Quality by Design Approaches in Pharmaceutical Developments

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Abstract

Quality by Design (QbD) is the new approach used for the quality of pharmaceuticals. It gives idea about use of quality by design to assure the quality of pharmaceuticals. The objective of the pharmaceutical development is to design a quality product and its manufacturing process to deliver the pharmaceutical products with quality assurance including quality and importance of the targeted product profile using Quality by Design. It gives idea on quality of pharmaceutical product by end product testing and quality of pharmaceutical product by Quality by Design. This book mainly highlights the elements of QbD, approaches of QbD and applications of QbD in manufacturing of pharmaceutical products and pharmaceutical development.

Keywords: QbD, elements, ICH guidelines, quality assurance

Introduction

Quality by Design (QbD) was first defined by the Dr. Joseph M. Juran [1]. Juran endorsed that most quality crises and issues emerge due to a lack of importance assigned to it during the planning of the product. Food Drug and Administration (FDA) in its current Good Manufacturing Practice for the 21st century initiated QbD and process analytical technology (PAT) with an objective to build quality into the product from its inception. QbD was described in ICH Q8, Q9 and Q10 guidance. In ensuring quality of the manufactured products, QbD is an important transition from the traditional quality by testing (QbT) perspective, which ascertains the product's quality by verifying it with approved regulatory specifications at the end of the manufacturing process. FDA is encouraging the application of QbD principles to pharmaceutical development since it promotes product and process understanding to build quality into a product [1]. The Abbreviated New Drug Application product submissions have included Quality by Design principles from January 1, 2013. In 2006, Merck and Co's Januvia (sitagliptin) became the first product to be approved, which had incorporated QbD principles during its product development [2]. During the scale-up of a product, from the formulation development to the production-scale, there appears to be a great

deal of unpredictability along with poor understanding, which results in unexpected failures. Failure of products to comply with their specifications would result in either rejection or reprocessing of the batch, with increased cost and regulatory burden. Post-approval changes, even of non-critical nature require pre-approval. Thus, lack of product and process understanding results in a wide communication gap between the regulatory bodies and the pharmaceutical companies [3]. QbD is thus a systematic, scientific, risk-based, holistic and proactive approach that begins with pre-defined objectives and emphasis on product, process understanding and process control [4]. It essentially necessitates designing and developing the product and the manufacturing process to achieve the predefined product quality objectives [5]. QbD identifies characteristics that are vital to quality from the patient's point of view and converts them into critical quality attributes (CQAs) that the product should possess. Further, it establishes the limits, the design space, for the critical process parameters (CPPs) and critical material attributes (CMAs) affecting the CQAs. The innovative risk-based approach is adopted to identify the CMAs and CPPs. Within the design space, the process remains unaffected and consistently manufactures the desired product [6]. Design space is obtained by employing design of experiment (DoE), a statistical tool to optimise the variables of CMAs and CPPs. This knowledge is then used to implement a flexible and robust manufacturing process that can adapt and yield stable product overtime. Knowledge-based commercial manufacturing ensures enough regulatory flexibility for setting specifications and post-approval changes. In addition, QbD principles promote innovation and continuous improvement and thus represent amalgamation of ICH Q8, ICH Q9 and ICH Q10.

The salient features of QbD include:

1. Product is designed to meet patient needs and performance requirements.
2. Process is designed consistently to meet the product quality attributes.
3. Understand the impact of raw materials and process parameters on product quality.
4. The critical sources of process variability are identified and controlled.

This review looks into the salient features of QbD components with an aim of understanding its application in pharmaceutical development. It discusses target product profile (TPP), quality target product profile (QTPP), critical quality attributes (CQAs) of the product and design of experiments (DoE) for obtaining design space for critical material attributes (CMAs) and critical process parameters (CPPs)[7]. The fundamentals of risk-based strategy and its capacity in recognizing and grading CMAs and CPPs are further discussed.

Quality

"The degree to which a set of inherent properties of a product, system or process fulfils requirements" (ICH Q9). "Good pharmaceutical quality represents an acceptably low risk of failing to achieve the desired clinical attributes."

Pharmaceutical Quality by Testing

Product quality is ensured by raw material testing, drug substance manufacturing, a fixed drug product manufacturing process, in-process material testing, and end product testing. If they meet the manufacturer's proposed and FDA approved specifications or other standards such as USP for drug substance or excipients, they can be used for the manufacturing of the products [8]. Since a few tablets out of several million are tested, drug manufacturers are usually expected to conduct extensive in process tests, such as blend uniformity, tablet hardness, etc; to ensure the outcome of in-process testing also meets the FDA approved in-process testing specifications. Manufacturers are also not permitted to make changes to the operating parameters specified in the batch record or other process changes without filing supplements with the FDA. As a result, the FDA has been overwhelmed by the number of Chemistry, Manufacturing, and Controls (CMC) supplements filed in recent years. For example, in 2005 and 2006, the FDA Office of Generic Drugs received over 3,000 CMC supplements annually [9]. This combination of fixed manufacturing steps and extensive testing is what ensures quality under the traditional system. Limited characterization of variability, inadequate understanding to identify and quantify critical process parameters, and caution on the part of regulators leads to a very rigid and inflexible specifications that prohibit the release of products that may have acceptable clinical performance [10]. Significant industry and FDA resources are spent debating issues related to acceptable variability, need for additional testing controls, and establishment of specification acceptance criteria. Often these are concentrated on acceptance limits or statistical aspects. FDA reviewers' conservatism results from the fact that manufacturers may not understand how drug substance, excipients, and manufacturing processes affect the quality of their products and they do not share this information with FDA reviewers. Under the traditional regulatory evaluation system, all products are treated equally without regard to the risk to the consumer [11]. This has placed too much review time on low-risk products and more significantly, takes away needed resources from the review of high-risk products. CMC review assessments of complex dosage forms (modified release products, topicals and transdermals) as well as narrow therapeutic

index (NTI) drugs differ only marginally from those of simple dosage forms (many immediate release solid oral products). Further, all CMC information in applications are sometimes evaluated equally, without differentiation of criticality, resulting in the requirement of intensive resources for each application. Product quality and performance are achieved predominantly by restricting flexibility in the manufacturing process and by end product testing. Presently regulatory review system places little or no emphasis on how the design of an effective and efficient manufacturing process can ensure product quality. As a result, the complexities of process scale-up, particularly for complex dosage forms are often not recognized. Product specifications often are derived using test data from one or more batches, and mechanistic understanding does not play a significant role in this process. Finally, the burdensome regulatory requirement of supplements imposed on manufacturers for executing minor and incremental changes to manufacturing processes and controls inhibits continuous improvement and strategies for the implementation of continuous "real time" assurance of quality.

Pharmaceutical Quality by Design

QbD is 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 Q8(R). QbD means designing and developing formulations and manufacturing processes to ensure predefined product quality. Thus, QbD requires an Understanding and controlling formulation and manufacturing process variables influence product quality. Relevant documents from the International Conference on Harmonization of Technical Requirements for Registration of Pharmaceuticals for Human Use (ICH), ICH Q8, Pharmaceutical Development, along with ICH Q9, Quality Risk Management, and ICH Q10, Pharmaceutical Quality Systems, indicated that how quality by design acts to ensure drug product quality.

ICH Q8 defines quality as "The suitability of either a drug substance or drug product for its intended use. This term includes such attributes as the identity, strength, and purity." ICH Q6A emphasizes the role of specifications stating that "Specifications are critical quality standards that are proposed and justified by the manufacturer and approved by regulatory authorities." [12] Pharmaceutical QbD is a systematic, scientific, risk-based, holistic and proactive approach to pharmaceutical development that begins with predefined objectives and emphases product and processes understanding and process control [13]. It means designing and developing formulations and manufacturing processes to ensure predefined product quality objectives. QbD

identifies characteristics that are critical to quality from the perspective of patients, translates them into the attributes that the drug product should possess, and establishes how the critical process parameters can be varied to consistently produce a drug product with the desired characteristics [14]. In order to do this the relationships between formulation and manufacturing process variables (including drug substance and excipient attributes and process parameters) and product characteristics are established and sources of variability identified. This knowledge is then used to implement a flexible and robust manufacturing process that can adapt and produce a consistent product over time.

Fig 1: Overview of QbD

Thus, some of the QbD elements may include,

- Define quality target product profile that describes the use, safety and efficacy of the product.
- Design and develop product and manufacturing processes.
- Identify critical quality attributes, process parameters, and sources of variability.
- Establish a control strategy for the entire process
- Control manufacturing processes to produce consistent quality over time.

Under the QbD concept, pharmaceutical quality for generic drugs is assured by understanding and controlling formulation and manufacturing variables. End product testing confirms the quality of the product and is not part of the manufacturing consistency or process control. Under QbT a product specification is often set by observing data from a small number of batches believed to be acceptable and then setting acceptance criteria that required future batches to be the same. Under QbD consistency comes from the design and control of the manufacturing process and the specification of drug product under QbD should be clinically relevant and generally determined by product performance. QbD requires an understanding how formulation and process variables influence product quality. These discussions have generally focused on the development of new drugs. Drawing on these discussions and some specific aspects of the development of generic products, a QbD development process may include & begin with a target product profile that describes the use, safety and efficacy of the product & Define a target product quality profile that will be used by formulators and process engineers as a quantitative surrogate for aspects of clinical safety and efficacy during product development & Gather relevant prior knowledge about the drug substance, potential excipients and process operations into a knowledge space. Use risk assessment to prioritize knowledge gaps for further investigation & Design a formulation and identify the critical material (quality) attributes of the final product that must be controlled to meet the target product quality profile & Design a manufacturing process to produce a final product having these critical material attributes & identify the critical process parameters and raw material attributes that must be controlled to achieve these critical material attributes of the final product. Use risk assessment to prioritize process parameters and material attributes for experimental verification. Combine prior knowledge with experiments to establish a design space or other representation of process understanding & establish a control strategy for the entire process that may include raw material controls, process controls and monitors, design spaces around individual or multiple unit operations, and final product tests. The control strategy should include expected changes in scale and can be guided by a risk assessment & continually monitor and update the process to assure consistent quality Design of experiments (DOE), risk assessment, and process analytical technology (PAT) are tools that may be used in the QbD process when appropriate. The difference between QbD for NDA and ANDA products is most apparent at the first step of the process. For an NDA, the target product profile is under development while for the ANDA product the target product profile is well established by the labelling and clinical studies conducted to support the approval of the reference product

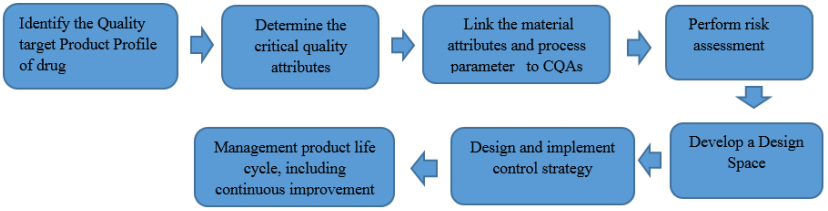
Table 1.

Table 1: Current Vs QbD approach to pharmaceutical development

Conventional Product Development	QbD Approach(Ideal)
Quality assured by end product testing and inspection and mainly an empirical approach.	Quality built into product & process by design, based on scientific understanding and a systematic approach
Data intensive submission – disjointed information without "big picture"	Knowledge rich submission – showing product knowledge & process understanding
Specifications based on batch history	Specifications based on product performance requirements
"Frozen process" disallowing changes	Flexible process within design space, allowing continuous improvement
Focus on reproducibility – often avoiding or ignoring variation	Focus on formulation and process robustness – understanding and controlling variation

"Quality is built in by design, not tested in"

"Quality by design is about doing things consciously.



Flow diagram (Key Aspects of QbD)

Flow diagram (Key Aspects of QbD)

Advantages of QbD

- It provides a higher level of assurance of drug product quality.
- It offers cost savings and efficiency for the pharmaceutical industry.
- It increases the transparency of the sponsor understands the control strategy for the drug product to obtain approval and ultimately commercialize.
- It makes the scale-up, validation and commercialization transparent, rational and predictable.

- It facilitates innovation for unmet medical needs.
- It increases efficiency of pharmaceutical manufacturing processes and reduces manufacturing costs and product rejects.
- It minimizes or eliminates potential compliance actions, costly penalties, and drug recalls.
- It offers opportunities for continual improvement.
- It provides more efficiency for regulatory oversight:
- It streamlines post approval manufacturing changes and regulatory processes.
- It more focused post approval CGMP inspections.
- It enhances opportunities for first cycle approval.
- It facilitates continuous improvement and reduces the CMC supplement.
- It enhances the quality of CMC and reduces the CMC review time [15].

Elements of pharmaceutical quality by design

In a pharmaceutical QbD approach to product development, an applicant identifies characteristics that are critical to quality from the patient's perspective, translates them into the drug product critical quality attributes (CQAs), and establishes the relationship between formulation/manufacturing variables and CQAs to consistently deliver a drug product with such CQAs to the patient. QbD consists of the following elements:

1. A quality target product profile (QTPP) that identifies the critical quality attributes (CQAs) of the drug product
2. Product design and understanding including the identification of critical material attributes (CMAs)
3. Process design and understanding including the identification of critical process parameters (CPPs) and a thorough understanding of scale-up principles, linking CMAs and CPPs to CQAs
4. A control strategy that includes specifications for the drug substance(s), excipient(s), and drug product as well as controls for each step of the manufacturing process
5. Process capability and continual improvement

Quality Target Product Profile that Identifies the Critical Quality Attributes of the Drug Product

QTPP is a prospective summary of the quality characteristics of a drug product that ideally will be achieved to ensure the desired quality, taking into account safety and efficacy of the drug product. QTPP forms the basis of design for the development of the product. Considerations for inclusion in the QTPP could include the following [16];

- Intended use in a clinical setting, route of administration, dosage form, and delivery system(s)
- Dosage strength(s)
- Container closure system
- Therapeutic moiety release or delivery and attributes affecting pharmacokinetic characteristics (e.g., dissolution and aerodynamic performance) appropriate to the drug product dosage form being developed
- Drug product quality criteria (e.g., sterility, purity, stability, and drug release) appropriate for the intended marketed product.

Identification of the CQAs of the drug product is the next step in drug product development. A CQA is a physical, chemical, biological, or microbiological property or characteristic of an output material including finished drug product that should be within an appropriate limit, range, or distribution to ensure the desired product quality. The quality attributes of a drug product may include identity, assay, content uniformity, degradation products, residual solvents, drug release or dissolution, moisture content, microbial limits, and physical attributes such as color, shape, size, odor, score configuration, and friability. These attributes can be critical or not critical. Criticality of an attribute is primarily based upon the severity of harm to the patient should the product fall outside the acceptable range for that attribute. Probability of occurrence, detectability, or controllability does not impact criticality of an attribute. It seems obvious that a new product should be adequately defined before any development work commences. However, over the years, the value of predefining the target characteristics of the drug product is often underestimated. Consequently, the lack of a well-defined QTPP has resulted in wasted time and valuable resources. A recent paper by Raw *et al*. [17] illustrates the significance of defining the correct QTPP before conducting any development. Also, QbD examples exemplify the identification and use of QTPPs [18].

Product Design and Understanding

Over the years, QbD's focus has been on the process design, understanding, and control, as discussed in the ICH Q8 (R2) guidance. It should be emphasized that product design, understanding, and control are equally important. Product design determines whether the product is able to meet patients' needs, which is confirmed with clinical studies. Product design also determines whether the product is able to maintain its performance through its shelf life, which is confirmed with stability studies. This type of product understanding could have prevented some historical stability failures.

The key objective of product design and understanding is to develop a robust product that can deliver the desired QTPP over the product shelf life. Product design is openended and may allow for many design pathways. Key elements of product design and understanding include the following:

- Physical, chemical, and biological characterization of the drug substance(s)
- Identification and selection of excipient type and grade, and knowledge of intrinsic excipient variability
- Interactions of drug and excipients.
- Optimization of formulation and identification of CMAs of both excipients and drug substance.

To design and develop a robust drug product that has the intended CQAs, a product development scientist must give serious consideration to the physical, chemical, and biological properties of the drug substance. Physical properties include physical description (particle size distribution and particle morphology), polymorphism and form transformation, aqueous solubility as a function of pH, intrinsic dissolution rate, hygroscopicity, and melting point(s). Pharmaceutical solid polymorphism, for example, has received much attention recently since it can impact solubility, dissolution, stability, and manufacturability. Chemical properties include pKa, chemical stability in solid state and in solution, as well as photolytic and oxidative stability. Biological properties include partition coefficient, membrane permeability, and bioavailability. Pharmaceutical excipients are components of a drug product other than the active pharmaceutical ingredient. Excipients can aid in the processing of the dosage form during its manufacture; protect, support, orenhance stability, bioavailability, or patient acceptability; assist in product identification; or enhance any other attribute of the overall safety, effectiveness, or delivery of the drug during storage or use[19]. They are

classified by the functions they perform in a pharmaceutical dosage form. Among 42 functional excipient categories listed in USP/NF, commonly used excipients include binders, disintegrants, fillers (diluents), lubricants, glidants (flow enhancers), compression aids, colors, sweeteners, preservatives, suspending/dispersing agents, pH modifiers/buffers, tonicity agents, film formers/coatings, flavors, and printing inks. The FDA's inactive ingredients database [20] lists the safety limits of excipients based on prior use in FDA-approved drug products. It is well recognized that excipients can be a major source of variability. Despite the fact that excipients can alter the stability, manufacturability, and bioavailability of drug products, the general principles of excipient selection are not well-defined, and excipients are often selected ad hoc without systematic drug-excipient compatibility testing. To avoid costly material wastage and time delays, ICH Q8 (R2) recommends drug-excipient compatibility studies to facilitate the early prediction of compatibility. Systematic drugexcipient compatibility studies offer several advantages as follows: minimizing unexpected stability failures which usually lead to increased development time and cost, maximizing the stability of a formulation and hence the shelf life of the drug product, and enhancing the understanding of drugexcipient interactions that can help with root cause analysis should stability problems occur.

Formulation optimization studies are essential in developing a robust formulation that is not on the edge of failure. Without optimization studies, a formulation is more likely to be high risk because it is unknown whether any changes in the formulation itself or in the raw material properties would significantly impact the quality and performance of the drug product, as shown in recent examples. Formulation optimization studies provide important information on the following:

- Robustness of the formulation including establishing functional relationships between CQAs and CMAs
- Identification of CMAs of drug substance, excipients, and in-process materials
- Development of control strategies for drug substance and excipients.

In a QbD approach, it is not the number of optimization studies conducted but rather the relevance of the studies and the utility of the knowledge gained for designing a quality drug product that is paramount. As such, the QbD does not equal design of experiments (DoE), but the latter could be an important component of QbD. Drug substance, excipients, and in-process materials may have many CMAs. A CMA is a physical, chemical, biological, or microbiological property or characteristic of an input material that should be

within an appropriate limit, range, or distribution to ensure the desired quality of that drug substance, excipient, or in-process material. For the purpose of this paper, CMAs are considered different from CQAs in that CQAs are for output materials including product intermediates and finished drug product while CMAs are for input materials including drug substance and excipients. The CQA of an intermediate may become a CMA of that same intermediate for a downstream manufacturing step. Since there are many attributes of the drug substance and excipients that could potentially impact the CQAs of the intermediates and finished drug product, it is unrealistic that a formulation scientist investigate all the identified material attributes during the formulation optimization studies. Therefore, a risk assessment would be valuable in prioritizing which material attributes warrant further study. The assessment should purchase common scientific knowledge and the formulator's expertise. A material attribute is critical when a realistic change in that material attribute can have a significant impact on the quality of the output material. Product understanding includes the ability to link input CMAs to output CQAs. The steps taken to gain product understanding may include the following:

1. Identify possible known input material attributes that could impact the performance of the product.
2. Use risk assessment and scientific knowledge to identify potentially high risk attributes.
3. Establish levels or ranges of potentially high-risk material attributes.
4. Design and conduct experiments, using DoE when appropriate.
5. Analyze the experimental data and apply first principle models to determine if an attribute is critical.
6. Develop a control strategy. For critical material attributes, define acceptable ranges. For non critical material attributes, the acceptable range is the range investigated. When more than one excipient is involved, these defined acceptable ranges may be termed formulation design space.

Process Design and Understanding

A pharmaceutical manufacturing process usually consists of a series of unit operations to produce the desired quality product. Unit operations may be executed in batch mode or in a continuous manufacturing process. A unit operation is a discrete activity that involves physical or chemical changes, such as mixing, milling, granulation, drying, compression, and coating. A process is generally considered well-understood when all critical sources of variability are identified and explained, variability is managed by the process, and product quality attributes can be accurately and reliably predicted. Process

parameters are referred to as the input operating parameters (e.g., speed and flow rate) or process state variables (e.g., temperature and pressure) of a process step or unit operation. A process parameter is critical when its variability has an impact on a critical quality attribute and therefore should be monitored or controlled to ensure the process produces the desired quality. Under this definition, the state of a process depends on its CPPs and the CMAs of the input materials. Process robustness is the ability of a process to deliver acceptable drug product quality and performance while tolerating variability in the process and material inputs [21]. The effects of variations in process parameters and material attributes are investigated in process robustness studies. The analysis of these experiments identifies CPPs that could affect drug product quality and establishes limits for these CPPs (and CMAs) within which the quality of drug product is assured.

Steps to establish process understanding are very similar to those of product understanding and include the following:

1. Identify all possible known process parameters that could impact the performance of the process
2. Use risk assessment and scientific knowledge to identify potentially high-risk parameters.
3. Establish levels or ranges of these potentially high-risk parameters
4. Design and conduct experiments, using DoE when appropriate.
5. Analyze the experimental data and, when possible, determine scalability and apply first principle models to determine if a process parameter is critical. Link CMAs and CPPs to CQAs when possible.
6. Develop a control strategy. For critical parameters, define acceptable ranges. For noncritical parameters, the acceptable range is the range investigated. When more than one process parameter or material attribute is involved, these defined acceptable ranges may be termed process design space.

While developing a strategy for investigating both product design and understanding and process design and understanding, studies can be designed in such a way that both the objectives of product and process understanding are achieved simultaneously. In addition, an interactive (or interdependent) relationship among material attributes, process parameters, and product attributes can be more easily developed when such analyses are performed in carefully planned and designed experimental studies. ICH Q8 (R2) defines design space as the multidimensional combination and interaction of input variables (e.g., material attributes) and process parameters that have been demonstrated to provide assurance of quality. Parameter movements that

occur within the design space are not subjected to regulatory notification. However, movement out of the design space is considered to be a change and would normally initiate a regulatory postapproval change process. Design space is proposed by the applicant and is subject to regulatory assessment and approval. Thus, design space is the direct outcome of analysis of the DoE data or validated models such as first-principle models. Design space may be scale and equipment dependent. Therefore, the design space determined at laboratory scale may need to be justified for use at commercial scale. Approaches for justification may include geometric considerations, kinematic considerations, heat and mass transfer, or dimensionless numbers as well as continual verification during commercial manufacturing. Justification is needed because the mechanistic understanding of pharmaceutical unit operations may be limited and scale-up is largely based on general rule of thumb and trial-and-error approaches; however, when mechanistic understanding or reliable empirical models (i.e., extensive process understanding) exists, then the design space can be translated across scale.

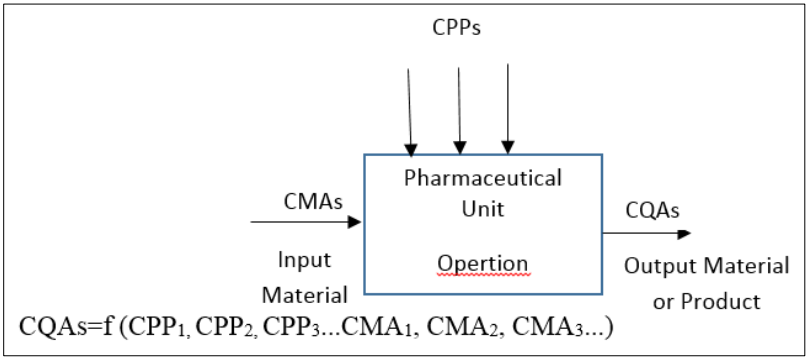


Fig 2: Link input critical material attributes (CMAs) and critical process parameters (CPPs) to output critical quality attributes (CQAs) for a unit operation

Pharmaceutical products are frequently manufactured by a combination of unit operations. For example, tablets prepared by direct compression may simply involve blending and compression. However, when tablets are prepared by wet granulation, unit operations may involve blending, granulation, wet milling, drying, dry milling, blending for lubrication, compression, coating, and packaging. In such cases, the output of the first unit operation becomes an input of subsequent unit operations. Process understanding could be conducted on each unit operation or a combination of unit operations to determine CMAs, CPPs, and CQAs [22].

Control Strategy

The knowledge gained through appropriately designed development studies culminates in the establishment of a control strategy. Level 1 utilizes automatic engineering control to monitor the CQAs of the output materials in real time. This level of control is the most adaptive. Input material attributes are monitored and process parameters are automatically adjusted to assure that CQAs consistently conform to the established acceptance criteria.

Level 1 control can enable real-time release testing and provides an increased level of quality assurance compared to traditional end-product testing. It should be noted that adoption of process analytical technology (PAT) is not the only way to implement real-time release testing (e.g., the use of predictive models as a surrogate for traditional release test, where the model may be defined in terms of traditional in-process measurements).

Level 2 consists of pharmaceutical control with reduced end-product testing and flexible material attributes and process parameters within the established design space. QbD fosters product and process understanding and facilitates identification of the sources of variability that impact product quality. Understanding the impact that variability has on in-process materials, downstream processing, and drug product quality provides an opportunity to shift controls upstream and to reduce the reliance on end-product testing.

Level 3 is the level of control traditionally used in the pharmaceutical industry. This control strategy relies on extensive end-product testing and tightly constrained material attributes and process parameters. Due to limited characterization of the sources of variability and inadequate understanding of the impact that CMAs and CPPs have on the drug product CQAs, any significant change in these requires regulatory oversight. Significant industry and regulatory resources are spent debating issues related to acceptable variability, the need for additional controls, and the establishment of acceptance criteria. In reality, a hybrid approach combining levels 1 and 2 can be used. ICH Q8 (R2) defines a control strategy as a planned set of controls, derived from current product and process understanding that ensures process performance and product quality.

- Control of input material attributes (e.g., drug substance, excipient, in process material, and primary packaging material) based on an understanding of their impact on process ability or product quality.
- Product specification
- Controls for unit operations that have an impact on downstream

processing or product quality.

- In-process or real-time release testing in lieu of end-product testing.
- A monitoring program for verifying multivariate prediction models.

Process Capability and Continual Improvement

Process capability measures the inherent variability of a stable process that is in a state of statistical control in relation to the established acceptance criteria. Table II shows the definition, calculation formula, and description of process capability indices [23] that are useful for monitoring the performance of pharmaceutical manufacturing processes. Calculations based on the inherent variability due to common cause of a stable process (i.e., in a state of statistical control) result in process capability (Cp and Cpk) indices. When the process has not been demonstrated to be in a state of statistical control, the calculation needs to be based on sample standard deviation of all individual (observed) samples taken over a longer period of time; the result is a process performance index (Pp and Ppk). A state of statistical control is achieved when the process exhibits no detectable patterns or trends, such that the variation seen in the data is believed to be random and inherent to the process.[24]

When a process is not in a state of statistical control, it is because the process is subject to special cause (source of intermittent variation in a process). Special causes can give rise to short-term variability of the process or can cause long-term shifts or drifts of the process mean. Special causes can also create transient shifts or spikes in the process mean. On the other hand, common cause is a source of inherent variation that is random, always present, and affects every outcome of the process. In a QbD development process, the product and process understanding gained during pharmaceutical development should result in early identification and mitigation of potential sources of common cause variation via the control strategy. The manufacturing process will move toward a state of statistical control, and, once there, the manufacturer will continue to improve process capability by reducing or removing some of the random causes present and/or adjusting the process mean towards the preferred target value to the benefit of the patient. In a non-QbD approach, common cause variation is more likely to be discovered during commercial production and may interrupt commercial production and cause drug shortage when it will require a root cause analysis.

Process capability can be used to measure process improvement through continuous improvement efforts that focus on removing sources of inherent variability from the process operation conditions and raw material quality. Ongoing monitoring of process data for Cpk and other measures of statistical

process control will also identify when special variations occur that need to be identified and corrective and preventive actions implemented.

Continuous improvement is a set of activities that the applicant carries out in order to enhance its ability to meet requirements. Continual improvements typically have five phases as follows [25]:

- Define the problem and the project goals, specifically.
- Measure key aspects of the current process and collect relevant data.
- Analyze the data to investigate and verify cause-and effect relationships. Determine what the relationships are, and attempt to ensure that all factors have been considered. Seek out root cause of the defect if any.
- Improve or optimize the current process based upon data analysis using techniques such as design of experiments to create a new, future state process. Set up pilot runs to establish process capability.
- Control the future state process to ensure that any deviations from target are corrected before they result in defects. Implement control systems such as statistical process control, production boards, visual workplaces, and continuously monitor the process. Continuous improvement can be applied to legacy products. Legacy products usually have a large amount of historical manufacturing data. Using multivariate analysis to examine the data could uncover major disturbances in the form of variability in raw materials and process parameters. Continuous improvement could be achieved by reducing and controlling this variability. Newer processes associated with a design space facilitate continuous process improvement since applicants will have regulatory flexibility to move within the design space (ICH Q8).

Pharmaceutical quality by design tools

Prior Knowledge

Although not officially defined, the term “prior knowledge” has been extensively used in workshops, seminars, and presentations. In regulatory submissions, applicants often attempt to use prior knowledge as a “legitimate” reason for substitution of scientific justifications or conducting necessary scientific studies. Knowledge may be defined as a familiarity with someone or something, which can include information, facts, descriptions, and/or skills acquired through experience or education. The word “prior” in the term “prior knowledge” not only means “previous,” but also associates with ownership and confidentiality, not available to the public. Thus, for the purpose of this paper, prior knowledge can only be obtained through experience, not

education. Knowledge gained through education or public literature may be termed public knowledge. Prior knowledge in the QbD framework generally refers to knowledge that stems from previous experience that is not in publically available literature. Prior knowledge may be the proprietary information, understanding, or skill that applicants acquire through previous studies.

Risk Assessment

ICH Q9 quality risk management indicates that "the manufacturing and use of a drug product, including its components, necessarily entail some degree of risk. The evaluation of the risk to quality should be based on scientific knowledge and ultimately link to the protection of the patient and the level of effort, formality, and documentation of the quality risk management process should be commensurate with the level of risk." The purpose of ICH Q9 is to offer a systematic approach to quality risk management and does not specifically address risk assessment in product development The risk assessment tools identified in ICH Q9 are applicable to risk assessment in product development also. The purpose of risk assessment prior to development studies is to identify potentially high-risk formulation and process variables that could impact the quality of the drug product. It helps to prioritize which studies need to be conducted and is often driven by knowledge gaps or uncertainty. Study results determine which variables are critical and which are not, which facilitates the establishment of a control strategy. The outcome of the risk assessment is to identify the variables to be experimentally investigated. ICH Q9 [26] provides a non-exhaustive list of common risk assessment tools as follows:

- Basic risk management facilitation methods (flowcharts, check sheets, etc.)
- Fault tree analysis
- Risk ranking and filtering.
- Preliminary hazard analysis
- Hazard analysis and critical control points.
- Failure mode effects analysis
- Failure mode, effects, and criticality analysis & Hazard operability analysis & Supporting statistical tools.

Mechanistic Model, Design of Experiments, and Data Analysis

Product and process understanding is a key element of QbD. To achieve these objectives, in addition to mechanistic models, DoE is an excellent tool that allows pharmaceutical scientists to systematically manipulate factors according to a pre specified design. The DoE also reveals relationships between input factors and output responses. A series of structured tests are designed in which planned changes are made to the input variables of a process or system. The effects of these changes on a predefined output are then assessed. The strength of DoE over the traditional univariate approach to development studies is the ability to properly uncover how factors jointly affect the output responses. DoE also allows us to quantify the interaction terms of the variables. DoE is important as a formal way of maximizing information gained while minimizing the resources required. DoE studies may be integrated with mechanism-based studies to maximize product and process understanding. When DoE is applied to formulation or process development, input variables include the material attributes (e.g., particle size) of raw material or excipients and process parameters (e.g., press speed or spray rate), while outputs are the critical quality attributes of the in-process materials or final drug product (e.g., blend uniformity, particle size or particle size distribution of the granules, tablet assay, content uniformity, or drug release). DoE can help identify optimal conditions, CMAs, CPPs, and, ultimately, the design space. FDA scientists have shown the use of DoE in product and process design in recent publications.

Process Analytical Technology

The application of PAT may be part of the control strategy [27]. ICH Q8 (R2) identifies the use of PAT to Understanding Pharmaceutical Quality by Design 781 ensure that the process remains within an established design space. PAT can provide continuous monitoring of CPPs, CMAs, or CQAs to make go/no go decisions and to demonstrate that the process is maintained in the design space. In-process testing, CMAs, or CQAs can also be measured online or inline with PAT. Both of these applications of PAT are more effective at detecting failures than endproduct testing alone. In a more robust process, PAT can enable active control of CMAs and/or CPPs, and timely adjustment of the operating parameters if a variation in the environment or input materials that would adversely impact the drug product quality is detected.

Application of PAT involves four key components as follows: [28]

- Multivariate data acquisition and analysis
- Process analytical chemistry tools
- Process monitoring and control
- Continuous process optimization and knowledge management.

Multivariate data acquisition and analysis requires building scientific understanding about a process and identifying critical material attributes and process parameters that affect product quality and integrating this knowledge into the process control, which is essentially the same as the process understanding in the context of QbD. Process analytical chemistry tools provide real time and in situ data about the status of the process. Multivariate data analysis takes the raw information from the PAT tools and connects it to CQAs. Based on the outcome of the data analysis, process controls adjust critical variables to assure that CQAs are met. The information collected about the process provides a basis for further process optimization. Studies in FDA laboratories indicated the promise of several PAT tools and chemometric approaches. [29] During the last decades, a sharp increase in the use of the Quality by Design (QbD) concept was observed in the titles of pharmaceutical technology and engineering papers. Quality cannot be tested into the final product but it should be built in by design. Nowadays, Pharmaceutical development moves away from the traditional quality by testing (QbT) towards quality by design (QbD) [30].

QBD approach in development and optimization of rosigilatazone maleate

Qbd approach decreases the defects and variability in products by setting quality target product profile (QTTP) process, by understanding its product design, risk assessment, control strategy and continual improvement.

Setting up of QTTP for the formulation

Based on the reference list drug, targets and requirements are set up.it includes routes of administration, strength, drug releases.

Study of CQA of formulation and process

When the critical quality attributes are controlled, the requirements of a developed and formulated product such as safety, efficacy, performance, stability are satisfied. Only the crucial quality attributes should be identified. Initially risk assessment was made and the manufacturing process has been not established in detail for the development of formulation. Risks were rated

based on assumption that for each formulation attribute that changed on optimized manufacturing process would be established. Critical variables are polymer levels (carbopol 934, Sodium carboxymethyl cellulose, ethyl cellulose) in the formulation as well as talc and magnesium stearate levels. Hardness, Drug release and ex-vivo muco-adhesion time were considered as process variables.

Formulation development

Defining design space

ANOVA was used to study the effect of independent variables on dependent variables and to generate space based on contour plots.

Defining control strategy

The controls include parameters and attributes such as drug substance, drug product, and materials.A cost effective formula is selected with minimal trials based on QbD approach [31].

Quality by design approach in formulation and development of aceclofenac loaded microsponges

Microsponge is defined as porous, inert units which are made up of synthetic polymers and act as a shield to the ensure drug from degradation which can be easily entrapped in the form of creams, lotions, and powders [32]. Topical polymeric Microsponge formulation of Aceclofenac was formulated using ethyl cellulose and eudragit ES 100. Solubility analysis of drug and polymer reveals that the internal phase suitable for the preparation of microsponges was acetone and external phase should be liquid paraffin. To produce microsponges with good physical and morphological characteristics the required polymer concentration was found to be 11% and 13% w/w of the internal phase for both the polymers. The volume of internal and external phase required to prepare good microsponges was found to be 20mL of internal and 50mL of the external phase. The minimum concentration of the emulsifier PVA required to produce microsponges was found to be 0.75% w/v. The minimum speed and time of stirring was found to be 2000 rpm for 90 Min. The ratio of drug: polymer required to produce microsponges with good encapsulation efficiency was found to be from 7:1 to 13:1. Below this ratio, the microsponges formed had low capacity encapsulation of the drug. Above this range there was no further increase in the encapsulation efficiency. Hence, it was concluded that 11: 1 to 13: 1 were optimum ratios of drug: polymer to produce good microsponges. Critical quality attributes such as selection of the type and concentration of emulsifier, selection of internal and external phase,

selection of speed and time of stirring required for preparation were identified and was used to develop QbD approach[33]. In factorial design, the amount of drug (ACF): polymer (EC) ratio (X1), amount of PVA Concentration (X2), Internal Phase Concentration (X3) and Speed (X4) were taken as independent variables while percentage yield (Y1), percentage E. E (Y2). Particle sizes (Y3), percentage cumulative drug release (Y4) were selected as dependent variables for both factorial designs. The microsponges after check point analysis which gave better physical, morphological and % encapsulation in either of the polymers were selected for incorporation into the gel. The release profile of the Aceclofenac in the form of microsponges loaded topical gel was compared with that of the pure Aceclofenac Topical Gel. The microsponges topical gel could sustain the drug release over a period of 8 hours when compared to the 96% release after 6 hrs from the pure Aceclofenac. By model fitting of the data obtained from the drug release profile we can conclude that drug release mechanism was Higuchi (Matrix) Model [34].

Quality by design in the development of dry powder inhalers

A dry powder inhaler is a formulation –device combination delivery system and is defined as "the product comprised of two or more regulated components that are physically, chemically or otherwise combined or mixed and produced as a single entity. Dry powder inhalers are complex formulations as compared to conventional dosage forms [35]. Firstly device and formulation interconnecting features should work together to aerosolize the drug and deliver it to the site of action. Apart from this, patient behaviour also plays a significant role in the product delivery, deposition in the lungs and hence bioavailability. The breathing pattern and the disease pathology could significantly affect the dose assumption especially when a DPI with flow rate dependent performance is used. The product quality in terms of respirable dose may be affected by the improper product handling by the patient. Handling errors of inhaler devices are common in real life and are associated with an increased rate of severe COPD exacerbation. QbD tools help in understanding of the interaction of the two product components and in monitoring their contribution on the product performance enabling the minimization of the patient errors during the device preparation and inhalation [36].

Secondly, the DPI manufacturing process exhibit low process capability. Variability is large as compared to the product specifications and it should be redesigned to attenuate the significant root causes of variance. Many DPI formulations are physical mixtures of a coarse carrier, usually α-lactose monohydrate and a micronized low dose of API with an aerodynamic particle

size ranging between 1 and 5μm. This limitation favours lack of API homogeneity in the original blend and during powder dosing either in the unit dose or device reservoir. The weight variability during capsule or blister fillings is also a potential risk factor due to the rheological characteristics of the fines and the low dose requirements of the powder mixture [37].

Thirdly, QbD tools could be particularly helpful in DPIs development because environmental humidity is a crucial factor that needed to be considered during the development and production stages since it negatively affects both the chemical stability of the API and the aerosolization of the powder bed. The adsorption of water on the surface of microparticles has a significant impact on the capillary forces, solid bridge formation and electrostatic forces. High relative humidity may increase inter-particulate forces due to increased capillary interactions resulting in the formation of larger agglomerates which are less breakable. Lactose monohydrate may dissolve and then recrystallize resulting in solid bridges among crystals producing stronger agglomerates that do not disperse in an air flow [38].

The Critical Material Attributes (CMAs) refer to properties of the raw materials important for the DPI product such as the API crystal form, purity, stability and particle size distribution. The Critical Process Parameters (CPPs) are the process variables such the mixing time/rate, the spray drying operating conditions etc. which have a major impact to the selected CQAs. One of the key components consisting the various phases of the QbD initiative is the Risk Assessment (RA).RA is a systematic process of organizing information to support a risk decision and is a key activity of the QbD based methodology. It is a very valuable tool that contributes to gaining process knowledge by identifying and ranking the criticality of the parameters affecting this process through DoE and other mathematical tools. Ranking the variables in terms of their importance on products. Quality from a patient perspective,is usually based on assessing the Risk Priority number (RPN)[39].The most important sources of variability in DPIs development and production can be categorised as follows:

1. Quality characteristics of drug substance and excipients

- Microparticles production process (milling, mechanofusion, spray drying.)
- Powder manufacturing process (API-carrier blending, soft pellets production.)
- Device filling process
- Environmental conditions

- Design of the delivery device
- Primary packaging materials

The physicochemical properties of the drug substance play a significant role in powder handling, its aerosolization after inhalation and its fate in vivo. Different polymorphs and crystallinities affect solubility and absorption of the API. Particle size distribution and other physicochemical properties are the other critical parameters that should be considered for assuring delivery of the API to the target site of a specific disease. The same features are equally important for the excipients when used. Carriers have an active role in DPIs clinical performance and their particle size distribution, shape and surface characteristics are engineered to meet specific requirements. It is thus becoming obvious how many variables are affecting the performance of a DPI and consequently the absolute need to manage the whole process with the "statistical thinking hat" while looking only towards the patient [40].

The effect of processing methods, such as jet milling, mechanofusion, ball milling and spray drying, and type of excipients (leucine, isomalt and magnesium stearate) was investigated using principal component analysis (PCA)and other statistical parameters like moisture uptake, particle size, densities, Hausner ratio, Carr's index, cohesion, fine particle dose(FPD)and fine particle fraction (FPF). The PCA approach allow the discrimination among the branches. considering FPD and FPF as the most important parameters for the characterization of the in vitro powder aerosolization, the jet milling combined with mechanofusion, in presence of leucine or magnesium stearate, produced particles with better performance. Spray drying powder having excellent aerosolization property show a reduced drug load due to higher amount of the excipients required to optimize the aerodynamic pattern. Milling is a common process used to micronize APIs before blending with excipients. This multivariate process can be individually studied using DoE, as it drastically affects the quality of the powders and their behaviour. A crystalline material is preferred as starting material and the most common CPPs to vary and investigate are milling (or grinding nozzle) pressure, feed (or pushing nozzle) pressure and feed rates [41].

The optimization of air-jet milling process of ibuprofen using DoE methodology was recently performed applying a CCD where the grinding and pushing nozzle pressures were varied from 20 to 110 psi.Output variables included yield and particle diameters at the 50th and 90th percentile. The DoE approach elucidated the optimal milling conditions, which were used to micronize another non-steroidal anti-inflammatory drug using the optimized

milling conditions. The milled ibuprofen powders showed a high in vitro respirability (FPF of 67–85%). Importance of powder milling was pointed out and conditions during storage duration and temperature significantly affected performance.

A screening DoE as a statistical tool for the exploration of amikacin spray drying process, through the establishment of mathematical relationships between six CQAs of the finished product and five CPPs. The surface-active excipient did not benefit the CQAs of the spray dried powders for inhalation. The spray drying feed solution required the inclusion of 10% (v/v) ethanol in order to produce powders with the desired aerodynamic performance. The Pareto chart illustrated the effect on FPD of each factor and their interactions. The presence of the surface-active excipient (factor D) had a large negative effect on powder's respirability. But interaction between excipient presence and ethanol content (CD) had a positive effect and it was identified as the only statistically positive interaction. Finally, the drying temperature (factor A) increased the amount of deposited powder smaller than 5μm. An optimization work followed and a CCD was applied in order to identify positive combinations of the production parameters of amikacin spray-dried powders with the intent to expand the experimental space defined in the previous half fractional factorial design. It was observed that amikacin respirability was maximized by the addition of ethanol. Expanding the design space towards smaller ethanol levels, including its complete absence, revealed the crucial role of this solvent on the morphology of the produced particles. Peclet number and drug solubility in the spraying solution helped to understand the formation mechanism of these amikacin spray-dried particles: amikacin is poorly soluble in water ethanol mixture therefore accumulating and precipitating at the surface, resulting in shell particle formation with voids and low density. A similar finding was published when mixtures of acetone and methanol at different molar ratios were applied to dissolve celecoxib and PLGA: the drug and polymer molecules exhibited different diffusion rates during the process of particle formation, resulting in a non-homogenous drug distribution in the resulting particles (Wan *et al*., 2013). Within the same context a central composite face centred design (CCF) with five factors at three levels was built to investigate the spray drying parameters and insulin concentration on the product characteristics. DoE and multivariate data analysis (MVDA) were employed to study the effect of process parameters on the characteristics of spray dried insulin particles. The work illustrates the use of the principal component analysis (PCA) to visualize differences and correlations in the spray-dried samples. PCA is a projection method used to

reduce complexity and to visualize patterns in complex data sets. It was observed that the first three principal components described 74% of the total variation in the data set, which originated from insulin concentration (PC1), inlet drying air temperature (PC2) and nozzle gas flow rate (PC3). A loading plot of PC1 and PC2 described the relationship between observations and variables: MMAD, mass median diameter, yield, tap density and droplet size all increased with increasing insulin concentration, whereas the degradation product “high molecular weight protein” content decreased with increasing insulin concentration [42].

A mannitol based co-spray dried formula was produced with different excipients and meloxicam as the model active agent. The RA performed and the interdependence between QTPPs and CQAs, and between CQAs and CPPs was structured, evaluated one by one and then the interaction was rated on a three-level scale. This scale reflected the impact of the parameters' interaction on the product as high, medium or low. Pareto diagrams showed the ranked parameters according to their potential impact on product quality. Particle size of the API had the highest impact on the desired quality of the final product. It was followed by pulmonary irritation or toxicity properties, wettability and solubility. Microcomposite meloxicam particles were prepared by high pressure homogenization and cospray drying. The optimization of the coating composition with mannitol, PVA and leucine resulted in decreased toxicity and irritation of meloxicam and also increased the wettability. A QbD risk based approach was also employed in the construction of a ciprofloxacin DPI. The interdependent rating of the QTPPs and CQAs was calculated using a specific RA software. Pareto charts also give a graphical overview of the hierarchy of CQAs and CPPs based on their calculated numerical difference of their influence on the aimed quality of the finished product. The particle size of the API was the factor with the highest impact on the quality of the final product. This factor was followed by wettability and dissolution properties. Among the CPPs for the product construction by spray drying, the powder composition and in particular the type of adjuvant,was found to have the highest impact on the desired product's quality. The principles of QbD, using DoE were also applied to prepare and optimize proliposomal DPI [43].

The rifapentine loaded proliposomes for the treatment of tuberculosis were prepared in a single step by spray drying method and the independent variables were optimized using a factorial design approach. The work investigated the effect of drug: hydrogenated soya phosphatidylcholine ratio and type of charged lipid on the CQAs, namely mass median diameter, liposomal vesicle size, encapsulation efficiency, MMAD and FPF. Contour

plots and multiple regression analysis were used to explain the effect of selected independent variables on dependent variables. Contour plot is a graphical technique for representing a 3-dimensional surface by plotting constant z slices, called contours, on a 2dimensional format. That is, given a value for z, lines are drawn for connecting the (x, y) coordinates where that z value occurs. The contour plot is an alternative to a 3-D surface plot. The results showed that both the independent variables were found influencing positively MMAD and negatively the FPF values. Within the same field, a QbD approach was adopted to the production process of liposome-based cationic adjuvant formulation These types of structures aim to be carriers of vaccines capable of eliciting both humoral and cell-mediated immune responses againstco-administered antigen.The applied DoE allowed for the identification of the optimal operating space (OOS) suitable for the production of a final product with the desired CQAs. The operating space is the best set of parameters inside the control space, determined statistically, which enable to accommodate and minimize any natural variability in CPPs and CQAs. In this work the OOS was given by a feed flow rate (1.5 mL/min), a low outlet temperature (75 °C), a medium aspirator rate (90%) and in the area of low feedstock concentration and high atomizing air-flow [44].

QBD in the development of antibiotics and antimalarials

Quality-by-design (QbD) approach was used in development of combination therapy for antimalarial-antibiotics using Azithromycin (Antibiotics) and Chloroquine (Antimalarial) drugs. The design space is defined as a manufacturing area of the product including Equipment, Material, and Operators and Manufacturing Conditions. The design space should be well defined prior to regulatory approval. For responses dissolution at 45 minutes performed and no significant difference observed. Complete release observed at these time points. Binder addition time had a significant impact on disintegration time and tablet dissolution at 45 min. Dissolution decreased with increasing binder addition time. Binder addition time and Kneading time showed impact on tablet disintegration time dissolution at 45 min. Kneading time has significant impact on tablet dissolution at 45 min. Conclusion: The experiments performed by Quality by Design are sufficient to identify the critical process parameters and design space to have good quality product [45].

QBD in the development of antitubercular drugs

The gastro-retentive drug delivery system can improve controlled delivery of the drugs by continuously releasing the drug for a longer period of time at the absorption site ensuring its optimal bioavailability. Rifampicin is

the vital component in the current therapeutic for dormant TB bacilli and is currently one of the frontline drugs recommended by WHO. It has many pitfalls like short half-life, adverse effects pH-dependent degradation, bioavailability problems and concentration dependent auto-induction of its own metabolism resulting decreased bioavailability after repeated oral administrations. Rifampcin is an antimicrobial agent and it should be released initially as loading dose to achieve its minimum inhibitory concentration (MIC) to elicit required therapeutic effect in body. A minimum of 17.11 % should be released as initial loading dose theoretically. Risk assessments using failure mode and effects analysis was done to depict the effects of specific failure modes. A box –Behnken design was used to investigate the effect of amount of sodium bicarbonate, pore former HPMC and glyceryl behenate on percent drug release and floating lag time. A BBD with 3 factors,3 levels and 15 runs was selected for the optimization study Percent drug release in 1 hours,4 hours,8 hours,floating lag time were selected as dependant variables were selected as dependent variables while floating duration will be observed for each Design of experiments (DOE) and will be correlated with other dependent variables..All statistical treatments of DoE were performed using Design expert software.Main plots, interaction plots residual plots and overlaid contour plots were generated using Minitab software.All experimental trials were randomized to exclude any bias. Further the model was evaluated for best fit using parameters, coefficient of determination, adjusted, predicted, adequate precision. The manufacturing method employed is relatively simple and can easily be adopted in industries [46].

Isoniazid

Critical quality attributes depend on dosage form designed, type of formulation and manufacturing method and is selected amongst many possible options. An overall risk assessment of the formulation or process variables was executed using FMEA method. Using method the failure modes can be identified that could have great [47]

QBD approach in the development of topical cream formulation

There is a growing interest in increasing the standards of dosage forms through implementation of more structured development and manufacturing procedures. QbD is recognized as a revoluntary approach to product development and manufacturing. Dosage forms for topical application are intended to produce the required therapeutic action at specific targets in the with least side effects. Creams and emulsions represent a promising pharmaceutical vehicle for skin drug delivery in spite of their thermodynamic

instability. It remains a challenge for pharmaceutical technology. A cream is a semisolid emulsion containing one or more active substances, dissolved or dispersed and may be defined as a biphasic system in which the dispersed or internal phase is finely and uniformly dispersed in the continuous or external phase. According to the dispersed phases nature it is of two types ; an oil-in – water cream or a water –in –oil cream[[48].Pharmaceutical industries have spent significant efforts to ensure product quality and to yield pharmaceuticals as cost efficient as possible. They perform sophiscated processes and technologies and it does not present a rational understanding of critical variables and control strategies which is necessary to ensure the product quality. Employing QbD principles to a complex formulation such as cream, an effective product development with an optimized formulation ad a continuous and robust manufacturing processes can be easily achieved. The initial step is to predefine the final quality profile. QTPP comprises cream quality parameters that should be ideally achieved at the final stage of the product development, considering its safety and efficacy. The second step is to identify critical quality parameters. Once the dosage form is selected, the product development using QbD approach is initiated The main purpose of the product design is to develop a robust cream that can therapeutic objectives and quality attributes, remaining stable over long period of time. The physicochemical and biological properties of drug substance have a significant effect on drug product performance. These properties must be identified to produce the right dosage form and to select appropriate drug concentration, excipients and process parameters. During pre-formulation studies, properties such as solubility partition coefficient, particle size, permeability, melting point and molecular weight need to be identified due to their specific role I percutaneous permeation. The quality attributes of drug substance will ensure that the drug product meet its CQAs and must be controlled within the defined specifications. Special consideration must be given to excipient selection because of their influence on the final product performance and stability.in cream formulation, excipients are used to improve drug solubility and to incorporate it at the target site (solvents), to control drug release and cream viscosity (thickeners), to improve drug skin permeability (chemical permeation enhancers) to enhance drug and formulation stability (antioxidants, emulsifiers and buffers) and to prevent microbial growth and contamination (preservatives). At this stage, special consideration must be given to drug solubility because it will dictate the excipient selection due to its impact on diffusion through each skin environment and release pattern from the dosage form vehicle, final cream uniformity and stability. Compatibility among excipients and drugs must be evaluated to anticipate any stability

features and possible incompatibilities in the final formulation. There are different accepted methods for drug and excipients compatibility analysis. The accelerated stability test is the common to evaluate chemical incompatibility for topical formulation development. During cream formulation production, the first mechanical process carried out is the mixture of both the aqueous solution and oily phases by adding the dispersed to the continuous phases or the continuous to the dispersed phase. Prior to mixing, different excipients are dissolved in the phase in which they are soluble. The next step in cream production is the homogenisation phase. Agitators, mechanical mixers, rotor stators, homogenizers or ultrasonic devices could be employed to ensure uniform excipient dispersion and droplet size reduction. To remove cream air pockets, a deration through vacuum with low speed mixing is turned on to the system. Homogenisation time and vacuum pressure are significant process variables that can affect physical stability. Visual inspection is a useful and simple confirmatory test to ensure solid dissolution or uniformity system. Microscopic visualizations can also be performed to select homogenization speed and time to enable proper incorporation of the active substance into the base.

An initial risk assessment is performed to identify and prioritize high risk variables that may influence identified cream Critical quality attributes. It is done to determine the material attributes and process parameters that are critical and the ones which are needed to be experimentally investigated and controlled to ensure quality. Using risk approach, the starting point must be identification of all material attributes and process parameters that can influence product CQAs to ascertain which of these parameters needed to be further studied and controlled, an ishikawa diagram is constructed. A risk estimation matrix is carried out to prioritize material attributes and process parameters that were demonstrated to be a potential risk factor for cream CQAs. CMAs and CPPs influence one or more cream CQAs and it must be identified to develop an adequate cream formulation. Critical variable identification is the preliminary step in the optimization methodology and is established through a screening process. A screening design is an experimental planning where a relatively large number of factors is simultaneously evaluated using a small number of experiments. Different experimental designs such as full factorial, fractional factorial and placett –burmann designs are usually used for screening purposes. Variable that show criticality in the previous phase are optimized through a DoEs. The optimization step helps to specify CMAs and CPPs optimal settings. Response surface designs such as central composite design and box behnken are the most usual models to predict the optimal CMAs and CPPs ranges Software packages are available

to simplify experimental design procedure and assist in results interpretation: MODDE, Design expert Design –Ease and JMP [49].

QBD approach in development of acyclovir microsponges

Acyclovir is a potent, specific antiviral drug which is active against herpes simplex viruses' types I and II and varicella zoster virus1. QbD was applied to generate design space, using QTPP, CQA, and risk assessment. Microsponges of acyclovir were developed by 23 factorial designs. Three variables Drug: Polymer ratio (X1), Concentration of surfactant (X2) and Stirring speed (RPM) (X3) at two levels low and high were selected and response surface plots were generated. The microsponges were prepared by Quassi-emulsion solvent diffusion method. Various characterizations that were carried out include entrapment efficiency, percentage yield, particle size determination, in-vitro drug release studies and kinetic modelling of drug release. Statistical analyses of batches and surface response studies were done to understand the effect of various independent variables on the dependent variables. Lastly it was concluded that microsponges of Acyclovir using QbD approach were successfully developed [50].

QBD approach in development of sterile dosage forms

The first step is to define the product performance upfront and identify CQAs. Sterility testing ensures sterility of that particular unit, but does not ensure sterility of the dosage form. Sterility is ensured only by process validation. This emphasizes an application of QbD to SDFs. Primary and secondary packaging have to be designed according to patient requirements. The packaging process has to be developed to produce assurance of quality. Control space dictates process control, the control of input materials and container closure system, and the control of the end point. The following are few examples of the impact of primary packaging materials on the quality attributes of SDFs. The primary concern of any packaging is the extractable and leachables. It is more important for SDFs. The primary or secondary packaging material is expected not to provide toxic or harmful components in the formulation. Some of the commonly observed unwanted components are – plasticizers, heavy metals, phthalates, and polyaromatic hydrocarbons. Guidance for Industry titled – "Container Closure Systems for Packaging of Human Drugs and Biologics" provides guidance on the information of packaging materials needed on drug products [4]. Attachment C of the guidance provides information on various extraction studies. It is important to obtain qualitative and quantitative profiles on plastics and elastomers to be used as the packaging components. The following tests are recommended -

USP <661> and USP <381> for the characterization of plastics and elastomers, respectively, and USP <87> and USP <88> for the biological reactivity of plastics and elastomers, respectively. The leachable can also come into the product from an indirect contact (e.g., imprinting on the bottle or adhesives, inks or varnish from labels) or from surrounding air.The QbD principles were applied to a packaging system which was utilized for 12 products. It was observed that when operated within the design space, the leachable profile was predictable. The Lyophilization process provides unique advantages and has been used in many products. In this article, lyophilization is considered as a packaging step rather than a part of formulation manufacturing. In a research article by Mockus *et al*. [12], Bayesian treatment was added to the primary drying modeling. There are three critical steps in freeze-drying:

- Freezing of the drug solution in partially stoppered vials,
- Primary drying to produce a cake, and
- Desorption phase for secondary drying.

During the freezing step, the temperature at which the first crystals of ice appear is termed as a nucleation temperature. Nucleation temperature is affected by several formulation and process factors. In the primary drying step, temperature should not go beyond the eutectic temperature or else the cake could collapse. Some of the factors affecting the primary drying could be the composition of formulation, pressure differential, rubber stopper resistance for water vapor release, heating rate etc. The main goal of this study was to determine the duration of primary drying. The number of temperature. Gauges and their correct placements are critical in determining the exact primary drying end point. In this study, it was shown that the resistance of dry layer mass transfer was product specific and it was a function of the nucleation temperature. Authors developed a mathematical model to predict the end point of primary drying time. In general, for the freeze-drying process, the design space would generally vary for different products. Cannon and Shemeley studied the effect of vial design on the sublimation rate during the primary drying of lyophilisation cycle. The sublimation rate was influenced by the heat and mass transfer rates. The composition of glass vials could affect the thermal conductivity. Other factors influencing the process were the vial diameter, the vial's bottom radius, and the fill volume. The bottom concavities did not substantially influence the sublimation rate.

Packaging aspects must be considered during the development of SDFs. The packaging process parameters may affect the final product quality. During

the development of packaging for sterile products, it is important to understand the impact of material attributes and process parameters on CQAs. It is essential to identify and control the sources of variability. It is also critical to continue to monitor these throughout the lifecycle of the product [51]. The fat-soluble vitamins lipid injectable emulsion, a parenteral supplement, commonly used for hospitalized patients to meet daily requirements of fat-soluble vitamins. The quality target product profile and critical quality attributes were defined based on a comprehensive understanding of fat-soluble vitamins lipid injectable emulsions. The emulsions were prepared using a high-pressure homogenization method. Critical quality attributes (CQAs) were identified using risk assessment tools such as fishbone diagram and risk estimation matrix. The assay, mean droplet size, polydispersity index, zeta potential, and the volume-weighted percentage of fat greater than 5 μm (PFAT5) were identified as CQAs. Accordingly, three critical formulation and process parameters for the emulsions were the percentage of emulsifier, homogenization pressure, and homogenization recirculation. The design space was obtained via a design of experiment (DoE), and an optimum formulation was successfully prepared. All physicochemical attributes of the optimal formulation were within the design space (i.e., droplet size: 217.2±0.37 nm; polydispersity index: 0.115±0.012; PFAT5: less than 0.05%; zeta potential: -34.6±1.09 mV; and viscosity: 20.95 mPa at 0.1 s-1). The optimal formulation remained acceptable physicochemical stability at 25 ± 2°C/60% RH ± 5% RH over a 12-month period. Safety of the optimal emulsion was evaluated as acceptable through the determination of lysophospholipid content and an in vitro haemolysis assay. An optimal lipid injectable emulsion for fat soluble vitamins can be successfully prepared using a QbD approach. Fat-soluble vitamins lipid injectable emulsion is a complex formulation that needs to be developed by using a QbD approach to achieve a high quality and safety product. A sensitive HPLC-MS method, DLS and light obscuration techniques were used as quality control tools to examine the CQAs of the emulsion, which including the assay, droplet size, PDI, zeta potential, and PFAT5. The application of DoE was beneficial to understand the impact of variation to control the entire process and subsequent quality risks. It was found that the percentage of egg lecithin, homogenization pressure, and recirculation were the most significant factors affecting the emulsion droplets. Additionally, the PFAT5 can be used as a crucial characteristic of the emulsion to direct the manufacturing process for the emulsion. The optimal formulation and design space established by CDD successfully lay within the QTPP requirements. The morphology study, rheology study, and long-term stability study were carried out for further evaluation of the emulsion with respect to its physical

stability. In the view of all results, a high-quality, safe and stable lipid injectable emulsion for fat-soluble vitamins had been prepared by following the QbD steps. This study has provided a deep insight into the association between parenteral safety issues and an in-depth understanding of lipid injectable emulsion [52].

Application of QBD approach for erythropoietin alpha purification

In biopharmaceutical manufacturing, quality should always be targeted to ensure safety and efficacy. Design-of-experiments–based approaches have been explored to rapidly and efficiently achieve an optimized yield and an increased understanding of a product and process variables affecting the product's critical quality attributes in the biopharmaceutical industry; this system is known as the quality-by-design approach. Changes in three critical process parameters-buffer pH, flow rate, and loading amount were evaluated. Process characterization was conducted on a scaled-down model previously validated by comparison with data from a large-scale production facility. Seven critical quality attributes relative aggregate content, host cell protein, host cell deoxynucleotides, endotoxin, Z-value (N-glycan score), relative content of charge isomers, and step yield were analyzed. Multivariate regression analysis was performed to establish statistical prediction models for performance indicators and quality attributes; accordingly, we constructed contour plots and conducted a Monte Carlo simulation to clarify the design space. As a result of the optimization analysis of the purification process, it was confirmed that proven acceptance ranges were optimized as follows: loading amount (mg/mL) 0.4–4.0, buffer pH 7.0–8.0, and flow rate (mL/min) 0.5–1.6[53].

Conclusion

QBD is an important approach to get the quality of the pharmaceutical products. QbD approach reduced time consuming in order to prove the quality assurance of the pharmaceutical products when compare with conventional approach. Therefore, QbD approach is important in the field of modern pharmaceutical research. QbD gives idea on all aspects including drug product quality profile, input variables for optimization technique, validation of QbD methodology, and scale up process using software based QbD. Hence, QbD approach can be useful in the field of modern pharmaceutical research to produce economic pharmaceutical products with best quality assurance.

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