ISSN: 2349-5448

Intercontinental Journal of Pharmaceutical Investigations and Research (ICJPIR)

ICJPIR |Vol.11 | Issue 1 | Jan - Mar -2024

www.icjpir.com

DOI : https://doi.org/10.61096/icjpir.v11.iss1.2024.1-12

Research

Quality By Design In Pharmaceutical Product Development

Karthick. M[*1], Nivetha. M[1], Divyaparvathi. R[1], Manivannan. R[2], Abinayasri. M[3], Ajay. T[3], Krishnaveni. S[3], Mohamed Aslam. M[3], Mohanraj. G[3]

[1]Assistant Professor, [2]Professor & Principal, [3]B.Pharm Final Year Students, Department of Pharmaceutics, Excel College of Pharmacy, Komarapalayam, Nammakal - 637303, Tamil nadu, India.

*Author for Correspondence: M. Karthick
Email: karthickm.m4@gmail.com

Published on: 23 Jan 2024

Published by:
DrSriram Publications

2024| All rights reserved.

Creative Commons Attribution 4.0 International License.

Abstract

The current strategy for pharmaceutical quality is called "Quality by Design." This essay outlines the application of pharmaceutical quality by design, or QbD, in the creation of new pharmaceutical products. It describes the Quality by Design and identifies some of its constituent parts. Every unit operation has its own set of process parameters and quality criteria. The prospects and procedures associated with Quality by Design for pharmaceutical products development in manufacturing of tablets are explained. Pharmaceutical development seeks to create high-quality products and production processes that reliably yield the desired product performance. Quality ought to be incorporated into items by design rather than being tested into them. Key components of Quality by Design, as well as the Quality goal product profile and essential quality criteria, are included. Further it is explained with a scientific example conducted by US FDA case study on QbD approach in brief for an immediate-release dosage form for the drug acetriptan and it differentiates the traditional approach vs QbD approach.

Keywords: product profile (QTPP), Process analysis technology (PAT), Critical process parameter (CPP). Quality by Design (QbD), Pharmaceutical product development, Critical quality attributes (CQA), Quality target.

INTRODUCTION

QUALITY BY DESIGN

The word "quality" is often mentioned (QbD). Quality is defined as "suitability for the intended use" in a qualitative sense. The pioneer Dr. Joseph M. Juran created the idea of quality by design (QbD). According to him quality should be built into a product from the start, and the majority of quality crises and issues originate from poor product design.(1)

Quality by Design is defined in the ICH Q8 guideline as “A systematic approach to development that begins with predefined objectives and emphasizes product and process understanding and process control, based on sound

science and quality risk management.

ICH quality guidelines from Q8 to Q11 are always recommended by regulatory bodies. Over the years, pharmaceutical QbD has evolved with the issuance of (Pharmaceutical Development) ICH Q8 (R2), (Quality Risk Management) ICH Q9, (Pharmaceutical Quality System) ICH Q10 and (Development and Manufacture of Drug Substance) ICH Q11 have been issued, as have the conclusions of FDA-EMA's parallel assessment of Quality-By-Design elements of marketing applications.[2]

QbD can be used in any stage of the drug development life cycle mainly it should be applied in the early development stage at this time they can build quality into the product from the beginning itself, also ensure that the product is continuously meeting its quality.

During the analytical method process by applying QbD principles errors in the identification of physical attributes can be minimized by developing a proper analytical method with proper validation and calibration which gives the better-quality product and processes efficacy, and regulatory flexibility can be attained.

QBD can be applied to various analytical methods which include

- Chromatographic techniques like (High-performance liquid chromatography)
- A hyphened technique like LC-MS.
- Analysis of genotoxic impurities.
- Karl-fisher titration for determination of moisture content.

APPLICATION OF IN-PROCESS ANALYTICAL TECHNOLOGY[4]

The asset of using process analytical technology in the pharmaceutical industry is to prevent errors in ongoing processes.

Table 1: PAT applications used in the pharmaceutical industry are given below

APPLICATION	PAT TOOL	STATISTICAL CHEMO METRIC METHOD	RESULT
Wurster coatingprocess	NIRS	PLS	Can be used for monitoring the wurster coating process
To compare thequality of pharmaceutical excipient	Raman spectroscopy	PCA	The proposed approach can form the basis for a risk reduction management system
To optimize a tablet formulation	NIRS Raman spectroscopy	PCA	Tablet formulation canbe designed by using QBD
To determine the quantification of active pharmaceutical ingredients using PAT	Fluorescence spectroscopy	PLS	A rapid and non- destructive method was developed simultaneous quantification of two active pharmaceuticalingredients in a tablet formulation
To develop a new Method using	DART-MSHPLC	Not required	A rapid process development method
Analysis in real-time mass spectrometry with PAT			It was proposed using process analytical technique (PAT)
To investigate online quantitative monitoring of alcohol precipitation	NIRS	PSO, LS-SVM, PLS	Can be used as a process analyzer for non-invasive and online quantitative monitoring of alcohol precipitation

NIRS: Near-infrared spectroscopy, PLS: Partial Least Squares, PCA: Principal Component Analysis, QBD: Quality by Design, DART-MS: Direct Analysis in Real Time Mass Spectroscopy, HPLC: High-performance liquid chromatography, PSO: Particle Swarm Optimization LS-SVM: Least Square Support Vector Machines.

KEY ELEMENTS OF QbD[7]

The following are the key elements of QbD that are essential to understand the process of quality product development.

QUALITY TARGET PRODUCT PROFILE (QTPP)

(QTPP) Quality Target Product Profile, when talking about product quality, the phrase QTPP can be a logical extension of the word TPP. This has been completedby outlining the intended properties of a therapeutic product while also taking its potential negative effects and safety issues into account. Quantity, strength, instrumentation, closure system, and identification are among the QTPP's indefinite-quantity types and purity.

CRITICAL QUALITY ATTRIBUTES (CQAs)

It can be used in several ways to guarantee a product's quality, safety, efficacy, and stability. The quality of the finished product can also be determined, measured, and monitored to make sure that it stays within reasonable bounds. These are critical properties of that should be within an appropriate range or limits. Critical quality attributes are the relationship between critical material attributes and critical process parameter that helps to identify safety and efficacy.

CRITICAL MATERIAL ATTRIBUTES (CMAs)

When a genuine change in a parameter renders a product incapable of meeting a QTPP, it is crucial to fail. When making a choice, it's crucial to take into account the uniqueness of each input material as well as how much change one is ready to do which criteria are crucial. Drug substance, excipient, and in-process material quality standards must be met by CMAs that are within an acceptable range or ranges.

CRITICAL PROCESS PARAMETER (CPPs)

This means that to produce the needed product quality and process consistency, any quantifiable input or output of a method step must be handled. Those criteria's used in a process are known to be method parameters. Here is how it would go before or during procedures that have the potential to significantly affect the look, purity, and yield of the finished product, parameters are checked.

Fig 1: List of tools

QUALITY RISK MANAGEMENT[5]

The FDA has given us the green light to assess and manage risk earlier in the drug development cycle. Risk assessment is a valuable science-based process, and the Q8 Pharmaceutical Development guidance encourages the application of scientific approaches and risk management to the development of a product and manufacturing processes. "RISK," refers to both the possibility and the magnitude of harm. By assessing the risks involved, the overall quality of a technique or process can be improved.

A few risk assessment methods are described in ICH guideline Q9

- FMEA Failure Mode Effects Analysis
- FMECA Failure Mode, Effects, and Criticality Analysis
- FTA Fault Tree Analysis
- HACCP Hazard Analysis and critical control points
- Hazard Operability Analysis
- Preliminary Hazard Analysis
- Risk ranking and filtering
- Supporting applied mathematics tool

FAILURE MODE EFFECTS ANALYSIS (FMEA)

FMEA enables an assessment of possible process failure modes and their likely impact on results and/or product performance. It is an effective technique for summarizing the key failure types, the contributing factors, and the expected outcomes of these failures.

FAILURE MODE, EFFECTS, AND CRITICALITY ANALYSIS (FMECA)

FMEA could be expanded to include an examination of the seriousness of the effects, their probability of occurring, and their detectability, creating a Failure Mode Effect and Criticality Analysis (FMECA; It is a structured approach that applies technical and scientific principles to analyze, evaluate, prevent, and control the risk or adverse consequence(s) of hazard(s) due to the design, development, production, and use of products.

FAULT TREE ANALYSIS (FTA)

The FTA tool is a strategy that presupposes that a product or process will not work as intended. This tool assesses system (or sub-system) failures one at a time, but by locating causal linkages, it can aggregate numerous causes of failure. Combinations of fault modes are represented at each level of the tree using logical operators.

HAZARD ANALYSIS AND CRITICAL CONTROL POINTS (HACCP)

HACCP is a systematic, proactive, and preventive tool for assuring product quality, reliability,and safety. It is a structured approach that applies technical and scientific principles to analyze,evaluate, prevent, and control the risk or adverse consequence(s) of hazard(s) due to the design,development, production, and use of products.

HAZARD OPERABILITY ANALYSIS (HAZOP)

HAZOP is based on a theory that assumes that risk events are caused by deviations from the design or operating intentions. The tool consists of:

1. The identification of the possibility that the risk event happens.
2. The qualitative evaluation of the extent of possible injury or damage to health that could result.
3. A relative ranking of the hazard using a combination of severity and likelihood of occurrence, and
4. The identification of possible remedial measures.

RISK RANKING AND FILTERING

Risk ranking and filtering is a tool for comparing and ranking risks. "Filters," in the form of weighting factors or cut-offs for risk scores, can be used to scale or fit the risk ranking to management or policy objectives.

SUPPORTING STATISTICAL TOOLS[3]

Statistical tools can support and facilitate quality risk management. They can enable effective data assessment, aid in determining the significance of the data set(s), and facilitate more reliable decision-making. A listing of some of the principal statistical tools commonly used inthe pharmaceutical industry is provided:

- Control Charts
- Design of Experiments (DOE)
- Histograms
- Pareto Chart
- Process Capability Analysis.

DESIGN SPACE

The multidimensional combination and interaction of input factors such as material qualities and process parameters are known as experimental design, and it has been shown to give assurance of excellence. To enhance process development and production optimization, pharmaceutical development scientists have started using computer-aided process design (CAPD) and process simulation. The design space for the gel was created utilizing a D-optimal design from a total of 15 gel batches, taking into account the five parameters of ethanol, water, carbomer, acid-neutralized fraction, and reactor temperature. For the design of experiments, a variety of mathematical models are available, including the Placket-Burman, Box-Banker, Taguchi, Surface Design, Full, and Fractional factorial designs.

The following are steps to build process understanding that are quite similar to those for product understanding:

1. List all potential known process variables that could affect how well the process works.
2. Utilize scientific understanding and risk assessment to determine potentially risky factors
3. Set these possibly high-risk factors' amounts or ranges.
4. Examine the trial results and, if at all possible the ability to scale and the use of first principle models to establish the criticality of a process parameter.

CONTROL STRATEGY[8]

Input material management, process controls, monitoring, and design space-to-end product specifications are a few examples of control strategies that can be utilized to guarantee consistent quality parts of a control plan process monitoring, batch release testing, in-process controls, comparability testing, consistency testing, and procedural control are all examples of quality assurance. Testing of the finished product is part of an all-encompassing strategy for creating high-quality items, along with raw material standards and technique controls. A planned set of controls, developed from current product and process knowledge that ensures process performance is referred to as a control strategy, and the calibration of the output, process controls, standards, and design space are all included in the quality control strategy.

RISK EVALUATION

When we use the word "risk," we're referring to both the potential for harm and its potential severity. A technique or process' overall quality can be raised by evaluating the risks involved.The objective of a risk assessment is to determine essential qualities that affect how well a thing turns out

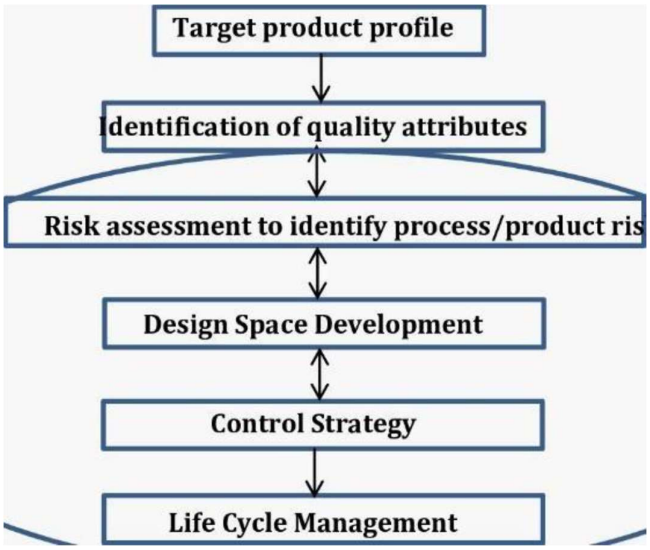

Fig 2: Flow of Risk Evaluation Test [7]

QbD MANUFACTURING PROCESS FOR TABLETS:

The most popular oral solid dosage form is a tablet, which can be produced primarily by direct compression or supplemented with either dry granulation or wet granulation to meet specific formulation needs.
The objective is to sufficiently comprehend processes to:

- Create a mathematical model (often a polynomial model) linking the critical process parameter (CPP) to critical quality attributes (CQA) .
- Collecting data through the process.
- Supplying the information to sophisticated computer systems that have Real-time monitoring of the CPP and CQA.

Data gathered in CQA during a procedure or research project at low and high CPP values of mathematical equations with several variables using improvement models that explain the item or the processes. PAT instrumentation combined with multivariate analysis offers tools for efficient process monitoring and control, enabling the detection of multivariate analysis of correlations between many factors such as starting resources, working conditions, and finished goods.[9] They contain pharmaceuticals and a variety of excipients, which only a few processing steps finding a process control tool that first correlates crucial material characteristics of dry powder to produce tablets with consistent quality attributes second, can combine with their tableting qualities to be monitored and managed in real-time so that the variation is according to the restrictions of the relevant material property. [9-10]

BASIC CHARACTERISTICS OF SINGLE MATERIAL FOR DIRECTCOMPRESSION:

Regarding the ideas of QbD and PAT, there is a need for the materials (excipients) to be characterized in terms of crucial qualities and steps of the tablet manufacturing procedure and the execution of the tablet using a risk-based methodology. As depicted in Figure 3, the tablet press itself is a multi- stage procedure that involves the following significant processes at each station: die loading, metering, pre- compression, main compression, tablet ejection, and take-off from the bottom punch. [11] By adjusting, it is possible to regulate the weight of the variation in powder bulk density or filling time caused by changes in turret speed and/or feed frame speed that may affect the dosing position with the present tablet press, the punch displacement, which is manually adjusted by adjusting the distance between the main compression rollers, determines the minimum in die tablet thickness. [11-13] An essential understanding of the QbD process in material compressibility is the relationship between main compression force and tablet weight, as will be covered in the following section.

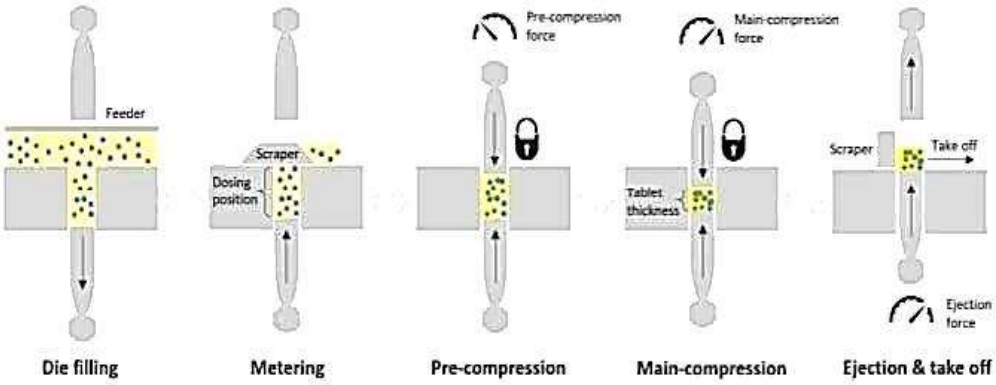

Fig 3: Major Steps in Natoli BLP-16 Rotary Tablet Press.

COMPRESSION

Tablet ability, which encompasses compressibility and compatibility, is a broad term used to describe how tablets are compressed (Figure 4). Tablet ability is the capacity to create tablets with specific characteristics. It is frequently described as having tensile strength as a result ofthe tableting pressure of the tablets. It's important to keep in mind that the most important factor is porosity. For evaluating various materials consequently, in sequence to more closely follow the tablet creation, volume diminution, compressibility must be measured against time. [13]

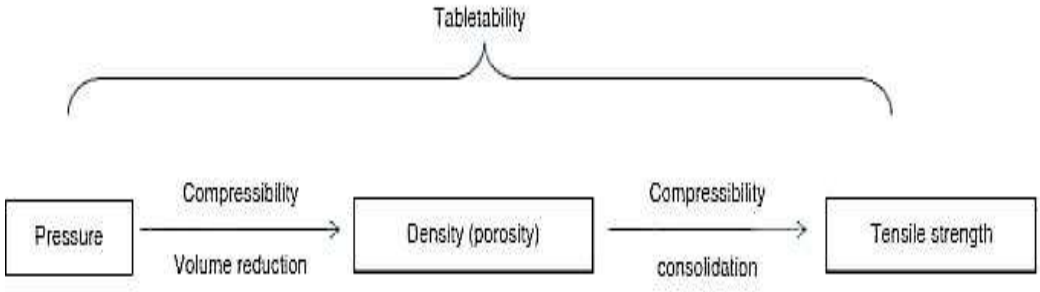

Fig 4: Definitions around the compression of Tablets including the term tabletability, compressibility & compatibility.

QbD IMPLEMENTATION

Modern process analytical technologies (PAT) sensors and process control techniques were integrated with the continuous direct compaction process to monitor process performance within the design space and maintain constant product quality. As illustrated in Figure 5, this CQA and CPP measurement data were gathered using the emerson deltav OPC system to enable a hierarchical three-level process control system created by the ISA 95 standard. [15]

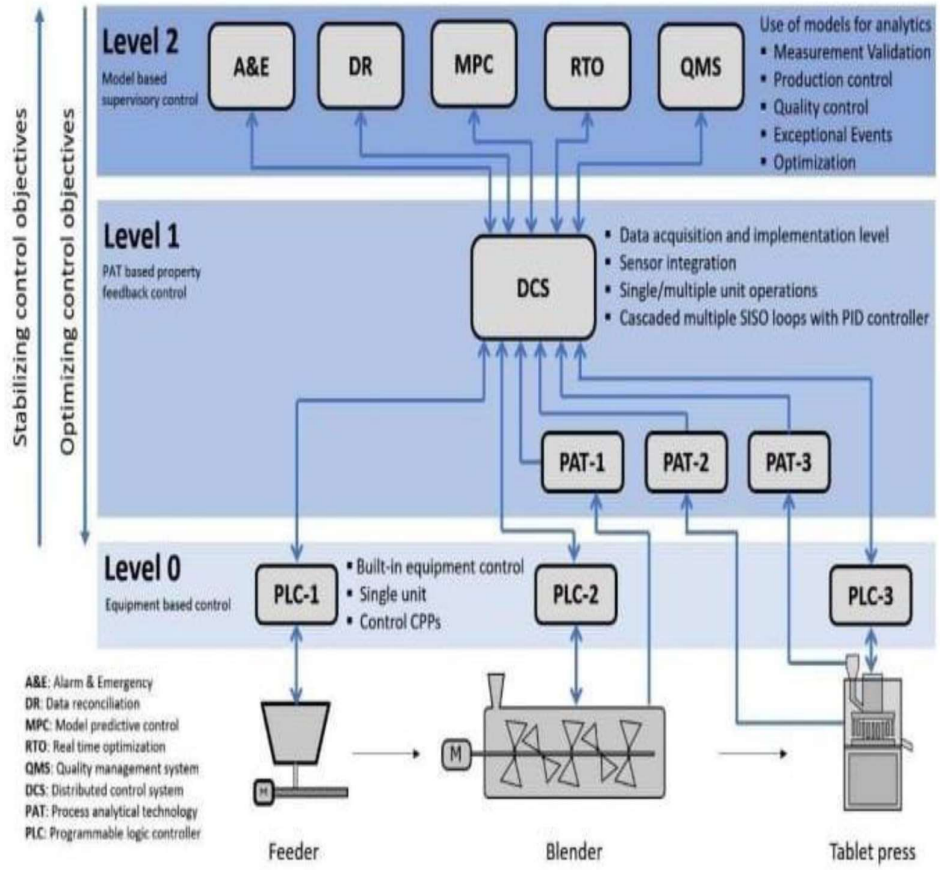

Fig 5: A hierarchical three-level process control for direct compaction

Tablet weight, relative density, strength, and major compression force were specifically named as the critical quality characteristics of the tablet press. As a result, an internal design for real-time tablet weight measurement based on a Mettler Toledo ME 4001E mass balance was taken into consideration. As a result, in the sections that follow, a data reconciliation technique for tablet weight measurement is shown and explored to improve the QbD implementation in a continuous rotary tablet press.

DATA RECONCILIATION FOR TABLET PRESS

Figure 6 depicts roughly the system's internal design for real-time tablet weight measurement and control. Tablets that have been excited by the tablet press are gathered in a container that is above an electronic scale. The corresponding tablet production rate can be obtained by taking the first-order derivative of the total tablet weight measurement. A tablet weight measurement (1, mg) is then calculated by dividing the tablet production rate by turret speed and number of stations, as shown below

$$\text{Wt.} = \frac{\text{Tablet production rate}}{\text{Turret speed x No. of stations}}$$

Where the total number of tablets generated per unit of time is determined by the turret speed. When using the first-order derivative to estimate tablet output, 100 tablets were used. The authors proposed that a shifting window time for 100 tablets does not filter out the process dynamics and that a total count of 100 tablets is representative of determining the mean tablet weight. However, when tablet samples are pneumatically weighed, serious mistakes might sometimes happen. As a result, to eliminate the measurement uncertainty and implement a data reconciliation method, with this tablet weight scale, serious mistakes are made.

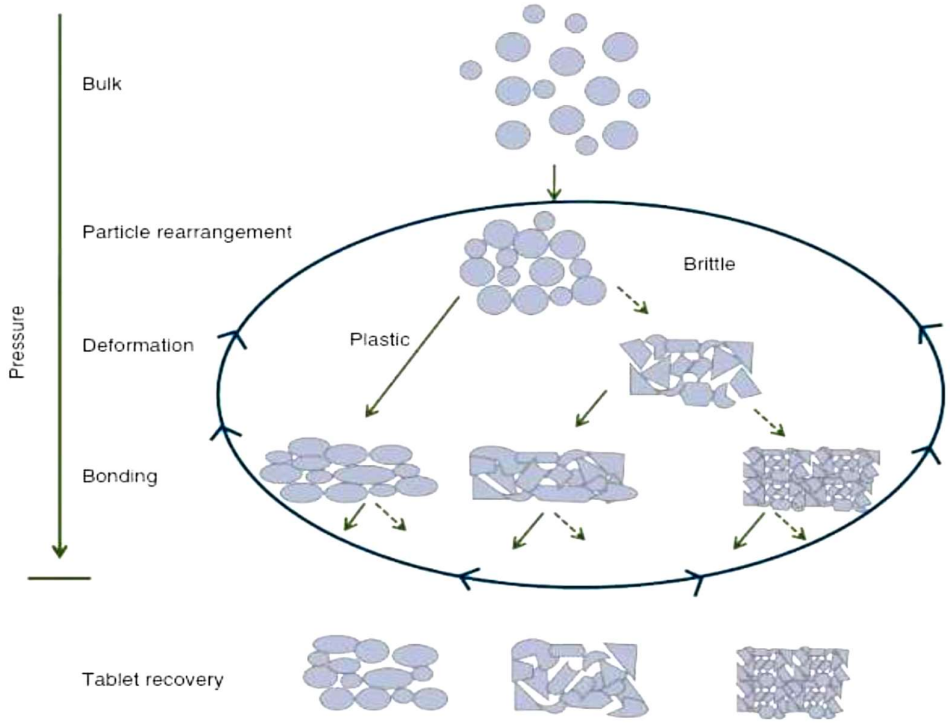

Fig 6: A schematic depiction of processes contributing to the formation of shapedproducts under pressure. (15)

INSTRUMENTATION / SENSORS

Accurate time-resolved force and displacement measurements are required for a quantitative description of the tableting event. Even compaction simulators made specifically for data, good data are not always acquired. Due to scientific purposes requiring a specific level of precision and accuracy, making the instrumentation specifically for each user still seems beneficial and validates it with particular attention.(16)

MECHANISM OF COMPACTION AND FORMULATION

After overcoming the forces of attraction and friction, the particles are first dispersed and packed more tightly under pressure. Where two areas of very high pressure co-exist when the edges of two particles collide, the particles will deform (based on the characteristics of the material). Regarding composite particles, it depends on the structure of the particle (intra- particle porosity, level of agglomeration, and particle failure toughness), in which the main process is deformation. Depending on the particle structure (intra-particle porosity, degree of agglomeration, and particle failure strength) for composite particles. (16-17)

EVALUATION AND PARAMETERS

The press characteristic, or time-displacement function, of the punches determined by the machine's geometry and acting as a consequence of the force (pressure) function, is significant because, particle deformation in the tablet that is time-dependent; considering the tablet's technical attributes, not to mention the tablet's release independently from a set of predetermined process parameters. To effectively use DOE and PAT as formulation and analysis tools, a mechanistic understanding of the structure of the materials, fundamental attributes, and the effect of processes.

QUALITY BY DESIGN (QbD) APPROACHES FOR COMPRESSION STEP OFTABLETING

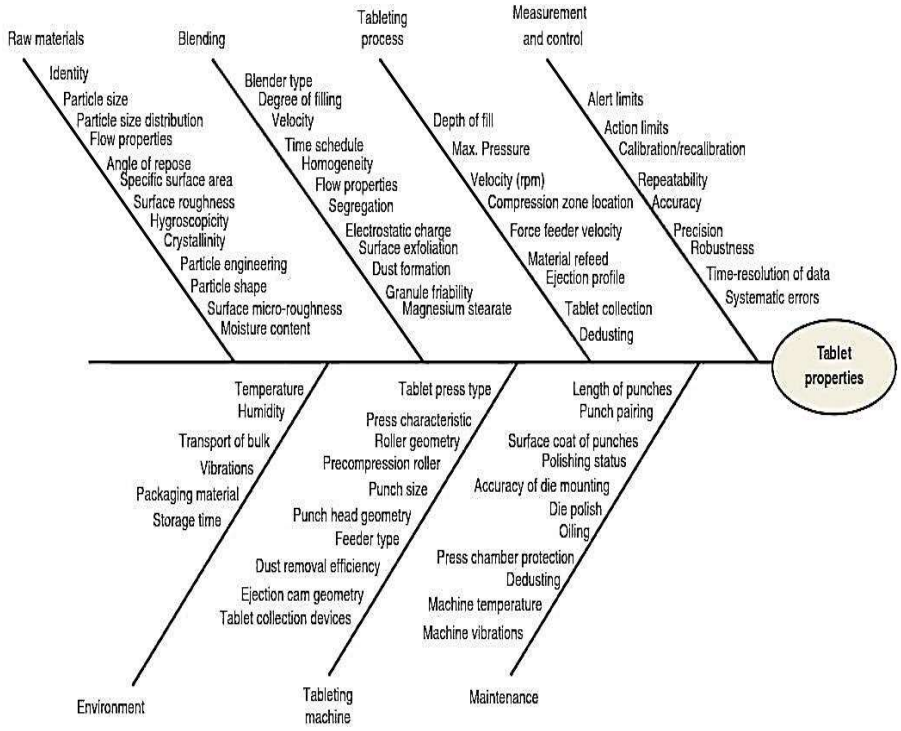

Fig 7: An overview of factors that may affect the mechanical properties of directcompression tablets

SCIENTIFIC EXAMPLES

USFDA has published two QbD implementation case studies. Quality by design for ANDAs: An example of immediate release tablets Quality by design forANDAs: An example of modified release tablets. These FDA case study examples are outstanding in understanding the implementation of the QbD process for product development. For the in–depth understanding of the readers, we havedemonstrated this example of the QbD approach in brief for an immediate-release dosage formfor the drug acetriptan.

Table 2: Acetriptan tablets, 20 mg based on the RLD labeling, patent literature, andreverse engineering.

INGREDIENTS	FUNCTION	COMPOSITION (mg/tablet)
Acetriptan, USP	API	20.0
Lactose monohydrate, NF	Filler	64-86
Microcrystalline cellulose	Filler	72-92
Croscarmellose sodium, NF	Disintegrant	2-19
Magnesium stearate, NF	Lubricant	2-6
Talc, NF	Glidant/Lubricant	1-10
Total weigh		200

QUALITY TARGET PRODUCT PROFILE (QTPP)

For ANDAs, the Target should be established early in product development based on the properties of the drug material, the characterization of the Reference Listed Drug (RLD) product, and consideration of the RLD label and expected patient population.

CRITICAL QUALITY ATTRIBUTES (CQAs)

Any physical, chemical, biological, or microbiological attributes related to the safety and efficacy of the product is called CQAs. The identification of CQAs was dependent on the extentof the harm to a patient incurred by failure to meet the drug product's quality attribute. Based on the assay, content uniformity, dissolution, and degradation products have been considered as CQAs.

CRITICAL MATERIAL ATTRIBUTES (CMAs)

The same types of excipients as the RLD product were chosen. For formulation development,an in-silicon simulation was conducted to evaluate the potential effect of Acetriptan PSD on in vivo performance, and a d90 of 30 micrometers or less was selected. Initial excipient binarymixture compatibility studies identified a potential interaction between Acetriptan and magnesium stearate. The interaction was found to be negligible.

QUALITY RISK MANAGEMENT (QRM)

QRM helps in identifying the extent of the impact of CMAs and CPPs on CQAs. Based on thesignificant risk CMAs possess to identified CQAs, Acetriptan particle size distribution,MCC/Lactose ratio, Croscarmellose sodium, talc, and Mg. stearate levels have been chosen asCMAs.

TWO FORMULATION DEVELOPMENT DESIGN OF EXPERIMENTS (DOE)WAS CONDUCTED

The first DOE investigated the impact of acetriptan PSD and levels of intra-granular lactose, microcrystalline cellulose, and Croscarmellose sodium on drug product CQAs. The second DOE studied the levels of extra-granular talc and magnesium stearate on drug product CQAs.

Table 3: Acetriptan tablets, 20 mg based on the RLD labeling, patent literature, and reverse engineering.

INGREDIENTS	COMPOSITION (mg/tablet)
Acetriptan	20.0
Intra-granular excipients	
Lactose Monohydrate, NF	79.0
Microcrystalline Cellulose	79.0
Croscarmellose Sodium, NF	79.0
Talc, NF	10.0
Extra-granular excipients	
Mg. stearate, NF	1.2
Talc, NF	5.5
Total Weight	200.0

QbD APPROACH OF IMMEDIATE RELEASE GENERIC ACETRIPTANTABLETS

CRITICAL PROCESS PARAMETERS (CPPs)

Roller compaction (RC) was selected as the granulation method (Dry Granulation) due to the potential for thermal degradation of acetriptan during the drying step of a wet granulation process. Roller pressure, roller gap, and mill screen orifice size were identified as CPPs for the roller compaction, and integrating milling process step and acceptable ranges were identified through the DOE.

CONTAINER CLOSURE SYSTEM

The proposed generic drug product is expected to be labeled for storage at 25°C with excursions permitted up to 15 – 30°C to be consistent with the RLD.

MICROBIOLOGICAL ATTRIBUTES

Accelerated stability analysis of the final batch shows that the drug has poor water activity and is unable to sustain microbial growth. For generic acetriptan tablets 20mg, the regular microbiological examination is unnecessary because of low water behavior and test on inboundraw materials.

CONTROL STRATEGY

A control strategy was developed which incorporates the material attributes and process parameters defined during the initial risk assessment as potentially high-risk variables.

PRODUCT LIFECYCLE MANAGEMENT

During the product life cycle, the procedure will be tracked and new information acquired willbe used to make adjustments to the control strategy if necessary.

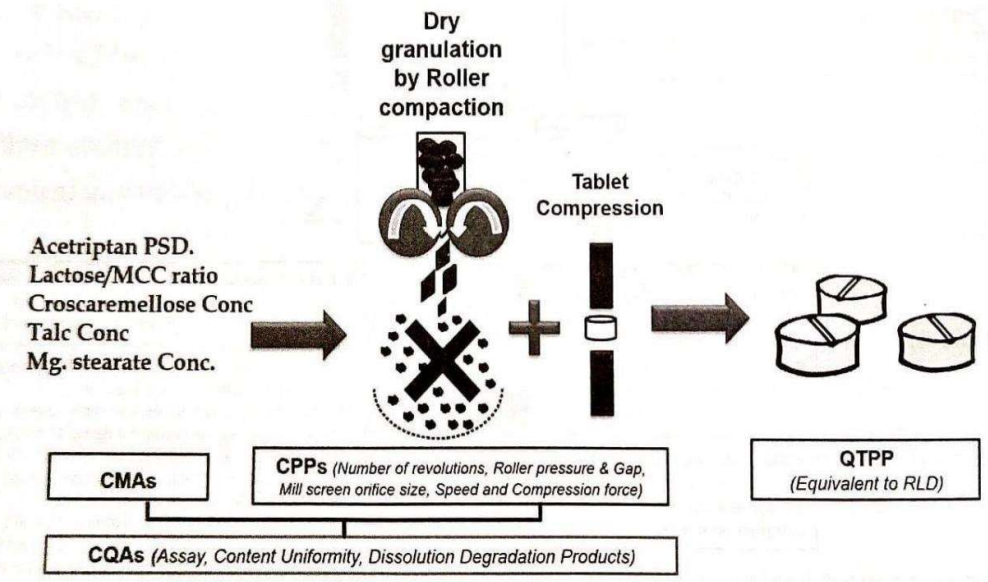

Fig 8: Illustration of the preparation of generic acetriptan tablets with identified by CMAs, CPPs and CQAs. [12]

Table 5: Traditional Product Development Vs QbD Approach [17]

ASCEPTS	TRADITIONAL	QbD
Pharmaceutical development	Empirical	Systematic; multivariateexperiments.
Manufacturing process	Fixed	Adjustable with in design space; opportunities for innovation.
Process Control	In process testing for go/no-go; offline analysiswide or slow response	PAT is utilized for feedbackand feed forward in real- time.
Product specifications	Primary means of quality control; based on batch data	Part of the overall controlstrategy, based on the desired product performance.
Control strategy	ainly by intermediate product and nd product testing	Risk-based; controlled shifted up stream, real-timerelease.
Life cycle management	Reactive time problem and OOS; Post approval changes needed	Continual improvementenabled within the design space.

CONCLUSION

QbD is increasingly becoming an important and widely technique in pharmaceutical development. It means designing and developing formulations and manufacturing process to ensure predefined product quality objectives. Implementing QbD concept in product development provide quality medicines to patients, production improvements to manufacturers with significantly reduce batch failures and drug regulatory bodies will have greater confidence in the robust quality of products they are been asked to approve. As such QbD is promising scientific evidence in quality assurance in pharma industry. QbD methodology helps in identifying and justifying target product profiles, product and process understanding. Also helps in continuous improvement.
There is a need for vigorous and well-funded research programs to developed new pharmaceutical manufacturing platforms in the future.

REFERENCES

1. Mallikarjun PN, Kumari P, Kumar SM, Sowmya G. An overview on quality by design in pharmaceutical product development.

2. Chandramouli R. Review on quality by design approach (Qbd). Curr Trends Biotechnol Pharm. 2021 Dec 23;15(4):447-54.
3. Soni S, Sahu P, Dikkatwar MS. Quality by design: modern approach in pharmaceutics for quality pharmaceuticals. J Pharm Neg Results.2023Feb13:2052-62.
4. Patel H, Parmar S, Patel B. A comprehensive review on Quality by Design (QbD) in pharmaceuticals development. Vol. 4(5); 2013.
5. Bhise JJ, Bhusnure OG, Mule ST, Mujewar IN, Gholve SB, Jadhav PU. A review on quality by design approach (QBD) for pharmaceuticals. J Drug Deliv Ther.2019Jun30;9;3-s:1137-46.
6. Savitha S, Devi K. Quality by design: a review. J Drug Deliv Ther. 2022 Apr 20;12(2-S):234-9. doi: 10.22270/jddt.v12i2-S.5451.
7. Patil AS, Pethe AM. Quality by Design (QbD): A new concept for development of quality pharmaceuticals. Int J Pharm Qual Assur. 2013 Apr;4(2):13-9.
8. Darkunde SL. A review on quality by design. Int J Pharm Chem Anal. 2018;5(1):1-6.
9. Pramod K, Tahir MA, Charoo NA, Ansari SH, Ali J. Pharmaceutical product development: A quality by design approach. Int J Pharm Investig. 2016;6(3):129-38. doi: 10.4103/2230-973X.187350, PMID 27606256.
10. Nadpara NP, Thumar RV, Kalola VN, Patel PB. Quality by design (QBD): A complete review. Int J Pharm Sci Rev Res. 2012;17(2):20-8.
11. Zhang L, Mao S. Application of quality by design in the current drug development. Asian J Pharm Sci. 2017 Jan 1;12(1):1-8. doi: 10.1016/j.ajps.2016.07.006, PMID 32104308.
12. Charoo NA, Shamsher AA, Zidan AS, Rahman Z. Quality by design approach for formulation development: a case study of dispersible tablets. Int J Pharm. 2012 Feb 28;423(2):167-78. doi: 10.1016/j.ijpharm.2011.12.024, PMID 22209997.
13. Yu LX, Amidon G, Khan MA, Hoag SW, Polli J, Raju GK et al. Understanding pharmaceutical quality by design. AAPS J. 2014 Jul;16(4):771-83. doi: 10.1208/s12248-014-9598-3, PMID 24854893.
14. Purohit D, Saini M, Pandey P, Tripathy S, Dureja H. Implementation of quality by design:A review. Appl Clin Res Clin Trials Regul Aff. 2019 Aug 1;6(2):99-111. doi: 10.2174/2213476X06666190117120029.
15. Ghaemmaghamian Z, Zarghami R, Walker G, O'Reilly E, Ziaee A. Stabilizing vaccines via drying: quality by design considerations. Adv Drug Deliv Rev. 2022 Aug 1;187:114313. doi: 10.1016/j.addr.2022.114313, PMID 35597307.
16. Alshaer W, Nsairat H, Lafi Z, Hourani OM, Al-Kadash A, Esawi E et al. Quality by design approach in liposomal formulations: robust product development. Molecules. 2022 Dec 20;28(1):10. doi: 10.3390/molecules28010010, PMID 36615205.
17. Sousa AS, Serra J, Estevens C, Costa R, Ribeiro AJ. A quality by design approach in oral extended-release drug delivery systems: where we are and where we are going? J Pharm Investig. 2023 Mar;53(2):269-306. doi: 10.1007/s40005-022-00603-w.
18. Chakravarthy PS, Grandhi S, Swami R, Singh I. Quality by design-based optimization and development of cyclodextrin inclusion complexes of quercetin for solubility enhancement. Biointerface Res Appl Chem. 2023;13(5):424.
19. Nowack M, Endrikat J, Guenther E. Review of Delphi-based scenario studies: quality and design considerations. Technol Forecasting Soc Change. 2011 Nov 1;78(9):1603-15. doi: 10.1016/j.techfore.2011.03.006.
20. Singh B, Beg S. Quality by design in product development life cycle. Chron Pharmabiz. 2013 Nov 28;22:72-9.