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Enhancing Analytical Method Development through Quality by Design: A Review

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Abstract

A proactive, science-based approach to pharmaceutical development and manufacture, Quality by Design (QbD) intentionally incorporates quality into the product from the outset rather than testing it after the fact. In order to guarantee product performance and consistency, this methodology entails creating a "design space" that comprises essential components including materials, machinery, process parameters, and operating circumstances. A detailed comprehension and rationale of this design space are prerequisites for regulatory approval. To guarantee product dependability, QbD places a strong emphasis on defining and managing Critical Quality Attributes (CQAs) and Critical Process Parameters (CPPs).Through Analytical Quality by Design (AQbD), which emphasises methodical method development, performance monitoring, and risk assessment to guarantee dependable analytical results, the concepts of QbD are expanded into the analytical domain. Design of Experiments (DoE) is a crucial tool for effectively optimising process and procedure variables. In particular, a popular response surface methodology in DoE for investigating component interactions and optimising multivariable systems is the Central Composite Design (CCD). Using QbD and AQbD reduces development time, cost, and variability while improving method robustness, product performance, and process understanding. Furthermore, it promotes on-going development across the product lifetime and provides more regulatory flexibility. All things considered, these methods aid in the creation of pharmaceutical items that are effective, reliable, and of excellent quality.

Keywords: Process Analytical Technology (PAT), Central Composite Design, Design of Experiments, Analytical Quality by Design, Quality by Design, and Critical Quality Attributes.

Introduction

The core idea of Quality by Design (QbD) is that rather of being tested into a product at the end, quality should be incorporated into it from the beginning. The phrase"design space" refers to the comprehensive environment in which a product is manufactured, encompassing equipment, raw materials, personnel, and processing conditions. Regulatory approval is typically granted once this design space is clearly defined and scientifically justified.Moving outside of the design area necessitates a careful assessment of how such changes impact product quality, whereas operating within it guarantees constant quality. By using the QbD framework to consider different influencing elements as tools,developers can systematically assess and control their impact on final product attributes. These evaluations form an essential part of the regulatory submission dossier. Quality Risk Management (QRM) is based on crucial process factors during product development. Establishing the Quality Target Product Profile (QTPP), which describes the desired quality attributes of the finished product, is crucial before starting development operations. To guarantee product efficacy and safety, the QTPP directs the selection of design space elements, performance standards, and manufacturing controls.

Defining Quality and QbD

In the context of QbD, the term *quality* refers to the suitability of a product for its intended use, encompassing attributes such as identity, potency, purity, and safety. QbD has been endorsed by global regulatory authorities, including the U.S. Food and Drug Administration (FDA) and the International Council for Harmonisation (ICH), as a methodical and scientifically based approach to drug development. It starts with predetermined goals and stresses a thorough comprehension of the product and its manufacturing process, as well as strong control measures founded on risk management and good science. The QbD concept was originally introduced by quality management pioneer Dr. Joseph M. Juran, particularly in his seminal work *Juran on Quality by Design*. In the pharmaceutical industry, QbD aims to enhance awareness of product efficacy, safety, and consistent quality. Its application involves analytical tools and scientific methodologies that provide comprehensive data throughout all stages of product development and manufacturing. These tools not only improve efficiency and performance but also help reduce risk. In recent years, QbD has been successfully implemented in the development of both traditional and advanced pharmaceutical dosage forms. The FDA has published specific guidance supporting the QbD framework, especially for biotechnology-based products and immediate/modified-release dosage forms. Regulatory agencies

continuously promote the adoption of ICH guidelines—specificallyICH Q8 (Pharmaceutical Development), Q9 (Quality Risk Management), Q10 (Pharmaceutical Quality System), and Q11 (Development and Manufacture of Drug Substances)—to ensure global consistency and high-quality standards in pharmaceutical manufacturing.

1.1 Objectives of Quality by Design

In pharmaceutical development, Quality by Design (QbD) is a methodical, scientifically based strategy that starts with well-defined objectives. It places a strong emphasis on a thorough comprehension of procedures and end products, underpinned by sound quality risk management guidelines. The following are the main goals of putting QbD into practice:

a) Establishing scientifically justified product quality specifications that reflect the desired clinical outcomes.
b) Enhancing process understanding to minimize variability and reduce the risk of defects, thereby improving overall product consistency.
c) Increasing effectiveness in the creation and production of pharmaceuticals.
d) Encouraging greater cause-and-effect analysis and regulatory flexibility to support well-informed decision-making.

1.2 Quality by Design's Benefits for Industry

(1) The QbD framework enhances process robustness, ensuring consistent performance even under variable conditions, thereby increasing confidence in product quality.
(2) It promotes a deep comprehension of the process and the final output, resulting in more intelligent and effective development choices.
(3) QbD improves the success rate of technology transfer from research and development to the quality control or manufacturing departments.
(4) Defining the design space in advance minimizes the need for post-approval changes, helping companies avoid costly regulatory updates.
(5) It supports ongoing enhancement across the product lifecycle, promoting the uptake of cutting-edge methods and technology.

Pharmaceutical QbB	**Analytical QbD**
Quality Target Product Profile (QTPP)	Analytical Target Profile (ATP)
Critical Quality Attributes (CQAs)	Critical Quality Attributes (CQAs)
Perform Risk Assessment	Conduct Risk Assessment
Establish Design Space	Define Method Operable Design Region (MODR)
Control Strategy	Analytical Control Strategy
Implement Life Cycle Management	Apply Analytical Life Cycle Management

Difference between Pharmaceutical QbD and Analytical QbD

- 2. Analytical Quality by Design: This method of developing analytical methods is structured and grounded on science, according to the International Council for Harmonisation (ICH). It starts with well-defined goals and concentrates on developing a thorough comprehension of the procedure and approach as well as strong process control. Like its cousin in pharmaceutical QbD, AQbD is based on good scientific principles and quality risk management, and it strives to create procedures that are dependable, well-characterized, and appropriate for their intended use.

AQbD uses a lifecycle approach and includes a number of essential elements and resources, such as:

- Analytical Target Profile (ATP)
- Critical Quality Attributes (CQA)
- Risk Assessment
- Method Development and Optimization using Design of Experiments (DoE)
- Method Operable Design Region (MODR)
- Control Strategy
- Method Validation
- Continuous Method Performance Monitoring

Figure 2 illustrates the AQbD lifecycle along with each of these tools.

Historically, both pharmaceutical product development and analytical method optimization were performed using the One Factor At a Time (OFAT) approach. In this method, only one variable is changed within a specified range while keeping all others constant. Although this approach is simple, it is inefficient—it requires a high number of experiments and fails to detect interactions between variables, potentially leading to suboptimal results.

To overcome these limitations, Design of Experiments (DoE) is employed. DoE is a powerful statistical tool that enables the simultaneous study of multiple factors and their interactions, often resulting in better optimization with fewer experiments. It includes various experimental designs, such as screening and optimization models, that are central to both analytical and pharmaceutical QbD. This research highlights both theoretical foundations and practical applications of DoE in implementing QbD for analytical and pharmaceutical development.

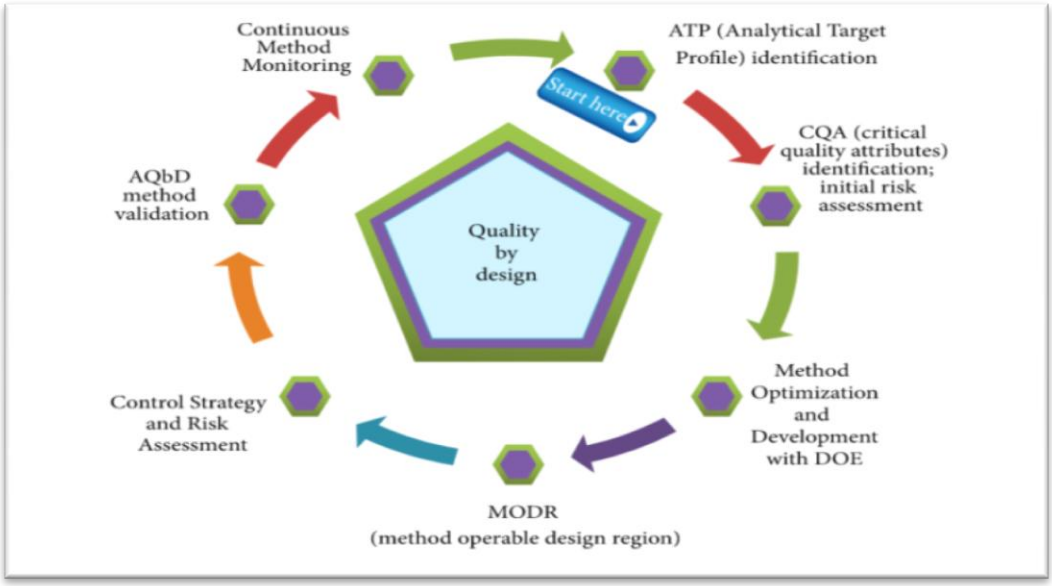


Figure No. 1:AQbD tools and life cycle

2.1 ToolsOF Analytical Quality By Design

Quality by Design (QbD) encompasses all facets of pharmaceutical development, enabling the creation of high-quality products and robust manufacturing processes that consistently deliver desired safety and efficacy outcomes. By applying the QbD approach, pharmaceutical development gains a comprehensive understanding of both the product and its manufacturing process.

Analytical methods are essential to the pharmaceutical development process. Integrating QbD principles into analytical method development is both logical and recommended, as it enhances regulatory flexibility, minimizes out-of-specification (OOS) results, and leads to more robust and cost-effective analytical methods.

I. Profile of Analytical Targets (ATP)

Analytical Quality by Design (AQbD) starts with the Analytical Target Profile (ATP), which defines the analytical technique's intended use and provides a basis for method selection, design, and development.

Performance characteristics of analytical analytical methods (AMPC)

The Analytical Target Profile's (ATP) specifications are met by the Analytical Method Performance Characteristics (AMPC). These traits can be divided into groups according to the source of variation:

a) Systematic variability (associated to bias), encompassing metrics like specificity, accuracy, and linearity.

b) Random (aleatory) variability, which includes characteristics such as limit of quantification (LOQ), precision, and limit of detection (LOD).

AMPC may additionally cover the method's resilience and range in addition to these. A combined performance requirement, usually encompassing both accuracy and precision, is often advised to be included in ATP. The best analytical method, whether chromatographic, spectrophotometric, microbiological, or another, should be chosen based on the definitions of ATP and AMPC.

I. **Risk Assessment**

Risk assessment is a structured process used to organize and evaluate existing knowledge and data to support informed decision-making. It involves three key components:

a) **Risk Identification** : A systematic process that uses stakeholder input, theoretical evaluations, and historical data to pinpoint potential sources of risk or hazard.

b) **Risk analysis** is the process of looking at and assessing the risks connected to the hazards that have been identified in order to determine their nature and possible consequences.

c) **Risk evaluation**: Using qualitative or quantitative metrics, the analysed hazards are compared to predetermined criteria to ascertain their overall importance and priority.

Method Development and Validation

To comprehend the robustness and ruggedness of the method, define MODR and look at possible multivariate interactions using DoE.

II. **Control Strategy**

Determine the system's appropriateness and control space; adhere to the technique

III. **Continuous Improvement**

By continuously monitoring method performance against the Analytical Target Profile (ATP), analysts can proactively identify and address any deviations or out-of-trend results. This approach supports timely updates using the latest analytical and process technologies.

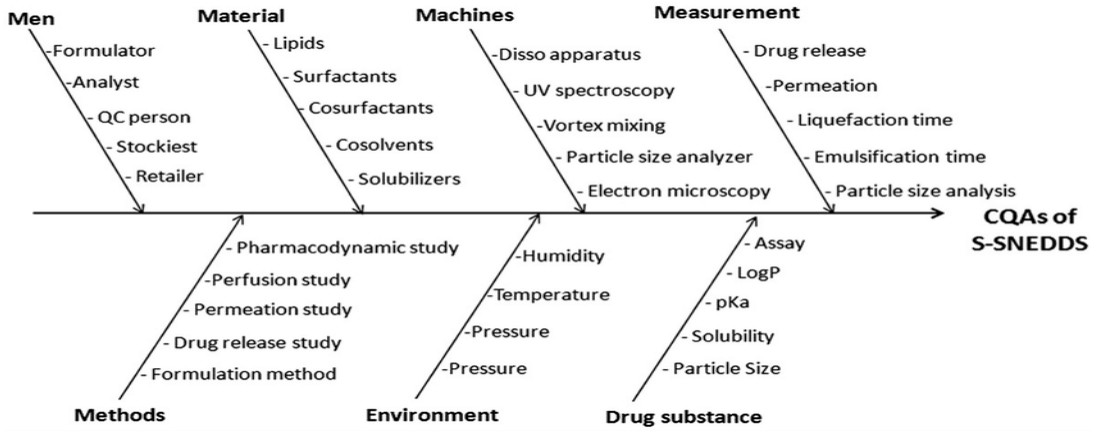


fig.3. Fishbone Diagram

4. Design of Experiment (DoE)

Design of Experiment (DoE) is a robust statistical approach widely used to address industrial process challenges and optimize both process and product design. During process analysis, experiments are conducted to identify which input variables significantly affect the output and to determine the optimal levels of these inputs to achieve the desired results. This methodology is also known as experimental design or designed experiments.DoE provides pharmaceutical scientists with a systematic framework to manipulate multiple factors simultaneously according to a predetermined experimental plan. A well-constructed design relies on a thorough understanding of the product and effective control of the entire manufacturing process. When combined with mechanism-based studies, DoE enhances the overall knowledge of product and process behavior. Essentially, DoE applies statistical tools to systematically identify and quantify cause-and-effect relationships between input variables (independent variables, xi) and output responses (dependent variables, y). This is achieved by developing mathematical models of the form y = f(xi), which describe the studied process or phenomenon. The primary goals often include determining conditions that optimize the process performance.

Among the many advantages of DoE are the following:

• Determining which critical process parameters (CPPs) have the biggest influence.

• Determining the ideal factor settings that enhance product quality and guarantee that Critical Quality Attributes (CQAs) maintain low variability

within intended parameters.

• Knowing how factors interact, which is a significant benefit over conventional One Factor At a Time (OFAT) testing, in which each variable is examined separately without taking synergistic effects into account.

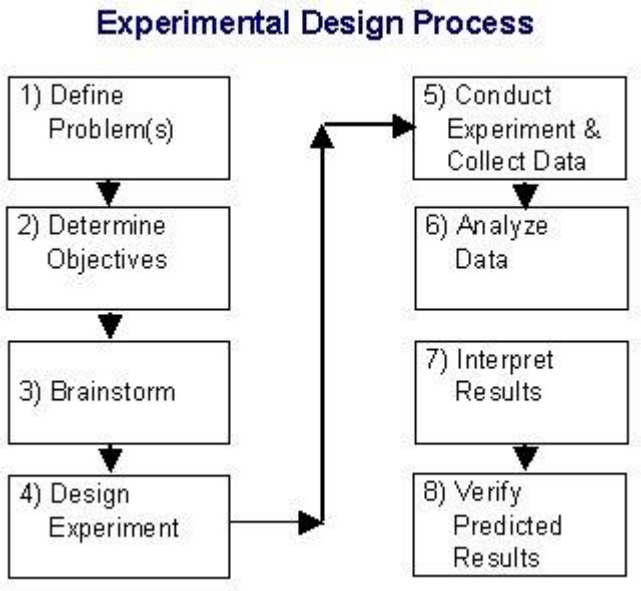


Fig 4.Steps of Design of Experiment (DoE)

The efficient application of Design of Experiments (DoE) techniques is made possible by defined protocols and principles. Establishing the study's goals and response variables, picking pertinent variables and their magnitudes, picking the best kind of experimental design, and carrying out the experiment are usually the steps involved in these processes. The type of process being researched, the resources available, and the purpose of the investigation (such as screening, characterisation, or optimisation) all influence the variables chosen for a DoE, including the number of factors, their levels, and the selection criteria. In essence, Planning the experiment, carrying out the experimental runs, and utilising a variety of statistical methods to evaluate the data gathered in order to produce trustworthy and impartial findings are the main components of DoE. Each DoE starts by deciding which system or process is being studied and outlining the issue that needs to be fixed. The construction of particular objectives, which in turn determine the choice of suitable performance indicators or response variables, is guided by this original problem statement. The behaviour of the system should be quantitatively reflected in these response variables. The subsequent stage entails identifying the variables that affect the response variable, choosing the number of experimental runs, categorising or discretising these variables, and Choosing an appropriate experimental design matrix—a crucial step in the procedure. Conducting the experiment in accordance with the design matrix and methodically gathering data comprise the third phase. Lastly, statistical tools like Analysis of Variance (ANOVA) and related techniques are used to analyse the data. The outcomes are then analysed to improve the procedure or obtain a better understanding of system behaviour.

Types of Design of Experiments (DoE)

Design of Experiments (DoE) is a systematic and organized approach used to identify and understand the relationships between input factors (independent variables) and output responses (dependent variables).

DoE can be categorized into the following types:

1. **Factorial Designs**
   a) Single Factorial Design
   b) Two-Factorial Design
2. **Fractional Factorial Designs**
3. **Screening Designs**
   a) Plackett-Burman Design
   b) Fractional Factorial Design
   c) Two-Level Full Factorial Design
4. **Optimization Designs**
   a) Box-Behnken Design
   b) Central Composite Design (CCD)
   c) Three-Level Design
5. **Factorial Design**

Several elements are simultaneously changed at two or more levels in a factorial design in order to evaluate each one's impact separately as well as in combination. The 2^k full factorial design, which is one of the most used factorial designs, tests k factors at two levels, usually called "low" and "high." Two-factor designs, for instance, have four experiments; three-, four-, five-, and six-factor designs have eight, sixteen, thirty-two, and sixty-four

experiments, respectively. A minus sign (−) is frequently used to indicate the lower levels of each factor, and a plus sign (+) is used to indicate the higher levels. In order to express an intermediate value of the component, middle or centre level (zero) is occasionally included.

		Independent Variable 2	
		Level 1	Level 2
Independent Variable 1	Level 1	Dependent Variable	Dependent Variable
	Level 2	Dependent Variable	Dependent Variable

Fig. Example of a 2×2 Factorial Designs

2. Fractional Design:

Full factorial experiments often demand a large number of runs, which can be resource-intensive. To address this, a fraction of the total runs—such as one-half (½), one-quarter (¼), or another fraction—can be selected and performed instead of the complete set. This approach is known as a fractional factorial design.

3. Screening Experimental Design

When there are numerous possible input variables that potentially affect one or more response variables, an experimental design known as a screening design is employed. Its goal is to determine which factors are most important so that only those be examined in more detail in subsequent studies. By eliminating less important factors early on, this reduces time and expense.

The general approach to carrying out a screening experiment consists of:

1. Assessing whether a screening design is necessary.
2. Evaluating the number of runs that can realistically be performed, balancing the information gained against the resources required.
3. Listing all possible variables and conducting a feasibility assessment.

The selected screening design aims to isolate the most influential input factors affecting the output. The results may be generated using specialized design software, combined with the researcher's understanding of the system and cost considerations. This approach enables the elimination of less significant factors, allowing focus on the most impactful variables for further experimentation.

3.1 Placket-Barman Designs

In 1946, mathematicians R.P. Plackett and J.P. Burman created a particular class of fractional factorial designs known as Plackett-Burman designs. In the early stages of testing, when little is known about the system, these designs are especially helpful. They effectively assist in determining the most important formulation or process variables. Plackett-Burman designs operate on the assumption that two-way interactions between factors are negligible, allowing the focus to remain on main effects.One of the key advantages of this design is its ability to evaluate many variables using a relatively small number of experiments. These designs typically require a number of runs that are multiples of four (i.e., 4n, where n = 1, 2, 3, ...). The maximum number of factors that can be studied in such a design is one less than the number of experiments conducted. For example, an eight-run Plackett-Burman design can investigate up to seven different factors, making it highly efficient for screening purposes.

Run	Factors										
	A	*B*	*C*	*D*	*E*	*F*	*G*	*H*	*J*	*K*	*L*
1	1	1	-1	1	1	1	-1	-1	-1	1	-1
2	-1	1	1	-1	1	1	1	-1	-1	-1	1
3	1	-1	1	1	-1	1	1	1	-1	-1	-1
4	-1	1	-1	1	1	-1	1	1	1	-1	-1
5	-1	-1	1	-1	1	1	-1	1	1	1	-1
6	-1	-1	-1	1	-1	1	1	-1	1	1	1
7	1	-1	-1	-1	1	-1	1	1	-1	1	1
8	1	1	-1	-1	-1	1	-1	1	1	-1	1
9	1	1	1	-1	-1	-1	1	-1	1	1	-1
10	-1	1	1	1	-1	-1	-1	1	-1	1	1
11	1	-1	1	1	1	-1	-1	-1	1	-1	1
12	-1	-1	-1	-1	-1	-1	-1	-1	-1	-1	-1

Fig. Example of a 12 Run Plackett-Burman design.

4. Optimization Experimental Design

4.1 Box-Behnken Design

Donald Behnken and George E. P. Box introduced the Box-Behnken Design (BBD) in 1960. This kind of response surface methodology (RSM) makes it possible to optimise procedures with the fewest possible experimental runs. BBD only needs three levels for each factor and is categorised as a rotatable or nearly rotatable design. BBD excludes experimental points at the corners of the experimental space, in contrast to central composite designs. Rather, the design incorporates many central points for estimating experimental error and positions points at the midpoints of the edges.

To standardise their values over the same scale, the factors are coded and expressed in terms of experimental units (e.g., eu). Each factor typically has a total range of 2 e.u., with the low level being coded as -1, the high level as +1, and the centre as 0. Comparison and analysis are made easier by this standardisation.

Regarding the experimental design,

$N = 2k(k - 1) + C_0$

This is the formula used to determine the total number of runs (N) needed for a BBD.

Where:

N is the total number of experimental runs,

C_0 is the number of centre points, and

k is the number of components.

Because it requires fewer experiments than complete factorial designs while still capturing significant interactions and response surface curvature, this design is very effective for process optimisation.

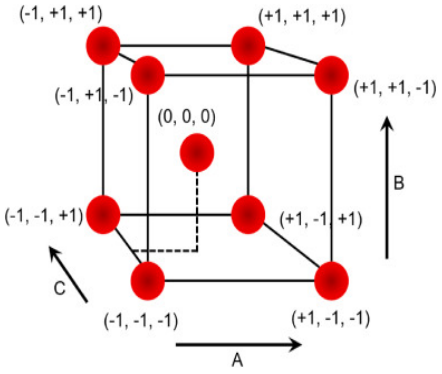


Fig. 9 Example of BBD for 3 factors representation

4.2 Central Composite Design

In response surface methodology (RSM), a Central Composite Design (CCD) is a popular experimental design that works especially well for creating a second-order (quadratic) model of a response variable. Because fewer experimental runs are needed, this method offers an effective substitute for doing a complete three-level factorial experiment.The concept was first introduced in the seminal 1951 paper "On the Experimental Attainment of Optimum Conditions" by G. E. P. Box and K. B. Wilson. CCD was specifically developed to support process optimization studies, enabling researchers to collect data efficiently, cost-effectively, and comprehensively.Unlike traditional one-factor-at-a-time methods, statistical techniques such as RSM allow for the simultaneous analysis of multiple variables and their interactions. For instance, in a particular study involving organosolv pretreatment of rice straw, CCD was applied to assess how variables such as temperature, time, and ethanol concentration affected responses like residual solids, lignin recovery, and hydrogen production.

A **Box-Wilson Central Composite Design** typically consists of:

- A factorial or fractional factorial core with center points (to estimate experimental error),
- Plus additional axial or “star” points to detect curvature in the response surface.

This combination enables the modeling of complex relationships between independent variables and the measured outcome. Using CCD, a second-order polynomial regression equation is fitted to the data, generally represented as:

$$\mathbf{y = \beta_0 + \Sigma\beta_i X_i + \Sigma\beta_{ij} X_i X_j + \Sigma\beta_{ii} X_i^2 + \varepsilon}$$

Where:

- y is the predicted response,
- $X_1, X_2, \ldots, X_k$ are the independent (input) variables,
- β terms are regression coefficients,
- ε represents the random error.

This modeling approach is valuable for determining the optimal conditions of a process and gaining insight into how individual variables, as well as their interactions and nonlinear effects, influence the outcome.

A **Central Composite Design (CCD)** typically involves three types of experimental runs:

1. **2^k factorial trials**
2. **2^k axial (or star) trials**
3. **Center point trials**

Here, *k* represents the number of independent variables (factors) under investigation. For example, when three factors (*k = 3*) are being studied, the design includes various experimental runs that represent distinct combinations of factor levels. Each experimental point corresponds to a unique condition in the design space, as typically illustrated in a CCD diagram.

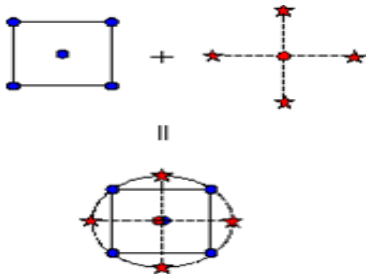


Fig.4.2.1: Generation of central composite design for two factors

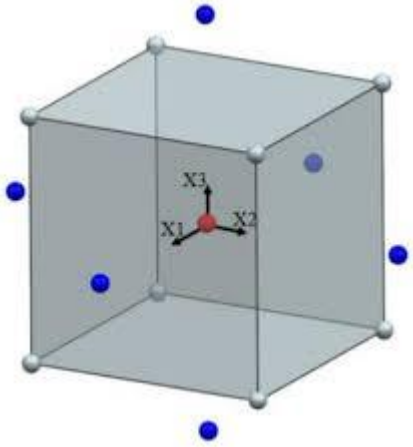


Fig.4.2.2: Visualization of original type rotatable CCD for three factors: X1, X2 and X3.

The centre point, which is the red point at coordinates (0, 0, 0) in a Central Composite Design (CCD), is essential for identifying curvature in the response surface. Estimating the coefficients of the quadratic terms in the regression model is greatly aided by these considerations. When estimating quadratic effects, axial points—usually six blue dots at a set distance, α, from the centre—are also crucial, and factorial points—usually

A cube with side length 2 has eight grey spots at its corners that aid in the estimation of linear coefficients and two-way interaction effects. The CCD structure needs to be expanded into four or more dimensions when working with more than three elements.

In CCD, each factor is studied at three primary levels—low, medium, and high—which correspond to coded values of −1, 0, and +1, respectively. Coded units are the term used to describe these levels. If a factor's actual minimum and maximum values are represented by X_min and X_max, the actual value X corresponding to a coded value can be determined using a linear transformation:

X = b × (coded value) + a

Where;

- **b** is the scale factor
- **a** is the shift factor
- **X** is the actual (uncoded) factor value

To calculate **b** and **a**:

b = 2 / (X_max − X_min)

a = −(X_max + X_min) / (X_max − X_min)

Three primary categories can be used to further classify CCD:

- These include Central Composite Face-Centerd (CCF),
- Central Composite Circumscribed (CCC),
- and Central Composite Inscribed (CCI).

Each type has specific geometrical arrangements suited for different experimental needs.

4.2.1 Central composite circumscribed (CCC): The factor levels in a CCD are ultimately extended to the design space's outer boundaries. Usually organised around corner points, which are shown by red dots in Figure 3, the CCD model forms the central factorial part of the design. New extreme values for each factor are introduced by the axial or star points (green dots) that radiate outward along each axis from the central point (blue). Every element is assessed at five different levels in this arrangement. By adding star points, the range of factor settings is successfully extended beyond the typical lowand high levels, enhancing the model's ability to detect curvature in the response surface.

These designs exhibit circular, spherical, or hyperspherical symmetry, depending on the number of factors, and require five levels per factor to maintain that symmetry. By adding star points to an existing factorial design, the Circumscribed Central Composite Design (CCC) is formed, which is recognized for its rotatability—a desirable property ensuring uniform prediction variance at equal distances from the center point.

4.2.2 Inscribed central composite (CCI): The star points in the Central Composite Inscribed (CCI) design are positioned based on the factors' real limits, which means that the factor levels are constrained to stay inside the designated experimental bounds. The CCI design is essentially a smaller version of the Central Composite Circumscribed (CCC) design. The CCI model is created by compressing the CCC layout by α (alpha) to fit inside the specified bounds. rotatability, a statistical characteristic that guarantees constant prediction accuracy at equal distances from the design centre, is maintained by both CCI and CCC designs.

4.2.3 Face cantered (CCF): This design sets α (alpha) to 1 and positions the star points in the centre of each factorial space face. As a result, each piece requires three layers. Face-Centered Central Composite Designs (CCF) cannot be rotated. Three varieties of Central Composite Designs (CCD) are frequently employed when dealing with two elements. The Central Composite Circumscribed (CCC) design covers the biggest experimental space, whereas the Central Composite Inscribed (CCI) design clearly examines the smallest. The spherical arrangement of the CCC design revolves around the factorial cube.

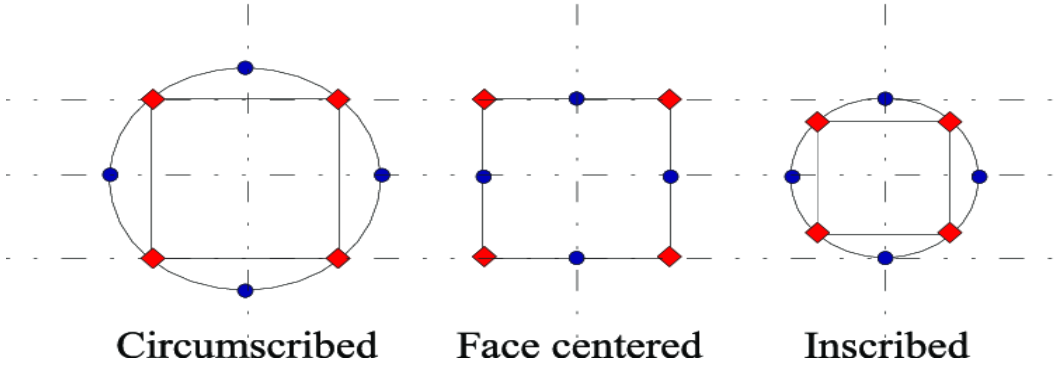


Fig : Comparison of the three types of central composite design

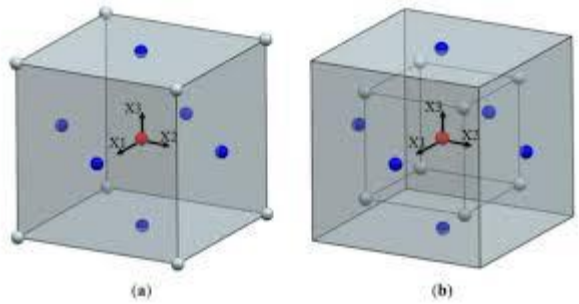


Fig Visualization of (a) face-centred CCD (b) and inscribed CCD for three factors: X1, X2 and X3

4.2.3Applications :

1. **Engineering Applications**: Computer simulation is extensively used in engineering, where engineers must design products and processes. Due to the high cost and complexity of physical experiments, computer models are often employed to simulate physical properties.
2. **Research and Development**: Simulations play a vital role in the research and development sector, supporting innovation and experimentation.
3. **Safety Assessments**: Central Composite Design (CCD) is widely utilized in computer modeling for conducting safety evaluations and risk assessments.
4. **Process Optimization**: Simulation aids in the optimization of operational parameters and process conditions for improved efficiency.
5. **Chemical and Engineering Research**: Both chemical and engineering fields rely heavily on simulation tools for modeling reactions, systems, and processes.
6. **Human Factors Engineering**: Applied research in human factors engineering uses simulation to analyze and improve interactions between humans and systems.

7. **Neural Networks**: Simulation techniques are also applied in training and evaluating neural networks, contributing to advancements in artificial intelligence.

5. Defining Design Space (DS) / Method Operable Design Region (MODR)

Experimental designs utilize a design space to maintain quality control. Within this defined space, no additional regulatory requirements are necessary. However, operating outside this space mandates regulatory approval. Design of Experiments (DOE) is favored because it enhances understanding of the process and product, enables monitoring at each stage, facilitates thorough prior planning, and helps manage process variations. The design space is a multidimensional region that ensures data quality while being constrained by boundaries representing failure limits. Therefore, the analytical method must be validated under various conditions within this space. Design spaces can either be specific to individual unit operations or encompass multiple operations within a single, unified space. They can be established using graphical approaches or numerical techniques such as desirability functions, which optimize output responses to satisfy multiple criteria simultaneously.

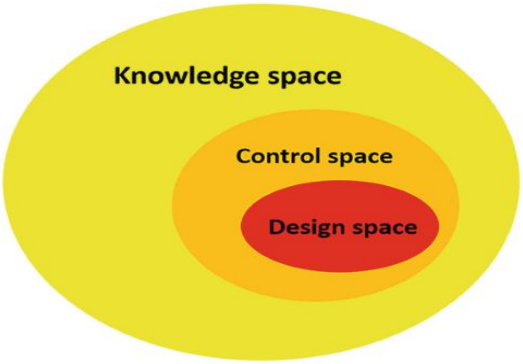
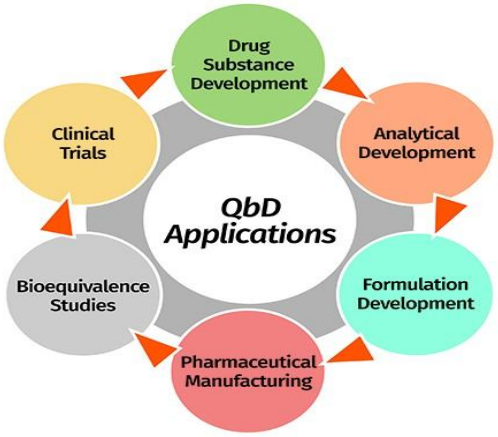


Fig. Defining Design Space

6. PAT (Process Analytical Technique)

The FDA's initiative to implement Process Analytical Technology (PAT) in formulation aims to embed quality directly into products. PAT involves real-time measurement of quality and performance parameters during processing to ensure the final product consistently meets required standards. According to ICH Q8, PAT is used to keep processes within a predefined Design Space, emphasizing science-based quality control to minimize patient risk. PAT helps identify critical process variables that impact product quality and mandates online monitoring of key Critical Quality Attributes (CQAs). Common PAT tools include near-infrared (NIR), infrared (IR), Raman spectroscopy, and turbidity probes. The PAT framework encompasses tools for experimental design, data analysis, process control, and continuous improvement. Process measurements can be classified as at-line, online, or in-line. PAT supports Quality by Design (QbD) by enabling real-time process monitoring and enhancing understanding of the relationship between technology and product quality.

Application Of QbD



Conclusion:

In conclusion, the pharmaceutical industry's implementation of Quality by Design (QbD) aims to lower product variability and flaws, which enhances product development and production effectiveness. By emphasizing robust formulation and process design, defining clear specifications, and leveraging tools such as prior knowledge, risk assessment, and Process Analytical Technology (PAT),QbD facilitates continuous improvement throughout the product lifecycle. This systematic approach strengthens quality assurance, minimizes the need for post-approval modifications, lowers costs, and ultimately supports the creation of safe and effective pharmaceutical products.

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CONFLICT OF INTREST

The authors declare that there is no conflict of intrest.

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