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Quality by Design (QbD): A Comprehensive Review.

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ABSTRACT: In this era of competition quality has been given the prime magnitude and failure to meet such quality allied goals produces massive shift of company in share of market. Pharmaceutical industry needs a regulatory compliance so as to get their product approved for marketing and as the pharmaceutical industry moves toward the implementation of pharmaceutical QbD, a common terminology, understanding of concepts and expectations are necessary. This understanding will facilitate better communication between those involved in risk-based drug development and application review of the drug. This review provides an overview of the modern pharmaceutical quality by design (QbD), clarifies the concept and describes its objectives. Quality-by-design (QbD) is a systematic approach to drug development, which begins with predefined objectives, and uses science and risk management approaches to acquire product and process understanding, and ultimately process control. The prime reason behind adoption of QbD is the regulatory requirements. The application of QbD in the formulation of drug and process design is based on a good understanding of the sources of variability and the manufacture process. It is a cost and time efficient approach in design and manufacturing, with DoE, risk assessment, and PAT as its tools to achieve a better understanding on the materials and processes, which make the QbD approach available and feasible to the pharmaceutical field. With its broad implementation in the pharmaceutical manufacture, drug products with high and reproducible quality can be expected. QbD comprises of a systematic approach with its elements including QTTP, CQAs, CPPs, CMAs, DOE, and control strategy.

[Key Words: Quality by design (QbD), Design of experiment (DoE), Process analytical technologies (PAT), Critical process parameters (CPP), Critical Quality Attributes (CQA), Critical Material Attributes (CMA), Quality risk management (QRM), Design Space (DS)]

I. INTRODUCTION TO QBD

Medicine is well known as special goods and in the pharmaceutical production industries, based on innovation, manufacturing and quality, the product quality is the most important issue.

Quality has been given the utmost importance by all regulatory bodies for pharmaceutical products. Quality means customer satisfaction in the terms of service, product, and process. Multitude of these quality related activities reflect the need for companies to excel in the global competition. Customer demands perfection in quality, reliability, low cost and timely performance of the product or service. Quality assurance is of substantial concern in the pharmaceutical industry, as described by Good Manufacturing Practices (GMP) requirements. This concept should be present throughout the pharmaceutical product lifecycle to ensure product quality and GMP compliance and it includes the management of (among others) equipment, procedures, environment and staff, as well as all kinds of reagents/ materials/references or data and deliverables.[1]

The traditional Quality by Testing (QbT) approach tests product quality by checking it against the already approved regulatory specifications at the end of manufacturing stream at great cost and effort. The development commonly relies on One-Factor-At-a-Time (OFAT) method or the trial-and error approach. The OFAT method is run by selecting a starting point, or baseline set of levels, for each factor, and then successively varying each factor over its range with the other factors held constant at the baseline level. After all the tests are performed, a series of graphs are usually constructed to show how the response variable is affected by varying each factor with all other factors held constant. The major drawback of the OFAT strategy is that it fails to consider any possible interaction between the factors. An interaction is the failure of one factor to produce the same effect on the response at different levels of another factor.[2] There is a prominent deal of

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unpredictability in the scaling up of product from research and development to the production scale and reasons for failure are generally not understood. The failure of products to comply with their specifications can amount to either rejection of the batch or reworking of the batch with increased cost and regulatory burden. Post approval changes even of noncritical nature will need to be preapproved by the regulatory authorities. For critical products, the wastage of a batch can be challenging for a pharmaceutical company especially in the terms of sustaining market competition.

Thus lack of product and process understanding results in a wide communication gap between regulatory bodies and the manufacturing companies which underscores the need for intensive regulatory oversight.

To overcome the limitation of GMP, FDA launched current Good Manufacturing Practices (cGMP) in 2002.[3] The cGMP places emphasis on "software" during the manufacturing, namely management level, and specifies staff's responsibility clearly and precisely. In contrast, GMP attaches a great importance on the qualification and training details of the staff rather than their duties, and these relatively lower requirements are still broadly used in many developing countries. After the cGMP was carried out, there's still another problem, that is, when compared with other industries, such as aircraft, automobile and electronic industries, the specification of pharmaceutical industry is way more rigid and fixed. However, it is not practically possible to keep all the parameters of the entire conditions constant and the environment may vary in small degrees inevitably. Then, the problem is in the approval documents for a new product to be handed over to FDA, the applicant can only write specific number in the report, as 'the authenticity of the process' and 'details' are quite critical in cGMP, it may happen that product's batches fail to meet the rigid specifications. To solve this problem, the FDA and the International Conference on Harmonization (ICH) began to learn from the other industries, and with the aim of improving pharmaceutical drug quality and safety to achieve a desired state for pharmaceutical manufacturing on the basis of scientific and engineering knowledge QbD was introduced into the Chemical Manufacturing Control (CMC) review pilot program in 2004. The function and efficacy of QbD, Design Space and real-time release had been evaluated through the CMC project. This leads to notable transformation in the pharmaceutical quality regulation, to a more scientific and risk-based approach from an empirical process.

Quality by Design (QbD) is defined in the ICH Q8 guideline as 'a systematic approach to development that begins with predefined objectives and emphasizes product and process understanding and process control, based on sound science and quality risk management' 51, which is in accordance with FDA's current drug quality system ideology of 'quality cannot be tested into products; it should be built-in or should be by design.' [4] Quality by design (QbD) is a concept first introduced by the quality pioneer Dr. Joseph M. Juran. Dr. Juran believed that quality should be designed into a product, and that most problems and quality crises relate to the way in which a product was designed in the first place.[5]

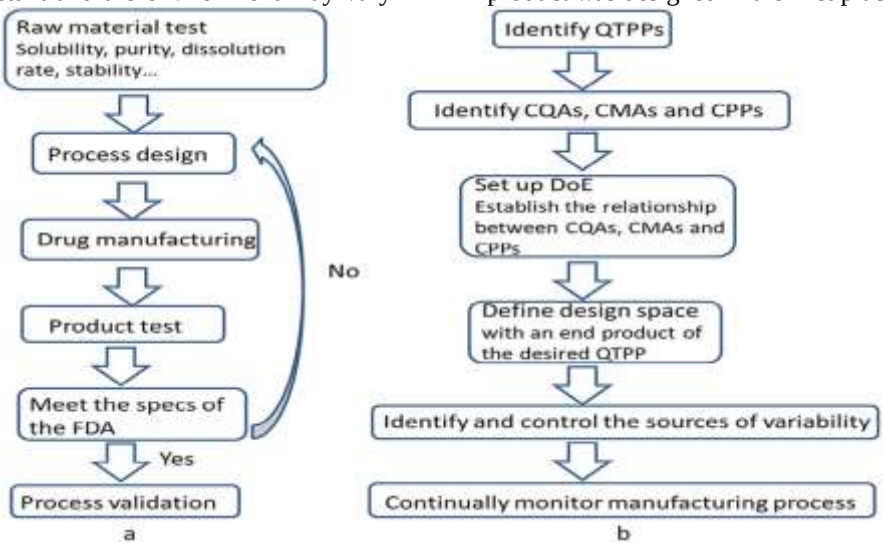

Fig.1 : Comparison between (a) Quality by Testing (QbT) and (b) Quality by Design (QbD)

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Over the years, pharmaceutical QbD has evolved with the issuance of ICH Q8 (R2) (Pharmaceutical Development), ICH Q9 (Quality Risk Management), and ICH Q10 (Pharmaceutical Quality System). In addition, the ICH Q1WG on Q8, Q9, and Q10 Questions and Answers; the ICHQ8/Q9/Q10 Points to Consider document; and ICH Q11 (Development and Manufacture of Drug Substance) have been issued, as have the conclusions of FDA-EMA's parallel assessment of Quality-By-Design elements of marketing applications.[6-11] These documents provide high level of directions with respect to the scope and definition of QbD as it applies to pharmaceutical industry. QbD approach is also a advantageous tool for the submission of INDA, NDA or ANDA in ICH countries.[12]

Generally, QbD approach emphasizes on the design to attain the preferred quality attributes or performances, process parameters that have an impact on the quality of final products, and knowledge for better understandings of the important formulation. In a QbD concept, the regulatory load is not much because there are broader limits and ranges based on the process and product understanding. Currently, QbD is vastly employed in the various industries in order to improve method robustness to close the quality gaps and reduce the failure attempts.[13]

II. ELEMENTS OF QBD

2.1 QTPP (Quality Target Product Profile)

QTPP forms basis of the design for the development of product. It gives information about the drug at a particular time in development, and provides a statement of the overall intent of the drug development program. Generally, the QTPP is organized in accordance with the key sections in the drug labelling and links the drug development activities to specific concepts intended for inclusion in the drug labelling.[14] Hence it can be described as a prospective summary of the quality characteristics of a drug product that ideally will be achieved to ensure the desired quality, taking into account the safety and efficacy of the drug product.[5]

Considerations for inclusion in the QTPP could include the following [6]:

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

Thus, the lack of a well-defined QTPP can result in waste of valuable resources and time. International Society of Pharmaceutical Engineers (ISPE) Product Quality Lifecycle Implementation (PQLI) calls this the Pharmaceutical Target Product Profile.[15] The QTPP is not a specification because it includes tests such as stability or bioequivalence that aren't carried out in batch to batch release. The QTPP should only include the patient relevant product performance. For example, if particle size is critical to the dissolution of a solid oral product, then the QTPP should include dissolution but not particle size. Particle size would be a critical material attribute and would be thus included in the process description and control strategy. The QTPP should not be mechanism based but should be performance based.

QTPP is a definition of product intended use and a pre-definition of quality targets (with respect to safety, efficacy and clinical relevance) and thus summarizes the quality attributes of the product which are required to provide safety and efficacy to the patient.[14]

2.2 CQAs (Critical Quality Attributes)

Identification of the CQAs of the drug product is next step in the development of drug product. They are derived from the QTPP and are used to guide the product and process 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.[6] The CQAs also decide the limit or range for the acceptance of quality product to ensure the expected quality of the product.[16]

CQA can be used to describe the elements of the QTPP (such as dissolution) and also to describe mechanistic factors (such as hardness and particle size) that determine the product performance. Thus CQA is used to express both aspects of product performance and determinants of product performance.[14]

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The quality attributes of a drug product may include the identity, assay, content uniformity, drug release or dissolution, degradation products, moisture content, residual solvents, microbial limits, and physical attributes such as shape, size, color, odor, score configuration, and friability. These attributes can be critical or not critical. Criticality of an attribute is essentially based upon the severity of harm that can occur to the patient if the product falls outside the acceptable range for that attribute. Probability of detectability, occurrence or controllability does not impact criticality of an attribute. [5] CQA is generally assumed to be an attribute of the final product, but it is also feasible to indicate a CQA of an intermediate or a raw material.

2.3 CMAs (Critical Material Attributes)

The CMAs include physical, chemical, biological, or microbiological properties or characteristics of an input material. They are the first category of factors that can cause variability of CQAs and are associated with the composition of formulation preparation.[17] CMAs should be within an appropriate range, limit or distribution to ensure the desired quality of that drug substance, excipient, or in-process material. CMAs can be directly linked to the raw materials and the manufacturing process parameters. Independent CMAs are the best way to provide a mechanistic link of the product quality to the critical process parameters in the manufacturing process of the product. Differentiating between CMAs (properties) and multi-faceted performance tests is part of the movement away from quality by testing (QbT) to quality by design (QbD).

The evolution of ICH Q8 is also consistent with making a distinction between CMA and performance tests.

The 2004 Q8 draft (21) put CQA and performance tests into the same pile of physiochemical and biological properties:

"The physicochemical and biological properties relevant to the performance or manufacturability of the drug product should be identified and discussed. These could include formulation attributes such as pH, osmolarity, ionic strength, lipophilicity, dissolution, redispersion, reconstitution, particle size distribution, particle shape, aggregation, polymorphism, rheological properties, globule size of emulsions, biological activity or potency, and/or immunological activity. Physiological implications of formulation attributes such as pH should also be addressed."

The final version of Q8 (8) made clear that this section would focus on product performance:

"The physicochemical and biological properties relevant to the safety, performance, or manufacturability of the drug product should be identified and discussed. This includes the physiological implications of drug substance and formulation attributes. Studies could include, for example, the development of a test for respirable fraction of an inhaled product. Similarly, information supporting the selection of dissolution vs. Disintegration testing (or other means to ensure drug release) and the development and suitability of the chosen test could be provided in this section."[14]

Defining the CMAs on this mechanistic physical property level makes it the best link to the manufacturing process variables. The CMAs are considered different from CQAs in that the CQAs are for output materials including product intermediates and finished drug product while the CMAs are for input materials including the drug substance and the excipients. The CQA of an intermediate may become a CMA of that same intermediate for a downstream manufacturing step.

As there are many attributes of a drug substance and excipients that can potentially impact the CQAs of the intermediates and finished drug product, it is irrational that a formulation scientist can investigate all the identified material attributes during the formulation optimization studies. Thus, a risk assessment would be valuable in prioritizing which material attributes mandate a further study. A material attribute is critical when a change in that material attribute can have an impact on the quality of the output material. Product understanding includes the ability to link the input CMAs to the output CQAs.

2.4 CPPs (Critical Process Parameters)

CPPs are the second category of potential factors likely to cause variability of CQAs and these are linked with the manufacturing process of the formulations.[16] These parameters are monitored before or in process that influence the appearance, impurity, and yield of final product quality significantly.[18] Process parameters are referred to as the input operating parameters (e.g., flow rate and speed) or process state variables (e.g., pressure and temperature) of a process step or unit operation. A parameter is critical when a realistic change in that parameter can cause the product to fail to meet the QTPP and has a significant effect on the product quality. The most definitive way to

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identify critical and noncritical parameters is by the scientific investigations that involves controlled variations of the parameters. The focus in the process development report is on the additional studies that build this knowledge. These studies can be conducted on pilot scale or lab scale and it does not need to be conducted under cGMP. When sensitivity of a process parameters is established, this can be used to design the appropriate control strategies. Because of broadness of the CPP definition it is possible for two investigators to examine the same process and come to a different set of CPP. The set of CPP is not unique, but the chosen set must be sufficient to ensure product quality.[14]

While the process design and understanding includes identification of CPPs and a thorough understanding of scale-up principles, linking CMAs and CPPs to CQAs is of a very special importance. From the viewpoint of QbD, CMAs and CPPs can vary within the established Design Space without any significant influence on CQAs, and as a result, the quality of final product will meet the QTPP.

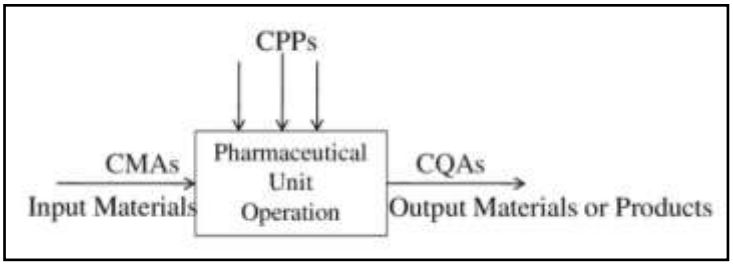

Fig.2 : Link between input critical material attributes (CMAs) and critical process parameters (CPPs) to output critical quality attributes (CQAs) for a unit operation

III. TOOLS OF QBD

The concept of QbD has two components – the science of manufacturing and the science underlying the design. Upon understanding the elements of QbD and the steps for QbD implementation, it is important to be intimate with the commonly used tools in QbD, including risk assessment, design of experiment (DoE), and process analytical technology (PAT)

3.1. Risk assessment

Risk is defined as the combination of probability of the occurrence of harm and the severity of that harm. Risk assessment helps to increase quality of method or process.[19] Risk assessment is a systematic process of organizing information to support a risk decision to be made within a risk management process. Also it is determinant for effect of input variable on the method or processes. From risk assessment one can recognize the critical attributes that are going to affect final quality of product. A risk assessment is helpful for the effective communication between FDA and industry, research/development and manufacturing and among multiple manufacturing sites within company. It comprises of identification of hazards, and the analysis and evaluation of risks which associated with the exposure to those hazards. It is the first step of quality risk management process; the others are risk control and risk review. Risk control includes decision making to reduce and/or accept the risks, it's objective is to reduce the risk to an acceptable level. At the final stage, the results/output of the risk management process are reviewed to take into account the new experience and knowledge. Throughout the risk management process, risk communication, the sharing of information about risk and risk management between the parties (including industry and regulators, industry and the patient, within a company, industry or regulatory authority, etc.), should be ongoing at any stage of the process of risk management. The included information might relate to the nature, existence, severity, probability, form, acceptability, detectability, control, treatment, or other aspects of risks to quality.

Principles of quality risk management are: [19]

- Evaluation of the risk to quality which eventually links to protection of the patient based on scientific knowledge
- Adequate effort taken; formality and documentation of the quality risk management process should be done in accordance with the level of risk involved.

There are three components of risk assessment, that is, risk identification, risk analysis and risk evaluation.[7]

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1) Risk Identification: The systematic use of information to identify the potential sources of harm (hazards) that are referring to the risk question or problem description, which can include theoretical analysis, historical data, informed opinions, and the concerns of stakeholders.
2) Risk Analysis: The estimation of the risk associated with identified hazards.
3) Risk Evaluation: The comparison of the estimated risk to given risk criteria using a qualitative or quantitative scale to determine the significance of risk.

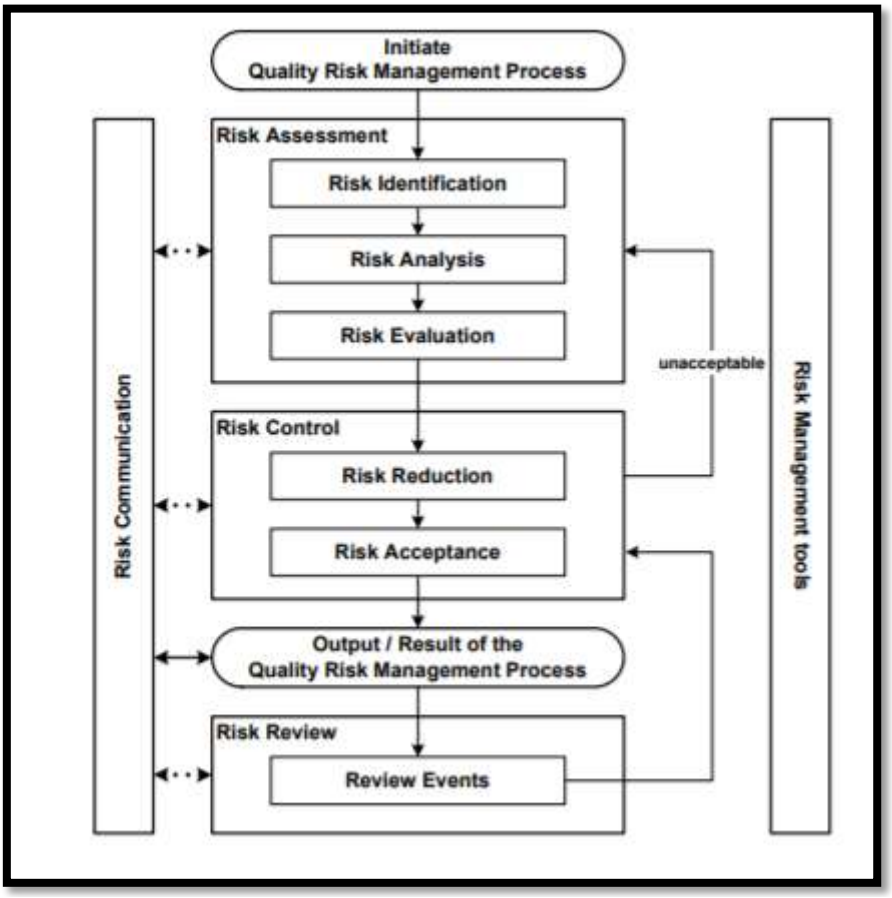

Fig.3 : Quality Risk Management

The above components aim at giving answers to the following three questions in the pre-formulation study, [7]

1. What might/can go wrong?
2. What is the likelihood (probability) that it will go wrong?
3. What are the consequences (severity)?

The evaluation of the risk to quality should be based on scientific knowledge and ultimately link to the protection of the patient, the level of effort and formality.[6,7]

Risk management is joint responsibility of quality unit, business development, engineering, regulatory affairs, production operations, sales and marketing, legal, statistics and clinical department.[24]

ICH Q9 provides a non-exhaustive list of 9 common risk management tools as follows : [7]

1. Basic risk management facilitation methods (Ishikawa fishbone diagram, flowcharts, checks sheets, etc.)
2. Fault tree analysis (FTA)
3. Failure mode and effects analysis (FMEA)
4. Failure mode, effects, and criticality analysis (FMECA)
5. Hazard analysis and critical control points (HACCP)
6. Hazard operability analysis (HAZOP)
7. Preliminary hazard analysis(PHA)
8. Risk ranking and filtering
9. Supporting statistical tools.

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It might be appropriate to adapt these tools for use in specific areas that are pertaining to the drug substance and the drug product quality. In accordance to the implementation of QbD, risk assessment has the priority over DoE. Among the tools, Ishikawa fishbone diagram and FMEA are widely used approaches for risk assessment, either separately or in combination.[20,21]

The risk factors in fishbone diagram are classified into broad categories, while the FMEA could identify the failure modes that have the highest chance of causing the product failure, which means each of the factors in the Ishikawa fishbone diagrams will be ranked later in FMEA analysis. FMEA method can be used to perform an quantitative risk assessment, identifying the CQAs that have the highest chance of causing product failure. The outcome of an FMEA analysis are risk priority numbers (RPN) for each combination of the failure mode severity, occurrence probability, and the likelihood of detection. [18]

Rank order scores on the basis of its severity, detectability, and occurrence of risk are assigned to the critical material attributes (CMAs), ranging between 1 and 10 each, to calculate the risk priority number (RPN) as per the formula given below.[22]

$$\text{RPN} = \text{Severity(S)} \begin{pmatrix} 5 \\ 4 \\ 3 \\ 2 \\ 1 \end{pmatrix} \times \text{Occurrence(O)} \begin{pmatrix} 5 \\ 4 \\ 3 \\ 2 \\ 1 \end{pmatrix} \times \text{Detectability(D)} \begin{pmatrix} 5 \\ 4 \\ 3 \\ 2 \\ 1 \end{pmatrix}$$

where the first parameter **S** is **severity** which measures how severe would be the effect which a given failure mode would cause. The parameter S was ranked as 5- catastrophic; 4 - critical; 3 - serious; 2 - minor; and 1- negligible or no effect.

The next parameter **O** is the **occurrence probability** which analyzes the likelihood of an event to occur. The parameter O was ranked as 5 - frequent; 4 - probable; 3 - occasional; 2 - remote; and 1 - improbable to occur.

The last parameter **D** is **detectability** which denotes the ease with which a failure mode can be detected and was ranked 1 - easily detectable; 2 - highly detectable; 3 - moderately detectable; 4 - low or remotely detectable; and 5 - hard to detect or absolutely uncertain. [23]

Thus, higher the detectable a failure mode is, the lesser would be the risk (also risk-rank) to product quality

Once the risk is assessed it is grouped into three categories.[24]

1. High-risk factors that should be stringently controlled, typical high-risk factors that can be fixed at the time of method development that includes data analysis methods and sample preparation methods.
2. Potential noise factors,
3. Factors that can be explored experimentally to determine acceptable ranges.

3.2 DoE (Design of Experiments)

Statistics is a mathematical science pertaining to collection, analysis, interpretation and presentation of the data, which is applicable to a wide variety of academic disciplines. DoE also known as Statistical experimental design, is the methodology of how to plan and conduct experiments in order to extract the maximum amount of information with the lowest number of analyses or experiments. A designed experiment is a tool or set of tools that is used for gathering test data.

Typical characteristics of an experimental design are planned testing, data analysis approach, simultaneous factor variability and scientific approach.[25]

In the beginning of the twentieth century, British Statistician Sir Ronald Fisher introduced the concept of applying statistical analysis during the planning stages of research rather than at the end of experimentation. Although developed primarily for agricultural purposes, Fisher highlighted the need to consider statistical analysis during the planning stages of research rather than at the final phases of experimentation. As he emphasized in his famous quote: “to consult the statistician after an experiment is finished is often merely to ask him to conduct a post mortem examination. He can perhaps say what the experiment died of”. [26]

DoE is an excellent tool which allows pharmaceutical scientists to systematically manipulate the factors according to a pre-specified design. A good design is based on sound cognition of the product and the effective management of whole process during manufacturing. DoE studies work together with mechanism-based studies to attain better product and process understanding. [18]

The design of experiments includes a series of applied statistics tools used to systematically classify and quantify cause and-effect relations between variables or input factors (xi – independent variables) and output responses (y – dependent variables) through the establishment of mathematical models (y = f(xi)) in the studied

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process or phenomenon, which may result (if that is the objective) in finding the conditions and settings under which the process becomes optimized.
Such relationships permit the:

- determination of the most prominent factors (CPPs) among the useful many;
- identification of optimum factor settings leading to better product performance and assuring CQA values lying within specifications with minimum variability;
- elucidation of interactions between the factors, an important advantage over the conventional way of experimentation, where each factor is studied independently of the others (One-Factor-At-a-Time or OFAT experimentation). [26]

These relationships allow mapping of process behaviour at different factor levels, known as design space, i.e., the multidimensional combination and interaction of input variables (e.g., material attributes) and process parameters that have been demonstrated to provide assurance of the product quality.[6]

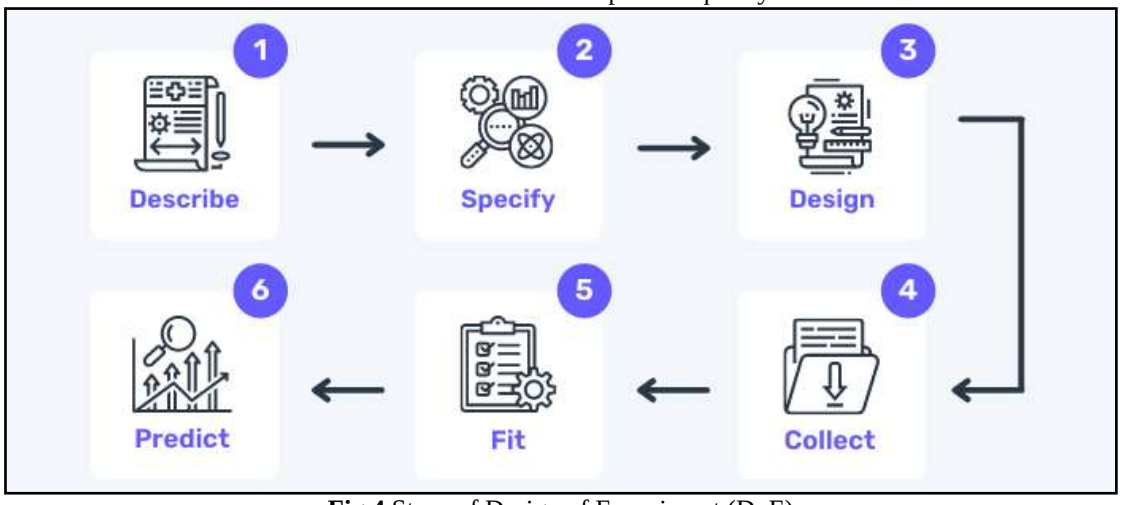

Fig.4 Steps of Design of Experiment (DoE)

Well-established general guidelines and procedures are available to support implementation of the DOE methods. These steps include defining the objectives and the response variables, determining factors, levels, experimental design type and the experiment execution. Variables in the DOE such as the number of factors, the levels, and the logic to select them usually depends on type of investigation (screening, characterization, or optimization), process type and available resources.[27] DOE can be viewed as being composed of a series of steps: the planning, the execution of experiment, and the analysis of collected experimental data using the various statistical methods in order to draw objective and valid conclusions.

Each DOE starts with the selection of process/system and recognizing the investigation problem. The problem statement then leads to establishment of the objectives based on which the performance indicator (response variable) needs to be defined. The response variable should represent a quantitative measure of system behaviour. As an essential step in the whole process, the factors affecting the performance indicator and how they are discretized, the number of experimental runs, and a suitable array need to be defined in the second stage.[28] The next stage covers the performance of the experiment according to the designed array and collection of data. The last step includes data analysis using statistical tools (ANOVA and associated statistical methods) and interpretation of results, leading to a better understanding of system behaviour or its optimization.

There are 4 interrelated steps in building a design:[29]

1. Define the objective
2. Define the variable that will be controlled during experiment and their level /ranges of variation.
3. Define the variable that will be measured during experiment-Response variable
4. Choose among the variable standard design-the one that is compatible with the objective.

DoE is a reasonable method for determining the relationship between the inputs and

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the outputs of a process. It can help to identify the optimal conditions, CMAs, CPPs, and, ultimately, the Design Space. It is wise to establish a Design Space through DoE for the multivariate experiments. ICH Q8 defines the 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."[6]

The selection of experimental design and formulation or process factors are the key elements in regard to achieving the objective of the study. The domain of the study needs to be demarcated within the levels of the factors selected, realistically and the extrapolations beyond the data space is not generally permitted. However, all variables cannot be controlled and can have a considerable effect on the outcome of the experimental design. Hence, while selecting an appropriate study design, either both systematic and random variable should considered or that the variables are sufficiently controlled and do not have an impact on the study design is assumed and hence not be incorporated into the design. Depending on the number of variables to be considered and the levels of variables, appropriate screening designs should be selected to minimize the number of experiments which also directly or indirectly minimizes the cost and on the other hand provides information to the greatest extent possible.[30]

3.2.1 SCREENING DESIGNS

A 'screening design' refers to an experimental design which can be applied when a large number of potential causative factors have to be examined, to identify the most important factors that may have an effect on one or more of the responses of interest. This will reduce the number of factors to be investigated in the further experimentations. In order to eliminate unimportant factors before investing money and time in a more elaborate experiment, screening should be performed.[31]

The screening design has valuable features such as:

- It helps to improve quality control process by determining the upper and the lower control limits of a certain variable.
- Process can be refined by the identification of the influencing factors in a less expensive way.
- Minimizes the number of experiments while maximizing the information.
- Another feature is that the quality of product can be improved through a structured approach, while maintaining the ideas and information in an understandable and readable format.
- Results can be checked in an efficient and reliable manner as it is a mathematical expression and the information gained can be used to optimize a process, and the repeatability of a process can be maintained.

The strategy which is followed in all screening experiments is as follows:[25]

1. Identification of the need to run a screening design.
2. Determination of the practicality of number of runs – the trade-off between the information gained versus the expense of the experiments.
3. All the variables are noted and feasibility performed.

A screening run is the one which isolates the input factors that are most important to the output. Output could be from the software used for screening designs and the researcher's own knowledge of system, with the cost factors in mind. This leads to the elimination of those factors which are deemed to be of minor significance to the desired output, based on the results of the screening experiments.

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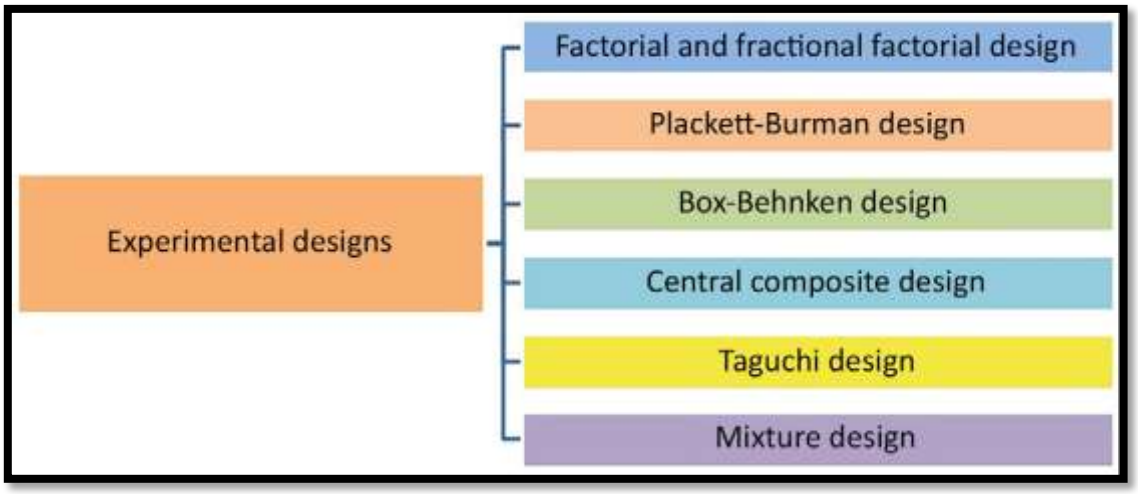

Fig. 5 Commonly used experimental designs

3.2.1.1 Factorial Design

In a factorial design, the levels of factors are varied independently at two or more levels. The effects can be attributed to the factors and their interactions can be assessed efficiently. The simplest of these designs are the 2K full factorial designs which evaluate k factors at two levels, usually "low" and "high" levels. Hence, a two factor, the two-level factorial design will consist of four experiments and as the factors increase to 3, 4, 5, and 6 it consists of 8,16, 32, and 64 experiments. The levels of the factors are represented by (-) minus for lower level and (+) plus for a higher level. A zero level is also sometimes included, to represent the centre or mid-value of the variable.

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

Fig. 6 Example of a 2×2 Factorial Design

3.2.1.2 Plackett-Burman Designs

The Plackett-Burman designs are a part of fractional factorial designs, developed by mathematicians R.P. Placket and J.P. Burman in 1946. These designs are used to identify the most important formulation or process factors at the early stage of experimentation when complete knowledge about the system is not available. These designs should be used to study the main effects when two-way interactions are expected to be negligible. The Plackett-Burman designs are an excellent way to study many factors in minimal experiments, thus finds use in screening factors. Their main feature is that they all involve 4n experiments,

where n¼1, 2, 3…, n. The maximum number of factors that can be evaluated is 4n_1, that is, in an eight-experiment Placket-Burman design, only seven factors can be studied

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

Fig. 7 Example of a 12 Run Placket-Burman design.

3.2.1.3 Central Composite Design

It is a progression of factorial design and is also known as the Box-Wilson central composite designs and finds use in response surface design and optimization. It includes factorial or fractional factorial design, experiments at centre, and experiments at axes (axial points) as part of design. In central composite design, if the distance from centre point to fractional point is equal _1. Then, the distance from central point axial point will be >1 and it is the same in case of all axial points (if the value is less than one, then axial point lies inside the cube). Central composite design deals with extreme high and low values. To minimize the variations related to regression coefficients along with estimation of block effects independently orthogonally blocked designs are utilized. Number of factors, number of experiments, and the fraction chosen decides the number of orthogonal blocks. Rotatable designs provide the preferred property of constant prediction variance at all points that are equidistant from the design centre, thus improving the quality of the prediction. They are especially useful in sequential experiments previous factorial experiments can be modified by adding axial and centre points.

Central composite designs are mainly classified into three types, namely:

- Central composite circumscribed (CCC),
- Central composite inscribed (CCI), and
- Central composite face centred (CCF).

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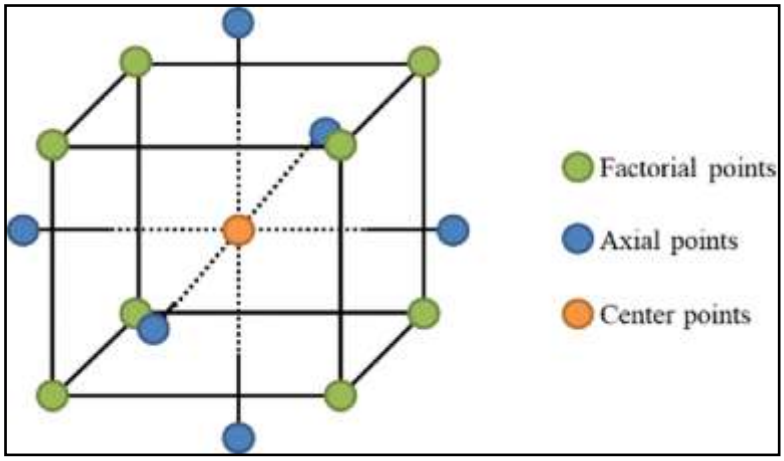

Fig. 8 Example of CCD for 3 factors representation

3.2.1.4 Box-Behnken Design

The BBD was developed by George E. P. Box and Donald Behnken in 1960, it is a class of rotatable designs or nearly rotatable designs. Only three levels for each factor are used and the domain lies within the original factorial shape. The design is represented by a cube as shown in Fig. 9 but experimental points are at the midpoint of edges of process space rather than at the corners and centres of the faces i.e.√2, i.e. 1.414 e.u. from the centre. Factors are subjected to process of coding and are expressed in experimental units or e.u. Coding is an analogous procedure which brings all the factors in the same range. For example, for a two-level experiment, the lower level is designated as -1 and the higher level as +1, thus for a factor, the range is 2 e.u. Use of this permits the interpolation and allocation of central point (0,0) in the design. Thus, the central point will be 1 e.u. N¼2k (k_1)+C0 defines the number of experiments required for the BBD as optimization technique, where N is number of experiments, C0 is number of central points, and k represents the number of factors.

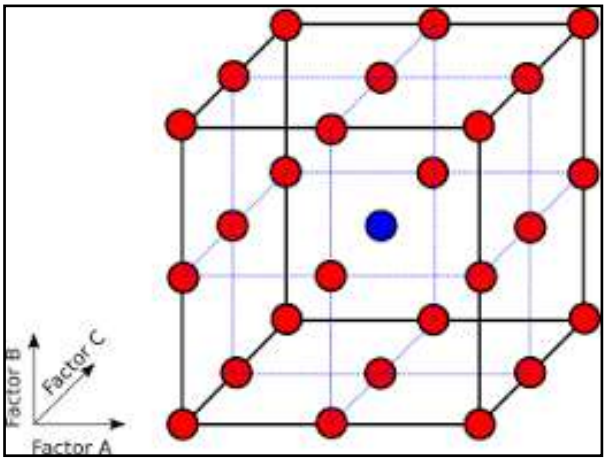

Fig. 9 Example of BBD for 3 factors representation

3.2.1.5 Taguchi Design

These experimental designs proposed by Japanese engineer Genichi Taguchi is an array of statistical techniques used to improve the quality of a product and to ensure the reliability of a process. It utilizes two, three, and mixed level fractional factorial designs. These designs are based on the fact that not all factors that cause variability can be controlled. Factors other than controllable factors are called noise factors (uncontrollable). Taguchi designs are useful in identification of controllable factors (control factors) that minimize the effect of the noise factors.[32] During experimentation, noise factors are varied forcing variability to occur. Based on this optimal control factor settings are selected, leading to a robust process or product.

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To make experiment cost effective and within minimum time, Taguchi design is very useful. Taguchi estimates the factors affecting response mean and variation by concentrating mostly on the main effects. It utilizes an orthogonal array which balances factor levels which are weighted equally. By orthogonal arrays estimation of one factor is not effected by other factor, in this design each factor is assessed independently of all other factors.

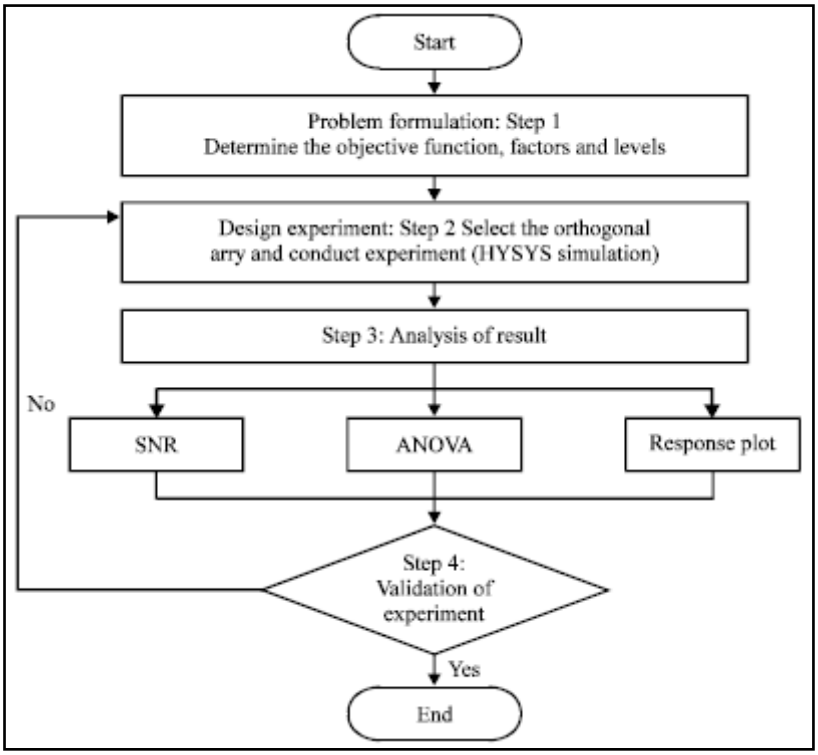

Fig. 10 Flow diagram of Taguchi Method

RUN	Control factor and levels		
	A	B	C
1	1	1	1
2	1	2	2
3	1	3	3
4	2	1	2
5	2	2	3
6	2	3	1
7	3	1	3
8	3	2	1
9	3	3	2

Fig. 11 A basic Taguchi L9 orthogonal array

3.2.1.6 Mixture Designs

Mixture designs are one of the response surface experiments where component of mixture are the factors and the function of each ingredient is considered as a response. The sum of all ingredients is a constant total, which is equal to 100% or 1. The constant total represents a constraint on the mixture experiments that indicates independence among all factors. The mixture factors or the formulation factors which have an impact on the formulation and whose proportions are to be varied in the experiments.

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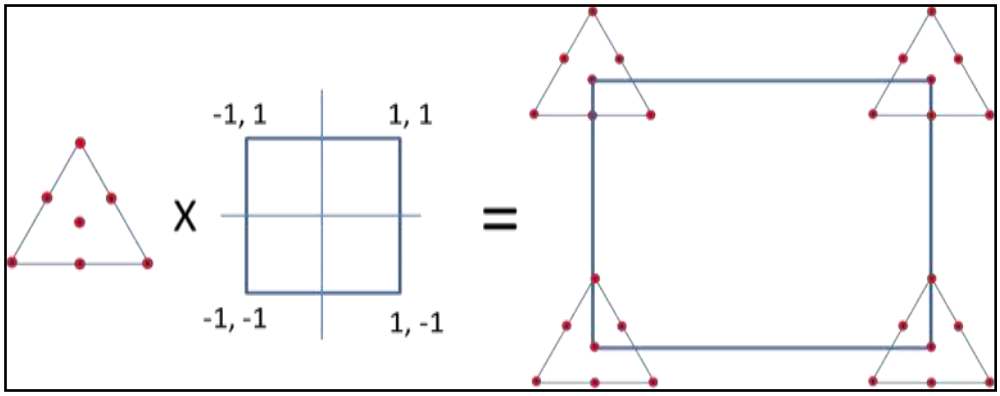

Fig. 12 Example of a simplex lattice design which gives us 7 points, and performing each of those at the 4 combinations for the process variables which ends up giving a total of 28 points in the design.

3.2.2 Choice of experimental design

The most important part of a DoE process, choosing an appropriate experimental design, is critical for the success of the study. The choice of experimental design depends on a number of aspects , including the nature of the problem and/or study (e.g., a screening, optimization, or robustness study), the factors and interactions to be studied (e.g., four, six, or nine factors, and main effects or two-way interactions), and available resources (e.g., time, labour, cost, and materials). Using previous knowledge of a product or previous experiments to identify possible interactions among the input process parameters before performing an experiment also plays a key part in selecting an appropriate experimental design.[29]

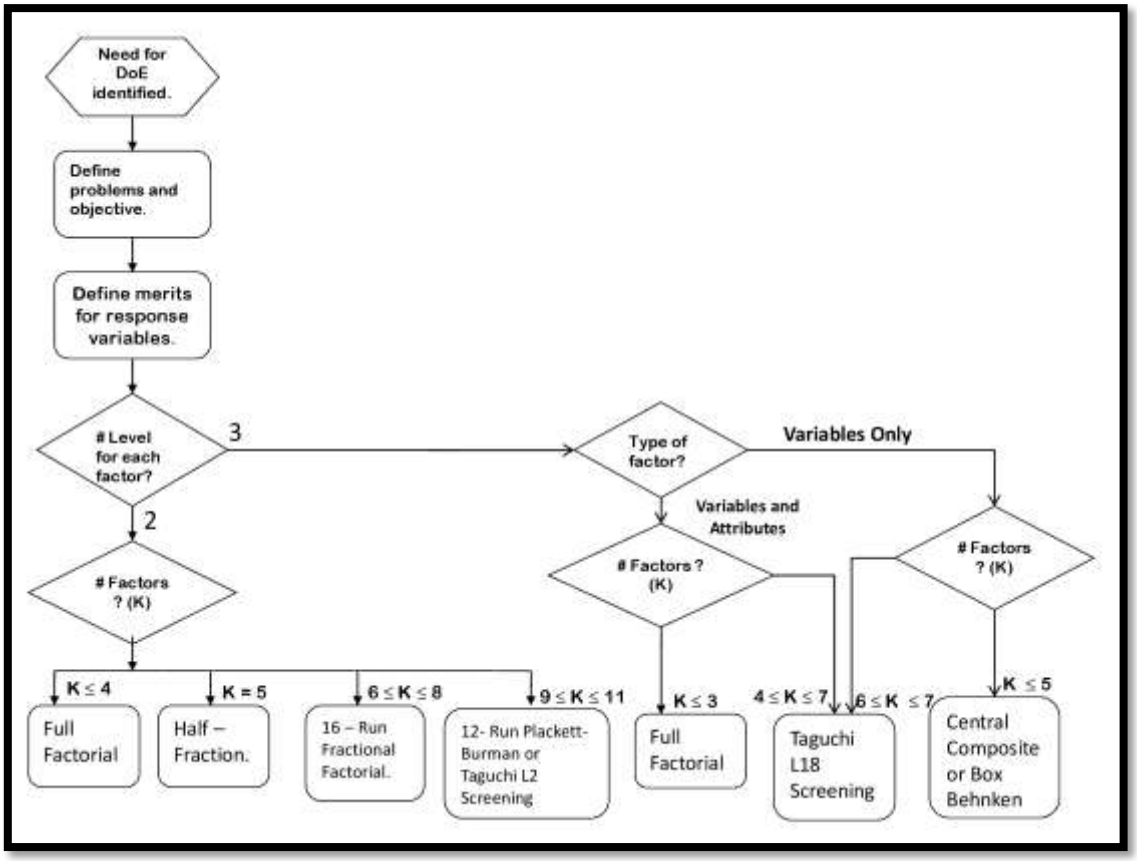

Fig. 13 Decision tree for choosing an Experimental Design

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3.2.3 Defining Design Space (DS) / Method Operable Design Region (MODR)

Experimental designs work on the basis of setting up of a design space. Working within the design space does not need any separate guidelines, but once the formulation designer steps out of the design space, a post-marketing changes approval needs to be taken from the regulatory agency. The reason why DOE is being preferred both by scientists and also the regulatory agencies is because it helps in increasing the knowledge about the process and product; keeps a regular track of the process at every stage; prior planning is easy and if there are any shifts in process during the run, they can be regulated has been defined as a multidimensional space which includes any combination of the variables that have been demonstrated to provide assurance of quality of the data produced by the method. The DS is limited by the so-called edges of failure, outside which method performances are not acceptable. Thus, the analytical method should be designed and validated not only under one fixed condition, but under a range of conditions.

It is possible to either "establish independent Design Spaces for one or more unit operations, or to establish a single Design Space that spans multiple operations".[6]

Design space region may be obtained by graphical optimization from overlaid counter plots of output responses (Ys) as functions of input factors (Xs) (Figure 14). Alternatively, the multiple response optimizations may be estimated by numerical techniques of desirability functions. Desirability functions are usually design to achieve different criteria, for example to maximize, minimize, and target optimization of the output responses (Figure 15) [33]

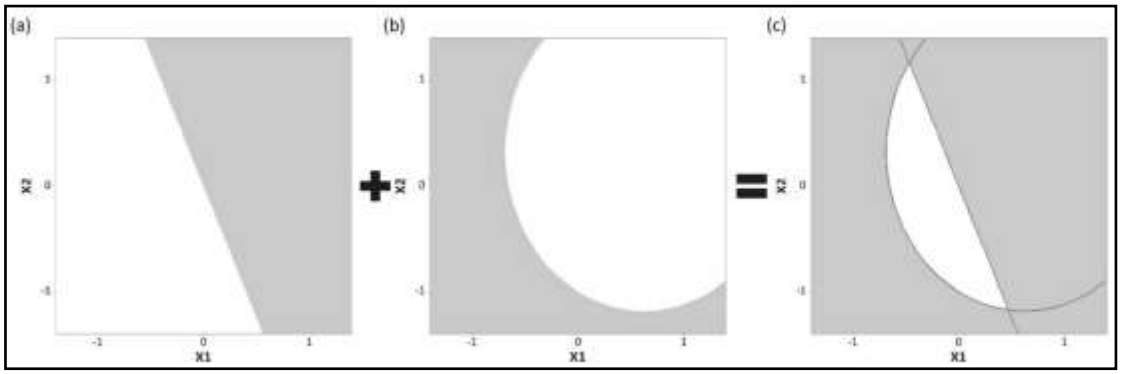

Fig. 14 – Design space (white regions) obtained from counter plot of output response Y1 (a), from counter plot of output response Y2 (b), and from overlaid counter plot of output responses Y1 and Y2 (c) as function of input factors X1 and X2.

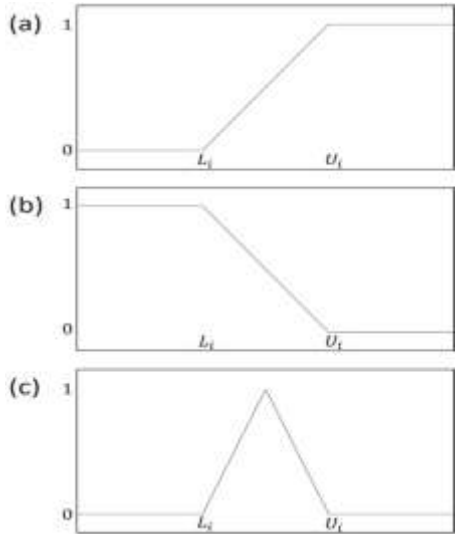

Fig. 15 – Desirability functions to maximize (a), minimize (b), and target optimization, usually used in multiple response optimization.

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Fig. 16 Defining Design Space

3.2.4 Advantages of the DoE:

- Helps to handle experimental error.
- Helps to determine the important variables that need to be controlled and find the unimportant variables that need not be controlled.
- Eliminates the confounding of effects whereby the effect of design variables is mixed up.
- Helps to measure interactions, which is very important.
- Allows extrapolation of data and search for the best possible product within the test variable ranges.
- Allows plotting graphs to depict how variables are related and what level of variables give the optimum product. Use of statistical models shows us the interrelationship between variables.

3.2.5 DoE Software

Good DoE software helps users follow the regressive modelling approach. It should guide them in carefully choosing model terms on the basis of graphical tools and statistics, and it should verify a model and its significance based on statistics in addition to verifying unaccounted residuals. Graphical tools play a key part in understanding and presenting statistical analysis results, so make sure that they deliver a smart way to diagnose, analyse, predict, and present the results in two and three dimensions.

Some examples of commonly used such software are:

- ❖ Design Expert
- ❖ Minitab
- ❖ Chemoface
- ❖ Develve
- ❖ DOE++
- ❖ EXSTAT
- ❖ Statgraphics Centurion

3.3 Control Strategy

As per ICH Q11, "Control Strategy is designed to ensure that a product of required quality will be produced consistently."

A control strategy can include: [11]

- Control of input material attributes (e.g., raw materials, packaging materials, and in-process materials) which have impact on process ability or product quality.
- Finished product specification(s).
- Controls for unit operations that have an impact on downstream processing or product quality (e.g., the impact of size reducing technique, particle size on drug release).
- In-process or real-time release testing instead of end-product testing (e.g., measurement and control of CQAs during processing example: temperature).

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Fig. 17 Strategy control and improvement

3.4 PAT (Process Analytical Technique)

The FDA's initiative to involve process analytical technique (PAT) in formulation process because it believes "the quality cannot be tested into products but it should be built in or should be designed." PAT is defined as "Tools and systems that utilize real-time measurements, or rapid measurements during processing, of evolving quality and performance attributes of in-process materials to provide information to ensure optimal processing to produce final product that consistently conforms to established quality and performance standards". ICH Q8 identifies the use of PAT to ensure that the process remains within an established Design Space. The concept originates from the desire of the regulators to shift control of product quality toward a science-based approach that explicitly attempts to reduce the risk to patients by controlling the manufacturing based on explicit understanding of the process. It is useful in designing, analyzing, and controlling the manufacturing process by utilizing engineering and scientific principles. PAT is used for identification of the process variables which affect the quality of product. For enhanced robustness and improved control over the process, there is a need of online monitoring of some CQAs. Some of the commonly used PAT tools include near infrared, infrared, Raman, focused beam reflectance measurement, and turbidity probes. Multidimensional spectral data generated by PAT are needed to be analyzed by data analysis tools and multivariate data acquisition.[34]

From a PAT standpoint, a process is considered well understood when :[18]

1) All critical sources of variability are identified and explained;
2) Variability is managed by the process; and
3) Product quality attributes can be accurately and reliably predicted.

For the understanding of scientific, risk-managed pharmaceutical development, manufacture, and quality assurance, many tools are available in the PAT framework. They can be categorized into four classes according to the PAT guidance:[4]

(1) Multivariate tools for design, data acquisition and analysis;
(2) Process analyzers;
(3) Process control tools;
(4) Continuous improvement and knowledge management tools.

As defined by FDA's PAT guidance document, whether to remove the sample or not, process analysis can be divided into three categories, namely at-line, on-line and in-line:[4]

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(1) Atline: Measurement where the sample is removed, isolated from, and analyzed in close proximity to the process stream;
(2) Online: Measurement where the sample is diverted from the manufacturing process, and may be returned to the process stream;
(3) In-line: Measurement where the sample is not removed from the process stream and can be invasive or non-invasive.

It is apparent that PAT is effective in helping QbD implement. It can do the job of real-time monitoring of the process without interruption to get the technological parameters and material parameters on-line. PAT enhances understanding of technology (including the relationship between CQA and CPP), which leads to accomplishment of quality improvement and register simplification.

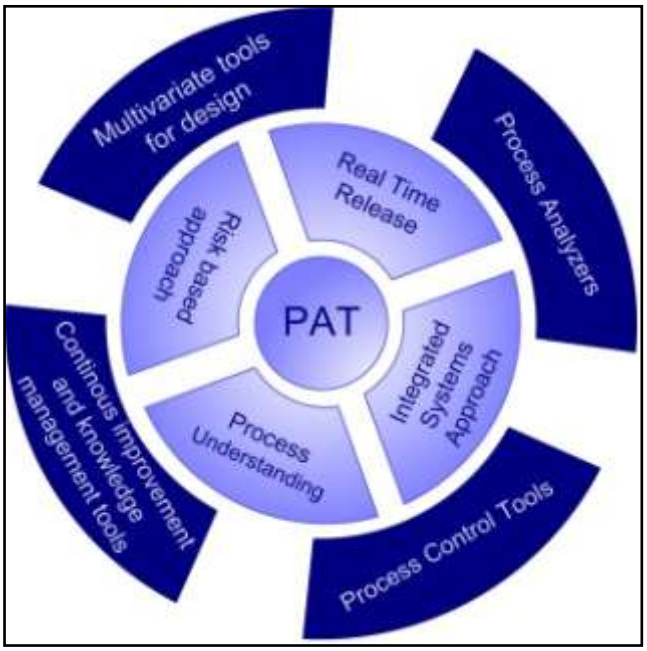

Fig. 18 Industrial perspective of Process Analytical Technique (PAT)

3.4.1 Advantages of PAT

• Improves process safety by detecting the unstable intermediates during process.
• Improves product quality and robustness.
• Prevents the rejection of batches.
• Reduces cost by significant reduction in the sampling and analysis.
• Increases automation of process for better control during the process.

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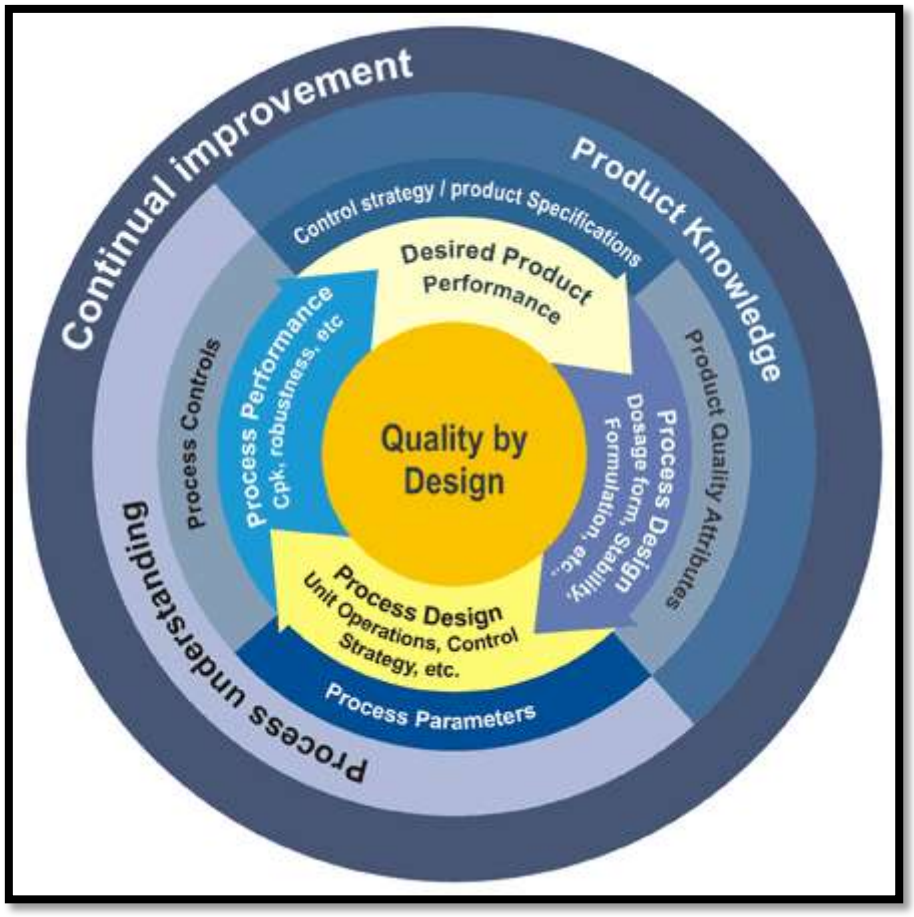

Fig. 19 Overview of QbD

4.1 Advantages of QbD can be summarized as,

- Patient safety and product efficacy are the primary focused.
- Better understanding of the process.
- Real-time controls (fewer batch controls) and realistic risk perceptions.
- Science based risk assessment is carried, and there is implementation of more efficient and effective control of change which minimizes batch failure. And the innovative process validation approaches leads to less validation burden.
- It provides wider acceptability by regulatory agencies. If the composition or process parameters remain within the design space, then resubmission for the post-approval changes is not required and thus reduces cost.
- Uniformly improves the overall life cycle of the product (i.e., controlled, and patient guided variability) and it also provides a space for invention of new techniques by continuous improvement throughout life cycle.
- Improves the yield at lower cost with fewer investigations, reduced testing, etc.
- QbD also provides efficient technology transfer data which helps in easy transfer from bench to the manufacturing site.
- The developed method will be more robust which gives greater level of confidence in case of variations in conditions, and also offers greater regulator confidence in final product.
- Provides screening and identification of critical parameters using risk based approach.
- Contributes substantially to realize the safer and beneficial options.
- Returns on investment/cost savings.

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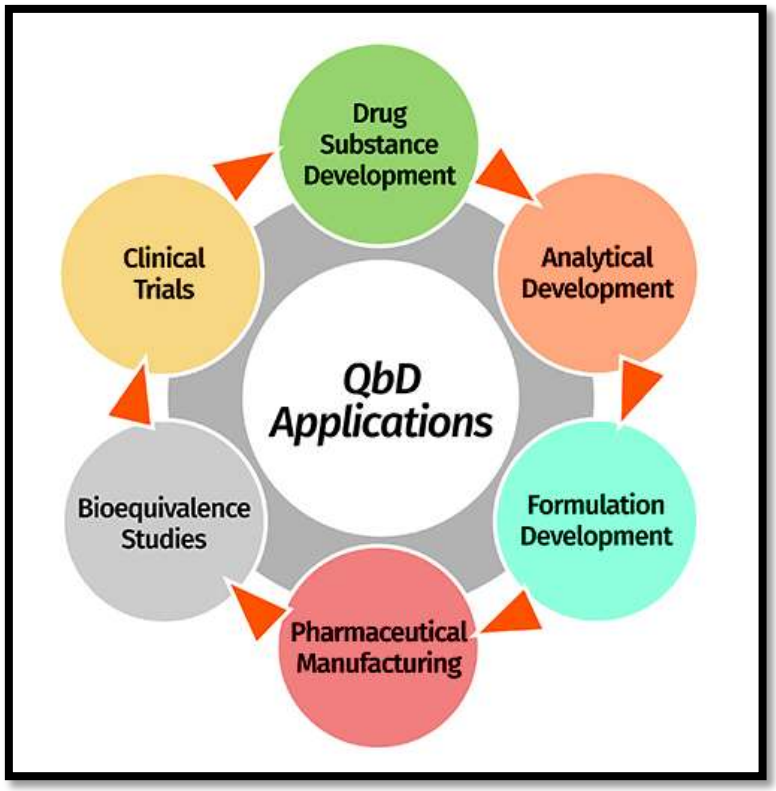

Fig. 20 Applications of QbD

QbD can be applied for various analytical methods which include,[71]

- Chromatographic techniques like HPLC (For stability studies, method development, and determination of impurities in pharmaceuticals).
- Hyphenated technique like LC–MS.
- Advanced techniques like mass spectroscopy, UHPLC, and capillary electrophoresis.
- Karl Fischer titration for determination of moisture content.
- Vibrational spectroscopy for identification and quantification of compounds e.g. UV method.
- Analysis of genotoxic impurity.
- Dissolution studies.
- To biopharmaceutical

IV. CONCLUSION:

Nowadays, much of the scientific basis is already in place for the implementation of QbD. The goal of implementing pharmaceutical QbD is to reduce product variability and defects, thereby enhancing product development and manufacturing efficiencies and post-approval change management. It is achieved by designing a robust formulation and manufacturing process and establishing clinically relevant specifications. The key elements of pharmaceutical QbD includes the QTPP, product design and understanding, process design and understanding, and continual improvement. Prior knowledge, risk assessment, DoE, and PAT are tools to facilitate QbD implementation. Finally, product and process capability is assessed and continually improved post-approval during product lifecycle management. In QbD, product and process understanding is the key enabler of assuring quality in the final product and process. QbD has huge importance in the area of pharmaceutical processes like drug development, formulations, analytical method and biopharmaceuticals. QbD has also replaced previously used frizzed approach of process development by providing a design space concept. Moving within design space would not require post approval changes thereby reducing the cost involved.

REFERENCE:

[1]. Dispas, etal. "'Quality by Design' approach for the analysis of impurities in pharmaceutical drug products and drug", TrAC Trends in Analytical Chemistry,

International Journal of Pharmaceutical Research and Applications
Volume 7, Issue 5 Sep-Oct 2022, pp: 1116-1138 www.ijprajournal.com ISSN: 2456-4494

(2018), 101: 24-33. DOI: 10.1016/j.trac.2017.10.028.

[2]. Montgomery Douglas C. "Design and analysis of experiments." 8th Edition, John Wiley & Sons,Inc. Publication. (1984). ISBN 978-1-118-14692-7

[3]. Pharmaceutical Quality for the 21st Century A Risk-Based Approach Progress Report Department of Health and Human Services U.S. Food and Drug Administration May 2007. https://www.fda.gov/about-fda/center-drug-evaluation-and-research-cder/pharmaceutical-quality-21st-century-risk-based-approach-progress-report

[4]. "PAT — A Framework for Innovative Pharmaceutical Development, Manufacturing, and Quality Assurance Guidance for Industry", OCTOBER 2004, Docket Number: FDA-2003-D-0032. Issued by: Center for Veterinary Medicine Office of Regulatory Affairs & Center for Drug Evaluation and Research. https://www.fda.gov/regulatory-information/search-fda-guidance-documents/pat-framework-innovative-pharmaceutical-development-manufacturing-and-quality-assurance

[5]. M. A. Khan, etal. "Understanding Pharmaceutical Quality by Design", The AAPS Journal, **(2004)** 16. DOI: 10.1208/s12248-014-9598-3.

[6]. GUIDANCE DOCUMENT "Q8(R2) Pharmaceutical Development", NOVEMBER 2009, Docket Number: FDA-2005-D-0154. Issued by: Center for Drug Evaluation and Research & Center for Biologics Evaluation and Research https://www.fda.gov/regulatory-information/search-fda-guidance-documents/q8r2-pharmaceutical-development

[7]. GUIDANCE DOCUMENT "Q9 Quality Risk Management", JUNE 2006, Docket Number: FDA-2005-D-0334. Issued by: Center for Drug Evaluation and Research & Center for Biologics Evaluation and Research https://www.fda.gov/regulatory-information/search-fda-guidance-documents/q9-quality-risk-management

[8]. GUIDANCE DOCUMENT "Q10 Pharmaceutical Quality System", APRIL 2009, Docket Number: FDA-2007-D-0370. Issued by: Center for Drug Evaluation and Research & Center for Biologics Evaluation and Research https://www.fda.gov/regulatory-information/search-fda-guidance-documents/q10-pharmaceutical-quality-system

[9]. GUIDANCE DOCUMENT "Q8, Q9, & Q10 Questions and Answers -- Appendix: Q&As from Training Sessions (Q8, Q9, & Q10 Points to Consider)", AUGUST 2012, Issued by: Center for Drug Evaluation and Research & Center for Biologics Evaluation and Research https://www.fda.gov/regulatory-information/search-fda-guidance-documents/q8-q9-q10-questions-and-answers-appendix-qas-training-sessions-q8-q9-q10-points-consider

[10]. "ICH QUALITY IMPLEMENTATION WORKING GROUP POINTS TO CONSIDER (R2) ICH-Endorsed Guide for ICH Q8/Q9/Q10 Implementation", Document date: 6 December 2011. https://www.google.com/urlsa=t&source=web&rct=j&url=https://database.ich.org/sites/default/files/Q8_Q9_Q10_Q2526As_R4_Points_to_Consider_0.pdf&ved=2ahUKEwjtr_fju9f6AhUCheYKHagODTIQFnoECBEQAQ&usg=AOvVaw28fH2sUxRsEZsjYQuPjs31

[11]. GUIDANCE DOCUMENT "Q11 Development and Manufacture of Drug Substances", NOVEMBER 2012, Issued by: Center for Drug Evaluation and Research & Center for Biologics Evaluation and Research https://www.fda.gov/regulatory-information/search-fda-guidance-documents/q11-development-and-manufacture-drug-substances

[12]. Prajapati, et al. "Failure Mode Critical Effect Analysis and Design of Experiment-Based Robust Chromatographic Method for Simultaneous Estimation Lornoxicam and Eperisone Hydrochloride", Journal of chromatographic science, **(2020)**, 58(10): 929-939. DOI: 10.1093/chromsci/bmaa064

[13]. Vishal C Gurumukhi, Sanjaykumar B Bari, "Quantification and Validation of Stability-Indicating RP-HPLC Method for Efavirenz in Bulk and Tablet Dosage Form using Quality by Design (QbD): A Shifting Paradigm", Journal of Chromatographic Science, **(2022)**, 60(2):

143–156. DOI: 10.1093/chromsci/bmab061

[14]. Robert A et al. "Quality by design: concepts for ANDAs." The AAPS journal **(2008)**, 10(2): 268-76. Doi:10.1208/s12248-008-9026-7

[15]. "Product Quality Lifecycle Implementation (PQLI)" International Society for Pharmaceutical Engineering. https://ispe.org/initiatives/pqli

[16]. V. Krishna et al. "QbD-driven formulation development and evaluation of topical hydrogel containing ketoconazole loaded cubosomes", Materials science & engineering. C, **(2021)** 119, 111548. DOI: 10.1016/j.msec.2020.111548

[17]. Waghule, etal. "Improved skin-permeated diclofenac-loaded lyotropic liquid crystal nanoparticles: QbD-driven industrial feasible process and assessment of skin deposition", Liquid Crystals, **(2020),** 48: 1-19. DOI: 10.1080/02678292.2020.1836276.

[18]. Lan Zhang, Shirui Mao, "Application of quality by design in the current drug development", Asian Journal of Pharmaceutical Sciences, **(2017)** 12(1). DOI: 10.1016/j.ajps.2016.07.006

[19]. Sangshetti, etal. "Quality by Design Approach: Regulatory Need", Arabian Journal of Chemistry, **(2014)**, 101. DOI: 10.1016/j.arabjc.2014.01.025.

[20]. Patwardhan K, et al. "A quality by design approach to understand formulation and process variability in pharmaceutical melt extrusion processes", J Pharm Pharmacol**, (2015)**, 67(5): 673–684. DOI: 10.1111/jphp.12370

[21]. Bousses C, et al. "Using an innovative combination of quality-by-design and green analytical chemistry approaches for the development of a stability indicating UHPLC method in pharmaceutical products", Journal of Pharmaceutical and Biomedical Analysis, **(2015)**, 115: 114–122. DOI: 10.1016/j.jpba.2015.07.003

[22]. Md Noushad et al. "Risk Assessment Integrated QbD Approach for Development of Optimized Bicontinuous Mucoadhesive Limicubes for Oral Delivery of Rosuvastatin", AAPS PharmSciTech **(2018)**, 19(3): 1377-1391. DOI: 10.1208/s12249-018-0951-1

[23]. Shah B, etal. "Intranasal delivery of Venlafaxine loaded nanostructured lipid carrier: risk assessment and QbD based optimization", Journal of Drug Delivery Science and Technology, **(2016)**, 33(3): 7–50. DOI: 10.1016/j.jddst.2016.03.008

[24]. Sangshetti, etal. "Quality by Design Approach: Regulatory Need", Arabian Journal of Chemistry, **(2014)**, 101. DOI: 10.1016/j.arabjc.2014.01.025

[25]. Vanaja, K. & Rani, R.H, "Design of Experiments: Concept and Applications of Plackett Burman Design", Clinical Research & Regulatory Affairs, **(2008)**, 24: 1-23. DOI: 10.1080/10601330701220520

[26]. N Politis, etal. "Design of experiments (DoE) in pharmaceutical development", Drug Development and Industrial Pharmacy, **(2017)**, 43(6): 889-901. DOI: 10.1080/03639045.2017.1291672

[27]. Jankovic, etal. "Designing the design of experiments (DOE) – An investigation on the influence of different factorial designs on the characterization of complex systems", Energy and Buildings, **(2021)**, 250: 111298. DOI: 10.1016/j.enbuild.2021.111298.

[28]. M. A. Farooq, etal. "An innovative approach for planning and execution of pre-experimental runs for Design of Experiments", European Research on Management and Business Economics, **(2016),** 22(3): 155-161. DOI: 10.1016/j.iedee.2014.12.003.

[29]. Gujral, etal. "An updated review on design of experiment (doe) in pharmaceuticals", Journal of Drug Delivery & Therapeutics, **(2018)**, 8(3): 147-15. DOI: 10.22270/jddt.v8i3.1713

[30]. V. K Rapalli, etal. "Chapter 13 - Application of QbD Principles in Nanocarrier-Based Drug Delivery Systems, Pharmaceutical Quality by Design", Academic Press, **(2019)**, 255-296. DOI: 10.1016/B978-0-12-815799-2.00014-9

[31]. Vanaja, K. & Rani, R.H, "Design of Experiments: Concept and Applications of Plackett Burman Design", Clinical Research and Regulatory Affairs, **(2008)**, 24(1): 1-23. DOI: 10.1080/10601330701220520.

[32]. Ghica, etal. "Response surface methodology and Taguchi approach to assess the combined effect of formulation

factors on minocycline delivery from collagen sponges", Pharmazie, **(2013),** 68(5): 340-8. DOI: 10.1691/ph.2013.2101.

[33]. Fukuda, etal. "Design of Experiments (DoE) applied to Pharmaceutical and Analytical Quality by Design (QbD)", Brazilian Journal of Pharmaceutical Sciences, **(2018),** 54. DOI: 10.1590/s2175-97902018000001006.

[34]. John D,George L. Reid, "An Introduction To Process Analytical Technology", June 21, 2017 https://www.pharmaceuticalonline.com/doc/an-introduction-to-process-analytical-technology-0001

[35]. 57 Final Report from the FDA-EMA pilot program for the parallel assessment of quality-by-design elements of marketing applications FDA published the final report of its join pilot program with the European Medicines Agency (EMA) for the parallel assessment of sections of applications relevant to quality by design in April 2017 https://www.fda.gov/drugs/pharmaceutical-quality-resources/final-report-fda-ema-pilot-program-parallel-assessment-quality-design-elements-marketing