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Research Article

Formulation and Evaluation of Herbal-Based Emulsomal Nebulizing Solution Containing *Abroma Augusta* and *Boerhavia Diffusa* for Inhalational Treatment of Cystic Fibrosis-Associated Lung Conditions

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Abstract

Background: Cystic fibrosis (CF) is a chronic genetic disorder characterized by viscous mucus accumulation and persistent pulmonary infections. Conventional therapies often suffer from limited drug penetration, poor bioavailability, and systemic side effects. The present study aimed to develop a herbal-based emulsomal nebulizing system incorporating *Abroma augusta* and *Boerhavia diffusa* extracts for targeted pulmonary delivery in CF-associated lung conditions.

Methods: Emulsomes were prepared by thin-film hydration using tripalmitin, phosphatidylcholine, and cholesterol as core components. Optimization was performed via Central Composite Design considering lipid and phospholipid concentrations as independent variables. The formulations were evaluated for particle size, zeta potential, drug content, entrapment efficiency, compatibility (FTIR, DSC, XRD), morphology (SEM, TEM), in vitro release, and stability. The optimized batch (F10) was further processed into a nebulizing solution (EN1–EN3) and analyzed for aerosol suitability.

Results: The optimized formulation exhibited a mean particle size of 211 nm, zeta potential –34.5 mV, and high entrapment efficiency (77.5%), confirming nanoscale stability. SEM and TEM revealed spherical, smooth vesicles with a core-shell structure. The nebulizing solution (EN3) demonstrated nanosized droplets (168 ± 2 nm), pH within physiological limits (5.57–5.77), and sustained drug release of 73.89% over 8 hours. The formulation remained stable for three months under ICH storage conditions without significant physicochemical changes.

Conclusion: The developed herbal emulsomal nebulizing system effectively enhanced solubility, stability, and controlled release of phytoconstituents, demonstrating potential for pulmonary delivery in cystic fibrosis-associated lung inflammation and infection. Further in vivo and clinical evaluations are warranted to validate its therapeutic efficacy and safety.

Keywords: *Abroma augusta*, *Boerhavia diffusa*, emulsomes, nebulizing solution, cystic fibrosis, pulmonary delivery, nanocarrier.

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1. Introduction

Cystic fibrosis (CF) is a chronic, life-limiting autosomal recessive disease primarily caused by mutations in the Cystic Fibrosis Transmembrane Conductance Regulator (CFTR) gene, leading to dysfunctional chloride ion transport across epithelial cells (Elborn, 2016). The resulting impairment in ion exchange causes dehydration of airway secretions, accumulation of viscous mucus, and persistent bacterial colonization in the lungs, contributing to progressive bronchiectasis and respiratory failure (Ratjen & Döring, 2019). Despite the availability of CFTR modulators, current therapies remain focused largely on symptom management through mucolytics, bronchodilators, antibiotics, and physiotherapeutic airway clearance methods (Clancy & Jain, 2019; Ramsey et al., 2019). However, these treatments are often limited by poor drug penetration into mucus plugs, inadequate lung deposition, systemic side effects, and frequent antimicrobial resistance.

Nanotechnology-based pulmonary delivery systems have emerged as a promising alternative to overcome these challenges by enabling targeted, controlled, and sustained delivery of therapeutics directly to the respiratory tract (Labiris & Dolovich, 2003). Among such systems, emulsomes hybrid nanocarriers that integrate the structural advantages of liposomes and solid lipid nanoparticles offer superior encapsulation efficiency, biocompatibility, and stability. Their unique core-shell architecture, consisting of a solid lipid core surrounded by phospholipid bilayers, supports high loading of lipophilic drugs and provides sustained release, improved mucus penetration, and enhanced pulmonary retention upon nebulization (Sivaramakrishnan & Reddy, 2020).

In recent years, herbal-based formulations have gained increasing attention in respiratory therapeutics due to their multifaceted pharmacological profiles and favorable safety margins. *Abroma augusta* (Devil's cotton), a traditionally used medicinal plant, exhibits potent anti-inflammatory, antioxidant, and mucolytic properties that may aid in reducing mucus viscosity and airway inflammation (Borah et al., 2020). Similarly, *Boerhavia diffusa* (Punarnava) demonstrates significant bronchodilatory, immunomodulatory, and antioxidant activities, beneficial in chronic airway conditions associated with oxidative stress and inflammation (Kumar et al., 2018). Nevertheless, the therapeutic utility of these herbal extracts in CF remains unexplored, and their poor aqueous solubility limits their pulmonary bioavailability when administered through conventional routes.

2. Rationale of the Study

The management of CF-associated pulmonary infections and mucus hypersecretion requires localized,

sustained, and safe drug delivery strategies. Herbal bioactives with mucolytic and anti-inflammatory effects could complement existing therapies and reduce treatment-related toxicity. However, achieving effective pulmonary delivery of phytoconstituents is challenging due to low solubility and limited permeability.

Incorporating *Abroma augusta* and *Boerhavia diffusa* extracts into an emulsomal nebulizing system offers a dual advantage: enhanced solubility and bioavailability of lipophilic phytoconstituents, and targeted deposition in the lower respiratory tract. The emulsomal design is particularly suitable for inhalation therapy as it facilitates mucus penetration, provides sustained release, and minimizes systemic exposure. This approach aligns with the current trend of developing hybrid nanocarriers for site-specific delivery of herbal compounds in chronic pulmonary disorders.

Therefore, the study proposes to develop and characterize a herbal-based emulsomal nebulizing solution for effective inhalational management of CF-related lung conditions. This work integrates traditional herbal pharmacology with advanced nanocarrier technology, offering a potential translational framework for natural bioactives in pulmonary therapeutics.

3. Objectives of the Study

- To formulate an emulsome-based nebulizing solution containing extracts of *Abroma augusta* and *Boerhavia diffusa* for pulmonary delivery.
- To evaluate the physicochemical characteristics of the developed emulsomes, including particle size, zeta potential, encapsulation efficiency, and aerosol performance.
- To assess in vitro release kinetics and stability of the herbal emulsomal formulation.
- To determine the in vitro antioxidant, anti-inflammatory, and mucolytic activities of the formulated extracts.
- To explore the potential of the developed herbal emulsomal nebulizing solution for improving pulmonary delivery and therapeutic efficacy in cystic fibrosis-associated lung conditions.

4. Materials and Methods

4.1 Materials

Ethanollic extracts of *Abroma augusta* and *Boerhavia diffusa* were procured from authenticated herbal suppliers and taxonomically verified. Tripalmitin was employed as the lipid core material, while phosphatidylcholine and cholesterol constituted the phospholipid bilayer. Tween 80 was utilized as a surfactant, and butylated hydroxytoluene (BHT) was added as an antioxidant. Chloroform and ethanol served as organic solvents, whereas phosphate-buffered saline (PBS, pH 7.4) was used as the hydration medium. All

reagents and solvents were of analytical grade and used without further purification.

4.2 Preparation of Emulsomes

Emulsomes were prepared using the thin-film hydration method (Sivaramakrishnan & Reddy, 2020). Briefly, the lipid components tripalmitin, phosphatidylcholine, and cholesterol were accurately weighed and dissolved in chloroform. The ethanolic extracts of *A. augusta* and *B. diffusa* were incorporated into the organic phase. The solvent mixture was evaporated under reduced pressure using a rotary evaporator (Buchi R-215) at $45 \pm 2^\circ\text{C}$ to obtain a thin lipid film on the flask wall. The film was hydrated with PBS (pH 7.4) under gentle agitation to yield multilamellar vesicles, which were then probe-sonicated (Sonics Vibra-Cell) for 5 minutes at 40%

amplitude to reduce vesicle size and form nanosized emulsomal dispersions.

2.3 Experimental Design

Optimization of formulation variables was performed using Central Composite Design (CCD) implemented in Design-Expert® software (Version 13). Two independent factors were evaluated lipid concentration (X_1) and phospholipid concentration (X_2) at five levels ($-\alpha$, -1 , 0 , $+1$, $+\alpha$). The dependent responses measured were particle size (nm), drug content (%), and entrapment efficiency (%). A total of 13 experimental runs (F1–F13) were generated and analyzed to determine the optimal formulation (Table 1).

Table 1. Independent variables and their coded levels used in the CCD design						
Factor	Units	$-\alpha$	-1	0	$+1$	$+\alpha$
Lipid (X_1)	g/mL	1.293	1.5	2.0	2.5	2.707
Phospholipid (X_2)	g/mL	2.293	2.5	3.0	3.5	3.707

4.4 Evaluation Parameters

4.4.1 Particle Size and Zeta Potential

Particle size distribution and zeta potential were determined by Dynamic Light Scattering (DLS) using a Malvern Zetasizer Nano ZS. The emulsomal dispersion was diluted with double-distilled water to prevent multiple scattering effects, and measurements were performed at $25 \pm 1^\circ\text{C}$ in triplicate. Results were expressed as mean $\pm$ SD. The optimized formulation exhibited nanoscale particle size, low PDI (< 0.3), and a high negative zeta potential, indicating colloidal stability.

2.4.2 Fourier Transform Infrared Spectroscopy (FTIR)

FTIR spectroscopy (Shimadzu IR Affinity-1) was employed to investigate drug–excipient compatibility. Dried samples were mixed with KBr and scanned over $4000\text{--}400\text{ cm}^{-1}$. Spectra of individual components were compared with that of the optimized formulation to detect any shifts or disappearance of characteristic peaks. The retention of principal bands confirmed the absence of chemical interactions.

2.4.3 Differential Scanning Calorimetry (DSC)

DSC thermograms were recorded using a PerkinElmer DSC 4000 to evaluate thermal behavior, crystallinity, and drug–excipient compatibility. Samples (3–5 mg) were sealed in aluminum pans and heated from 30°C to 300°C at $10^\circ\text{C}/\text{min}$ under a nitrogen atmosphere. Changes in melting endotherms were analyzed to confirm encapsulation and matrix transition.

2.4.4 X-Ray Diffraction (XRD)

XRD analysis was conducted using a Bruker D8 Advance diffractometer with $\text{Cu K}\alpha$ radiation ($\lambda = 1.5406\text{ \AA}$), operating at 40 kV and 30 mA. Diffraction patterns were recorded over $2\theta = 5^\circ\text{--}60^\circ$ at a scanning rate of $2^\circ/\text{min}$. The disappearance or reduction of sharp crystalline peaks in the emulsomal samples compared to

pure drug confirmed partial amorphization, enhancing solubility and dissolution.

2.4.5 Scanning Electron Microscopy (SEM)

The surface morphology of emulsomes was examined using SEM (JEOL JSM-6390LV). Samples were mounted on aluminum stubs, gold-coated under vacuum, and imaged at 10 kV. The images provided insights into shape, smoothness, and aggregation of vesicles.

2.4.6 Transmission Electron Microscopy (TEM)

Ultrastructural examination was carried out using TEM (JEOL JEM-2100) to visualize internal morphology and confirm the core-shell structure. A drop of diluted emulsomal suspension was placed on a carbon-coated copper grid, negatively stained with phosphotungstic acid, air-dried, and imaged at 200 kV.

2.4.7 Entrapment Efficiency (EE%)

Entrapment efficiency was determined via ultracentrifugation (15,000 rpm, 60 min, 4°C). The supernatant was analyzed using a UV–Visible spectrophotometer (Shimadzu UV-1800) at $\lambda_{\text{max}} = 262\text{ nm}$ (*B. diffusa*) and 284 nm (*A. augusta*). EE% was calculated using:

$$EE\% = \frac{\text{Total drug} - \text{Free drug}}{\text{Total drug}} \times 100$$

4.4.8 Drug Content

Drug content was analyzed by lysing 1 mL of emulsomal suspension with methanol or ethanol, followed by dilution and spectrophotometric analysis at the same λ_{max} values. The percentage drug content was calculated as:

$$\% \text{Drug Content} = \frac{\text{Estimated Drug}}{\text{Theoretical Drug}} \times 100$$

4.4.9 In Vitro Drug Release

In vitro release was studied using the dialysis bag diffusion method (MWCO: 12,000–14,000 Da). One milliliter of emulsomal dispersion was enclosed in the dialysis membrane and immersed in 100 mL PBS (pH 7.4) at 37 ± 0.5 °C under magnetic stirring (100 rpm). Aliquots (2 mL) were withdrawn at predetermined intervals (0–12 h) and replaced with fresh buffer. Absorbance was measured spectrophotometrically, and cumulative drug release was calculated.

4.4.10 Stability Studies

Stability of the optimized emulsomal formulation was assessed under refrigerated (4 ± 2 °C) and accelerated (25 ± 2 °C, 60% RH) conditions as per ICH Q1A(R2) guidelines. Samples were analyzed at 0, 15, and 30 days for particle size, zeta potential, entrapment efficiency, drug content, and physical appearance. Formulations maintaining consistent parameters were considered stable.

4.5 Formulation of Nebulizing Solution

The optimized emulsomal batch (F10) was dispersed in sterile 0.9% normal saline containing BHT to prepare nebulizing formulations (EN1–EN3). These were evaluated for physicochemical parameters including pH, clarity, drug content, aerosolization performance, in vitro release, and short-term stability to ensure suitability for pulmonary administration.

5. Results and Discussion

5.1 Optimization and Evaluation of Herbal Emulsomes

The emulsomal formulations were optimized using a Central Composite Design (CCD) by varying lipid and phospholipid concentrations as independent variables, while particle size, drug content, and entrapment efficiency were taken as dependent responses. Among the experimental runs, the optimized batch (F10) demonstrated superior physicochemical characteristics, with a mean particle size of 211 nm, zeta potential -34.5 mV, drug content 80.3%, and entrapment efficiency 77.5%, indicating satisfactory encapsulation and colloidal stability.

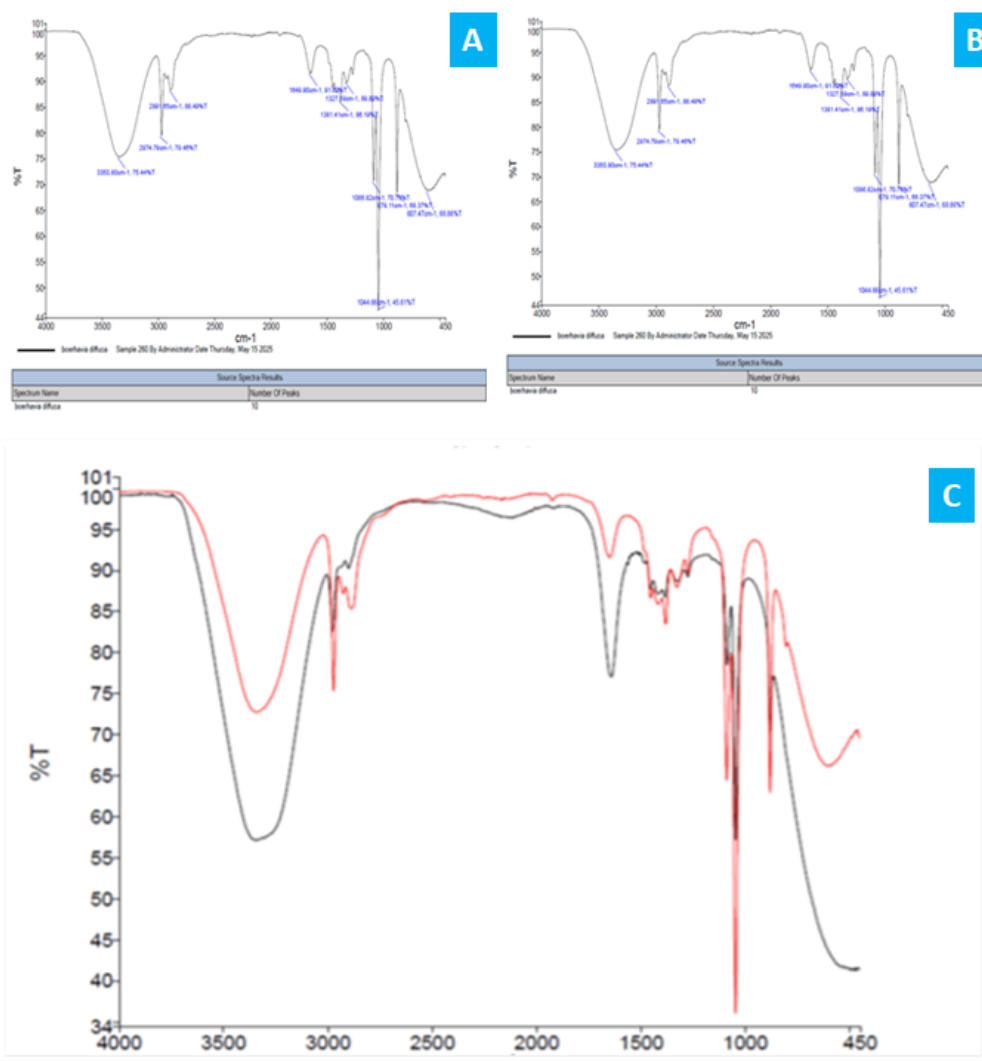


Figure 1. FTIR spectra of (A) *Abroma augusta*, (B) *Boerhavia diffusa*, and (C) combined spectra illustrating drug-excipient compatibility in the optimized emulsomal formulation.

FTIR analysis of *Abroma augusta* and *Boerhavia diffusa* extracts confirmed the absence of any major drug-excipient incompatibility, suggesting that the active constituents retained their chemical integrity within the lipid matrix. This compatibility was further validated by the overlapping characteristic peaks of the herbal extracts and excipients in the optimized formulation, indicating no new bond formation.

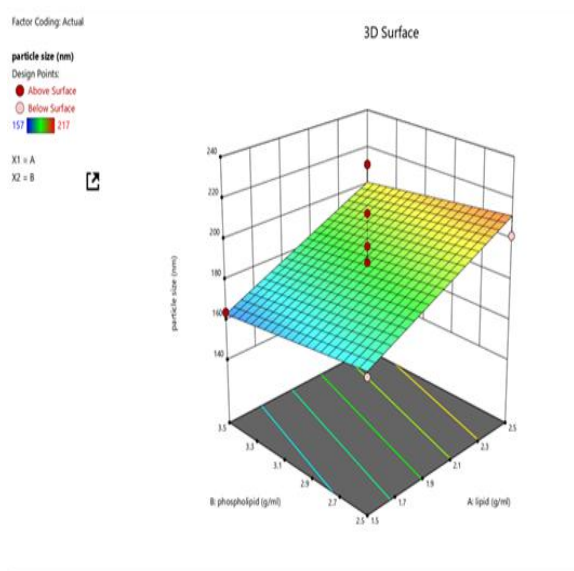
5.2 Effect of Independent Variables

The optimization plots revealed that both lipid and phospholipid concentrations significantly influenced the particle size and entrapment efficiency. An increase in lipid concentration tended to enlarge vesicular size, whereas higher phospholipid levels improved drug loading and stability. The interaction between the two factors was crucial for achieving an optimal vesicle size within the nanoscale range (<250 nm), which is essential for pulmonary delivery. The overlay plot indicated that batch F10 met the desired criteria for all three responses with a high desirability factor.

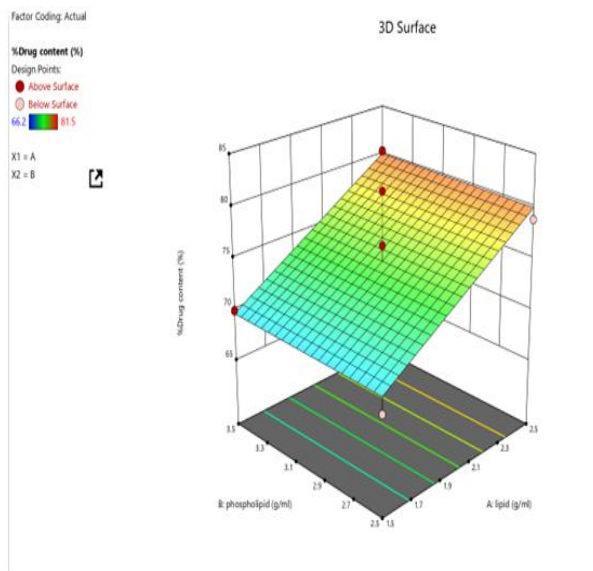
Table No 2. Observed response in Central Composite Design of phytochemical loaded emulsome						
Std	Run	Factor 1 A: Lipid g/ml	Factor 2 B: Phospholipid g/ml	Response 1 particle size nm	Response 2 %Drug content %	Response 3 % Entrapment Efficiency %
11	1	2	3	189	76.3	72.9
10	2	2	3	213	81.5	76.89
3	3	1.5	3.5	164	69.9	66
12	4	2	3	197	74.7	69.9
13	5	2	3	157	68	64
6	6	2.70711	3	217	80.6	76.42

Formulation and Evaluation of Herbal-Based Emulsomal Nebulizing Solution Containing Abroma Augusta and Boerhavia Diffusa for Inhalational Treatment of Cystic Fibrosis-Associated Lung Conditions

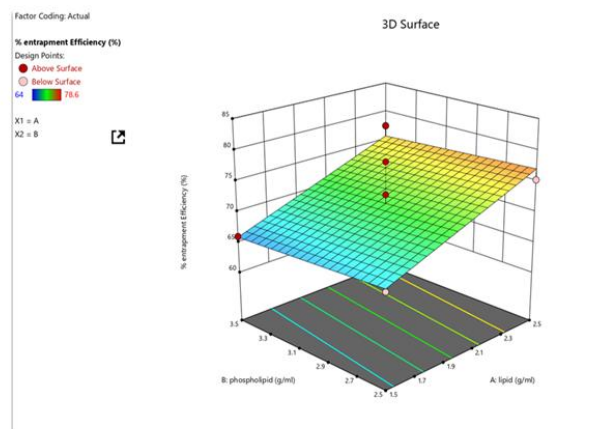
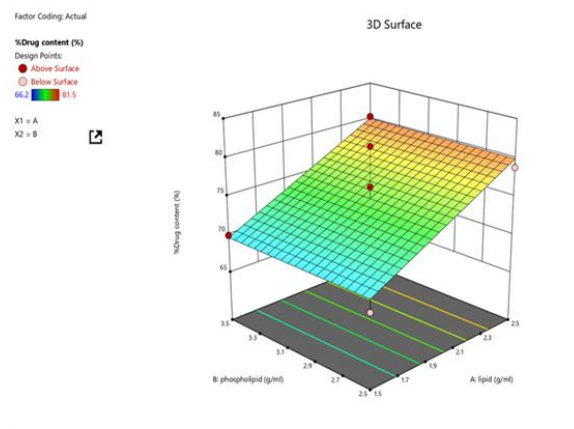
7	7	2	2.29289	209	80	76.9
8	8	2	3.70711	178	77.8	72.02
9	9	2	3	164	70.1	66
4	10	2.5	3.5	211	80.3	77.5
5	11	1.29289	3	164	66.2	65
1	12	1.5	2.5	171	67.9	66.8
2	13	2.5	2.5	202	78.8	75.3



Effect of independent variable on particle size

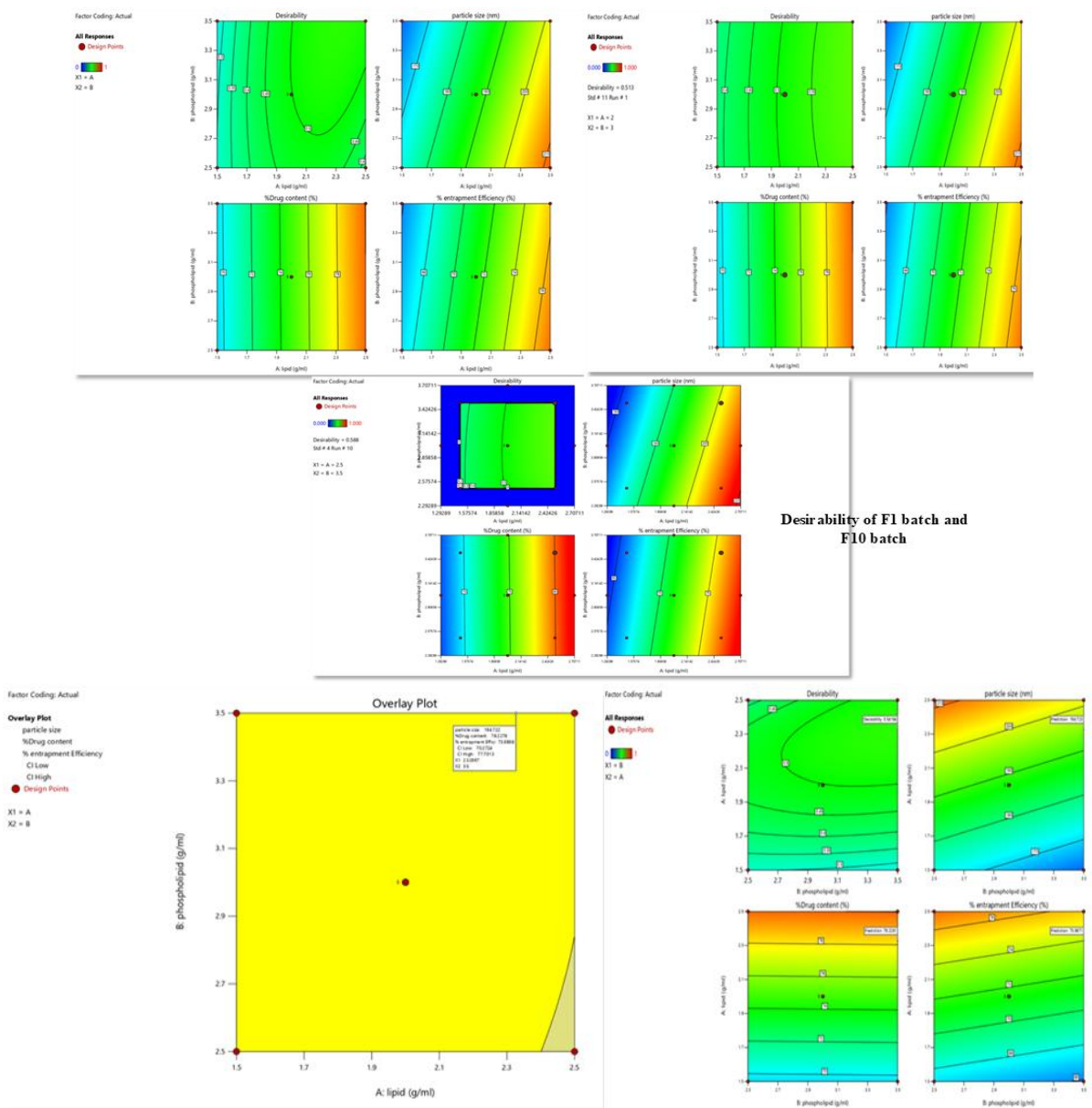


Effect of independent variables on % Drug content



Effect of independent variables on % Entrapment Efficiency

Formulation and Evaluation of Herbal-Based Emulsomal Nebulizing Solution Containing *Abroma Augusta* and *Boerhavia Diffusa* for Inhalational Treatment of Cystic Fibrosis-Associated Lung Conditions



Overlay plot for optimization of F10 batch
Figure 2. Effect of Independent variables on Dependent variables

5.3 Solid-State Characterization

The DSC thermogram of the optimized batch exhibited thermal shifts compared to pure components, confirming successful encapsulation of phytoconstituents within the emulsomal core. Similarly, XRD patterns showed a marked reduction in peak intensity, indicating the transition of crystalline drug into an amorphous or molecularly dispersed state, which favors improved dissolution and release kinetics.

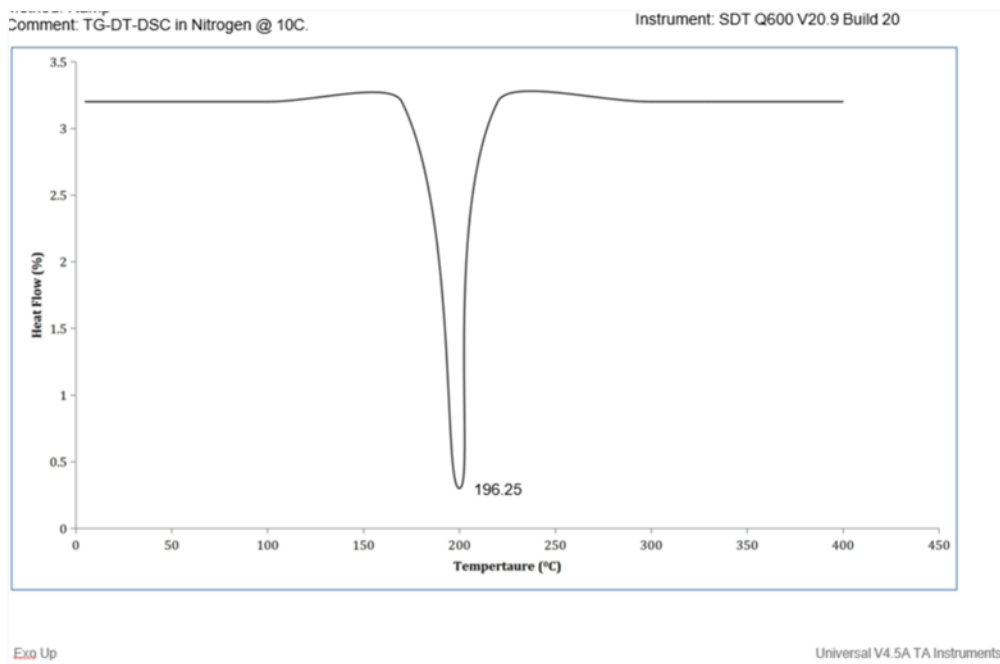


Figure 3. DSC of optimized batch F10

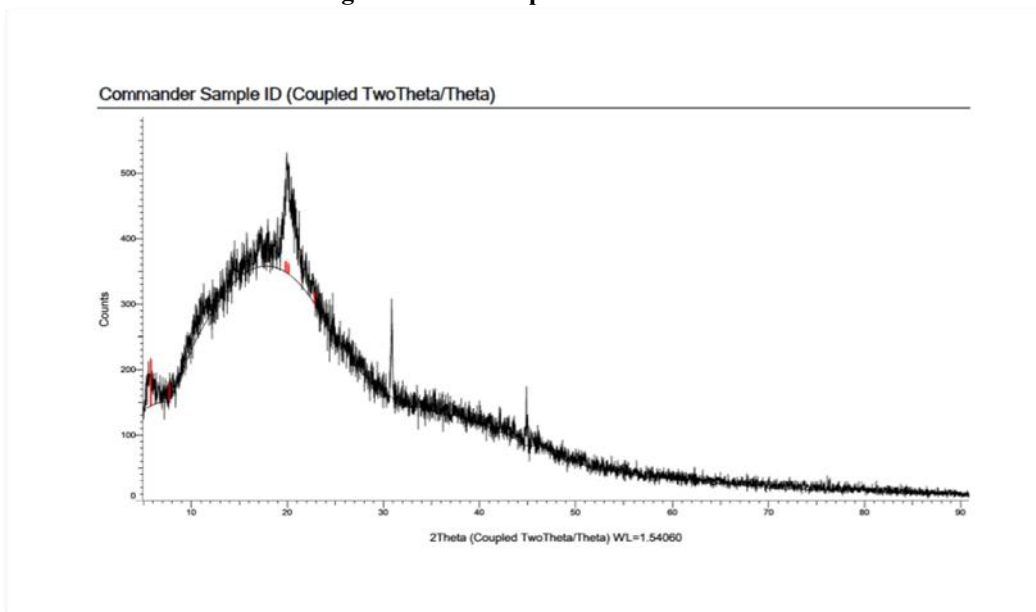


Figure 4. XRD of optimized batch F10

5.4 Surface Morphology

SEM and TEM micrographs of batch F10 revealed spherical to slightly oval vesicles with smooth surfaces and uniform size distribution in the nanometer range. TEM images further confirmed the core-shell bilayer structure typical of emulsomes, validating their suitability as carriers for lipophilic herbal constituents.

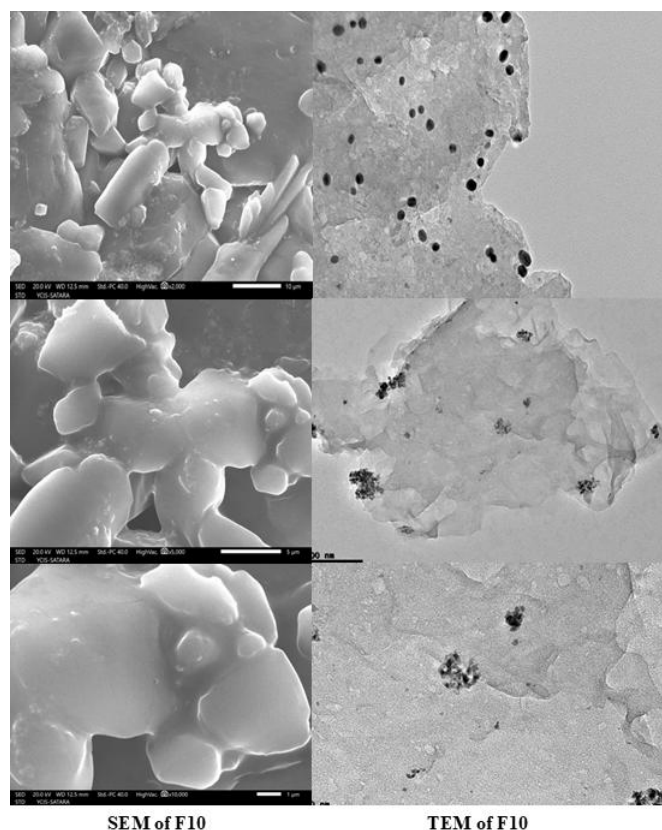


Figure 5. SEM and TEM Analysis of Optimized Batch F10 Showing Uniform, Spherical Emulsomal Particles

5.5 Stability Studies of Emulsomal Dispersion

The optimized emulsomal batch (F10) was subjected to stability evaluation as per ICH guidelines under both refrigerated and long-term storage conditions. The formulation retained its uniform appearance for one month, with only minor flocculation observed after 30 days at ambient conditions, indicating acceptable physical stability for a nanosuspension system.

Table 3. Stability of optimized batch of emulsome F10

Sr.no	Time period	Appearance	Storage condition: 25°C±2°C 60% RH ±5%RH (long term), 5°C±3°C (Refrigerated)
1	Initial	Uniform mixture	
2	After 10 days	No major changes	
3	After 20 days	Slight change in texture	
4	After 30 days	Slightly flocculated	

5.6 Development of Nebulizing Solution

To achieve respirable particle dimensions suitable for inhalation therapy, batch F10 was further processed by controlled sonication, reducing the mean size to 168 nm. A slight decrease in drug content (to 79.17%) and entrapment efficiency (to 75.33%) was noted, likely due to mechanical disruption of vesicles and partial drug leakage. The pH values (5.57–5.77) of the nebulizing formulations (EN1–EN3) were within the physiologically acceptable range for pulmonary delivery, minimizing potential irritation.

Table No 4. Particle Size and pH of Herbal-Based Emulsomal Nebulizing Solutions (Mean ± SD)

Formulation Code	Particle Size (nm)	pH
EN1	172 ± 2	5.72
EN2	170 ± 2	5.57
EN3	168 ± 2	5.77

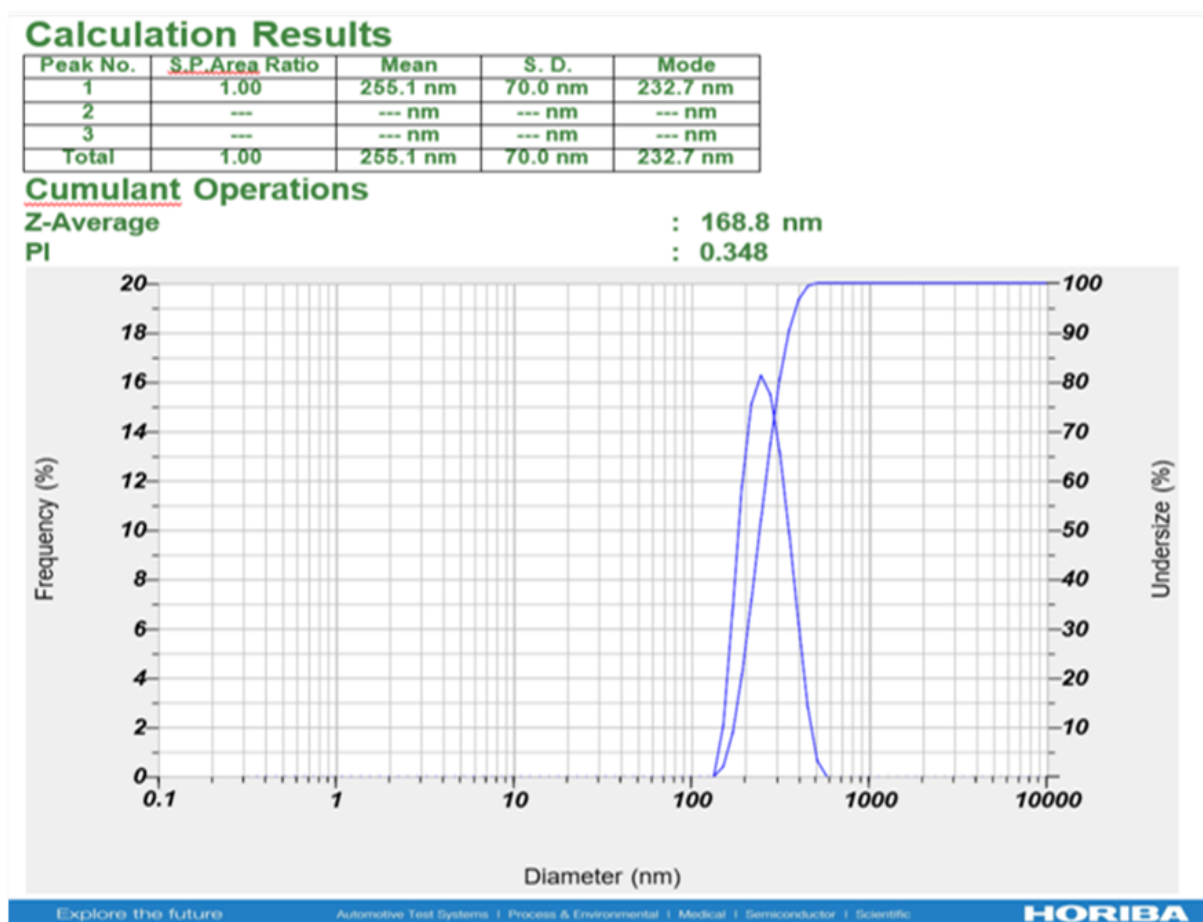
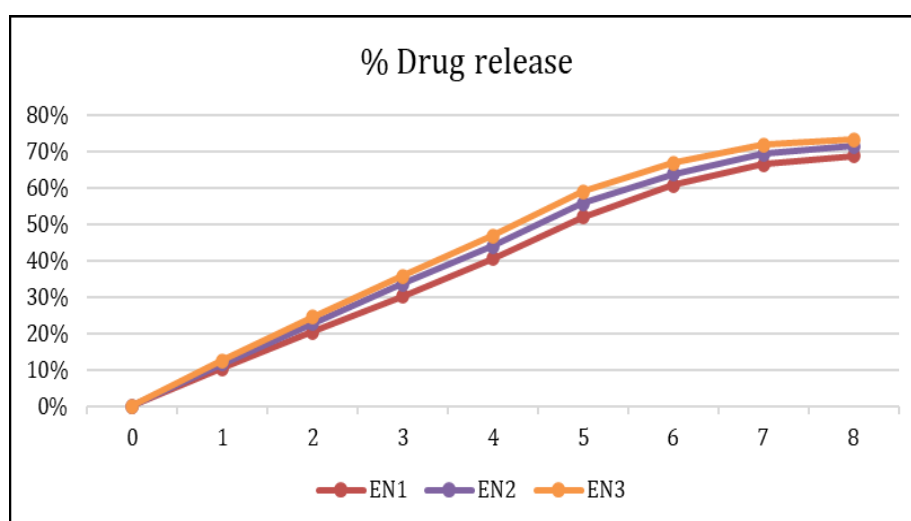


Figure 6. Particle size of optimized batch F10

5.7 In Vitro Drug Release

The optimized nebulizing solution (EN3) exhibited a sustained drug release profile, achieving 73.89% release over 8 hours, which suggests prolonged residence time in the pulmonary tract and potential for improved

therapeutic efficacy in cystic fibrosis-associated infections. The biphasic release pattern may be attributed to initial surface drug diffusion followed by sustained diffusion from the lipid matrix.



5.8 Stability of Nebulizing Solution

The EN3 batch-maintained clarity, pH stability (6.24 → 6.0), and consistent drug release (>72%) during a 3-

month study under both refrigerated and accelerated conditions, indicating good formulation robustness and shelf stability suitable for nebulization.

Table No 5. Stability study data for 3-month time period (EN3 batch)

Sr.no	Stability period	study	Appearance	pH	In-vitro release	Drug
1	Initial		Good clarity, appearance	stable	6.24	73.89%
2	After 1 month		Clear & stable		6.16	73.82%
3	After 2 month		Clear & stable		6.04	73.13%
4	After 3 month		Clear & stable		6.0	72.93%

Conclusion

The integration of *Abroma augusta* and *Boerhavia diffusa* extracts into an emulsomal nanocarrier system significantly improved their aqueous dispersibility, physicochemical stability, and controlled release potential. The optimized herbal-based emulsomal nebulizing formulation exhibited nanoscale particle size and a stable negative zeta potential, favoring efficient deep lung deposition through nebulization. The formulation demonstrated excellent stability, sustained release, and compatibility with inhalation therapy, indicating its suitability for pulmonary delivery. Overall, the developed herbal emulsomal platform presents a promising approach for the inhalational management of cystic fibrosis-associated lung inflammation and infection. However, further in vivo and clinical investigations are essential to substantiate its therapeutic efficacy and safety.

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