

MONTHLY KNOW HOW

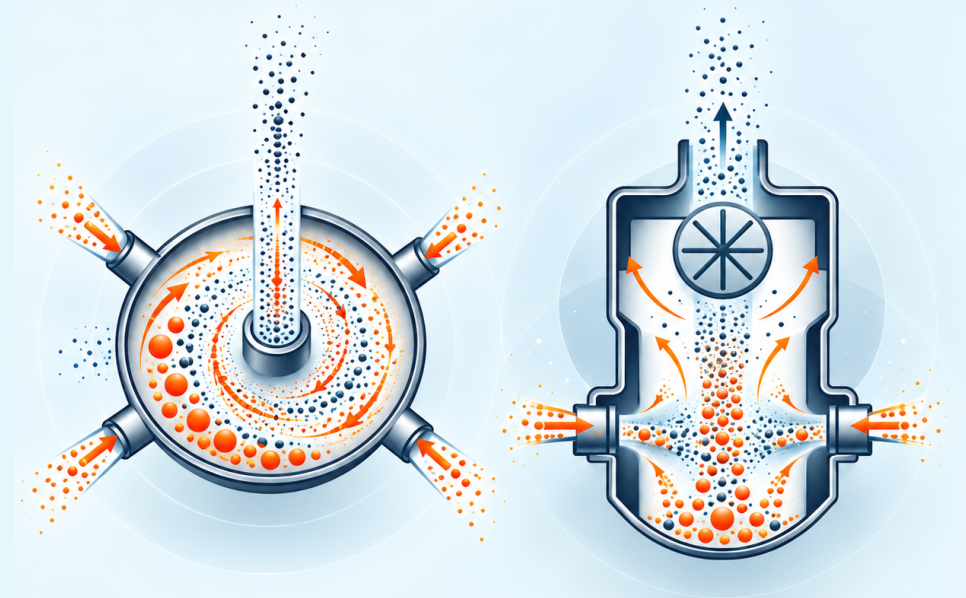
Micronization Process Control & Troubleshooting Guide

Connecting mill conditions, particle properties, and downstream
performance

2026

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Connect the process change to the performance problem.

The useful investigation is not the largest analytical panel. It is the shortest evidence chain that can distinguish the plausible mechanisms.



WHAT THIS GUIDE DOES

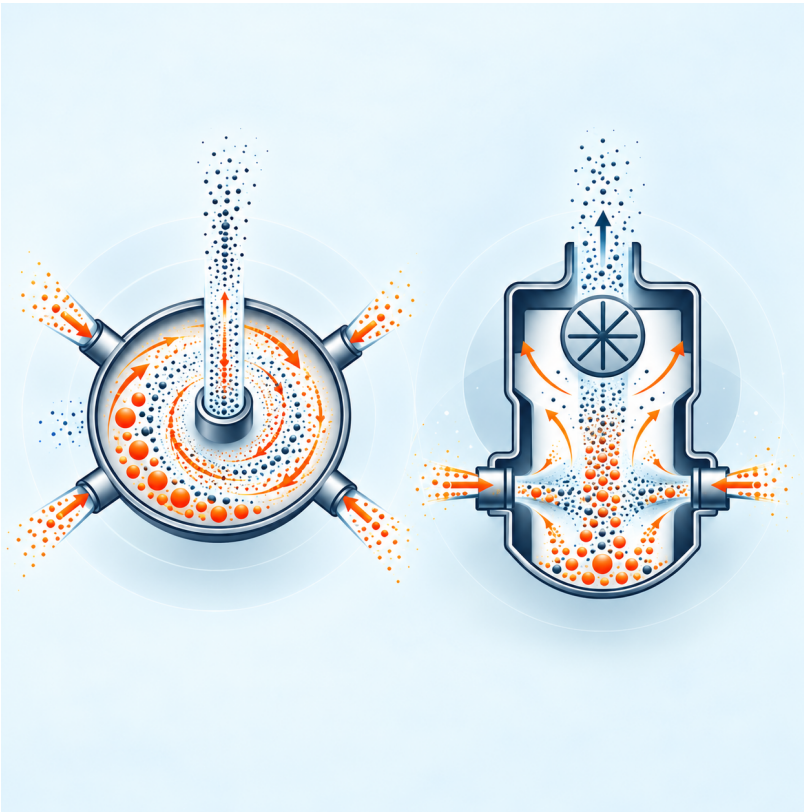
Provides a practical sequence for comparing process history, particle properties, moisture response, time, and application performance. It is designed for process engineering, formulation, analytical, QA/QC, and troubleshooting teams.

IMPORTANT LIMIT

This guide supports investigation and does not replace validated methods, site procedures, product specifications, change-control systems, or regulatory requirements.

Do not transfer a control rule from one jet mill to another.

The classification mechanism determines which process variables belong in the investigation.



SPIRAL / PANCAKE JET MILL

Cut-size control: aerodynamic separation inside the vortex.

- Grinding gas pressure / flow
- Feed rate and solids loading
- Feed injector (venturi) pressure
- Chamber and outlet geometry
- Nozzle condition and wear
- Gas dew point and inlet temperature

FLUIDIZED-BED OPPOSED JET MILL

Cut-size control: dynamic classifier integrated with the grinding zone.

- Classifier wheel speed
- Grinding gas pressure / flow
- Feed rate and solids loading
- Classifier airflow and holdup
- Nozzle / liner wear
- Gas dew point and inlet temperature

Eight steps from symptom to supported action.

Keep the sequence explicit so analytical results remain connected to the problem that triggered the investigation.

01**DEFINE THE SYMPTOM**

State the performance change in measurable terms.

02**COMPARE PROCESS HISTORY**

Identify what changed in the operating window.

03**CHECK THE FULL PSD**

Compare D10, D50, D90, tails, and curve shape.

04**CHECK MORPHOLOGY / BET**

Look for changes in accessible area or fracture structure.

05**CHECK MOISTURE / SOLID STATE**

Use representative RH and a method suited to the material.

06**TEST THE ACTUAL FAILURE**

Measure flow, caking, dissolution, dispersion, or aerosol performance.

07**ADD TIME WHEN NEEDED**

Compare fresh material with defined conditioning or storage intervals.

08**CONFIRM BEFORE ACTION**

Change the process only when the proposed chain is supported.

Compare the suspect lot with a known-good operating window.

Process records are often the fastest route to a plausible mechanism.

Variable	Reference lot	Suspect lot	Difference / comment
Mill type			
Feed material / grade			
Feed PSD			
Feed moisture			
Feed rate			
Grinding gas pressure			
Grinding gas flow			
Feed injector (venturi) pressure			
Classifier speed, if applicable			
Classifier airflow, if applicable			
Gas dew point			
Gas inlet temperature			
Product temperature			
Run duration / start-stop events			
Nozzle / liner wear or erosion			
Cleaning / maintenance / configuration change			

LOOK FOR COMBINATIONS

A changed outcome is often caused by an interaction: lower feed rate at unchanged energy input, higher classifier speed with increased holdup, changed feed moisture with a tighter cut, or wear that alters the flow field.

PSD is the first measurement, but D50 is not the whole answer.

Illustrative values only. The lower tail, upper tail, width, and measurement dispersion can change while the median remains within specification.

Reference vs suspect lot

Metric	Reference	Suspect
D10	1.4 μm	0.9 μm
D50	4.2 μm	4.0 μm
D90	9.8 μm	9.5 μm
Interpretation	Baseline	More fines despite similar D50

Seven questions to ask

- Did the median move?
- Did the lower tail move?
- Did the coarse tail move?
- Did the distribution widen or develop a shoulder?
- Is the difference reproducible across preparations?
- Could dispersion conditions explain the difference?
- Have both lots been run through a dispersion-pressure titration?

PRESSURE TITRATION

For laser diffraction of cohesive micronized powders, compare both lots across a controlled dispersion-pressure series. A difference that disappears at higher dispersion energy may reflect agglomeration or dispersion state rather than a true primary-particle shift.

BET can confirm that accessible surface changed. It cannot tell you why by itself.

Separate geometry, fracture structure, and solid-state interpretation.

PSD / IMAGING

What changed in size or shape?

Equivalent-sphere size, fines, aspect ratio, fragmentation, agglomeration.

BET SSA

Did accessible surface area change?

Sensitive to size, roughness, cracks, porosity, shape, and aggregation state.

SOLID-STATE METHOD

Did molecular order or surface energetics change?

DVS, XRPD, DSC, IGC, microcalorimetry, or spectroscopy depending on the question.

INTERPRETATION RULE

A higher BET value is evidence of higher accessible surface area. It is not proof of amorphization. Always compare BET with PSD, morphology, density assumptions, and the surface- or solid-state method selected for the suspected mechanism.

Compare moisture response with the surface area that is available to sorb water.

A rise in uptake per gram can be geometric. The more discriminating signal is uptake that changes out of proportion to BET.

MOISTURE RESPONSE RELATIVE TO BET

Compare uptake per gram with accessible surface area, or normalize the DVS response to BET when the method supports it.

PATTERN A • MOSTLY GEOMETRIC

BET increases and total moisture uptake rises by approximately the same proportion. Surface-area-normalized uptake remains similar. This supports a predominantly geometric explanation, provided other evidence is consistent.

PATTERN B • SURFACE-STATE CHANGE

Moisture uptake rises more than BET predicts, or a method-specific transition appears. Investigate amorphous/disordered material, altered surface energy, or another surface-state mechanism.

Method note: DVS can quantify low amorphous fractions in some materials, but only with a validated material-specific protocol. In the 2021 terbutaline sulfate study, surface-area-normalized moisture uptake was used to separate amorphous-content effects from new crystalline surface exposure.

Add methods only when they resolve a specific uncertainty.

The objective is not analytical completeness. It is discrimination between competing mechanisms.

Surface and solid-state methods

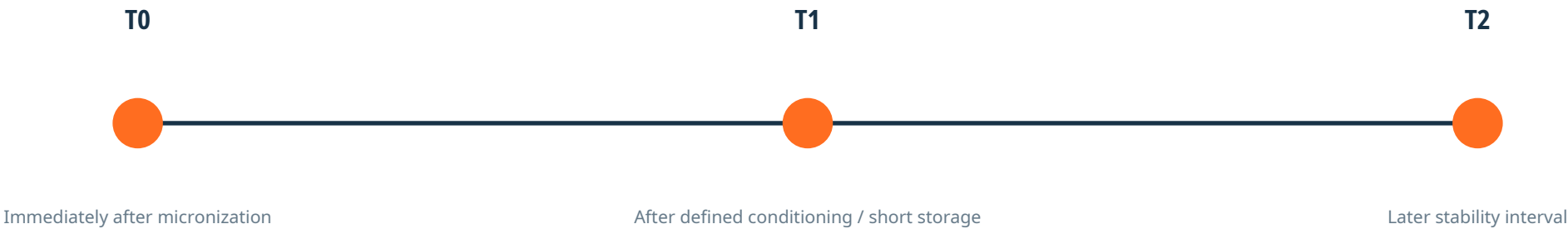
XRPD	Bulk crystalline change; routine sensitivity may be limited for very small surface fractions.
DSC	Thermal transitions, crystallinity changes, and recrystallization where suitable.
Inverse gas chromatography	Surface-energy distributions relevant to cohesion, adhesion, wetting, and formulation behavior.
Isothermal microcalorimetry	Sensitive energetic evidence for amorphous or disordered material.
Raman / IR	Chemical or solid-state differences where spectra are discriminating.

Measure the performance that matters

FLOW	Shear cell, flow function, wall friction where relevant, feeder performance
CAKING	DVS/moisture, caking strength, time under load, storage RH/T
DISSOLUTION	PSD, BET, wetting, agglomeration, solid state, dissolution test
DISPERSION	Wettability, sinkability, agglomerate structure, morphology, surface chemistry
AEROSOL	Cascade impaction (NGI or ACI), fine particle fraction, agglomeration strength, moisture sensitivity

Freshly micronized surfaces can evolve.

Do not assume the material characterized at release is identical after conditioning or storage.



Property	T0	T1	T2
D10 / D50 / D90			
BET SSA			
Moisture response relative to BET			
Flow / caking metric			
Application performance			

The direction of BET change is material- and mechanism-dependent. Use defined intervals and storage conditions rather than assuming surface area will always rise or fall.

Use patterns as screening logic, not automatic root-cause determinations.

Observation	PSD	BET	Moisture response relative to BET	First interpretation
Product becomes finer; BET rises	Changed	Higher	Rises roughly in proportion to BET	Predominantly geometric size reduction
PSD similar; BET higher; uptake tracks BET	Similar	Higher	Similar after normalization	Roughness, cracks, porosity, morphology, or aggregation change
PSD similar; BET similar	Similar	Similar	Higher after normalization	Surface / solid-state or chemistry change
PSD similar; BET higher; uptake exceeds BET	Similar	Higher	Higher than BET predicts	Milling altered more than particle dimensions
More fines; poorer flow	Lower tail	May rise	Similar after normalization	Fines-driven cohesion may dominate
PSD passes; caking increases	Similar	Variable	Higher than BET predicts	Investigate moisture-sensitive surface change
PSD passes; dissolution changes	Similar	Variable	Variable	Investigate wetting, surface area, solid state, and agglomeration
Apparent PSD coarsens in storage	Apparent	Variable	Variable	Check agglomeration / caking before assuming particle growth

Where DVS is being used quantitatively, normalize only when the method and material support that interpretation. Surface-area normalization is not a universal correction for all sorption mechanisms.

Every branch should tell you what to do next.

Use the tree to prevent a single analytical result from becoming the conclusion.

Q1 • DID THE MILLING PROCESS CHANGE?

YES: Document the changed variable(s), then continue to Q2.

NO: Continue to Q2 using the material comparison.

Q2 • DID THE PSD CHANGE?

YES: Test whether the PSD shift can explain the failure; continue to Q3 if not sufficient.

NO: Continue to Q3.

Q3 • DID MORPHOLOGY OR BET CHANGE?

YES: Assess whether the surface-area / morphology change matches the failure; continue to Q4.

NO: Continue to Q4.

Q4 • DID MOISTURE RESPONSE OR SOLID STATE CHANGE?

YES: Test relevance within the actual environmental window; continue to Q5.

NO: Continue to Q5 and reconsider other mechanisms.

Q5 • DID THE DOWNSTREAM PROPERTY CHANGE UNDER CONTROLLED TESTING?

YES: A supported process, property, and performance link exists. Define and confirm corrective action.

NO: Do not change the process yet. Revisit the hypothesis, measurement conditions, and alternative mechanisms.

A supported mechanism should lead to a controlled decision.

The target is a stable operating window, not the finest powder the equipment can produce.

RESTORE THE OPERATING WINDOW

Return the process toward historically acceptable feed rate, gas conditions, classifier setting, or temperature.

BACK OFF AN UNNECESSARILY AGGRESSIVE CUT

Fine enough for performance is the objective. Extra milling intensity can add surface change without product value.

CONTROL FEED VARIABILITY

Feed PSD, moisture, crystallinity, and mechanical properties can change milling behavior at identical equipment settings.

CONTROL THE POST-MILLING ENVIRONMENT

Tighter RH, temperature, open-handling, packaging, or transfer control may reduce variability.

EVALUATE CONDITIONING

For some materials, controlled humidity or temperature can relax or recrystallize milling-induced disorder. Confirm experimentally.

ADJUST THE CONTROL STRATEGY

If PSD alone does not predict performance, combine process parameters, PSD, one relevant material attribute, and the performance test.

REGULATED MANUFACTURING

In regulated manufacturing, process changes and post-micronization conditioning steps fall under change control and may require revalidation or regulatory assessment. Follow the applicable site quality system and product commitments.

A passing D50 does not end the investigation.

Illustrative case only. Values are fictional and are not acceptance limits.

MILL TYPE

Fluidized-bed opposed jet mill with dynamic classifier.

Problem

A micronized active ingredient passes its particle-size specification but forms weak agglomerates during storage and shows poorer flow during dispensing.

Reference vs suspect

Metric	Reference	Suspect
D10	1.3 µm	1.0 µm
D50	4.0 µm	3.9 µm
D90	9.2 µm	8.9 µm
BET SSA	1.8 m²/g	2.2 m²/g

Process comparison

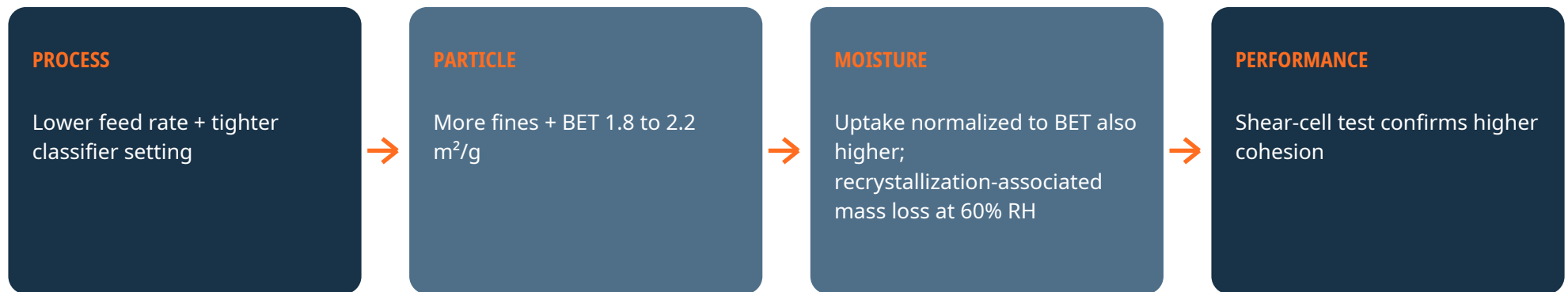
- Feed rate was lower than the historical range
- Grinding gas setting was unchanged
- Classifier setting was tighter
- No abnormal wear or maintenance change was recorded

Initial interpretation

The lot has more fines and a 22% higher BET surface area. Those observations can increase moisture uptake per gram without requiring a new surface state. The investigation therefore compares DVS behavior relative to BET before drawing a solid-state conclusion.

The additional evidence makes the reasoning stronger.

The conclusion comes from several independent measurements that align with the observed failure.



Corrective study

The mill is returned toward the historical operating window while maintaining the required product PSD. The new batch is evaluated using PSD, BET, DVS, and shear testing. The downstream flow behavior returns to the expected range.

What the example teaches

- D50 never failed
- BET alone was not treated as proof of amorphization
- Moisture uptake was interpreted relative to BET
- The DVS transition provided additional material-specific evidence
- The root-cause chain ended with the actual handling problem

BOUNDARY

This worked example demonstrates reasoning, not a universal test sequence. The correct panel depends on the material, process, and downstream risk.

A one-page record keeps the evidence chain visible.

Use this as a working sheet or adapt it to the site deviation / CAPA system.

OBSERVED PROBLEM

Deviation / symptom

Where observed

Measurable reference performance

MILLING CONDITIONS

Mill type

Feed rate

Grinding gas pressure / flow

Injector pressure

Classifier setting if applicable

Gas dew point / inlet temperature

Wear / maintenance changes

PARTICLE CHARACTERIZATION

D10 / D50 / D90

Fines / span

Morphology

BET SSA

SURFACE / MOISTURE

DVS RH range

Moisture response relative to BET

Solid-state method / result

DOWNSTREAM PERFORMANCE

Flow / caking / dissolution / dispersion / aerosol

Controlled-test result

HYPOTHESIS & ACTION

Process, property, and performance hypothesis

What result would disprove it?

Corrective action

Change-control / validation requirement

Start small. Expand only when the evidence requires it.

A practical investigation usually begins with process history + full PSD + the measurement closest to the failure.

Minimum useful starting panels

INCREASED CAKING

Process history + PSD + moisture response relative to BET + caking / flow

CHANGED DISSOLUTION

Process history + PSD + surface / morphology assessment + dissolution

UNEXPECTED FLOW LOSS

Process history + PSD / fines + shear or feeder test

AEROSOL PERFORMANCE SHIFT

Process history + PSD + NGI/ACI + fine particle fraction + moisture / agglomeration evidence

Ten rules to keep

- 01 Define the symptom before choosing the test
- 02 Match the variables to the actual mill type
- 03 Compare against a known-good process window
- 04 Read the whole PSD, not D50 alone
- 05 Use dispersion-pressure titration when agglomeration may affect PSD
- 06 Treat BET as accessible surface area, not amorphous-content proof
- 07 Interpret moisture uptake relative to available surface area when appropriate
- 08 Measure the downstream property that actually matters
- 09 Include time when the powder may evolve
- 10 Change the process only through the applicable quality and change-control route

Sources, companion resources, and laboratory support.

The guide is a working aid; use the original literature and validated site methods for technical decisions.

Selected references

- [1] Midoux N, Hošek P, Pailleres L, Authelin JR. Micronization of pharmaceutical substances in a spiral jet mill. Powder Technology 104(2), 113-120 (1999). DOI: [10.1016/S0032-5910\(99\)00052-2](https://doi.org/10.1016/S0032-5910(99)00052-2).
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- [5] Bagwan NUS, Sheokand S, Kaur A, et al. Role of surface molecular environment and amorphous content in moisture sorption behavior of milled Terbutaline Sulphate. Eur J Pharm Sci 161, 105782 (2021). DOI: [10.1016/j.ejps.2021.105782](https://doi.org/10.1016/j.ejps.2021.105782).

Continue the investigation

COMPANION ARTICLE

Micronization by Jet Milling: How Classification, Milling Intensity, and Time Change Surface Properties

powdertechology.info/?p=11350

CALCULATORS & TOOLS

Use PTI calculators and diagnostic tools alongside the interpretation in this guide.

powdertechology.info/calculator-suite/

LABORATORY SUPPORT

Delft Solids Solutions provides contract testing and characterization, with its laboratory working in accordance with ISO 17025.

solids-solutions.com