

Quality by Design (QbD) in Pharmaceutical Development: Analytical and Regulatory Perspectives

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ABSTRACT

Background: Quality by Design (QbD) is a structured, risk-based approach that embeds quality into pharmaceutical development through scientific rationale, analytical controls, and formulation strategies. It is supported by ICH guidelines Q8 (Pharmaceutical Development), Q9 (Quality Risk Management), and Q10 (Pharmaceutical Quality System), ensuring product consistency, regulatory compliance, and patient safety.

Aim: This review aims to critically evaluate the principles, tools, and applications of QbD in pharmaceutical sciences, focusing on its role in dosage form design, analytical method development, and regulatory submissions.

Methods: Relevant scientific literature, regulatory documents, and case studies were reviewed to explore the implementation of QbD tools, including the Quality Target Product Profile (QTPP), Critical Quality Attributes (CQAs), Design of Experiments (DoE), and risk assessment methodologies.

Results: QbD adoption has demonstrated significant benefits in minimizing process variability, reducing development costs, and improving manufacturing robustness. Its application extends to advanced drug delivery systems, including nanocarriers, thereby facilitating innovation while enhancing regulatory acceptability and global harmonization.

Conclusion: QbD is a transformative framework that strengthens pharmaceutical development by integrating science- and risk-based principles. Endorsed by regulatory bodies such as the FDA and ICH, it continues to optimize complex formulations, elevate product quality, and improve healthcare outcomes worldwide.

Keywords: QbD, QTPP, CQAs, DoE, Risk Assessment, Drug Delivery, Nanocarriers

1. INTRODUCTION

Pharmaceutical development aims at two main goals, that is making a great product as well as the establishment of a reliable production procedure that allows the final product to be effective as intended. Firstly, the scientific knowledge acquired from drug creation, exploration and manufacturing helps in defining the design criteria, requirements and control methods. Due to this knowledge, creating a solid framework that guides performance and quality during the entire cycle of a product is more seamless ^[1]. The successful use of drug development research data underpins effective risk minimisation systems. Testing is not enough to guarantee product quality; product design itself must include key quality characteristics. The changes to manufacturing and production procedures Lifecycle management and development should be interpreted as means for improving knowledge and enlarging design space ^[2]. In addition, the integration of ideas of studies that produce unexpected results can be beneficial in the development procedure. The applicant's suggested design space must undergo regulating review along with obtained consent. The alterations do not apply to the activities carried out within the designated area for design purposes ^[3]. This is considered outside the pre-established design limits, which triggers the formal change process with the management approved by the regulation at the exit of the baseline. The product also needs to regularly satisfy patient demands, as well as guarantee maximum performance during their life. There are many different ways in which the development of products between companies and products can be addressed. Multiple presentation modes can be used to clarify key ideas ^[4]. An applicant can decide to develop their product in an experimental manner, systematically, or by combining the two methods. Throughout the product life cycle, a methodical approach known as Quality by Design (QbD) integrates existing knowledge and research findings by applying using knowledge management concepts, employing quality risk management strategies, and designing experiments (DoE) (as described in ICH Q10) ^[5]. Managers can better understand the company's strategic framework and raise the likelihood of achieving the desired level of product quality by adopting such a methodical approach. Additionally, information acquired is used to update and improve knowledge of a product and process over the course of its life cycle ^[6]. Scientific approaches offer comprehensive along with detailed information from product creation to manufacture. The QbD framework successfully lowers risks by increasing manufacturing efficiency and product quality. Standardized formulas have been successfully created in modern practice using the QbD approach. Specific QbD requirements have been released by the USFDA for both immediate and delayed release therapeutic formulations and biotechnology-based medications ^[7]. Scientific approaches offer comprehensive and detailed information from product creation to manufacture. The QbD framework successfully lowers risks by increasing manufacturing efficiency and product quality. Specific QbD requirements have been released by the USFDA for both immediate and delayed release therapeutic formulations and biotechnology-based medications ^[8]. Regulatory bodies are always advocating for the application of ICH quality standards, including Q8, Q9, Q10, and Q11. For the purpose to promote a deeper scientific comprehension of significant processes and the QbD method was developed to improve product quality. This framework emphasizes the establishment of controls and tests grounded in scientific principles in order to fill in knowledge gaps in the field of pharmaceutical research and application ^[9]. A continuous improvement architecture that integrates a systematic approach to pharmaceutical development known as QbD, supports the product lifecycle. This approach uses manufacturing process design and optimization to continuously guarantee and preserve the desired degree of final product quality ^[10]. Instruction guided by mathematical models facilitates the systematic acquisition and application of topic knowledge, both individually and in integrated contexts. Based on rigorous risk assessment and scientific concepts, QbD emphasizes not just reducing diagnostic tests but also ensuring accurate diagnoses at the optimal time ^[11]. Using QbD facilitates the evolution of robust, robust processes that ensure compliance with ICH standards. The drug industry consequently takes an active part in QbD initiatives. Within the QbD framework, an environmentally optimal analytical approach is built by carefully assessing the variables that affect process robustness ^[12]. This approach facilitates the gradual improvement and refinement of analytical techniques. The literature has well-established techniques for incorporating QbD concepts into analytical procedures in a way that is comparable to how they are used in production processes. Techniques like benchmarking, identifying important quality characteristics (CQAs), including design-phase issues, and conducting comprehensive risk assessments can all be beneficial for developing analytical methods. The new trend highlights how management teams must adjust to these advancements in order to meet future regulatory requirements and product quality standards, even though pharmaceutical companies have not generally adopted it ^[13]. Industries are adopting this strategy quickly due to its many advantages and straightforward control techniques. Organizations such as the European Federation of Pharmaceutical Industries and Associations (EFPIA), the Analytical Technology Group (ATG), and Pharmaceutical Research and Manufacturers of America (PhRMA) provide thorough suggestions and guidance for the concurrent use of Quality by Design (QbD) principles ^[14]. Regulatory agencies and the pharmaceutical business are constantly striving to enhance the products' quality, safety, and therapeutic efficacy in order to guarantee that pharmaceutical goods directly impact patient health ^[15]. However, issues like manufacturing failures, financial limitations, inconsistent quality control of the final product, scale-up restrictions, and strict regulatory requirements have become major roadblocks for

researchers and the pharmaceutical sector. In order to ensure a methodical, sequential evaluation of formulations, regulatory agencies have placed an increasing emphasis on the use of QbD in the creation of pharmaceutical products. These failures not only impede product development but also make regulatory compliance more difficult, requiring the implementation of strong quality assurance strategies to ensure manufacturing efficiency and product reliability. This approach reduces the likelihood of failure and increases product robustness by simplifying the identification, assessment, and mitigation of high-risk materials and processes. As a result, QbD has significantly raised the success rate of pharmaceutical development by advancing a science-driven, risk-based framework that ensures regulatory compliance and product reliability.

Design: The product is meticulously designed to satisfy both functional specifications and patient expectations. In order to adhere to established criteria for product excellence, the manufacturing process is systematically organized. A comprehensive comprehension of the manner in which initial raw materials and essential processing variables influence product quality is established. The primary process variability sources are located and successfully managed. To ensure consistent product quality throughout its lifecycle, the process is perpetually monitored and refined ^[16].

Quality: Quality constitutes an essential element inside the QbD framework, which is characterized by the adherence to specified criteria to ensure its identity, potency, and quality of a product for its designated application ^[17-18].

2. QUALITY BY DESIGN (QbD)

QbD constitutes a logical framework for growth that begins with clearly defined Priorities and goals and an exhaustive awareness of the product as well as the associated processes, in compliance with ICH guideline Q8 (R1). This approach seamlessly integrates rigorous risk management strategies and is fundamentally grounded in robust scientific principles. QbD serves as a comprehensive framework for the formulation, evaluation, and oversight of manufacturing processes, incorporating in-process, monitoring essential quality parameters in real time, as required by the FDA's Process Analytical Technology (PAT) guidelines. Furthermore, it underscores the paramount importance of being aware of the interplay somewhere between the production procedure and the performance characteristics of both raw and processed materials. Regarding the quality and safety of the finished product ^[17-18].

2.1. History of QbD

The notion of excellence through design as well as its subsequent application within engineering methodologies was originally articulated by Dr. Joseph M. Juran. Edwards Deming further elaborated on the QbD foundation all over the year 1986. In an attempt to improve manufacturing efficiency and product quality, the FDA introduced a revised framework entitled 21st Century Current Good Manufacturing Practices (cGMP): A Risk-Based Strategy for the Year 2002. The integration of QbD principles can significantly advance the development of novel products, the implementation of industrial quality management protocols, and the automation processes in the study and creation of pharmaceuticals as well as manufacturing ^[19].

2.2. Principles of QbD

Decision-making is informed by both risk assessment and knowledge acquisition; A methodical framework is employed for the development of processes; Ongoing enhancement contributes to the establishment of capable processes.

2.3. Objectives of QbD ^[20-21]

QbD's main goal is to guarantee and uphold product quality through a methodical framework. The essential components of this approach include:

1. Maintaining consistent product quality throughout its lifecycle.
2. Enhancing practical knowledge during the development phase.
3. Improving product efficiency by reducing variability through a comprehensive understanding of processes, design controls, and optimization techniques.
4. Achieving superior outcomes in quality assessments.
5. Establishing a robust foundation for the implementation of QbD principles.

6. Enhancing the design, knowledge and command of products and methods to increase process capability while minimizing product variability and errors.
7. Meeting clinically relevant performance-based standards for product quality.
8. Increasing the efficiency of manufacturing and product development processes.
9. Enhancing management of post-approval changes and conducting thorough root cause analyses.
10. This framework is applicable to drug ingredients as well as medication products.
11. Reducing failure rates and improving product performance.
12. Establishing a working range that does not compromise product quality.
13. Minimizing waste, project rejections, and costs while simultaneously enhancing manufacturing efficiency.

2.4. Advantages of QbD ^[22]

Putting QbD into practice presents several significant advantages, including:

1. Enhancement of product quality through a thorough and methodical comprehension of the production process.
2. Provision of a robust scientific foundation for pharmaceutical development.
3. Elevation of commercial and operational standards to achieve excellence.
4. Promotion of the advancement and application of sophisticated technological capabilities.
5. Facilitation of continuous improvements in product consistency and quality.
6. Assurance of accuracy and reliability in manufacturing and development processes.
7. Effective identification and resolution of process-related challenges.
8. Support for strategic and informed decision-making throughout the product development lifecycle.
9. Mitigation of compliance risks and improvement of adherence to regulatory requirements.
10. Optimization of processes to eliminate defective batches and ensure consistent quality.
11. Contribution to the production of superior, safer, and more effective pharmaceutical products.
12. Acceleration of drug development processes while ensuring safety.
13. The use of QbD equips the production crew with a thorough knowledge of the criteria governing the development process and their interrelationships, thereby greatly lowering the probability of failure by aiding teams in risk assessment and appropriate response.
14. It provides a thorough knowledge of critical material as well as process variables and how they affect the end product's quality of the pharmaceutical product.
15. By adopting QbD, organizations can minimize variability between batches and enhance consistency across production runs.
16. The QbD framework integrates quality into the production process through the establishment and control of essential characteristics.
17. This facilitates intermediate checkpoints for product evaluation throughout the process, thereby simplifying root cause analysis.

2.5. Prospects of QbD ^[23-25]

QbD presents a multitude of advantages, which include the following:

- Decreasing expenses, increasing manufacturing efficiency and minimizing waste through the implementation of effective methodologies.
- Fostering a comprehensive understanding of all processes and products involved.
- Addressing complex scientific challenges within valuable industries.
- Establishing cost-effective, adaptable, and flexible systems that can respond to evolving demands.
- Integrating robust risk management strategies to ensure compliance and maintain quality standards.

2.6. Key Activities & Elements of QbD

QbD represents a knowledge based, risk-oriented, comprehensive, along with proactive methodology for pharmaceutical product development, with the objective of enhancing product aspects. It necessitates that both the drug product and the associated processes be meticulously planned and designed prior to the initiation of experimental procedures.

2.6.1. Clinical Development

- Conducting preclinical and non-clinical investigations to establish foundational knowledge.
- Engaging in clinical research to confirm safety and efficacy.
- Implementing process scale-up to ensure readiness for manufacturing.
- Achieving market acceptance through the maintenance of consistent product quality.

2.6.2. Production

- Enhancing facility and spatial design to promote operational efficiency.
- Establishing real-time quality control mechanisms.
- Performing comprehensive technical process analyses to facilitate ongoing improvement.

2.6.3. Management Strategy

- Engaging in decision-making processes that are informed by risk assessment.
- Promoting ongoing enhancement throughout all phases of development and production.
- Guaranteeing uniform product performance through anticipatory management practices.

2.7. Quality by Design (QbD) Implementation Plan: Seven Strategic Steps

- Employ a systematic and expert design methodology to establish quality objectives.
- Conduct a thorough evaluation of organizational processes and methodologies to identify deficiencies.
- Facilitate workshops and training sessions on design quality for all team members.
- Review professional recommendations and findings to enhance strategic approaches.
- Develop a comprehensive plan that encompasses cost projections and implementation strategies.
- Outsource specific tasks as necessary to ensure proficiency and efficiency.
- Engage an impartial expert as a project management consultant to oversee implementation and maintain objectivity.

2.8. Important Attributes about QbD [26-32]

2.8.1. QTPP

The QTPP delineates the essential quality requirements as well as characteristics necessary for as well as development and design of a medication. The primary objective of the QTPP is to meet established quality standards while ensuring the product's effectiveness and safety. Key components of QTPP include following aspects:

- Purity and contamination control
- Stability and dissolution characteristics
- Bioavailability and bioequivalence
- Dosage and administration guidelines
- Pharmaceutical formulation
- Visual appearance
- Product identity
- Overall quality
- Marketing and promotional strategies

The QTPP specifies the critical attributes required to guarantee the caliber and performance among a medical item, tailored to its intended use as well as method of administration. Clearly defined quality metrics, such as CQAs as vital for patients as well as consumers to evaluate the effectiveness and security of the product.

2.8.2. Advantages of QTPP

- Enhances effectiveness along with risk management and identification of potential risks.
- Fosters timely decision-making regarding interventions that have the potential to preserve life.
- Supports the generation and dissemination of knowledge to advance product development.
- Guarantees that the pharmaceutical item is developed & manufactured in compliance according to quality standards, legal regulations, and anticipated in vivo performance criteria.

2.9. CQAs

CQAs encompass the chemical, biological, and physical and microbiological qualities that need to be maintained inside the designated thresholds to guarantee the purity and safety of a product. These attributes are relevant to excipients, API and intermediates, because they have an important part in both item development and safety assessments.

Key considerations regarding CQAs include the following:

- The necessity of sustaining CQAs within defined parameters throughout various distribution channels and across different geographic regions.
- The direct influence of CQAs on product safety, quality, and advancements in analytical methods.
- Application of analytical methodologies, such as HPLC, for the evaluation and regulation of CQAs in particular drug compositions.

2.10. Design Area

Within the product design phase, concept of design area involves understanding the connections between process variables and key material characteristics. This understanding facilitates development of comprehensive design strategies for projects that may involve multiple components. According to FDA guidelines, the design phase should prioritize acquiring sufficient knowledge about the product and its functionality, without necessitating complete system control at the outset.

2.11. Evaluation of Risk

Evaluation of risk constitutes systematic methodology for identification, analysis, prioritization of potential risks, considering their likelihood and severity. This process entails the anticipation of potential harm and the evaluation of its implications for product safety and quality. Effective risk management as articulated in ICH Q9, serves as foundational framework for risk assessment within the realms of pharmaceutical development and manufacturing.

Key components of this process include:

- The application of robust risk assessment and mitigation strategies to ensure patient safety, which is a critical element of the overall approach.
- The management of hazards associated with the evaluation of finished products, process management, and raw materials.
- The integration of technical expertise to align risk management practices with regulatory requirements.

This approach guarantees that development of pharmaceutical products is both patient-centered along with grounded in scientific principles^[33]. Risk assessment tools have a vital part in the identification and evaluation about key parameters within realms about pharmaceutical development and manufacturing. These threat assessments foster improved communication and collaboration among regulating agencies like the FDA, subject matter experts, research and development teams, and production units. Such tools enable effective modeling, sampling, and coordination throughout various stages of production. ICH Q9 rules delineates several formal methodologies for conducting threat assessments, which include:

- FMEA, which identifies possible modes of failure and their impacts with respect to processes or products. An extension of this the Failure Modes, Effects, and FMECA technique incorporates criticality evaluations to prioritize hazards.
- FTA, which is used to ascertain that root causes system failures and visually represents the interrelationships among these causes.
- HACCP, which aims till identifying and managing hazards that are essential to guaranteeing the safety and quality of the product.
- Risk Activity Analysis, which evaluates actions that may exacerbate process-related risks.
- Initial Risk Assessment, which provides a preliminary evaluation of potential hazards to guide further investigation.

3. PAT

An integrated framework known as PAT is developed to validate and regulate design, operational parameters, and production processes, thereby ensuring product quality. PAT emphasizes the real-time analysis of essential material characteristics and manufacturing parameters for the procedure to maintain consistent aspect in the final product. This systematic approach enhances comprehension of the process and control, facilitating along with production of superior pharmaceutical items that comply with regulatory standards^[34]. To enhance product quality and minimize waste in pharmaceutical fabricating, PAT employs nonstop fabricating methodologies. This approach represents a shift from traditional batch production methods to a more dynamic, real-time framework. By centering on CQAs of the ultimate item and their correlation with CPPs, PAT facilitates production of refined, high-quality outputs while simultaneously reducing waste and lowering manufacturing costs. The real-time evaluations provided by PAT yield immediate and actionable insights, thereby promoting greater process robustness and efficiency. This feedback mechanism reinforces control over critical factors, including particle size distribution, concentration, content uniformity, polymorphism, and other vital quality attributes. Furthermore, PAT functions as a key instrument in enabling RTTRT, thereby ensuring quality and consistency of the product.

2.12. Key Tools in Process Analytical Techniques (PAT)

1. **Real-Time/Inline Analytical Tools:** These tools permit for real-time prepare checking and control to ensure manufacturing quality.
2. **Programs for downstream processing:** Enhance post-production phases to guarantee effectiveness and quality.
3. **Multivariate Statistical Methods:** To analyze intricate data sets and facilitate sound decision-making, apply sophisticated statistical approaches.

PAT offers a thorough framework for enhancing production procedures and producing pharmaceutical goods of consistently high quality by combining various tools ^[35].

3.2. Strategy for Control

A control technique speaks to a systematic framework employed throughout the drug development process to recognize and address factors contributing to product variability. This strategy encompasses all facets of the manufacturing process, including:

- **Process Development:** Ensuring that manufacturing processes are effectively designed and optimized is essential. The management of resources, components, and materials utilized in the production of therapeutic products serves as a prime example of the inputs involved in these processes.
- **Facilities and Equipment:** Maintaining reliable equipment and state-of-the-art infrastructure.
- **Operating Procedures:** To ensure uniformity, it is essential to establish consistent protocols.
- **Process controls:** Monitoring and adjusting variables to maintain the integrity of the final product.
- **Final Product Requirements:** Ensuring that the ultimate item reliably meets the foreordained quality measures.

The principal objective of the control methodology is to preserve the quality of the pharmaceutical item throughout its entire lifecycle, thereby ensuring safety, efficacy, and adherence to regulatory requirements ^[36].

3.3. Elements of Effective Strategy ^[37]

- Methodology Testing
- Delivery Output Testing
- Compliance Testing
- In-Process control
- Procedural control

4. TOOLS FOR PHARMACEUTICAL QbD DESIGN

At present, the pharmaceutical sector employs a range of QbD frameworks, as illustrated Table I.

4.1. Plackett-Burman (PB) Plan

PB plans are widely recognized as prominent instances of non-regular experimental designs ^[38]. PB designs are commonly utilized for screening purposes due to their capacity to evaluate different parameters with a negligible number of experimental trials ^[39].

4.2. CCD Plan

CCD presented by Box and Wilson in 1951, was initially conceived for application in consecutive tests. This plan consolidates F factorial focuses, nc center runs, and 2k pivotal focuses, because it coordinating two-level factorial focuses (either full or factorial) with 2k hub focuses. The consecutive nature of the plan is hence apparent. The expansion of pivotal focuses encourages the compelling estimation of unadulterated quadratic terms by pleasing the ebb and flow of the framework. In spite of the fact that the concept was at first created for successive experimentation, it has moreover demonstrated to be profoundly beneficial for non-sequential bunch reaction surface tests ^[40-41].

4.3. FCD Plan

FCD which is characterized by three levels, represents a particular instance of central composite design (CCD) when the value of α is set to 1 ^[42].

4.4. Box-Behnken Plan

Box and Behnken (1960) presented the Box-Behnken plan (BBD), which comprises an arrangement of three-level plans capable at modeling second-order reaction surfaces. This plan is predicated on the detailing of fragmented, adjusted piece plans. In various scientific studies, particularly those necessitating response surface methodology (RSM), the requirement for evenly spaced three-level designs is prevalent, thereby rendering the BBD a highly effective alternative to the central composite design (CCD) ^[43].

4.5. Star Design Plan

A star design provides an efficient approach for the estimation of a quadratic demonstrate. The overall number of exploratory runs essential for a star plan is spoken to by the expression $2k + 1$, where k denotes the number of components included within the ponder ^[44].

4.6. Center of Gravity Design

The Central Composite Design (CCD) has been adapted for use in center of gravity configurations. This modification comes about in a diminishment of the full number of exploratory runs to $4k + 1$ ^[45].

4.7. Equiradial Design

Equiradial designs represent first-degree response surface methodologies characterized by the arrangement of N points in a regular polygon configuration centered around a specified point of interest within a circular framework ^[46].

4.8. Taguchi Designs

The Taguchi design methodology, recognized as an "off-line quality control" approach within the realm of experimental design, is primarily aimed at enhancing the performance of processes and products during their development phases. This methodology systematically assesses system variability by identifying the underlying causes of such variability and determining optimal settings for control factors to achieve desired outcomes. A distinctive feature of the Taguchi design is its classification of variables into two categories: signal factors, which are controllable inputs within the system, and noise factors, which represent uncontrollable variables that are either impractical or exceedingly challenging to manage. By meticulously regulating critical variables, the Taguchi design contributes to the robustness and reliability of pharmaceutical formulations and manufacturing processes ^[47-48].

4.9. Optimal Designs

To ensure maximum efficiency in the estimation of model coefficients, an optimal design methodology requires the improvement of an exact show, the depiction of the variable space, and the selection of an appropriate number of design points. A key advantage of these advanced design techniques is their inherent adaptability, which allows for continuous modifications. This adaptability encompasses the ability to conduct experiments in successive phases and to incrementally incorporate design points as needed, thereby enhancing both the efficiency and reliability of the process ^[49-50].

4.10. Rechtschaffner Designs

The incorporation of first-order interactions and principal effects within the model is essential for the design ^[51-53].

Table I Different Quality by Design (QbD) Approaches Utilized in Pharmaceutical Development.

Experimental Design	Description	Ref.
Plackett-Burman (PB) design	- In a Plackett-Burman (PB) design, the number of experimental runs (n) must always be greater than four. Plackett and Burman originally developed these designs for values of n up to 100, with the exception of $n = 92$. While standard fractional factorial designs are characterized by the number of runs being a power of two, all other PB designs are classified as non-regular experimental designs. - These designs are widely utilized for screening significant factors in optimization studies, particularly in pharmaceutical research and industrial applications. By systematically evaluating multiple variables with a minimal number of experimental runs, PB designs facilitate the	39

	identification of key influencing factors, making them an invaluable tool in statistical modeling and process optimization.	
Central Composite Design (CCD)	- In a first-order model or a first-order model incorporating two-factor interactions, factorial points establish a variance-optimal design, while center runs provide essential insights into system curvature. The experimental design consists of three distinct components, each fulfilling a specific function. - A resolution V fraction is particularly important for optimally estimating variance, ensuring accurate representation of both linear terms and two-factor interactions. Quadratic terms are determined using axial points, whereas interaction effects can only be identified through factorial points. In the absence of axial points, the evaluation is limited to the cumulative effect of quadratic terms. - Notably, axial points do not contribute to assessing interaction effects; instead, center runs play a crucial role in estimating quadratic terms and pure error, thereby enhancing model precision and robustness. This structured experimental framework ensures a comprehensive understanding of factorial interactions and curvature effects, ultimately improving the reliability and predictive capability of the mathematical model.	40-41
Box-Behnken Design	- This model enables efficient process optimization while minimizing the number of experimental runs, making it particularly effective for analyzing quadratic response surfaces due to its second-order polynomial structure. - By defining a multidimensional region of interest at the midpoints of a cube's edges, replicated center points enhance the accuracy and robustness of the optimization process, ensuring greater reliability and precision in the resulting mathematical model.	43
Star Design	- The step size (α), which represents an equal shift in both positive and negative directions, is used to generate various factor combinations from a central experimental point. When two factors are considered, the star design corresponds to a 45° rotated two-factorial design (FD) with an additional center point. - This design ensures statistical efficiency and robustness in experimental analysis by maintaining both orthogonality and rotatability, thereby enhancing the reliability and accuracy of the experimental outcomes.	44
Center of Gravity Design	- To optimize the geometric design space, a minimum of four points along each coordinate axis is selected from the central point (center of gravity) within the factorial region, where the experimental process is initiated. - Regardless of the dimensionality of the geometric space, only experiments yielding significant and relevant data are incorporated into the design framework, ensuring efficiency, accuracy, and robustness in the optimization process.	45
Equiradial designs	- A distinct advantage of this experimental design is its ability to rotate freely at any angle without compromising its intrinsic properties. The experimental setup consists of five design points positioned along the circumference of a circle, with a central point forming a pentagonal configuration across six experimental runs. - This geometric arrangement ensures statistical efficiency and robustness in data analysis, facilitating a comprehensive evaluation of response variability while maintaining design integrity.	46
Taguchi Design	- This experimental design employs two orthogonal arrays, which serve as structured frameworks for conducting systematic experiments. The outer array incorporates noise factors to account for process and environmental variability, while the inner array consists of signal (or control) elements that facilitate process optimization. - Taguchi's orthogonal arrays include two-level, three-level, and mixed-level fractional factorial designs (FFDs). The optimal process parameters are identified through the internal design using control elements, whereas	47-48

	the external design evaluates response behavior under variable noise conditions. To ensure a comprehensive analysis, each experimental run systematically integrates the inner and outer designs, enabling a robust and reliable optimization process.	
Optimal Design	- Expanding an experimental design may alter the original domain shape; in such cases, a D-optimal design can be employed for further investigation and refinement. This approach facilitates the incorporation of additional terms in either direction, enabling model expansion and enhancing predictive accuracy. Furthermore, D-optimal designs identify optimal new test runs that align with the extended model, thereby improving experimental efficiency. - Experiments conducted in separate blocks can be integrated into a unified dataset, increasing analytical flexibility and ensuring a comprehensive evaluation of the experimental factors. Depending on the study's objectives, D-optimal designs can be effectively applied in conjunction with factorial, central composite, or mixed designs. - These methodologies have been extensively utilized in factor screening, formulation development, and process optimization, consistently delivering robust and reliable results.	49-50
Rechtschaffner design	- With the exception of the five-factor design, which allows for the independent estimation of primary effects, saturation designs generally lack orthogonality and balance. Although their application in factor effect studies is relatively limited, these designs offer significant potential in pharmaceutical formulation, providing valuable insights for process development and optimization. - Their strategic implementation enhances experimental efficiency, enabling the systematic evaluation of formulation variables and manufacturing parameters to improve process robustness and product quality.	51-53

5. APPLICATIONS OF QbD APPROACH

At present, QbD methodology has been successfully applied across various domains within pharmaceutical research, as illustrated Table II.

5.1. Within the improvement of ordinary drug delivery framework

5.1.1. Tablets

The investigation conducted by Dholariya Y.N. et al. explains the optimization of hydrochlorothiazide (HCTZ) bilayered tablet definitions through the application of the QbD strategy. The study meticulously assessed and optimized critical formulation variables utilizing surface response plots, polynomial equations, and a 2^2 factorial design (FD). A comprehensive chance appraisal was performed to assess the impact of different handle and detailing parameters on key quality traits, particularly the disintegration time (DT) of the immediate-release layer and the overall mediate discharge time (T) of the sustained-release lattice within the bilayered tablets. The findings underscored the potential of bilayered tablet technology as a viable alternative to conventional dosage forms, particularly through the identification of high-risk variables during the risk assessment phase, which were targeted for further enhancement. The validation batch, developed in accordance with the design model, exhibited a minimal percentage error in predictions, showing a solid relationship between exploratory and expected reaction values. The relationship plots revealed high R-values, affirming the model's exceptional predictive capability and fit accuracy. The employment of statistical methodologies in this study not only facilitated the precise optimization of formulation factors but also contributed to the development of a robust formulation. This approach ensured the formulation's sensitivity and regulatory compliance, enabling the medication to be delivered in a biphasic release pattern. Furthermore, the integration of QbD principles with advanced statistical techniques is crucial for enhancing process understanding, enabling root cause analysis, and establishing comprehensive control strategies for effective formulation and process development^[54]. In the form of a gastro-retentive bilayer tablet, Singh and colleagues systematically developed a steady fixed-dose combination of lamivudine and zidovudine, which shown both controlled mediate discharge and floating-bioadhesive properties. The formulation was created using isopropyl alcohol as a granulating agent within a non-aqueous granulation process. A strategic selection of polymers was employed in the fabrication of effervescent floating-bioadhesive bilayer tablets to achieve the

desired drug release profile and prolonged gastric retention. To facilitate robust formulation development, FCC plan was utilized to efficiently optimize CMAs. The resulting tablets underwent comprehensive evaluation, focusing on essential critical quality attributes (CQAs), such as buoyancy time (Tb), bioadhesive strength (BS), and drug release characteristics. The optimized bilayer tablet formulation demonstrated superior gastroretentive efficacy compared to conventional immediate-release dosage forms. In vivo validation of the gastroretentive properties of the enhanced formulation was conducted through gamma scintigraphic studies on healthy human volunteers. The findings indicated a significant increase in gastric residence time, with the improved formulation exhibiting retention for up to 6 hours, in contrast to the 1-hour retention observed with the marketed immediate-release formulation. The successful development of a robust and effective gastro-retentive drug delivery system with enhanced therapeutic potential was accomplished through the fastidious application of QbD standards nearly progressed detailing strategies ^[55].

5.1.2. Gelatin hard capsules

Hard capsules are broadly utilized in the research and manufacturing of pharmaceutical dosage forms due to their ability to encapsulate a diverse range of formulations and pharmacological agents. Pharmaceutical companies employ hard capsules to enclose various therapeutic compounds, thereby ensuring both stability and precise dosage. A systematic investigation was conducted to assess the effect of varieties in purge difficult gelatin capsules on the quality characteristics of the ultimate pharmaceutical item. The essential objective of this consider was to evaluate basic quality parameters (CQPs) of purge difficult gelatin capsules both inside person bunches (intra-batch) and over distinctive clusters (inter-batch). This evaluation aimed to determine the reliability and consistency of these capsules in relation to established quality standards. The findings of the study indicated that the variability among hard capsules was notably consistent, with all measured CQPs falling within the acceptable limits. Furthermore, automated endpoint detection techniques were employed to analyze the disintegration time of the capsules, revealing uniform performance across batches. These results underscore the efficacy of hard gelatin capsules as a preferred dosage form in drug administration and affirm their robustness and reliability in pharmaceutical formulations ^[56].

5.2. In improvement of novel drug delivery framework

Over the past six decades, DDS have undergone significant advancements, fundamentally altering the landscape of pharmaceutical research and therapeutic interventions. The inception of the controlled drug delivery era occurred between the 1960s and 1980s, during which a diverse array of devices and systems was developed for administration via various routes to address a multitude of therapeutic needs. The primary objectives of these increasingly sophisticated formulations, which incorporate both natural and synthetic pharmacological agents, are to optimize drug delivery, minimize antagonistic impacts, upgrade security and persistent adherence, and progress overall therapeutic adequacy. Extensive research efforts have led to the creation of solid, semisolid, and liquid dosage forms through innovative formulation techniques designed to facilitate controlled and modified drug release. The evolution of DDS has progressed from the concept of a Magic Bullet to the modern nanoscopic time, wherein focused on nanocarriers have gotten to be an unmistakable reality. Notable advancements in targeted drug delivery, particularly for solid tumors, have been achieved through pioneering technologies such as PEGylation and both active and passive targeting strategies, which leverage the improved penetrability and maintenance (EPR) impact. Subsequently, the DDS segment has experienced a marked increase in patent applications and acquisitions, with projections indicating sustained growth in the coming decades. In light of these headways, it is basic to guarantee the pharmaceutical quality of DDS improvement. This may be viably accomplished by executing the standards of QbD, which require a comprehensive understanding and precise control of definition factors. The ICH has set up rule Q8 (and its changed adaptation, Q8(R2)), which gives an organized system for the application of logical strategies and quality chance administration in item development and manufacturing. It is basic allude to" to allude to with relevant regulatory specialists to guarantee the appropriateness of ICH rule Q8 within the improvement of DDS. The effective usage of ICH Q8 ought to illustrate both prepare and administrative adaptability to encourage QbD-based entries whereas keeping up the astuteness of licensed pharmaceutical advancements and shielding mental property ^[57].

5.3. QbD approach in advancement of nanocarriers

Pharmaceutical improvement has experienced a noteworthy change with the presentation of QbD, transitioning from a traditional knowledge exchange model to a more integrated, knowledge-based approach. The essential objective within the advancement of a DDS is to define a vigorous item and set up an productive fabricating process that reliably guarantees the required execution and helpful viability of the ultimate pharmaceutical item. Key strategies in formulation development include the use of experimental design methods that promote systematic identification and optimization of essential representational and process variables. By setting

accurately characterized parameters to preserve ideal execution, broad testing and development room investigation can make strides item quality. This systematic approach improves the overall effectiveness and reliability of DDS by minimizing variability and ensuring overall batch consistency. Numerous successful drug submission systems using nanocarrier have been developed within the QBD framework. These advanced formulations use QBD principles to improve drug stability, kinetic release, bioavailability and target distribution. The following sections thoroughly examine the effective use of QBD in the development of nanocarriers and its impact on modern pharmaceutical innovation.

5.3.1. Liposome

Surface-modified liposomes, which are functionalized with monoclonal antibodies or specific functional groups on their exterior vesicular lamella, have demonstrated effective drug-targeting properties. In particular, glycosylated liposomes that are ligand-anchored have been developed as targeted drug delivery systems for the brain, leveraging their ability to traverse the blood-brain barrier (BBB) via glucose transporter 1 (GLUT1) mediated transport. This targeted approach significantly enhances drug delivery to the brain, thereby improving treatment efficacy for neurological disorders. Glycosylated liposomes are increasingly regarded as promising carriers due to their superior drug transfer efficiency, prolonged in vivo circulation, ease of synthesis, enhanced stability, and suitability for brain-targeted delivery. These advantages position them as a viable strategy for overcoming the physiological challenges associated with drug delivery to the central nervous system (CNS). However, despite their remarkable targeting capabilities, surface-modified liposomes face several limitations that hinder their widespread application. Key challenges include potential immunogenicity, formulation complexity, high production costs, and variability in therapeutic response among patients. Addressing these challenges through advanced formulation techniques and optimization of surface modifications may further enhance their therapeutic potential in brain-targeted drug delivery [58-59].

5.3.2. Proliposomes

The QBD principle was systematically used in the development of proliposomes for the soluble drug lopinavir (LPV). The formulation development process was directed by patient-oriented QTPP and CQAS. A comprehensive think about on chance appraisal was conducted to distinguish potential dangers that may influence CQA within the last item. After recognizing CMAS, especially lipid-to-drug proportion and carrier sum, a total FCC plan was utilized for optimization. The CQA of the proliposomal arranging included the ice viability of the ice of the sedate released after 60 min, vesicle degree, and cure degree. Wording optimization was accomplished by numerous direct relapse examination (MLR) to clarify the numerical connections between the distinguished CMA and CQA. Ideal CMAs were decided utilizing numerical optimization and craved utilitarian strategies, driving to dialect demonstrating sedate discharge of >95% and vesicle estimate of $659.7 \text{ Å} \pm 23.1 \text{ nm}$ inside 60 min. The optimized proliposome definition appeared a move from gem to shapeless from solid-state structures to shapeless. This is usually associated with improved solubility and bioavailability. Besides, oral bioavailability of proliposome details was essentially more prominent than unadulterated LPV and the as of now accessible lopinavir/ritonavir (LPV/RTV) combinations. Moreover, proliposomes based on the Worldwide Conference on Consonant Conditions (I) contained soundness for up to 6 months. These comes about highlight the potential of proliposomes as a viable technique to move forward verbal bioavailability of dissolvable drugs such as LPV, which gives critical focal points in detailing soundness and restorative viability [60].

5.3.3. Nanoliposomes

In a recent investigation, a hydrophilic pharmaceutical agent was effectively encapsulated within chitosan-coated nanoliposomes (CHNLPs) utilizing the QbD system. The essential objective of the ponder was to evaluate the impact of different preparing parameters on the CQAs of the CHNLPs, specifically focusing on coating efficiency (%CE), particle size, and encapsulation efficiency (%EE). A thorough risk analysis was conducted to identify key factors for the screening plan think about, which included temperature, sonication term, mixing speed, the organic-to-aqueous proportion, and the concentrations of the sedate, lipid, cholesterol, and chitosan. Moreover, an extra examination was performed to assess the vigor of the plan space. Upon optimization, the final CQAs of the CHNLPs were determined to be 33.4% for %EE, 111.3 nm for particle size, and 35.2% for %CE. The design space of the CHNLP formulation demonstrated both resilience and suitability for its intended application, as indicated by the close alignment between anticipated and actual responses. The findings of this study suggest that the challenges associated with scaling up the production of nano-liposomal formulations can be significantly mitigated through the optimization of critical processing factors. By carefully controlling these essential parameters, the scalability and reproducibility of the CHNLP formulation can be enhanced, thereby ensuring consistent quality throughout large-scale manufacturing processes [61].

5.3.4. Polymeric nanoparticles

To develop and characterize paclitaxel (PTX)-charged nanoparticles (NPS), research is conducted simultaneously, identifying and treating key sources of variability that affect the design and manufacturing process. A comprehensive risk assessment was conducted to assess the impact of various processes and formulation parameters such as zeta potential, average particle size, and encapsulation efficiency (EE) on NPS critiques. NP optimization was achieved by Box-10 (BB) design. Potential risk factors were identified using Ishikawa diagrams and examined using Plackett-Burman Design (PB). An extended analytical technique that characterizes NPS by adding X-ray diffraction (XRD), scanning electron microscopy (SEM), gas chromatography (GC), atomic force microscopy (AFM), differential scan calorimetry (DSC), and Fourier transform electron microscope (FTEM). It was watched that PTX passed from the gem into the shapeless state amid the embodiment prepare. Besides, NPS appeared homogeneous, round and smooth morphology without the remaining dichloromethane. An examination of in vitro cyto-toxicity showed up that NPs mounted on PTX showed up more than 2% anticancer activity compared to free PTX. These comes about highlight the significance of QBD standards for the optimization of complex medicate conveyance frameworks (DDS) to guarantee vigorous detailing improvement and made strides helpful adequacy. The systematic approach pursued in this study promotes the production of scalable and optimized DDS-based DDS with nanoparticles with improved performance capabilities [62]. We developed Zolmitriptan-Poly (D, L-Lactide-Co-Glycolide) (PLGA) nanoparticles (NPs) and poloxamers to the brain using quality according to the design (QBD). Using 24 randomized complete fact designs (FDs), we effectively optimized key quality attributes (CQAs), including minimum particle size and maximum encapsulation efficiency (EE). PLGA/poloxamer-NPs were synthesized, with particle sizes ranging from 165.4 to 245.4 nm, leading to particle sizes ranging from 43.32% to 100%, and EE values ranging from 48.96% to 95.97%. PLGA/poloxamer-NPs were synthesized. Fourier transform infrared (FTIR) spectroscopy and powder x-ray (XRD) characterization of NPS showed no significant interaction between drugs and excess during the drug loading process. TEM analysis of transmission electron microscopy (TEM) confirmed that the NPS has a uniform spherical morphology. In vivo studies showed that PLGA/poloxamer NPs significantly improved the delivery of drugs to the brain, achieving a 14.13 increase in brain targets compared to free drugs. Furthermore, these NPs showed improved migraine efficacy. This aims to the potential of this formulation of nanoparticles from the brain to improve the therapeutic efficacy of zolmitriptan in migraine treatment. This study demonstrates the successful application of the QBD principle in the development of brain-targeted drug delivery systems to ensure excellent treatment outcomes and optimal formulation parameters [63].

5.3.5. Solid lipid nanoparticles

Rivastigmine (RHT)-incorporated solid lipid nanoparticles (SLNs) were meticulously created and optimized through the comprehensive Quality by Design (QbD) methodology, which emphasizes the importance of systematic planning and process control to ensure consistent quality in pharmaceutical formulations. The intricate formulation process employed a combination of advanced techniques, specifically homogenization and ultrasonication, and incorporated essential components such as Poloxamer-188 serving as a stabilizing agent, Compritol 888 ATO acting as the lipid matrix, and Tween-80 utilized as a surfactant to enhance the overall formulation stability and efficacy. In order to rigorously evaluate the influence of pivotal formulation parameters on the resultant product's characteristics, a 3³ full factorial design (FD) was meticulously implemented, allowing for a structured exploration of the interactions between variables. The research endeavour was meticulously directed towards clarifying and revealing the intricate effects that the drug-to-lipid ratio (denoted as X₁), the concentration of surfactant (designated as X₂), and the length of time for homogenization (represented as X₃) exert on the pivotal quality attributes (CQAs) of the formulation, which encompassed the dimensions of the particles (Y₁), the polydispersity index (PDI) (Y₂), and the encapsulation efficiency expressed as a percentage (%EE) (Y₃), thereby contributing significantly to a holistic and comprehensive understanding of the overall performance metrics associated with the formulation under scrutiny. In order to ensure the statistical significance of these critical variables, which included not only their primary effects but also their quadratic and cubic interactions, in addition to two-factor interactions (2FI), a rigorous and meticulous evaluation was conducted through the implementation of advanced statistical methodologies such as analysis of variance (ANOVA) and multiple linear regression (MLR), thereby establishing a robust and reliable analytical framework that underpins the findings derived from this exhaustive investigation. Ultimately, the systematic approach adopted in this study not only elucidates the complex interplay between the aforementioned factors and the resultant CQAs but also lays the groundwork for future research endeavours aimed at optimizing formulation strategies within the pharmaceutical sciences, thereby enhancing the efficacy and safety of drug delivery systems. The optimized formulation of SLNs exhibited a remarkably small particle size measuring 82.5 ± 4.07 nm, a highly favourable PDI of 0.132 ± 0.016 , and an impressive encapsulation efficiency of $66.84 \pm 2.49\%$, signifying the successful integration of the aforementioned components. The rigorous structural characterization that was meticulously conducted through the utilization of advanced techniques such as X-ray diffraction (XRD) and differential scanning calorimetry (DSC) has unequivocally revealed that the RHT, or the relevant pharmaceutical compound, was present within the lipid matrix in a structural state that was not entirely crystalline, thereby indicating a notable degree of partial

amorphization, a phenomenon which is often considered highly desirable in the context of enhancing both the solubility of the drug and its bioavailability in biological systems. Furthermore, *in vitro* and *ex vivo* diffusion studies demonstrated that the SLN formulation significantly facilitated the release of RHT when compared to the unmodified drug solution, conforming to the Higuchi kinetic model, which is indicative of a controlled release mechanism. Furthermore, an exhaustive histological analysis of the nasal mucosa substantiated the formulation's compatibility with biological tissues, as there was an absence of discernible signs of mucosal damage, thereby enhancing its viability as a safe and efficacious approach for intranasal drug administration. Collectively, this research underscores the successful implementation of the QbD framework in the optimization of RHT-loaded SLNs, ultimately culminating in the development of a meticulously designed, efficient, and targeted intranasal delivery system that boasts significantly improved drug release characteristics and therapeutic potential ^[64]. Lipid nanoparticles, commonly referred to as LNPs, were innovatively formulated utilizing the Quality by Design (QbD) methodology, which has been specifically tailored to significantly enhance the transdermal permeability of the chemotherapeutic agent 5-fluorouracil (5-FU), with the overarching objective of improving its therapeutic efficacy in treating non-melanoma skin cancer. The formulation process was executed through a sophisticated water-in-oil-in-water (w/o/w) double emulsion-solvent evaporation technique, which is recognized for its ability to encapsulate hydrophilic drugs within lipid matrices effectively. In order to systematically evaluate and meticulously refine the various formulation parameters, a sophisticated Artificial Neural Network (ANN) model was implemented, which serves as a powerful computational tool for data analysis and predictive modeling. This advanced computational strategy not only facilitated the development of a well-defined design space but also enabled a thorough evaluation of the formulation data, culminating in the optimization of the overall process employed in the preparation of the lipid nanoparticles. In this study, two distinct ANN models were meticulously constructed and their results validated the assumption that both the input and output parameters remained comfortably within the predefined design space, thereby ensuring the robustness and reliability of the formulation developed. The optimized formulations were subsequently assigned Critical Quality Attributes (CQAs), which were meticulously aligned with the established Quality Target Product Profile (QTPP), thus ensuring a consistent and high standard of product quality throughout the development process. By adhering rigorously to the principles of QbD while simultaneously integrating advanced ANN-based modeling into the formulation process, the final formulations successfully achieved the desired quality standards, all while remaining well within the established design space parameters. The findings articulated in this study underscore the remarkable effectiveness of synergistically combining QbD frameworks with sophisticated computational modeling techniques in the optimization of LNP-based drug delivery systems. This innovative approach holds considerable promise for significantly enhancing the skin permeability of 5-FU, which ultimately contributes to the advancement of safer and more effective therapeutic strategies in the battle against non-melanoma skin cancer ^[65].

5.3.6. Microsponges

A microsphere-based drug delivery system (MDDC) was successfully formulated using a twofold emulsion dissolvable dissemination procedure, coordinates with rotor-stator homogenization. The primary objective was to develop an MDDC formulation suitable for gel incorporation. To achieve this, QTPP and CQAs were systematically identified and defined in accordance with QbD principles. Additionally, a Failure Mode, Effects, and Criticality Analysis (FMECA) was conducted within the framework of Quality Risk Management (QRM) to determine the Critical Material Attributes (CMAs) and Critical Process Parameters (CPPs) essential to formulation robustness. The identification of CPPs and CMAs was based on a comprehensive analysis, integrating process knowledge, literature review, principal component analysis (PCA), and partial least squares (PLS) statistical modeling. The FMECA approach highlighted several key CMAs, including acetone (ACT), ethyl-cellulose (EC), dichloromethane (DCM), chitosan (CTS), Span 80 (S80), Tween 80 (T80), and the water ratios in primary and multiple emulsions. Meanwhile, solvent removal stirrer type and rotation speed were identified as critical CPPs influencing the final formulation. To establish a design space, a one-factor response surface methodology (RSM) was employed, enabling the assessment of the relationship between particle size (a key CQA) and CPPs. The impact of CPPs on particle size distribution was rigorously analyzed using statistical modeling, which facilitated process optimization. The selection of CMAs and CPPs was further supported by historical multivariate statistical data, prior formulation expertise, and literature insights related to microsphere design and processing parameters. Statistical evaluations, including PCA and PLS, were conducted using SIMCA 13 (Umetrics AB, Sweden), while Design-Expert® V8 (Stat-Ease, Inc., Minneapolis, USA) was employed to optimize identified CPPs using a one-factor design approach. Additionally, the influence of CPPs on particle size distribution (Span) and characteristics (D_{10} , D_{50} , and D_{90}) was systematically assessed through statistical modeling. Future research should focus on a stepwise experimental validation of the identified CMAs using a Design of Experiments (DoE) approach. This would begin with screening studies to identify key formulation variables, followed by RSM-based characterization and optimization. These findings will contribute to the establishment of a robust manufacturing process control strategy, ensuring product quality, consistency, and regulatory compliance ^[66].

5.3.7. Transgel

To enhance the transdermal penetration of pioglitazone (PZ), Prasad et al. developed an advanced transdermal drug delivery system (TDDS) by encapsulating PZ within a carbopol-based transgel, incorporating both proniosomes and niosomes. The formulation was systematically optimized following the Quality by Design (QbD) methodology, with evaluations conducted on entrapment efficiency, transdermal flux, and particle size. The study results indicated high drug encapsulation efficiency and a marked improvement in transdermal flux, establishing the transgel system as a promising carrier for enhanced skin permeation. A comparative analysis demonstrated that the proniosomal transdermal system exhibited a 3.16-fold increase in transdermal activity compared to the control PZ ethanol-buffer formulation (3:7), as confirmed through confocal laser scanning microscopy (CLSM). Additionally, in vivo pharmacokinetic studies revealed that the bioavailability of the carbopol-based transgel formulation was 2.26 times higher than that of a conventional tablet formulation. Furthermore, the anti-diabetic efficacy of the transgel system surpassed that of commercially available tablet formulations, indicating its potential as an effective transdermal delivery vehicle for pioglitazone. These findings emphasize the superiority of the optimized transgel system over traditional formulations, demonstrating its potential to enhance bioavailability and improve therapeutic efficacy in transdermal pioglitazone delivery^[67].

5.3.8. Nanostructured lipid carriers

Nanostructured lipid carriers (NLCs) loaded with aceclofenac were successfully developed and characterized using the Quality by Design (QbD) approach, followed by an evaluation of their stability and transdermal penetration potential. The microemulsion technique was employed for NLC synthesis, incorporating lipids and surfactants identified as Critical Material Attributes (CMAs). To optimize the formulation, a 3³ full factorial design (FD) was implemented, systematically analyzing Critical Quality Attributes (CQAs) such as polydispersity index (PDI), zeta potential, particle size, entrapment efficiency, and in vitro drug release. A comprehensive investigation assessed the influence of CMAs, including surfactant concentration, oil-to-lipid ratio, and lipid type, on particle size and entrapment efficiency to achieve an optimized formulation. The optimized NLC formulation, incorporated into a carbopol gel, underwent rheological and textural characterization, followed by in vitro and in vivo evaluations. The results indicated that the aceclofenac-loaded NLCs exhibited high drug loading capacity, superior entrapment efficiency, and nanometric spherical morphology. In vitro release studies, analyzed using the Korsmeyer-Peppas equation, demonstrated Fickian diffusion kinetics, characterized by an initial burst release followed by sustained drug release over 48 hours, establishing a biphasic release profile. Compared to a commercial formulation, the NLC-based gel displayed enhanced ex vivo skin permeability, increased cellular uptake in hyperkeratinocytic HaCaT cell lines, and superior rheological and textural properties. Furthermore, in vivo studies on carrageenan-induced edema in mice suggested that the aceclofenac-loaded NLC hydrogel holds strong potential as an alternative for targeted transdermal drug delivery across multiple skin layers. These findings highlight the efficacy of NLC-based hydrogel formulations in enhancing transdermal drug delivery, offering promising implications for topical anti-inflammatory therapy^[68]. A Quality by Design (QbD) approach was employed in a recent study to develop and characterize nanostructured lipid carriers (NLCs) loaded with salicylic acid (NLC-SA). A systematic risk assessment was conducted to identify Critical Material Attributes (CMAs) and Critical Process Parameters (CPPs) essential to formulation optimization. The formulation utilized Compritol 888 ATO as the solid lipid, Miglyol 812 as the liquid lipid, and Cremophor RH60® as the surfactant, with ultrasonication serving as the primary preparation method. Risk assessment was performed using Lean-QbD Software and Stat-Soft Inc. Statistica for Windows 11. Key Critical Quality Attributes (CQAs)—including particle size, particle size distribution, and aggregation were identified as dependent variables. Additionally, parameters such as pH, lipid solubility of the active pharmaceutical ingredient (API), entrapment efficiency, dissolution efficiency, and dissolution rate were considered to have moderate significance in influencing the formulation's characteristics. The solid lipid-to-liquid lipid ratio, surfactant concentration, and ultrasonication duration were identified as CMAs and CPPs, serving as independent variables. A 2³ factorial design (FD) was employed to systematically evaluate the impact of these variables on the overall performance of the formulation. The optimized NLC-SA formulation was achieved with a solid lipid-to-liquid lipid ratio of 7:3, a surfactant concentration of 5%, and an ultrasonication time of 20 minutes. The resulting NLC-SA exhibited a mean particle size of 114 ± 2.64 nm and a particle size distribution of 0.857 ± 0.014 . In vitro drug release studies demonstrated that the NLC-SA formulation exhibited superior drug release compared to a reference salicylic acid-loaded microparticle formulation, indicating potentially enhanced therapeutic efficacy. These findings underscore the effectiveness of a QbD-driven approach in optimizing NLC-based drug delivery systems, demonstrating their potential for improved topical drug administration.^[69]

5.3.9. Pickering Emulsion

Unlike conventional emulsions, which rely on surfactants for stabilization, Pickering emulsions are stabilized by solid particles, thereby reducing the risk of adverse effects commonly associated with traditional emulsions. In

this study, a water-in-oil (w/o) Pickering emulsion was developed using starch as a stabilizing agent, following a Quality by Design (QbD) approach. A screening design was implemented to identify critical factors and process parameters influencing key quality attributes. To enhance emulsion stability, a design space was established by optimizing both the internal aqueous phase volume and starch concentration. The results indicated that higher starch concentrations significantly enhanced emulsion stability. Mechanical and rheological analyses demonstrated that the incorporation of starch and additional lipids increased the viscosity of the formulation, thereby improving stability. Furthermore, biocompatibility and non-irritating properties were confirmed through *in vitro* cytotoxicity assays conducted on human skin cell lines (HaCaT and Df), where cell viability exceeded 90%, indicating self-preserving properties. In conclusion, the integration of QbD principles facilitated the development of an optimized Pickering emulsion with favourable structural and organoleptic characteristics, supporting its potential as an effective vehicle for topical drug delivery. ^[70]

5.3.10. Solid self-nanoemulsifying oily preparations

A solid self-nanoemulsifying oily formulation (S-SNEOF) was systematically designed and optimized to improve the bioavailability and targeted delivery of lopinavir. The formulation process began with the identification of the Quality Target Product Profile (QTPP) and Critical Quality Attributes (CQAs), followed by a Failure Mode, Effects, and Criticality Analysis (FMECA) to assess potential risks. Preliminary investigations identified Maisine (lipid), Tween 80 (emulsifier), and Transcutol HP (cosolvent) as the Critical Material Attributes (CMAs). A D-optimal mixture design was utilized to optimize the formulation. The resulting nanoemulsion, characterized through *ex vivo* permeation studies, *in vitro* dissolution testing, and globule size analysis, exhibited a globule size of 53.16 nm. To enhance drug loading capacity and stability, the optimized lopinavir SNEOFs (OPT-L-SNEOFs) were adsorbed onto a porous carrier (Aeroperl), followed by the incorporation of microcrystalline cellulose (MCC) as a diluent before tablet compression. *In situ* single-pass intestinal perfusion (SPIP) studies demonstrated significantly improved absorptivity of the SNEOFs compared to the pure drug. Furthermore, oral bioavailability studies confirmed a substantial enhancement in drug absorption over the unformulated drug. These findings highlight the potential of the optimized S-SNEOF formulation to facilitate intestinal lymphatic transport of lopinavir, presenting a promising strategy for effective HIV management in sanctuary sites. ^[71]

5.3.11. Nano-capsules

A starch-based nanoparticulate carrier system (StNC) was developed for the topical delivery of lipophilic bioactive compounds, with formulation optimization conducted using a Quality by Design (QbD) approach. Key formulation variables influencing zeta potential and particle size distribution were systematically assessed. StNC formulations were prepared via the emulsification-solvent evaporation method, and an optimal formulation was selected for comprehensive characterization. The morphology of the optimized StNCs was examined using atomic force microscopy (AFM) and transmission electron microscopy (TEM), while Fourier transform infrared spectroscopy (FTIR) and differential scanning calorimetry (DSC) were employed to analyze potential molecular interactions within the formulation. The biological properties of the formulation were evaluated through *in vitro* and *in vivo* studies, including human volunteer trials to assess biological sensitivity and irritation potential. Results indicated that lipid content and surfactant concentration were the primary factors influencing particle size distribution. The optimized StNC formulations demonstrated high physical stability, with a zeta potential of approximately $+33.6 \pm 6.7$ mV. The QbD-driven optimization process provided valuable insights into formulation parameters, leading to the development of a robust and stable starch-based nanoparticulate carrier system. These findings highlight the potential of StNCs as efficient vehicles for the topical administration of lipophilic bioactive compounds, offering promising applications in advanced drug delivery ^[72].

5.4. Quality by Design (QbD) in process control

5.4.1. Dissolution Testing

The development of amorphous solid dispersions (ASDs) of efavirenz was undertaken using Soluplus® and HPMCA-HF polymers to enhance solubility, stability, and dissolution rate. A Quality by Design (QbD) approach was employed to optimize the formulation, utilizing a user-defined quadratic model within the Design of Experiments (DoE) framework to evaluate the influence of HPMCA-HF and Soluplus® concentrations on formulation performance. A prototype formulation, incorporating Soluplus® as the carrier with 30% efavirenz loading, was initially prepared, and granular extrudates of efavirenz ASDs were assessed for saturation solubility and dissolution rate. Comprehensive solid-state characterization was performed using atomic force microscopy (AFM), differential scanning calorimetry (DSC), Fourier transform infrared (FTIR) spectroscopy, and powder X-ray diffraction (XRD). Analysis through XRD and DSC confirmed the transformation of efavirenz from a crystalline to an amorphous state, thereby demonstrating enhanced solubility and dissolution characteristics. The optimized formulation, identified through DoE, comprised Soluplus® and HPMCA-HF in a 60:20 ratio and exhibited the highest dissolution rate. Stability studies conducted over six months under International Council for

Harmonization (ICH) conditions indicated that while the prototype ASD formulation displayed instability, the optimized ASD batch successfully retained its amorphous state and dissolution profile when stored at 40°C and 75% relative humidity (RH). These findings underscore the successful application of QbD principles in optimizing ASDs for efavirenz, leading to enhanced dissolution performance and long-term stability, thereby improving the oral bioavailability of poorly soluble drugs^[73]. A Quality by Design (QbD)-based multivariate analytical approach was employed to assess the *in vitro* dissolution profiles and predict the *in vivo* performance of nifedipine immediate-release capsules. The formulation was evaluated using a Design of Experiments (DoE) methodology, wherein key dissolution variables were identified, including dissolution apparatus type (USP 1, basket apparatus; USP 2, paddle apparatus), dissolution medium composition (volume, ethanol content, and pH), operator conditions, and rotational speed (rpm) of the paddle or basket. The dissolution characteristics of nifedipine capsules were analyzed using multiple linear regression (MLR) under conditions simulating administration with various liquids, including water, orange juice, and an alcoholic beverage. The MLR-derived mathematical model facilitated the optimization of dissolution parameters, enabling the establishment of an *in vitro*–*in vivo* correlation (IVIVC). Notably, IVIVC was successfully demonstrated under *in vitro* conditions mimicking the co-administration of capsules with orange juice and ethanol. Furthermore, MLR analysis revealed that the ethanol concentration in dissolution studies could be reduced from 47% v/v to 20% v/v without affecting the dissolution outcomes. This finding underscores the potential to refine dissolution testing methodologies to better simulate real-life administration scenarios while accurately predicting the formulation's pharmacokinetic behavior^[74].

5.4.2. Spray drying

Spray drying is an extensively utilized technique for the drying of biologicals, offering a cost-effective and efficient alternative to lyophilization. In this study, a whole inactivated influenza virus (WIV) vaccine was stabilized using spray drying, with process optimization guided by the Design of Experiments (DoE) approach. A systematic screening and optimization of critical process parameters was performed to assess their impact on product quality attributes and to predict optimal formulation conditions. The study examined the influence of key process variables, including feed flow rate, intake air temperature, and nozzle gas flow rate, on the powder characteristics of the WIV vaccine, such as particle size, residual moisture content (RMC), and powder yield. The resulting vaccine powders displayed diverse physical properties, with powder yields ranging from 42% to 82%, RMC values between 1.2% and 4.9%, and particle sizes spanning 2.4 to 8.5 μm . Hemagglutination assays confirmed that the antigenicity of the WIV vaccine remained preserved following spray drying. The optimal spray drying conditions were identified using descriptive models generated through DoE software, facilitating the production of a dried WIV powder with tailored properties. Notably, the spray-dried vaccine powders retained antigenic stability even after three months of storage at 60°C. The Quality by Design (QbD) framework enabled the development of a thermostable WIV vaccine powder with the desired physical properties, positioning it as a promising candidate for pulmonary delivery. This study underscores the successful application of DoE and QbD principles in optimizing spray drying processes, demonstrating their potential for the development of stable, high-quality vaccine formulations^[75].

5.4.3. Tablet Coating

The impact of disintegrants on the hardness and disintegration time of rapidly disintegrating tablets (RDTs) was systematically evaluated using the Quality by Design (QbD) framework. Ibuprofen, aspirin, and ascorbic acid were selected as model drugs based on their varying water solubility profiles. A combined optimal design approach was employed to assess the influence of different disintegrants on tablet mechanical strength and disintegration kinetics. The study findings indicated that higher concentrations of disintegrants, including sodium starch glycolate (modified starch), croscarmellose sodium (modified cellulose), and crospovidone (cross-linked polyvinylpyrrolidone), generally prolonged disintegration time. However, specific disintegrant combinations demonstrated synergistic effects, resulting in enhanced tablet disintegration. Notably, a crospovidone–sodium starch glycolate blend significantly reduced the disintegration time of aspirin RDTs, while crospovidone combined with sodium starch glycolate or croscarmellose sodium accelerated the disintegration of ibuprofen RDTs, particularly under high compression pressures. Furthermore, the crospovidone–microcrystalline cellulose (MCC) combination facilitated faster tablet disintegration by promoting water uptake into the matrix, whereas sodium starch glycolate extended the disintegration time of ascorbic acid RDTs, likely due to its high-water solubility. Graphical optimization analysis established a design space, enabling the selection of tailored disintegrant combinations and compression pressures to achieve the desired tablet hardness and disintegration characteristics. The QbD-driven approach proved to be an effective strategy in elucidating the interactions between formulation variables and process parameters, ensuring the consistent quality and performance of RDT formulations^[76-77].

5.4.4. Analytical Processes

The Quality by Design (QbD) approach offers a structured framework for the development and optimization of analytical methodologies, enabling a systematic evaluation and comparative analysis of different techniques to achieve optimal method performance. A comprehensive risk assessment, integrated with effective risk management strategies, is performed to ensure the robustness and ruggedness of the selected method. Following risk assessment, the methodology undergoes rigorous stress testing to identify potential vulnerabilities and enhance its reliability. By providing detailed insights into method performance, this approach facilitates targeted refinements and supports the development of a well-defined control strategy for risk mitigation. The implementation of this strategy ensures method consistency and dependability, allowing the analytical method to perform as intended following validation ^[77].

5.5. Quality by Design (QbD) approach in chromatographic techniques

5.5.1. Method development & optimization strategy for high performance-liquid chromatography (HPLC)

Weiyong and Henrik have developed a systematic three-step strategy for pharmaceutical assay and impurity testing utilizing High-Performance Liquid Chromatography (HPLC). A fundamental aspect of this approach involves the screening of multiple columns and mobile phases, incorporating various organic modifiers to enhance separation efficiency. Additionally, a Plackett-Burman (PB) design was employed to simultaneously optimize multiple parameters within the analytical method. To expedite the optimization process, Dry-Lab, a commercially available chromatographic method development software, was used to conduct computer simulations, significantly reducing the number of experimental trials required for method development. Once optimal separation conditions were established, PB experimental designs were further applied to refine and enhance method robustness, ensuring its accuracy and reliability ^[78]. Peter et al. implemented an Ultra-Performance Liquid Chromatography (UPLC) method, integrated with specialized analytical software, to achieve the separation of impurities in Vancomycin using a Quality by Design (QbD) framework in combination with Design of Experiments (DoE). Compared to conventional gradient-based High-Performance Liquid Chromatography (HPLC) methods, the UPLC-based approach demonstrated notable advantages in terms of efficiency and analytical performance. The QbD-optimized UPLC method, utilizing a sub-2- μm ACQUITY UPLC column, successfully resolved 26 Vancomycin impurities, whereas the traditional HPLC approach detected only 13 impurities. These results underscore the superior resolving power and analytical efficiency of the UPLC-based methodology, reinforcing its potential as a robust and enhanced technique for impurity profiling in pharmaceutical analysis ^[79]. A stability-indicating High-Performance Liquid Chromatography (HPLC) method was developed following Quality by Design (QbD) principles to assess the stability of eberconazole nitrate (EBZ). The study evaluated EBZ under various stress conditions, including thermal, oxidative, photolytic, and hydrolytic degradation in neutral, acidic, and basic environments. Degradation of EBZ was observed across all tested conditions, following pseudo-first-order kinetics. These findings suggest that to enhance the stability of EBZ and mitigate degradation under such stress conditions, topical formulations containing EBZ should be formulated with antioxidants to improve product stability ^[80].

5.5.2. Development and validation of rapid ultra-high-performance liquid chromatography

A reliable and precise reversed-phase ultra-high-performance liquid chromatography (UHPLC) method was developed for the quantitative determination of total benzalkonium chloride, a widely used preservative in pharmaceutical formulations. The method was systematically optimized using a Quality by Design (QbD) approach, employing Fusion AE® software to ensure optimal chromatographic performance. Key high-performance liquid chromatography (HPLC) parameters, including gradient time and mobile phase composition, were carefully assessed and refined. To achieve efficient separation, a gradient elution technique was utilized with an ACE Excel 2 C18-AR column. The aqueous mobile phase consisted of 10 mM ammonium phosphate buffer (pH 3.3), while the organic mobile phase comprised a methanol/acetonitrile mixture (85:15, v/v). Detection was performed using a UV detector set at 214 nm. The optimized method successfully achieved baseline separation of the primary benzalkonium chloride homologues (C12 and C14) within two minutes. A linear response was observed over the concentration range of 0.025 to 0.075 mg/mL, demonstrating exceptional precision and accuracy. Method validation further confirmed its reliability, with recovery values ranging from 99% to 103%, ensuring compliance with regulatory and quality control standards. This UHPLC method provides a highly efficient, robust, and rapid approach for the precise quantification of benzalkonium chloride in pharmaceutical formulations ^[81].

5.5.3. Development of hydrophilic interaction liquid chromatography

For the first time, a hydrophilic interaction liquid chromatography (HILIC) method was developed using an Analytical Quality by Design (AQbD) approach, combined with a gradient elution strategy, to enable the simultaneous analysis of olanzapine and its seven related compounds. To optimize method performance, critical

process parameters (CPPs) including column temperature, initial aqueous phase composition, and linear gradient duration were systematically identified and refined. To ensure robustness and reliability, critical quality attributes (CQAs) were established based on the separation efficiency of critical analyte pairs. The interrelationship between CQAs and CPPs was thoroughly examined using predictive modeling based on the Rechtschaffen design. A comprehensive design space was explored during optimization, facilitating the selection of optimal chromatographic conditions that ensured peak symmetry and maximum resolution. The finalized HILIC method demonstrated high precision, accuracy, and reproducibility, making it a reliable tool for quality control and regulatory assessment of olanzapine and its related impurities in pharmaceutical formulations^[82].

5.5.4. Screening of column used for chromatography

Connie et al. conducted a comprehensive review of analytical columns, extensively utilized and manufactured by leading column suppliers. Their study provided detailed insights into evaluation criteria and experimental design parameters, offering a systematic approach to column selection within the framework of Quality by Design (QbD). A total of seven reverse-phase high-performance liquid chromatography (RP-HPLC) columns were rigorously assessed as a critical component of method development, ensuring robustness and reliability through comparison with predefined performance criteria. The findings from this study offer valuable guidance for analytical scientists, facilitating the development of reliable and durable chromatographic methods aligned with QbD principles. These results serve as a practical reference for method development, particularly in ensuring efficiency and reproducibility in analytical workflows. Moreover, the expanding application of QbD in the selection of ultra-performance liquid chromatography (UPLC) columns underscores its growing significance in modern analytical science and pharmaceutical quality assurance^[83-84].

5.5.5. High performance-liquid chromatography (HPLC) method development for drug products/substances

Monks et al. introduced an innovative approach for the development of high-pressure reversed-phase liquid chromatography (RP-HPLC) methods, utilizing Quality by Design (QbD) principles. Within this framework, four critical parameters pH of the aqueous eluent, gradient time, stationary phase, and column temperature were systematically evaluated through a comprehensive column database and advanced computer modeling tools. This strategic methodology ensures enhanced chromatographic performance, as well as greater method robustness and reliability. In a related study, Awotwe-Otoo et al. incorporated key QbD components to develop and optimize an analytical method for protamine sulfate. The optimization process was further refined using response surface methodology (RSM) with a Box-Behnken design (BB design) to assess interactions, main effects, and quadratic effects of critical method parameters on analytical responses. The predicted results demonstrated a tailing factor ranging from 1.02 to 1.45 and a peak resolution between 1.99 and 3.61 for the four peptide peaks of protamine sulfate, meeting the established method performance criteria under optimized conditions. These findings underscore the effectiveness of QbD-driven method development in producing highly accurate and reproducible analytical techniques for pharmaceutical quality control^[85-86]. One of the widely used strategies in compliance with International Council for Harmonisation (ICH) guidelines in analytical method development focuses on the Quality by Design (QbD) methodology, which takes a systematic approach to creating strategies for developing highly reliable and robust methodologies. Prompted by the effectiveness of QbD-based approaches in ensuring method consistency, reliability, and regulatory compliance, the pharmaceutical industry is increasingly embracing these concepts. In addition, the QbD perspective promotes continuous improvement, allowing analytical methodologies to be optimized and refined over time to enhance method performance and quality. One of the tasks regularly performed by analytical chemists has traditionally relied on High-Performance Liquid Chromatography (HPLC). This technique remains a cornerstone for impurity profiling, method development, and stability studies. Additionally, Karl Fischer titration continues to be the gold standard for determining moisture content in pharmaceutical formulations. Analytical methods play a fundamental role in biomedical research, facilitating both qualitative and quantitative assessments of pharmaceutical products through descriptive studies. Liquid Chromatography-Mass Spectrometry (LC-MS) is commonly used for generating highly accurate and reliable analytical results. Moreover, sophisticated separation methods, including capillary electrophoresis and ultra-high-performance liquid chromatography (UHPLC), along with mass spectrometry, provide unparalleled sensitivity and resolution, making them invaluable for intricate analytical studies. Furthermore, specialized analytical methods are employed for the detection and quantification of genotoxic impurities, ensuring product safety while reinforcing regulatory compliance and quality assurance in pharmaceutical development^[88]. The application of Quality by Design (QbD) principles to the development of analytical methods offers significant advantages. Analytical Quality by Design (AQbD) follows a systematic approach, with its primary objective being the establishment of a highly reliable analytical method that maintains consistent performance throughout the entire lifecycle of a pharmaceutical product. This strategic approach is particularly beneficial for pharmaceutical products containing the same active ingredient, as it ensures method consistency and reproducibility across

various stages of research, development, and manufacturing. By adopting a structured framework, AQbD facilitates the optimization and validation of analytical methodologies, ultimately enhancing their accuracy, precision, and compliance with regulatory standards in pharmaceutical quality control [77]. Analytical methodologies now integrate Quality by Design (QbD) principles to facilitate the detection and analysis of biological metabolites, pharmaceutical contaminants, and active pharmaceutical ingredients (APIs). A fundamental component of Analytical QbD (AQbD) involves defining process development objectives, enhancing product and process knowledge, and establishing an Analytical Target Profile (ATP). The AQbD framework also necessitates the development of rigorous testing strategies to evaluate diverse analytical approaches, achieve a comprehensive understanding of the methodology, and optimize the Method Operating Design Region (MODR) to improve method performance and reliability. Furthermore, systematic risk assessment and method validation are conducted throughout all stages of the product lifecycle to ensure long-term stability and robustness [89]. The FDA's Process Analytical Technology (PAT) initiative focuses on real-time monitoring of critical process parameters (CPPs) and critical quality attributes (CQAs) to enhance the efficiency, reliability, and quality of pharmaceutical manufacturing. The integration of PAT systems within manufacturing processes improves operational efficiency, minimizes rework, and ensures regulatory compliance. To enforce its effective implementation, regulatory bodies have established stringent criteria, promoting enhanced process control and product uniformity. The role of CPPs during post-processing phases is particularly crucial, as they directly influence the final product's CQAs. Furthermore, the implementation of PAT, when complemented by continuous manufacturing technology (CMT), significantly reduces waste, enhances process predictability, and improves product quality. A comprehensive understanding of upstream and downstream process dynamics allows for better control of common cause variations, leading to greater manufacturing consistency and efficiency. The combined application of PAT and CMT facilitates a higher degree of automation, sustainability, and regulatory compliance in the pharmaceutical industry, ensuring the production of high-quality pharmaceutical products with minimal environmental impact [90-92]. The effective implementation of a Process Analytical Technology (PAT) framework necessitates the integration of advanced analytical instruments and sophisticated software tools to facilitate real-time monitoring of critical process parameters (CPPs). Key methodologies employed in PAT-driven pharmaceutical manufacturing include Design of Experiments (DoE), comprehensive raw data acquisition, and rigorous statistical analysis, all of which contribute to precise process optimization and enhanced control strategies. To ensure continuous monitoring and analysis of CPPs, cutting-edge spectroscopic techniques, such as fiber optics, Raman spectroscopy, and Near-Infrared Spectroscopy (NIRS), are widely employed. These real-time analytical approaches enhance process understanding, support proactive decision-making, and ensure compliance with stringent regulatory requirements. By leveraging advanced PAT methodologies, pharmaceutical manufacturers can achieve greater process efficiency, reduced variability, and improved product quality, ultimately fostering a more robust and sustainable manufacturing paradigm within the industry [93].

5.6. Quality by Design (QbD) approach in vaccine development

The application of Quality by Design (QbD) principles plays a pivotal role in accelerating the development of vaccine manufacturing processes at a commercial scale. A comprehensive risk assessment was conducted by integrating historical data with a scientific understanding of the production process, enabling the systematic identification of critical process parameters (CPPs) within the existing manufacturing platform. To further refine process optimization, multiple Design of Experiments (DoE) studies were performed to thoroughly evaluate key parameters and their interactions, ensuring the development of a robust and well-optimized manufacturing strategy. The strategic integration of QbD enhances process understanding, strengthens control mechanisms, and improves overall operational efficiency in vaccine production. Ultimately, this approach contributes to higher product quality, consistency, and regulatory compliance, reinforcing the scientific and regulatory framework necessary for advanced vaccine manufacturing [94]. This process development strategy proved highly effective in meeting stringent deadlines and resource constraints while successfully achieving program objectives. The successful implementation of this approach was attributed to the integration of a risk- and experiment-driven strategy aligned with Quality by Design (QbD) principles. A comprehensive risk assessment enabled the classification of process parameters into three distinct categories: (i) parameters with a high impact on product quality or potential strain sensitivity, (ii) parameters with a significant impact but effectively managed through established control strategies, and (iii) parameters with minimal influence. This categorization approach facilitated a targeted experimental characterization of critical parameters, while leveraging historical production and development data for non-critical variables. Given the time-intensive nature of experimental execution, prioritizing essential process parameters significantly reduced the number of required experiments, thereby accelerating process development timelines. Additionally, optimized resource allocation minimized staff requirements for data mining and documentation, further enhancing operational efficiency. A key contributor to this project's success was the implementation of a licensed platform approach, which was supported by extensive manufacturing data and a well-defined control strategy. The involvement of cross-functional experts across development and production facilitated the widespread adoption of the platform process, enabling informed risk

assessments and data-driven decision-making. Furthermore, the integration of a well-characterized scale-down model equipped with validated analytical assays provided a real-time experimental evaluation framework, enhancing process sensitivity to deviations and ensuring rapid troubleshooting and resolution. When compared to traditional vaccine development programs, this approach demonstrated a marked improvement in efficiency, leveraging a pre-existing framework to streamline development. Without the use of QbD tools, systematically prioritizing experiments and optimizing resource allocation would have been significantly more challenging, even with access to extensive historical data. Notably, the successful application of QbD methodologies to a legacy platform process, which was not originally designed within a QbD framework, highlights the adaptability and versatility of this strategy. While the integration of pre- and post-QbD processes presents inherent complexities, this case study demonstrates the feasibility of incorporating legacy processes into a QbD-driven framework, resulting in a robust and optimized manufacturing process. Beyond accelerating development timelines, this integration is anticipated to deliver long-term benefits across the entire product lifecycle, reinforcing process robustness, consistency, and regulatory compliance^[95].

5.7. Quality by design (QbD) approach in development of botanical drug products

A notable example of the application of Quality by Design (QbD) principles in pharmaceutical manufacturing is the production of botanical medicine products, specifically the ethanol precipitation unit operation involved in the processing of Danshen (*S. Miltiorrhiza Bunge*). Through a comprehensive risk assessment, critical process parameters (CPPs) such as ethanol consumption, concentrate density, and setting temperature were systematically identified. To evaluate the efficacy of the ethanol precipitation method, the recovery of four active pharmaceutical ingredients (APIs) and the removal of saccharides were analyzed. The impact of these key process parameters on overall process performance was systematically assessed using a Design of Experiments (DoE) approach. Experimental data revealed that higher concentrate density significantly enhanced saccharide removal, yet was associated with a reduction in API recovery. Additionally, excessive ethanol consumption influenced the recovery behaviours of different APIs, highlighting the complex interplay between process variables. The DoE-based analysis facilitated the establishment of a well-defined design space, providing an in-depth understanding of the interrelationships between material attributes, process parameters, and method performance. These findings underscore the effectiveness of the QbD framework in optimizing botanical medicine production, ensuring greater process understanding, reproducibility, and quality control^[96].

5.8. Manufacture of polyacrylamide corn fiber gum using the Quality by Design (QbD) method

The application of Quality by Design (QbD) principles enabled the systematic transformation of corn fiber gum (CFG) into polyacrylamide-grafted corn fiber gum (PAAm-g-CFG) through an optimized polymerization process. The grafting reaction was meticulously fine-tuned by adjusting acrylamide and initiator concentrations, ensuring the desired copolymer characteristics were achieved. The successful grafting of acrylamide onto CFG was confirmed through advanced spectroscopic and analytical techniques, including ¹H NMR, mass spectrometry, attenuated total reflectance Fourier-transform infrared spectroscopy (ATR-FTIR), X-ray diffraction (XRD), and differential scanning calorimetry (DSC). Rheological analysis of the grafted copolymer dispersion revealed its compliance with the Herschel-Bulkley model, demonstrating shear-thinning behavior. Viscoelastic studies indicated that increasing concentrations of PAAm-g-CFG resulted in enhanced viscosity, signifying its predominantly liquid-like properties. Additionally, muco-adhesion assessments confirmed the superior adhesive strength of PAAm-g-CFG in comparison to conventional bioadhesive polymers, including guar gum, xanthan gum, chitosan, karaya gum, gelatin, and Moringa oleifera gum. Furthermore, thermal stability evaluations validated the enhanced thermal resilience of PAAm-g-CFG, underscoring its potential as an innovative biomaterial for pharmaceutical and biomedical applications^[97].

5.9. Pharmacogenomics using the Quality by Design (QbD) method

The integration of pharmacogenomics into drug research and discovery, particularly in the wake of the Human Genome Project, has transformed pharmaceutical development. When combined with the Quality by Design (QbD) framework, this approach enables the development of high-quality pharmaceutical products by systematically optimizing drug formulation and therapeutic efficacy. The emergence of functional and structural pharmacogenomics as fundamental components of modern drug discovery has facilitated a more targeted and efficient therapeutic development process. Genetic data plays a pivotal role in identifying and evaluating potential therapeutic targets, while high-throughput screening enhances lead optimization. Additionally, the integration of bioinformatics databases and computational methodologies enables a comprehensive assessment of drug-receptor interactions, drug transporters, and metabolizing enzymes. These technological advancements contribute to a more systematic and rational approach to drug development, ultimately leading to improved efficacy and safety profiles. The convergence of pharmacogenomics and QbD represents a paradigm shift in pharmaceutical research, fostering the development of personalized and precision medicine to optimize patient outcomes^[98].

Pharmacogenomics plays a pivotal role in optimizing drug formulations and repurposing previously unsuccessful medications for novel therapeutic applications. The identification of disease-associated genetic markers has significantly advanced the development of next-generation drug delivery systems, including vaccines, immunological agents, DNA- and gene-based therapies, and anticancer drugs. Moreover, pharmacogenomic insights enable the evaluation of formulation polymers and their influence on pharmacokinetic and pharmacodynamic properties, facilitating rational formulation optimization. Despite its transformative potential, the widespread implementation of pharmacogenomics remains constrained by high costs and limited accessibility to advanced technologies. However, with ongoing technological advancements and the integration of Quality by Design (QbD) principles, pharmacogenomics is poised to revolutionize drug discovery and formulation. This convergence is expected to drive the development of safer, more effective pharmaceutical products, ultimately shaping the future of precision medicine and personalized therapeutics^[99].

5.10. QbD approach in dissolution and drug stability enhancement

A design space for the felodipine solid mixture (FSM) was successfully established using the Box–Behnken (BB) experimental design, followed by the determination of its control space to optimize solubility and dissolution while preventing felodipine crystallization from a supersaturated solution. The study systematically evaluated critical material attributes (CMAs) and critical process parameters (CPPs), including the proportions of hydroxypropyl methylcellulose (HPMC), polymeric surfactant (Inutec®), and Pluronic® F-127, as well as the preparation method—either physical mixing (PM) or solvent evaporation (SE). Results indicated that a stable design space could not be achieved using the PM approach when Pluronic® content was below 45.1 mg. The optimal operating ranges for FSM formulation were identified as 16–23 mg of Inutec®, 49–50 mg of Pluronic®, and 83–100 mg of HPMC, with SE emerging as the preferred preparation method. The ternary mixture of HPMC, Pluronic®, and Inutec® not only enhanced dissolution rates and inhibited felodipine crystallization but also regulated drug release from the tablet matrix through the incorporation of Carbopol® 974. The implementation of the Quality by Design (QbD) approach facilitated the development of a once-daily controlled-release (CR) formulation of felodipine, ensuring enhanced solubility, dissolution, and long-term stability^[100].

5.11. QbD approach in stability enhancement

Karmarkar et al. implemented Quality by Design (QbD) principles to develop a stability-indicating high-performance liquid chromatography (HPLC) method for the quantitative analysis of a drug compound and its degradants. A primary challenge in method development was the inadequate resolution between the drug degradant and the oxidative degradant of the preservative, as well as between the preservative and another drug degradant. To address these chromatographic challenges, Design of Experiments (DoE) was applied using Fusion AETM software (SMatrix Corporation, Eureka, CA). Key method parameters including initial hold duration (2.5, 5, or 10 min), mobile phase buffer pH (2.9 ± 0.2), column temperature ($50 \pm 5^\circ\text{C}$), and initial acetonitrile (ACN) concentration ($2 \pm 1\%$) were systematically optimized to achieve enhanced peak separation in HPLC analysis. The optimal conditions identified for complete resolution of the two critical peak pairs included a buffer pH of 3.1, an initial hold period of 2.5 min, a column temperature of 50°C , and an initial ACN concentration of 3%. The integration of QbD-driven optimization facilitated the development of a robust and reliable HPLC method, ensuring well-defined design and operating spaces. This strategic approach significantly enhanced method reproducibility and robustness, ultimately improving analytical performance within the specified operating range^[101].

5.12. QbD approaches in animal cell culture process

The identification of critical process parameters (CPPs) that significantly impact critical quality attributes (CQAs) is a fundamental component of Quality by Design (QbD) implementation in upstream bioprocessing for therapeutic protein production. Establishing proven acceptable ranges (PARs) for CPPs based on experimental data and aligned with CQA acceptance criteria ensures process robustness and product quality. In accordance with International Council for Harmonisation (ICH) guidelines Q8, Q9, and Q10, the QbD framework follows a structured approach, encompassing risk analysis, work package definition, scale-down model qualification, range studies, and process characterization. A validated scale-down model serves as the cornerstone of this architectural framework, facilitating a reliable correlation between small-scale experimental trials and commercial-scale manufacturing data. To enhance the predictive capability and accuracy of the model, various scale-down criteria were systematically refined. Once validated, the scale-down system was employed to systematically investigate cause-and-effect relationships between process parameters and quality attributes. This approach enables a comprehensive assessment of process variability, ensuring a well-characterized and stable manufacturing process for therapeutic proteins. Ultimately, this strategy contributes to enhanced product consistency, regulatory compliance, and process reliability in biopharmaceutical production^[102].

5.13. QbD approach in immuno-assays

In recent years, the application of Quality by Design (QbD) principles has expanded beyond pharmaceutical manufacturing to include analytical chemistry, particularly in the optimization of offline assays, such as immunoassays, through online process analytical technologies. Although analytical QbD is a relatively recent advancement, concepts such as statistical quality control and target-oriented development have long been employed as design control measures in diagnostic assays. However, most research has predominantly focused on specific tools and partial implementations, with few studies detailing the comprehensive evolution of QbD-based immunoassays. The increasing adoption of Design of Experiments (DoE) in refining immunoassay parameters has significantly contributed to enhancing robustness, particularly by introducing noise factors early in development. This approach enables the selection of parameters that are less susceptible to external variations, such as temperature fluctuations, equipment differences, and analyst inconsistencies. A systematic and objective risk management strategy translates method-related risks into patient safety considerations, further reinforcing the importance of analytical QbD. Moreover, critical quality attributes (CQAs) of pharmaceutical products, process performance, and acceptable patient risk profiles serve as essential determinants for critical material attributes (CMAs). Despite these advancements, the real-world implementation of QbD in analytical methodologies remains limited due to the inherent complexity of pharmaceutical development, which requires the integration of analytical support, regulatory compliance, chemistry, manufacturing, and clinical testing. A significant challenge lies in achieving the full integration of QbD principles across product development, bridging patient-centered considerations with offline analytical methodologies, including immunoassays. While QbD concepts and statistical quality tools are often applied independently, the establishment of a seamlessly integrated development framework remains an ongoing pursuit. Achieving true integration requires the synthesis of extensive empirical knowledge with a structured QbD approach. However, this level of harmonization has yet to be fully realized, underscoring the need for further advancements in the field ^[99].

Table II Applications of the QbD technique in pharmaceuticals

DRUG DELIVERY SYSTEM			
Formulation	QbD design	Parameter	Ref.
Tablets	A Two factorial design	The independent variables in this study include medication concentration, total polymer ratio, and super-disintegrants concentration. The evaluated responses comprise disintegration time and the time required for drug release from the matrix system. These parameters play a critical role in optimizing formulation performance and ensuring controlled drug delivery.	54
Hard gelatin capsules	-	Key Critical Quality Attributes (CQAs) in pharmaceutical formulations include disintegration time, drying loss, sulfated ash content, sulfur dioxide levels, and weight and dimensional specifications. These attributes play a crucial role in ensuring product quality, consistency, and compliance with regulatory standards.	56
Nanoliposomes	Risk analysis	Key process variables influencing formulation performance include particle size, coating effectiveness, and encapsulation efficiency. Several critical factors affecting these parameters include sonication duration, stirring speed, temperature, organic-to-aqueous phase ratio, and the concentrations of fat, cholesterol, chitosan, and the active pharmaceutical ingredient (API). Optimizing these variables is essential to ensure enhanced stability, controlled drug release, and improved bioavailability in pharmaceutical formulations.	61
Polymeric Nanoparticles	BB design, PB design	Key Critical Quality Attributes (CQAs) in pharmaceutical formulations include zeta potential, average particle size, and entrapment efficiency. These attributes are essential for ensuring formulation stability, drug delivery performance, and overall product quality.	62

Solid lipid nanoparticles	3 ³ factorial design	The independent factors influencing formulation performance include surfactant concentration, homogenization time, and drug-to-lipid ratio. The qualitative characteristics or dependent variables assessed in the study comprise particle size, entrapment efficiency percentage, and polydispersity index (PDI). These parameters play a critical role in determining the stability, uniformity, and effectiveness of the drug delivery system.	64
Microsponges	FMECA, One-factor response surface method	The Critical Material Attributes (CMAs) in primary and multiple emulsions include the proportions of water, Tween 80, Span 80, ethyl cellulose, dichloromethane, chitosan, and acetone. These components play a crucial role in determining the stability, emulsification efficiency, and physicochemical properties of the formulation, directly influencing drug encapsulation, release kinetics, and overall product performance.	66
Transgel	-	The Critical Process Parameters (CPPs) influencing formulation performance include the type of stirrer, rotational speed, transdermal flux percentage, and particle size. These parameters play a pivotal role in determining drug diffusion rates, formulation stability, and overall transdermal drug delivery efficiency, thereby ensuring optimal therapeutic outcomes.	67
Nanostructured lipid carriers	3 ³ factorial design	The Critical Material Attributes (CMAs) essential for formulation development include lipids, oil-to-lipid ratio, and surfactant concentrations. These components significantly influence the physicochemical properties and performance of the final product. Key Critical Quality Attributes (CQAs) that determine formulation stability and efficacy comprise zeta potential, in vitro drug release profile, entrapment efficiency, particle size, and polydispersity index (PDI). These parameters are essential for ensuring optimal drug encapsulation, controlled release kinetics, and consistent particle distribution, thereby enhancing therapeutic performance and product quality.	68
Pickering emulsions	-	The concentration of starch and the amount of internal aqueous phase are critical formulation parameters that influence the stability, structural integrity, and performance of the final pharmaceutical system. Optimizing these factors is essential for achieving controlled drug release, improved encapsulation efficiency, and enhanced product consistency.	70
Oily compositions with solid self-nano emulsification	FMECA	The Critical Material Attributes (CMAs) essential for formulation development include Maisine, Tween 80, and Transcutol HP. These components play a key role in determining the physicochemical properties, solubility enhancement, and stability of the pharmaceutical system, directly influencing drug delivery efficiency and bioavailability.	71
Nano-capsules	-	Particle size distribution and zeta potential are critical physicochemical parameters that influence the stability, dispersibility, and bioavailability of pharmaceutical formulations. These attributes play a pivotal role in ensuring uniformity, optimizing drug delivery efficiency, and maintaining formulation integrity throughout the product lifecycle.	72
PROCESS CONTROL			

Process	QbD Design	Parameter	Ref.
Dissolution	Multivariate analysis	Key experimental parameters influencing dissolution and formulation performance include solution volume, ethanol content, pH, operator conditions, rotational speed (RPM), and the type of dissolution equipment used. These factors play a critical role in ensuring consistent drug solubility, dissolution rate, and analytical reproducibility, ultimately impacting pharmaceutical quality and regulatory compliance.	74
Spray drying	DoE	Key process variables influencing formulation efficiency and product quality include feed flow rate, intake air temperature, and nozzle gas flow rate. These parameters play a crucial role in ensuring optimal process conditions, particle size control, and overall stability of the final product.	75
Tablet Coating	Combined optimal design	Hardness and disintegration time are critical quality attributes (CQAs) in pharmaceutical tablet formulations, directly influencing mechanical strength, drug release profile, and patient compliance. Optimizing these parameters is essential to ensure formulation stability, efficacy, and regulatory compliance in oral solid dosage forms.	76
CHROMATOGRAPHIC TECHNIQUES			
Purpose	QbD design	Parameters	Ref.
Development of an HPLC method or optimization approach	PB design	Pharmaceutical assays and impurity testing are fundamental components of quality control and regulatory compliance in drug development and manufacturing. These analytical evaluations ensure the accuracy, potency, and purity of pharmaceutical formulations while identifying and quantifying potential impurities that may arise during synthesis, processing, or storage. The implementation of validated analytical methodologies is essential for maintaining product safety, efficacy, and adherence to regulatory standards.	78
Rapid UHPLC development and validation	Fusion AE in conjunction with the QbD approach	Mobile phase composition and gradient time are critical parameters in chromatographic method development, directly influencing separation efficiency, resolution, and analytical reproducibility. The selection of appropriate mobile phases ensures optimal analyte retention and peak symmetry, while gradient time modulation enhances selectivity and sensitivity, enabling precise quantification of pharmaceutical compounds and impurities.	81
Development of HILIC	The design of AQbD and Rechtschaffen	The Critical Process Parameters (CPPs) in chromatographic method development include temperature, initial aqueous phase content, and linear gradient duration. These parameters play a pivotal role in optimizing separation efficiency, peak resolution, and analytical precision. The Critical Quality Attributes (CQAs) consist of the Critical Pairs of Substances Separation Criterion, which ensures effective discrimination between closely eluting compounds, thereby enhancing method robustness, reproducibility, and regulatory compliance.	82
Screening of column used for RP-HPLC and ULC	Systematic approach	-	84

HPLC method development for drug products/ substances	BB design	Key analytical responses in chromatographic method optimization include interaction effects, primary and quadratic effects, tailing factor, and peak resolution. These parameters are essential for evaluating separation efficiency, peak symmetry, and method robustness, ensuring optimal chromatographic performance and regulatory compliance.	86
BIOMEDICAL APPLICATIONS			
Process	QbD Design	Parameters	Ref.
Vaccine development	Risk and experimental based strategy	Minimal influence on critical quality attributes (CQAs), posing negligible risk to product performance and safety. Although the impact on CQAs is significant, a robust and well-characterized control method effectively mitigates variability, ensuring process reliability. A substantial effect on CQAs, where variability may lead to strain sensitivity, requiring rigorous monitoring and risk mitigation strategies to maintain product consistency and efficacy.	95
Creation of Botanical Medicine Products	Risk assessment methods	Key process parameters influencing formulation stability and efficiency include concentrate density, setting temperature, and ethanol consumption. These factors play a critical role in optimizing precipitation efficiency, solvent removal, and overall process performance, ensuring consistent product quality and regulatory compliance.	96
Polyacrylamide corn fiber gum synthesis	-	The concentrations of acrylamide and initiator are critical parameters in polymerization reactions, directly influencing reaction kinetics, polymer structure, and overall material properties. Optimizing these variables ensures controlled polymer growth, enhanced stability, and improved performance in pharmaceutical and biomedical applications.	97
Pharmacogenomics	-	Lead optimization, bioinformatics library databases, and genetic data analysis play a pivotal role in drug target selection and assessment. The integration of computational approaches facilitates the identification of promising drug candidates, enabling a systematic evaluation of molecular interactions, pharmacokinetics, and therapeutic potential. The use of genetic data further enhances target validation, contributing to the development of precision medicine and novel therapeutic strategies.	98
Immuno-assays	-	Temperature fluctuations, equipment variability, and analyst-related factors are critical sources of variability in pharmaceutical analysis and quality control. These parameters can influence experimental reproducibility, analytical precision, and overall method robustness. Implementing strict environmental controls, standardized operating procedures, and rigorous analyst training is essential to ensure consistent and reliable analytical outcomes.	99
Dissolution and solubility enhancement	BB design	The Critical Process Parameters (CPPs) essential for formulation development and material synthesis include hydroxypropyl methylcellulose (HPMC) content, synthesis methods, and polymeric surfactants such as Inutec® and Pluronic®. These parameters play a crucial role in determining drug encapsulation efficiency, stability, and controlled release profiles,	100

		ultimately influencing the performance and quality of the final pharmaceutical product.	
Stability enhancement	-	"The initial hold time, the pH of the mobile phase buffer, column temperature, and the initial percentage of acetonitrile were optimized to achieve the best chromatographic separation. The initial hold time was selected to ensure a stable baseline before the gradient started, allowing for a better resolution of the analyte peaks. The pH of the mobile phase buffer was adjusted to maintain optimal ionization of the analyte, thus enhancing the sensitivity and reproducibility of the method. The column temperature was carefully controlled to minimize variability in retention time and to improve the resolution of the chromatographic peaks. Lastly, the initial acetonitrile concentration was set to optimize the balance between retention time and peak sharpness, contributing to a higher-quality separation of components."	101
Animal cell culture process	-	Cause-effect relationships	102

6. BENEFITS OF QbD IN WORKPLACE ^[103]

The developed approach demonstrates enhanced robustness and reliability when subjected to varied conditions, ensuring consistent performance across diverse operational settings. As the methodology undergoes further refinement, a deeper understanding of its fundamental principles and applications is achieved. This strategic framework facilitates a seamless transition from research and development (R&D) to quality control, significantly enhancing the success rate of method transfer. Furthermore, meticulous planning during the development phase minimizes manufacturing disruptions and ensures regulatory compliance, thereby mitigating the need for costly post-approval modifications. This approach also fosters the advancement of novel methodologies and supports continuous process improvements throughout the product lifecycle, ensuring sustained efficiency and adherence to regulatory standards.

7. QbD's BENEFITS FOR THE FOOD AND DRUG ADMINISTRATION ^[104]

A systematic, data-driven framework streamlines decision-making by ensuring that analytical methods and conclusions are based on rigorous scientific principles. This approach prioritizes scientific rationale over empirical observations, fostering more reliable and predictive analytical outcomes. Furthermore, it enhances the integration and compatibility of analytical techniques across diverse systems and processes, promoting consistency, efficiency, and reproducibility in scientific research and industrial applications. By establishing a structured and objective methodology, this framework supports robust analytical development, ultimately contributing to advancements in precision-driven disciplines.

8. REGULATORY ASPECTS OF QUALITY BY DESIGN (QbD) APPROACHES

According to the International Council for Harmonization (ICH) Q10 guidelines on the Pharmaceutical Quality System, analytical methods play a fundamental role in the overall control strategy for pharmaceutical manufacturing. Analytical Quality by Design (AQbD) has emerged as a systematic approach aimed at ensuring the reliability and quality of pharmaceutical products. This framework encompasses critical parameters associated with the drug substance, excipients, and drug product components, including finished product specifications, facility requirements, instrument operating conditions, analytical procedures, and testing frequency. The principle of "right analytics at the right time" is integral to the pharmaceutical product development cycle, and the implementation of QbD principles further strengthens this concept by systematically identifying and mitigating variability in analytical method development. The U.S. Food and Drug Administration (FDA) has acknowledged the significance of AQbD in regulatory submissions, with multiple new drug applications (NDAs) incorporating AQbD principles receiving regulatory approval. This underscores the pivotal role of QbD in enhancing the robustness, reliability, and regulatory compliance of analytical methodologies in pharmaceutical development ^[105]. Continuous process verification and process control are critical for monitoring product quality trends, enabling a comprehensive evaluation of drug-excipient interactions and critical quality attributes (CQAs) throughout the experimental phase. To address these requirements, the pharmaceutical industry has increasingly embraced Analytical Quality by Design (AQbD) as a fundamental strategy for ensuring method robustness and

regulatory compliance. Despite the long-standing enforcement of current Good Manufacturing Practice (cGMP) regulations, the U.S. Food and Drug Administration (FDA) has issued warning letters to pharmaceutical companies for failing to implement adequate risk management systems in analytical methodologies. This highlights the industry's need to enhance systematic risk assessment and control strategies in analytical method development. The integration of AQbD principles into pharmaceutical quality assurance fosters a proactive approach to risk mitigation, thereby improving the reliability, reproducibility, and regulatory acceptance of analytical techniques. Quality assurance professionals recognize QbD as an effective strategy for minimizing method failures while ensuring the stability and dependability of analytical procedures. The concurrent development and validation of analytical methods within the QbD framework play a pivotal role in maintaining product quality and regulatory compliance. Given the importance of accurate and reliable analytical data in pharmaceutical formulation and manufacturing, there is an increasing emphasis on integrating AQbD principles alongside rigorous analytical method development. Although analytical method development is not explicitly linked to design space in the ICH Q8 (R2) guidelines, it remains integral to enhancing method robustness and process understanding. Analytical methodologies serve as key indicators of process and product robustness, ensuring the sustained quality of pharmaceutical products throughout their lifecycle^[106].

9. CHALLENGES

Although Quality by Design (QbD) is essential for enhancing the quality and consistency of medical products, its implementation remains challenging due to a limited general understanding of pharmaceutical processes. A comprehensive scientific knowledge of production methods is critical to ensuring the efficacy, safety, and quality of the final product. To facilitate the adoption of QbD, pharmaceutical companies actively engage in collaborative efforts, while regulatory agencies, particularly the U.S. Food and Drug Administration (FDA), have prioritized the incorporation of key elements into regulatory guidelines. These elements include criteria for selecting and rejecting quality attributes, standards for regulatory review, and specifications for various analytical methodologies. However, eight primary obstacles to the widespread implementation of QbD have been identified, with the impact of each challenge varying depending on the pharmaceutical product type and its intended therapeutic application. Addressing these barriers is crucial for the successful integration of QbD principles into pharmaceutical development and manufacturing, ultimately ensuring product quality, consistency, and regulatory compliance^[107]. The implementation of Quality by Design (QbD) principles in pharmaceutical manufacturing presents several significant challenges that must be systematically addressed. Among these, four primary obstacles have been identified, each influencing the efficacy and feasibility of QbD adoption across the industry:

1. **Internal Misalignment:** Smooth implementation is hampered by conflicts between cross-functional domains, such as production and research and development (R&D) or between the legal and quality assurance departments.
2. **Practitioner Uncertainty:** Due to ambiguous implementation schedules and expenses, QbD practitioners encounter numerous difficulties.
3. **Limited Knowledge of Critical Quality Attributes (CQAs):** Data management issues arise from a lack of understanding of CQA concepts and insufficient technology resources for execution.
4. **Engagement of Suppliers and Contract Manufacturers:** It is still crucial to make sure that suppliers and contract manufacturers are committed to and aligned with QbD implementation^[108].

The remaining five difficulties have a direct bearing on organizational supervision and management:

1. **Limited Familiarity with QbD:** Because there is not any clear, uniform industry requirements, managers frequently don't grasp QbD programs well enough.
2. **Inadequate Legal Framework:** Stakeholders are not sufficiently protected by the stated legal protections and the distribution mechanisms already in place.
3. **Lack of Inter-Governmental Coordination:** The smooth implementation of QbD is hampered by a lack of cooperation among governmental organizations.
4. **Voluntary Industry Interaction:** The broad adoption of QbD projects is now constrained by the lack of a mandate requiring businesses to participate.
5. **Difficulties with Practical Implementation:** Although there are difficulties with practical application, cooperation between companies and governmental organizations provides a mechanism to successfully address and resolve these problems^[109].

10. PRESENT CIRCUMSTANCES

The International Council for Harmonization (ICH) Q8 guidelines on drug development emphasize the importance of stringent controls and a comprehensive understanding of manufacturing processes to ensure the production of high-quality pharmaceuticals. Throughout the drug development lifecycle, product attributes and their associated

processes, including performance evaluation, must be assessed with a focus on efficacy, risk management, and comprehensive data analysis. However, a detailed examination of every aspect of the final product's quality is not always mandatory. With strong managerial support, Process Analytical Technology (PAT) can be leveraged to ensure that manufactured products consistently meet predefined quality standards. To uphold these standards, regulatory authorities require insight into a company's technical expertise, decision-making processes, and management strategies through well-defined legal frameworks. According to the Center for Research and Analysis at the U.S. Food and Drug Administration (FDA), Quality by Design (QbD) promotes a structured and systematic approach to product and process design and development. The key elements of QbD include: (i) Identifying Critical Quality Attributes (CQAs) to establish precise product specifications. (ii) Correlating raw materials with CQAs to facilitate effective risk assessment. (iii) Defining manufacturing processes and critical process parameters (CPPs). (iv) Establishing a design space to optimize process performance. (v) Addressing identified challenges through continuous improvement strategies. (vi) Implementing long-term product management for sustained quality assurance. As a strategic priority, QbD principles benefit both pharmaceutical organizations and their contractual partners, fostering regulatory compliance and operational efficiency. Furthermore, adherence to manufacturing protocols and process controls strengthens quality assurance measures, enhances supply chain reliability, and improves delivery timelines, thereby reinforcing the efficacy and consistency of pharmaceutical production^[110-113].

11. FUTURE PERSPECTIVES

The adoption of Quality by Design (QbD) principles in the pharmaceutical industry continues to expand, with an increasing emphasis on event-driven approaches in both production and drug development. However, several challenges hinder full implementation, including limited access to manufacturing facilities and insufficient collaboration with Process Analytical Technology (PAT) departments. Although current manufacturing output may meet acceptable quality standards, addressing the complexities of traditional PAT approaches, which rely on control mechanisms, remains a significant challenge. Regulatory agencies, such as the European Medicines Agency (EMA), actively support QbD adoption through collaborative initiatives, while the European Union has introduced the concept of "deferral" to enhance regulatory flexibility. The EMA recognizes the emphasis on quality in QbD-driven projects and fully supports regulatory applications that adhere to its principles. To maintain compliance with quality standards, the integration of mathematical and analytical techniques, including risk management strategies, is essential throughout drug research, development, and manufacturing. The ICH Q8–Q12 guidelines serve as primary references for QbD implementation in both the United States and Europe, with ongoing updates reflecting advancements in manufacturing and analytical methodologies. With regulatory requirements now mandating the application of QbD principles in drug development, the use of experimental designs has become essential, particularly in industrial settings. The selection of optimal design strategies depends on resource availability and risk tolerance concerning decision-making errors (e.g., Type I and Type II errors in hypothesis testing). Low-resolution screening designs, including Plackett-Burman Designs (PBDs), Taguchi designs, and Fractional Factorial Designs (FFDs), are frequently used for initial parameter screening; however, these approaches are limited to linear response models. When nonlinear responses emerge, or when a more precise response surface characterization is required, more sophisticated designs must be employed. By establishing a comprehensive understanding of formulation and manufacturing variables, QbD ensures pharmaceutical quality, supported by rigorous product testing. Within the Chemistry, Manufacturing, and Controls (CMC) review framework for abbreviated new drug applications (ANDAs), QbD enables science-based pharmaceutical quality evaluations. From a patient-centered perspective, QbD facilitates the identification and control of critical process parameters (CPPs) to consistently produce high-quality pharmaceutical products. This approach systematically establishes the relationship between critical quality attributes (CQAs) and desired product characteristics, while analyzing the impact of formulation and production processes. Factors such as active pharmaceutical ingredient (API) properties, excipient characteristics, process parameters, and product attributes are comprehensively assessed to ensure robust formulation development. To maintain process consistency and reproducibility, manufacturers define operational ranges based on critical material attributes (CMAs) and process parameters, setting upper and lower limits to regulate manufacturing variability. The implementation of real-time release testing (RTRT), a key feature of QbD, enables process-based quality control, reducing reliance on traditional batch testing while ensuring compliance with predefined quality standards. Unlike conventional quality assurance systems, which depend on batch testing, QbD emphasizes process capability evaluation, often utilizing the Six Sigma approach to demonstrate manufacturing reproducibility. The successful integration of QbD principles into drug development relies on adherence to predefined design spaces, ensuring continuous quality improvement while maintaining regulatory compliance. The optimization of drug delivery systems (DDSs) benefits from statistical modeling techniques, which enhance formulation robustness and enable the development of highly controlled and responsive pharmaceutical products. The extensive application of QbD in pharmaceutical manufacturing guarantees the production of high-quality, reproducible formulations, reinforcing scientific and regulatory standards. Furthermore, QbD is increasingly recognized as a universal manufacturing paradigm,

applicable beyond the pharmaceutical industry, with the ICH Q8 guidelines outlining the essential tools required for its successful implementation. Beyond industrial applications, QbD has profoundly influenced academic research, with scholars acknowledging its role in advancing drug formulation and development strategies. By enabling the production of safer, more effective, and cost-efficient pharmaceuticals, QbD fosters patient-centered innovations while addressing regulatory expectations. Unlike traditional Quality by Testing (QbT), which relies on empirical batch data, QbD establishes impurity acceptance criteria based on biological safety thresholds and scientific certification. While toxicological evaluations may contribute to quality assessments, safety and clinical studies remain the primary determinants of acceptable impurity levels. The integration of QbD modernizes pharmaceutical manufacturing guidelines, enhances quality control measures, and improves upon conventional regulatory models. Despite its widespread implementation, ongoing efforts are required to refine QbD methodologies, generate relevant data, and strengthen collaboration among industry stakeholders. As the scientific understanding of formulation and process factors within the QbD framework continues to evolve, the optimization of complex DDSs will become increasingly feasible. To fully realize QbD's potential, sustained collaboration between pharmaceutical companies and regulatory agencies is essential to enhance integration strategies and ensure long-term success.

12. CONCLUSION

A comprehensive understanding of pharmaceutical products and manufacturing processes, coupled with a commitment to continuous quality improvement, is fundamental to the Quality by Design (QbD) paradigm. One of the key advantages of QbD is the incorporation of the Target Product Profile (TPP), which serves as a strategic framework for enhancing pharmaceutical quality. A QbD-driven approach to drug development offers significant benefits to manufacturers, patients, and regulatory agencies by improving process control, product consistency, and compliance with quality standards. The regulatory framework supporting QbD is anticipated to have a profound impact on the pharmaceutical industry, reinforcing its role as a scientifically robust methodology essential for pharmaceutical manufacturing and quality assurance. Given that regulatory approval is a critical prerequisite before market authorization, the growing adoption of QbD principles and associated technologies underscores their indispensability in modern pharmaceutical manufacturing rather than being transient trends. The QbD framework provides a time- and cost-efficient approach to pharmaceutical design and production, employing tools such as Process Analytical Technology (PAT), Design of Experiments (DoE), and risk assessment methodologies to enhance the understanding of raw materials and manufacturing processes. This makes QbD not only a viable but also a highly practical strategy within the pharmaceutical industry. Its application extends beyond pharmaceutical processing to analytical chemistry, improving both online process analytical technologies and offline analytical methodologies, including immunoassays. As ensuring product quality remains a fundamental priority for pharmaceutical manufacturers, the establishment of a robust design space through QbD minimizes intra- and inter-batch variability, which is frequently encountered in pharmaceutical manufacturing. By embedding quality into both manufacturing and product development processes, QbD promotes continuous process improvement and significantly reduces variability. A well-structured Pharmaceutical Quality System (PQS) is essential for identifying and implementing process and product improvements, developing strategies for variability reduction, and fostering innovative advancements in pharmaceutical manufacturing. Ultimately, the PQS framework enables the pharmaceutical industry to consistently meet stringent quality standards, reinforcing its commitment to patient safety and regulatory compliance.

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