

Discrete Element Method in Pharmaceutical Engineering: A Critical Review of Powder Processing, Tablet Manufacturing, and Pulmonary Drug Delivery

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ABSTRACT: Pharmaceutical manufacturing relies on powders, granules, and agglomerated materials whose particle-scale interactions can determine blend uniformity, feeding stability, die filling, compaction, coating, milling, and aerosol performance. The Discrete Element Method (DEM) offers direct access to these interactions, but its engineering value depends less on visualization than on how convincingly model parameters are calibrated, transferred, and validated against process- or product-relevant measurements. This critical review evaluates DEM across powder handling, continuous and batch blending, feeding, die filling, granulation, milling, tablet compaction, coating, and pulmonary drug delivery. Building on earlier application-focused and calibration-oriented reviews, the present review applies an evidence-oriented framework that asks whether material characterization is linked to calibration, whether numerical verification and independent validation are documented, whether numerical scaling preserves the relevant physics, and whether the final comparison is made against a meaningful pharmaceutical endpoint. Studies reviewed from 2020-2026 increasingly report production-scale blending, experimentally validated continuous processing, calibrated compression models, DEM-based coating prediction, digital-twin workflows, and CFD-DEM analysis of dry-powder inhalers. At the same time, parameter non-uniqueness, coarse-graining, cohesion, computational cost, and weak transferability between formulations and operating conditions remain major barriers to predictive use. DEM is

therefore most useful when it is embedded in experimentally anchored, uncertainty-aware multiscale workflows that connect particle-scale mechanisms with measurable critical quality attributes and dose-delivery outcomes.

Keywords: *Discrete element method; pharmaceutical engineering; tablet manufacturing; die filling; powder blending; tablet coating; dry powder inhaler; CFD-DEM.*

1. INTRODUCTION

Powders and granules are used throughout pharmaceutical manufacturing, from handling and blending to granulation, milling, die filling, tableting, coating, and inhaled formulations. Their bulk behavior can be difficult to predict because it depends on particle size, shape, friction, cohesion, packing, and interactions with processing equipment. DEM is particularly useful in this setting because it represents the powder as individual particles and calculates their motion and contacts over time. Reviews of pharmaceutical DEM have documented applications across material transport, storage, blending, granulation, milling, compression, and film coating, while more recent work has extended these ideas to industrial-scale process analysis and device-oriented problems (Ketterhagen et al., 2009; Yeom et al., 2019). In dry-powder inhalers, the biomedical relevance is especially direct because airflow, particle collisions, de-agglomeration, and deposition all affect delivery of the respirable dose (Zheng et al., 2021). It does not present DEM as a new method for pharmaceutical engineering; that foundation is already well established (Ketterhagen et al., 2009; Yeom et al., 2019; Zheng et al., 2023). Instead, it examines a more difficult question: when does a DEM model move from mechanistic illustration to a model that can credibly support process development, scale-up, troubleshooting, or device design. The distinction is important because pharmaceutical decisions depend on measurable outcomes such as blend uniformity, feed-factor stability, residence-time distribution, tablet mass, compaction response, coating variability, emitted dose, and fine-particle fraction. Recent studies increasingly report these endpoints, but the strength of experimental anchoring and the transferability of calibrated parameters still vary considerably across applications (Toson et al., 2021; Sivanapillai et al., 2023; Benque et al., 2024; Jajcevic et al., 2024a, 2024b; Mahto et al., 2025; Alizadeh Behjani et al., 2026). It is organized around four critical questions rather than around unit operations alone. First, are DEM parameters calibrated against experiments that reproduce the relevant flow or stress regime? Second, are

numerical verification and independent validation documented separately from parameter fitting? Third, are numerical simplifications such as spherical particles, particle upscaling, reduced stiffness, or cohesion scaling reported and tested for sensitivity? Fourth, do the reported outputs connect to a practical pharmaceutical or device-relevant endpoint, for example content uniformity, granule-size evolution, die mass, tablet mechanical response, fine-particle fraction, or device deposition? These questions allow older foundational studies and recent industrial work to be compared on a common basis (Ketterhagen and Wassgren, 2022; Rouabah et al., 2022; Jajcevic et al., 2024).

The novelty is not a claim that DEM has been overlooked in pharmaceutical manufacturing. Earlier reviews established the range of DEM applications and discussed important issues in model setup, calibration, and process simulation (Ketterhagen et al., 2009; Yeom et al., 2019; Ketterhagen and Wassgren, 2022; Zheng et al., 2023). The present review extends that literature by applying a common evidence-oriented lens across solid-dose manufacturing and pulmonary drug delivery. In particular, it examines whether material characterization informs contact-model selection, whether numerical verification, calibration, and independent validation are distinguished, whether numerical scaling is tested rather than assumed, and whether the final comparison is made against a pharmaceutical or pulmonary performance endpoint. Using the same evidential lens across applications helps distinguish primarily mechanistic studies from those that are beginning to support quantitative engineering decisions. This article is a critical narrative review rather than a systematic review or meta-analysis. The literature base was developed from foundational pharmaceutical DEM reviews and expanded through targeted searches and reference chaining to identify more recent peer-reviewed studies. Search terms combined "discrete element method" or "DEM" with pharmaceutical powder, blending, continuous mixing, feeding, die filling, granulation, milling, tablet compaction, coating, dry powder inhaler, CFD-DEM, calibration, validation, coarse graining, and digital twin. Greater weight was given to studies published from 2020 to 2026 because this period contains much of the recent shift toward industrial-scale simulation, experimental validation, and process- or product-level endpoints.

Studies were included when DEM was a substantive part of the modelling framework and when the paper provided information relevant to at least one of the review questions:

parameter calibration, numerical verification or scaling, experimental validation, transferability, or linkage to a pharmaceutical or pulmonary performance measure. Foundational older studies were retained when they established a method or application that remains influential. Studies were not ranked numerically because the applications differ in scale and validation targets; instead, the review compares the strength and scope of the evidence supporting each modelling claim. Figure 1 summarizes the application map synthesized from Yeom et al. (2019), Zheng et al. (2021), Rouabah et al. (2022), Zheng et al. (2023), and the recent application studies reviewed here.

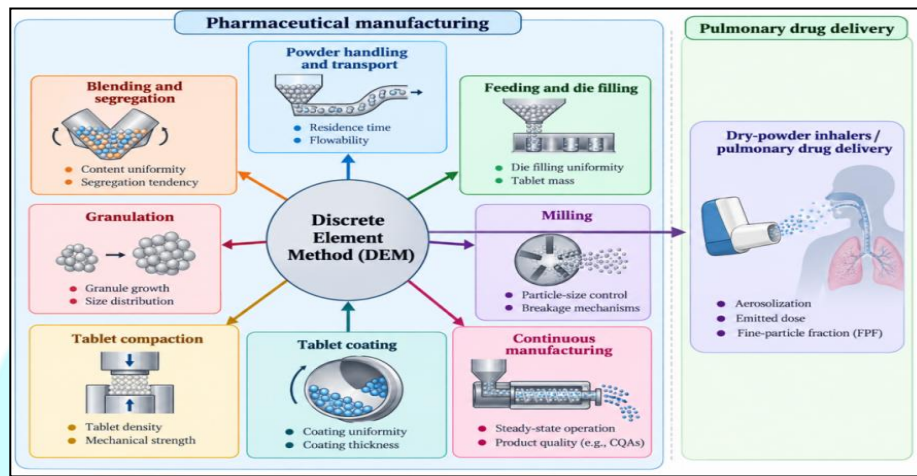


Figure 1. Application map for DEM in pharmaceutical manufacturing and pulmonary drug delivery.

2. FUNDAMENTALS OF THE DISCRETE ELEMENT METHOD

In soft-sphere DEM, particles are allowed a small numerical overlap when they come into contact. The overlap is not a physical penetration; it is used by the contact law to calculate forces. Particle translation and rotation are then obtained from Newton's laws of motion, with the total force and torque assembled from particle-particle, particle-wall, body, and any externally imposed interactions. This contact-by-contact description is the defining feature of the original distinct-element formulation and remains the basis of modern DEM implementations (Cundall and Strack, 1979; Yeom et al., 2019).

$$m_i \, dv_i/dt = \sum_j (F_{n,ij} + F_{t,ij}) + m_i g + F_{ext,i} \quad (1)$$

$$I_i \, d\omega_i/dt = \sum_j (T_{t,ij} + T_{r,ij}) + T_{ext,i} \quad (2)$$

Here, m_i and I_i denote particle mass and moment of inertia, v_i and ω_i are translational and angular velocities, F_n and F_t are normal and tangential contact forces, and the torque terms account for tangential and rolling contributions. The exact force law

depends on the selected contact model. Linear spring-dashpot and Hertz-Mindlin-type models are widely used, while cohesive powders may require adhesive extensions. Because explicit DEM resolves short contact events, the numerical time step must remain sufficiently small relative to contact dynamics; this is one reason simulations become expensive as particles become finer or stiffer (Yeom et al., 2019; Ketterhagen and Wassgren, 2022).

The contact law determines how overlap, relative motion, friction, damping, rolling resistance, and, when needed, cohesion is converted into contact forces and torques. This matters in pharmaceutical systems because real powders are rarely ideal spheres with simple surfaces. Fine APIs and excipients may be irregular, rough, porous, lubricated, or cohesive. In practice, friction and rolling resistance are often adjusted to reproduce bulk flow, while cohesive parameters may be needed when attractive forces strongly affect the powder response. Reviews of pharmaceutical DEM therefore emphasize that many input values should be treated as effective model parameters that require calibration, not as universal material constants (Yeom et al., 2019; Coetzee, 2017; Ketterhagen and Wassgren, 2022).

Real pharmaceutical powders commonly contain broad size distributions and non-spherical particles, but representing every physical particle at industrial scale is usually impractical. Modelers therefore simplify particle shape, narrow the represented size distribution, or use coarse-grained parcels. Spherical particles are computationally efficient, while clumps or other non-spherical representations can better capture interlocking and rotational resistance at higher computational cost. Coarse graining can also change contact number, mass scaling, cohesion, and segregation behavior, so an upscaled model should be recalibrated and validated rather than assumed to be dynamically equivalent to the original powder (Coetzee, 2017; Coetzee, 2019; Ketterhagen and Wassgren, 2022).

3. MODEL PARAMETERIZATION, CALIBRATION, AND VALIDATION

Verification, calibration, and validation address different questions and should not be treated as interchangeable. Numerical verification asks whether the implemented model is being solved with adequate numerical fidelity, for example by checking time-step sensitivity and, in coupled CFD-DEM, the influence of grid or resolution choices.

Calibration estimates effective model parameters by fitting selected experimental responses, whereas validation tests the calibrated model against measurements that were not used for fitting. Keeping these steps distinct reduces the risk that numerical agreement with a calibration target is interpreted as evidence of predictive validity (Yeom et al., 2019; Ketterhagen and Wassgren, 2022). Parameterization is one of the most important sources of uncertainty in DEM. Directly inserting literature values or single-particle measurements does not guarantee that a simulation will reproduce bulk powder behavior, because simplified particle shape, unresolved roughness, fines, surface treatment, and cohesion can all shift the effective response. For this reason, DEM calibration is commonly based on bulk tests such as angle of repose, shear-cell response, bulk density, compression behavior, or hopper discharge. Calibration should also reflect the stress and flow regime of the intended process. Recent pharmaceutical studies have followed this approach by calibrating against laboratory tests before moving to full-scale blending simulations (Coetzee, 2017; Ketterhagen and Wassgren, 2022; Benque et al., 2024; Mostafaei et al., 2025). Because several parameter combinations can reproduce the same single bulk response, calibration against one target alone may be non-identifying. Where practical, multi-objective calibration using more than one independent bulk response—for example angle of repose together with shear-cell, density, or discharge behaviour—provides a stronger basis for selecting a parameter set and for testing whether it remains valid outside the calibration condition (Coetzee, 2017; Ketterhagen and Wassgren, 2022). Calibration and validation should be kept separate. Reproducing the same test used to fit the parameters only shows that the calibration objective was met; it does not demonstrate predictive performance. Independent validation may use concentration profiles, residence-time distributions, die mass, discharge behavior, tablet weight, or other process and product measurements. Benque et al. (2024), for example, compared simulated concentration differences with production-scale HPLC sampling in a tote blender. Alizadeh Behjani et al. (2026) compared DEM predictions with experimental tablet-weight and residence-time data in a rotary tablet press. These examples illustrate a stronger validation strategy because the model is judged against measurements that were not simply the calibration target (Benque et al., 2024; Alizadeh Behjani et al., 2026). Figure 2 summarizes the resulting evidence-oriented workflow from characterization and calibration through numerical simulation, independent validation, and engineering use, based on Coetzee

(2017), Ketterhagen and Wassgren (2022), Rouabah et al. (2022), and Jajcevic et al. (2024).

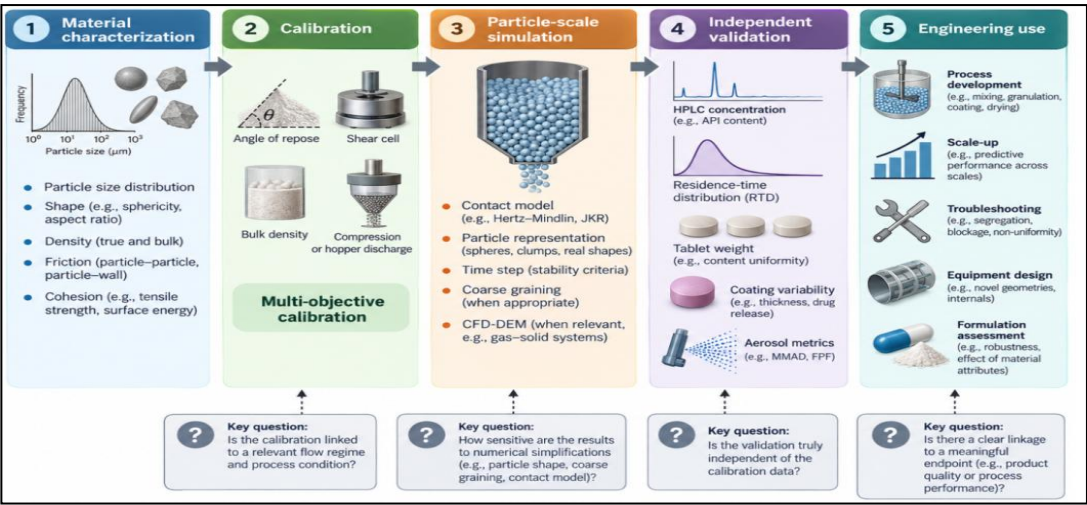


Figure 2. Evidence-oriented workflow for pharmaceutical DEM.

Table 1. DEM inputs, practical calibration targets, and consequences of parameter uncertainty in pharmaceutical powder simulations (Yeom et al., 2019; Coetzee, 2017; Ketterhagen and Wassgren, 2022).

Model component	Typical DEM parameter	Experimental anchor	Main risk if poorly specified
Particle geometry	Diameter distribution; aspect ratio; clump geometry	Laser diffraction/sieving; microscopy/image analysis	Incorrect packing, percolation, segregation and contact network
Bulk flow resistance	Static friction; rolling friction	Shear cell; angle of repose; hopper discharge	Wrong flow regime, shear localization or residence time
Collision dissipation	Coefficient of restitution; damping	Drop/collision tests or calibrated bulk response	Unrealistic bouncing and kinetic energy dissipation
Cohesion	Surface energy or effective cohesive force	Tensile/shear tests; flow-function measurements	Severe error for fine APIs and cohesive blends
Particle stiffness	Young's modulus or effective contact stiffness	Compression/contact data; sensitivity analysis	Time-step inflation or unrealistic deformation
Wall interaction	Particle-wall friction/cohesion	Wall-friction tests using equipment material	Incorrect discharge, feeder behavior and die filling

4. DEM APPLICATIONS IN PHARMACEUTICAL MANUFACTURING

4.1 Powder transport, feeding, and die filling

Die filling links powder flow directly to tablet mass and dose consistency. In a rotary tablet press, powder has only a limited time to enter each moving die cavity, so filling is sensitive

to flowability, cohesion, bed height, feeder kinematics, and the interaction between powder and equipment surfaces. Early DEM studies established the influence of particle size, shape, and filling speed (Wu, 2008), while later GPU-enhanced simulations extended the analysis to forced feeders and industrially relevant geometries. Li et al. (2023), for example, used DEM to resolve particle-scale transport in a KG-Pharma RoTab feed-frame system, whereas Alizadeh Behjani et al. (2026) combined DEM with tablet-weight and residence-time measurements to quantify cohesion-sensitive die filling in a rotary press. Feeding upstream of the press is equally important because fluctuations generated in loss-in-weight feeders can propagate through a continuous line. Bhalode and Ierapetritou (2020) combined bulk calibration with DEM to examine how pharmaceutical material properties affect continuous powder feeding, and later work has used DEM to resolve the interaction between screw transport, agitation, powder holdup, and local flow structure. These studies strengthen a recurring message: feeder design cannot be separated from powder properties, and validation should include an operational quantity such as feed factor, mass-flow variability, or residence-time response rather than flow visualization alone (Ketterhagen and Wassgren, 2022; Alizadeh Behjani et al., 2026).

In practice, a feeder or die geometry that performs well with a free-flowing excipient may behave quite differently with a cohesive or API-rich blend. A useful DEM model should therefore be tested across the relevant range of material properties and operating conditions, rather than being validated at a single point and then transferred without evidence (Ketterhagen and Wassgren, 2022; Alizadeh Behjani et al., 2026).

4.2 Blending and segregation

Blending is one of the most established pharmaceutical uses of DEM because the method can track individual particle histories and local composition. The same capability also makes it useful for studying segregation, which may arise from differences in particle size, density, shape, or cohesive behavior. DEM studies commonly evaluate mixing indices, spatial concentration, residence histories, and particle motion as functions of fill level, rotation speed, baffle configuration, and loading sequence (Ketterhagen et al., 2009; Yeom et al., 2019). More recent studies have begun to move beyond laboratory-scale demonstrations. Alizadeh Behjani et al. (2020) used DEM to study continuous pharmaceutical mixing and introduced a mixing metric intended to identify API

agglomeration. Toson et al. (2021) then demonstrated a more explicit validation workflow for continuous mixing, while Zheng et al. (2022) used GPU-enhanced DEM to examine granular dynamics in a full-scale continuous blender. Yang et al. (2023) validated a continuous-blender model against experimentally measured residence-time distributions and used the model to assess hold-up mass and operating conditions. For tumbling systems, Mostafaei et al. (2023) compared blending behaviour across scales, and more recent industrial studies connected DEM predictions to HPLC sampling, tablet tensile-strength models, and commercial-scale equipment (Benque et al., 2024; Boehling et al., 2024; Mostafaei et al., 2025). Salloum et al. (2025) further showed that DEM-guided mixer and deflector design could be assessed against UV/Vis measurements. Together, these studies show a progression from mixing indices toward validation against traceable experimental and downstream quality measures.

4.3 Granulation and milling

Granulation and milling are more difficult to model than dry blending because particle properties can evolve during processing. In granulation, agglomerates form, strengthen, deform, or break; in milling, particles fragment and may undergo solid-state changes. DEM can resolve collision frequency, impact energy, bond formation, contact-force histories, and local kinematics, but prediction of final size distributions requires an additional breakage, bonding, or liquid-bridge model. Rouabah et al. (2022) demonstrated a calibrated DEM workflow spanning handling and processing, and Rouabah et al. (2025) later compared numerical granule-growth predictions with experiments in high-shear wet granulation. These studies illustrate why granulation models require validation beyond equipment motion. This is a key difference from many blending studies: in blending, the same particles can often be followed throughout the process, whereas granulation and milling require the model to represent changing particle identity, size, bonding state, or breakage history. As a result, a model that predicts mixer kinematics accurately may still fail to predict the evolving product distribution unless the transformation law itself is calibrated and validated. Recent milling studies provide the complementary case. Krok et al. (2021) coupled bonded-particle DEM with a clustering method to analyse breakage of pharmaceutical granules during ball milling, while Abouhakim et al. (2022) used DEM-derived milling energy to interpret comminution and amorphisation of omeprazole-

magnesium material. Such work is particularly useful because milling performance depends not only on residence and collision statistics but also on whether the model links those statistics to breakage or solid-state transformation. The remaining limitation is that calibrated breakage parameters are often material- and mill-specific, so transfer between formulations or milling technologies should not be assumed. A fixed-particle DEM model may reproduce equipment motion while still failing to predict the final granule or particle-size distribution. For that reason, the underlying particle transformation model should be validated independently whenever breakage, bonding, or liquid-mediated agglomeration is a central process mechanism. This increases model complexity and parameter uncertainty, but it is necessary if the intended output is product prediction rather than equipment visualization (Ketterhagen et al., 2009; Yeom et al., 2019). Rouabah et al. (2025) provide a useful example of how this limitation can be addressed. Rouabah et al. (2025) developed and experimentally evaluated a DEM framework for high-shear wet granulation using a 0.5 L granulator. Their analysis incorporated cohesive interactions and used a post-processing routine to identify agglomerates and follow granule-size evolution. Agreement between simulated and experimental granule-growth kinetics is important because it moves validation beyond general powder motion toward the evolving product attribute that the operation is intended to control. At the same time, the study also illustrates why transfer to other formulations is not automatic: liquid content, binder distribution, primary-particle morphology, and agglomerate-breakage rules can change the effective interaction physics and must be reconsidered for each material system (Rouabah et al., 2025).

4.4 Tablet compaction

Tablet compaction transforms a loose powder bed into a dense porous compact through rearrangement, elastic-plastic deformation, fragmentation, bonding, and unloading. Standard DEM describes rearrangement and evolving contact networks well, but conventional contact formulations become increasingly demanding as coordination number and deformation rise. Gao et al. (2021) developed and verified a quantitative DEM calibration strategy for pharmaceutical powder compression using an elasto-plastic contact model, while Giannis et al. (2021) used a multi-contact formulation to represent high-density compaction of microcrystalline cellulose. These approaches are important because they move beyond qualitative force-chain visualization toward comparison with bulk

compression response. The main attraction of DEM in compaction is access to internal contact forces and particle-scale rearrangement that are difficult to measure experimentally during compression. However, predictions of tensile strength, capping, lamination, or porosity still depend on constitutive assumptions and validation. For this reason, DEM and continuum approaches such as FEM are often better viewed as complementary: DEM is strongest when particle-scale contacts and rearrangement dominate, whereas continuum methods become attractive when the compact behaves more like a dense deformable body (Giannis et al., 2021; Ketterhagen et al., 2009).

A 2026 study by Najafian et al. further illustrates the value of particle-scale analysis for mini-tablets. Najafian et al. (2026) examined how fill weight, particle size, and particle-size distribution affected contact-force transmission in narrow die cavities. The simulations indicated that particle size strongly influenced force heterogeneity and that force-chain organization, rather than particle force magnitude alone, governed the macroscopic response. This is relevant to personalized and pediatric dosage forms because mini-tablets reduce the ratio between die diameter and particle size, making confinement and local force networks more prominent. The study nevertheless reinforces the need for experimentally calibrated contact parameters before such force maps are interpreted as quantitatively predictive.

4.5 Coating and other particulate operations

DEM has also been applied to tablet coating, where circulation, residence time, collision exposure, tablet shape, spray interception, and breakage can influence final quality. Ketterhagen et al. (2021) combined DEM with tablet-impact experiments to identify coating conditions associated with tablet breakage. Pasternak et al. (2023) coupled DEM with resolved spray measurements to model coating in lab-scale drum coaters, while Sivanapillai et al. (2023) performed multi-scale experimental validation of DEM predictions for coating variability. Liu et al. (2024) extended DEM-DDM analysis to intra-tablet coating uniformity and non-spherical tablet shapes. These studies go beyond using circulation time alone as a surrogate for coating performance by comparing model predictions with coating- or damage-related measurements. Despite this progress, coating remains a multiphysics problem. Tablet trajectories can be resolved by DEM, but coating thickness and uniformity additionally depend on spray-field geometry, droplet transport,

shadowing, deposition, spreading, drying, and film formation. Consequently, a DEM model that reproduces tablet circulation is not automatically predictive of coating quality. The strongest recent workflows therefore combine DEM with spray measurements, CFD or droplet models, and independent coating measurements (Pasternak et al., 2023; Sivanesapillai et al., 2023; Liu et al., 2024).

Table 2. Major DEM application domains and their connection to pharmaceutical or biomedical performance.

Application	Primary DEM outputs	Pharmaceutical/biomedical relevance	Ref
Blending	Particle trajectories; mixing index; local composition; segregation	Content uniformity; API distribution; process scale-up	Benque et al. (2024); Boehling et al. (2024); Mostafaei et al. (2025)
Die filling / feed-frame transport	Mass flow; die occupancy; residence time; composition	Tablet mass and dose consistency	Bhalode and Ierapetritou (2020); Li et al. (2023); Alizadeh Behjani et al. (2026)
Granulation	Collision/bonding events; agglomerate growth; residence time	Granule size and flowability for downstream tableting	Rouabah et al. (2022); Rouabah et al. (2025)
Milling	Impact energy; collision frequency; breakage history	Particle-size control; dissolution and processability	Krok et al. (2021); Abouhakim et al. (2022)
Compaction	Contact networks; force chains; density/porosity evolution	Tablet strength, defects and manufacturability	Gao et al. (2021); Giannis et al. (2021); Najafian et al. (2026)
Dry-powder inhaler	Particle trajectories; agglomerate break-up; wall/device collisions	Aerosolization, emitted dose and pulmonary delivery	Zheng et al. (2021); Sulaiman et al. (2022); Zhu et al. (2023); Saeid et al. (2025)
Tablet coating	Tablet trajectories; spray exposure; coating distribution; impact severity	Coating uniformity; film quality; tablet breakage	Ketterhagen et al. (2021); Pasternak et al. (2023); Sivanesapillai et al. (2023); Liu et al. (2024)
Upstream continuous feeding	Mass flow; feed factor; residence/holdup; flow pattern	Composition stability and disturbance propagation in continuous manufacturing	Bhalode and Ierapetritou (2020); Li et al. (2023)

5. CFD-DEM AND PULMONARY DRUG-DELIVERY APPLICATIONS

Some pharmaceutical and biomedical particulate processes cannot be described adequately as dry granular motion because the surrounding fluid strongly affects particle trajectories. CFD-DEM coupling addresses this by solving a continuum fluid field while DEM tracks individual particles and their contacts. This is particularly relevant for inhalers and

fluidized systems, where drag and pressure effects act together with particle-particle and particle-wall collisions. The added physical detail also adds model uncertainty: drag correlations, turbulence treatment, grid resolution, particle size, and contact parameters all influence the result. CFD-DEM is therefore more expressive than one-way particle tracking, but not automatically more accurate unless these assumptions are justified and validated (Zheng et al., 2021). Dry-powder inhalers provide a clear biomedical example because device performance depends on turning a stored powder formulation into an aerosol that can reach the respiratory tract. During inhalation, carrier-drug detachment, agglomerate break-up, particle-wall impacts, airflow structure, and deposition can all affect the emitted and respirable fractions. Zheng et al. (2021) reviewed the use of CFD together with DPM and DEM for analyzing flow patterns, trajectories, de-agglomeration, and deposition in DPI systems, showing how particle-scale modeling can contribute directly to inhaler design (Zheng et al., 2021). DEM is especially attractive when de-agglomeration is controlled by contact mechanics because contacts within an agglomerate can be represented explicitly. The difficulty is scale. Fine inhaled particles are typically small enough that a realistic dose may contain far more particles than can be resolved individually in a practical full-device simulation. As a result, DPI studies often rely on representative agglomerates, coarse graining, or multiscale strategies. Those simplifications should be reported clearly because they can influence the predicted break-up and deposition behavior (Zheng et al., 2021; Ketterhagen and Wassgren, 2022).

Recent CFD-DEM studies have examined both device-specific mechanisms and the computational compromises needed to model them. Liu et al. (2021) proposed a representative-particle coarse-graining strategy to reduce the cost of carrier-based DPI simulations while retaining fine-particle-fraction trends. Alfano et al. (2022) used DEM to study deaggregation and discharge from a capsule-based DPI, highlighting the contribution of capsule motion and collisions. Sulaiman et al. (2022) examined transport and aerosolization in the ELLIPTA® device, and Zhu et al. (2023) quantified how aperture size alters flow and particle behaviour in a capsule-based inhaler. More recent work has incorporated electrostatic and van der Waals forces (Saeid et al., 2025), coupled an inhaler with downstream airway geometries (Gou et al., 2025), and used CFD-DEM to optimize grid and chamber geometry with fine-particle fraction as a performance endpoint (Liu et al., 2026). The field is therefore moving from device-flow description toward endpoint-

based design, although predictions remain sensitive to adhesion, electrostatics, inhalation profile, and coarse-graining assumptions. Figure 3 shows the principal output used to assess aerosolization based on Zheng et al. (2021), Sulaiman et al. (2022), Zhu et al. (2023), and Saeid et al. (2025).

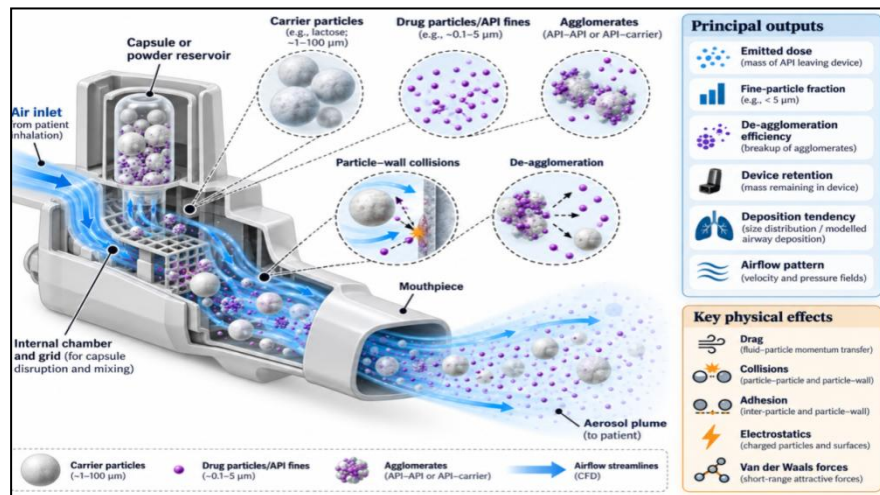


Figure 3. Simplified CFD-DEM representation of a carrier-based dry-powder inhaler.

6. RECENT EVIDENCE: FROM QUALITATIVE SIMULATION TO PREDICTIVE ENGINEERING

The studies reviewed from 2020-2026 increasingly combine calibration, independent validation, and process-relevant endpoints. In continuous mixing, Toson et al. (2021) and Yang et al. (2023) used experimental process responses to test DEM predictions rather than relying only on qualitative particle patterns. In tablet coating, Sivanesapillai et al. (2023) explicitly assessed model predictivity across scales and conditions. Benque et al. (2024) used calibrated DEM and production-scale HPLC sampling to diagnose axial nonuniformity in an industrial tote blender. Jajcevic et al. (2024a) developed a high-fidelity DEM-based digital-twin calibration workflow for continuous direct compression, and the companion validation study (Jajcevic et al., 2024b) tested model response to concentration disturbances. Mahto et al. (2025) addressed the difficult link between calibration and coarse-graining and validated the calibrated parameter strategy using tablet-press experiments. Collectively, these examples indicate a shift in the selected literature from visual plausibility toward quantitative process response. The same trend is visible in granulation, compaction, and inhalation-device research, but the validation endpoints differ. Rouabah et al. (2025) validated granule-growth kinetics in a high-shear granulator;

Alizadeh Behjani et al. (2026) compared tablet weight and residence-time behavior while varying particle cohesion during rotary-press die filling; and Najafian et al. (2026) used calibrated DEM to analyze force networks in mini-tablet compaction. In DPI research, Sulaiman et al. (2022) and Zhu et al. (2023) used CFD–DEM to connect airflow, collision histories, and powder release to aerosol-performance indicators, while Saeid et al. (2025) examined electrostatic effects. The comparison reveals an important difference in maturity: bulk manufacturing applications can often be validated against mass, concentration, or mechanical measurements, whereas DPI studies require simultaneous confidence in transient airflow, particle contacts, adhesion, de-agglomeration, and aerosol endpoints. Accordingly, a more sophisticated coupled model is not automatically a more predictive one.

Table 3. Selected studies illustrating the shift toward calibrated and experimentally validated pharmaceutical DEM.

Study	Scale / system	Calibration or validation feature	Why it matters
Benque et al. (2024)	Industrial tote blender	Dynamic angle-of-repose calibration; production HPLC sampling	Demonstrates experimentally anchored process diagnosis and equipment redesign
Boehling et al. (2024)	Two pharmaceutical blender types	Small-scale calibration; cross-scale comparison; quality linkage	Shows how DEM may support scale transfer and downstream tablet-property prediction
Mostafaei et al. (2025)	Commercial-scale cone and hoop blenders	Compression/ring-shear based calibration and experimental comparison	Addresses realistic process variables at commercial scale
Alizadeh Behjani et al. (2026)	Rotary tablet press	Tablet weight and residence-time distribution validation	Links cohesion-sensitive DEM behavior to measurable manufacturing outcomes
Giannis et al. (2021)	High-density tablet compaction	Calibration against MCC compaction response	Extends DEM to dense multi-contact mechanics rather than dilute flow only
Toson et al. (2021)	Continuous powder mixer	Calibration plus experimental process validation	Establishes a validated DEM workflow for continuous oral-solid manufacturing
Sivanesapillai et al. (2023)	Tablet coating across scales	Experimental coating-variability measurements and uncertainty assessment	Tests coating predictivity rather than particle circulation alone
Jajcevic et al. (2024b)	Continuous direct-compression digital twin	Validation against concentration-disturbance response	Separates calibration workflow from independent process validation
Mahto et al. (2025)	Calibrated/coarse-grained pharmaceutical powder	Tablet-press experimental validation	Directly tests how far calibrated parameters can survive coarse graining

Table 4 compares recent studies using a common evidential lens. The comparison is qualitative rather than a numerical ranking: it identifies which part of the calibration-verification-validation-endpoint chain each study addresses and which uncertainty remains outside its scope. Viewed in this way, the central research gap becomes clearer: calibrated DEM has been demonstrated in many settings, but parameter transfer across materials, scales, equipment, and pharmaceutically or device-relevant endpoints is still tested far less often.

Table 4. Critical comparison of selected 2022–2026 pharmaceutical and pulmonary DEM studies

Study	Application / scale	Model/contact approach	Validation endpoint	Strongest contribution	Remaining limitation
Rouabah et al. (2022)	Handling / processing	Calibrated cohesive DEM	Bulk tests and process behaviour	Shows one calibration framework across several operations	Transfer across formulations and industrial scale remains limited
Sulaiman et al. (2022)	ELLIPTA® DPI	CFD-DEM carrier/API transport	Aerosolization /device behaviour	Connects flow and particle interactions in a commercial DPI geometry	Adhesion and representative-particle assumptions affect generalization
Zhu et al. (2023)	Capsule DPI	CFD-DEM	Device-dependent aerosol performance	Relates aperture geometry to particle dispersion	Device-specific geometry and formulation
Benque et al. (2024)	Industrial tote blender	Calibrated cohesive DEM	Production-scale HPLC concentration	Uses plant-scale sampling to diagnose and redesign mixing	One formulation/equipment family
Boehling et al. (2024)	Two blender types	Calibrated DEM + quality linkage	Cross-scale blending and tensile-strength model	Links mixing history to downstream tablet property	Transfer tested across limited blender/material space
Jajcevic et al. (2024a, 2024b)	Continuous direct-compression digital twin	High-fidelity DEM calibration and validation workflow	Concentration-disturbance response	Embeds DEM within a process-level calibration and validation framework	High-fidelity DEM is computationally unsuitable for direct real-time use without model reduction
Rouabah et al. (2025)	High-shear wet granulation	Cohesive/bonding DEM	Experimental granule-growth behaviour	Connects particle interactions to granule evolution	Granulation parameters remain formulation-specific
Saeid et al. (2025)	Carrier-based DPI	DEM with electrostatic + van der Waals forces	Dispersion/coating metrics	Adds surface-force physics often omitted in DPI DEM	Electrostatic inputs and device transfer need further validation

Study	Application / scale	Model/contact approach	Validation endpoint	Strongest contribution	Remaining limitation
Alizadeh Behjani et al. (2026)	Rotary tablet press	Cohesive DEM	Tablet weight/variability and RTD	Validates both process dynamics and final mass outcome	MCC-based system; broader formulation transfer remains open
Najafian et al. (2026)	Mini-tablet compaction	DEM calibrated using compaction experiments	Experimental compaction response used for parameter calibration	Resolves force-chain effects of particle size and polydispersity	Findings remain specific to the tested confined geometry and calibrated material system
Sivanesapillai et al. (2023)	Tablet coating / multiple scales	DEM coating model	Measured coating variability across scales/conditions	Explicitly evaluates predictive uncertainty and scale effects	Spray/film physics still partly external to DEM
Mahto et al. (2025)	Calibration and coarse graining	Bulk-calibrated DEM + ANN-supported parameterization	Tablet-press validation	Directly tests parameter robustness under coarse graining	Generalized limits remain powder- and scale-dependent
Gou et al. (2025)	Turbuhaler + airway	CFD-DEM-DPM	Transport and airway deposition patterns	Extends device simulation into integrated airway geometry	Clinical deposition validation and patient variability remain limited

7. CRITICAL LIMITATIONS AND RESEARCH GAPS

7.1 Model and physics limitations

At the model-physics level, computational cost and scale disparity remain major constraints. Industrial processes may contain enormous numbers of physical particles, while fine pharmaceutical powders require small spatial and temporal scales. Common shortcuts include coarse graining, restricted size distributions, spherical particles, and reduced stiffness. These choices can make simulations feasible, but they may also change the predicted flow, segregation, contact network, or cohesion. Studies should therefore report particle scaling, stiffness assumptions, time-step criteria, and sensitivity checks clearly enough for readers to judge the effect of these numerical simplifications (Coetzee, 2019; Ketterhagen and Wassgren, 2022; Zheng et al., 2021). Fine-particle interaction physics adds a second layer of uncertainty. Cohesion, humidity, electrostatics, surface-energy heterogeneity, and nanoscale roughness can strongly affect powders for which

surface forces are important relative to particle weight. In many practical DEM studies, several microscopic effects are represented through effective cohesive parameters rather than modelled separately. This is useful for calibration, but it limits transferability when formulation or environmental conditions change. The electrostatics study by Saeid et al. (2025) is a useful step toward representing additional surface-force physics, but broader validation across devices and material systems is still needed (Yeom et al., 2019; Ketterhagen and Wassgren, 2022; Saeid et al., 2025).

7.2 Evidence, transferability, and translation limitations

At the evidence level, calibration is often non-unique: different combinations of friction, rolling resistance, stiffness, damping, and cohesion can reproduce a similar bulk response. Coetzee (2017) described this identifiability problem broadly, and pharmaceutical studies continue to encounter it when scaling fine powders or transferring parameter sets between unit operations. Mahto et al. (2025) directly addressed calibration and coarse-graining for pharmaceutical powder and showed that the usable parameter space remains constrained by the degree of particle scaling. The practical implication is that calibration should be multi-objective whenever possible and should be challenged under a stress state or operating condition that was not used during fitting. Parameter transfer between batches, humidity conditions, formulations, scales, and equipment materials should be demonstrated rather than assumed (Ketterhagen and Wassgren, 2022; Jajcevic et al., 2024a, 2024b). Validation should also target an endpoint that matters to the process, product, or device. For manufacturing, suitable targets include blend uniformity, tablet mass, residence time, tensile strength, porosity, or other measurable quality attributes. For inhaler applications, meaningful outputs include emitted dose, fine-particle fraction, deposition, and de-agglomeration behaviour. Particle trajectories can explain mechanisms, but qualitative agreement alone should not be presented as proof of predictive accuracy. Reproducibility additionally requires sufficient reporting of the contact law, interaction parameters, particle representation, wall properties, calibration procedure, validation data, time-step choice, and major numerical simplifications (Benque et al., 2024; Alizadeh Behjani et al., 2026; Zheng et al., 2021; Coetzee, 2017; Ketterhagen and Wassgren, 2022).

The principal unresolved evidence gap is transferability. Many models reproduce one calibration experiment or one operating condition, but fewer show that the same

parameterization predicts a second material state, process scale, operating range, or downstream quality endpoint. The strongest recent studies are beginning to close this gap through production-scale sampling, residence-time measurements, coating experiments, tablet-press validation, and paired calibration-validation workflows (Toson et al., 2021; Sivanesanpillai et al., 2023; Benque et al., 2024; Jajcevic et al., 2024a, 2024b; Mahto et al., 2025; Alizadeh Behjani et al., 2026). Nevertheless, transfer across formulation composition, humidity, particle-size scaling, and equipment remains insufficiently tested.

A related translation gap concerns endpoint integration, especially for pulmonary delivery. Manufacturing studies increasingly connect DEM to concentration, tablet mass, tensile strength, or granule growth, whereas DPI studies face a longer chain from contact mechanics to aerosol generation and deposition. Future DPI work should report not only particle trajectories and collision statistics but also independent aerosol metrics under multiple inhalation profiles and, where possible, deposition measurements. Figure 4 summarizes how model-physics limitations and evidence limitations accumulate across the development chain: uncertainty introduced during calibration can propagate through parameter transfer, coarse graining, endpoint validation, and ultimately any proposed real-time or digital-twin use. The schematic is synthesized from Coetzee (2017), Ketterhagen and Wassgren (2022), Jajcevic et al. (2024a, 2024b), Mahto et al. (2025), and Alizadeh Behjani et al. (2026).

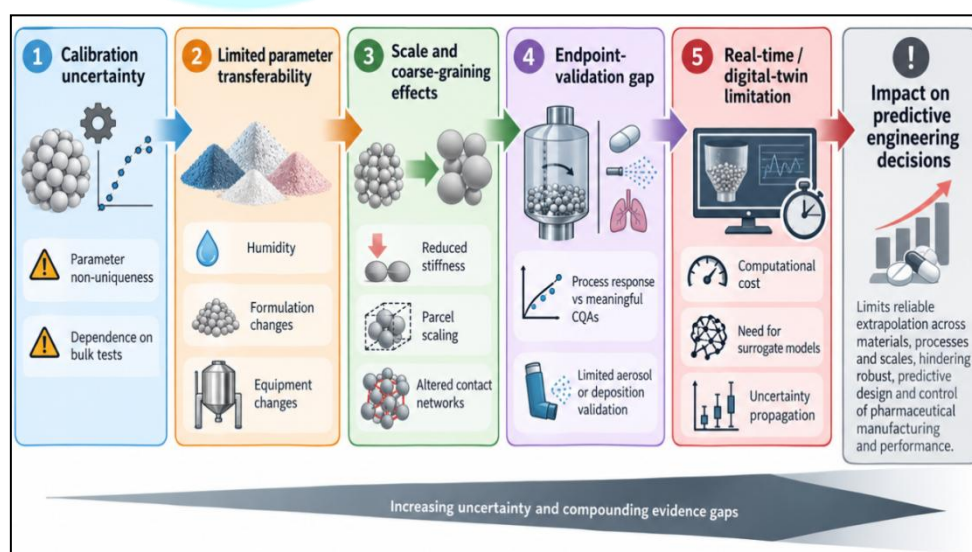


Figure 4. Consolidated evidence gaps that currently limit transfer from calibrated DEM to predictive pharmaceutical engineering.

8. FUTURE DIRECTIONS

Future progress will likely depend on integrating DEM with experiments, process analytical technology (PAT), uncertainty analysis, and faster surrogate models rather than treating it as an isolated simulator. A practical architecture is already visible in recent work: high-fidelity DEM can be used offline to identify particle-scale mechanisms and generate validated response data, while reduced-order or data-driven models provide faster optimization, monitoring, or control calculations. The high-fidelity digital-twin work of Jajcevic et al. (2024a, 2024b) is important in this context because it embeds DEM within a broader process-level calibration and validation workflow. At the same time, digital-twin terminology should be used carefully. A three-dimensional DEM model of equipment is not, by itself, a digital twin; useful pharmaceutical digital twins require continuing correspondence with the physical process, data integration, and a model that supports monitoring, prediction, or decision making. Because full DEM is computationally expensive, a realistic architecture may therefore combine offline high-fidelity DEM with faster hybrid or surrogate models for repeated or near-real-time use (Chen et al., 2020; Ketterhagen and Wassgren, 2022; Jajcevic et al., 2024a, 2024b). Future studies should also report how uncertainty in friction, cohesion, contact laws, and particle-size scaling propagates to the final critical quality attribute rather than presenting a single deterministic prediction. For biomedical-device research, the strongest DEM applications are those in which particle contact mechanics are directly connected to a measurable device or dose-delivery outcome. Dry-powder inhalers already provide a well-established example because de-agglomeration and deposition are central to device performance. Other powder-based biomedical or pharmaceutical manufacturing applications may also benefit, but the biomedical claim should be supported by a clear mechanistic link and experimental validation rather than by labeling a general powder process as biomedical (Zheng et al., 2021; Ketterhagen et al., 2009).

9. CONCLUSION

DEM is now an established mechanistic tool for pharmaceutical powder processing and pulmonary drug-delivery research, but the recent literature shows that its engineering value depends on the quality of the evidence surrounding the simulation. The most convincing studies distinguish numerical verification from parameter calibration and independent

validation, document numerical scaling, and compare predictions with a process-, product-, or dose-delivery endpoint. Across applications, three requirements should define future claims of predictive capability: validation under more than one relevant condition, explicit reporting of parameter and coarse-graining uncertainty, and verification against an endpoint that is meaningful for product quality or device performance. Accordingly, DEM is most valuable not as a stand-alone virtual experiment, but as part of an experimentally anchored, multiscale, uncertainty-aware engineering workflow.

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