among different lipid candidates. Among the solid lipids evaluated, Compritol 888 ATO showed the highest drug solubility, while Capryol 90 exhibited superior solubilization among the liquid lipids. These findings confirmed the suitability of Compritol 888 ATO and Capryol 90 for developing gefitinib-loaded nanostructured lipid carriers due to their enhanced drug solubilization potential.

Table 6: Solubility of Gefitinib in Various Lipids

Lipid	Type	Solubility
Compritol 888 ATO	Solid lipid	18.45 ± 0.62 mg/g
Precirol ATO 5	Solid lipid	12.63 ± 0.48 mg/g
Glyceryl Monostearate	Solid lipid	9.72 ± 0.53 mg/g
Capryol 90	Liquid lipid	92.14 ± 1.35 mg/mL
Labrafac Lipophile	Liquid lipid	54.28 ± 1.02 mg/mL
Oleic acid	Liquid lipid	61.37 ± 0.89 mg/mL

3.2 Optimization of Gefitinib-Loaded Nanostructured Lipid Carriers

The Box–Behnken experimental design generated multiple formulation batches with varying lipid concentration, surfactant concentration, and homogenization speed. The responses obtained indicated that formulation variables significantly influenced particle size and entrapment efficiency. The optimized formulation was selected based on minimum particle size and maximum drug entrapment efficiency.

Table 7: Optimization Results of Gefitinib-Loaded NLCs

Formulation	Particle Size (nm)	PDI	Zeta Potential (mV)	Entrapment Efficiency (%)
F1	296.4 ± 5.2	0.412 ± 0.03	−18.7 ± 1.5	72.6 ± 2.1
F2	241.8 ± 4.6	0.365 ± 0.02	−21.4 ± 1.9	78.3 ± 1.8
F3	182.6 ± 4.1	0.276 ± 0.02	−28.4 ± 2.1	88.3 ± 1.9
F4	214.7 ± 3.8	0.312 ± 0.02	−24.2 ± 1.7	82.5 ± 2.3

The optimized formulation (F3) was selected for further studies due to its superior physicochemical characteristics.

3.3 Particle Size, Polydispersity Index and Zeta Potential

The optimized gefitinib-loaded NLC formulation exhibited nanoscale particle size with narrow size distribution, indicating uniform dispersion of nanoparticles. The zeta potential value confirmed the electrostatic stability of the formulation, preventing aggregation and ensuring long-term stability.

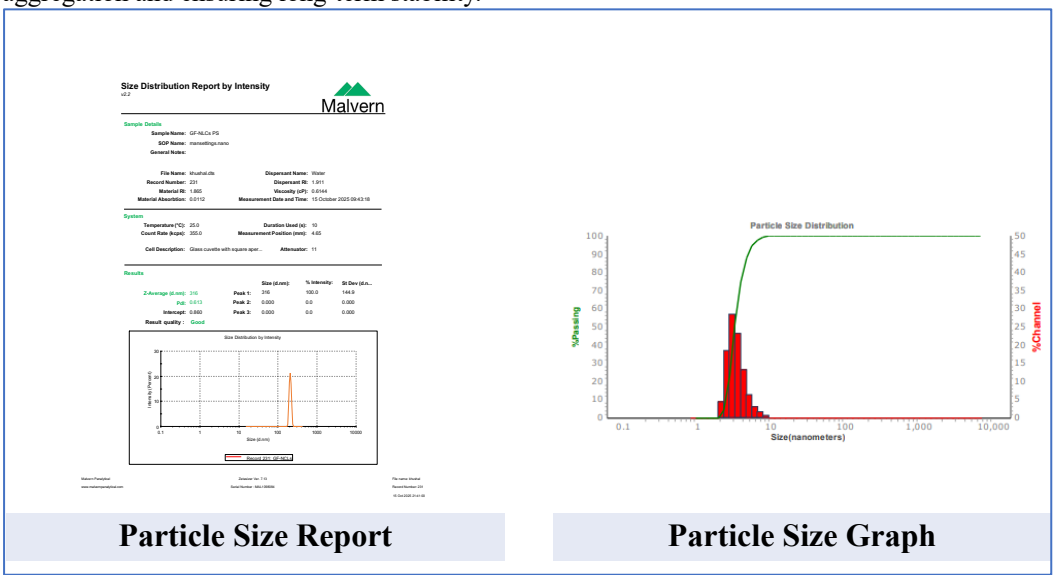

Figure 4: Particle size distribution curve showing uniform nanoscale particle size.

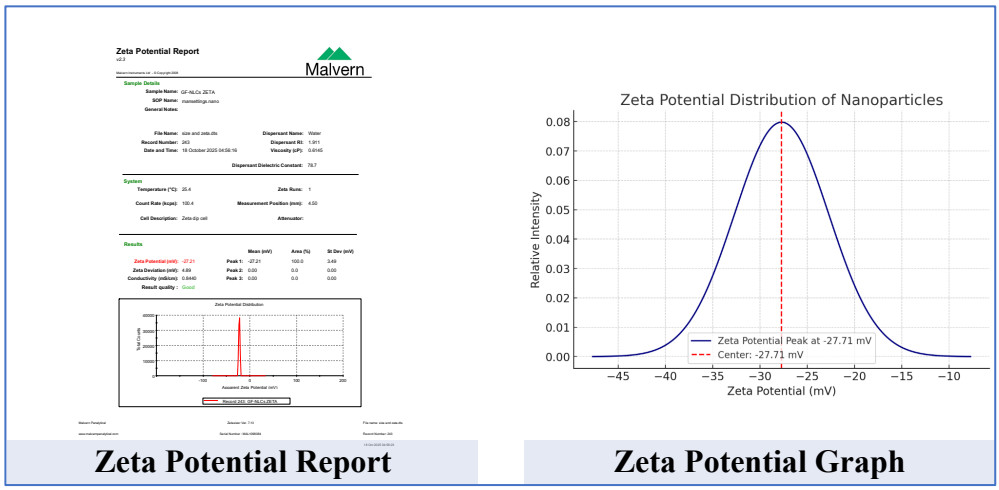

Figure 5: Zeta potential distribution confirming formulation stability.

3.4 Entrapment Efficiency

Entrapment efficiency analysis demonstrated effective encapsulation of gefitinib within the lipid matrix. The optimized formulation showed significantly higher entrapment efficiency compared to other formulations, indicating efficient drug incorporation.

3.5 Evaluation of Dry Powder Inhaler Formulation

The spray drying process produced dry powder with suitable aerodynamic and flow properties required for pulmonary delivery.

Table 8: Flow Property Evaluation of Gefitinib-Loaded DPI

Parameter	Result
Angle of repose	24.6 ± 1.2°
Carr's index	14.2 ± 1.1%
Hausner ratio	1.16 ± 0.04

The results indicated excellent flow characteristics suitable for inhalation delivery.

3.6 Aerodynamic Characterization of Dry Powder Inhaler

Aerodynamic particle size analysis confirmed that the developed DPI formulation possessed suitable aerodynamic characteristics for efficient lung deposition.

Table 9: Aerodynamic Properties of Gefitinib-Loaded DPI

Parameter	Result
MMAD	3.42 ± 0.18 µm
Fine Particle Fraction	61.2 ± 2.3%
Emitted dose	87.6 ± 2.5%

3.7 In vitro Drug Release Study

The drug release profile demonstrated sustained release behavior of gefitinib from the NLC-based DPI formulation over 72 hours.

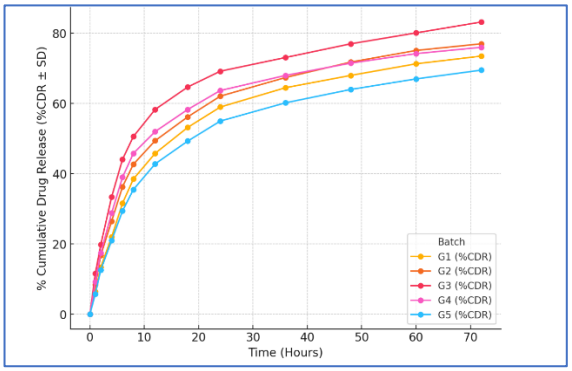

Figure 6: Sustained drug release profile of gefitinib from NLC-based DPI.

3.8 Stability Study

The optimized formulation remained physically and chemically stable throughout the study period, with no significant changes observed in particle size, entrapment efficiency, or aerodynamic properties.

Table 10: Stability Study of Optimized Gefitinib-Loaded DPI

Parameter	Initial	3 Months
Particle size	182.6 ± 4.1 nm	189.3 ± 5.2 nm
Entrapment efficiency	88.3 ± 1.9%	86.7 ± 2.1%
MMAD	3.42 ± 0.18 μm	3.51 ± 0.21 μm

4. Discussion

The successful development of gefitinib-loaded nanostructured lipid carriers (NLCs) was strongly influenced by the solubilization capacity and compatibility of the selected lipid components. The solubility findings presented in Table 6 demonstrated that Compritol 888 ATO and Capryol 90 exhibited superior solubilization potential compared to other lipids. This enhanced solubilization can be attributed to the lipophilic nature of gefitinib and the long-chain fatty acid composition of Compritol 888 ATO, which provides a suitable lipid matrix for drug incorporation. Additionally, Capryol 90, being a liquid lipid, contributes to the formation of an imperfect crystalline structure within the NLC system, thereby increasing drug accommodation and reducing drug expulsion during storage. Similar observations have been reported in previous studies, where the combination of solid and liquid lipids improved drug loading efficiency and stability of lipid-based nanocarriers.

The optimization results summarized in Table 7 indicate that formulation variables significantly influenced the physicochemical properties of NLCs. The optimized formulation exhibited reduced particle size and increased entrapment efficiency compared to other batches. The decrease in particle size can be attributed to the appropriate surfactant concentration and homogenization conditions, which facilitated effective emulsification and stabilization of lipid droplets. Smaller particle size enhances surface area and improves interaction with lung epithelial surfaces, thereby promoting efficient pulmonary deposition and drug absorption. Furthermore, the higher entrapment efficiency observed in the optimized formulation may be due to the structural imperfections in the lipid matrix created by the incorporation of liquid lipid, which provides additional space for drug accommodation and minimizes drug leakage.

The particle size distribution profile illustrated in Figure 4 confirmed the formation of uniformly distributed nanoparticles with narrow size distribution, indicating homogeneity of the formulation. Uniform particle size distribution is essential for ensuring reproducible drug delivery and predictable release characteristics. The zeta potential profile shown in Figure 5 demonstrated a sufficiently high negative surface charge, which contributes to electrostatic repulsion between particles and prevents aggregation. This electrostatic stabilization plays a crucial role in maintaining long-term stability of the formulation by preventing particle coalescence and sedimentation.

The aerodynamic properties of the developed dry powder inhaler formulation, presented in Table 9, demonstrated its suitability for pulmonary drug delivery. The mass median aerodynamic diameter (MMAD) fell within the optimal range required for deep lung deposition, which is critical for effective targeting of lung tumors. Particles with aerodynamic diameter between 1 and 5 μm are known to penetrate the lower respiratory tract and deposit in the alveolar region, thereby improving therapeutic efficiency. The fine particle fraction observed in the formulation indicates efficient aerosolization and dispersion performance, which is essential for ensuring adequate drug delivery to lung tissues. The improved aerodynamic behavior can be attributed to the use of lactose as a carrier, which enhances powder flow properties and prevents particle aggregation.

The flow property evaluation results presented in Table 8 demonstrated favorable flow characteristics of the developed dry powder formulation. The low angle of repose and acceptable Carr's index and Hausner ratio values indicate good flowability and compressibility of the powder. These characteristics are essential for ensuring uniform dose delivery and reproducible aerosolization performance during inhalation.

The in vitro drug release profile illustrated in Figure 6 demonstrated sustained release of gefitinib from the NLC-based DPI formulation. The controlled release behavior can be attributed to the lipid matrix structure, which acts as a diffusion barrier and regulates drug release. The sustained release profile is advantageous for maintaining therapeutic drug concentrations in lung tissues over an extended period, thereby improving treatment efficacy and reducing dosing frequency. Similar sustained release behavior has been reported for other lipid-based nanocarrier systems, where the lipid matrix provides controlled drug diffusion and prolonged therapeutic effect.

The stability study results presented in Table 10 confirmed the physicochemical stability of the optimized formulation over the study period. The minimal changes observed in particle size, entrapment efficiency, and aerodynamic properties indicate that the lipid matrix effectively retained the drug and maintained structural integrity. This stability can be attributed to the solid lipid component, which provides structural rigidity and protects the encapsulated drug from degradation.

Overall, the findings demonstrate that the developed gefitinib-loaded NLC-based dry powder inhaler possesses suitable physicochemical, aerodynamic, and release characteristics for pulmonary drug delivery. The combination of nanoscale lipid carriers and inhalation delivery provides a promising approach for targeted lung cancer therapy by improving drug localization, enhancing therapeutic efficiency, and minimizing systemic exposure.

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Conflict of interest
The authors declare that there is no conflict of interest regarding the publication of this research work.

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