Predictable scale-up in continuous pharmaceutical extrusion

A practical guide to validating method transfer through residence time, energy balance, and extruder fill level

Scale-up succeeds or fails on **physics**

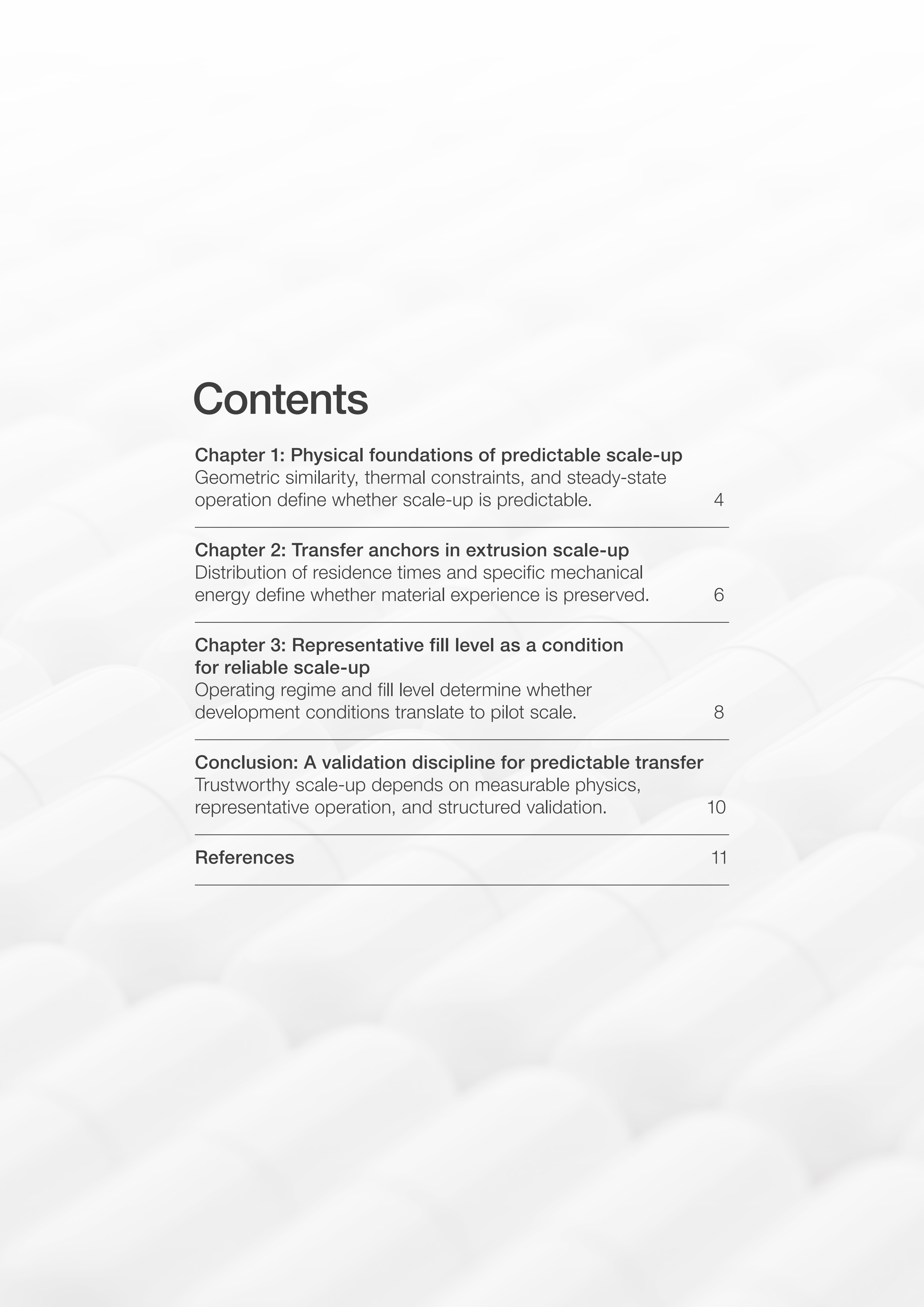
Scale-up is often framed as a proportional adjustment

> Scale-up is not proportional adjustment. It is preservation of material experience.

Transfer between development and pilot scale is governed by physics, not proportion. Material behavior inside a twin-screw extruder depends on geometry, fill level, mechanical energy input, and thermal balance. When these factors shift, material history—and potentially critical quality attributes of the final product—shift with them.

For formulation and process teams, the objective of scale-up is not simply to increase throughput, but to do so without altering the materials' experience.

This document presents a structured approach to scale-up in continuous twin-screw processing, grounded in physical constraints and focused on transfer reliability.



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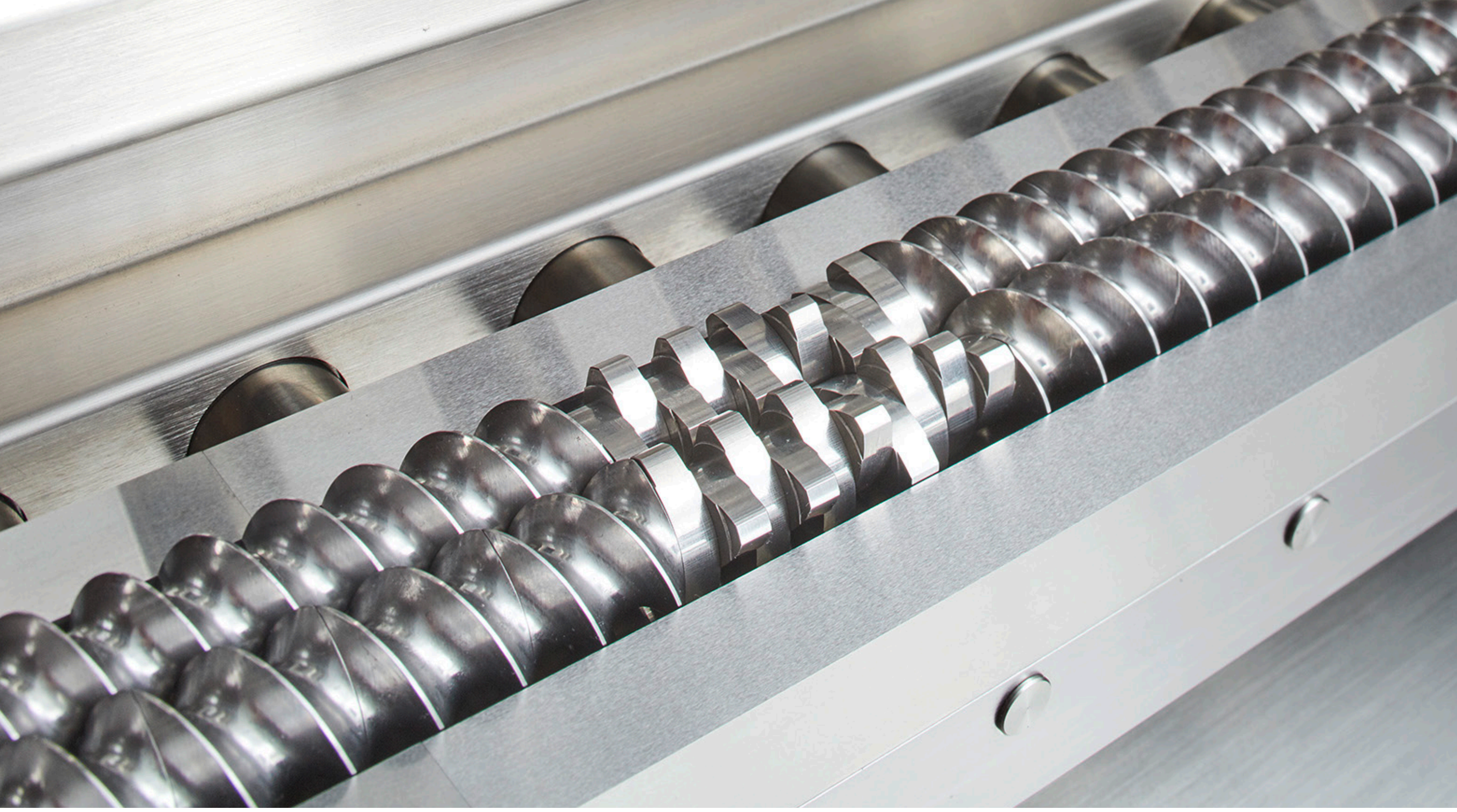


Chapter 1

Physical foundations of predictable scale-up

Geometric similarity, thermal constraints, and steady-state operation define whether scale-up is predictable

Field notes: Scale-up is constrained by physics, not defined by throughput

- Preserve geometric similarity before adjusting process parameters.
- Validate under representative fill level and realistic thermal conditions.
- Confirm steady-state behavior before transferring scale.

Scaling a twin-screw extrusion process is often described as a proportional adjustment: increase screw diameter, increase feed rate, maintain temperature, and expect comparable output. While these adjustments are necessary, they are not sufficient to ensure process equivalence.

Extrusion does not scale by geometric enlargement alone. It scales when the material undergoes the same mechanical, thermal, and residence-time history at larger scale as it did during development. Mechanical energy input governs shear exposure. Shear influences melting and distributive mixing. Residence time distribution affects how long the materials are under thermal and mechanical stress. Thermal balance determines whether that exposure results in controlled transformation or degradation. When any of these conditions shift, material history and potentially critical quality attributes of the final product shift with them.

Geometric similarity enables physical equivalence

Twin-screw extrusion is governed by geometry as much as by parameter settings. The relationships between outer screw diameter (D_0), inner diameter (D_i), barrel length (L), and screw configuration define the transport and mixing regime within the barrel.

For comparable physics to apply across scales, geometric relationships must be preserved across instruments, from small scale to large scale:

- Consistent L/D ratio
- Consistent D_0/D_i ratio
- Comparable free volume per unit length
- Equivalent screw configuration philosophy

These relationships define the internal shear field, fill behavior, and transport mechanisms. When preserved, material experiences comparable shear rates, distributive mixing, and residence patterns. When altered, transport and mixing conditions change even if screw speed and feed rate appear proportionally scaled.

Volumetric scale-up approaches assume that geometric similarity across instruments preserves the filling level and shear conditions.[1] If geometry differs, scaling relationships lose predictive value. Processing literature reinforces this principle. Mixing efficiency and material transport are inseparable from screw configuration and barrel geometry.[2] While geometric similarity does not guarantee successful scale-up, it does help establish the conditions under which predictable scale-up is possible.

Surface-to-volume constraints and thermal balance

As extruder diameter increases, volume scales proportionally to the cube of the diameter (D^3) while surface area scales only in relation to the diameter squared (D^2). The relative heat-transfer surface available per unit material therefore decreases with larger scale.[3] Larger systems dissipate heat less efficiently relative to throughput, and viscous dissipation becomes a more significant contributor to melt temperature.

Regression-based scale studies across 11 mm, 16 mm, and 24 mm systems demonstrate that feed rate adjustment alone does not preserve material experience at larger diameters.[3] Maintaining comparable specific mechanical energy consumption requires screw speed adjustments as diameter increases. The operating window expands with scale, but its position and boundaries shift.

Development processes that depend heavily on external heat extraction introduce thermal conditions that may not translate proportionally at larger diameters. More scalable operation relies on mechanical energy input and stable fill behavior to establish thermal equilibrium. Processes that approximate adiabatic behavior during development translate more predictably across scales.[1]

Steady state as a prerequisite for transfer

Instability observed at laboratory scale is not corrected by increasing diameter. At very low feed rates, specific feed load (SFL) can fall below representative fill levels. Under these conditions, residence time distribution contracts, plug-flow tendencies may emerge, and material transport becomes dominated by feed displacement rather than controlled mixing.[1] Although such conditions may appear stable, they do not reflect the regime required at larger scale.

Studies evaluating volumetric scale-up under low-throughput conditions show that residence time equivalence deteriorates when fill level is insufficient.[1] Regimes dominated by plug-flow tendencies at development scale can lead to mismatched specific mechanical energy behavior and altered axial mixing during transfer. Therefore, processes operating with apparent stability at smaller laboratory scales present elevated transfer risk. Predictable scale-up requires stable steady-state operation at representative fill levels.

What scaling really changes

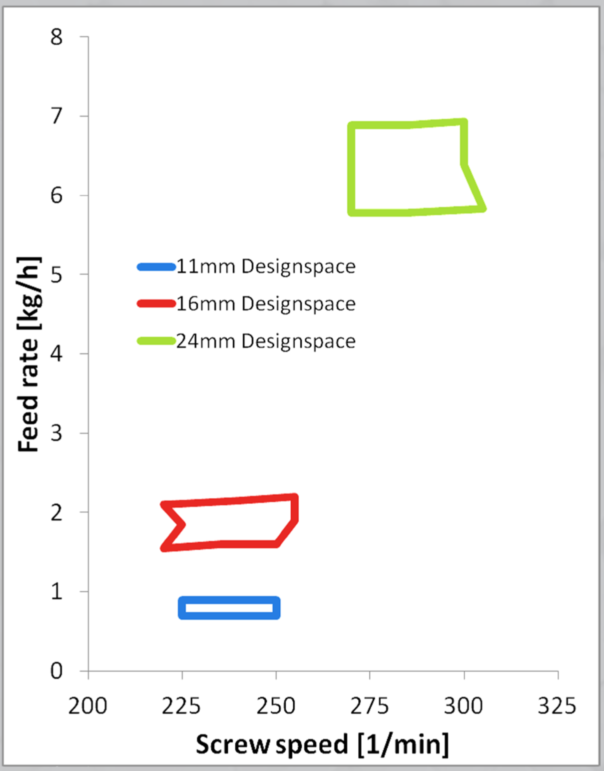


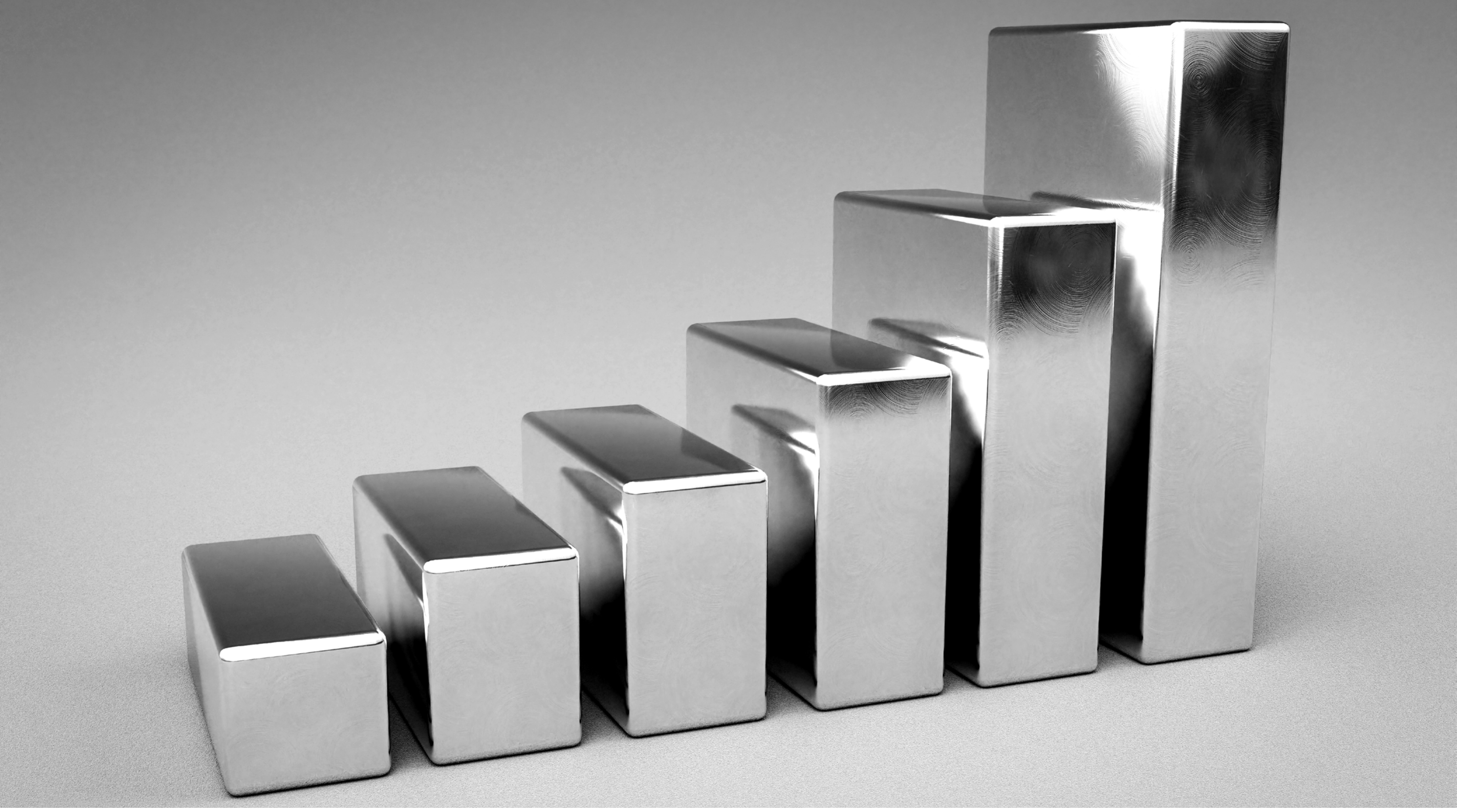
Figure 1. These operating windows were derived from experimental runs across 11 mm, 16 mm, and 24 mm extruders.

The shape and position of each window illustrate a key constraint: As diameter increases, heat-transfer efficiency decreases relative to material volume. To preserve material experience, screw speed must be adjusted alongside feed rate.

For development teams, this means lab-scale conditions cannot be translated proportionally without verifying energy input and residence behavior at the next scale.

Scale-up is not a simple translation. It is an adjustment that requires a recalibration within physical limits.

See the complete scale-up analysis.



Chapter 2

Transfer anchors in extrusion scale-up

Residence time distribution and specific mechanical energy define whether material experience is preserved

Field notes: Predictable scale-up begins with representative physics

- Do not validate transfer from very low-throughput or under-filled conditions.
- Confirm RTD and SMEC under fill levels intended for pilot scale.
- Resolve torque and thermal instability before increasing diameter.

Geometric similarity and thermal discipline establish the conditions for scale-up. They do not confirm equivalence. Verifying that the material experience remains consistent across scales requires measurable transfer anchors.

In twin-screw extrusion, two parameters govern material history more directly than diameter or throughput: residence time distribution (RTD) and specific mechanical energy consumption (SMEC). Together, they define duration under stress and mechanical work per unit mass. If either shifts, material experience shifts with it.

Residence time distribution as a measure of material exposure

Residence time is often reduced to a mean value, but the mean alone does not capture material experience.

A twin-screw extruder does not behave as an ideal plug-flow reactor in which all elements exit simultaneously. Instead, material elements experience a distribution of residence times shaped by conveying geometry, kneading sections, fill level, pressure development, and screw speed.[1] Axial dispersion and backmixing define this distribution.

RTD width and symmetry influence melting, mixing, degradation, and reaction pathways. A narrow distribution with controlled axial mixing suggests uniform exposure. Conversely, extended tailing indicates that a portion of the material remains significantly longer than the mean residence time, which increases degradation risk for heat- or shear-sensitive APIs.

Experimental scale-up studies show that matching mean residence time alone does not ensure comparable RTD shape across scales.[1] At low fill levels, RTD narrows and plug-flow behavior may dominate; as fill increases, axial mixing intensifies and the distribution broadens. These shifts alter material exposure even when screw speed and feed rate appear proportionally scaled.

The Peclet number, a value expressing the ratio of material flow to heat or mass diffusion, serves as a scale-independent indicator of axial mixing. Similar Peclet number values across scales suggest comparable transport-to-dispersion balance.[1] When development conditions approach plug-flow behavior, equivalent axial mixing at larger diameter should be verified rather than assumed.

Scale-up discipline therefore requires characterizing RTD shape, not just its average.

Specific mechanical energy as a measure of mechanical history

If RTD defines exposure time, SMEC defines exposure intensity.

Specific mechanical energy consumption represents mechanical work per unit mass and is derived from torque, screw speed, and throughput. Unlike screw speed alone, SMEC reflects the combined effect of load and mass flow.

Volumetric scale-up assumes that scaling feed rate with diameter preserves fill and shear conditions. In practice, SMEC equivalence does not always follow directly from simple volumetric scaling.[1] In some cases, a scaling factor below three more accurately preserves energy per mass, reflecting heat transfer and realistic processing constraints.[1]

SMEC is also coupled to fill behavior. As feed rate and fill level increase, mechanical input is distributed across more material, reducing energy per unit mass. Conversely, low fill levels can produce artificially elevated SMEC values.

Matching screw speed and throughput alone does not guarantee equivalent mechanical history. SMEC must be evaluated explicitly.

RTD and SMEC are not independent

RTD and SMEC interact through fill level and shear regime.

A low fill level may shorten RTD while increasing specific mechanical exposure. A higher fill level may broaden RTD while reducing energy per unit mass. Plug-flow conditions can reduce axial mixing while maintaining apparent residence time equivalence.

As extruder diameter increases, surface-to-volume effects and heat transfer constraints further influence this coupling.[3] Larger systems may require screw speed adjustments to maintain SMEC while preserving RTD shape.

Predictable scale-up therefore requires simultaneous consideration of these factors:

- RTD width and symmetry
- Peclet number or equivalent mixing indicator
- SMEC equivalence across scales
- Fill level consistency

Transfer cannot be validated by a single parameter.

Structured scale transfer under geometric continuity

Element	11 mm	16 mm	24 mm
Geometry	Preserved	Preserved	Preserved
Operating parameters	Feed adjusted	Feed adjusted	Feed + speed adjusted
Material experience	Baseline	SMEC & RTD matched	SMEC & RTD matched

These operating windows were derived from regression-based experiments across geometrically similar 11 mm, 16 mm, and 24 mm systems. Feed rate scaled with diameter, but screw speed required adjustment at 24 mm to preserve SMEC and RTD.

The results demonstrate a structured scale-up approach: Preserve geometry, adjust for physical constraints, and verify material experience rather than assume proportional equivalence.[2]

What this means for tool selection

Platforms with consistent L/D ratio, screw architecture, and free volume scaling enable predictive SMEC and RTD mapping and reduce empirical iteration during transfer.

Explore the scalable pharma extrusion platform

Chapter 3

Representative fill level as a condition for reliable scale-up

Scale-up cannot be validated from under-filled or plug-flow regimes

Field notes: Scale-up depends on representative operation

- Do not use low-throughput runs as scale-up references.
- Confirm fill level reflects intended pilot conditions and verify RTD and SMEC under those conditions.
- Resolve torque and thermal instability before increasing diameter.

Scale-up rarely fails as a result of diameter increases. More often, it fails because the development conditions used to justify transfer were not representative of the intended operating regime.

In early formulation work, feed rates are frequently kept low to conserve API and accelerate iteration. While efficient, very low throughput alters fill behavior and transport mechanisms inside the extruder, and therefore it also alters the material experience that scale-up seeks to preserve.

Specific feed load (SFL) provides a practical indicator of this shift. When SFL falls below representative levels, the barrel operates in a partially filled regime and transport becomes increasingly governed by drag flow rather than pressure-driven mixing.

Under these conditions, certain phenomena are observed:

- Residence time shortens rapidly with increasing feed rate
- Axial mixing diminishes
- Plug-flow tendencies may emerge

Volumetric scale-up studies document this behavior under low-throughput laboratory conditions.[1] When development runs operate at very low SFL, matching mean residence time across scales becomes unreliable because RTD shape shifts and equivalence deteriorates.

A lab-scale process validated under under-filled conditions may appear stable while operating in a regime that does not translate to pilot scale.

Plug-flow, mixing, and transfer risk

Plug-flow-dominated behavior is not inherently problematic. In some contexts, narrow RTD may be advantageous. The issue arises when such behavior is unintentionally used as the reference condition for scale-up.

Scale-transfer investigations show that plug-flow regimes at development scale can lead to mismatched specific mechanical energy behavior and altered axial mixing at larger diameter.[1] Because fill level and geometry interact differently at scale, equivalent transport and dispersion cannot be assumed.

Operationally, this misalignment often appears during transfer in various forms:

- Torque shifts
- Melt temperature drift
- Changes in solid-state behavior of the material, affecting crystallinity or amorphous solid dispersion
- Variability in downstream material performance

The root cause is rarely scale-up in isolation. More often, development conditions were misaligned with the regime required at pilot or production scale.

If the Peclet number indicates strong plug-flow behavior at lab scale, axial mixing equivalence at larger diameter should be verified rather than assumed.

Stability is a prerequisite

Instability present at laboratory scale does not resolve through scale-up.

Processes exhibiting fluctuating torque, oscillating melt temperature, or inconsistent fill level are operating near physical boundaries. Larger systems tend to amplify these conditions due to surface-to-volume constraints and increased mechanical load, increasing the risk of parameter drift and CQA variability.

Documented scale-up evaluations confirm that residence time equivalence across scales requires sufficient fill level.[1] At very low SFL, RTD behavior shifts; only at representative fill levels does residence time begin to stabilize between scales.

Validation should be performed under the same operating regime intended for production.

Geometric continuity as a scale-up criterion

Geometric continuity preserved

- Consistent L/D ratio across scales
- Consistent D_0/D_i ratio and free volume scaling
- Identical screw configuration philosophy
- SMEC and RTD mapped predictively across diameters

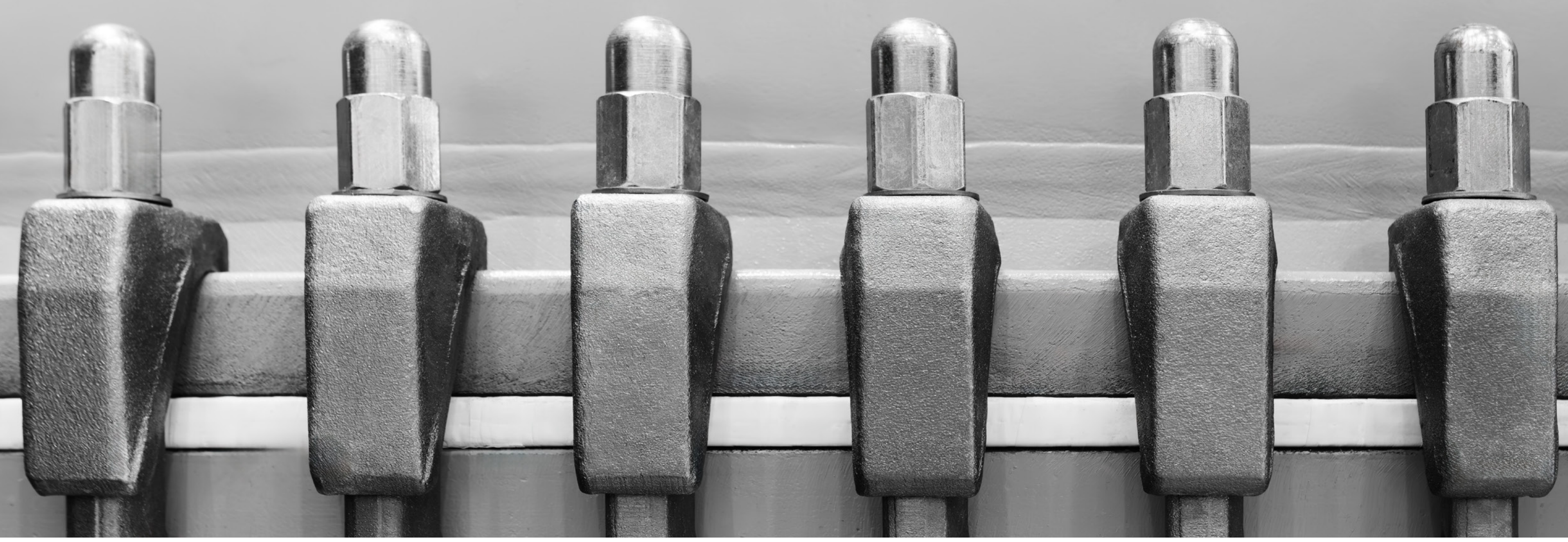
Geometric continuity altered

- Different L/D ratios between lab and pilot
- Changes in ID/OD ratio or channel geometry
- Modified screw architecture at larger scale
- Additional empirical adjustment required to re-establish equivalence

Structured scale-transfer investigations demonstrate that predictive mapping of SMEC and RTD across scales depends on preserving geometric relationships.[2] When architecture remains consistent, transfer can be validated through measurable equivalence. When geometry differs, equivalent shear and transport behavior must be re-established experimentally.

Platform architecture should be evaluated as a primary factor in scale-up reliability.

Explore scalable twin-screw platforms



Conclusion

Implementing validation discipline for predictable scale-up

Predictable scale-up in twin-screw extrusion depends on preserving material experience as extruder diameter and mass throughput increase. When shear exposure, residence behavior, fill level, or thermal balance shift, critical quality attributes of the final product can shift with them.

Residence time and mechanical energy define exposure across a given scale. Fill level and geometric similarity determine whether those stresses are applied consistently across scales.

Scale-up challenges rarely originate in diameter alone. More often, development conditions do not necessarily reflect the regime required at pilot or production scale. Under-filled operation, plug-flow-dominated behavior, or unstable torque and temperature profiles introduce misalignment that becomes visible only during transfer.

A defensible scale-up therefore requires these features:

- Preservation of the geometric similarity of used extruders
- Confirmation of RTD shape, not only mean values
- Verification of SMEC equivalence
- Operation at representative fill levels
- Demonstration of stable steady-state behavior

These conditions are achievable, but they are not self-enforcing. Continuous extrusion demands ongoing measurement, parameter control, and disciplined process management. It is not a set-and-forget system.

Successful scale-up benefits from experienced process insight, robust equipment designed for geometric similarity, and application expertise that extends beyond initial development.

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Stage	Development	Pilot / scale validation	Production
Scale-up role	Establish representative operating regime	Verify SMEC and RTD equivalence across scale	Maintain validated operating window under GMP
Transfer focus	Characterize RTD and energy baseline	Confirm geometric continuity and energy balance	Sustain steady-state performance at commercial scale
Typical throughput	Grams to low kg/h	Intermediate scalable throughput	Commercial-scale continuous throughput

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