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Review Article

APPLICATION OF DESIGN OF EXPERIMENTS FOR OPTIMIZING CRITICAL QUALITY ATTRIBUTES (CQA) IN ROUTINE PHARMACEUTICAL PRODUCT DEVELOPMENT

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ABSTRACT

Purpose: QbD is a helpful tool in building quality products and to understand critical process parameters which affects the manufacturing of drug products. It helps to build control strategy which helps to maintain quality throughout its life cycle.

Approaches: The major approach in QbD is through DOE which includes either screening or optimization done by various designs like plackett-Burmann, Box-Behnken design, Fractional Factorial design, Central Composite design, Mixture design etc.

Findings: QbD approach helps in formulating and maintaining quality in the drug product. It helps to identify the critical quality attributes and process parameters which are likely to affect the quality of the drug product through screening design.

Conclusions: Adopting QbD concepts into manufacturing of the drug product has its advantage of reducing development and marketing costs. It also helps in meeting regulatory requirements.

Key Words: QbD, DOE, Process optimization, QTPP, CQA.

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INTRODUCTION

QbD (Quality by Design) is the modern approach for building quality in the drug product and not just tested into the product. According to ICH Q8(R1) guideline, "QbD is a systemic risk based proactive approach to pharmaceutical development that begins with predefined objectives and emphasizes product & process understanding and process control based on sound science and quality risk management".[1]

QbD is concerned with predicting the quality through linking the critical material attributes (CMA) and critical process parameters (CPP) of the drug product.[2] QbD uses multivariate experiments to understand product and process and establishes a design space using design of experiments (DOE).[3] DOE is an organised method to determine the relationship between the inputs and outputs of a process. In pharmaceutical development, CMA & CPP include the factors or input variables, while CQAs (Critical Quality Attributes) include solubility and dissolution.

As each unit operation involved in manufacturing has many input variables and CQAs, it is experimentally impossible to investigate all of them due to lack of time and high risk. The researchers must use the prior knowledge and experience along with the risk management to identify critical input and output variables, however the process parameters are investigated by using DOE.[3] All likely combinations of raw material attributes and process

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parameters that need to be realised by the process to ensure that the CQAs stay within the required ranges (control space) can be called as the design space (DS) of the process.[4]

After the design of experiments are executed, the results are analysed and studied to identify the cause and effect relationship between the input parameters and responses. Finally scaling up the experiments to intermediate or large scale manufacturing followed by continuous improvement along with life-cycle management are done.[5]

ADVANTAGES OF QbD AND DOE

- The ability to improve process leads to better innovation.
- Less batch failures due to systematic approach and efficient technology transfer.[6]
- QbD helps to determine the quality of the product by assessing the level of risk associated with manufacturing of the drug product.
- Allows to implement new technology and approaches to improve manufacturing without regulatory scrutiny.[1]
- It helps in reducing the overall costs of manufacturing and increase revenues due to reduced rework and faster entry to market.[7]
- DOE helps in the screening of important factors and optimization of quality and performance of a product.
- It increases robustness of the tests of product and process.

DOE

DOE is an efficient and a structured procedure for planning experiments so that the data obtained can be analysed to yield valid and objective conclusions.[6]

Commonly Used Types of Design of Experiment

1. **Screening Design :** Screening designs are effective way to identify the significant effects. The term screening design refers to experimental plan that is intended to find a few significant factors from a list of many potential ones.This type of design not only provides limited amount of information about the individual variables in a given system but also requires fewest number of runs for a given variable.[6]

2. **Response Surface Design (RSD) :** Once a screening experiment has been performed and the significant factors are determined, the next step is often to perform RSD in order to produce a prediction model, to determine curvature, detect interactions among the factors and to optimize the process. The model that is frequently used to estimate the response surface is the quadratic model given with a eq.[8]

$$y=\beta_{\circ}+\sum_{i=1}^{p}\beta_{\circ}\ \beta_i X_i+\sum_{\substack{i=1\\ i\neq j}}^{p}\beta_{\circ}\sum_{j=1}^{p}\beta_{ij}X_i+\sum_{i=1}^{p}\beta_{ii}X_i^2$$

Where,

$\beta_{\circ}$= the overall mean response

β_i=the main effect for each factor (i=1, 2, 3….p)

β_{ij}=the two way interaction between ith and jth factors

β_{ii}=the quadratic effect for the ith factor[8]

3. **Fractional Factorial Design :** This design requires many runs in order to resolve this use only a fraction of the runs specified by the factorial design. In general a fraction such as ½, ¼ etc..,of the runs are called for by the full factorial. This design can be used when experiments are costly and when the full factorial has number of design points.[8]

4. **Placket-Burmann Design :** Plackett-Burmann design is a two level fraction factorial design commonly used for screening. In these designs the number of runs are in multiples of 4. The disadvantage of this design is that it does not consider the interactions that occur between independent variables, hence its use in optimization is limited.[9]

5. **Box-Behnken Design :** This design is an independent quadratic equation design which does not have a fractional factorial design. It requires only three levels for each of the three factors(+1, 0 and -1). It employs 15 experimental runs with 3 factors at 3 levels and is economical than central composite design(CCD) due to less no. of trials.

6. **Mixture Design :** These designare used when the quality characteristics of the finished product depend on proportions of substances and not on their quantities in the product

7. Central Composite Design : This designis most commonly used for non-linear responses which require second order model. It is quite popular design in response surface optimization during product development in pharmaceutics. [10]

STEPS INVOLVED IN QbD AND DOE

Prior to the development of DOE, QTPP and CQA must be identified by risk assessment. Basic steps in QbD is as in Fig. 2.

Quality Target Product Profile (QTTP) : According to FDA QTPP is defined as those quality attributes which are related to safety and efficacy of the drug product. Eg.sterility, purity, stability etc., it is important as it defines the product performance. Eg.Dissolution, Solubility etc.

Critical Quality Attributes (CQA) : After QTPP is assigned, the next step is to identify CQAwhich may be physical, chemical, biological or microbiological characteristic which should be present within certain limit to ensure that the desired response or product quality is met. Eg.particle size, drug-excipient ratio etc.

Quality Risk Management (QRM) : According to FDA, QRM is defined as a systemic process to assess and control the risk to quality of the drug product throughout its life cycle.7(Fig.1)

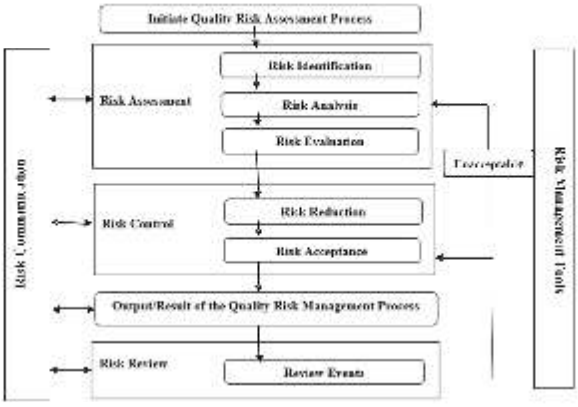


Fig. 1: Steps involved in risk management[7]

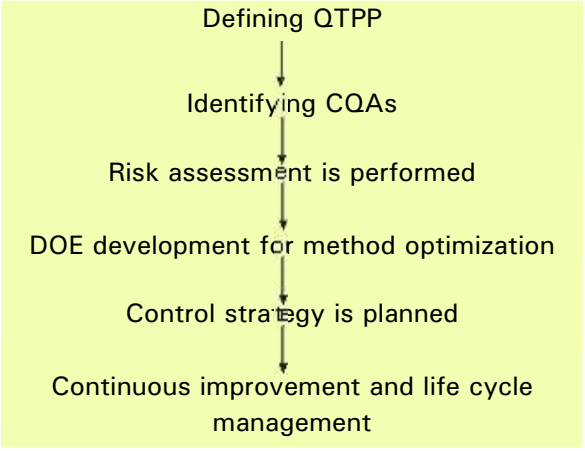
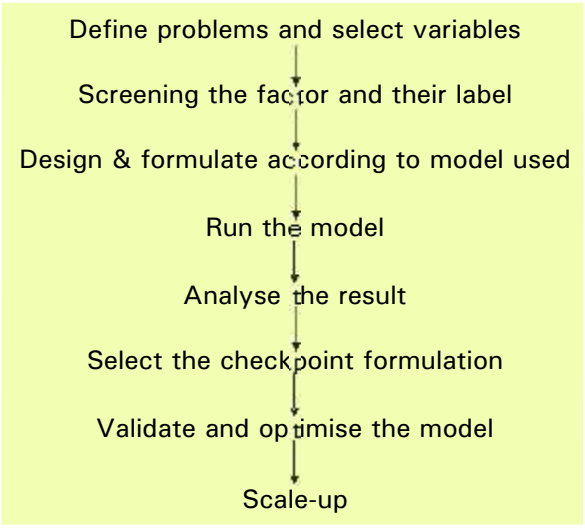


Fig. 2: steps in QbD[6,11]

Basic steps in DOE



DOE approach has the following basic steps:

1. **Defining the input and output variable and range:**
   The variables and their range can be defined by prior knowledge and risk assessment. Suitable screening design is used to identify range of variables. The variables must be CQA or closely related to it.[7]

2. **Selection of appropriate experimental design and performing the run:**
   Based on the purpose of the study (eg.screening, optimization, etc.), factors and interaction involved in the experimental design can be selected. Available resources like time, cost, labour and materials must also be

considered in selecting the experimental design. After selecting the suitable design, the model is run by performing the required experiments according to the model selected.

3. Analysing the results by illustrating the design space based on the type of the study:

Design space can be tabulated or graphically represented by any one of the following methods:

a) Contour plots:

It is a graphical representation of the relationship between 3 numerical variables in two dimension. Two variables are represented in X & Y axes and third one is for contour level. Better contouring quality and performance can be obtained by changing the resolution of rectangular grid. It can also interactively identify, label, colour and move contour level. It is useful for determining or displaying acceptable ranges for process parameters.

b) Three dimensional plots:

These plots are opted for the simultaneous study of the effect of 2 input variables on an output variable.

c) Overlay plots:

It is mostly used when more than one quality characteristic is present in the design space. The overlay plot indicates the combination of all the factors showing the possible results within the acceptable ranges.[7]

4. Validating and optimizing the model:

After analysing the results, a best fit combination of factors is selected and optimized. The combination is validated through scaling up of the formulation.[10]

After following these above four steps control strategy is planned:

According to ICH Q10, a control strategy is a planned set of control derived from current product and process understanding that assures process performance and product quality. It ensures that the process is maintained within the limits derives from the design space.

A control strategy includes the following:

- Control of input variables based on the impact they have on process and product quality.
- Control of procedure followed and facilities available.
- Control of operations which can be possibly impact the processing of the product or its quality.[7]

Continuous improvement and life-cycle management:

After the method is optimized and validated, it can be validated for routine processing and the method processing can be monitored. It is done by using tracking system suitability data, method related investigation and so forth.

Life-cycle management is a controlled strategy used for implementation of design space in commercial stage. It includes the use of risk assessment tools at the right time and stage, which helps to prevent method failure and better understanding on the design space and control strategy.[11]

APPLICATIONS OF QbD

1. **QbD in Dissolution Testing :** As dissolution is the most important quality control attribute for any pharmaceutical product, QbD is helpful in optimizing the drug composition in order to achieve the specified dissolution profile.

2. **QbD in Bioequivalence Testing :** QbD is used in optimizing the generics to obtain desired pharmacokinetic profile that matches with the reference listed drug's (RLD)pharmacokinetic parameters like $C_{max,}$ T_{max}, AUC etc. which are considered as CQAs.

3. **QbD in Stability Testing :** It gives a better knowledge of the product stability and shelf life. Specifications relating to concentration of degradants and efficacy of finished product can be prepared.[12]

4. **QbD in Formulation Develop-ment :** It can be used for developing a quality product and manufacturing process with consistent performance.

5. **QbD in CMC(Chemistry Manufacturing and Control) Review Offices :** It helps in science based assessment in the "Office ofNew Drug Quality Assessment"(ONDQA). To evaluate the quality of product, to determine the

level of risk associated with manufacture and design of the product in "Office of Generic Drugs" (OGD).[1]

6. **QbD in Process Optimization :** It can be used for process optimization and establishing process knowledge by implementing PAT (Process Analytical Technology) monitoring tools along with multivariate data analysis (MVDA).[5]

7. **QbD in Analytical Method Development :** Analytical methods used for the analysis of active pharmaceutical ingredient (API) and drug products for an integral part of quality by design concept as outlined in ICHQ8 guidelines. In order to develop robust, stability indicating analytical methods, a solid set of design requirements must be established in order to meet the required specification of the method.[9]

CONCLUSION

QbD is an innovative and robust technology which is very helpful to various industries including pharmaceuticals. It builds quality into the drug with less expenditure and with its predictory profile, formulation development has become easier and better. It helps to clear regulatory requirements with less risk and time. Finally it severs as an excellent tool in formulating and maintaining the quality in drug products and in optimization of various unit operations with its PAT tools.

GLOSSARY

QbD ="QbD is a systemic risk based proactive approach to pharmaceutical development that begins with predefined objectives and emphasizes product & process understanding and process control based on sound science and quality risk management".

DOE =DOE is an organised method to determine the relationship between the inputs and outputs of a process.

Process optimization =Process optimization is the discipline of adjusting a process so as to optimize some specified set of parameters without violating some constraint.

QTPP = It is defined as the quality attributes which are related to safety and efficacy of drug product.

CQA = It is physical,chemical, biological or microbiological characteristics which should be present within certain limit to ensure that the desired response or product quality is met.

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