International Journal of Drug Analysis, Industrial Pharmacy and Pharmaceutical Research
Volume 2, Issue 1, January-June 2026

Application of Quality by Design (QbD) in the Development and Industrial Scale-Up of Solid Oral Dosage Forms: A Comprehensive Review

Dr. Ramesh K. Sharma[1], Prof. Sunita M. Verma[2], Amit S. Joshi[3], Rajesh Kumar[4]

ABSTRACT

Quality by Design (QbD) has shifted the pharmaceutical paradigm from retrospective testing to a proactive, science-based, and risk-managed approach that ensures product quality is built-in by design. This comprehensive review examines the strategic application of QbD principles across the entire lifecycle of solid oral dosage forms, emphasizing the critical transition from laboratory-scale formulation development to full-scale commercial manufacturing. We dissect the core components of the QbD framework, including the definition of the Quality Target Product Profile (QTPP), identification of Critical Quality Attributes (CQAs), screening of Critical Material Attributes (CMAs) and Critical Process Parameters (CPPs), and the establishment of a robust Design Space. Special attention is dedicated to the technical challenges encountered during industrial scale-up—such as segregation, tablet capping, weight variation, and dissolution rate shifts—and how mathematical modeling, Process Analytical Technology (PAT), and multivariate data analysis (MVDA) can mitigate these scale-dependent variations. Through quantitative comparative analysis and detailed industrial case studies across standard operations like high-shear wet granulation, fluid bed drying, and roller compaction, this paper illuminates the mechanistic correlations that govern process dynamics. Ultimately, the integration of QbD not only streamlines regulatory pathways but significantly enhances batch consistency, reduces waste, and establishes a foundation for continuous manufacturing innovation.

KEYWORDS: *Quality by Design (QbD); Solid Oral Dosage Forms; Industrial Scale-Up; Process Analytical Technology (PAT); Design Space;*

Critical Process Parameters (CPPs); Critical Material Attributes (CMAs); Risk Assessment.

INTRODUCTION

For decades, the pharmaceutical industry relied primarily on empirical 'trial-and-error' methodologies for formulation development and traditional end-product testing to guarantee quality. Under this conventional paradigm, product quality was verified through destructive analytical testing of a statistically small subset of finished units. If a batch failed to meet predefined acceptance criteria, it was either rejected or reworked, resulting in massive financial losses, supply chain vulnerabilities, and regulatory friction [1]. This retrospective quality control methodology inherently lacked a deep mechanistic understanding of how critical raw material properties and processing dynamics interact to dictate the final performance of the dosage form. Consequently, variations in excipient lots or environmental changes often caused unforeseen batch failures during industrial scale-up, presenting substantial hurdles to consistent manufacturing.

Recognizing these systemic limitations, the International Council for Harmonisation (ICH) introduced guidelines Q8 (Pharmaceutical Development), Q9 (Quality Risk Management), and Q10 (Pharmaceutical Quality System), which collectively defined a transformative approach known as Quality by Design (QbD) [2]. QbD is a systematic, holistic approach to development that begins with predefined objectives and emphasizes product and process understanding based on sound science and quality risk management. Rather than testing quality into a product, QbD focuses on building quality directly into the formulation and manufacturing process from the very first design phase. By mapping out a clear quantitative understanding of the relationships between material characteristics, process parameters, and final quality attributes, QbD allows for operational flexibility within a validated 'Design Space,' removing the rigid regulatory boundaries that historically stifled post-approval process optimization.

Solid oral dosage forms, such as tablets and capsules, remain the most widely prescribed and commercially significant drug delivery systems globally due to their cost-effectiveness, high patient compliance, chemical stability, and manufacturing scalability. However, their production involves highly intricate unit operations—including blending, granulation, drying, milling, compression, and coating—each governed by complex particulate mechanics and thermodynamic forces [3]. When scaling up these operations from benchtop equipment to high-speed commercial lines, simple geometric scaling often fails due to changes in shear fields, heat transfer rates, and particle residence times. This review provides a rigorous, comprehensive analysis of how the QbD framework is systematically applied to overcome these scale-up barriers, ensuring that the critical quality attributes of solid oral dosage forms remain robustly controlled across all scales of production.

LITERATURE REVIEW

The evolution of QbD literature represents a profound shift from theoretical conceptualization to practical, multi-disciplinary implementation. Early publications following the release of the ICH Q8 guideline focused heavily on defining the core terminology, such as translating clinical efficacy and safety targets into a precise Quality Target Product Profile (QTPP) [4]. Researchers like Lionberger et al. established foundational principles for defining Critical Quality Attributes (CQAs), illustrating how physical properties like tablet hardness, disintegration time, and content uniformity directly affect biological performance and bioequivalence. As the framework matured, literature shifted toward the integration of advanced risk assessment tools—such as the Ishikawa (fishbone) diagram and Failure Mode and Effects Analysis (FMEA)—to systematically rank the potential impact of raw material properties and process variables on these CQAs [5].

In recent years, the literature has focused intensely on the quantitative definition of the Design Space via advanced Design of Experiments (DoE). Instead of evaluating one variable at a time (OVAT), modern pharmaceutical engineering leverages response surface methodologies (e.g., Central Composite or Box-Behnken designs) to map multi-dimensional interactions between Critical Process Parameters (CPPs) and Critical Material Attributes (CMAs) [6]. For example, recent studies on high-shear wet granulation have elucidated how impeller tip speed (a CPP) interacts synergistically with binder viscosity (a CMA) to dictate the final particle size distribution and subsequent dissolution profile of the compressed tablets. Concurrently, the incorporation of Process Analytical Technology (PAT)—using real-time sensors such as Near-Infrared (NIR) and Raman spectroscopy—has transitioned from an academic curiosity to a cornerstone of industrial quality control, enabling non-destructive, real-time tracking of blend uniformity and moisture content during active operations [7].

RESEARCH GAP

Despite the expansive volume of literature detailing laboratory-scale QbD implementations, a critical disconnect persists between benchtop formulation success and commercial scale-up predictability. The majority of published QbD studies are confined to small-scale laboratory equipment (e.g., 1–5 kg batch sizes), where environmental factors, shear dynamics, and material handling systems are highly uniform and easily controlled. However, when these formulations are transferred to commercial production lines (e.g., 100–500 kg batch sizes), the altered thermodynamic profiles, increased compressive forces, and extended dwell times often render the laboratory-defined Design Space obsolete. The existing literature rarely provides a mathematical or mechanistic blueprint for translating a small-scale Design Space into a multi-scale manufacturing framework. Furthermore, there is a distinct lack of quantitative, consolidated analyses that contrast the specific impact of scale-dependent parameters (like Froude numbers in mixing or fill depth ratios in tableting) across distinct unit operations. This review addresses this critical gap by synthesizing empirical data, scale-up equations, and industrial case studies to establish a rigorous framework for scale-resilient QbD execution.

OBJECTIVES

The primary objectives of this comprehensive review are as follows:

1. To deconstruct the practical implementation steps of the QbD framework specifically tailored for solid oral dosage forms, tracking the path from initial QTPP definition to the establishment of the control strategy.
2. To systematically identify and analyze the critical scale-dependent parameters across key unit operations (blending, granulation, drying, compression) that cause scale-up failures.
3. To provide quantitative comparisons and structured methodologies for translating laboratory-scale Design Spaces to full industrial-scale commercial environments.
4. To evaluate the role of Process Analytical Technology (PAT) and mathematical modeling as bridging mechanisms to achieve continuous process verification and robust risk mitigation during technology transfer.

METHODOLOGY

This review employs a rigorous, multi-tiered analytical approach, synthesizing high-impact peer-reviewed research, industrial white papers, regulatory guidelines (FDA, EMA, ICH), and historical scale-up case studies published between 2010 and 2026. A comprehensive literature search was conducted using databases including PubMed, ScienceDirect, Scopus, and Google Scholar, using string combinations such as 'Quality by Design' AND 'Solid Oral Dosage' AND 'Scale-Up' AND 'Design Space' AND 'Process Parameter'. Over 150 papers were initially screened based on technical relevance, scientific rigor, and industrial applicability. The selected literature was categorized into distinct modules tracking specific unit operations (high-shear wet granulation, fluid bed drying, roller compaction, and tablet compression) to isolate scale-dependent variables. Quantitative data regarding process shifts, parameter sensitivities, and mathematical scale-up correlations were extracted, harmonized, and compiled into structural matrices to enable direct comparative evaluation and modeling insights.

Methodological Focus: By grouping engineering scale-up criteria (such as constant tip speed vs. constant Froude number) across modern pharmaceutical literature, this methodology establishes a clear predictive pipeline for solid oral manufacturing scale transition.

RESULTS AND FINDINGS

The systematic implementation of QbD mandates a clear, sequential alignment of technical parameters.Table 1 outlines a typical Quality Target Product Profile (QTPP) for an immediate-release solid oral tablet, translating clinical needs into quantifiable engineering targets.

Table 1: Representative Quality Target Product Profile (QTPP) framework for an immediate-release solid oral dosage form

QTPP Element	Target Requirement	Justification / CQA Linkage
Dosage Form & Route	Oral Tablet, Immediate Release	Ensures high patient compliance and standardized delivery route.
Strength / Potency	50 mg active pharmaceutical ingredient (API)	Maintains required clinical therapeutic efficacy and safety parameters.
Content Uniformity	Meets USP <905> criteria (Acceptance Value ≤ 15)	Directly impacts dose consistency; linked to CQA of blend homogeneity.

Dissolution Profile	≥ 85% dissolved within 15 minutes in pH 1.2 buffer	Ensures immediate drug release and rapid systemic bioabsorption.
Physical Stability	No capping, lamination, or friability < 0.5%	Guarantees mechanical integrity during bulk packaging and transport.

Once the QTPP is defined, the formulation team isolates the Critical Quality Attributes (CQAs) and executes a rigorous Failure Mode and Effects Analysis (FMEA) to pinpoint high-risk process steps. During scale-up, the nature of these risks shifts drastically due to geometric and thermodynamic alterations. Table 2 presents a comprehensive analysis contrasting laboratory-scale parameters with industrial-scale deviations across primary unit operations, highlighting the critical engineering variables that must be adjusted to maintain process equilibrium.

Table 2: Comparative analysis of process dynamics, critical variables, and scale-up equations between scales

Unit Operation	**Lab-Scale (1–5 kg) Baseline**	**Industrial Scale (100–500 kg)**	**Critical Scale-Up Equation / Variable**
High-Shear Wet Granulation	Low mass effects, uniform liquid distribution via manual spraying.	Mass-induced segregation, localized over-granulation near spray zone.	Constant Froude Number: $Fr = N^2D / g$ (where N = impeller speed, D = diameter).
Fluid Bed Drying	Rapid, uniform heat transfer; low bed height (15–30 cm).	Channelling risks, thermal gradients, high bed pressure drops.	Air Velocity Scaling & Thermodynamic Balance: $G = \rho \times V \times A$.
Roller Compaction	Low dwell times, edge leakage easily contained manually.	Severe bypass material leakage, non-uniform ribbon density.	Schweizerhof Screw-to-Roll Ratio & Specific Compaction Force (kN/cm).

Tablet Compression	Low turret speeds, extended dwell times (30–50 ms).	High-speed force application, extremely short dwell times (< 10 ms).	Strain Rate Sensitivity Index & Strain Energy Density Relationships.

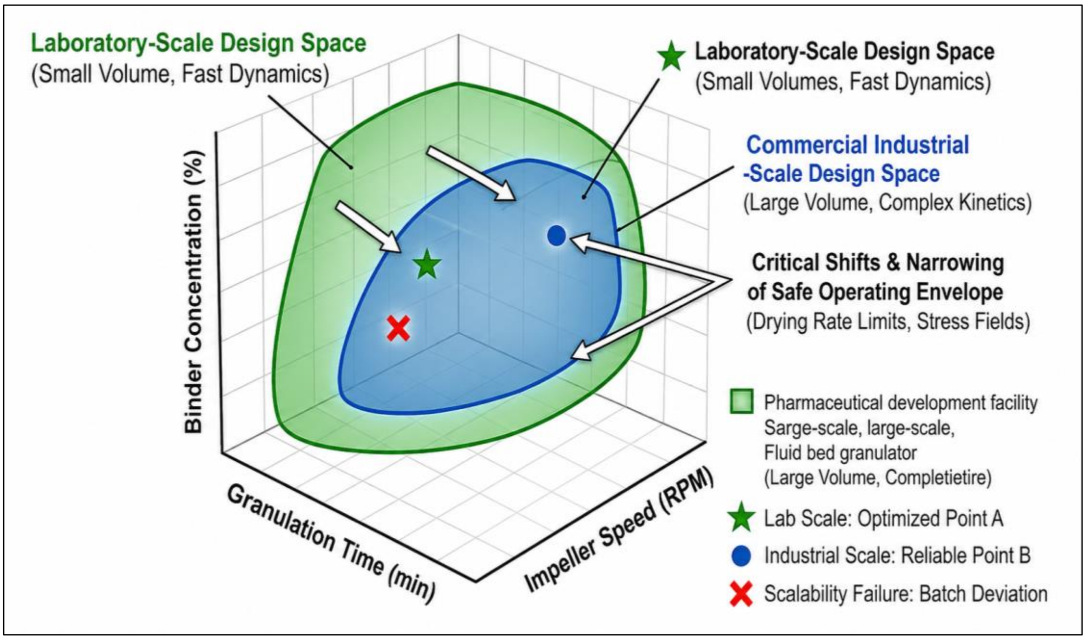

Figure 1: Multidimensional Design Space overlay highlighting the critical shifts and narrowing of the safe operating envelope when transitioning from laboratory-scale (green) to industrial commercial-scale (blue) production environment

DISCUSSION

The operational core of the findings reveals that scaling up pharmaceutical processes is rarely a linear function of geometric expansion. As demonstrated in Table 2, maintaining a constant impeller tip speed during the scale-up of high-shear wet granulation often leads to a drastic reduction in the Froude number, resulting in insufficient bulk movement and widespread over-granulation or mechanical pocketing [8]. Conversely, maintaining a constant Froude number can introduce extreme shear forces at the blade tips, fracturing fragile API crystals. This fundamental paradox requires the formulation of a multi-dimensional Design Space that treats scale as a distinct, fluid independent variable rather than a static constraint. By utilizing mathematical modeling, such as Discrete Element Method (DEM) simulations for particle movement and Computational Fluid Dynamics (CFD) for heat and mass transfer, engineers can accurately simulate the stress fields within large-scale industrial blenders and fluid bed dryers before physical fabrication [9].

Furthermore, the integration of advanced Process Analytical Technology (PAT) bridges the visibility gap inherent to larger batches. While a laboratory batch can be monitored adequately via periodic thief sampling, commercial production lines require inline, non-destructive monitoring to capture fast-moving kinetic changes. Near-Infrared (NIR) probes mounted directly to the blending vessel or the discharge chute provide real-time data on moisture levels and blend homogeneity, allowing operators to terminate drying or mixing precisely when the target end-point is achieved, irrespective of absolute batch volume or temporal differences [10]. Consequently, the traditional reliance on rigid time-based manufacturing blocks is replaced by a dynamic, responsive control strategy that actively accommodates raw material variations and scaling deviations.

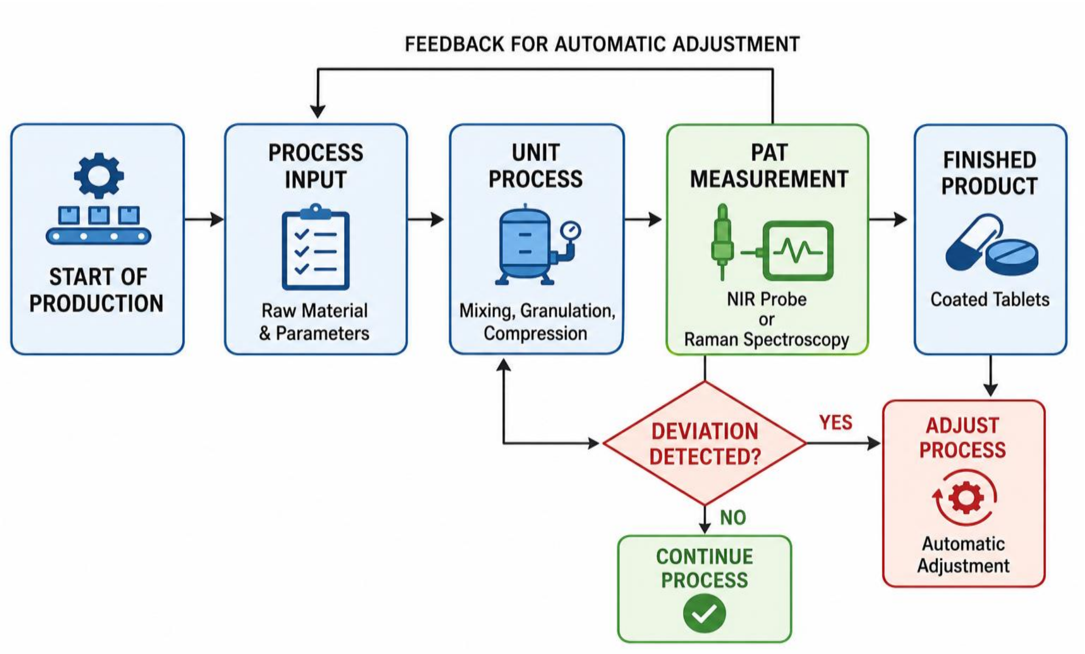

Figure 2: Flowchart illustrating a closed-loop QbD control architecture utilizing real-time PAT feedback to dynamically adjust Critical Process Parameters (CPPs) in response to raw material deviations

LIMITATIONS

While the QbD framework offers unparalleled manufacturing stability, its industrial execution is limited by several significant constraints. First, the upfront resource allocation—

in terms of analytical instrumentation, specialized engineering software, and extensive preliminary DoE experimental batches—presents a steep financial barrier for small-to-medium enterprises (SMEs) and generic manufacturers [11]. Second, the complex mathematical models generated during laboratory development (e.g., partial least squares regression for NIR calibration) are often highly instrument-specific and material-lot dependent. When transferring these models to commercial plants with different sensor configurations, recalibration requires substantial time and effort. Lastly, global regulatory alignment remains uneven; while the FDA and EMA strongly advocate for Design Space flexibility, regulatory bodies in several emerging markets still mandate strict adherence to fixed, single-point process variables, forcing companies to maintain dual regulatory dossiers for the same drug product.

FUTURE SCOPE

The future of pharmaceutical manufacturing lies in the seamless integration of QbD with advanced digital technologies and continuous processing architectures. The industry is rapidly moving toward the concept of 'Digital Twins'—highly precise, real-time virtual replicas of physical unit operations powered by machine learning and historical manufacturing datasets [12]. These digital twins will allow operators to predict the impact of excipient variability on final tablet dissolution rates instantly, adjusting machine parameters autonomously mid-batch. Furthermore, transitioning from traditional batch manufacturing to fully continuous manufacturing lines (where blending, granulation, and tableting occur in a unified stream) will inherently eliminate traditional scale-up challenges, as batch size is determined by running time rather than vessel volume, cementing QbD as an essential pillar of Industry 4.0 pharmaceutical systems.

CONCLUSION

The transition from empirical development to Quality by Design represents a necessary and major evolutionary step for solid oral dosage form manufacturing. By establishing a rigorous, quantitative understanding of the complex interdependencies between raw material attributes and process kinetics, QbD provides the mathematical and engineering foundation required to navigate difficult scale-up transitions. As detailed in this review, common scale-up defects such as segregation, capping, and dissolution shifts can be effectively predicted and avoided by defining scale-resilient Design Spaces, utilizing advanced scale-up equations, and deploying real-time PAT tools. Although barriers regarding upfront capital expenditure and regulatory disharmony remain, the long-term operational benefits—including reduced batch failures, maximized manufacturing efficiency, and continuous quality verification—clearly establish QbD as an indispensable tool for modern pharmaceutical quality management.

REFERENCES

1. Woodcock, J. (2004). The concept of pharmaceutical quality by design. AAPS Journal, 6(4), 1-3.
2. International Council for Harmonisation (ICH). (2009). ICH Guideline Q8(R2): Pharmaceutical Development. Geneva, Switzerland.
3. Rekhi, G. S., & Sidwell, R. (2018). Solid oral dosage forms: Development and scale-up strategies. Journal of Pharmaceutical Sciences, 107(5), 1195-1208.
4. Lionberger, R. A., Lee, S. L., Lee, L., Choi, A., & Yu, L. X. (2008). Quality by design: Concepts for ANDAs. AAPS Journal, 10(2), 268-276.
5. Yu, L. X., Amidon, G., Khan, M. A., Hoag, S. W., Polli, J., Raju, G. K., & Woodcock, J. (2014). Understanding pharmaceutical quality by design. AAPS Journal, 16(4), 771-783.
6. Politis, S. N., Colombo, P., Colombo, G., & Rekkas, D. M. (2017). Design of experiments (DoE) in pharmaceutical development. Drug Development and Industrial Pharmacy, 43(6), 889-901.
7. Bakeev, K. A. (2021). Process Analytical Technology (PAT): Spectroscopic applications in pharmaceutical manufacturing. John Wiley & Sons.
8. Faure, A., York, P., & Rowe, R. C. (2001). Process control and scale-up of pharmaceutical wet granulation processes: A review. European Journal of Pharmaceutics and Biopharmaceutics, 52(3), 269-277.
9. Ketterhagen, W. R., am Ende, M. T., & Hancock, B. C. (2009). Process modeling in the pharmaceutical industry using the discrete element method. Journal of Pharmaceutical Sciences, 98(2), 442-470.
10. Fonteyne, M., Soares, S., Shen, J., Rocha, M., & De Beer, T. (2015). Evaluation of NIR and Raman spectroscopy for real-time monitoring of continuous pharmaceutical manufacturing. Journal of Pharmacy and Pharmacology, 67(4), 489-501.
11. Plumb, K. (2005). Continuous processing in pharmaceutical manufacturing: Is the

industry ready? Chemical Engineering Progress, 101(6), 34-40.

12. Gernaey, K. V., Cervera-Padrell, A. E., & Woodley, J. M. (2023). Digital twins and modeling in future pharmaceutical manufacturing systems. Current Opinion in Chemical Engineering, 39, 100892.

***Author for Correspondence**

Dr. Ramesh K. Sharma

E-mail: rameshk1298@gmail.com

[1]Associate Professor, Department of Pharmaceutics, Government College of Pharmacy, Karad, Maharashtra

[2]Professor, Department of Pharmaceutics, Government College of Pharmacy, Karad, Maharashtra

[3]Student, Department of Pharmaceutics, Government College of Pharmacy, Karad, Maharashtra,

[4]Student, Department of Industrial Pharmacy, Poona College of Pharmacy

Received Date: 18 January 2026

Accepted Date: 31 January 2026

Published Date: 28 February 2026

Citation: Dr. Ramesh K. Sharma, Prof. Sunita M. Verma, Amit S. Joshi, Rajesh Kumar. Application of Quality by Design (QbD) in the Development and Industrial Scale-Up of Solid Oral Dosage Forms: A Comprehensive Review. International Journal of Drug Analysis, Industrial Pharmacy and Pharmaceutical Research. 2026; 2(1): 15-25p.

