

Article

Advancing Dry Powder Inhalers: A Complete Workflow for Carrier-Based Formulation Development

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Abstract

Background/Objectives: Carrier-based dry powder inhaler (DPI) formulations remain the predominant platform for respiratory drug delivery. However, integrated development frameworks that align upstream particle engineering with downstream manufacturing are underdeveloped. This study aimed to develop a comprehensive Quality-by-Design (QbD) strategy that systematically connects jet milling, formulation design, and blending scale-up for carrier-based DPI products containing micronized crystalline active pharmaceutical ingredient (API). **Methods:** Phenytoin was selected as a model API to investigate process–formulation–performance relationships. Jet milling parameters were optimized to generate three distinct API particle size distributions while monitoring solid-state integrity. A design of experiments (DoE) evaluated the impact of API particle size and lactose fines level on aerodynamic performance (fine particle fraction, FPF) and powder processability (flowability, compressibility). High-shear and low-shear blending techniques were compared, and a novel V-shell blending scale-up methodology was developed based on maintaining particle fall velocity and total strain across multiple scales (one-, two-, and eight-quart). **Results:** Optimized jet milling produced inhalation grade API particles with controlled amorphous content localized to high-energy processes. DoE analysis identified a design space in which API D_{v90} of 2.9–4.5 μm and coarse lactose $<96\%$ maximized both aerosolization and blend flowability. Low-shear blending achieved superior lung delivery (FPF $62.6 \pm 1.7\%$) compared with high-shear mixing ($50.1 \pm 1.5\%$). The particle-velocity-based scale up strategy produced statistically equivalent FPF and ED across all scales ($p < 0.01$), with content uniformity ($\text{RSD} \leq 5\%$) and variability comparable to commercial DPIs. **Conclusions:** This integrated QbD framework demonstrates that the co-optimization of particle size engineering, formulation composition, and blending dynamics is essential for achieving robust and scalable DPI products. The approach offers a material-sparing, efficient pathway from API characterization through commercial scale manufacturing and is broadly applicable to respiratory drug development.

Keywords: dry powder inhaler; jet milling; carrier-based formulation; low shear mixing; high shear mixing; scale-up; quality by design (QbD); pharmaceutical manufacturing

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1. Introduction

1.1. Pulmonary Drug Delivery: Clinical Rationale

The inhalation route has long been utilized for the treatment of pulmonary disorders and is now recognized as one of the most efficient and safe methods of drug delivery [1]. By enabling direct deposition of active pharmaceutical ingredients (APIs) at the site of action within the lungs, this approach minimizes systemic exposure and allows for reduced therapeutic doses. Several delivery strategies have been developed to target the deep lung effectively [2]. For instance, nebulizers generate fine aerosols from drug solutions or suspensions that are inhaled passively over 5–20 min, depending on the treatment regimen. Pressurized metered-dose inhalers (pMDIs) deliver a measured amount of drug as a solution or suspension via a single, coordinated inhalation synchronized with actuation of the device. Among these technologies, dry powder inhalers (DPIs) have gained particular prominence due to their portability, propellant-free design, and capacity for efficient pulmonary deposition.

1.2. Dry Powder Inhalers and Their Advantages

Dry powder inhalers (DPIs) have gained prominence as an effective alternative to other inhalation systems [3]. A typical DPI consists of a device containing a dry powder formulation, where performance largely depends on the interplay between powder formulation and device design. The formulation must yield a powder that is both physically stable and readily dispersible—an inherently challenging balance. For efficient deposition in the lungs, particles must generally be smaller than 5 μm in aerodynamic diameter, but fine powders are cohesive and difficult to disperse [4].

1.3. Carrier-Based Systems

A range of both advanced and conventional strategies have been employed to optimize powder dispersibility in DPI formulations. Advanced formulation focuses on engineering tailored particles obtained by co-processing the API with suitable excipients into composite particles. This can be achieved via techniques such as spray-drying, spray freeze-drying, emulsion-based methods, or supercritical antisolvent processes [5]. In contrast, conventional methods rely on physically blending micronized API with carrier excipients—carrier-based formulations—to improve flow and dispersion. Traditional carrier-based formulations represent the most widely used approach in marketed DPI products (such as fluticasone, salmeterol, and tiotropium). This approach is particularly suitable for highly potent APIs with low dosage targets (1–15% of API), with minimal need for solubility enhancement [3]. Ultimately, the selection of the best formulation strategy should be guided by the target product profile and the physicochemical characteristics of the API—whether amorphous or crystalline—as well as the required delivered dose and bioavailability objectives [6]. While composite particles produced by techniques such as spray drying offer several advantages, including compatibility with biologics and the ability to achieve higher drug loadings, carrier-based formulations rely on excipients with extensive commercial precedent and typically present lower stability risks for APIs that can be maintained in a crystalline state [3]. This contrasts with metastable amorphous dispersions, which are susceptible to phase transitions during storage, handling, or processing, particularly under higher humidity conditions. Given their widespread adoption and cost-effectiveness, carrier-based systems remain a cornerstone of inhalation product design, making it essential to understand the particle-particle interactions that govern their performance.

1.3.1. Mechanism: Particle-Excipient Interactions in Carrier-Based Systems

In carrier-based dry powder inhaler formulations, the dispersibility of micronized API (typically 1–5 μm) is enhanced by mixing it with carriers such as lactose monohydrate. These larger particles serve two critical functions: they effectively carry the API particles from the capsule or device to the upper airway and aid in dispersing the cohesive API particles during the inhalation, thereby promoting deposition of the API as individual particles or small agglomerates [6,7]. Effective aerosolization relies on the stable adhesive interactions between the drug and carrier surfaces, promoting effective distribution of drug particles and ensuring consistent aerosolization. These phenomena make the aerosolization process easier to achieve and enhance its reproducibility. The establishment and maintenance of these particle-particle interactions depends critically on multiple manufacturing stages. Recognizing and managing these interdependencies is therefore essential for achieving robust, high-performing DPI products.

1.3.2. The Manufacturing Workflow: Key Process Stages

The development of carrier-based DPI formulations requires careful control across multiple interlinked manufacturing stages, notably crystallization, micronization, blending, and capsule or device filling. Each stage contributes to the final product's performance.

Micronization

Micronization determines API particle size, shape, and surface characteristics such as rugosity, surface energy, cohesiveness, amorphous content, electrostatic charge, and polymorphism. The relationship between crystallinity and aerosol performance is multifactorial, as any modification of crystallinity through particle engineering can simultaneously affect morphology, electrostatic charge, and surface energy [8].

Several micronization techniques are available [8]. Jet milling is a widely adopted and scalable approach that produces fine powders with narrow particle size distributions. In this process, high-velocity gas streams accelerate particles, inducing interparticle collisions that reduce size. However, jet-milled powders often exhibit irregular shapes, rough surfaces, and elevated electrostatic charge, which can impair flowability and handling [9]. Moreover, localized amorphization may occur on particle surfaces, followed by potential recrystallization under humid storage conditions. This recrystallization can promote particle growth through solid-bridge formation between amorphous surfaces, potentially shifting particles outside the respirable range [8]. Because jet milling parameters have cascading effects throughout the formulation's lifecycle, they should be optimized with downstream blending and aerosol performance in mind.

Formulation Design and Lactose Fines

Following micronization, the micron-sized API particles are blended with selected excipients. The standard strategy is a ternary system with API, coarse lactose, and a small fraction (usually <15%) of fine lactose. The mechanisms governing these multi-component interactions have been extensively investigated [10–12]. Collectively, these theories highlight both surface level adhesion phenomena and bulk powder dynamics as key determinants of DPI performance. Several theories have been proposed to rationalize how fine lactose modifies API-carrier interactions and hence aerosolization performance. The most cited theories include the “active sites” concept [13], which assumes preferential occupation of high-energy surface sites on the carrier by fines, thereby passivating these regions for API adhesion; and the “agglomerates” or “multiplets” theory [10], which attributes the fines effect to the formation of mixed API-fines clusters that are more readily detached by aerodynamic drag than isolated API particles. More recently, the viscoelastic damping

mechanism has been proposed, in which fines are responsible for dissipating impact energy, thereby reducing effective press-on forces and facilitating API detachment [12]. The coexistence of these theories underlines that fines-mediated behavior is complex and motivates the use of a statistical approach to develop formulations. In addition to lactose, the use of force control agents such as magnesium stearate (MgSt) can improve formulation performance, stability, and flowability by reducing surface energy, passivating high-energy binding sites, and providing lubrication effects [4,14].

Blending Mechanism and Scale-Up

Beyond the formulation composition, the mixing process mechanism and input energy profoundly affect particle-particle interaction, dictating blend uniformity, stability, and aerosolization efficiency. The energy of a mixture is dependent on the mechanism, speed, and duration, and several studies have proposed approaches to quantify the mixing energy [15–17] and correlate it with the aerodynamic performance. Mixing processes can be classified as high- or low-shear. While scale up strategies for high-shear have been well established [15], no validated methodology currently exists for scaling up low-shear blending of carrier-based DPI formulations containing fine particle fractions. A successful blending process must yield a homogeneous mixture that consistently delivers uniform doses and can be seamlessly scaled for manufacturing. The scale up of high-shear mixing processes has been successfully achieved based on the mixing energy [15]. For low shear tumble blending, parameters such as the Froude number ($Fr = r\omega^2/g$) or tangential speed are commonly used as a scale-up criteria [18]. However, their applicability is limited: the Froude number originates from continuum mechanics and was first introduced to quantify the hydrodynamic resistance of floating bodies and to support ship-scale testing [19]. In contrast, powder blending processes operate in a regime where the characteristic system dimensions are on the order of the particles' mean free path [18]. Moreover, the Froude number does not account for fill level, a parameter known to dramatically influence mixing [20]. Despite being the most widely applied scale-up criterion for such systems, there is no evidence in the literature supporting the Froude number or the tangential speed's suitability for powder blending applications. Furthermore, Horibe et al. [21] demonstrated that the properties of mixtures prepared in a V-blender across scales ranging from 1.45 L to 130 L were independent of the Froude number. Alexander et al. proposed a scale up approach for low shear mixing of coarse mixtures based on the fall pattern and fill fraction in V-shell blenders correlating the particle velocity to the radius and rotational speed of the vessel [22]. However, this method has not been validated for mixtures containing a small percentage of fine particles typical of carrier-based inhalation powder.

Consequently, the formulation composition and process parameters must be optimized in concert, accounting for both the chemical and physical characteristics of the API. Given this complexity, a universal “one-solution-fits-all” strategy remains elusive—underscoring the need for a structured, mechanism-driven, and material-efficient framework for DPI development.

1.4. Knowledge Gap and Study Objectives

Despite extensive progress in the field of DPI development, systematic, material sparing, and scientifically grounded frameworks that connect key process stages—micronization, formulation screening, blending technology selection, and process scale-up—remain underdeveloped. This gap is particularly evident for low-shear blending processes involving fine-particle systems, where limited mechanistic understanding continues to hinder efficient, scalable product development.

To address this challenge, the present study employs an integrated Quality by Design (QbD) approach using Phenytoin as a model compound for the development of a carrier-based dry powder inhaler formulation. The investigation spans the entire manufacturing workflow—from jet milling to the final product evaluation—with the overarching goal of establishing a structured, resource-efficient and scalable development strategy.

The primary objective was to systematically evaluate how milling and blending processes influence the critical quality attributes (CQAs) of the DPI product. Specifically, the work aimed to do the following:

1. Identify key material and process parameters relevant to standard DPI development workflows
2. Establish practical, material-sparing strategies that enable a seamless transition from a new API to a scalable carrier-based formulation
3. Evaluate the influence of mixing energy under both low- and high-shear conditions on powder homogeneity and aerosolization performance
4. Develop and validate a predictive scale-up methodology for low-shear blending of carrier-based powders

To accomplish these objectives, a comprehensive experimental strategy was designed to systematically assess the interdependencies between formulation and process parameters. It is important to note that while the systematic methodology presented here, encompassing DoE-driven formulation screening, blending mechanism comparison, and particle velocity-based scale-up, is broadly transferable to other APIs, the specific quantitative correlations and optimal process parameters are compound-dependent. APIs with different surface energies, hygroscopicity, or polymorphic stability may exhibit altered drug-carrier adhesion dynamics, altered sensitivity to fines content, and potentially different mixing technology preferences. Therefore, the workflow should be replicated for each new API, but the specific design space and performance metrics must be re-established empirically for each compound.

The subsequent section details the materials employed, the jet milling conditions investigated, the design of experiments (DoE) for formulation screening, and the blending methodologies under both low- and high-shear regimes.

This integrated framework established the foundation for the systematic experimental studies presented in the subsequent sections.

2. Materials and Methods

2.1. Materials

Phenytoin was purchased from Spectrum Chemical Mfg. Corp. Respitose® SV003 (coarse lactose) and Lactohale® L230 (fine lactose) were obtained from DFE Pharma. V Caps Plus DPI grade capsules (size 3) were purchased from Lonza, Capsugel division. High Resistance RS01 inhalers were purchased from Amcor. Ultra-purified water was produced on-site using a Milli-Q® purification system. HPLC-grade methanol, acetonitrile, isopropanol, ammonium phosphate dibasic, phosphoric acid (85%), ammonium hydroxide, and hexane were acquired from Fisher Scientific.

2.2. Manufacturing

2.2.1. Jet Milling for Target Particle Size Distributions

With the materials procured and characterized, the first critical manufacturing stage, jet milling, was systematically optimized to generate three distinct particle size distributions for subsequent formulation development.

Phenytoin API was micronized using an MC50 spiral jet mill (Micro-Macinazione, Lonza, Switzerland), operating with nitrogen as the grinding gas. Milling conditions were selected to produce three well-differentiated particle size distributions (PSDs):

- A fine fraction (target Dv50 $\approx$ 1.6 μ m)
- An intermediate fraction (Dv50 $\approx$ 1.8 μ m),
- A coarse fraction (Dv50 $\approx$ 2.7 μ m).

Grinding pressure and feed rate were maintained constant with each batch, as summarized in Table 1. This controlled approach enabled a systematic assessment of particle-size effects on powder behavior, blending performance, and aerosolization efficiency in later stages of development. The specific energy consumption (E_{sp} , kJ/g) for each milling condition was calculated following the methodology described by Midoux et al. [9], providing a quantifiable link between processing energy and resulting particle characteristics.

Table 1. Jet mill process parameters used to target fine, intermediate and coarse fraction of phenytoin. PF—feeding pressure, PG—grinding pressure, F_{feed} —feeding rate, E_{sp} —specific energy.

Batch	P _F (bar)	P _G (bar)	F _{feed} (kg/h)	E _{sp} (KJ/g)
Fine fraction	7.0	6.0	0.10	1.5
Intermediate fraction	5.5	4.5	0.10	1.2
Coarse fraction	3.5	2.5	0.30	0.3

2.2.2. Formulation Screening by Low Shear Mixing

Following the generation of three well-defined jet-milled phenytoin fractions, formulation screening was performed to assess how particle size distribution influences drug-excipient interactions under controlled low-shear blending conditions.

A preliminary DoE was conducted using Turbula® T2F (WAB, Muttenz, Switzerland) with a central composite DoE with three center-point replicates ($2^3 = 8$ factorial runs + 4 axial points + 3 central point repetitions = 15 total runs) was employed using Design-Expert® software (Version 11, Stat-Ease Inc., Minneapolis, MN, USA), investigating the effects of:

- API concentration (1–10%),
- Fine lactose concentration (1–15%)
- API Dv90 (2.9–5.7 μ m).

Response variables included:

- Fine particle fraction (FPF, %)
- Emitted dose (ED, %)
- Conditioned bulk density (CBD, g/mL)
- Compressibility (%)

The central composite design was selected to evaluate curvature and to generate a predictive model capable of identifying the region that would optimize the response. The optimization criteria aimed to maximize FPF and ED and CBD, while minimizing compressibility to ensure acceptable powder flowability for capsule filling. This resulted in 15 formulations, each prepared in 20 g batches, as summarized in Table 2.

Table 2. Experimental design matrix for feasibility trials, detailing the percentage of fines, API content (%), and API particle size (Dv90) for each trial condition evaluated.

Trial	A	B	C	D	E	F	G	H	I	J	K	L	M	N	O
Fines (%)	15	15	1	15	1	1	1	15	1	15	8	8	8	8	8
API (%)	1	10	10	1	1	10	1	10	5.5	5.5	1	10	5.5	5.5	5.5
API Dv90 (µm)	2.9	2.9	2.9	5.7	5.7	5.7	2.9	5.7	3.3	3.3	3.3	3.3	3.3	3.3	3.3

All components were sieved through a 500 µm screen to remove oversized agglomerates. Blending followed a geometric addition strategy to promote uniform API addition in this low-energy process, especially critical given the low dose drug and multi-modal particle sizes. The procedure involved:

- i. Preparation of the pre-blend, a mixture of coarse and fine lactose.
- ii. Dividing the pre-blend in three parts and the API in two parts.
- iii. Adding 1/3 of the pre-blend, 1/2 of the API and another 1/3 of the pre-blend to the Blending and mixing for 25 min at 32 rpm.
- iv. Adding the remaining 1/2 of the API and 1/3 of the pre-blend and mixing for an additional 25 min at 32 rpm.

The formulation design space established through low-shear screening provided the foundation for understanding optimal API-excipient interactions. To evaluate whether these interactions could be preserved during manufacturing scale-up, and to compare how different blending mechanisms influence product performance, the selected formulation was then scaled and blended using both a high-shear and a low-shear blending mechanism.

2.2.3. Scale-Up to High Shear Mixer

Scale up was performed using a TMG high shear mixer from Glatt (Binzen, Germany) with a batch size of 20 g to 150 g, containing 5.5% of API, 8.0% of fine lactose, and 86.5% of coarse lactose. A two-factor, three-level full factorial DoE without replicates ($3^2 = 9$ factorial runs), created using Design-Expert® software (Version 11, Stat-Ease Inc., Minneapolis, MN, USA), was conducted by varying the impeller speed (400–750 rpm) and mixing time (3–7 min), yielding scale-independent mixing energies of 1.2–11.4 mJ (Table 3). Based on the literature indicating that both impeller speed and mixing time influence performance [17], the objective of the full factorial design was to determine the main effects and any interactions for the specific phenytoin formulation. The response variable evaluated was fine particle fraction (FPF).

Table 3. Mixing parameters and calculated mixing energies for high shear blending design-of-experiments trials using a Glatt TMG mixer.

Trial	Mixing Speed (RPM)	Mixing Time (min)	Mixing Energy (mJ)
1	750	3	4.9
2	750	5	8.1
3	750	7	11.4
4	400	3	0.7
5	400	5	1.2
6	400	7	1.7
7	575	3	2.2
8	575	5	3.7
9	575	7	5.1

All components were sieved through an 850 µm sieve prior to blending. All pre-blend mixtures were prepared as described previously. The API was then added between two equal layers of the pre-blend.

The mixing energy calculation for high shear mixing trials was done according to Thalberg et al. [15], as described in Equation (1). The mixing energy is scale-independent and relates to the Fine Particle Fraction (FPF) according to Equation (2). This strategy can be used to ensure a similar product performance upon scale-up with a similar vessel and stirred geometry. Moreover, it is a process development tool, as it provides a relationship between energy and product performance, allowing for performance optimization.

$$ME = 8\pi^3 m f^3 r^2 t \quad (1)$$

$$FPF = \left[A + \frac{B}{1 + e^{-k_1 ME}} \right] \times e^{-k_2 ME} \quad (2)$$

where m is the carrier particle mass, f is the impeller frequency, r is the bowl radius, and t is the mixing time. A and B are model constants representing system-specific maximum FPF, k_1 and k_2 are rate constants related to the loading of drug.

2.2.4. Scale-Up to Low Shear Mixer (V-Shell)

Low shear mixing was scaled using a V-Shell blender (Patterson Kelley, East Stroudsburg, PA, USA), to determine whether the performance observed during Turbula-based formulation screening could be maintained under a scalable tumble blending process. The blend was prepared as follows:

- i. Sieving the fine and coarse lactose and the API, totaling 125 g of powder,
- ii. Pre-blending the sieved fine and coarse lactose for 30 min at 32 rpm,
- iii. Dividing the pre-blend in three parts and the sieved API in two parts
- iv. Adding 1/3 of the pre-blend, 1/2 of the API and another 1/3 of the pre-blend to the blender and mixing for 30 min at 32 rpm
- v. Adding the remaining 1/2 of the API and 1/3 of the pre-blend and mixing for an additional 30 min at 32 rpm.

Following sampling for content uniformity and aerodynamic performance testing, the blend was subjected to two extended mixing intervals, with a total mixing time of 60 min and 120 min at 32 rpm.

To understand how particle velocity and fill fraction influence particle motion within tumbling V-shell blenders, a surrogate blend of 79.5% coarse lactose (SV003) and 20.5% fine lactose (LH230) was evaluated in a transparent 3D-printed one-quart V-shell. The fill fraction ranged from 20% to 80%, and the rotation speed from 4.5 and 32.3 rpm. This corresponds to fall velocities of 9.6 and 35.9 cm/s, according to Equation (3), where R is the shell radius, Ω is the rotational speed, g is the gravitational acceleration and d is the average particle size [22].

$$\text{Particle fall velocity} = R\Omega^{\frac{2}{3}} \left(\frac{g}{d} \right)^{\frac{1}{6}} \quad (3)$$

Preserving the particles' fall velocity and the fill fraction has been shown to lead to similar fall patterns across scales [22]. Unlike the high shear mixing process development, the present methodology for low shear mixing has not been validated for coarse and fine carrier-based formulations. While these scale-independent dynamics were used to explain segregation in previous work [22], here it was hypothesized that:

- fine particles move in tandem, cohesively with the larger coarse particles while falling, minimizing diffusion-driven separation and

- preserving the same macroscopic tumbling regime across scales would maintain analogous mixing dynamics between fine and coarse particles.

It is worth noting that the proposed methodology is sensitive to these assumptions: although they are expected to hold for typical carrier-based formulation development scenarios, they may begin to break down at sufficiently high fines contents or for particle density ratios that deviate substantially from unity.

The fall patterns in the operating space of the one-quart V-shell were observed and the pattern transition regions recorded. The scale up to a two-quart V-shell was performed using the same preparation strategy and fill fraction (27%), while adjusting the rotational speed (19 rpm) to match the target fall velocity of 36 cm/s, according to Equation (3). The mixing times of 102 min and 204 min were selected to maintain an equivalent total number of revolutions relative to small scale blending. Further scale up to an eight-quart V-shell required adjusting the fill fraction to 22% to achieve an 800 g batch size, while operating at 9.5 rpm to again maintain the fall velocity at 36 cm/s. Blending was conducted for 204 and 408 min, preserving scale-independent particle kinematics.

2.3. Characterization

2.3.1. Particle Size Distribution

The particle size distribution (PSD) of micronized phenytoin was measured using a Malvern Mastersizer 3000 (Worcestershire, UK) equipped with a Hydro MV wet-dispersion unit. Laser diffraction was performed using 0.1% w/v solution of Span® 85 in Heptane as the dispersing medium. Approximately a 30 mg sample was dispersed by vortex prior to introduction into the analysis cell. The suspension was fed into the dispersion unit until an obscuration level of 11–12% was achieved and maintained. Continuous stirring and ultrasonic energy were applied to ensure complete deagglomeration and dispersion of the particles.

All measurements were conducted in triplicate, and the mean values were reported. PSD results are expressed as Dv10, Dv50, and Dv90, corresponding to the particle diameters below which 10%, 50%, and 90% of the total particle volume contained, respectively.

2.3.2. Scanning Electron Microscopy

Scanning Electron Microscopy (SEM) was conducted to evaluate the particle morphology of the carrier-based formulation. Samples were sputter-coated (Anatech Hummer 6.2) before imaging (Hitachi Model SU3500). Micrographs were acquired at magnification 200X, SEM operated at an accelerating voltage of 5.6–5.7 kV.

2.3.3. X-Ray Powder Diffraction

X-ray powder diffraction (XRPD) was used to assess the crystalline characteristics of the micronized API. Measurements were performed using a Bruker D2 Phaser diffractometer equipped with a Cu K α radiation source ($\lambda = 1.5418 \text{ \AA}$) operated at 30 kV and 10 mA. Powder samples were gently leveled into standard flat sample holders to minimize preferential orientation. Diffraction patterns were collected over a 2θ range of 3–50°, with a step size of 0.02° (2θ).

2.3.4. Rheological Characterization by FT4

Bulk density and compressibility of the formulation development blends were evaluated using a Freeman FT4 rheometer (Freeman Technology, Tewkesbury, UK). Powders were conditioned using three consecutive conditioning cycles, with the standard FT4 blade in a 25 mm split vessel. Following conditioning, the powder bed was compressed to 1.0 kPa and held under load for 60 s using the vented piston. The compression and hold

sequence was subsequently repeated at normal pressures of 2.0 kPa, 4.0 kPa, 6.0 kPa, 8.0 kPa, 10.0 kPa, 12.0 kPa, and 15.0 kPa. The conditioned bulk density was calculated as the mass to volume ratio immediately after conditioning. Compressibility was defined as the percentage increase in bulk density upon compression at 15.0 kPa, relative to the conditioned bulk density.

2.3.5. High Performance Liquid Chromatography (HPLC)

Phenytoin content was quantified by using a modified version of the phenytoin sodium USP method [23] to achieve a shorter run time. An Agilent HPLC Model 1290 (Agilent Technologies, Santa Clara, CA, USA) was equipped with a reverse-phase Waters CORTECS C18 column (PN 186007093, 1.6 μ m, 2.1 $\times$ 50 mm). An isocratic method with a 65/21/14 50 mM ammonium phosphate buffer (pH 2.5)/MeOH/ACN (v/v/v) mobile phase at a flow rate of 0.4 mL/min was used with 10 μ L injection volume. The column temperature was maintained at 40 $^{\circ}$ C, and samples held at ambient temperature. Detection was performed at 220 nm (band-width 4.0 nm). The total run time was 4 min, with phenytoin eluting at approximately 2 min.

Linearity was confirmed between 3–25 μ g/mL with $R^2 = 1.000$, $Y = 5.62 \times 10^7 X + 1.49 \times 10^4$. Interference at the phenytoin retention time was not observed in any diluent injections nor in test article blanks (i.e., syringe filter, FSI components, bags for filter assay, etc). Solution stability was confirmed for up to 16 days with deviation in assay $\leq 2.0\%$. Reference standards were prepared at 25 μ g/mL phenytoin with mobile phase used as diluent for quantification; system suitability was assessed for every HPLC run with the following parameters accepted: standard agreement $\leq 2.0\%$, USP tailing ≤ 2.0 , K Prime ≥ 2.0 , USP Plate Count > 2000 , and working standard precision for the first five and subsequent bracketing standards with area and retention time %RSD $\leq 2.0\%$.

2.3.6. Blend Uniformity Analysis (BUA)

Approximately 60 mg of powder were sampled from multiple locations within the blender. Each sample was diluted with the HPLC mobile phase to target 27.5 μ g/mL phenytoin and quantified using the by HPLC (described in Section 2.3.6).

2.3.7. Aerosol Performance Characterization by Fast Screening Impactor (FSI) and Next Generation Impactor (NGI)

Aerosolization performance of the carrier-based formulations was evaluated primarily using Fast Screening Impactor (FSI) (Copley Scientific, Colwick, UK), with confirmatory testing on a Next Generation Impactor (NGI) (Copley Scientific, Colwick, UK) for selected blends. A high resistance RS01 dry powder inhaler (Amcor) was used for device actuation. A total of 25 mg of powder was hand-filled into size 3 DPI-grade capsules, and each condition was tested in triplicate.

FSI testing was performed at a flow rate of 60 L/min, corresponding to a 5 μ m aerodynamic cutoff, with an actuation volume of 4.0 L delivered over 4.0 s. Phenytoin was recovered from the capsule, inhaler, induction port (IP), pre-separator (PS), and filter, using dissolution in HPLC mobile phase and quantified by HPLC.

NGI testing was conducted at 65 L/min to generate a 4 kPa pressure drop, corresponding to a 3.7-s actuation (4.0 L total volume). To minimize particle bounce, all impactor stages were coated with 1 wt% Tween-20 in methanol and allowed to dry prior to testing. Phenytoin was recovered from the capsule, inhaler, IP, PS, impactor stages 1–7, micro-orifice collector (MOC), and the after filter, then quantified by HPLC.

2.4. Statistical Analysis

To assess the scalability of low shear blending, aerosol performance results were statistically compared using a Two One-Sided Test (TOST) approach. Equivalence was evaluated between:

- One-quart vs two-quart V-Shell
- One-quart vs eight-quart V-Shell

Performance metrics included emitted dose (ED) and fine particle fraction (FPF). Equivalence margins were set at 20% for ED and 15% for FPF, consistent with FDA guidance and commonly accepted FPF variability limits for marketed inhalation products.

Design Expert® software (version 11, Stat-ease Inc., Minneapolis, MN, USA) was used. Regression models were fitted using stepwise selection. Model adequacy assessed using ANOVA, lack-of-fit tests ($p > 0.05$), and R^2 .

3. Results and Discussion

Implementation of this integrated experimental strategy enabled the generation of a comprehensive dataset spanning all critical DPI development stages. The following section presents the outcomes of jet milling optimization, formulation screening under low-shear blending, and comparative scale-up performance between high- and low-shear blending processes.

3.1. Production of Distinct Particle Size Fractions via Jet Milling

Three batches of phenytoin API were successfully micronized under tailored jet milling conditions and characterized for particle size distribution and solid state, summarized in Table 4. As designed, higher milling energy produced smaller particle size, consistent with established spiral jet-milling behavior [9].

Table 4. Summary of jet-milled phenytoin characterization ($n = 3$). Dv10, Dv50, Dv90: particle diameter at 10th, 50th, and 90th percentiles by volume. RSD < 0.1% across the board.

Batch	PSD		
	Dv10 (μm)	Dv50 (μm)	Dv90 (μm)
Fine fraction	0.86	1.6	2.9
Intermediate fraction	0.88	1.8	3.2
Coarse fraction	0.94	2.7	5.7

To investigate whether increased milling intensity altered the solid-state properties of the API, the fine and intermediate fractions were analyzed using XRPD. XRPD diffractograms (Figure 1) are aligned with the literature for phenytoin free base [24], with no qualitative evidence of polymorphic transformation. The XRPD method used did not detect any amorphous content (no visible halo). However, conventional laboratory XRPD typically has a relatively high limit of quantification for amorphous material (approximately 5–10% [25]), meaning that a small amount of amorphous content may still be present on the particle surface but remain below the detection threshold. Such low-level amorphous content could influence particle properties if it subsequently crystallizes. This represents a critical attribute to monitor in later development stages and should be incorporated into jet-milling process optimization. If amorphous content cannot be fully avoided when targeting inhalation-range particle sizes via jet milling, a conditioning step may be considered in which the API is exposed to elevated temperature and relative humidity for a defined period to promote control crystallization. Alternatively, a less energetic micronization technology, such as wet milling, may be explored to reduce the risk of inducing amorphous regions in the material.

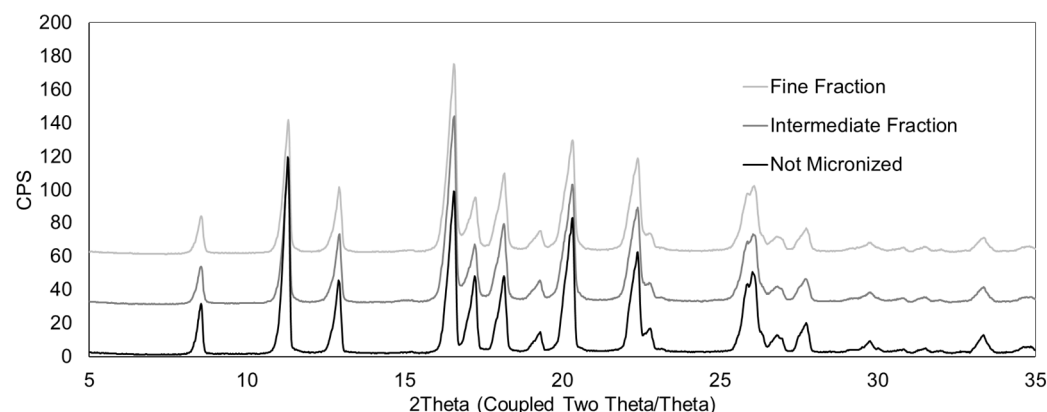


Figure 1. Comparison of XRPD patterns of Phenytoin micronized fractions and non-micronized material.

Collectively, these results demonstrate that jet-milling parameters can be tuned to achieve target particle size while minimizing undesirable solid-state disruptions.

3.2. Formulation Screening

3.2.1. Influence of Formulation Variables on Fine Particle Fraction

Formulation screening trials (A–O) were conducted using a DoE framework to evaluate the effect of API concentration, fines content, and API particle size (Dv90) on aerosolization performance under low shear blending. Aerodynamic performance was evaluated using emitted dose relative to total recovery (ED) and fine particle fraction relative to emitted dose (FPF). ANOVA was performed to quantify the relationships between formulation variables and these responses. Normalization to recovered dose was applied to minimize variability associated with early-stage blending and NGI handling. The DoE matrix and corresponding aerodynamic performance outcomes are summarized in Table 5, with response surface contour plots presented in Figure 2.

Table 5. Summary of aerodynamic performance results for formulation trials A–O, presenting average values (Av) and standard deviations (SD) for emitted dose by recovery (ED), fine particle fraction (FPF).

Trial	ED		FPF	
	Av (%)	SD (%)	Av (%)	SD (%)
A	85.3	1.7	66.5	2.6
B	85.5	3.2	71.7	0.9
C	83.6	1.9	70.1	0.9
D	87.1	3.4	48.9	1.1
E	76.8	3.6	54.7	7.8
F	85.5	2.4	45.9	4.3
G	77.0	2.9	47.7	2.5
H	92.1	1.3	42.5	1.8
I	80.4	2.7	71.4	1.1
J	88.0	1.0	65.6	5.1
K	82.4	1.4	65.4	2.0
L	87.2	1.3	70.3	0.9
M	86.5	1.6	69.3	0.8
N	84.4	0.7	68.9	0.6
O	85.4	0.6	68.2	2.5

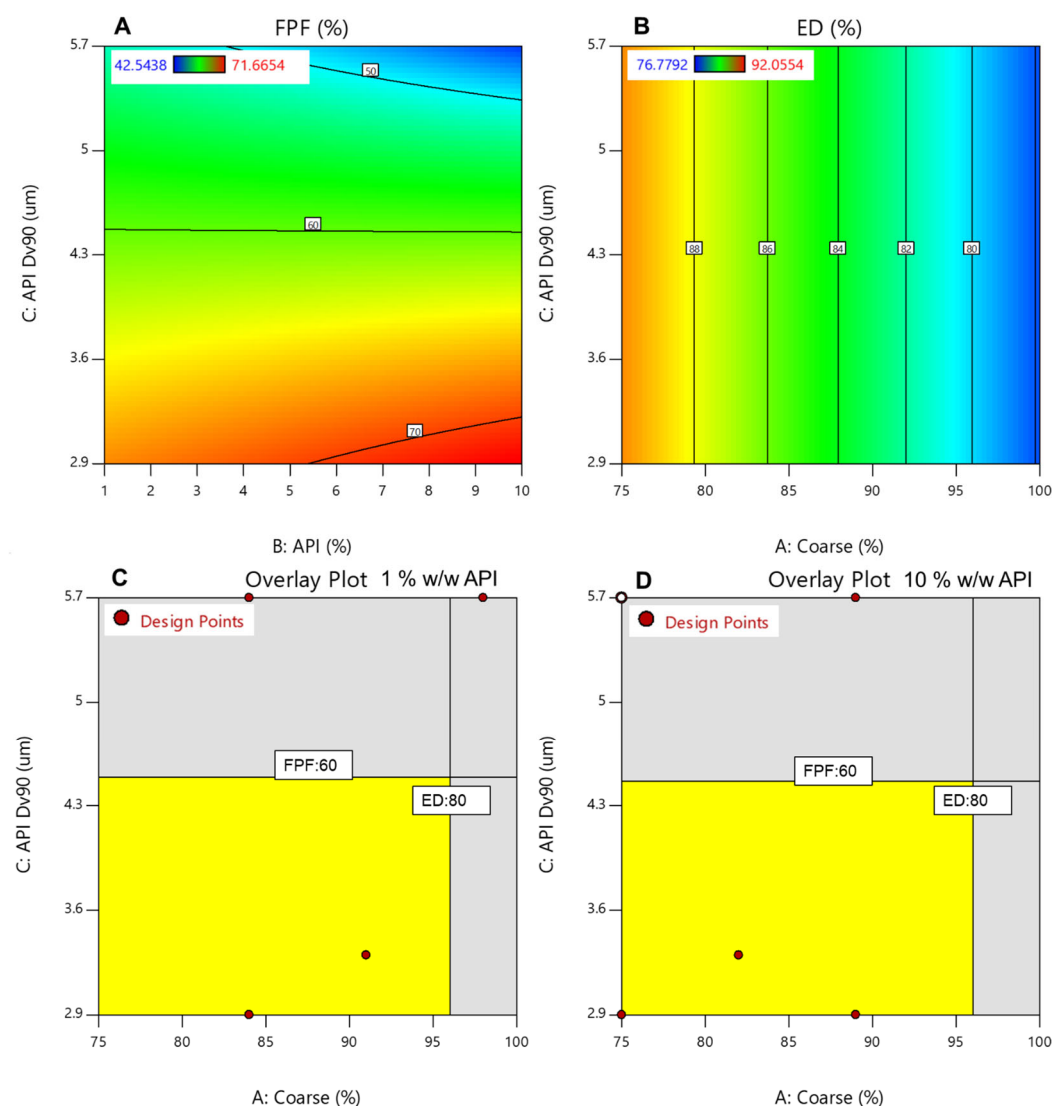


Figure 2. Contour plots showing DoE results for feasibility formulations: (A) fine particle fraction as per API Dv90 vs. API content, $R^2 = 0.9489$, p -value < 0.0001 , lack of fit > 0.07 ; Equation (4); (B) emitted dose as per API Dv90 vs coarse content, $R^2 = 0.7513$, p -value < 0.0001 , lack of fit > 0.2 , Equation (5); (C,D) overlay plot illustrating the combination of API Dv90 and coarse content, achieving both $FPF \geq 60\%$ and $ED \geq 80\%$, for 1% API and 10% API content.

Figure 2 illustrates the influence of formulation variables on aerosolization performance. Panel A demonstrates that the fine particle fraction of emitted dose (FPF) is primarily governed by API loading and particle size distribution, with strong model correlation ($R^2 = 0.95$). Consistent with established principles for inhalation products, smaller API particles (lower Dv90) lead to higher fractions of drug reaching the deep lung, i.e., greater deposition of drug in the deep lung. Interestingly, this effect becomes even more pronounced at higher API concentration (e.g., 10% loading), indicating that particle size plays an even more decisive role in product performance, confirming that the API properties exert increasing control over aerosol performance as loading increases.

Panel B shows emitted dose recovery (ED) as a function of coarse lactose content and API particle size.

$$\begin{aligned}
 FPF^3 &= 4.7 \times 10^5 + 2.0 \times 10^4 \text{ API}(\%) - 5.7 \times 10^4 \text{ API Dv90} - \\
 FPF^3 &= 4.7 \times 10^5 + 2.0 \times 10^4 \text{ API}(\%) - 5.7 \times 10^4 \text{ API Dv90} \\
 &\quad - 4.5 \times 10^3 \text{ API}(\%) \cdot \text{API Dv90}
 \end{aligned}
 \tag{4}$$

$$ED^{2.49} = 1.4 \times 10^5 - 8.8 \times 10^1 \text{Coarse}(\%) \quad (5)$$

3.2.2. Influence of Lactose Carrier Composition on Emitted Dose

ED exhibited a significant correlation with the coarse carrier fraction ($R^2 = 0.75$), whereas API concentration and particle size did not demonstrate statistical influence. Higher ED values were achieved at lower coarse lactose concentrations (i.e., higher fines content), consistent with the current understanding that fine lactose promotes formation of API–fine lactose agglomerates, facilitating drug detachment and improving dose emission from the capsule during actuation.

3.2.3. Morphological Evidence of Particle Interaction

Representative SEM micrographs (Figure 3) provide qualitative insights into powder-particle interactions across the formulations. Although inherently non-quantitative, the micrographs demonstrate a clear trend toward greater availability of free fines and more pronounced agglomeration at higher API loadings, particularly in lactose blends with elevated fines content. Notably, formulations containing 0% API and 16% fines exhibited substantially fewer unbound fines compared with those containing 1% API, regardless of fines level. This compositional shift fundamentally alters the balance between cohesive and adhesive forces, promoting agglomerate formation at the expense of direct surface adhesion to coarse lactose particles.

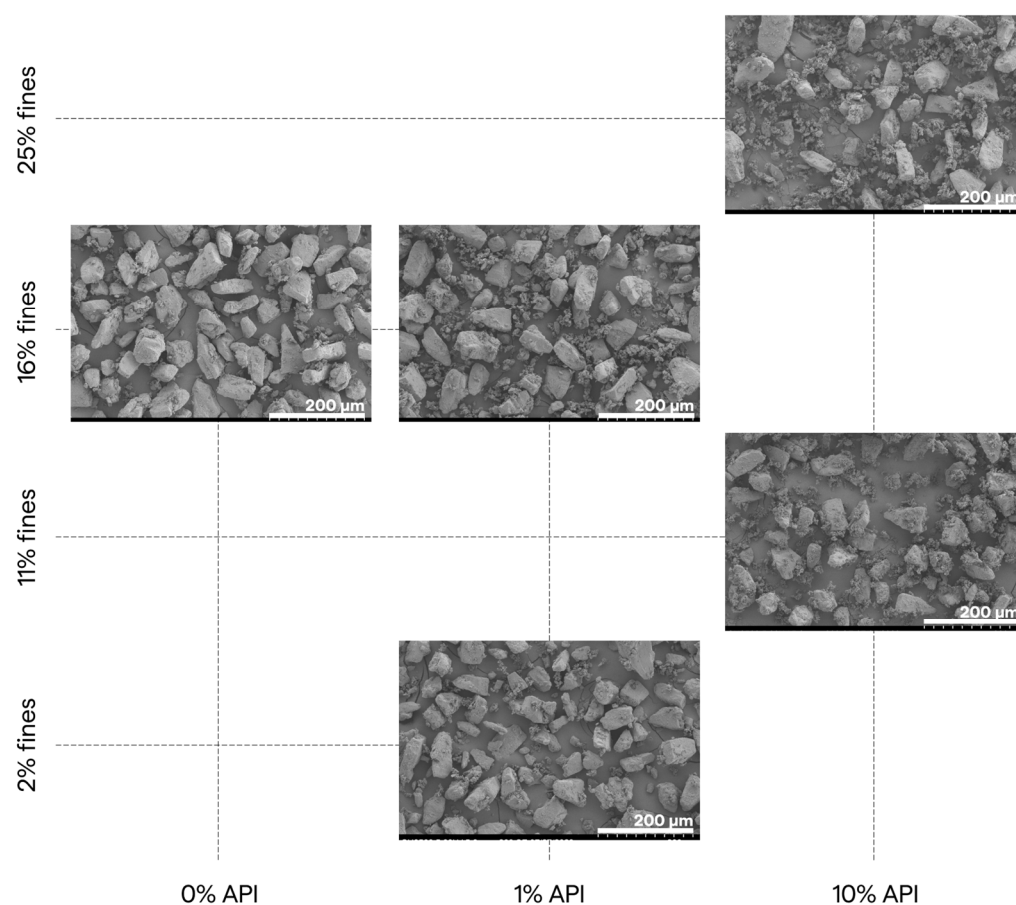


Figure 3. Scanning electron micrographs (200× magnification) of DPI blend surfaces, illustrating the effect of varying fines content and API load on particle interactions following blending.

3.2.4. Construction of the Formulation Design Space

The practical implication of these findings is highlighted by the overlay plots in Figure 2C,D, which define a formulation design space capable of meeting both aerosolization performance criteria. Specifically, targeting an API Dv90 of 2.9–4.5 μm and limiting the coarse lactose to below 96% enables simultaneous optimization of FPF (>60%) and ED (>80%). This integrated approach emphasizes that jet milling conditions and particle size specifications must be aligned with the requirements of the carrier composition, ensuring that micronization and blending are optimized in a coordinated manner to achieve robust aerosol performance.

Overall, accounting for the interdependencies between formulation components and manufacturing processes enables more predictable, efficient DPI development, and ultimately supports better clinical outcomes.

3.2.5. Interdependence Between Aerodynamic Performance and Rheology

Building upon the integrated strategy—where formulation design space informs jet milling targets—it is equally essential to evaluate how formulation variables affect downstream processability, particularly capsule filling. Just as particle size specifications inform micronization parameters, powder flowability must influence formulation selection and blending process optimization. This holistic approach ensures that formulation and DPI development is aligned across the entire workflow, from milling through blending to final encapsulation, reducing process risk and expediting translation to manufacture.

Powder flowability was evaluated using FT4 rheology to assess how formulation composition may impact downstream capsule, blister, or device filling performance. Achieving the right balance between optimal aerosol performance and robust manufacturability is essential during formulation selection. As shown in Figure 4, flow properties were strongly influenced by both fines and API load (%). Conditioned bulk density (CBD) and compressibility were inversely correlated: higher levels of fines and/or API reduced CBD while increasing compressibility. This trend is expected, as compressibility reflects the extent of powder densification under applied stress—materials with low CBD generally exhibit greater cohesive behavior and higher densification potential, which may lead to poor and inconsistent fill performance.

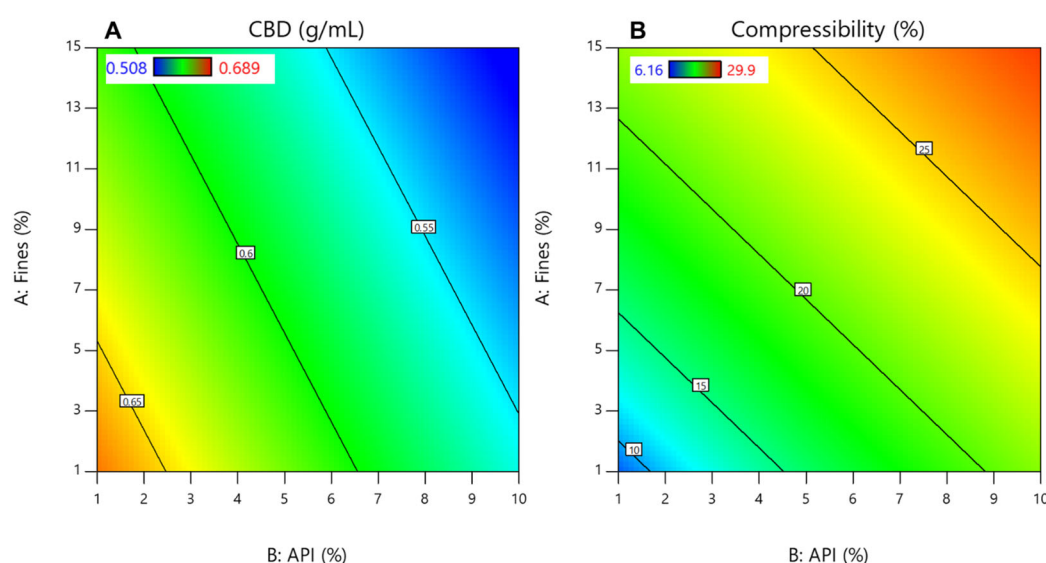


Figure 4. Response surface plots showing the effects of fines content and API percentage on (A) conditioned bulk density (CBD), $R^2 = 0.9477$, p -value < 0.0001, lack of fit > 0.1, and (B) compressibility, $R^2 = 0.9184$, p -value < 0.0001, lack of fit > 0.6 of the feasibility formulations.

Previous studies have demonstrated that high compressibility and low bulk density are increasingly prone to agglomeration, poor filling and inconsistent mass uniformity, ultimately compromising dose reproducibility and manufacturing efficiency [26]. Therefore, incorporating both CBD and compressibility criteria early in formulation development is essential to proactively mitigate downstream manufacturability risks and to achieve an optimal balance between aerosol performance and robust processing characteristics.

To minimize flowability-related challenges while retaining strong aerosol performance, fines content required careful optimization. Although reducing fines improves flowability and fill consistency, excessively low fines negatively impact drug detachment and deep-lung delivery. Therefore, a balanced fines level is essential to simultaneously support manufacturability and aerodynamic efficiency. Based on the design space, a formulation containing 8–15% fines and 5.5% API was selected for scale-up, as it best represents this critical balance point.

This selection completes the integrated development framework by ensuring that:

- Jet milling establishes API particle size targets that support efficient aerosolization.
- Formulation screening defines carrier composition requirements for stable drug-excipient interactions.
- Powder rheology confirms flowability suitable for reliable capsule filling and dose consistency.

By linking material attributes and process parameters across stages, this approach ensures that final DPI performance is optimized holistically rather than through isolated development steps.

3.3. Scale-Up to High Shear Mixing

A two-factor DoE was performed using the Glatt high-shear mixer (see Table 3) to evaluate the effect of mixing time and mixing speed (impeller rpm) on fine particle fraction (FPF, %). As shown in Figure 5 (left), both higher impeller speeds (RPM) and longer mixing durations (minutes) resulted in a reduction in FPF. The statistical model demonstrated a strong goodness of fit ($R^2 = 0.86$), confirming that increased mechanical stress in high-shear environments diminishes aerosolization efficiency.

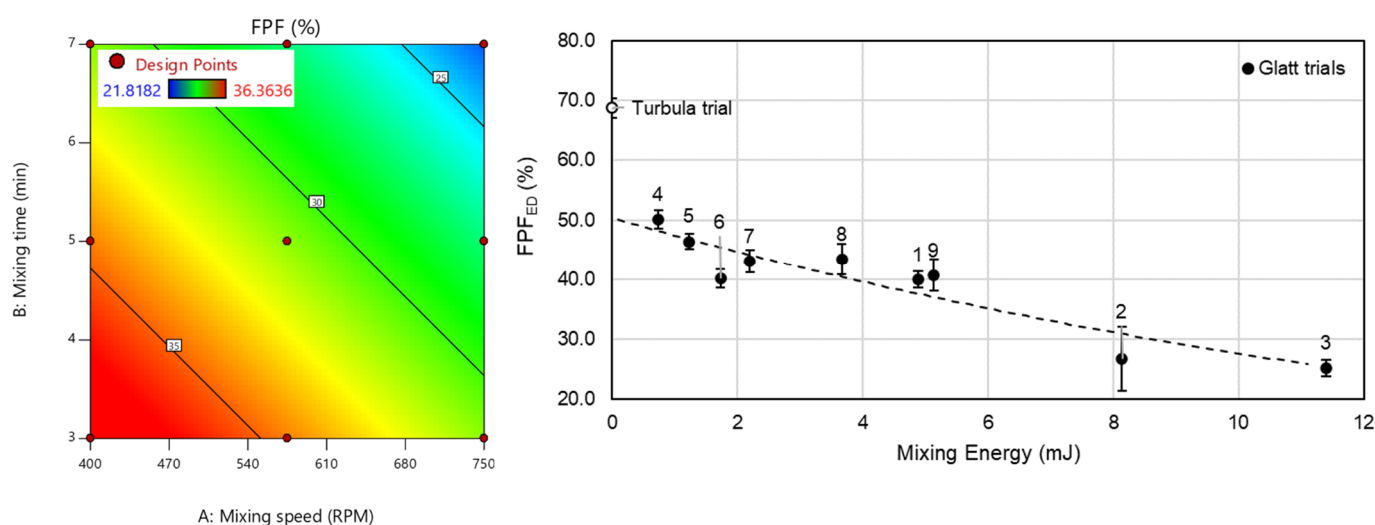


Figure 5. High shear mixing process development results. (Left): Contour plot showing the effect of mixing speed (RPM) and mixing time (minutes) on fine particle fraction (FPF, %) during scale-up of high-shear mixing using the Glatt mixer. $R^2 = 0.8611$, p -value < 0.01 . (Right): Fine particle fraction vs

mixing energy. The dotted line represents Equation (2) fitted to the data. $R^2 = 0.9946$, $A = 50.36$, $B = 0.00$, $k_1 = 102.84$, and $k_2 = 0.06$.

When the data were expressed in terms of scale-independent mixing energy, a further increase in mixing energy correlated with a continued decline in FPF (Figure 5, right). This relationship was accurately captured using Equation (2) ($R^2 = 0.99$; fit parameters: $A = 50.36$, $B = 0.00$, $k_1 = 102.84$, $k_2 = 0.06$), indicating that mixing energy is a predictive and unifying parameter for high-shear blending performance.

Notably, when compared with the Turbula® trial using a comparable formulation, included in Figure 5 (right) as an open marker, a substantial loss in aerodynamic performance was observed upon transferring the blending process to pilot-scale high-shear blending: while the Turbula® mixer achieved an FPF of $68.8 \pm 1.6\%$ (M, N and O in Table 2), the maximum FPF obtained in high-shear mixing trials was $50.1 \pm 1.5\%$.

This decline in FPF with increasing mixing energy can be attributed to intensified press-on forces generated during high-shear processing. Extended mixing durations and higher rotational speeds increase mechanical stresses at particle-particle and particle-blender interfaces, leading to stronger API-carrier adhesion that must be overcome during aerosolization. This enhanced drug-carrier adhesion hinders API detachment during inhalation, resulting in reduced fine particle fractions [4,17,27].

In contrast, low-shear mixing via the Turbula® imparts a gentle tumbling motion with lower collision intensity, minimizing excessive compaction while maintaining adequate API distribution across carrier surfaces. This gentler approach maintains a favorable balance between drug-carrier adhesion (for blend stability) and detachment efficiency (for lung delivery), preserving superior aerosol performance [28].

These findings emphasize the need for scale-up strategies specifically tailored to low-shear blending, particularly when this approach demonstrably outperforms high-shear processes for carrier-based DPI systems.

3.4. Scale-Up to Low Shear Mixing

3.4.1. Transfer from Turbula to V-Shell Blender and Comparison with High Shear Mixer

Low shear mixing trials were performed using a V-shell blender to reproduce the aerodynamic performance previously achieved with the Turbula® mixer. A formulation containing 15% fines—within the optimized design space—was selected for evaluation due to its robust performance in screening studies. This composition also served as a surrogate for the 8% fines formulation used in the high shear trials, enabling direct comparisons across mixing mechanisms. Blending was conducted for up to 120 min, with intermediate samples collected at 60 min for aerodynamic performance evaluation. As shown in Table 6, The V-shell process successfully replicated the target aerosol performance achieved with the Turbula® mixer, generating an FPF of $62.6 \pm 1.7\%$ at 1920 rotations (60 min).

Table 6. Summary of best performing formulation development and blending scale up trials. FPF—fine particle fraction, ED—emitted fraction.

Equipment	Formulation	Batch Size (g)	ED (%)	FPF (%)	FPD (mg)
Turbula	15% fines	20	76 ± 8.0	65.6 ± 5.1	0.68
Turbula	8% fines	20	80 ± 7.8	68.8 ± 1.6	0.76
V-shell	15% fines	125	76 ± 5.5	62.6 ± 1.7	0.70
V-shell	15% fines	125	91 ± 12.5	58.4 ± 1.2	0.70
Glatt	8% fines	150	79 ± 2.5	50.1 ± 1.5	0.50

Extended mixing beyond this point led to a modest increase in the ED, but a decline in fine particle fraction to $58.4 \pm 1.2\%$, suggesting the onset of excessive agglomeration under prolonged tumbling. In this case, agglomerates become easier to emit yet more resistant to dispersion during inhalation, resulting in reduced deep-lung delivery. These observations highlight the importance of mixing time optimization to prevent overmixing, which can disrupt the balance between adhesion (blend stability) and detachment (aerosolization efficiency).

Having confirmed that low-shear blending preserves superior aerosolization performance relative to high-shear methods for the studied phenytoin formulation, the key development focus shifts from formulation and blending mechanism selection to practical manufacturability and scalability: Can the favorable particle-particle interactions established at laboratory scale be maintained as the process transitions towards manufacturing-relevant batch sizes? To address this question, the following section details validation of a novel scale-up strategy for low shear blending of carrier-based DPI formulations.

3.4.2. Scale-Up Methodology for V-Shell Blender

Given the risks of both under- and over-mixing, establishing a robust and scalable low shear blending methodology is essential. We hypothesized that a previously reported methodology, originally developed to identify segregation patterns among coarse particles [22], could be adapted to characterize blending processes containing small fractions of fine particles. This approach assumes that fine particles adhere to larger particles via adhesive forces, thereby moving as a unified structure, with diffusion-driven separation considered negligible.

To map powder flow behavior across the operating range of the one-quart V-shell, the fall pattern was observed under different combinations of fill fraction and rotational speed. Four distinct flow regimes were apparent (Figure 6):

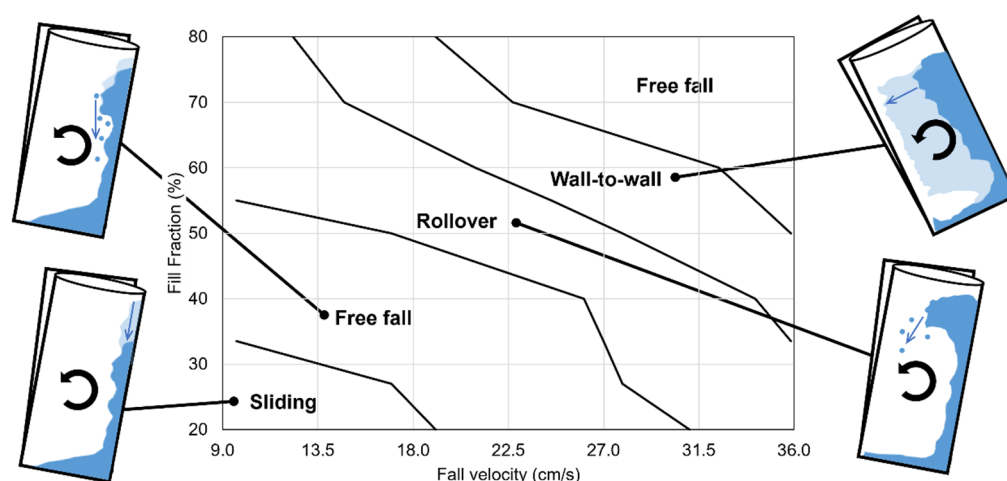


Figure 6. Scale-independent fall pattern diagram for V-blending with illustrations depicting movement of powder (blue).

Images of the V-shell under each flow regime can be found in Supplementary Materials Figure S1. This image has been presented in a poster at the Drug Delivery to the Lungs 2025 conference by the authors [29].

- **Sliding:** At low rotational speeds, powder movement occurs by sliding along the vessel wall, with limited convective motion. This regime becomes less prevalent at moderate to high fill fractions, where even modest speeds initiate partial free-fall.

- Free-fall: Once a critical combination of rotation speed and fill fraction is reached, centrifugal forces cause a fraction of the powder to detach from the pushing wall and fall freely through the vessel. This introduces greater powder bed disruption and improved mixing relative to sliding behavior.
- Rollover: The powder bed folds over itself in a tubular, wave-like motion that reflects higher mixing intensity than free-fall, driven by increased internal circulation within the bulk.
- Wall-to-wall: A highly turbulent regime in which powder continuously cascades between the pushing and receiving wall, forming a continuous falling curtain and maximizing convective mixing.

At sufficiently high speeds and fill fractions, aeration was observed—the bulk bed remained mostly static while only a small fraction circulated—an undesirable condition for DPI blends.

It remains unclear which flow regime is universally optimal, as the preferred pattern is likely formulation dependent and influenced by particle size, density, and cohesiveness. Thus, the intent of this work was not to prescribe a single optimal regime, but to determine whether maintaining consistent powder flow behavior and total strain (total revolutions) enables successful V-shell scale up. This methodology treats fall pattern as a scale-independent indicator of blending dynamics and uses fill fraction and particle fall velocity (Figure 6) as the basis of scale translation. During scale-up, adjustments to fill fractions to rotation speed can be made to preserve the same flow regime and mixing effectiveness across different blender volumes.

3.4.3. V-Shell Blended Scale-Up

One-Quart to Two-Quart V-Shell Blender

The scale-up methodology was first evaluated by transferring the process from a one-quart to a two-quart V-shell blender while maintaining a constant fill fraction of 27%. To preserve particle fall velocity, a critical parameter governing powder flow regime and mixing kinetics, Equation (3), was applied. Based on one-quart conditions, a target particle velocity of 36 cm/s was calculated. Maintaining equivalent velocity in the larger blender required reducing the rotation speed to approximately 19 RPM. Because total revolutions determine total strain imparted to the powder bed, mixing time was increased proportionally to offset the reduced rotational speed.

Comparison of the aerodynamic performance results obtained with the two-quart V-shell (FSI) and the one-quart V-shell (NGI) confirmed a similar over-mixing trend, with the FPF decreasing nearly in parallel as total revolutions increased (Figure 7). The two-quart blender achieved an FPF of $59.8 \pm 2.2\%$ at 1920 rotations and of $54.5 \pm 1.6\%$ at 3840 rotations, representing only a modest reduction relative to the one-quart scale. The ED values remained highly consistent across scales, with $83.4 \pm 1.4\%$ for the two-quart versus $85.9 \pm 1.0\%$ for the one-quart V-shell at equivalent strain. Minor differences in reported values are expected due to different analytical methods employed (NGI vs FSI), which vary slightly in sensitivity to fine particles recovery.

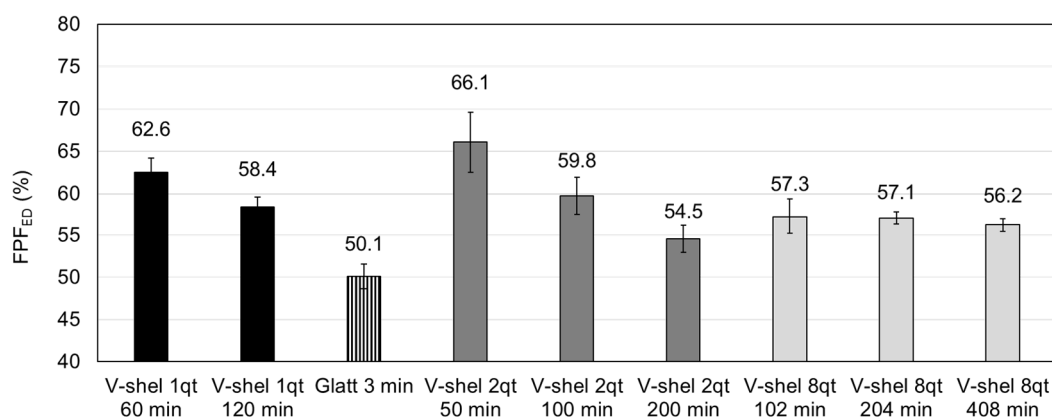


Figure 7. Comparison of FPF values for blends manufactured across V-shell blender scales and mixing times. Black bars: 1 Qt V-shell (1920–3840 rotations); striped bar: Glatt high-shear mixer (3 min); dark gray bars: 2 Qt V-shell (1920–3840 rotations); light gray bars: 8 Qt V-shell (1920–3840 rotations). Error bars represent standard deviation ($n = 3$).

Two-Quart to Eight-Quart V-Shell Blender

A second scale-up step was performed to ensure applicability to manufacturing-relevant batch sizes and to address two key considerations:

- Non-linear scale-up behavior: Batch size increases do not always scale proportionally with equipment size changes, often altering fill fraction requirements.
- Industrial relevance: The two-quart V-shell is insufficiently large for clinical-scale and commercial manufacturing, necessitating extrapolation to larger production scales.

An 800 g batch of the selected formulation was therefore blended in an eight-quart V-shell, resulting in a reduced fill fraction of 22% due to larger vessel geometry.

Content uniformity results confirmed consistent blending performance across scales, with all samples meeting specification ($RSD \leq 5\%$, 90–110% label claim), as summarized in Table 7. This level of homogeneity is particularly important for carrier-based DPI systems, where high potency APIs demand tight dose accuracy to ensure therapeutic consistency and patient safety.

Table 7. Content uniformity comparison for 2 Qt. and 8 Qt. V-shell blends ($n = 5$).

Trial	Average (%)	RSD (%)	Min (%)	Max (%)
2 Qt, 60 min	92	5	90	100
2 Qt, 102 min	94	2	91	96
2 Qt, 204 min	92	1	90	93
8 Qt, 102 min	102	2	99	103
8 Qt, 204 min	104	3	101	110
8 Qt, 408 min	103	1	102	105

The large-scale blending process exhibited lower variability overall, as reflected by the reduced standard deviations in both FPF and ED values (Figure 7). While a decline in FPF with extended mixing was again observed at the two-quart scale—consistent with one-quart behavior—FPF remained comparatively stable at the eight-quart scale. Although FPF values at the larger scale were slightly lower than those obtained with the one-quart blender at similar total revolution (~1980 rotations), they remained within the performance range of the two-quart results.

A plausible explanation is that at larger scales, particles experience fewer collisions per unit time and reduced cumulative shear stress, even when fall pattern and total number of rotations are preserved. This reduction in mechanical stress may decrease the press-on forces that otherwise facilitate redistribution of API across carrier surfaces. As a result, a greater fraction of the drug retains embedded surface irregularities rather than being optimally distributed for aerosolization. This finding aligns with literature showing that optimal DPI performance requires a careful balance of mixing energy, sufficient to deagglomerate and distribute API, but not so intense as to create irreversible adhesive bonds that hinder detachment during inhalation [4].

Despite the slight reduction in FPF at larger scale, the eight-quart V-shell blends still exhibited substantially superior aerodynamic performance compared with the high-shear Glatt-processed product (Figure 7), further confirming that low shear mixing is a more suitable approach for this carrier-based DPI system.

Statistical Equivalence Across Scales and Comparison to Commercial DPI Performance

Regulatory guidance for orally inhaled product requires, with 95% confidence, at least 90% of units in a batch to fall within 80–120% of the target delivered dose [30]. To evaluate scale-up robustness, a two one-sided test (TOST) procedure was performed to compare ED and FPF results from the one-quart V-shell against those from the two-quart and eight-quart blenders.

For ED, a 20% equivalence margin was selected to align with the regulatory expectations for delivered dose limits. In contrast, the FPF is a performance-defining CQA that is generally more sensitive to changes in formulation and processing conditions and does not have a generic variability recommendation. To ensure that potentially meaningful shifts in aerosol performance would not be masked by too wide an equivalence bound, a more conservative equivalence margin of 15% was selected for FPF (Figure 8). Statistical analysis demonstrated that the 90% confidence interval (CI) was fully contained within the equivalence interval ($p < 0.01$), establishing equivalence for both FPF and ED between one-quart versus two-quart and one-quart versus eight-quart blends at both 1920 and 3840 rotations. In other words, the observed differences are within the range of normal batch-to-batch variability and therefore not practically significant from a product performance perspective.

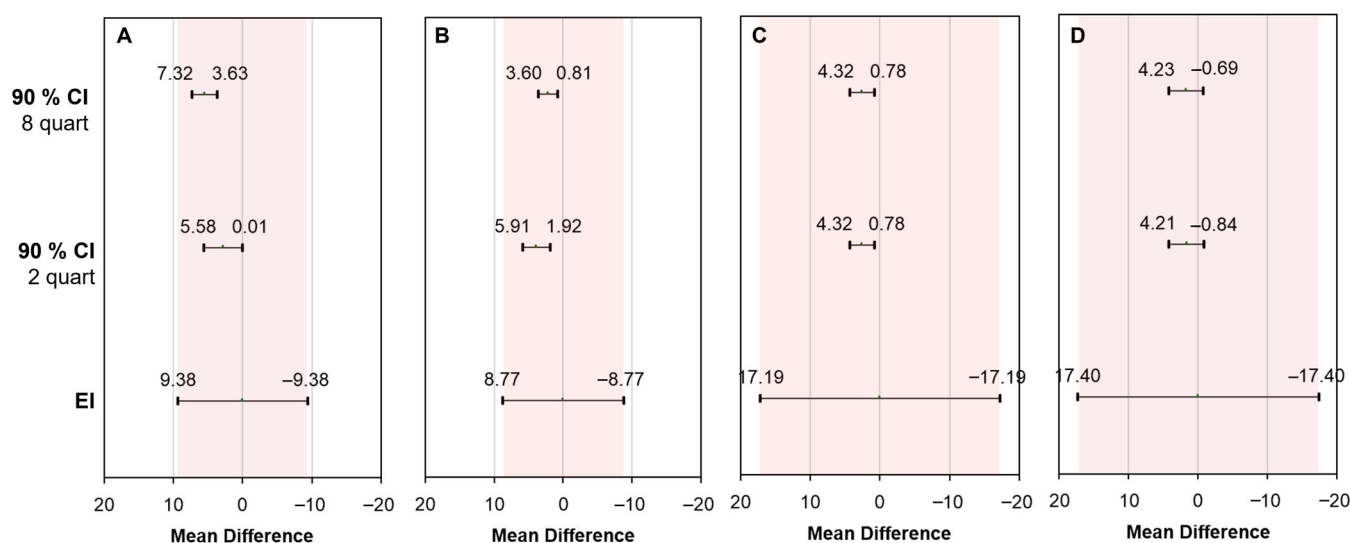


Figure 8. Summary of the results of the TOST procedure ($p < 0.01$). EI—Equivalence interval, 90%CI—90% confidence interval, red area—equivalence bounds, A—FPF at 1920 rotations, B—FPF at 3840 rotations, C—ED at 1920 rotations, D—ED at 3840 rotations.

In contrast, when the TOST procedure was performed comparing the one-quart trial at 1920 rotations with the two-quart trial at 3840 rotations, the equivalence criteria was not met. The 90% CI (5.69, 10.37) exceeded the predefined equivalence bounds (−9.38, 9.38) on the upper limit, indicating a statistically significant performance difference between these two conditions. This result reinforces the critical importance of maintaining equivalent mixing dynamics and total strain to ensure consistent aerodynamic performance during scale-up.

To contextualize the practical relevance of the observed performance variability, results were compared with those reported for commercially available carrier-based DPIs. For example, Trelegy Ellipta specifies a $\geq 90\%$ delivered dose for fluticasone furoate, umecclidinium, and vilanterol [31]. Although precise FPF data remain proprietary, Hamilton et al. reported relative standard deviations of up to 3.69% for the emitted dose and up to 4.55% for fine particle fraction with this drug-device combination [32].

Across all scales in the present study, variability remained comparable to or lower than these commercial benchmarks: FPF = $59.80 \pm 2.77\%$ (RSD = 4.63%) at 1920 rotations and $56.41 \pm 2.00\%$ (RSD = 3.55%) at 3840 rotations; ED = $85.25 \pm 1.83\%$ (RSD = 2.15%) at 1920 rotations and $85.83 \pm 1.53\%$ (RSD = 1.78%) at 3840 rotations. These results demonstrate that the particle-velocity-based scale up framework yields blend performance consistently that is aligned well with commercial DPI standards, supporting the robustness and manufacturability potential of this low-shear blending approach.

Critical Evaluation of Froude Number-Based Scale-Up

Traditional scale-up strategies for tumbling blenders typically rely on either the Froude number (Fr) or the tangential velocity as geometric scaling parameters. In the current study, Fr varied between 4.0×10^{-6} (eight-quart) and 2.0×10^{-7} (one-quart) across evaluated scales.

When applying a Fr-based approach to scale the one-quart process, the two-quart shell would require rotation at ~ 27 RPM (fall velocity = 46 cm/s), and the eight-quart shell at ~ 22 RPM (fall velocity = 62 cm/s). However, these calculated fall velocities substantially exceed the validated operating space established for the one-quart V-shell (Figure 6).

Extrapolation of flow regime boundaries revealed that the rollover and wall-to-wall transition would occur at much lower fall velocities—38 cm/s for a fill fraction of 27% (two-quart case) and at 39 cm/s for a fill fraction of 22% (eight-quart case)—both substantially lower than the fall velocities predicted by Fr-based scale-up (46 cm/s and 62 cm/s, respectively). Furthermore, extrapolating the boundary between the wall-to-wall regime and the second free-fall regime indicates that the same fill fractions would approach borderline conditions at 44 cm/s and 45 cm/s, respectively.

Although these trends require further validation, the results strongly indicate that operating under Fr-scaled conditions would likely induce transitions into different flow regimes (wall-to-wall or potentially free-fall), altering the fundamental mixing dynamics of the system. Such changes would violate the assumption of equivalent blending kinetics across scales, potentially compromising blend quality and aerodynamic performance. Accordingly, while Fr-based scale up may be appropriate for free-flowing powders, this work demonstrates that cohesive fine-particle systems require a different approach. Maintaining consistent particle fall behavior and total strain provide a more reliable basis for scale translation, supporting the particle-velocity-based scale up methodology implemented in this study.

4. Conclusions

This work establishes an integrated, quality-by-design framework for carrier-based dry powder inhaler (DPI) development, demonstrating that jet milling, formulation composition, blending technology, and downstream manufacturability are fundamentally interconnected rather than independent unit operations (Figure 9). The framework provides a rational, end-to-end pathway from API particle engineering process development to commercial-scale drug product production, enabling predictable performance and streamlined development.

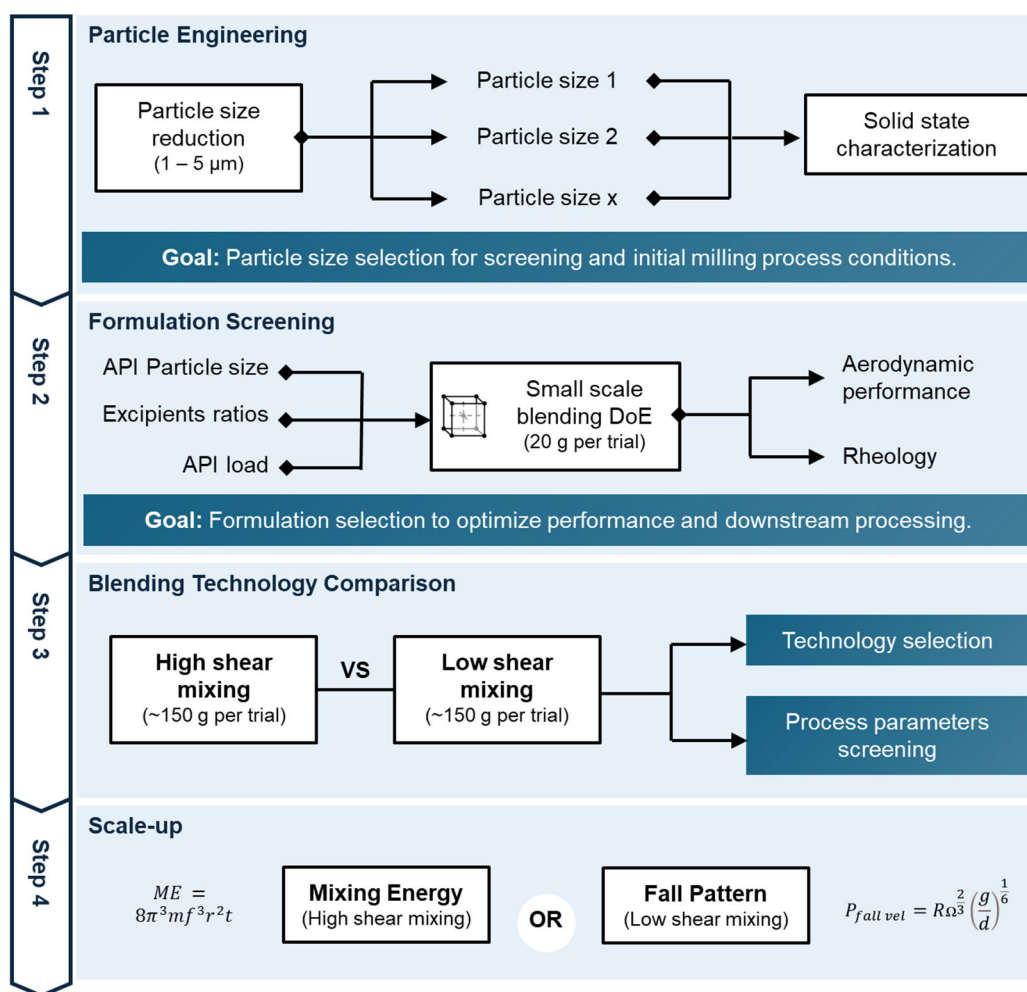


Figure 9. Systematic approach to rational DPI development from API characterization through commercial-scale manufacturing.

A robust design space was established by integrating jet milling parameters targeting an API Dv90 of 2.9–4.5 μm with a coarse lactose content below 96%. This combination maximized aerodynamic performance (FPF > 60%, ED > 80%) while maintaining acceptable powder flow for consistent capsule filling and preventing undesired solid-state transformations.

Comparative evaluation of blending technologies revealed that high-shear mixing disrupted the delicate balance between API–carrier adhesion and the detachment required for optimal aerosolization. For the phenytoin system studied, low-shear blending achieved a $62.6 \pm 1.7\%$ fine particle fraction compared to $50.1 \pm 1.5\%$ with high-shear blending, underscoring the need for formulation-specific process selection rather than equipment-driven decisions.

A key contribution of this work is the validation of a particle-velocity-based scale-up methodology for low-shear V-shell blending of carrier-based formulations containing fine particle fractions. Unlike conventional Froude number-based approaches, maintaining equivalent fall behavior and total strain across scales produced statistically equivalent aerodynamic performance in one-quart, two-quart, and eight-quart blenders ($p < 0.01$). Content uniformity ($\text{RSD} \leq 5\%$) and aerodynamic performance variability ($\text{RSD} 2\text{--}5\%$) met or exceeded commercial DPI standards. In contrast, Froude-based scaling could induce flow regime transitions at larger scales, potentially compromising blend uniformity and lung delivery—highlighting the value of flow-regime-aware scaling for cohesive formulations.

Overall, this material-sparing, workflow-integrated development strategy enables the following:

- More predictable development timelines
- Reduced material consumption during optimization
- Improved manufacturability and aerosolization robustness

The proposed framework is broadly applicable, as it is grounded in QbD principles and statistically driven evaluations that support systematic optimization of carrier-based formulations irrespective of the API. The particle-velocity-based scale-up methodology, being rooted in macroscopic flow behavior, is particularly suited for low-dose inhalation products and is not expected to be influenced by API-specific physicochemical variations. Future studies should extend this methodology to other APIs, alternative carriers, and advanced particle engineering approaches such as wet milling to fully realize its potential across the DPI development landscape.

Supplementary Materials: The following supporting information can be downloaded at: <https://www.mdpi.com/article/10.3390/pharmaceutics18020246/s1>, Figure S1—Pictures of the 1-quart V-Shell under the Four Distinct Flow Regimes.

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Abbreviations

The following abbreviations are used in this manuscript:

ACN	Acetonitrile
API	Active pharmaceutical ingredient
BUA	Blend uniformity analysis
CBD	Conditioned bulk density
CQAs	Critical quality attributes
DoE	Design of experiments
DPI	Dry powder inhaler
Dv10, Dv50, Dv90	Particle size percentiles—10th, 50th, 90th by volume (μm)
ED	Emitted dose

FPF	Fine particle fraction
FSI	Fast screening impactor
HPLC	High performance liquid chromatography
HSM	High shear mixing
LSM	Low shear mixing
IP	Induction port
MeOH	Methanol
MOC	Micro-orifice collector
MgSt	Magnesium stearate
NGI	Next generation impactor
PSD	Particle size distribution
QbD	Quality by design
SD	Standard deviation
TOST	Two one-sided test
XRPD	X-ray powder diffraction

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