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A REVIEW ON DESIGN OF EXPERIMENTS (DOE)

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ABSTRACT

Quality by design (QbD) is a new modern perspective towards the qualitative pharmaceutical development. Many pharmaceutical companies have used several Quality Management System (QMS) for instance ISO 9001. This is a systemic approach to design and development of the pharmaceutical formulations and manufacturing processes that ensures the predefined product quality. Pharmaceutical industry is moving towards quality. A process DOE was used to evaluate effects of the design factors on manufacturability and final product CQAs, and establish design space to ensure desired CQAs. Critical material and process parameters are linked to the critical quality attributes of the product. On the basis of the Information Company then design the product formulation and process to meet the product attributes. This leads to understand the impact of raw materials [critical material attributes (CMA)], critical process parameters (CPP) on the CQAs and identification and control sources of variability

KEYWORDS Quality by design, Design of experiment, Design space and critical materials attributes.

INTRODUCTION

The design of experiment (DOE) approach, process variables are first 'screened' to determine which are important to the outcome (excipients type, percentage, disintegration time (DT) etc. Second step is the 'optimization', when the best settings for the important variables are determined. It involves the use of 'mixture designs' for changing mixture composition and exploring how such changes will affect the properties of the mixture. [1, 2,3,4,5]

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

Advantages

- Better innovation due to the ability to improve processes.
- More efficient technology transfer to manufacturing.
- Less batch failures.
- Greater regulator confidence of robust products.
- Risk- based approach and identification.
- Innovative process validation approaches.
- For the consumer, greater product consistency.

Pharmaceutical Quality by Testing Product quality is ensured by raw material testing, drug substance manufacturing, a fixed drug product manufacturing process, in- process material testing, and end product testing. The quality of raw materials including drug substance and excipients is monitored by testing. If they meet the manufacturer's proposed and FDA approved specifications or other standards such as USP for drug substance or excipients, they can be used for the manufacturing of the products. Because of uncertainty as to whether. If pharmaceutical companies fulfill all requirements of FDA approved specifications or other standards such as USP for drug substance or excipients, they can be used for the manufacturing of the products. Finished drug products are tested for quality by assessing whether they meet. [6, 7, 8, 9, 2, 3]

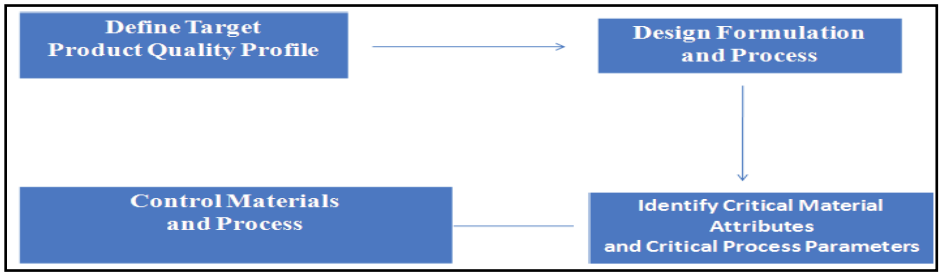

Figure 1: Risk assessment and design space

Pharmaceutical in quality by design

QBD means designing and developing formulations and manufacturing processes to ensure predefined product quality. According to ICH Q8 defines quality as "The suitability of either a drug substance or drug product for its intended use. This term includes such attributes as the identity, strength, and purity." The recent approach is QbD where if drug substance and excipients meet the specification the next step of unit operation is carried out such as Mixing, blending, drying, compression, coating etc. with fixed process parameters Quality in pharmaceuticals is very much important since it directly deals with patient's health and so Food and Drug Administration (FDA) has set stringent law for drug approval**.** If QbD explains "what to do," then PAT is a framework for "how to do". QbD is overarching philosophy articulated in both the cGMP regulations and in robust modern quality system. Thus some of the important QbD features include

- Define Product quality profile
- Design and develop Manufacturing Processes
- Identify and control the critical control parameters, Critical quality attributes and source of variability.
- Control the whole manufacturing process to produce quality product consistently over a period of time. Key steps for quality by design (Qbd). [10,11,12,13]

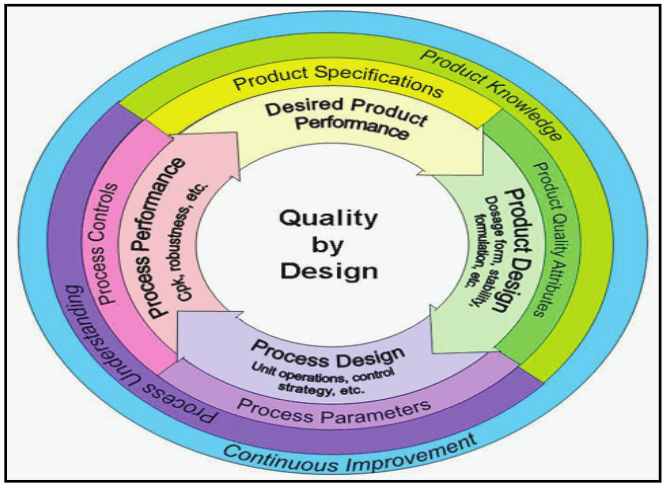

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Figure 2: Aspects of QBD include

ELEMENTS OF QUALITY BY DESIGN

QbD development process includes the following elements that accomplish the following steps as per fig-3.[11].

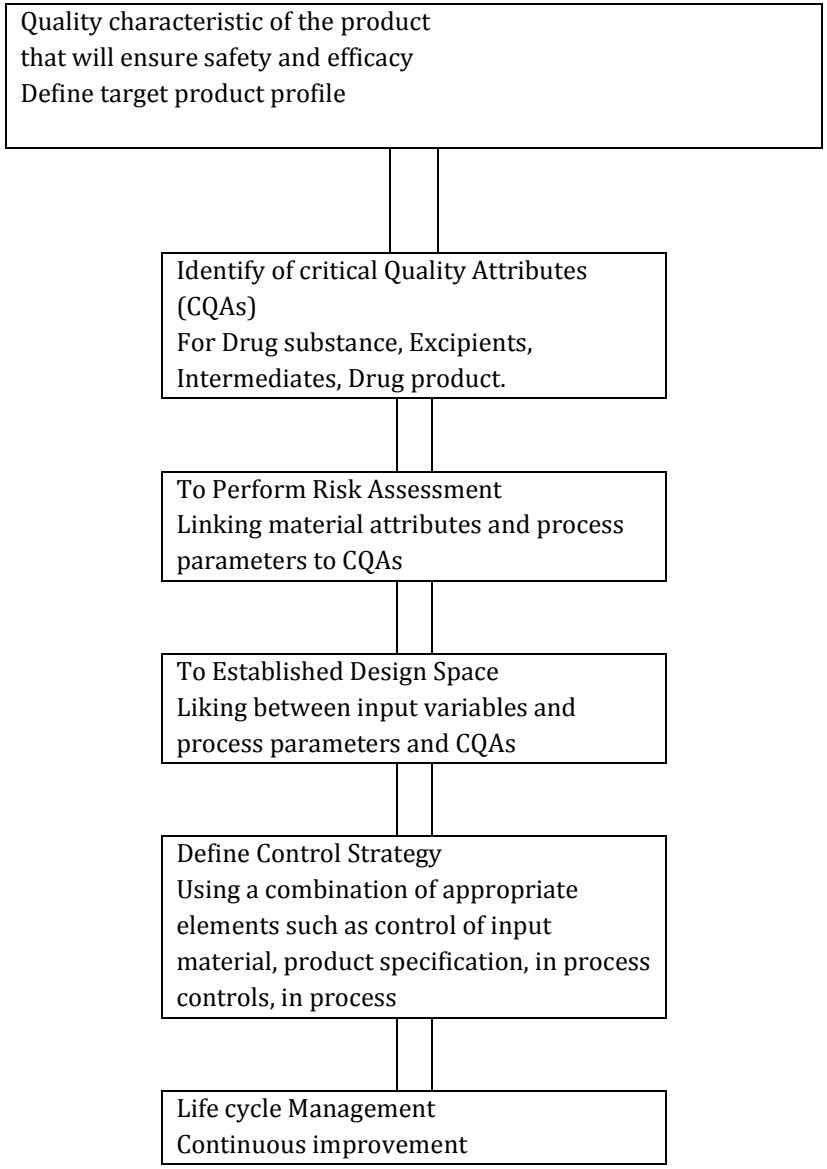

Figure 3: Quality by Design (QbD) Steps

FORMULATION BY QUALITY BY DESIGN AND DEVELOPMENT

In design and develop for pharmaceutical product that has the desirable TPQP, a product development must give serious consideration to the biopharmaceutical properties of the drug substance. The availability of drug substance may influence the number of studies and therefore, product understanding. The investigation of physical property, chemical property and biological property is termed as the preformulation in pharmaceutical science. Critical quality attributes (CQA) are physical, chemical, biological, or microbiological property or characteristic that must be controlled directly or indirectly to ensure the quality of the product. Critical process parameters (CPP) are process inputs that have a direct and significant influence on critical quality required when they vary within the operating range. Design of experiments (DOE) is a structured and organized method to determine the relationship among factors that influence outputs of that process variable.

Design of experiment and design space
Design of experiment

The applicant can choose to conduct pharmaceutical development studies that can lead to an enhanced knowledge of product performance over a wider range of material attributes, processing options and process parameters. Inclusion of this additional information in this section provides an opportunity to demonstrate a higher degree of understanding of manufacturing processes and process controls. This scientific understanding establishes the design space. In these situations, opportunities exist to develop more flexible regulatory approaches, for example, to facilitate: risk based regulatory decisions (reviews and inspections); manufacturing process improvements, within the approved design space described in the dossier, without further regulatory review; real time" quality control, leading to a reduction of end-product release testing.

To realize this flexibility, the applicant should demonstrate an enhanced knowledge of product performance over a range of material attributes (e.g. particle size distribution, moisture content, and flow properties), processing options and process parameters. This knowledge can be gained by, for example, application of formal experimental designs* or PAT*. Appropriate use of risk management principles can be helpful in prioritizing the additional pharmaceutical development studies to collect such knowledge. The below given comparison is chart current conventional approach and quality based design which is scientific approach encouraged by US food and drug administration. [14, 15, 16]

Current Approach	QbD Approach
Quality assured by testing and inspection	Quality built into product & process by design, based on scientific understanding
Data intensive submission – disjointed information without "big picture"	Knowledge rich submission – showing product knowledge & process understanding
Specifications based on batch history	Specifications based on product performance
"Frozen process," discouraging changes	Flexible process within design space, allowing continuous
Focus on reproducibility – often avoiding or ignoring	Focus on robustness – understanding and controlling

Table 1: Difference between Current and Qbd approach

The design and conduct of the pharmaceutical development studies should be consistent with their intended scientific purpose and the stage of the development of the product. It should be recognized that the level of knowledge gained, and not the volume of data, provides the basis for science-based submissions and their regulatory evaluation.

Design Space

the design space is the established range of process parameters that has been demonstrated to provide assurance of quality. In some cases design space can also be applicable to formulation attributes. Working within the design space is not generally considered as a change of the approved ranges for process parameters and formulation attributes. Movement out of the design space is considered to be a change and would normally initiate a regulatory post approval change process. The design space is the established range of process parameters and formulation attributes that have been demonstrated to provide assurance of quality. It forms the linkage between development and manufacturing design.

Establishment of Design Space through product and process design

Making changes to the formulation and manufacturing process during development generates valuable data that supports establishment of the design space. It is implied that both positive and negative results are important to understanding the design space. Minimum requirements are to provide data to support the proposed formulation and manufacturing process Reports should identify properties of the active ingredient, excipients and manufacturing process that are critical and that present significant risk to product quality and therefore should be monitored or otherwise controlled. Applicants can choose to perform additional development studies that enhance knowledge of product performance over a wider range of attributes, processing options and process parameters. Sharing such information with the regulatory bodies in the development report provides an opportunity to demonstrate a higher degree of understanding of manufacturing processes and process controls this effectively establishes the design space. This sharing of knowledge of the design space with the regulatory bodies will open the door to: True risk based reviews and inspections manufacturing process improvements within the approved design space without further regulatory oversight Real time quality control leading to a reduction in end product release testing

Regulatory and Business Advantages of using Design Space

Working within the design space is not generally considered as a change of the approved ranges for process parameters and product attributes. Result will clearly be less supplemental regulatory filings. Movement out of the design space is considered to be a change and would normally initiate a regulatory post approval change process. De-emphasize end product testing and may eliminate certain release tests. Process knowledge can eliminate redundant testing for those attributes that are demonstrated to be controlled in-process Diminish the burden for validating systems by providing more options for justifying and qualifying systems intended to control critical attributes of materials and processes

Challenges and Barriers to Implementation of Design Space

Fear of punishment resulting from sharing of full spectrum of knowledge and data generated to implement the concepts Industry is well experienced in the "current state" of design and needs better guidance on risk management and quality systems. Potentially higher upfront costs and expanded development timeline. [17, 18, 7,9,10]

CERTAIN KEY ASPECTS OF QBD

The Target Product Quality Profile (TPQP)

(TPQP) is a term that is a natural extension of TPP for product quality. It is the quality characteristics that drug product should possess in order to reproducibly deliver the therapeutic benefit. For example, TPQP of an immediate release solid oral dosage form includes.

- Tablet Characteristics
- Identity
- Assay and Uniformity
- Purity/Impurity
- Stability, and
- Dissolution time
- Disintegration time

Target product quality profile (TPQP) is a quantitative surrogate for dissolution safety and efficacy product to optimize a formulation and manufacturing process. International Society of Pharmaceutical Engineers (ISPE) Product Quality Lifecycle Implementation (PQLI) calls this the Pharmaceutical Target Product Profile. It includes quantitative, stability and release profile for safety products. Associations and Regulatory Authorities on the presentation of enhanced product and process understanding in regulatory dossiers.

Drug Substance and Excipients Properties

It is well recognized that excipients could be a major source of variability. Characterization and understanding of excipients' pharmaceutical properties depends on the function and characteristics of excipients. The characteristics of excipients are physical, chemical. Biological such as stability, solubility, particle size. Drug-excipients compatibility knowledge information is valuable in the design of formulation and manufacturing processes. Such information may be gained through theoretical investigation and experimental studies.

Formulation Design and Development

In order to design and develop a robust generic product that has the desirable TPQP, a product development scientist must give serious consideration to the biopharmaceutical properties of the drug substance. These biopharmaceutical properties include physical, chemical, and biological properties. Physical properties include physical description (particle size, shape, and distribution) polymorphism. Chemical property like partition co-efficient and chemical stability in solid or solution state. The goal of preformulation studies is to determine the appropriate salt and polymorphic form of drug substance evaluate understand its critical properties, and generate a thorough understanding of the material's stability under various processing and in vivo conditions, leading to an optimal drug delivery system.

Manufacturing Process Design and Development

It is important that the process and product design and development cannot be separated since a formulation cannot become a product without a process. Depending the product developed process knowledge, type of process, the scientist may be necessary to study before the completely the process design and development. The pharmaceutical industry has traditionally put emphasis on new drug discovery and development, and the complexity of drug product manufacturing operations is not well recognized. With the emphasis of QbD by the FDA an industry and drug product cost pressures; this trend is expected to change.

DESIGN OF EXPERIMENTS (DOE) [19, 20, 21, 22, 12, 15, 5]

Design of experiments (DOE) is an efficient procedure for planning experiments so that the data obtained can be analyzed to yield valid and objective conclusions. A structured, organized method for determine the relationship between factors affecting a process and the output of that process is known as "Design of experiment". In experiments, we deliberately change one or more process variables (or factors) in order to observe the effects the change will have on one more response variables. The (Statistical) design of experiments (DOE) is an efficient procedure for planning experiments so that the data obtained can be analyzed to yield valid & objective conclusions. DOE begins with determining the objective of an experiments & selecting the process factors for the study. A experiments design is the laying out of a detailed experiments plan in advance of doing the experiment will chosen experimental designs Maximize the amount of "Information" that can be obtained for a given amount of experimental effect

Benefits of Design of Experiments

- Experimental design involves manipulating the independent variable to observe the effect on the dependent variable. This makes it possible to determine a cause and effect relationship.
- As well as controlling the independent variable the experimenter attempts to eliminate unwanted extraneous variables.
- Control over extraneous variables is usually greater than in other research methods.
- Because of strict conditions and control the experimenter can set up the experiment again and repeat or 'check' their results. Replication is very important as when similar results are obtained this gives greater confidence in the results

Use of Design of experiment: Design of experiments is used to determine the causes of variation in the response, the find conditions under which the optimal (maximum or minimum) response is achieved, to compare responses at different levels of controlled variables & to develop a Model for predicting response.

Key steps for Design of experiments

Obtaining good results from a Design of experiments involves those seven steps.

- Set objective
- Select process variables
- Select an experimental design
- Execute the design
- Check that the data are consistent with the experimental assumptions.
- Analyze and interpret the results.

Related definitions

Some of the related definitions are stated below

- **Treatment:** Different combinations of conditions for rest.
- **Treatment levels:** The relative intensities at which a treatment will be set during the experiments.
- **Treatment factors (variables):** One of the controlled conditions of the experiments.
- **Experimental unit:** Subject on which a treatment will be applied & from which a response will be elicited also called measurement or response units.
- **Responses:** Outcomes that will be elicited from experimental units after treatments have been applied eq. hardness, friability (release of drug from a formulation).
- **Experimental design:** Rule for assigning treatment levels to experimental units.
- **Analysis variance (ANOVA):** Principal statically means for evaluating potential sources of variation in the responses.
- **Replication:** Observing individual response of multiple experimental units' under identical experimental conditions. It is use to detect Noise.

- **Randomization:** Non- systematic assignment of experimental units to treatments.

- **Confounding:** Design situation in which the effect of one factor or treatment can't be distinguished from another factor or treatment.

Characterization of a Good Experimental design: The following are the characteristics of a good experimental design.

- Avoidance of systematic error: Systematic errors lead to bias when estimating difference in response between treatments.
- Precise estimation: Achieved a relatively small random error , which in turn depends on:-
  - Random error in the responses.
  - The number of experimental units.
  - The experimental design employed.
  - Proper estimation of error

Limitations of Conventional Method: The classical method of experimentation is costlier & is restricted to one factor at a time & other factor being kept constants .This fails to show interaction effect that may exists between some of the factors consequent on which optimum concentration are difficult to be determined .

Advantages of Design of Experiments over conventional method: A single integrated design, which permits variations of more than one factor at a time & allows determination of interaction effects of well as provide more information on the man effects. Advantages of well planned experiments are:

- More information per experiments, reduced lead time, improve efficacy.
- Organized approved.
- Information reliability.
- Capability to the interactions & more reliable prediction.

Some reasons to model a process: Once we know the primary variables (factors) that affect the responses of interact, a number of additional objective may be pursued those include –

- Hitting a target
- Maximizing & minimizing a response
- Reducing a variation
- Making a process robust.
- Seeking multiple goals.

Key steps for Design of experiments (DOE): Obtaining good results from a Design of experiment (DOE) involves these steps:

A) Set objective
B) Select process variables
C) Select an experimental design
D) Execute the design
E) Analyze & interpret the results.

Selections of variables & their level

Process variables include both inputs & outputs i.e. factors & response. The most popular experimental design are tune level design because it is ideal for screening design , simple & economical ; it is also gives most of the information required to get to a multilevel response surface experiments if needed.

Selection of experimental design

The choice of an experimental design depends on the objectives of the experiments & the number of factors to be investigated.

Experimental design objective

- Comparative objective
- Screening objective
- Response surface (method) objective
- Optimizing response when factors are proportions of a mixture objective.
- Optimal fitting of a regression model objective.

This primary purpose of the experiments is to select or screen out the few important main effects from the many less important ones. These screening designs are those termed main effects designs

Screening Design (S.D)	Screening designs are effective way to identified significant main effects. The term "Screening design" refers to an experimental plan i.e. indented to find a few significant factors from a list of many potential ones.
Response Screening Design	Response screening design involves just the main effects & interactions or they may also have quadratic & possibly cubic terms to account for curvature model which may be appropriate to described a response
Fractional Factorial Design	Full factorial experiments can requires may runs. The solution to this problem is to use only a fraction of the runs specified by the full factorial design. In general, we pick a fraction such ½, ¼ etc. of the runs called for by the full factorial.
Placket – Burmam Design	These designs have run numbers that are in multiple of 4.placket Burmam (PB) designs are used for screening experiments because in PB designs, main effects are, heavenly confounded with two – factor interactions.
Box- Behnken Design	The Box- Behnken Design is an independent quadratic design which does not contain an embedded factorial or fractional factorial design. These designs are rotatable (or near rotatable) & requires 3 levels of each factors.

Table 2: Types of Design of Experiments commonly used

FULL FACTORIAL DESIGN

Full factorial design in 2 levels:

A common experimental design is one with all inputs factors set at 2 levels each. A full factorial design has 2^k run.

No. of factors	No. of runs
2	4
3	8
4	16
5	32
6	64

Table 3: No. of runs for Full Factorial Design

As shown in figure, when the number of factors in 5 or greater, a Full Factorial Design requires a large no. of runs & is not very efficient. Then a full factorial design or a Plackett – Burman Design is a better choice.

How to interpret Design of Experiments (DOE) results: Assume that we have a final model that has passed all the relevant tests (visual & quantitative) & we are ready to make conclusion & decisions. These should be response to the outputs dictated by the original experimental goals.[23, 24, 6, 7,8,12,13,15,16]

CONCLUSION

Nowadays, much of the scientific basis is already in place for the implementation of QbD. So, the Statistical optimization for pharmaceutical scientist is to define the formulation with optimum characteristics. Statistical optimization can also provide solutions to larger-scale manufacturing problems, which occasionally arise. Importantly, statistical optimization experimentation and analysis provides strong assurances to Regulatory Agencies regarding superior product quality.

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