



JOURNAL OF THE ROYAL LAUREATES ACADEMY

www.rlaindia.org

DESIGN SPACE AND PROCESS CONTROL STRATEGIES FOR ROBUST MANUFACTURING OF ORAL TABLETS: A RISK-BASED QUALITY BY DESIGN FRAMEWORK

Singh Rahul Saroj

Research Scholar, Jayoti Vidyapeeth Women's University, Jaipur, Rajasthan

Dr. Avinash Shah

Research Supervisor, Jayoti Vidyapeeth Women's University, Jaipur, Rajasthan

ABSTRACT

Robust manufacturing of oral tablets requires systematic management of formulation and process variability throughout the product lifecycle. A risk-based Quality by Design framework provides a scientific basis for identifying critical quality attributes, critical material attributes, and critical process parameters and for establishing an appropriate design space and control strategy. This paper examines the role of design space and process control in achieving consistent quality during tablet manufacturing. Particular emphasis is placed on risk assessment, experimental characterization, multidimensional design space, process analytical technology, in-process monitoring, process validation, and continued process verification. The design space provides a scientifically justified operating region within which combinations of material attributes and process parameters can produce tablets meeting predefined quality requirements. The control strategy translates this understanding into practical controls for materials, equipment, processing conditions, in-process characteristics, and finished-product quality. ICH Q8 identifies design space and control strategy as important elements of enhanced pharmaceutical development, while ICH Q10 emphasizes monitoring of process performance and product quality throughout the lifecycle.

Keywords: Design Space, Quality by Design, Oral Tablets, Risk Management, Process Control, Critical Process Parameters, Process Validation, Pharmaceutical Manufacturing

I. INTRODUCTION

Manufacturing oral tablets consistently requires control over a complex network of formulation and process variables. Although tablets appear relatively simple as dosage forms, their quality is influenced by powder properties, excipient functionality, blending behavior, granulation, drying, lubrication, compression, coating, and environmental conditions. Variability in these factors can produce differences in tablet weight, strength, friability, disintegration, dissolution, assay, and content uniformity. Traditional approaches may rely heavily on fixed operating limits and final-product testing, whereas Quality by Design emphasizes understanding the relationships among material attributes, process parameters, and product quality before routine manufacturing begins.

Design space is a central concept within enhanced QbD. ICH Q8 defines it as the multidimensional combination and interaction of input variables and process parameters demonstrated to provide assurance of quality. The concept is particularly valuable for oral tablet manufacturing because several parameters can interact. For example, granule moisture, particle-size distribution, lubricant concentration, compression force, and press speed can collectively influence tablet mechanical properties and dissolution. A scientifically established design space therefore provides a more realistic representation of manufacturing behavior than isolated parameter limits.

Risk management is essential for establishing such a design space. ICH Q8/Q9/Q10 implementation materials state that scientific rationale and quality risk management can be used to identify CQAs and CPPs and support development of the control strategy. Risk assessment helps determine which variables require detailed experimental investigation and which can be managed through routine controls. This prevents excessive experimentation while directing resources toward the factors most likely to affect product quality.

A robust control strategy must then ensure that manufacturing remains within an appropriate state of control. ICH Q10 describes process performance and product quality monitoring as mechanisms for assuring continued process capability, identifying sources of variability, and supporting continual improvement. FDA process-validation guidance similarly emphasizes a lifecycle approach in which process understanding developed during design is carried through qualification and continued process verification. This paper therefore examines how

design space and risk-based process control can be integrated into robust oral tablet manufacturing.

II. RISK-BASED IDENTIFICATION OF CRITICAL VARIABLES IN TABLET MANUFACTURING

A risk-based QbD framework begins by defining the desired quality characteristics of the oral tablet. The QTPP establishes the intended dosage-form characteristics and provides a basis for identifying CQAs. For immediate-release tablets, dissolution, disintegration, assay, content uniformity, hardness, friability, and stability may be important quality characteristics. For modified-release tablets, dissolution behavior across specified time points may have particular importance. The criticality of each attribute should be linked to its potential impact on product quality, safety, and efficacy.

The next stage involves identifying critical material attributes. API particle size and distribution can affect flow, blending, compression, and dissolution. Solid-state characteristics can influence stability and dissolution behavior. Excipients may affect powder flow, compaction, disintegration, and drug release. Moisture can be particularly important because it may alter powder cohesion, granule formation, compression behavior, and stability. Consequently, material specifications should be scientifically connected to process performance rather than viewed only as incoming-quality requirements.

Potential CPPs can then be identified for each manufacturing operation. During blending, mixing speed, blending time, fill level, and sequence of addition may influence blend uniformity. During wet granulation, liquid quantity, addition rate, impeller speed, and endpoint may influence granule characteristics. Drying conditions affect residual moisture. Milling influences particle-size distribution. Lubrication can affect tablet strength and dissolution. During compression, force, dwell time, turret speed, feeder operation, and machine settings may affect tablet quality. The relevance of each parameter depends on the particular formulation and equipment.

Risk assessment tools can help organize these relationships. Failure Mode and Effects Analysis, for example, can rank potential failure modes based on severity, occurrence, and detectability. Fishbone diagrams can identify possible sources of variability associated with materials, methods, machines, measurements, environment, and personnel. Such tools do not by themselves prove criticality, but they help formulate hypotheses for experimental

investigation. ICH implementation guidance emphasizes that risk assessment and scientific understanding should support CQA and CPP determination.

The risk assessment should be updated as knowledge accumulates. A parameter initially classified as potentially high risk may prove to have limited impact within the proposed operating range. Conversely, a parameter initially considered low risk may become important when scale, equipment, or raw-material characteristics change. QbD therefore treats risk management as a continuing activity rather than a one-time documentation exercise.

This approach establishes a logical connection between risk, experimentation, and control. Instead of attempting to control every manufacturing variable with equal intensity, the manufacturer can focus enhanced monitoring and experimentation on variables with demonstrated or plausible relationships to CQAs. Such prioritization is fundamental to establishing a meaningful design space and an efficient control strategy.

III. ESTABLISHMENT AND APPLICATION OF DESIGN SPACE

Design-space development requires experimental characterization of the relationships among material attributes, process parameters, and CQAs. DoE is frequently useful because it allows several factors to be studied simultaneously and can identify interactions that may remain hidden in one-factor-at-a-time experiments. For tablet manufacturing, a factorial, response-surface, or other appropriate experimental design can investigate selected formulation and process variables.

The resulting mathematical models can describe how CQAs change as process conditions vary. For example, a model may demonstrate that tablet hardness increases with compression force but decreases beyond a certain region because of changes in material behavior. Another model may demonstrate that dissolution is affected jointly by lubricant level and compression force. Multiple response models can subsequently be combined to identify regions where all relevant quality requirements are simultaneously satisfied.

The design space should therefore be viewed as a multidimensional region rather than a single numerical setting. ICH Q8 explicitly describes it as a multidimensional combination and interaction of input variables and process parameters demonstrated to provide assurance of quality. This concept allows manufacturers to accommodate normal process variation while maintaining product quality. For example, a modest increase in one parameter may be

acceptable when accompanied by a corresponding adjustment in another parameter, provided the combination remains within the demonstrated design space.

Model verification and confirmation experiments are essential. Predicted operating conditions should be tested experimentally to determine whether the observed product quality agrees with model predictions. Appropriate statistical criteria and practical manufacturing considerations should be used when evaluating the model. The design space should also consider measurement uncertainty and the realistic variability of raw materials and equipment.

Scale-up introduces additional considerations. Laboratory-scale mixing, granulation, drying, and compression behavior may not exactly reproduce commercial-scale behavior because equipment geometry, energy input, heat transfer, residence time, and material movement can change. The design space should therefore be supported by process knowledge relevant to the intended manufacturing scale. ICH Q8/Q9/Q10 implementation guidance recognizes that knowledge generated during development provides a foundation for process validation and can be further developed during technology transfer and commercial manufacturing.

The practical value of design space is that it shifts process control from rigid isolated values toward scientifically justified operating regions. However, establishment of a design space does not eliminate the need for monitoring. Manufacturing should continue to monitor critical parameters and product attributes to verify that the process remains in a state of control. Design space and control strategy are therefore complementary concepts: design space defines a demonstrated region of acceptable operation, while the control strategy provides mechanisms for maintaining routine manufacturing within appropriate limits.

IV. PROCESS VALIDATION AND LIFECYCLE MANAGEMENT

Process validation is the mechanism through which process understanding is demonstrated under manufacturing conditions. FDA's process-validation guidance describes a lifecycle approach encompassing process design, process qualification, and continued process verification. A risk-based QbD strategy strengthens process validation by identifying critical sources of variability and defining the controls required to maintain acceptable performance.

During process design, laboratory and pilot-scale experiments establish the relationship between formulation variables, process parameters, and CQAs. During process qualification,

the commercial manufacturing system is evaluated under defined operating conditions. Equipment qualification, facility suitability, operator training, analytical methods, and material controls are important supporting elements. The objective is to demonstrate that the integrated process can reproducibly manufacture product meeting predetermined quality requirements.

Continued process verification extends validation into routine manufacturing. ICH implementation guidance describes CPV as continuous monitoring and evaluation of manufacturing process performance and notes that it may use in-line, on-line, or at-line measurements. For oral tablets, CPV can involve monitoring tablet weight, compression force, hardness, dissolution trends, assay, content uniformity, environmental conditions, and other relevant parameters over time.

Lifecycle management is necessary because commercial processes rarely remain completely unchanged. Equipment may be replaced, suppliers may change, formulations may be optimized, manufacturing sites may change, and new technologies may become available. ICH Q12 provides a framework for managing postapproval CMC changes and supporting continual improvement. A strong design-space and control-strategy framework can facilitate scientific assessment of such changes.

Change management should consider whether a proposed change affects established CQAs, CPPs, or the approved design space. If sufficient process understanding exists, the effect of a change may be evaluated systematically using risk assessment and targeted experimentation. This can be more efficient than repeating an entire development program. However, regulatory reporting and approval requirements remain applicable according to the relevant jurisdiction.

Modern manufacturing can further strengthen lifecycle control through continuous manufacturing and advanced process monitoring. ICH Q13 provides scientific and regulatory considerations for development, implementation, operation, and lifecycle management of continuous manufacturing. Although continuous manufacturing differs from conventional batch tablet production, its emphasis on real-time process understanding and control illustrates the broader direction of pharmaceutical manufacturing toward more integrated control systems.

Thus, validation and lifecycle management should be regarded as extensions of QbD rather than independent activities. Development knowledge provides the scientific foundation, design space defines demonstrated operating regions, the control strategy maintains routine control, validation confirms capability, and continued monitoring generates new knowledge. Together, these elements form an integrated quality-management system.

V. CONCLUSION

Design space and process control are important components of a risk-based Quality by Design framework for robust oral tablet manufacturing. Tablet quality depends on complex relationships among material attributes, formulation variables, equipment characteristics, and process conditions. A systematic QbD approach begins by establishing the QTPP and CQAs and then uses risk assessment and experimentation to identify variables requiring enhanced understanding and control.

The design space provides a scientifically demonstrated multidimensional region in which combinations of input variables and process parameters can produce acceptable product quality. ICH Q8 identifies design space as an element of enhanced pharmaceutical development and links it with product and process understanding and control strategy. This approach is particularly useful for tablet manufacturing because individual process variables frequently interact, making isolated parameter limits insufficient to describe actual process behavior.

A robust control strategy translates development knowledge into routine manufacturing practice. Material controls, equipment controls, in-process measurements, process analytical technologies, statistical monitoring, and finished-product testing can work together to maintain a state of control. ICH Q10 emphasizes process-performance and product-quality monitoring, while FDA's process-validation framework supports continued verification throughout the product lifecycle.

In conclusion, the integration of risk assessment, design space, process control, process validation, and lifecycle management provides a comprehensive foundation for robust oral tablet manufacturing. The approach reduces dependence on final-product testing alone and encourages proactive management of variability. Future pharmaceutical manufacturing is likely to benefit from increased use of real-time monitoring, multivariate analytics, continuous manufacturing, and advanced process-control technologies. When supported by

appropriate scientific evidence and a strong pharmaceutical quality system, the risk-based QbD framework can contribute to consistent tablet quality, efficient manufacturing, and continual process improvement.

REFERENCES

1. Charoo, N. A., Shamsher, A. A. A., Zidan, A. S., & Rahman, Z. (2012). Quality by design approach for formulation development: A case study of dispersible tablets. *International Journal of Pharmaceutics*, 423(2), 167–178. <https://doi.org/10.1016/j.ijpharm.2011.12.024>
2. Chávez, P.-F., Lebrun, P., Sacré, P.-Y., De Bleye, C., Netchacovitch, L., Cuypers, S., Mantanus, J., Motte, H., Schubert, M., Evrard, B., Hubert, P., & Ziemons, E. (2015). Optimization of a pharmaceutical tablet formulation based on a design space approach and using vibrational spectroscopy as PAT tool. *International Journal of Pharmaceutics*, 486(1–2), 13–20. <https://doi.org/10.1016/j.ijpharm.2015.03.025>
3. Djuris, J., Medarevic, D., Krstic, M., Djuric, Z., & Ibric, S. (2013). Application of quality by design concepts in the development of fluidized bed granulation and tableting processes. *Journal of Pharmaceutical Sciences*, 102(6), 1869–1882. <https://doi.org/10.1002/jps.23530>
4. Grangeia, H. B., Silva, C., Simões, S. P., & Reis, M. S. (2020). Quality by design in pharmaceutical manufacturing: A systematic review of current status, challenges and future perspectives. *European Journal of Pharmaceutics and Biopharmaceutics*, 147, 19–37. <https://doi.org/10.1016/j.ejpb.2019.12.007>
5. Gupta, A., & Kumar, R. (2014). Quality by design approach for pharmaceutical product development: A review. *International Journal of Pharmaceutical Sciences and Research*, 5(10), 1–10.
6. Kushner, J., Langdon, B. A., Hicks, I., Song, D., Li, F., Kathiria, L., Kane, A., Ranade, G., & Agarwal, K. (2014). A quality-by-design study for an immediate-release tablet platform: Examining the relative impact of active pharmaceutical ingredient properties, processing methods, and excipient variability on drug product quality attributes. *Journal of Pharmaceutical Sciences*, 103(2), 527–538. <https://doi.org/10.1002/jps.23810>
7. 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. <https://doi.org/10.1208/s12248-014-9598-3>

8. Yekpe, K., & Abatzoglou, N. (2018). Developing a quality by design approach to model tablet dissolution testing: An industrial case study. *Pharmaceutical Development and Technology*, 23(6), 1–9. <https://doi.org/10.1080/10837450.2017.1392566>
9. Won, D. H., Park, H., Ha, E.-S., Kim, H.-H., Jang, S. W., & Kim, M.-S. (2021). Optimization of bilayer tablet manufacturing process for fixed dose combination of sustained release high-dose drug and immediate release low-dose drug based on quality by design (QbD). *International Journal of Pharmaceutics*, 605, 120838. <https://doi.org/10.1016/j.ijpharm.2021.120838>