

Particle Morphology as a Critical Material Attribute in Pharmaceutical Development: Characterization, Quality Impact, and Control Strategies

Murugesan Palanivelu¹, Jayaram Kamma², Prabakaran Ramachandran³, Padmakar Gandla⁴, Venkatanarayana Bypaneni⁵, Kishore Kumar Hotha⁶

¹Carnegie Pharmaceuticals LLC, New Jersey, USA

²Lupin, Somerset, USA

³Granules Pharmaceuticals Inc, Virginia, USA

⁴Catalent Pharma Solutions, Winchester, USA.

⁵Stira Pharmaceuticals LLC, New Jersey, USA

⁶Dr. Hotha's Life Sciences LLC, New Jersey, USA

Email: drhotha@drhothas.com

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Abstract

Particle morphology plays a key role in the physical, chemical, and processing properties of active pharmaceutical ingredients (APIs) and excipients. This review examines how particle size, shape, surface texture, and crystallinity influence pharmaceutical development and manufacturing. It outlines the main characterization methods, including scanning electron microscopy (SEM), transmission electron microscopy (TEM), atomic force microscopy (AFM), laser diffraction, dynamic light scattering (DLS), and Raman chemical imaging. The review also covers how particle morphology influences drug properties like dissolution rate, bioavailability, powder flow, compressibility, content uniformity, and aerodynamic behavior. Both top-down methods, such as milling and homogenization, and bottom-up methods, such as crystallization and spray drying, are discussed within the Quality by Design (QbD) framework. Regulatory guidelines from the International Council for Harmonization (ICH) and pharmacopeial standards are included. The article examines the role of particle shape in drug delivery for oral, pulmonary, and parenteral routes. Although there have been many advances, challenges remain in achieving reliable three-dimensional characterization, scaling up engineering methods, and creating standardized shape descriptors. This review aims to serve as a useful resource for scientists, formulators, and regulatory professionals seeking to leverage particle morphology to improve drug quality and performance.

In summary, research shows that particle morphology is an important material attribute in pharmaceutical development. It needs careful, risk-based characterization, clear, science-based specifications, and integrated control strategies throughout the product's lifecycle.

Keywords

Particle Morphology, Particle Size Distribution (PSD), Crystal Engineering, Pharmaceutical Characterization, Scanning Electron Microscopy (SEM), Dissolution Rate, Bioavailability, Quality by Design (QbD), Critical Quality Attribute (CQA), Critical Material Attribute (CMA), Drug Delivery, Powder Flow, ICH Guidelines

1. Introduction

The pharmaceutical industry must carefully control the properties of active pharmaceutical ingredients (APIs) and excipients to make sure drug products are consistent, safe, and effective. Particle morphology—including size, shape, surface texture, porosity, and internal microstructure—should be considered a potential CMA only when experimental evidence links its variability to CQAs for a specific formulation, process, dosage form, and route. In oral solids, crystal habit and shape can affect flow, compression, sticking, dissolution, and tablet performance outcomes [1]–[5]. For inhalation products, particle size, surface roughness, corrugation, and morphology directly influence aerosol dispersion, the fine-particle fraction, and aerodynamic performance, indicating that morphology is strongly route- and product-dependent [6]–[8]. Particle morphology should not be critical, but should be assessed using a product-specific risk-based evaluation supported by experimental links to CQAs, aligned with QbD and quality risk management per ICH Q8(R2) and Q9(R1) [9] [10]. Its clinical importance is underscored by the Biopharmaceutics Classification System (BCS), particularly for BCS Class II oral drugs, in which low solubility and slow dissolution limit bioavailability. For example, drugs such as piroxicam or griseofulvin are absorbed more effectively when micronized or nanosized, and these smaller forms greatly improve bioavailability compared to larger particles [11] [12]. These cases show that controlling particle morphology can directly affect therapeutic outcomes. Over the past 20 years, the role of particle morphology in pharmaceutical science has grown, supported by improved analytical tools, a deeper understanding of how structure affects properties, and increased regulatory focus on Quality by Design (QbD) principles [9].

Particle size directly affects how drug formulations adapt, remain stable, and are absorbed in the body [13]. Smaller particles have a greater surface area, which helps drugs dissolve faster and interact more effectively with cell membranes. The Noyes–Whitney equation shows that dissolution rate depends on surface area, highlighting the important connection between particle size and drug perfor-

mance [14]. Besides size, particle shape also influences powder flow, compaction, and aerodynamic properties. These factors are important for the manufacture and use of different dosage forms [15] [16].

The importance of particle morphology is further highlighted by the Biopharmaceutics Classification System (BCS), which estimates that 70% - 90% of drugs in development exhibit low bioavailability due to poor aqueous solubility [17]. For BCS Class II compounds (low solubility, high permeability), particle size reduction is a primary strategy to improve oral absorption [13]. Crystal engineering offers complementary approaches through manipulation of crystal habit, selection of polymorphic forms, and co-crystal formation [18].

The ICH Q6A guideline explicitly recommends particle-size testing for new drug substances intended for use in solid or suspension drug products, where particle size can significantly affect dissolution rates, bioavailability, and/or stability [19]. Decision trees in Q6A provide systematic guidance on when to establish particle size specifications. Furthermore, the ICH Q8(R2) Pharmaceutical Development guideline encourages a science-based approach to understanding how particle attributes affect drug product critical quality attributes [9].

Particle morphology is considered a critical material attribute (CMA) when changes in features such as size, shape, surface texture, porosity, or crystallinity clearly affect one or more critical quality attributes (CQAs) of the final drug product, as supported by scientific evidence. Whether particle morphology is classified as a CMA depends on the dosage form and the route of administration [20]. In pharmaceutical development, this connection is especially crucial when morphology influences dissolution rate, bioavailability, powder flow, compressibility, uniformity, stability, or aerodynamic performance. Within a Quality by Design (QbD) framework, labeling morphology as a CMA depends not only on its measurability but also on the strength of the scientific link between the material attribute and relevant product performance. Thus, particle morphology should be seen not just as a descriptive physical property but also as a potentially critical upstream factor affecting downstream product quality, processability, and control-strategy design.

This review addresses fundamental concepts of particle morphology in the pharmaceutical industry, including advanced measurement methods, the influence of morphology on drug quality, engineering strategies, regulatory considerations, and emerging trends. It is intended to serve as a clear, evidence-based guide for scientists and regulatory professionals applying particle morphology in drug development. Practical recommendations are provided for resolving common formulation and processing challenges, selecting suitable characterization techniques, and achieving regulatory compliance. Application of these insights can improve product quality, enhance process consistency, and align with evolving regulatory requirements.

To support compliance efforts, we have included a summary checklist of key regulatory checkpoints for particle morphology below. This list helps identify ma-

for decision criteria and documentation requirements for regulatory submissions:

2. Regulatory Checklist for Particle Morphology

- Determine the need for particle size and morphology control based on drug product type and route of administration (solid oral, inhaler, injectable, etc.).
- Consult ICH Q6A guidance and decision trees to assess whether particle size testing and specifications are required for the drug substance or product.
- Identify critical quality attributes (CQAs) where particle morphology directly impacts dissolution, bioavailability, content uniformity, flow, or stability.
- Select validated, pharmacopeia-accepted methods for particle characterization (e.g., microscopy, laser diffraction) where appropriate.
- Establish justified and scientifically supported specifications for particle size and, if required, shape descriptors.
- Document method validation, including accuracy, precision, and specificity, in accordance with ICH Q2.
- Evaluate control strategies for particle morphology using Quality by Design (QbD) or risk-based approaches as encouraged by ICH Q8(R2) and Q9.
- Prepare supporting data and rationale for regulatory dossiers, ensuring traceability from method selection to specification setting.

Adhering to this checklist facilitates the development of regulatory strategies and ensures comprehensive documentation of particle morphology throughout the drug lifecycle.

3. Particle Morphology as a Critical Material Attribute

In pharmaceutical development, a material attribute becomes critical—and is designated a Critical Material Attribute (CMA) only when its variability can be demonstrated, through risk assessment and experimental evidence, to significantly impact one or more Critical Quality Attributes (CQAs) of the final product [9] [10]. This determination is not universal: it is product-specific, route-dependent, and must be established through a structured, science-based evaluation rather than assumed by default. Particle morphology fits this definition in specific formulation and process contexts where a clear mechanistic or empirical link between morphological variability and product CQAs has been established, because it can influence both product performance and manufacturability.

For example, particle size directly affects surface area and dissolution behavior; particle shape and surface roughness influence powder flow, die filling, blending, and content uniformity; and crystallinity or surface energetics may affect physical stability, wettability, and downstream process consistency. However, these relationships are not inherently critical in all cases—they become critical only when their variability is shown to meaningfully impact the relevant CQAs for the specific dosage form and route of administration under development. The importance of morphology is therefore product-specific and route-dependent rather than universal.

In immediate-release oral products containing poorly soluble APIs, particle size and surface area may be designated critical because of their established impact on dissolution and bioavailability—a relationship that must be confirmed through formulation studies, dissolution testing, and, where applicable, in vivo or in vitro–in vivo correlation (IVIVC) data. In inhalation products, particle size, density, and shape factor may be critical because they govern aerodynamic deposition and therapeutic lung dose—a link that should be supported by aerodynamic particle size distribution (APSD) testing using impaction methods (e.g., ACI, NGI) per pharmacopeial requirements. In suspensions or injectable systems, particle size distribution, morphology, and tendency to aggregate may influence syringeability, redispersibility, and patient safety—but these relationships must be demonstrated, not assumed, and assessed in the context of the specific formulation, container-closure system, and patient population.

For this reason, assessing particle morphology should be an integral part of risk-based pharmaceutical development within the QbD framework. Early-stage studies should determine which morphological descriptors are relevant for the intended dosage form, establish their connection to CQAs through experimental studies or mechanistic understanding, and assess whether routine monitoring or formal specification setting is necessary. Critically, if no meaningful relationship between morphological variability and CQAs can be established at the relevant scale and operating ranges, then particle morphology need not be classified as a CMA, and simplified controls or reporting-only approaches may be justified. This approach aligns with QbD principles by linking material understanding to process design, analytical control, and lifecycle management.

When such a risk-assessed, evidence-supported relationship is established, particle morphology should be managed not just as a characterization endpoint but as a CMA that guides formulation strategy, process robustness, and justification of regulatory compliance. The designation should be revisited throughout the product lifecycle as new knowledge accumulates, consistent with ICH Q10 lifecycle management principles [21].

4. Fundamental Concepts of Particle Morphology

4.1. Definition and Scope

Particle morphology refers to the external form, internal structure, and surface characteristics of individual particles within a pharmaceutical powder [22]–[24]. It encompasses multiple dimensions: particle size (expressed as equivalent circular diameter, Feret diameter, or Martin diameter), particle shape (described by parameters such as aspect ratio, circularity, convexity, and elongation), surface texture (roughness, porosity), and crystallographic structure (polymorphic form, degree of crystallinity) [25]. For pharmaceutical applications, the term “particle morphology” is generally used in a broader context than simple particle size, acknowledging that shape and surface properties exert independent and often syn-

ergistic effects on material behavior [26]. The various particle morphologies commonly encountered in pharmaceutical powders are depicted in **Figure 1**.

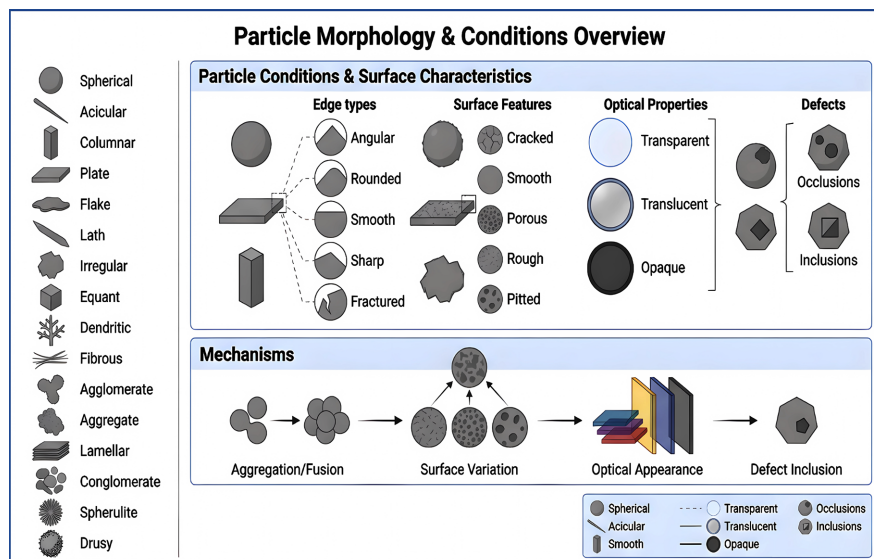


Figure 1. Common particle morphologies encountered in pharmaceutical powders. Each morphology exhibits distinct physicochemical and processing behavior.

4.2. Particle Size Parameters

For spherical particles, size is uniquely defined by diameter. However, pharmaceutical particles are rarely spherical, necessitating the use of equivalent diameter concepts [27]. Common size descriptors include: the equivalent volume diameter (d_v), the equivalent surface area diameter (d_s), the equivalent projected area diameter (EQPC), and Feret diameters (maximum and minimum distances between parallel tangent lines) [3]. The choice of size descriptor can significantly affect reported particle size distributions, as the same particle may yield different equivalent diameters depending on the measurement principle employed [28].

Particle size distributions (PSDs) are commonly expressed using percentile values (d_{10} , d_{50} [median], and d_{90}), along with span values [$(d_{90} - d_{10})/d_{50}$] to characterize distribution width [29]. The polydispersity index (PDI), particularly used for nanoparticle systems, provides a dimensionless measure of the breadth of the size distribution, with values below 0.2 indicating monodisperse systems [30].

4.3. Particle Shape Descriptors

Particle shape profoundly influences powder behavior, yet remains more challenging to characterize than size. Standardized shape descriptors have been developed to enable quantitative comparison [3] [31].

The aspect ratio $\left(AR = \frac{\text{Length}}{\text{Width}} \right)$ is defined as the ratio of the maximum Feret diameter to the minimum Feret diameter, providing a measure of particle elonga-

tion [3]. Values approaching 1.0 indicate equant (spherical/cubic) shapes, while higher values indicate increasing elongation. For pharmaceutical pellets, an upper limit of 1.1 on the aspect ratio has been recommended to ensure acceptable sphericity [31]. Circularity ($C = \frac{4\pi A}{P^2}$, where A is the projected area, and P is the perimeter) measures the deviation from a perfect circle, with $C = 1.0$ for a perfect sphere [3] [32]-[34]. Convexity ($C_x = \frac{A}{A_{hull}}$, Where A is the real projected area of the particle and total projected area of its convex hull) describes the ratio of particle area to convex hull area, indicating the presence of concavities. Elongation ($E = 1 - \text{Width/Length}$) quantifies the degree of stretching from a circular form [35]-[37]. **Figure 2** illustrates particle shape descriptors, including aspect ratio, circularity, convexity, and elongation.

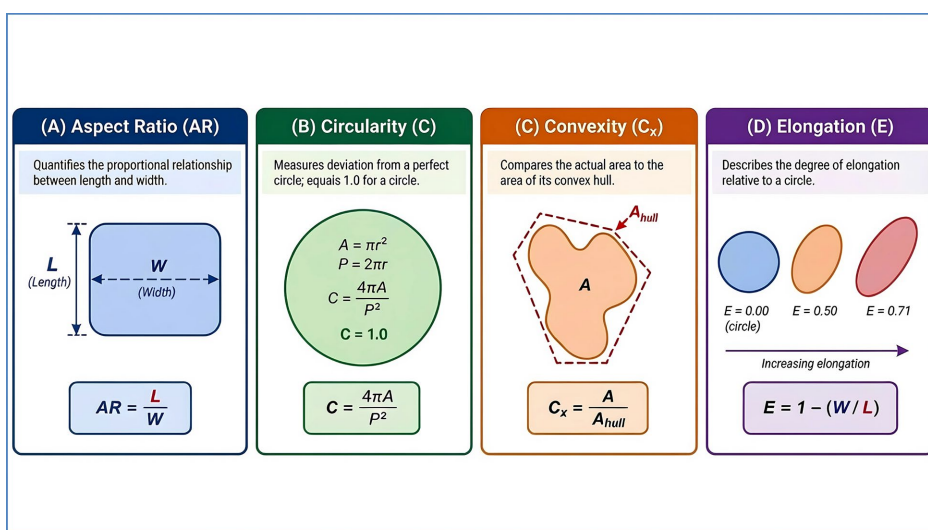


Figure 2. Key particle shape descriptors used in pharmaceutical characterization.

5. Characterization Techniques for Particle Morphology

Multiple analytical techniques are available for assessing particle morphology in pharmaceuticals, each offering distinct advantages and limitations regarding resolution, speed, sample requirements, and information output [31] [35]-[37]. Selection of an appropriate method depends on the specific features to be measured, the relevant particle size range, and the intended application of the results. Key considerations include regulatory acceptance, required level of detail, sample throughput, and the need for quantitative versus qualitative data. Regulatory guidelines such as ICH Q6A and the United States Pharmacopeia (USP) provide decision trees to guide the selection of suitable techniques, particularly for specification setting. A comparative overview of the main particle characterization techniques utilized in pharmaceutical development is provided in **Table 1**.

The relative positioning of major particle characterization techniques based on information content, resolution, and throughput is shown in **Figure 3**.

Table 1. Comprehensive comparison of particle characterization techniques used in pharmaceutical development [1] [38]-[41].

Technique	Size Range	Shape Info	Resolution	Key Advantages	Key Limitations
Optical Microscopy	1 μm - 1 mm	Yes	$\sim 0.5 \mu\text{m}$	Direct visualization; low cost; polarized light capability	Limited resolution; time-consuming; small sample size
SEM	10 nm - 1 mm	Yes	1 - 10 nm	High resolution; 3D surface detail; EDX capability	Vacuum required; conductive coating; cost
TEM	0.1 - 100 nm	Yes	$< 0.2 \text{ nm}$	Atomic resolution; crystal structure; gold standard	Complex sample prep; small field; expensive
AFM	1 nm - 100 μm	Z-axis	Sub-nm (Z)	No vacuum; ambient conditions; surface roughness	Slow scanning; tip artifacts; limited lateral resolution
Laser Diffraction	0.01 - 3500 μm	No	N/A	Rapid; high throughput; wide range; wet/dry	No shape info; assumes spherical; refractive index needed
DLS	0.3 nm - 10 μm	No	N/A	Fast; non-invasive; low sample volume; high sensitivity	Intensity-weighted; polydisperse limitations
Image Analysis	0.5 μm - 10 mm	Yes	$\sim 1 \mu\text{m}$	Automated; shape + size; high particle counts	Sample dispersion; calibration needed; 2D projection only
XRPD	Bulk	Indirect	N/A	Polymorph ID; crystallinity; non-destructive	Bulk measurement; no individual particle data
Raman Microscopy	$> 1 \mu\text{m}$	Yes	$\sim 1 \mu\text{m}$	Chemical + physical ID; non-destructive; in-situ capability	Fluorescence interference; slow mapping

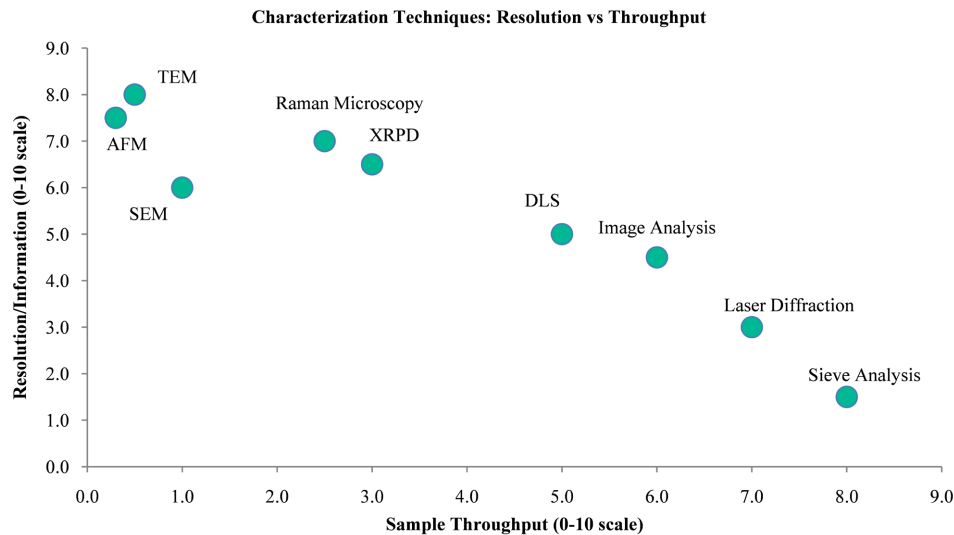


Figure 3. Qualitative comparison of particle characterization techniques plotted by information content/resolution versus sample throughput. Techniques in the upper-left quadrant (SEM, TEM, AFM) offer high resolution but lower throughput, while those in the lower-right (sieve analysis, laser diffraction) provide rapid bulk measurements with limited morphological detail. Adapted from Hickey *et al.* [1] and Preis *et al.* [41].

5.1. Microscopy-Based Techniques

5.1.1. Optical Microscopy

Optical microscopy remains a fundamental tool for pharmaceutical particle characterization, offering direct visualization of particle size, shape, and surface fea-

tures at magnifications up to $\sim 1000\times$ [42]. Polarized light microscopy enables the identification of crystalline particles by their birefringence properties, providing a simple method for distinguishing polymorphic forms [43]. The ICH Q6A guideline and pharmacopeial methods (USP <776>, Ph. Eur. 2.9.37) recognize optical microscopy as a primary method for particle size determination [18] [44]. However, the technique is limited by its optical resolution ($\sim 0.5\ \mu\text{m}$) and the relatively small number of particles that can be examined in practice.

5.1.2. Scanning Electron Microscopy (SEM)

SEM provides high-resolution images of particle surfaces at magnifications from $\sim 20\times$ to $>300,000\times$, revealing detailed morphological features including surface roughness, crystal faces, and agglomeration patterns [38] [45]. The technique is particularly valuable for examining particles in the 10 nm to 1 mm range and is considered essential for comprehensive morphological characterization of pharmaceutical powders [46]. Energy-dispersive X-ray spectroscopy (EDX) coupled with SEM enables simultaneous analysis of chemical composition [47]. SEM has been widely used to characterize API crystal habits, assess milling effects, evaluate coating uniformity in microparticles, and verify nanoparticle morphology [48] [49].

5.1.3. Transmission Electron Microscopy (TEM)

TEM is considered the “gold standard” technique for nanoparticle sizing and morphology characterization [38]. Operating at accelerating voltages of 80 - 300 kV, TEM can achieve atomic-scale resolution ($<0.2\ \text{nm}$), providing detailed information on particle size, shape, internal structure, and crystallographic orientation [50]. For pharmaceutical nanoparticles, TEM images should be accompanied by size distribution histograms generated from at least 200 particles for average size determinations and >3000 particles for distribution width measurements [51]. High-resolution TEM (HR-TEM) enables the observation of crystal lattice fringes, confirming crystalline structures in nanoparticulate drug formulations [52].

5.1.4. Atomic Force Microscopy (AFM)

AFM provides three-dimensional surface topography at sub-nanometer vertical resolution by scanning a sharp probe across the particle surface [53]. Unlike electron microscopy, AFM operates under ambient conditions without requiring vacuum or conductive coating, making it particularly suitable for moisture-sensitive pharmaceutical materials [54]. The technique excels at measuring surface roughness, adhesion forces, and mechanical properties at the single-particle level. In pharmaceutical applications, AFM has been used to characterize API crystal-face properties, assess surface-energy heterogeneity, and study particle-particle interactions relevant to powder flow and agglomeration [55] [56].

5.2. Ensemble and Bulk Characterization Techniques

5.2.1. Laser Diffraction

Laser diffraction is the most widely used technique for particle size analysis in the

pharmaceutical industry, covering a size range from ~0.01 to 3500 μm [1] [57] [58]. The technique measures the angular distribution of scattered light from a particle ensemble and uses Mie theory or the Fraunhofer approximation to calculate a volume-weighted particle size distribution. While offering excellent throughput and reproducibility, laser diffraction inherently assumes spherical-particle equivalence, providing no direct information about particle shape [59]. Pharmacopeial methods (USP <429>, Ph.Eur. 2.9.31) provide detailed guidance on method development and validation for laser diffraction measurements [60].

5.2.2. Dynamic Light Scattering (DLS)

DLS measures the hydrodynamic diameter of particles in suspension by analyzing the autocorrelation function of fluctuations in scattered light caused by Brownian motion [61]. The technique is particularly valuable for characterizing nanoparticles in the 0.3 nm to 10 μm range and is routinely used for quality control of pharmaceutical nanosuspensions, liposomes, and protein aggregates [62]. DLS provides the z-average diameter (intensity-weighted mean) and polydispersity index (PDI). However, the technique is sensitive to large particles or aggregates and does not provide shape information [63].

5.2.3. X-Ray Powder Diffraction (XRPD)

XRPD is a key solid-state analytical technique for identifying crystalline forms and assessing crystalline/amorphous phase composition in pharmaceutical solids [64]. While XRPD is not a direct particle-sizing method, it provides critical information on polymorphic form, crystallinity, and crystal structure, which may be associated with crystal habit and particle morphology. Preferred orientation effects in XRPD patterns can arise from anisotropic particle or crystal shapes, such as needle-like or plate-like morphologies, and may indicate non-random orientation of crystallites during sample preparation [65] [66]. The Scherrer equation enables estimation of crystallite size from diffraction peak broadening, linking bulk diffraction measurements to nanoscale crystalline-domain dimensions rather than true particle size [67] [68].

5.3. Advanced and Hybrid Techniques

Recent advances have led to analytical tools that combine physical and chemical characterization in a single system. For example, morphologically directed Raman spectroscopy (MDRS) combines automated particle imaging with Raman microspectroscopy, enabling measurement of particle size and shape, along with Raman-based chemical identification of individual particles [69] [70]. This approach has been applied to characterize API particle-size distribution in nasal suspension drug products and to support pharmaceutical product characterization. In particulate powder systems, combined automated image analysis and Raman spectroscopy can also classify particles at the individual-particle level based on both morphology and solid-form or chemical information.

Raman chemical imaging can chemically distinguish different ingredients in

finished pharmaceutical products while simultaneously providing spatial information on particle distribution, size, and shape. For example, fiber-array-based Raman hyperspectral imaging has been used to monitor the size, shape, and distribution of particles of acetylsalicylic acid, acetaminophen, and caffeine in commercial analgesic tablets at a high spatial resolution of approximately 1 - 1.25 μm [71]. Raman chemical imaging has also been validated for estimating micrometer-scale API particle size in tablets using traceable polystyrene microsphere standards [41].

Process analytical technology (PAT) tools, such as focused beam reflectance measurement (FBRM) and particle vision measurement/in situ video microscopy (PVM), enable real-time or in-line monitoring of particle size, size distribution, and particle-shape-related attributes during pharmaceutical crystallization and particle-processing operations [72]-[74].

Deep learning image analysis is now used to monitor crystal type, size, and shape during crystallization [75]. However, widespread adoption of these advanced methods can be difficult due to high costs, the challenge of integrating new technology into existing processes, the need for expert staff, and a lack of clear regulatory guidance. Regulatory acceptance of advanced and AI-driven techniques is evolving. While traditional PAT tools such as laser diffraction, FBRM, and certain forms of spectroscopy have been recognized by regulatory authorities within Quality by Design frameworks, newer technologies like automated image analysis and deep learning models are still considered emerging. Current regulatory positions emphasize the need for robust method validation, clear demonstration of data integrity, and scientific justification when proposing novel techniques in regulatory filings. Some agencies have published draft guidance or concept papers acknowledging the potential of AI and advanced analytics, but formal, harmonized guidance is limited. Sponsors considering adopting these technologies should engage regulators early, document performance characteristics, and be prepared to address questions about model transparency and reproducibility. As regulatory experience grows, more explicit acceptance criteria and standards are expected to emerge.

A structured, phased approach supports the effective adoption of advanced particle morphology techniques within organizations. Initiating pilot studies in development laboratories can demonstrate the method's benefits and assess its suitability. Cross-functional collaboration is essential for evaluating the compatibility of new technologies with existing workflows and determining optimal implementation points. For instance, limited-scale trials of advanced image analysis or parallel testing of morphologically directed Raman spectroscopy (MDRS) alongside current release methods can mitigate risk and facilitate staff training. Support and training from equipment suppliers further enhance implementation. Gradual, systematic deployment across products or sites enables continuous improvement and efficient resource allocation. Comprehensive documentation of feasibility assessments, performance metrics, and regulatory feedback underpins sustainable

adoption. These strategies enable organizations to realize the advantages of advanced particle morphology analysis while minimizing operational disruptions.

When preparing regulatory submissions that include advanced particle morphology techniques, some practical steps can help ensure strong documentation and smooth interactions with agencies. Clearly document validation experiments for each measurement method, covering specificity, accuracy, precision, range, and robustness. Give detailed descriptions of calibration procedures, standard operating protocols, sample preparation, and instrument qualification. Include examples of typical results, system suitability criteria, and representative images if needed. Explain how the data are used to set specifications or support control strategies for critical quality attributes. It also helps to prepare answers in advance for possible agency questions, such as why certain characterization techniques were chosen or how data variability is handled. Keep well-organized records of all method changes, references to regulatory guidelines, and direct communications with agencies about method acceptance. This level of detail can make the review process smoother and help gain regulatory approval for new analytical methods.

6. Impact of Particle Morphology on Drug Product Quality

Particle morphology exerts far-reaching effects on drug product quality, influencing dissolution, bioavailability, manufacturability, and stability. The relative impact of particle size versus particle shape can vary across different particle types. For example, in the case of poorly soluble BCS Class II drugs, reduction in particle size has been reported to increase dissolution rates by up to tenfold, whereas changes in particle shape may result in a two- to threefold difference in dissolution rate under otherwise identical conditions. Conversely, powder flowability is often more sensitive to particle shape: studies have shown that sphericity can improve flow indices by over 50%, even when particle size distribution remains constant, while the same degree of flow improvement may require reducing particle size by an order of magnitude. One comparative study found that, for direct-compression blends, particle shape was the dominant factor in achieving uniform die filling, whereas particle size was the predominant driver of rapid dissolution. Such quantitative comparisons underscore that the magnitude of size or shape effects depends on the specific quality attribute and product application (Podczec & Newton, 1999; Sun *et al.*, 2022). **Figure 4** summarizes the broad influence of particle morphology on the quality attributes of drug products.

The following sections examine the impact of particle morphology on drug product quality across multiple delivery systems. The magnitude and relevance of morphological effects vary substantially depending on the formulation type and route of administration. Consequently, the practical recommendations in each sub-section should be interpreted within their specific context.

Sections 6.1 and 6.2 address dissolution rate, bioavailability, and nanoparticle geometry, focusing on oral dosage forms and colloidal drug delivery systems such as nanosuspensions, nanocrystals, and lipid-based carriers. Sections 6.3 and 6.4

analyze conventional powder systems for oral solid dosage forms, specifically tablets and capsules, in which particle shape and size distribution are critical to processability. Section 6.5 Evaluators inhaled drug products, where the aerodynamic diameter and dynamic shape factor determine deposition within the respiratory tract. For parenteral suspensions, additional performance factors such as syringeability, sterility assurance, and redispersibility are relevant but are not comprehensively discussed in this review.

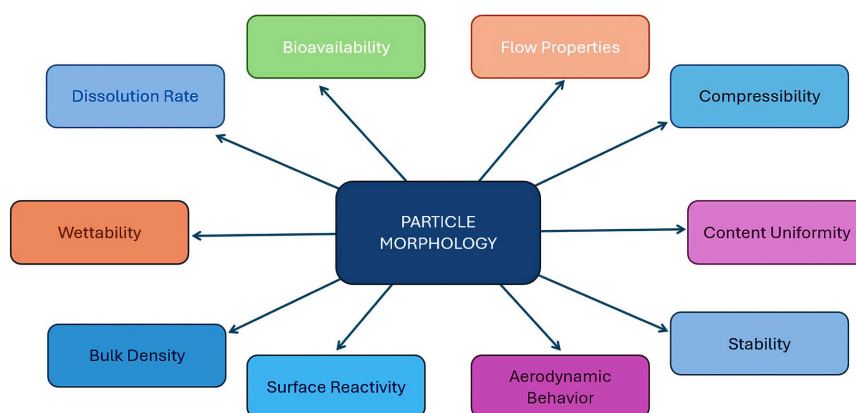


Figure 4. Schematic representation of the multifaceted impact of particle morphology on drug product quality attributes. Particle morphology directly or indirectly affects dissolution, bioavailability, flow properties, compressibility, content uniformity, stability, aerodynamic behavior, surface reactivity, bulk density, and wettability.

6.1. Dissolution Rate and Bioavailability

The relationship between particle size and dissolution rate is described by the Noyes–Whitney equation:

$$\frac{dM}{dt} = \frac{DA}{h} \times (C_s - C_t),$$

where M is the mass dissolved, D is the diffusion coefficient, A is the surface area, C_s is the saturation solubility, C_t is the concentration at time t , and h is the diffusion layer thickness [14]. Reducing particle size increases surface area (A), directly enhancing dissolution rate. For BCS Class II drugs, this relationship is of paramount importance [13] [17]. **Figure 5** shows simulated dissolution profiles demonstrating how decreasing particle size accelerates drug release, consistent with the Noyes-Whitney relationship.

Reduction in particle size consistently enhances dissolution performance and systemic exposure, particularly for poorly soluble drugs. Investigations involving aprepitant/MK-0869, rosuvastatin calcium, and esomeprazole formulations demonstrate that smaller particle size increases dissolution rate and pharmacokinetic exposure, as evidenced by higher C_{max} and/or AUC values [76]–[78]. Therefore, particle size should be considered a critical material attribute when experimental data establish its direct impact on dissolution, absorption, or bioavailability for a specific drug product.

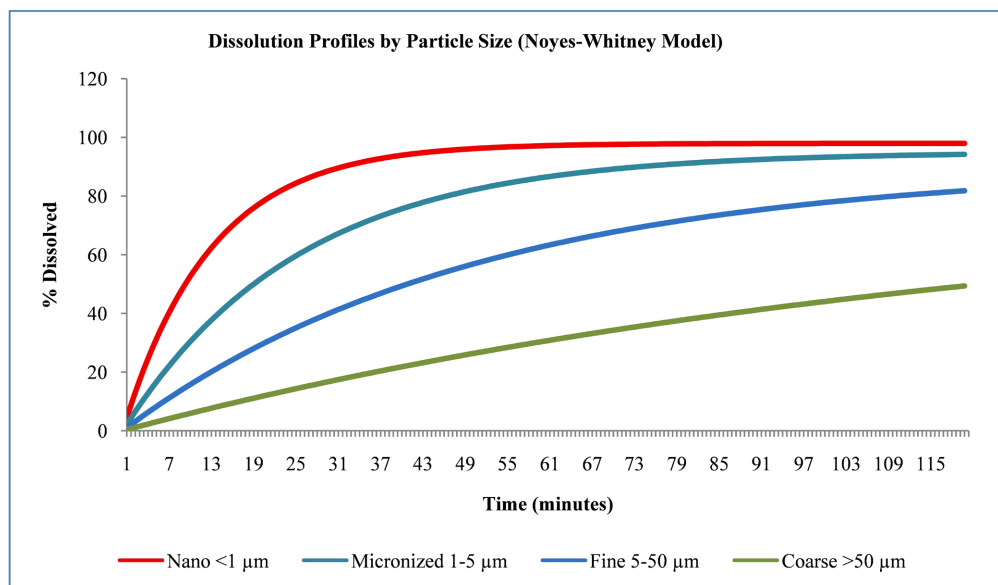


Figure 5. Simulated dissolution profiles showing the effect of particle size on drug release rate based on the Noyes–Whitney equation. Nanoparticles (<1 μm) exhibit the fastest dissolution, followed by micronized (1 - 5 μm), fine (5 - 50 μm), and coarse (>50 μm) particles. Data patterns are consistent with published findings [14] [79].

Beyond size, particle shape influences dissolution through differential exposure of surface area. Rod-shaped particles of dipyridamole exhibited different dissolution rates compared to prismatic or tabular habits of the same compound [18]. Crystal morphology engineering has been shown to modify the exposed crystal faces, altering surface energy and wettability and, consequently, affecting dissolution kinetics [80].

6.2. Nanoparticle Geometry and Cellular Uptake

Nanoparticle shape has emerged as a significant design parameter for drug delivery systems [81]. Studies by Banerjee *et al.* demonstrated that rod-shaped nanoparticles exhibit significantly higher cellular uptake and trans-epithelial transport in intestinal cell models than spherical particles of similar volume [82]. Nanoparticles smaller than 200 nm can traverse the intestinal mucus bilayer (pore size 10 - 200 nm) and be absorbed via endocytic, transcellular, and paracellular pathways [83]–[86]. **Table 2** summarizes representative examples of how particle size affects dissolution and bioavailability.

6.3. Powder Flow and Processability

Particle morphology is a primary determinant of powder flow behavior, which directly impacts manufacturing operations, including blending, die filling, and tablet compression [96] [97]. Spherical particles generally exhibit superior flow properties compared to irregular or acicular particles due to reduced inter-particle mechanical interlocking [26]. The Carr Index and Hausner Ratio serve as empirical indicators of flow behavior but are influenced by both size and shape [98].

Different particle engineering routes can produce micron-sized API with similar size specifications but dramatically different bulk powder properties due to variations in particle shape, size distribution, and surface energetics [99] [100].

Table 2. Summary of particle size effects on bioavailability and dissolution for selected pharmaceutical systems.

Drug/System	Particle Size	Key Finding	References
Aprepitant/ MK-0869	0.12 μm vs. 5.5 μm	Nanosized formulation gave ~4 $\times$ higher C_{max} in dogs.	[76]
Rosuvastatin Calcium	Nanoparticles vs. untreated/bulk drug	Nanoparticles gave ~2 $\times$ higher C_{max} and 1.5 $\times$ higher AUC	[77]
Esomeprazole multiparticulates	X50: 494 μm vs. 648 μm	Smaller particles dissolved faster; T50 dropped from ~61 to ~38 min.	[78]
Candesartan cilexetil	Nanoparticles/nanosuspension vs. commercial, bulk, or coarse drug	Nanoparticulate form improved solubility, dissolution, and bioavailability	[87]-[89]
Piroxicam	Micronized API vs. ethanolamine salt vs. succinic-acid co-crystal	Particle/solid form engineering improved dissolution of piroxicam	[90]-[92]
Quercetin	Nanocrystals, approximately 276 - 290 nm	Nanocrystals increased solubility and dissolution vs coarse quercetin	[93] [94]
Polymeric model NPs	50 - 1000 nm; sphere vs. rod vs. disc	Rod shaped particles had higher uptake and transepithelial transport	[92]
PLGA NPs (model)	~142 nm lopinavir-loaded PLGA nanoparticles	PLGA nanoparticles enhanced Caco 2 uptake, transport, and oral exposure.	[95]

To assist formulators in diagnosing and resolving powder-flow problems related to particle morphology, the following three-step checklist is recommended:

- **Step 1:** Assess particle shape (Aspect Ratio ≥ 1.5 or Circularity < 0.7)

Acicular (needle-like) or elongated particles mechanically interlock during flow, increasing the Carr Index above 25% and the Hausner Ratio above 1.35, indicating poor-to-very-poor flow (Carr, 1965). In blending and die-filling operations, this results in non-uniform die fill and weight variability in tablet presses. **Corrective action:** Consider milling to reduce the aspect ratio, or switch to a bottom-up particle-engineering technique (e.g., spray drying or controlled crystallization) that produces more equant (spherical) habits.

- **Step 2:** Evaluate surface roughness and fines content ($d_{10} < 10 \mu\text{m}$)

High surface roughness and an elevated proportion of fine particles ($< 10 \mu\text{m}$) increase inter-particle adhesive forces, leading to powder bridging, rat-holing in hoppers, and erratic feed rates. Micromeritics (2024) demonstrated that differences in particle shape were the dominant factor in Basic flowability energy (BFE) under low-stress blending conditions, while particle size dominated under con-

solidation (high-stress tablet pressing). **Corrective action:** Granulation, dry coating with colloidal silica (0.1 - 0.5% w/w), or blending with a spherical carrier can effectively reduce cohesion without altering particle size distribution.

- **Step 3:** Confirm flow by pharmacopoeial methods before specification-setting. Measure the Angle of Repose ($<25^\circ$ = excellent flow; $26^\circ - 30^\circ$ = good; $>40^\circ$ = very poor), Carr Index, and Hausner Ratio. Where possible, supplement with a powder rheometer (BFE/specific energy ratio) to decouple the contributions of size versus shape to the overall flow behavior. Document which morphological parameter is the primary driver to enable targeted corrective action.

6.4. Compressibility and Tablet Properties

Crystal morphology engineering has been shown to be an effective tool for tailoring tablet performance [80]. Mirza *et al.* showed that modifying the crystal habit of erythromycin A dihydrate by adding hydroxypropyl cellulose during crystallization resulted in morphologies with significantly different compaction behavior [80]. Needle-shaped crystals tend to exhibit preferential orientation under compression, potentially leading to anisotropic tablet structures [101].

6.5. Aerodynamic Behavior and Pulmonary Delivery

For inhaled drug delivery, particle morphology is arguably the most critical attribute determining therapeutic performance. The aerodynamic diameter, which depends on both geometric diameter and particle density, governs deposition in the respiratory tract [102]. Stokes' law predicts the settling velocity of particles in air, and deviations from spherical shape require the application of dynamic shape factors [103]. Engineered low-density particles, porous particles, and elongated particles have been developed to optimize the aerodynamic diameter-geometric size relationship [104].

Table 3 outlines key quality attributes that are influenced by particle morphology, including dissolution, bioavailability, powder flow, compressibility, content uniformity, and aerodynamic performance

7. Particle Engineering and Control Strategies

Control of particle morphology in pharmaceutical development requires more than selecting a particle-engineering technique; it requires an integrated strategy that links material attributes, analytical methods, process parameters, and product performance targets. A robust control strategy begins with identifying morphology-related risks, followed by selecting relevant descriptors such as $d_{10}/d_{50}/d_{90}$, span, aspect ratio, circularity, surface roughness, or crystallinity, depending on the dosage form and performance mechanism. These attributes should then be connected to the relevant CQAs through experimental studies and risk assessment. Once criticality is established, appropriate controls may include raw material acceptance criteria, in-process monitoring, endpoint definitions for milling or crystallization, process analytical technology (PAT) tools, and justified release

specifications. Thus, control strategies for particle morphology should be science-based, dosage-form specific, and aligned with the broader QbD framework.

Table 3. Impact of particle morphology on critical drug product quality attributes.

Quality Attribute	Morphological Factor	Effect	Significance
Dissolution rate	Particle size, surface area, shape	Inverse relationship with particle size	Critical for BCS Class II/IV
Bioavailability	Size, shape, surface chemistry	Enhanced with a smaller size and non-spherical shapes	Primary Efficacy driver
Powder flow	Shape, size distribution, surface roughness	Spherical > irregular; narrow PSD preferred	Manufacturing efficiency
Compressibility	Crystal habit, shape, porosity	Habit-dependent compaction behavior	Tablet quality
Content uniformity	Size, shape, surface energy	Better with matched API-excipient morphology	Dose precision
Aerodynamic behavior	Geometric size, density, shape factor	Governs respiratory tract deposition	Pulmonary drug delivery
Stability	Crystallinity, surface area, polymorphic form	Amorphous regions and high surface area may reduce stability	Shelf life

Particle engineering encompasses a range of techniques for producing particles with controlled size, shape, and surface properties tailored to specific pharmaceutical applications [79]. These methods are broadly classified into top-down (size reduction of bulk material) and bottom-up (controlled assembly from molecular or ionic precursors) approaches. **Figure 6** outlines the primary top-down and bottom-up particle-engineering approaches used in pharmaceutical manufacturing.

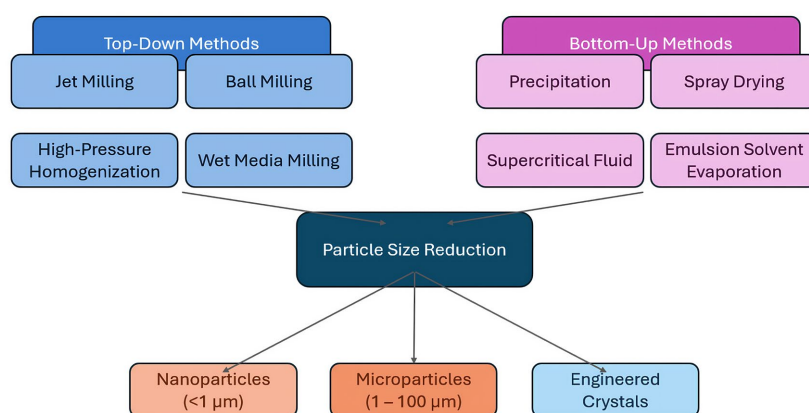


Figure 6. Classification of particle size reduction and engineering techniques in pharmaceutical manufacturing. Top-down methods apply mechanical energy to reduce bulk material, while bottom-up methods build particles from molecular precursors.

7.1. Top-Down Approaches

7.1.1. Mechanical Milling and Micronization

Jet milling, also known as air-jet or fluid-energy micronization, is a widely used

pharmaceutical particle-size reduction technique for producing micronized drug powders. Fluid-energy milling can reduce drug particles from approximately 20 - 100 μm to below 10 μm , while jet milling for inhalation products commonly produces particles in the 1 - 20 μm range, with typical API particle sizes around 2 - 5 μm depending on the product target and material properties [105]-[108]. Wet media milling with zirconium oxide beads has been successfully applied to produce nanosuspensions with particle sizes below 300 nm while maintaining crystalline integrity [94].

7.1.2. High-Pressure Homogenization

High-pressure homogenization subjects particle suspensions to extreme shear, cavitation, and impact forces at pressures of 100 - 2000 bar [109]. The technique is particularly effective for producing drug nanocrystals and nanosuspensions of poorly soluble APIs [110].

7.2. Bottom-Up Approaches

7.2.1. Controlled Crystallization

Crystallization is the most critical unit operation in API manufacturing, accounting for approximately 90% of API production [111]. Crystal habit modification through additive-mediated crystallization offers a powerful approach to tailoring particle morphology. For example, hydroxypropyl cellulose has been used to modify the crystal habit of erythromycin A dihydrate [80]. Sonocrystallization, employing ultrasonic energy to control nucleation and growth, produces smaller crystals with narrower size distributions [55].

7.2.2. Spray Drying

Spray drying converts drug-containing liquids into dried powdered forms with engineered morphologies [112]. Nano spray drying extends the accessible particle size range to the submicron and nanoscale. Spray drying is particularly effective for producing amorphous solid dispersions (ASDs) [113].

7.2.3. Supercritical Fluid Processing

Supercritical fluid techniques, particularly using supercritical CO_2 , offer an environmentally friendly approach to particle engineering [114]. The supercritical antisolvent (SAS) process, rapid expansion of supercritical solutions (RESS), and gas antisolvent (GAS) methods enable production of micro- and nanoparticles with controlled morphology and minimal residual solvent [114] [115].

7.2.4. Emulsion Solvent Evaporation

The emulsion solvent evaporation method is a widely utilized bottom-up particle engineering technique for producing biodegradable polymeric micro- and nanoparticles from preformed polymers such as PLGA and PLA [116]. In the single oil-in-water (O/W) emulsion variant, a hydrophobic drug and polymer are dissolved in a volatile organic solvent, then emulsified into an aqueous phase stabilized by polyvinyl alcohol (PVA). The solvent is subsequently removed by evapo-

ration, yielding smooth, spherical particles [117]. For hydrophilic drugs, the water-in-oil-in-water (W/O/W) double emulsion variant produces core-shell morphologies; however, encapsulation efficiency is generally lower due to drug partitioning into the external aqueous phase [118]. Particle size and morphology depend on homogenization energy, polymer concentration, surfactant concentration, and solvent evaporation rate [119]. A comparison of major particle engineering techniques and their corresponding pharmaceutical applications is presented in **Table 4**.

Table 4. Comparison of particle engineering techniques for pharmaceutical applications.

Technique	Typical Size Range	Particle Shape	Scalability	Key Applications
Jet Milling	1 - 10 μm	Irregular, angular	Excellent	Micronized APIs for oral/inhaled
Wet Media Milling	100 - 500 nm	Retained crystal habit	Good	Nanosuspensions; BCS Class II
High-Pressure Homogenization	100 - 800 nm	Irregular to spherical	Excellent	Nanocrystals; parenteral
Spray Drying	1 - 100 μm (nano: <1 μm)	Spherical, hollow	Excellent	ASDs; inhaled; encapsulation
Anti-solvent Crystallization	1 - 500 μm	Controlled habit	Good	Crystal engineering
Sonocrystallization	5 - 50 μm	Uniform crystals	Moderate	Narrow PSD; polymorph control
Supercritical Fluid (SAS)	0.1 - 100 μm	Spherical to needle	Moderate	Solvent-free; high purity
Emulsion Evaporation	1 - 50 μm	Spherical	Good	Microparticles; controlled release

7.3. Elements of a Control Strategy for Particle Morphology

A practical control strategy for particle morphology may be organized into five elements. First, the development program should identify which morphological features are likely to influence product quality for the intended route of administration and formulation platform. Second, fit-for-purpose analytical methods should be selected to quantify those features with sufficient sensitivity, robustness, and relevance. Third, acceptable ranges or specifications should be defined based on development data, process capability, and clinical or biopharmaceutical relevance. Fourth, manufacturing processes should be designed and monitored so that morphology remains within the intended design space; this may include control of crystallization conditions, milling energy, homogenization pressure, spray-drying parameters, or granulation conditions. Fifth, ongoing lifecycle management should assess whether morphology remains under control during scale-up, site transfer, and post-approval changes.

Depending on the product, control can be achieved through different combinations of material controls and process controls. For example, direct-compression products may place greater emphasis on particle shape and flow-related de-

scriptors, whereas poorly soluble immediate-release products may prioritize particle size distribution and surface area because these factors influence dissolution. In inhalation products, control strategies may need to extend beyond geometric particle size to include density, tendency to agglomerate, and aerodynamic behavior. This risk-based flexibility is important because the same morphological descriptor may be highly critical in one product type and only supportive in another.

8. Regulatory Framework and Pharmacopeial Standards

The regulatory framework governing particle morphology in pharmaceuticals spans international harmonized guidelines (ICH), regional pharmacopeias, and health authority expectations for quality-by-design submissions. The Biopharmaceutics Classification System (BCS) classifies drugs based on their aqueous solubility and intestinal permeability and is widely used to inform biowaivers and formulation strategies [ICH M9]. **Figure 7** illustrates the significance of particle morphology within the Biopharmaceutics Classification System.

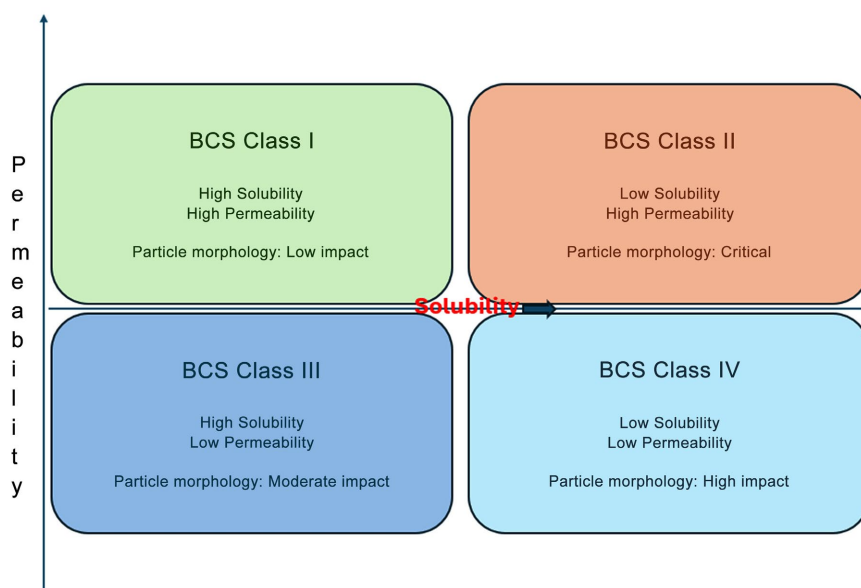


Figure 7. Biopharmaceutics Classification System (BCS) and the relevance of particle morphology to each class. Particle size reduction and morphology engineering are most critical for BCS Class II compounds. Adapted from ICH guidelines and Amidon *et al.* [17] [19].

8.1. ICH Guidelines

ICH Q6A provides the foundational guidance for particle size specifications [19]. Decision Tree #3 in Q6A systematically guides the assessment of whether particle-size testing should be included in drug-substance specifications. ICH Q8(R2) encourages a QbD approach to identifying and controlling material attributes that impact drug product quality [9]. ICH Q9 (Quality Risk Management) provides tools for assessing and managing risks associated with particle-related quality attributes [10]. ICH Q10 emphasizes ongoing monitoring of particle-related controls throughout the product lifecycle [21]. ICH Q12 enables post-approval

changes to particle specifications when supported by scientific understanding [120].

From a regulatory perspective, the control of particle morphology should be justified through a clear chain of evidence linking the selected morphological attribute to product CQAs and process performance. In practice, this means documenting why a given attribute is considered critical, how it is measured, what acceptance criteria are proposed, and how manufacturing controls maintain it within an acceptable range. When particle morphology is treated as a CMA, regulatory submissions are strengthened by demonstrating traceability from development studies through method selection, specification setting, process controls, and lifecycle monitoring. Such an approach is consistent with contemporary expectations for science- and risk-based pharmaceutical development.

8.2. Pharmacopeial Methods

Relevant regulatory guidelines and pharmacopeial standards for particle size and morphology are summarized in **Table 5**.

Table 5. Regulatory guidelines and pharmacopeial standards relevant to particle morphology.

Standard/ Guideline	Scope	Key Requirements	Particle Aspects
ICH Q6A	Specifications for new drug substances/products	Decision trees for particle size testing; acceptance criteria	Size distribution; polymorphism; morphology
ICH Q8(R2)	Pharmaceutical development	QbD approach; design space; CQA identification	CMA's including particle attributes
USP <429>	Light diffraction measurement	Method development; validation; reporting	Volume-weighted PSD; span
USP <776>	Optical microscopy	Particle size by microscopy	Size, shape, morphological ID
USP <786>	Subvisible particulate matter	Limits for injections; light obscuration	Count-based size limits
Ph.Eur. 2.9.31	Laser diffraction	Particle size analysis by laser light diffraction	Equivalent spherical diameter
Ph.Eur. 2.9.37	Optical microscopy	Particle size by image analysis	Size and shape parameters
Ph.Eur. 2.9.38	Analytical sieving	Sieving for particles > 75 µm	Mass-based PSD
JP 3.04	Particle size determination	Optical microscopy; analytical sieving	Morphology and size

9. Case Studies and Applications

9.1. Crystal Morphology Engineering of Erythromycin

Mirza *et al.* investigated the engineering of crystal morphology in erythromycin A dihydrate to tailor tableting performance [80]. Crystal habit modification was

achieved by adding hydroxypropyl cellulose (HPC) during crystallization from solution. The predicted BFDH morphology was compared with the observed morphologies, and molecular simulations were used to analyze the arrangements on the dominant crystal faces [(002), (011), and (101)]. The study demonstrated that additive-mediated crystallization can selectively modify crystal habit for direct compression tableting.

9.2. Morphologically Directed Analysis in Process Development

A notable case study demonstrated the power of combined image analysis and Raman spectroscopy for process troubleshooting. During the manufacture of a solid dosage form, the HPLC assay showed API content in tablets was occasionally lower than in the precompression blend. Morphologically directed Raman spectroscopy revealed that API particles exhibited a distinct spherical morphology, unlike excipients, thereby enabling process optimization to minimize API loss during equipment start-up [68] [69].

9.3. Piroxicam as a Case Study in Risk-Based Formulation Strategy Selection for Poorly Soluble Drugs

Piroxicam, a poorly soluble drug, has been investigated using multiple formulations and solid-state strategies, including particle-size control, salt formation, co-crystallization, and amorphous/polymeric solid dispersion. Particle-size and agglomeration studies showed that dissolution behavior of piroxicam powders and capsules can vary significantly even when the polymorphic form is unchanged, demonstrating that particle size, wetting, and agglomeration are important practical factors in dissolution performance [121]. Salt formation with ethanolamines has been reported to improve piroxicam bioavailability, while piroxicam co-crystals with carboxylic acid and phenolic conformers have been prepared and evaluated for solid-state properties, solubility, intrinsic dissolution rate, powder dissolution, and phase behavior [90]-[92]. PVP-based solid dispersions of piroxicam have also shown substantial dissolution enhancement, including solvent-prepared PVP K-30 dispersions and spray-dried or compressed-antisolvent piroxicam-PVP systems [122] [123]. Taken together, these studies indicate that formulation strategy selection should not assume that advanced crystal engineering is always superior; instead, development should begin with comparative screening of simpler approaches such as particle-size control and proceed to salt formation, co-crystallization, or amorphous solid dispersion only when needed based on dissolution performance, physical stability, manufacturability, scalability, analytical control, regulatory expectations, intellectual-property position, and commercial feasibility. FDA guidance also supports the need for appropriate specification setting for particle-size control and additional classification/characterization considerations for pharmaceutical co-crystals. Piroxicam has been reported to form a succinic acid co-crystal, including an acetonitrile-solvated piroxicam-succinic acid co-crystal containing both zwitterionic and non-ionized piroxicam molecules

[124].

9.4. Nanoparticle Shape and Intestinal Transport

Banerjee *et al.* systematically investigated the role of nanoparticle geometry in oral drug delivery using sphere-, rod-, and disc-shaped PLGA nanoparticles [82]. Using a triple co-culture model of intestinal cells (Caco-2/HT-29), the study demonstrated that rod-shaped nanoparticles exhibited significantly higher cellular uptake and transepithelial transport compared to spheres, regardless of the presence of active targeting moieties [82].

10. Emerging Trends and Future Perspectives

10.1. Artificial Intelligence and Machine Learning

Deep learning-based image analysis methods have been developed for real-time, in situ monitoring of crystal polymorphs, size, and shape during solution crystallization [75]. Machine vision, combined with deep learning, enables non-invasive online monitoring of granule particle morphology during fluidized-bed granulation [125]. Data-driven frameworks for predicting pharmaceutical particle size distributions using kernel mean embedding methods show promise for model predictive control [126].

10.2. Continuous Manufacturing and PAT Integration

Continuous manufacturing requires real-time monitoring and control of particle attributes [127]. PAT frameworks incorporating in-line laser diffraction, FBRM, and machine vision enable feedback control of particle size in continuous processes [128]. Model-based control strategies represent the convergence of QbD and PAT principles [72]-[74].

10.3. 3D Particle Characterization

Current characterization methods predominantly generate 2D projections of 3D particles. Advances in X-ray micro-computed tomography (μ CT), electron tomography, and confocal microscopy are enabling true three-dimensional characterization of pharmaceutical particles [129].

10.4. Personalized Medicine and On-Demand Manufacturing

Advances in 3D printing, microfluidics, and small-scale continuous processing are enabling on-demand manufacturing of personalized dosage forms with tailored particle attributes [130]. The development of compact, rapid-response analytical tools for particle characterization will be essential for enabling decentralized manufacturing models [131].

10.5. Limitations of the Current Evidence Base

While the evidence reviewed here supports the utility of particle morphology characterization in pharmaceutical development, several important limitations af-

fect the strength of the practical recommendations presented. First, morphology descriptors are not yet harmonized across laboratories and instrument platforms: aspect ratio, circularity, and convexity values obtained on one imaging system are often not directly comparable with those from another, limiting inter-study interpretation [ISO 9276-6:2008]. Second, the majority of characterization data in the published literature relies on 2D projected images—from optical microscopy, SEM, and automated image analysis—which cannot fully capture the three-dimensional geometry of irregular particles; this introduces systematic biases in shape parameter estimates, particularly for elongated or porous forms. Third, most bioavailability and dissolution studies demonstrate that the impact of particle morphology involves small numbers of formulations, single-drug compounds, or animal models; cross-study comparability is limited by differences in particle-size measurement methods, dissolution apparatus conditions, and animal species. Fourth, the case studies cited in Sections 9.1 - 9.4 are illustrative examples from specific compounds and should not be generalized without product-specific risk assessment. These constraints underscore the need for standardized shape descriptors, harmonized reporting practices, and adequately powered comparative studies before universal quantitative thresholds for particle morphology specifications can be recommended [132].

11. Conclusions

Particle morphology is a potential critical material attribute that affects the physical, chemical, and processing properties of pharmaceutical materials. This review shows how particle morphology influences everything from the molecular-level chemistry of crystal faces to powder behavior, spanning the entire process from API synthesis to the final dosage form.

The range of characterization techniques has expanded significantly, with advanced methods such as morphologically directed Raman spectroscopy (MDRS), deep learning-enhanced in situ imaging, and three-dimensional tomographic approaches complementing traditional microscopy and ensemble sizing methods. Integration of these techniques into process analytical technology (PAT) frameworks enables real-time monitoring and feedback control of particle attributes in continuous manufacturing processes. For example, a major pharmaceutical company successfully implemented MDRS as part of its PAT strategy during the scale-up of a solid oral dosage form, enabling automated detection of deviations in API polymorph distribution and prompt process adjustments. Similarly, real-time in situ imaging has been employed in continuous wet granulation processes to monitor granule growth and shape evolution, thereby improving batch consistency and enabling faster troubleshooting of upstream variability. These real-world applications highlight the practical impact of advanced particle characterization, demonstrating how such tools can strengthen product quality, support regulatory compliance, and streamline pharmaceutical manufacturing.

Particle engineering strategies, using both top-down and bottom-up methods,

provide flexible tools for designing particles with the right shape and size. The best approach depends on the drug's properties, the intended dosage form, and manufacturing needs.

Overall, the evidence reviewed here supports the view that particle morphology should be evaluated systematically and designated as a critical material attribute (CMA) only when a science-based risk assessment, supported by experimental data, establishes a meaningful link between morphological variability and specific product critical quality attributes (CQAs) for the intended dosage form and route of administration. As pharmaceutical development increasingly adopts Quality by Design (QbD), process analytical technology (PAT), and continuous manufacturing concepts, particle morphology is likely to play a more explicit role in integrated control strategies across the product lifecycle.

The integration of artificial intelligence, continuous manufacturing, and advanced analytical methods is anticipated to enhance control over particle morphology. As the field transitions from empirical approaches to rational particle design, a comprehensive understanding of the relationship between morphology and drug properties will be essential for the development of safe and effective medicines. Future research should prioritize the development of reliable, standardized methods for particle shape measurement to facilitate comparability across laboratories and systems. Ongoing initiatives, such as the ISO 9276-6:2008 guidelines, reflect efforts to harmonize particle shape analysis. Regulatory agencies, equipment manufacturers, and researchers are collaborating to establish common methodologies and conduct studies that inform shared standards. Although consensus exists on fundamental measurement principles, global harmonization remains incomplete, with regional guidelines differing in the acceptance and requirements for particle shape data in regulatory submissions. Continued collaboration, including working groups focused on technical standardization and cross-regional validation studies, is expected to advance harmonization. Next steps involve additional pilot studies, publication of draft guidance, and solicitation of feedback from industry and regulators. These efforts aim to increase consistency in regulatory requirements and comparability of results across the industry. Furthermore, implementing real-time, automated particle monitoring in manufacturing will enable in-process control of production. Addressing these challenges will facilitate translating advances in particle morphology into practical applications in drug development.

Conflicts of Interest

The authors declare no conflicts of interest regarding the publication of this paper.

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