

Artificial Intelligence-Driven Quality by Design in Pharmaceutical Formulation Development: Applications, Challenges, and Future Perspectives

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ABSTRACT

The development of pharmaceutical formulations is changing. It is moving away from trial-and-error ways. Now modern approaches rely on science and data. Quality by Design or QbD offers a structured way to develop medicines. It starts with defining the Quality Target Product Profile or QTPP. Then it identifies Critical Quality Attributes or CQAs. It also looks at Critical Material Attributes or CMAs and Critical Process Parameters or CPPs. Design of Experiments or DoE helps in planning studies. This leads to the creation of a design space and a control strategy. Traditional QbD methods may not work well when variables are complex. They may not handle effects or strong interactions between factors. Artificial intelligence machine learning and predictive models can help. These tools can find patterns in data from experiments, formulations and manufacturing. This review looks at how AI fits into every stage of formulation development. It covers preformulation excipient selection, compatibility prediction, formulation optimization and predicting CQAs. It also includes identifying CMAs and CPPs. AI helps with process monitoring, Process Analytical Technology or PAT design space development and control strategy design. Applications are shown in solid dosage forms, modified-release systems, nanoparticulate and lipid-based formulations, continuous manufacturing, personalized medicines and 3D-printed medicines. Some challenges exist. These include data, overfitting models, models that are hard to understand lack of validation difficulties in scaling up regulatory issues and the need for diverse expertise. New ideas, like twins, continuous process verification, hybrid models that combine mechanics and AI generative AI and federated learning may push the field forward. In the end AI should support science not replace it. Experimental verification and mechanistic understanding are still essential.

Keywords: Artificial Intelligence, Critical Quality Attributes, Machine Learning, Pharmaceutical Formulation Development, Quality by Design.

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INTRODUCTION

Pharmaceutical formulation development has traditionally followed a path. Formulators adjust excipients, process settings and manufacturing conditions one at a time until a product meets the required standards. This trial-and-error method has led to successful medicines over the years. It takes a long time. It uses a lot of resources. It often fails to explain how different formulation and process factors affect the final product quality.

Quality by Design or QbD marks a shift. It was first formally introduced in the ICH Q8 (International Council for Harmonisation, 2009) Q9 (International Council for

Harmonisation, 2005). Q10 (International Council for Harmonisation, 2008) guidelines. Of testing quality after production QbD builds quality into the product from the start. It begins with a Quality Target Product Profile or QTPP. Then it identifies the Critical Quality Attributes or CQAs. Risk assessment follows to find Critical Material Attributes and Critical Process Parameters. After that systematic Design of Experiments or DoE is used. The process ends with defining a design space and creating a control strategy. Regulatory agencies and the industry have widely accepted this approach as the way to make pharmaceutical products with quality built in not tested in afterward (Yu *et al.*, 2014).

With its strengths traditional QbD has real-world difficulties. Classical Design of Experiments or DoE becomes harder to manage when there are variables. This is especially true when interactions between variables are complex or nonlinear. Response Surface Methodology or RSM works with a few factors. It often fails to model highly nonlinear or discontinuous relationships.



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These kinds of patterns are common in complex dosage forms (Rantanen and Khinast, 2015).

Artificial intelligence or AI has emerged as a complement to QbD. AI includes machine learning, deep learning and other computational methods. These tools can learn nonlinear patterns from experimental data, historical records and manufacturing information (Kolluri *et al.*, 2022). They often make assumptions than traditional statistical models (Rowe and Colbourn, 2006). When carefully integrated into the QbD framework AI can improve risk assessment, sharpen design spaces, speed up optimization and help monitor and control processes in time.

This review aims to give a critical look, at how AI can be used within the QbD framework throughout the pharmaceutical formulation development lifecycle. It covers applications, challenges and future directions (Bannigan *et al.*, 2021).

Quality by Design: Conceptual Framework

QbD is an approach to development. QbD begins with predefined objectives. Emphasizes understanding of the product and the process. QbD relies on science and, on quality risk management of essential elements of QbD are summarized below.

Quality Target Product Profile (QTPP)

The QTPP is a prospective summary of the quality characteristics of a drug product that ideally will be achieved to ensure desired efficacy and safety, considering the intended route of administration, dosage form, delivery system, dosage strength, and pharmacokinetic characteristics. The QTPP forms the foundation from which CQAs are subsequently derived (Rathore and Winkle, 2009).

Critical Quality Attributes (CQAs)

CQAs are physical, chemical, biological, or microbiological properties or characteristics that must be maintained within an appropriate limit, range, or distribution to ensure the desired product quality. Common CQAs in oral solid dosage forms include assay, content uniformity, dissolution rate, hardness, friability, disintegration time, and stability-related attributes such as degradation product levels.

Risk Assessment and Critical Material/Process Attributes

Risk assessment tools such as Failure Mode and Effects Analysis (FMEA), Ishikawa (fishbone) diagrams, and risk-ranking matrices are used to identify which Material Attributes (CMAs) and Process Parameters (CPPs) have the greatest potential impact on CQAs (Fahmy *et al.*, 2012). This prioritization step focuses subsequent experimental effort on the variables most likely to affect product quality.

Design of Experiments and Design Space

DoE is used to systematically vary CMAs and CPPs to develop a mathematical relationship with CQAs. The multidimensional combination of material attributes and process parameters within which quality is assured is termed the design space (Politis *et al.*, 2017). Movement within the design space is not considered a change requiring regulatory approval, providing manufacturing flexibility once the design space is established and approved.

Control Strategy

A control strategy is a planned set of controls derived from current product and process understanding that ensures process performance and product quality. It may include specifications on raw materials, in-process controls, Process Analytical Technology (PAT), and finished product testing (Nasr, 2007).

Artificial Intelligence and Machine Learning: A Brief Overview

AI refers to computational systems capable of performing tasks that typically require human intelligence, including pattern recognition, prediction, classification, and decision-making. Machine learning, a subset of AI, involves algorithms that learn relationships from data without being explicitly programmed with fixed rules. In the context of pharmaceutical formulation, the most relevant AI/ML techniques are summarized in Table 1 (Chan *et al.*, 2019).

Unlike traditional statistical DoE models, which typically assume specific functional forms (e.g., linear, quadratic), many AI algorithms can approximate arbitrary nonlinear functions, making them well suited for capturing complex formulation-process-quality relationships (Rowe and Roberts, 1998). However, this flexibility comes at the cost of reduced interpretability and increased risk of overfitting when datasets are small, which is a common constraint in pharmaceutical development (Domingos, 2012).

Integration of AI Across the QbD Workflow

AI can be embedded at multiple stages of the QbD workflow, from early preformulation through to commercial process control, complementing each core QbD element (Simões *et al.*, 2020).

AI in Preformulation Assessment

Preformulation studies characterize the physicochemical properties of Active Pharmaceutical Ingredients (APIs), including solubility, dissolution rate, partition coefficient, polymorphism, hygroscopicity, and stability. AI-based Quantitative Structure-Property Relationship (QSPR) models can predict properties such as aqueous solubility, melting point, and permeability directly from molecular descriptors, reducing the need for exhaustive experimental characterization at an early stage (Boobier *et al.*, 2020). Machine learning models trained

on large pharmaceutical databases have also been applied to predict polymorph stability and the likelihood of successful salt or cocrystal formation, informing early API selection decisions.

AI in Excipient Selection and Compatibility Prediction

Selection of compatible excipients is critical to formulation success. AI models, including classification algorithms trained on historical drug-excipient compatibility data (e.g., differential scanning calorimetry and Fourier-transform infrared spectroscopy datasets), can predict the likelihood of physical or chemical incompatibility before experimental testing (Zhao *et al.*, 2006). Recommender-system-like approaches have also been explored to suggest suitable excipient combinations based on similarity to previously successful formulations with comparable APIs and desired release profiles.

AI in Formulation Optimization

Formulation optimization traditionally relies on RSM following DoE. AI-enhanced optimization replaces or augments RSM with ANN-based models, which are then coupled with optimization algorithms such as genetic algorithms, particle swarm optimization, or Bayesian optimization to identify optimal formulation compositions (Chen *et al.*, 2022). This hybrid ANN-genetic algorithm approach has been applied to optimize matrix tablets, microspheres, nanoparticles, and self-emulsifying drug delivery systems, often achieving comparable or superior predictive accuracy relative to classical polynomial models, particularly when relationships between variables are strongly nonlinear (Aksu *et al.*, 2012).

AI for Prediction of Critical Quality Attributes

AI models can predict CQAs such as dissolution profiles, tablet hardness, friability, content uniformity, and drug release kinetics from formulation composition and process parameters. Predictive models allow formulators to conduct rapid *in silico*

screening of formulation variables before committing to physical experiments, substantially reducing the number of experimental runs needed to identify a robust formulation (Han *et al.*, 2018).

AI for Identification of CMAs and CPPs

Feature importance techniques associated with tree-based ensemble methods (e.g., random forest variable importance, gradient boosting feature importance) and model-agnostic interpretability tools such as SHAP (SHapley Additive exPlanations) values can rank material attributes and process parameters according to their influence on CQAs (Lundberg and Lee, 2017). This provides a data-driven complement to traditional risk assessment tools, potentially refining the initial risk ranking based on quantitative evidence from experimental or historical datasets.

AI in Process Monitoring, PAT, and Real-Time Release Testing

Process Analytical Technology relies on real-time or near-real-time measurement of critical parameters during manufacturing, often using spectroscopic techniques such as Near-Infrared (NIR) or Raman spectroscopy. AI and chemometric models are used to convert raw spectral data into predictions of blend uniformity, moisture content, or drug concentration in real time, supporting Real-Time Release Testing (RTRT) and continuous manufacturing (Chen *et al.*, 2021).

AI in Design Space Definition and Control Strategy Development

AI models, when combined with Monte Carlo simulation or probabilistic approaches, can be used to generate probability-based design spaces that account for uncertainty in model predictions, rather than relying solely on deterministic boundaries derived from RSM. This can result in a more statistically robust design space definition and a control strategy that better reflects the true risk of producing out-of-specification product under

Table 1: Commonly Used AI/ML Techniques in Pharmaceutical Formulation Development.

Technique	Underlying Principle	Typical Pharmaceutical Application
Artificial Neural Networks (ANNs)	Layered interconnected nodes that learn nonlinear input-output relationships	Prediction of dissolution profiles, drug release kinetics, tablet properties
Support Vector Machines (SVMs)	Finds optimal hyperplane separating classes or fitting regression data	Classification of formulation success/failure, solubility prediction
Random Forests / Gradient Boosting	Ensemble of decision trees combined to improve prediction accuracy	Ranking of critical material attributes, CQA prediction
Gaussian Process Regression / Bayesian Optimization	Probabilistic modelling providing predictions with uncertainty estimates	Design space exploration, adaptive experimental design
Genetic Algorithms	Evolutionary optimization inspired by natural selection	Formulation optimization, multi-objective excipient selection
Deep Learning / Convolutional Neural Networks	Multi-layer networks capable of learning from complex/image data	Tablet coating defect detection, granule image analysis

Table 2: AI Applications Mapped to QbD Elements.

QbD Element	Conventional Approach	AI-Enhanced Approach
QTPP definition	Expert judgment, literature review	Text-mining and NLP of literature/regulatory databases to inform QTPP
CQA identification	Risk assessment, prior knowledge	Data-driven correlation analysis and feature selection
CMA/ CPP screening	FMEA, Ishikawa diagrams	Feature importance ranking (random forest, SHAP)
DoE and modelling	Factorial/RSM designs, polynomial models	ANN, SVM, Gaussian process regression models
Optimization	Desirability function on RSM models	Genetic algorithms, Bayesian optimization on ML models
Design space	Deterministic RSM-derived boundaries	Probabilistic/Monte Carlo-based design space
Process monitoring	Univariate/multivariate SPC, PAT with chemometrics	Deep learning-based spectral and image analysis, soft sensors
Control strategy	Fixed specifications and IPC limits	Adaptive, model-predictive control strategies

normal operating variability (Table 2) (International Council for Harmonisation, 2019).

Representative Application Areas

Oral Solid Dosage Forms

ANN-based models have been widely applied to predict tablet hardness, disintegration time, and dissolution profiles from formulation composition and compression force (Bannigan *et al.*, 2021). Genetic algorithm-coupled ANN models have been used to identify optimal formulations meeting multiple simultaneous quality targets, such as achieving a target dissolution profile while minimizing friability (Sun *et al.*, 2003).

Modified-Release and Matrix Systems

For extended-release matrix tablets, AI models can capture the complex, often nonlinear relationship between polymer type/level, drug loading, and resulting release kinetics, which may not follow classical release models (e.g., Higuchi, Korsmeyer-Peppas) closely across the entire compositional space. Machine learning models can complement mechanistic release models by predicting deviations attributable to formulation-specific factors.

Nanoparticulate and Lipid-Based Systems

Nanoparticle and liposome formulations involve numerous interacting variables (lipid ratio, surfactant concentration, sonication time, homogenization pressure) that influence particle size, polydispersity index, zeta potential, and encapsulation efficiency. AI-based QbD approaches, often combining DoE with ANN or SVM regression, have been used to model and optimize these multivariable systems more efficiently than RSM alone, particularly given the frequently nonlinear and interaction-heavy nature of nanoparticle formation processes (He *et al.*, 2021).

Continuous Manufacturing and Process Control

In continuous manufacturing platforms, AI-based soft sensors integrated with PAT data streams support real-time prediction of CQAs and can inform model-predictive control strategies that automatically adjust process parameters to maintain output within the approved design space, reducing batch-to-batch variability relative to fixed-setpoint control (Fonteyne *et al.*, 2015).

Personalized and 3D-Printed Formulations

AI models are increasingly explored to support personalized dosing, particularly in 3D-printed dosage forms, where machine learning can predict how printing parameters and formulation composition influence dose accuracy and release profile for patient-specific formulations, potentially enabling QbD principles to be extended to small-batch or individualized manufacturing (Elbadawi *et al.*, 2020).

CHALLENGES AND LIMITATIONS

Despite considerable promise, several important challenges must be addressed before AI-driven QbD can be routinely and confidently applied in pharmaceutical development and regulatory submissions (Table 3).

Data Quality and Availability

AI models are highly dependent on the quality, quantity, and representativeness of training data. Pharmaceutical development datasets are often small, heterogeneous across studies, and may contain inconsistent measurement conditions, limiting model generalizability. Sparse or imbalanced datasets increase the risk of overfitting, where a model performs well on training data but fails to generalize to new formulations or scales.

Model Interpretability (the 'Black-Box' Problem)

Many high-performing AI models, particularly deep neural networks, function as 'black boxes' that provide limited insight into the mechanistic basis of their predictions, which poses a challenge for fields that traditionally emphasize mechanistic understanding and transparent regulatory review (Vellido, 2020). Interpretability tools such as Local Interpretable Model-Agnostic Explanations (LIME) can partially address this gap but do not fully substitute for mechanistic understanding (Ribeiro *et al.*, 2016).

External Validation and Reproducibility

Many published AI-QbD models are validated only internally (e.g., cross-validation on the same dataset) rather than through independent external validation using new experimental batches, different equipment, or different sites. Without external validation, there is uncertainty regarding whether a model's predictive performance will hold under real manufacturing conditions.

Scale-Up and Technology Transfer

Models developed using laboratory-scale data may not directly translate to pilot or commercial scale due to differences in equipment geometry, mixing dynamics, and heat/mass transfer characteristics. Incorporating scale-independent dimensionless parameters or transfer-learning approaches may help address this limitation but remains an area requiring further methodological development (Muteki *et al.*, 2011).

Regulatory Considerations

Regulatory agencies have shown growing interest in AI applications for pharmaceutical development and manufacturing, as reflected in recent guidance and discussion papers on this topic (U.S. Food and Drug Administration, 2023). However, expectations regarding model validation, lifecycle management,

change control for adaptive/continuously learning models, and documentation of model development remain evolving areas.

Interdisciplinary Expertise Requirements

Effective AI-QbD implementation requires collaboration between formulation scientists, process engineers, data scientists, and regulatory affairs professionals. A lack of shared vocabulary and mutual understanding between these disciplines can lead to models that are statistically sound but pharmaceutically unrealistic.

EMERGING OPPORTUNITIES AND FUTURE PERSPECTIVES

Digital Twins and Digital Manufacturing

Digital twin technology, wherein a virtual model of a manufacturing process is continuously updated with real-time plant data, offers the potential to simulate process behavior under varying conditions without physical experimentation. Integration of AI-based digital twins with QbD could allow continuous refinement of the design space using ongoing production data, supporting post-approval change management (Rathore *et al.*, 2023).

Real-Time Data Analytics and Continuous Process Verification

Continuous Process Verification (CPV), the third stage of the process validation lifecycle (U.S. Food and Drug Administration, 2011), relies on ongoing monitoring of process performance. AI-based analytics applied to routinely collected manufacturing data can identify subtle trends or drifts before they result in out-of-specification product, enabling a more proactive, rather than reactive, approach to process control.

Personalized and On-Demand Formulations

As personalized medicine and point-of-care manufacturing become more feasible, AI-driven QbD principles could be

Table 3: Key Challenges in AI-Driven QbD and Potential Mitigation Strategies.

Challenge	Underlying Issue	Potential Mitigation
Limited data	Small experimental datasets typical of pharma development	Design-of-experiments-guided data generation; data augmentation; transfer learning
Black-box models	Limited mechanistic transparency	SHAP/LIME interpretability; hybrid mechanistic-ML models
Overfitting	High model flexibility vs. limited data	Cross-validation, regularization, simpler models where appropriate
Lack of external validation	Internal validation only	Independent test sets, multi-site/multi-batch validation
Scale-up uncertainty	Lab-to-plant differences	Dimensionless scale-independent variables; pilot-scale confirmation
Regulatory uncertainty	Evolving guidance on AI model lifecycle	Early regulatory engagement; transparent model documentation

adapted to support rapid, individualized formulation design while maintaining an auditable, risk-based quality framework appropriate for small-batch or single-unit production.

Hybrid Mechanistic-AI (Grey-Box) Models

A promising direction involves combining mechanistic pharmaceutical models (e.g., physiologically based pharmacokinetic models, mechanistic dissolution models) with data-driven AI components, creating 'grey-box' models that retain interpretability while benefiting from the pattern-recognition strengths of AI.

Generative AI and Large Language Models in Formulation Science

Generative AI and large language models are beginning to be explored for literature synthesis, formulation knowledge management, and generation of candidate formulation compositions based on learned patterns from historical development data. While still nascent in regulated pharmaceutical contexts, these tools may eventually support faster hypothesis generation during early formulation screening, subject to appropriate validation.

Federated and Collaborative Learning

Given that individual companies often possess limited proprietary datasets, federated learning approaches-in which models are trained collaboratively across multiple organizations without sharing raw data-may help build more generalizable AI-QbD models while preserving data confidentiality.

CONCLUSION

AI-driven QbD represents a meaningful evolution of the traditional QbD framework, offering the potential to model complex, nonlinear formulation-process-quality relationships more effectively than classical statistical approaches alone. Applications spanning preformulation, excipient selection, formulation optimization, CQA prediction, CMA/CPD identification, process monitoring, and control strategy development demonstrate the breadth of opportunity for AI integration across the pharmaceutical development lifecycle.

Nevertheless, realizing this potential requires addressing substantial challenges related to data quality and availability, model interpretability, external validation, scale-up translation, and regulatory alignment. AI should be regarded as a powerful decision-support tool that complements, rather than replaces, sound pharmaceutical science, experimental confirmation, and mechanistic understanding. With appropriate validation and a balanced integration of computational prediction and experimental verification, AI-enhanced QbD holds significant promise for accelerating the development of robust, high-quality pharmaceutical products (Paul *et al.*, 2021).

ABBREVIATIONS

AI: Artificial Intelligence; **AI/ML:** Artificial Intelligence/Machine Learning; **ANN:** Artificial Neural Network; **API:** Active Pharmaceutical Ingredient; **CMA:** Critical Material Attribute; **CMA(s):** Critical Material Attribute(s); **CNN:** Convolutional Neural Network; **CPV:** Continuous Process Verification; **CQA:** Critical Quality Attribute; **CQA(s):** Critical Quality Attribute(s); **CPP:** Critical Process Parameter; **CPP(s):** Critical Process Parameter(s); **DoE:** Design of Experiments; **FDA:** Food and Drug Administration; **FMEA:** Failure Mode and Effects Analysis; **FTIR:** Fourier-Transform Infrared Spectroscopy; **GA:** Genetic Algorithm; **ICH:** International Council for Harmonisation; **IPC:** In-Process Control; **LIME:** Local Interpretable Model-Agnostic Explanations; **LLM(s):** Large Language Model(s); **ML:** Machine Learning; **NIR:** Near-Infrared Spectroscopy; **NLP:** Natural Language Processing; **PAT:** Process Analytical Technology; **PBPK:** Physiologically Based Pharmacokinetic; **QbD:** Quality by Design; **QSPR:** Quantitative Structure-Property Relationship; **QTPP:** Quality Target Product Profile; **RSM:** Response Surface Methodology; **RTTR:** Real-Time Release Testing; **SHAP:** SHapley Additive exPlanations; **SPC:** Statistical Process Control; **SVM:** Support Vector Machine.

CONFLICT OF INTEREST

The authors declare that there is no conflict of interest.

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