IJPPR
INTERNATIONAL JOURNAL OF PHARMACY & PHARMACEUTICAL RESEARCH
An official Publication of Human Journals
ISSN 2349-7203
HUMAN

Human Journals
Review Article
September 2023 Vol.:28, Issue:2

QBD Concepts in Pharma Industries

IJPPR
INTERNATIONAL JOURNAL OF PHARMACY & PHARMACEUTICAL RESEARCH
An official Publication of Human Journals
ISSN 2349-7203
HUMAN

Jayanti Mukherjee[1*], Tadikonda Rama Rao[1], Sneha Yaramada[2], Ravi Anju[2], Rachuri Sateesh[2]

[1]Professor, Department of Pharmaceutical Analysis, CMR College of Pharmacy, Hyderabad, India.

[2]B. Pharm Final Year Students, CMR College of Pharmacy, Hyderabad. India.
Affiliated to Jawaharlal Nehru Technological University, Hyderabad (JNTUH), India.

Submitted: 18 August 2023
Accepted: 20 September 2023
Published: 30 September 2023

ijppr.humanjournals.com

Keywords: QBD, Risk Assessments, PAT, CQA, Multivariate trials, Critical Material Attributes

ABSTRACT

Quality by Design serves as a bridge between industry and drug regulatory authorities to move towards a scientific, risk-based holistic and proactive approach to the development of pharmaceutical products. In the context of pharmacy, QBD (Quality by Design) is based on a full understanding of how materials and process factors affect the quality profile of final products, in order to correctly comprehend the manufacturing processes. QBD is a term used generally by the FDA (Food and Drug Administration). A meticulous understanding of the sources of variability and the manufacturing processes is the foundation for the application of Quality by Design in drug formulation and process design. Prior knowledge, risk assessment, mechanistic models, design of experiments (DoE), data analysis, and process analytical technology (PAT) are examples of Quality by Design methods and research. Awareness of principles and expectations, as well as a consistent nomenclature, are required as the pharmaceutical business works towards the adoption of pharmaceutical Quality by Design. This information will allow for better communication between individuals involved in the development of risk-based medications and the review of drug applications.

INTRODUCTION

Manufacturing and innovation are the foundations of growth for the pharmaceutical industries. Designing and creating formulas and manufacturing procedures that guarantee the established product standards are included in quality by design. Quality by design (QBD) is a methodical approach to product creation that starts with predefined objects and places an emphasis on knowledge of the product and its processes as well as on controls based on reliable science, quality risk management and the product's efficacy and safety. Joseph Moses Juan, an American-born quality expert, created the Quality by Design (QBD) concept first. The Food and Drug Administration (FDA) recommended QBD in the field of pharmaceutical science. In general, the ICH (International Council of Harmonisation) approaches QBD as a scientific technique, and it adheres to three ICH criteria (Woodcock, 2004). The three approaches include ICH Q8: Pharmaceutical development, ICH Q9: Quality risk management and ICH Q10: Pharmaceutical quality system. A new initiative by the FDA known as cGMP for the 21st Century: A Risk-based Approach was introduced in 2002 (Nishendu *et al*., 2012). This article investigates pharmaceutical quality through design with a focus on solid oral dose forms of tiny molecules and explains how it might be utilized to guarantee pharmaceutical quality. The pharmaceutical sector puts a lot of effort into developing, producing and bringing new medications to market while also adhering to regulatory criteria to prove that the medications are both safe and effective. In order to identify key quality attributes (CQAs) based on risk assessments (RAs), pharmaceutical product development uses process analytical technology (PAT) and other testing to execute quality by design (QbD) in a methodical manner. The QbD begins with pre-established objectives and calls for understanding how formulation and process variables impact product quality (Nishendu *et al*., 2012). Saving money over time might be the two main advantages that spur the industry's urgent need for a paradigm change while also giving patients access to more reliable and durable products. The development of the idea of "Quality by Design" (QbD) will result in a significant shift in pharmaceutical quality regulation from an empirical technique to a more rational and risk-based systems approach. QbD (Figure 1) is a systematic, risk-based, proactive method for developing pharmaceuticals that start with predetermined goals and places an emphasis on knowledge process control based on trustworthy research, knowledge of the product and process, and excellent risk management.

The following advantages and practical dimensions may be derived from the information created during product development utilizing the QbD principles: greater operational

flexibility, greater sourcing flexibility for input materials, less end-process testing made possible by real-time quality control, fewer batches for rejection, less rework, quicker manufacturing, testing and batch paper/approval times and fewer resources needed for regulatory compliance and testing (Lionberger *et al.*, 2008; Looby *et al.*, 2011; Branca *et al.*, 2017). Quality, according to ICH Q8, is the suitability of a drug substance or drug product for the intended application. This phrase encompasses qualities like individuality, power and purity.

Quality by Design (QbD) for pharmaceuticals entails creating formulas and manufacturing procedures to meet predetermined product quality goals (Lawrence *et al.*, 2008). By identifying characteristics that are crucial to quality from the perspective of patients and translating them into the qualities that the drug product should possess, Quality by Design (QbD) establishes how the critical process parameters can be changed to consistently produce a drug product with the desired characteristics. To accomplish this, a connection is made between the characteristics of the product, its formulation, and the manufacturing process factors (such as the components of the medicine, its excipients, and its process parameters). Establishing in place a reliable, adaptable production process that can provide a consistent product across time uses this knowledge under the current Quality by Design (QbD) philosophy.

A deep grasp of the connections between product performance, product characteristics and process is required for QbD (Saurí *et al.*, 2017). Formulations are traditionally produced to pass the quality assurance tests indicated in product specifications. If a product is declared suitable for commercial use, it must pass quality control inspections. If a batch doesn't pass these tests, it is either reprocessed or rejected, which raises legal issues and adds a hefty financial burden. In order to identify key quality attributes (CQAs) based on risk assessments (RAs), the implementation of QbD in pharmaceutical product development is methodical and involves multivariate trials using process analytical technology (PAT) and other testing. The QbD starts with pre-established goals and necessitates knowledge of how formulation and process factors affect product quality (http://www.gmpcompliance.com/daten/download/FDAs_Quality_Initiative.pdf). Although end-product testing can attest to a product's quality, it is not permitted as an element of process control or consistency. A general QbD system with product attributes and process parameters is shown in Figure 1 while the current difference between QbD with the

conventional one is depicted in Table I (http://www.fda.gov/downloads/AboutFDA/CentersOffices/CDER/ucm103526.pdf).

ELEMENTS OF PHARMACEUTICAL QBD

A candidate for a pharmaceutical QbD approach to product development identifies characteristics that are essential from the viewpoint of the patient, converts them into the critical quality attributes (CQAs) of the drug product, and defines the link within formulation/manufacturing parameters and CQAs in order to safely deliver the medication with such CQAs to the patients. The subparts of QbD can be summarized as mentioned:

- Critical quality characteristics (CQAs) for the pharmaceutical product are listed in a quality target product profile (QTPP).
- CMAs are identified as part of product design and understanding.
- Process designing and comprehension tie up with CMAs, CPPs and CQAs to important process parameters with profound knowledge of scale-up concepts.
- A well-controlled plan involves the correct selection of the active pharmaceutical ingredients, excipient(s) and drug products to control at each stage of production.
- Process flexibility and ongoing development.

There are a number of claims made concerning the components of QbD, but the following parameters seem to be the most frequently accepted (Lionberger *et al*., 2008; Jaybhave *et al.*, 2021).

QTPP: It includes detailed dose form, administration methods, dosage strength(s), and other elements. It is an anticipated list of the qualities of a drug product that should be attained, considering the strength of the dosage forms and the container closure part of the medicine, as well as the factors controlling pharmacokinetic parameters (like dissolution and aerodynamic performance) and quality criteria of the dosage forms (like complying sterility test, content uniformity, stability parameters and the pattern of drug release) appropriate for the intended marketed product. The drug product needs to have these qualities in order to consistently provide the therapeutic benefit stated on the label. The QTTP helps formulation scientists develop formulation plans and maintain an efficient and well-focused formulation effort. Identification, content uniformity, dosage forms, purity of the medicine, stability of the dosage forms and labeling are all related to QTPP.

CQAs: These include features or properties of a finished drug product that are physically, chemically, biologically, or microbiologically stable. In order to guarantee the intended quality of the drug product, potential drug product CQAs should come within an appropriate limit, range, or distribution that is generated from the QTPP and/or prior knowledge. Raw ingredients (active pharmaceutical ingredients, excipients), intermediate products (in-process materials), and finished medicines are typically linked with CQAs. The required quality, safety and efficacy are examples of critical performance attributes (CQAs) for pharmaceutical products (Figure 2).

CQAs are QTPP subgroups that could be affected by the modification of the formulation or manufacturing variables (Ravendra *et al.*, 2015; Yu, 2008). Say, for instance, QTPP may incorporate extra pharma product quality parameters like strength and dosage form(s) that are not involved in CQA as these are constant throughout the drug development process. However, since those may be affected by manufacturing or in-process variables, CQA will also involve QTTP properties such as assaying of the medicines, content uniformity test for the finished product, dissolution and permeation flux. CQAs are difficult to measure or control on the soft floor of the pharmaceutical industry. Standard CQA parameters for pharmaceutical ingredients and pharmaceutical products are given in Table II.

CMA or Critical Material Attributes: A CMA is a physical, chemical, biological or microbiological property or characteristic of the material that guarantees the intended quality of that drug component, excipient or in-process material to be within an appropriate limit, range or distribution to ensure the desired product quality.

Critical Process Parameters (CPPs): These pharmaceutical manufacturing parameters are the key variables affecting the production process. CPPs are the attributes that are monitored to detect deviations in standardized production operations and product output quality or changes in CQA.

QUALITY RISK MANAGEMENT (QRM)

The FDA defines risk management as a proactive safeguarding approach developed to lower risk associated with products utilizing any number of procedures or techniques. Concerns to the drug's efficacy, and products are evaluated, regulated, shared, and assessed systematically throughout the product lifecycle (Lourenço *et al.*, 2012). Figure 3 provides a summary of a good example of handling risks procedure.

FAILURE MODE AND EFFECTS ANALYSIS/ FMEA: FMEA is among the most widely used risk-assessment methodologies in the pharmaceutical industry. It is a rigorous and preventative approach to identifying and minimizing any process flaws. Any errors or defects in a process, an ingredient, a layout, or any component of equipment are considered failure modes. The FMEA tool evaluates the consequences of these failures after failure modes have been discovered, and then gives them a commensurate priority. This tool is more sophisticated because it assesses how severe the effects will be it provides a crystal-clear indication of the circumstance.

FAILURE MODE, EFFECTS AND CRITICALITY ANALYSIS OR FMECA: This is an illustration of the above-mentioned FMEA tool that includes an examination of the seriousness of repercussions, their likelihood of occurring and their detectability. Every product's failure mechanism is identified, and utilizing FMECA, its significance is evaluated. If the level of risk increases from the urgency to a danger, remedial measures must be taken. This can be used to address industrial process risk and failure. As well as supporting control methods and other quality control procedures, the tool can be used to develop and enhance maintenance regimens for devices that are capable of being repaired.

FTA OR ANALYSIS OF FAULT TREES: This tool presupposes that a procedure or product won't perform properly. The results are represented aesthetically using a failure mode tree. This can be utilized to investigate complaints or deviations in order to fully comprehend their root causes and ensure that any intended adjustments would address the current issues without creating new ones.

QUALITY BY DESIGN TOOLS

Design of experiment (DOE) tools are used in QBD. Through the development of mathematical models ($y = f(x_i)$), the DoE is a structured and organized strategy for identifying the correlations between input factors (x_i - independent variables) affecting one or more output responses (y - dependent variables) (Tomba *et al*., 2013). Table III shows the various quality by-design tools in pharmaceutical manufacturing processes and dosage forms (Singh *et al.*, 2012; Jason *et al.*, 2013). Some of the tools are listed below:

Statistical design of experiments: The design of experiments (DoE) is a technique and method of determining the connection in a cause-effect relationship with the requisite accuracy and scope with the least amount of time, material, and other resources.

Factorial designs: Multiple independent variables are investigated in a factorial design. When testing two variables, multiple conditions are produced by combining each level of one independent variable with each level of the second independent variable.

Full factorial designs: In each complete trial or replication of the tests, the full factorial design generates experimental points utilizing all feasible combinations of the component values.

Fractional factorial designs: A fraction of the experimental runs from a complete factorial design are used in fractional factorial designs, which are experimental designs in statistics. The subset was chosen to use a small fraction of the resources and experimental runs needed for a full factorial design while still exposing information about the most crucial aspects of the problem under study. In other words, it takes advantage of the fact that many full factorial design tests are sometimes redundant and provide little to no new knowledge of the system.

Two- level factorial designs: In a full factorial DoE, the number of experiments rises dramatically as the number of factors and levels does as well. Experiment reduction can be achieved by limiting the DoE design to the same number of levels for each factor, such as two levels. DoE project goal-establishing activities involve identifying one or more intended outcomes as well as how to quantify and categorise them. These tasks are included in two-level factorial design tasks. The design or process is then modeled by choosing the input factors, levels, and interactions, then fitting them into specified Orthogonal Arrays (OA) (Kumar *et al.*, 2014; Hemlata *et al.*, 2015).

Three–level factorial designs: A 3k factorial design is how the three-level design is expressed. It denotes that k components are taken into account, each at three levels. These are known as low, middle, and high levels (typically). These levels are denoted by the numbers 0, 1, and 2.

Optimized designs: Engineering design methodology known as "design optimization" uses a mathematical definition of a design problem to enable choosing the best design from several possibilities.

Placket-Burman Designs (PB): For screening trials, Plackett-Burman (PB) designs are utilized because, in a PB design, main effects are typically significantly confounded with two-factor interactions.

Central Composite Design (CCD): A central composite design is a type of experimental layout that can be used in response surface methods to construct a second-order (quadratic) model of the response variable without doing a full three-level factorial experiment. Results from the planned experiment are obtained using linear regression, sometimes iteratively. When creating this design, coded variables are frequently employed.

Box-Behnken Designs (BBD): Higher-order response surfaces are produced using Box-Behnken designs, which require fewer runs than a typical factorial procedure. In a minimum of necessary runs, Box-Behnken designs (BBDs), a particularly effective response surface design, offer information just on the effect of experiment variables and total experimental error. As opposed to the common CCD, these designs produce minimal experimental runs and give the most information while also having excellent symmetry and rotatability.

Multivariate Data Analysis (MVDA): MVDA is a statistical method for analyzing data that is derived from many variables. One can estimate summary variables with the aid of MVDA. MVDA is a collection of statistical approaches that can assist users in searching through datasets with several parameters, such as tests run over the course of a batch or data from process sensors. The goal is to pinpoint the factors that contribute the majority of the variability. A statistical background is not necessary for the analysis and interpretation of results when the proper tools are used (Yerlikaya *et al.*, 2013; Brijesh *et al.*, 2015).

MANUFACTURING OF PHARMACEUTICAL DOSAGE FORMS

Dosage forms manufacturing process parameters are mostly limited by the capacities of the facility along with equipment, resulting in narrow ranges. However, there are exceptions such as lyophilization manufacturing operations, holding times and temperatures of the manufacturing floor. Unfortunately, the availability of materials and the accompanying prices frequently impose limitations on the ability to undertake edge-of-failure and spectrum-determining experiments. However, by employing the QbD approach, it becomes possible to overcome these limitations. QbD makes use of vicarious mathematical models, micro, worst-case scenarios, and simulations to assess the effects of the manufacturing process on product quality and interactive effects. The use of validated models in a QbD approach not only enables the study of parameter ranges for all unit operations but also enhances the full understanding of the unit operations. This valuable information and capability extend beyond simply defining broader operation ranges; they also assist in identifying potential failure points and investigating any discrepancies that may arise.

QBD FOR TABLETS

There are several types of QbD approaches (Figure 4) that can be applied in tablet manufacturing (Rahman *et al.*, 2010; Basalious *et al.*, 2011). Some commonly used types of QbD in this context are mentioned as follows.

DESIGN SPACE: The multimodal arrangement and interactivity involving input variables, such as formulation elements and process parameters that have been shown to offer confidence of superior quality for tablet manufacturing are referred to as design space. QbD principles aim to describe a design space that ensures the desired product quality attributes are met.

CRITICAL QUALITY ATTRIBUTES (CQAS): CQAs are the product characteristics that are crucial to ensuring the quality and performance of the tablet. These attributes are identified based on their consequences for the medication product's efficacy and safety. QbD involves the identification and understanding of CQAs and their relationship with formulation and process parameters.

RISK ASSESSMENT: QbD incorporates risk assessment techniques to identify and prioritize potential risks to product quality. These risks can arise from formulation variability, process variability, or other sources. For assessing and handling risks, risk assessment techniques like Failure Mode and Effects Analysis (FMEA) or Hazard Analysis and Critical Control Points (HACCP) can be used.

DESIGN OF EXPERIMENTS (DOE): DoE is a statistical tool used in QbD to systematically evaluate and optimize formulation and process parameters. By varying and controlling these parameters within defined ranges, DoE allows for the identification of key factors affecting product quality and the determination of their optimal values.

MULTIVARIATE ANALYSIS: Multivariate analysis techniques are employed in QbD to analyze complex data sets that involve multiple variables and responses. These methods enable the identification of correlations, interactions, and patterns within the data, which can aid in understanding and optimizing the tablet manufacturing process.

CONTROL AND MONITORING OF PROCESSES IN REAL TIME: QbD encourages the use of real-time process vigilance and control systems to ensure the consistency and quality of tablet production. These systems involve the use of advanced process analytical

technologies (PAT) such as spectroscopy, near-infrared (NIR) imaging, or Raman spectroscopy to monitor critical process parameters and make real-time adjustments as necessary.

It is noteworthy hereby that the specific QbD approaches employed in tablet manufacturing can vary depending on the company, product, and regulatory requirements. The implementation of QbD principles requires a systematic and science-based approach to optimize the tablet manufacturing process and ensure consistent product quality.

ADVANTAGES OF QBD

The application of QbD has several major benefits and challenges (Carolina *et al*., 2015)

- Lessens stability problems.
- Increases the aggression of your process.
- Increased traceability.
- Decrease the quantity of reprocessing.
- Increases bench stage output.
- Reduced development expenses.
- Lessens the challenges of the scale-up stage.
- Fulfilment of project goals.
- Adequate regulations are required (GMP).
- A higher return on investment.
- Better project budgetary control.
- Increases the safety and efficiency of the medication.
- A deliberate approach to development.
- Better understanding of the process.
- Shorter review timelines and quicker review clearance.
- The health of the pharmaceutical industry and a change in culture.

CHALLENGES TO QBD APPLICATION

• To use a scientific approach to locate actual risks.

• To launch the QbD application to carry out the action strategy.

• To find the ideal compromise between the conventional approach and QbD in terms of economic viability;

• To create of important information and methods for sharing and preserving it.

CONCLUSION

Therefore, we draw the conclusion that the Good Manufacturing Practises (GMP) should be included in pharmaceutical development based on the product life cycle approach while adhering to the expectations of regulatory authorities. In view to increase the likelihood that the product will meet its quality specifications and standards when it is delivered to the patient, quality should be regulated at every stage of the process while taking into account the multidisciplinary team, suppliers, and end user. Quality by Design, which is based on current guidelines and reference materials, aims to improve process understanding. It may be seen as a process that is established by document requirements in accordance with process knowledge and comprehension. It can be used with both old and new goods, although the bundle of supporting documents can be different. The QbD document suite is "active." As the knowledge base evolves, they may and should be changed. Pharmaceutical Quality by Design aims to enhance post-approval handling of changes, development of products, and manufacturing effectiveness by lowering product variability and imperfections. Finally, from the industry's point of view, QbD implementation presents a problem because it hasn't completely embraced its application to pharmaceutical product development. However, by implementing this idea, there will surely be a considerable increase in the quality and efficacy of the drug in terms of patient treatment, given the requirement for mapping and controlling the hazards recognized throughout the product's life cycle.

The rapid increase in interest in QbD and related tools suggests that the methodologies are not passing fads but are solutions to the requirements of contemporary production processes. With DoE, risk assessment, and PAT as its instruments to gain a deeper understanding of the materials and processes, QbD is a time- and money-efficient design and manufacturing strategy that is made available and practical for the pharmaceutical industry. It is possible to

predict therapeutic items with excellent and repeatable quality considering its widespread adoption in pharmaceutical manufacturing. Furthermore, QbD has expanded significantly outside the pharmaceutical (or closely related) industries to become a widely applicable manufacturing paradigm.

ACKNOWLEDGMENTS

Dr. Jayanti Mukherjee and the students of this review paper (Sneha, Anju, and Sateesh) would like to express their heartfelt thanks and gratitude to Dr. T. Rama Rao, Principal, CMR College of Pharmacy, Hyderabad, for his endless motivation and encouragement for this review write up.

FUNDING

No funding was associated with this review work presented in the manuscript.

CONFLICT OF INTEREST

The authors declare that they have no conflict of interest.

AUTHOR CONTRIBUTIONS

All authors contributed to the study's conception and design. Material preparation, data Collection was performed by Sneha, Anju and Sateesh. The first draft of the manuscript was written by Dr Jayanti Mukherjee and Dr T. Rama Rao. All authors commented on previous versions of the manuscript. All authors read and approved the final manuscript.

REFERENCES

1. A.R. Jaybhave, M. Shinde, R. Mogal, S. Narkhede, Dr. A. Jadhav. QbD Approach to Analytical RP-HPLC Method Development and Validation of Tenofovir Disoproxil Fumarate in Dosage Form. J. Pharm. Sci. & Res. Vol. 13(7), 2021, 381-386.
2. Basalious EB, El-Sebaie W, El-Gazayerly O. Application of pharmaceutical QbD for enhancement of the solubility and dissolution of a Class II BCS drug using polymeric surfactants and crystallization inhibitors: Development of controlled-release tablets. AAPS Pharm Sci Tech. 2011; 12(3):799–810.
3. BrancaM.A. Silva, Sílvia Vicente, Sofia Cunha, Jorge F.J. Coelho, Cláudia Silva, Marco Seabra Reis *et al*. Retrospective Quality by Design (rQbD) applied to the optimization of orodispersible films Int. J. Pharm. 2017; 528(2):655-663.
4. Brijesh Shah , Dignesh Khunt , Himanshu Bhatt , Manju Misra, Harish Padh . Application of quality by design approach for intranasal delivery of rivastigmine loaded solid lipid nanoparticles: effect on formulation and characterization parameters. Eur J Pharm Sci. 2015; 78, 54– 66.
5. Firat Yerlikaya , Aysegul Ozgen, Imran Vural, Olgun Guven, Ergun Karaagaoglu, Mansoor A Khan, Yilmaz Capan. Development and evaluation of paclitaxel nanoparticles using a Quality-by design approach. J Pharm Sci 2013;102(10):3748–3761.

6. Food and Drug Administration. Final Report on Pharmaceutical cGMPs for the 21st Century – A Risk Based Approach, http://www.fda.gov/ cder/ gmp/ gmp 2004/ GMP_ final report 2004.htm
7. Hemlata Patil , Xin Feng, Xingyou Ye, Soumyajit Majumdar, Michael A Repka. Continuous production of fenofibrate solid lipid nanoparticles by hot-melt extrusion technology: a systematic study based on a quality by design approach. AAPS J. 2015;17(1):194–205.
8. Jason Teckoe , Tracey Mascaro, Thomas P Farrell, Ali R Rajabi-Siahboomi. Process optimization of a novel immediate release film coating system using QbD principles. AAPS Pharm Sci Tech 2013;14(2):531–540.
9. http://www.gmpcompliance.com/daten/download/FDAs_Quality_Initiative.pdf
10. http://www.fda.gov/downloads/AboutFDA/CentersOffices/CDER/ucm103526.pdf
11. J Carolina Visser , Willem M C Dohmen , Wouter L J Hinrichs , Jörg Breitkreutz , Henderik W Frijlink , Herman J Woerdenbag. Quality by design approach for optimizing the formulation and physical properties of extemporaneously prepared Oro dispersible films. Int J Pharm. 2015; 485(1–2):70–76.
12. J. Saurí, M. Zachariah, R. Macovez, J.Ll. Tamarit, D. Millán, M. Suñé-Pou, E. García-Montoya. Formulation and characterization of mucoadhesive controlled release matrix tablets of captopril. J. Drug Deliv. Sci. Technol. 2017; 42: 215-226.
13. Kumar S, Gokhale R, Burgess DJ. Quality by design approach to spray drying processing of crystalline nanosuspensions. Int J Pharm. 2014;464(1–2):234–242.
14. Lawrence X Yu. Pharmaceutical quality by design: Product and process development, understanding, and control. Pharmaceutical Research. 2008; 25: 781–791.
15. Lionberger RA, Lee SL, Lee L, Raw A, Yu LX. Quality by design: concepts for ANDAs. AAPS J. 2008; 10:268–76.
16. Looby M, Ibarra N, Pierce JJ, Buckley K, O'Donovan E, Heenan M. Application of quality by design principles to the development and technology transfer of a major process improvement for the manufacture of a recombinant protein. Biotechnology Progress. 2011; 27:1718-29.
17. Lourenço V, Lochmann D, Reich G, et al. A quality by design study applied to an industrial pharmaceutical fluid bed granulation. Eur J Pharm Biopharm. 2012;81(2):438– 447.
18. Nishendu P. Nadpara, Rakshit V. Thumar, Vidhi N. Kalola, Parula B. Patel. Quality by design (QBD) a complete review. International Journal of Pharmaceutical Sciences Review and Research. 2012, 17: 20-28.
19. Ravendra Singh , Andrés D Román-Ospino , Rodolfo J Romañach , Marianthi Ierapetritou , Rohit Ramachandran. Real time monitoring of powder blends bulk density for coupled feedforward/feed-back control of a continuous direct compaction tablet manufacturing process. Int J Pharm, 2015;495(1):612–625.
20. Singh R, Ierapetritou M, Ramachandran R. An engineering study on the enhanced control and operation of continuous manufacturing of pharmaceutical tablets via roller compaction. Int J Pharm. 2012;438(1–2):307–326.
21. Teckoe J, Mascaro T, Farrell TP, et al. Process optimization of a novel immediate release film coating system using QbD principles. AAPS Pharm Sci Tech. 2013;14(2):531–540.
22. Tomba E., Facco P., Bezzo F. Latent variable modelling to assist the implementation of quality-by-design paradigms in pharmaceutical development and manufacturing: a review. Int J Pharm. 2013;457(1):283–297.
23. Woodcock J, The concept of pharmaceutical quality. American Pharmaceutical Review. 2004; 7:10–15.
24. Yu L.X. Pharmaceutical quality by design: product and process development, understanding, and control. Pharm Res. 2008;25(4):781–791.
25. Ziyaur Rahman, Ahmed S. Zidan, Muhammad J. Habib, Mansoor A. Khan. Understanding the quality of protein loaded PLGA nanoparticles variability by Plackett–Burman design. Int J Pharm. 2010;389 (1–2):186–194.

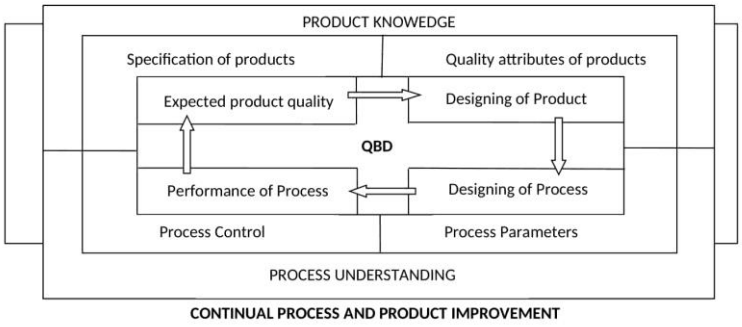

FIGURE 1: A typical QBD System

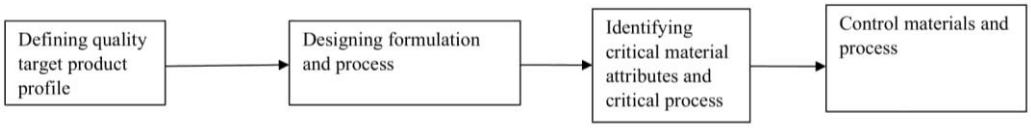

FIGURE 2: Overview of QbD: Target - Design – Implementation

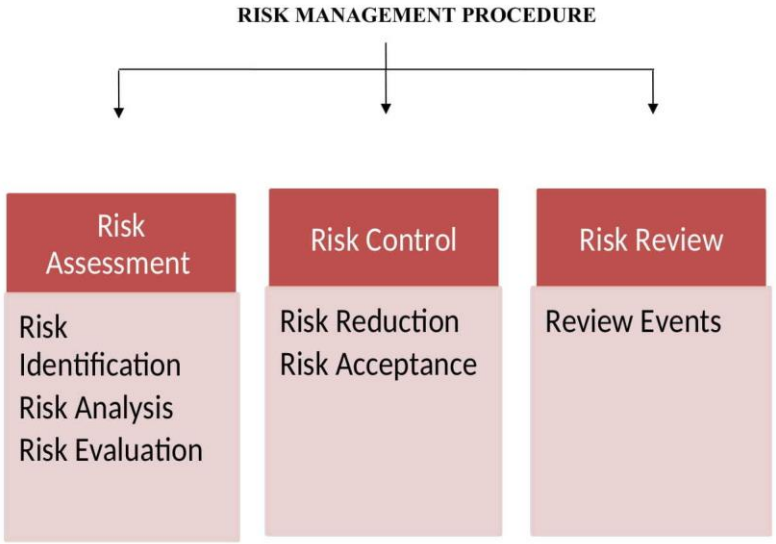

FIGURE 3: Steps of a quality risk management procedure

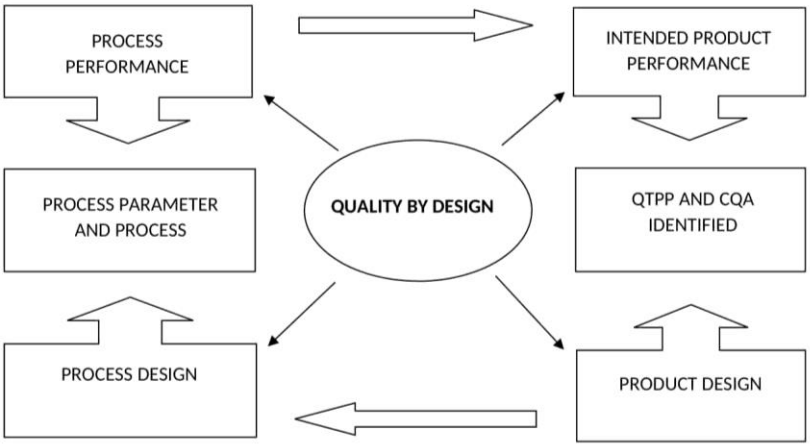

FIGURE 4: Implementation of QbD for development of tablets

Table I: Comparison between the Conventional approach and the Quality by Design approach [11]

Conventional Approach	QbD Approach
1. Examination and inspections ensure quality.	Quality is intentionally included into processes and products and is established on scientific knowledge.
2. It only contains entries that are data-intensive and include fragmented information lacking in perspective.	It comprises a contribution that is knowledge-rich and demonstrates both product and process understanding.
3. Any details used here are predicated on batch history.	Any parameters made in this case are based on the demands for product performance.
4. This place has a "fixed procedure," which always resists adjustments.	Within this design area, there is a "Flexible methodology" that enables ongoing development.
5. Focusing on reproducibility, it frequently minimises or disregards variation.	It emphasises robustness, which recognises and manages variation.

Table II: Standard CQAs for pharmaceutical ingredients and products

Pharmaceutical Ingredients	Pharmaceutical Products
Morphology	Morphology
Size of the particles	Detection
Morphic shapes	Determining hardness
Moisture content	Content Uniformity of dosage forms
Analysis of Residual solvents	Physical states
Organic contaminants	Performing dissolution studies
Chemical contaminants	Compounds of degradation
Heavy metallic residues	Moisture content
Remains after combustion	Determination of Assay
Determination of Assay	Limits of Microbiological values

Table III: Quality by design tools in pharmaceutical manufacturing and dosage forms [15 -24]

Pharmaceutical manufacturing	Different Dosage Forms	Standard Drugs	DoE	CMA	CPP	CQA
Fluid bed granulation	Tablets	Placebo tablets	i) Fractional Factorial Design for screening ii) CCD for optimization	i) Viscosity, ii) Temperature, iii) Concen of the aqueous dispersion binder	i) Inlet air temp, ii) binder spray rate iii) air flow rate	i)Particle size distribution , ii) bulk and tapped densities, iii) flowability, iv) angle of repose
Roller compaction	Tablets	Placebo tablets	Fractional Factorial Design	i) API composition, ii)API : excipient ratio	i) API flow rate, ii) lubricant flow rate, iii) pre-compression pressure	i) Weight variation, ii) Hardness testing, iii) Testing Dissolution, iv)Determining Ribbon density
Film coating	Coated tablets	Placebo tablets	Central Composite face centred response surface design	Percentage of solids in the coating dispersion	i) Inlet air temp, ii) air flow rate, iii)solid level in coating solution, iv) coating pan	i) Morphology, ii) disintegration time, iii) dissolution of the film coated tablets

					speed, v)spray rate	
Spray drying	Solid nanocrystalline dry powder	Drug Indomethacin	Full factorial design	Not applicable	i) Inlet temp, ii) flow rate, iii) aspiration rate	i) Particle size, ii) moisture content, iii) percent yield, iv) crystallinity
Hot-melt extrusion	Solid lipid nanoparticles or SLN	Drug Fenofibrate	Plackett Burman screening design	i) Conc. Of Lipid, ii) Conc. of surfactant	i)Screw speed, ii)barrel temp., iii) zone of liquid addition	i)Particle size, ii)polydispersity index (PDI), iii) zeta potential, iv) entrapment efficiency
Homogenization	Nanoparticles	Drug Paclitaxel	Box-Behnken Design	i) Surfactant concentration in aqueous phase	Homogenization rate	i)Average particle size, ii) zeta potential, iii) encapsulation efficiency
Homogenization	Solid lipid nanoparticle (SLN)	Drug Rivastigmine	Factorial design	i) Ratio of Drug to Lipid conc., ii) surfactant concentration	Homogenization time	i) Particle size, ii) PDI, iii) entrapment efficiency

o/w emulsification-solvent evaporation	Nanoparticles	Cycloserine-A	PB Design	i) Organic solvent to aqueous solvent ratio, ii) Conc. Of drug, polymer and surfactant	Stirring rate	i) Particle size of nanoparticles, ii) Encapsulation efficiency, ii) zeta potential, iv) burst release and dissolution efficiency
Physical mixture, solvent evaporation	Controlled release tablets	Drug Felodipine	Box-Behnken Design	i)Amount of polymer, polymeric surfactants and amount of Pluronic F127	Preparation technique	i) Checking the maximum solubility after 30 min., ii) Checking equilibrium solubility after 24 h, iii) Determining dissolution efficiency
Homogenate membrane method	Orthdispersible film	Theophylline	Central Composite Design	Glycerol and HPMC percentage	Drying temperature	i) Tensile strength, ii) elongation at break, iii) Young's Modulus, iv) disintegration time