WORLD JOURNAL OF PHARMACEUTICAL RESEARCH
SJIF Impact Factor 8.453
Volume 13, Issue 16, 559-579. Review Article ISSN 2277–7105

QUALTY BY DESIGN IN THE FORMULATION AND DEVELOPMENT OF DOSAGE FORMS

Amrutha O.* and Shijith K. V.

College of Pharmaceutical Sciences, Govt. Medical College, Pariyaram, Kannur, Kerala University of Health Sciences, Kerala-670503.

Article Received on
02 July 2024,

Revised on 22 July 2024,
Accepted on 12 August 2024

DOI: 10.20959/wjpr202416-33631

***Corresponding Author**
Amrutha O.
College of Pharmaceutical Sciences, Govt. Medical College, Pariyaram, Kannur, Kerala University of Health Sciences, Kerala-670503.

ABSTRACT

In this era the application of quality by design in pharmaceutical development has gained greater importance. International Conference on Harmonization and United States Food and Drug Administration (USFDA) emphasized the principles and applications of QbD in pharmaceutical development in their guidance for the industry. Among various mathematical modeling approaches, Design of Experiments (DoE) is widely applied for the implementation of QbD in both research and industrial settings. In QbD, product and process understanding are the key that enables the assurance of quality in the final product. Knowledge is achieved by establishing models correlating the inputs with the outputs of the process. By establishing mathematical relationship between Critical Process Parameters (CPPs) and Material Attributes (CMAs) with the Critical Quality Attributes (CQAs), a design space is defined. Consequently, the process understanding is well assured and rationally leads to a final product that meets the Quality Target Product Profile (QTPP). It is important to recognize that quality cannot be tested into products, i.e., quality should be built in by design. The prime objective of QbD is to generate quality and safety employing very first design steps. This review details the concept of pharmaceutical quality by design (QbD), steps of implementing QbD and their salient features.

KEYWORDS: Quality target product profile, Critical quality attributes, Critical material attributes, Critical process parameters, Control strategy, DoE.

INTRODUCTION

Quality by design is a concept first developed by quality pioneer Dr. Joseph M. Juran who believed that quality should be built into product. The US Food and Drug Administration encourages the implementation of QbD principles and risk-based approaches in drug product development, manufacturing, and regulation.[1]

The pharmaceutical Quality by Design (QbD) is a systematic approach to development that starts with predefined objectives and focusing on product and process understanding and process control, based on sound science and quality risk management. QbD includes designing and developing formulations and manufacturing process which assures defined quality and product specifications.

FDA's emphasis on QbD began with the realisation that increased testing does not necessarily improve product quality. Quality must be built into the product. 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).[1]

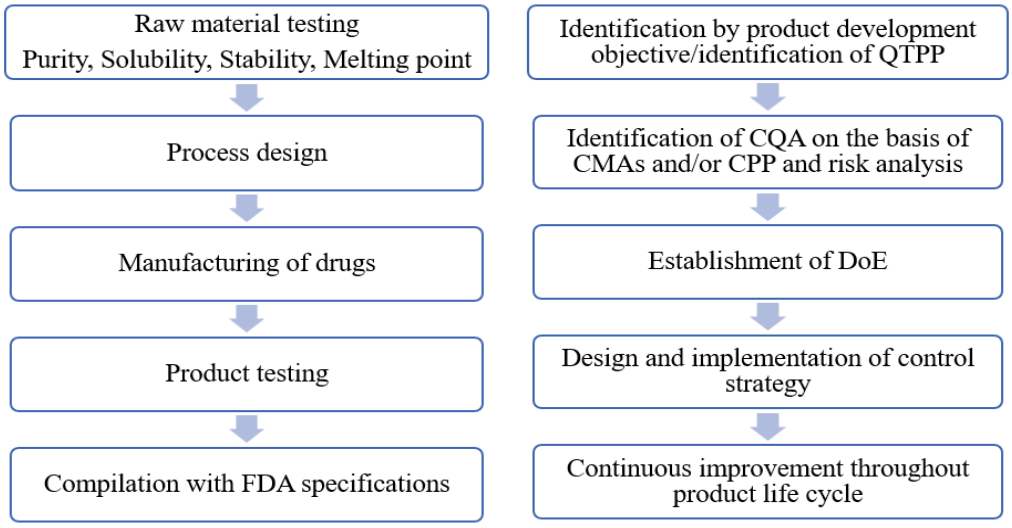

Figure 1: Comparison between (A) quality by test and (B) quality by design.

Table 1: Traditional approach vs QbD approach.

Traditional approach	QbD approach
Starts with trial and error	Starts with predefined objectives
Quality is assured by end product testing and inspection	Quality is built into product and process by design
Rigid process, discourage changes	Flexible process within design space

	allowing continuous improvement.
Focus on reproducibility, often ignoring or avoiding variations	Focus on robustness, understanding and controlling variations
Limited understanding of process and critical process parameters	Emphasis product and process understanding

Basic terminology and fundamentals of quality by design

According to ICH guidelines Q8-Q10, implementing QbD involves understanding key concepts and terminology.

1. Target product profile

The target product profile is a crucial element of QbD which describes the important features of proposed therapeutic product. In other words, TPP may be regarded as the vibrant summary that varies with increase in the awareness and understanding of the drug product. Therefore, TPP must be frequently updated during the process of therapeutic product development to achieve robust improvement in product quality.[2]

2. Quality target product profile

The quality target product profile serves as the basis of design for the development of the product. QTPP is a prospective summary of excellence features of a therapeutic product that must be attained to confirm desired features, considering efficacy, and safety concern of the therapeutic formulation. It owns a decisive part in describing the aim of the drug product under development. An ideal QTPP must explain the quality, efficacy, and safety of the target formulation for the intended patient population.[2]

Quality concern of QTTP includes

- Identification of active molecule, purity or assay
- The molecular weight, structural conformation
- The physiochemical characteristic of product (Melting point, Solubility, pH, Polymorphism)
- The dosage form and therapeutic target
- The dosage strength (Concentration).

Safety concern of QTTP includes

- The product stability
- Scientific data studies like pharmacokinetics, pharmacology, toxicology, and clinics

- Contraindications and adverse reactions
- Container closure system

Efficacy concern of QTTP includes

- Delivery/release of bioactives
- Bioavailability
- Marketed product.[2]

3. Critical quality attributes

A CQA refers to a physical, chemical, biological, or microbiological property or characteristic that should be within an appropriate limit, range, or distribution to ensure the desired product quality. CQAs are commonly associated with the drug substance, excipients, intermediates (In-process materials) and drug product.

CQAs for solid dosage forms typically encompass factors that impact the product's purity, potency, drug release characteristics, and stability. CQAs for other delivery system can additionally include more product specific aspects such as aerodynamic properties for inhaled products, sterility for parenterals, and adhesion properties for transdermal patches. For drug substances, raw materials and intermediates, the CQAs can also include those properties such as particle size distribution, bulk density that affect CQAs of the drug product.

Potential critical quality attributes (CQAs) for the drug product, identified from the quality target product profile or existing knowledge, serves as guiding principles for product and process development. The list of potential CQAs can be modified when the formulation and manufacturing process are chosen and as product knowledge and process understanding increase. Quality risk management can be used to prioritize the list of potential CQAs for further evaluation. An iterative process of quality risk management and experimentation identify relevant CQAs that assesses the extent to which their variation can have an impact on the quality of the drug product.[3]

4. Critical material attributes

CMAs are self-governing input variables that governs the quality of drug product by directly influencing the CQAs. It outlines the properties of the input drug moiety and excipients used to achieve QTPP. It must remain within a suitable restricted limit to achieve resultant drug

product with all the desired quality. CMAs primarily include active and inactive introductory raw substances or excipients, that have direct association with the CQAs of drug moiety.[2]

5. Critical process parameters

A process parameter is a measure that expresses the status of the process or unit operation. They are concerned with proposed process being employed for the preparation of pharmaceutical products and offer direct influence on the CQAs. CMAs can also impact important parameters that could influence the process performance as well as inconsistency in product characteristics. The CPPs have a major effect on the physical appearance, product stability, presence of impurity and yield of finished product.

6. Design space

The design space can be used to illustrate or describe the relationship between the process input (Material Attributes and Process parameters) and the critical quality attributes.[3]

7. Control Strategy and Continuous improvement

Control strategy is used to make sure that a product of required quality will be produced consistently. The elements of the control strategy discussed in Section P.2 of the dossier should explain and justify how in-process controls and the controls of input materials (drug substance and excipients), intermediates (in-process materials), container closure system, and drug products contribute to the quality of the final product. The controls should be based on product, formulation and process understanding and should include, at a minimum, control of the critical process parameters and material attributes. After formulation development is completed, control must be obviously discrete and must trust on a risk-concerned methodical knowledge of the process and formulation variables, ultimately leading to incessant progress.[3]

Steps of quality by design implementation

1. Identification of product development objectives
2. Identification of critical quality attributes on the basis of critical material attributes and/or critical process parameters and risk analysis
3. Establishment of experimental design
4. Designing and implementation of control strategy/policy
5. Continuous improvement throughout product life cycle[2]

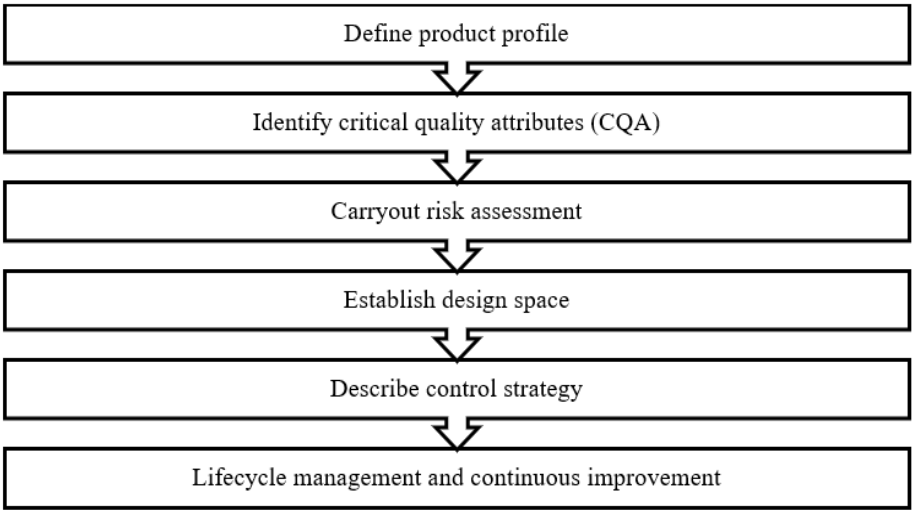

Figure 2: Steps of quality by design implementation.

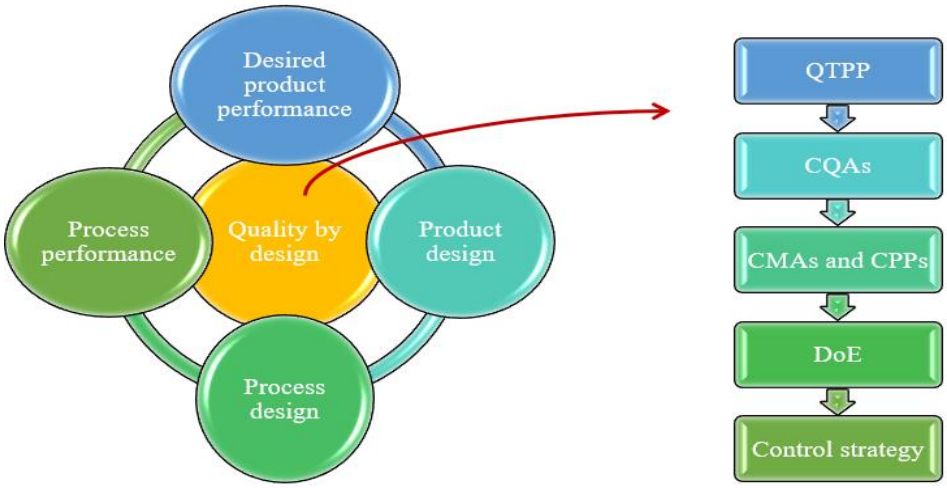

Figure 3: Quality by design approach to product and process development.

1. Identification of the product development objectives

Product development objectives must be identified by the manufacturer in the beginning of product development process to satisfy the existing requirement for the intended product with a view to provide superior therapeutic effectiveness. Based on the previously available literature and prior experience, the objectives of pharmaceutical product development are drawn as TPP. QbD requires a target product profile, it may be called as Quality target product profile which defines the expectations in final product. The TPP can play a central role in the whole drug discovery and development processes like optimization, planning and decision making, and designing of clinical research strategies.[2]

2. Identification of critical quality attributes on the basis of critical material attributes and/or critical process parameters and risk analysis

Next step in the implementation of QbD is the determination of CQAs considering of CMAs and/or CPPs. Selection of correct CMAs/CPPs is crucial, as they directly affect the CQAs. Basically, CQAs originate from QTPP and or earlier information employed to govern the product and process development, consequently CQAs are assessed for risk management.[2] Risk may be defined as the probability of occurrence of harm and the severity of that harm. Risk assessment helps to enhance the quality of method or process. From the risk assessment one can identify the critical attributes that are going to affect the final quality of product. A risk assessment is helpful for effective communication between FDA and industry, research/development and manufacturing and among multiple manufacturing sites within company.[4] Risk management is a planned safety programme meant to reduce the product risk by implementing one or more risk valuation tools. Assessment of CQAs is done by risk assessment according to ICH guidance Q9. Risk assessment is an organised method for evaluation, regulation and risk analysis of quality of intended formulation throughout the product development process.

Methods of risk assessment: Some methods of risk assessment are mentioned in ICH guideline Q9 as follows

- Failure Mode Effects Analysis (FMEA)
- Failure Mode, Effects and Criticality Analysis (FMECA)
- Fault Tree Analysis (FTA)
- Hazard Analysis and Critical Control Points (HACCP)
- Hazard Operability Analysis (HAZOP)
- Preliminary Hazard Analysis (PHA)
- Risk ranking and filtering
- Supporting statistical tools.

ICH guideline Q9 gives description of risk management and various terminologies associated with it, like risk acceptance, risk analysis, risk assessment, risk communication, risk control, risk evaluation, risk identification, and risk management. Quality management policies should indicate the procedures and practices to the tasks of assessing, controlling, communicating and reviewing risk. Risk reduction is the actions taken to lessen the probability of occurrence of harm and the severity of that harm.[4]

1. Establishment of experimental design

DoE is a key tool of QbD. During the product development DoE is employed for statistical optimization of formulation and process parameters. Optimization is the process of determining the finest probable composition or operating conditions considering all the factors that influence the results in any experiment. Optimization is defined as the execution of organized approaches to achieve the best amalgamation of product/or process features under a specified set of conditions. Optimization aims to discover the best possible values of dependent variables by varying certain independent variables which ultimately leads to improved quality, reduced manufacturing cost and safety of the product. The development and optimization of pharmaceutical products have been done by taking into consideration of only one factor at a time (OFAT approach). In this approach one of the factors is varied within an appropriate range or level, whereas the other factors are retained constants.

The OFAT approach does not allow to evaluate the interaction between the factors and it also necessitates very high run of experiments, which ultimately leads to insufficient conduction of the development and optimization. Thus, DoE was created to overcome these limitations because it provides better results with very few experimental runs. DoE is broadly employed in research as well as industrial settings. It allows the pharmaceutical experts to scientifically change the parameters as per the requirements of predefined design and reveals the relations among input and output variables.[2]

The advantages of DoE are

- It takes fewer experimental run to attain an optimum formulation.
- It helps to develop the best solution in the presence of additional challenging objectives.
- It possesses the strong ability to identify the problem and find solutions to those problems in an extraordinary way.
- It provides a thorough understanding of the formulation and also aids to identify the significant and nonsignificant input variables.
- DoE helps to evaluate and augments robustness of the experimental performance.
- It permits or allows alteration in formulation variables (ingredients) or process variable individualistically.
- Identify experimental error with ease and protect a remarkable amount of resources such as time, cost, materials, and effort.
- It helps to simulate the product or process performance by model equation(s).

- Estimate and enhance the statistical connotation of the projected model(s).
- It predicts the formulation performance without going through experimental preparation.
- DoE helps to evaluate and identify the probable interactions between the selected variables.
- It facilitates decision making by response mapping prior to conduct of subsequent experimentation.
- Offers rational suppleness in experimentation to assess the product system.[2]

After defining the QTPP and CQAs, the significant independent factors (i.e. CMAs and CPPs) are selected using DoE and then optimize the results by finding the conditions that meet the optimal values of the CQAs (i.e. response surface designs). Thus, a DoE can be divided into screening and optimization designs and can be considered as step 1(screening) and step 2 (optimization). When there are several factors that can influence the results, the screening designs are applied before the response surface designs with the aim of selecting the significant factors. When the process involving formulation development is well known, then this step may be omitted. Response surface methodology is applied for the formulation optimization. Response surface designs can be classified into two types: one in which variables or factors influencing the response can be adjusted independently of each other such as central composite designs or box Behnken designs and the other one in which variables corresponds to the components of a mixture, where the levels depend on each other, such as mixture designs.[5]

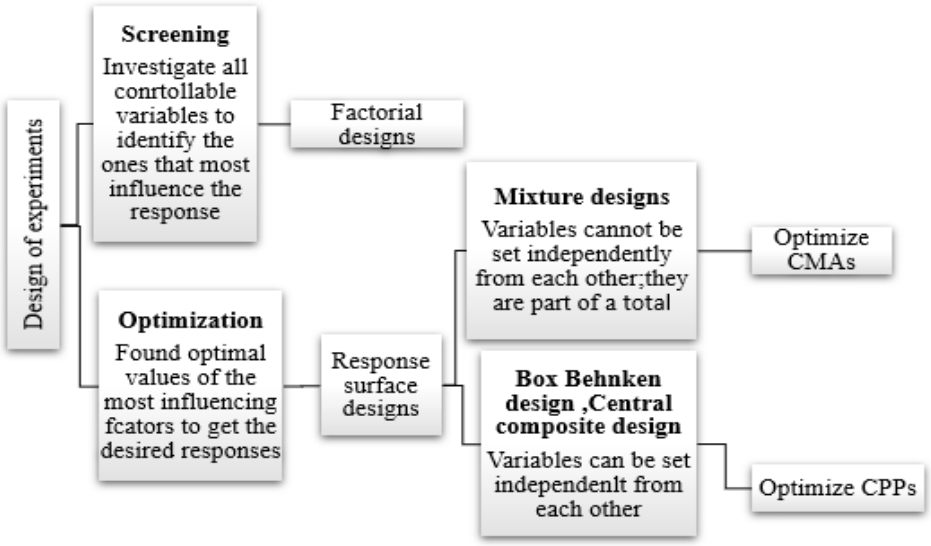

Figure 4: Flowchart highlighting the differences between screening and optimization designs of experiment.

Factorial designs

Factorial designs are typically employed as screening designs prior to the implementation of a more complex statistical study to investigate the factors that most influence responses. All controllable variables (i.e. the dependent variables such as materials, temperature and pressure are investigated and those that have greatest impact on the process will be identified by the end of the study. Therefore, it is beneficial to apply factorial design before using designs to optimize the formulations.[5]

A classical approach for a factorial design is called 'one factor at a time' (OFAT), which is a less efficient approach. In this approach the researcher analyses different responses by changing one factor while holding other factors as constants. This approach is less effective, simple and intuitive and can be considered where there are small number of factors that may affect the response. Another disadvantage of OFAT is that it discards the interaction between the factors. Inorder to overcome these limitations 2^k full factorial or the two-level fractional factorial designs are used which provide the information about the interaction between the factors, require less runs and therefore are less time and resource consuming.[5] Full FDs comprise studying the influence of all factors at various levels and the interaction among them. The simplest FD comprises the study of two factors at two levels, with appropriate coding of each level. FDs are considered symmetric, if each factor has the same number of levels and FDs are considered asymmetric if the number of levels differs for each factor. Full FDs are also termed as fully crossed design. An FFD creates experimental trials considering factorial points and creates a linear polynomial equation.[2]

In a 2^k full factorial design, 2 stands for the number of levels ('+' means high '-' means low values) of each factor and k means the number of evaluated factors. For example, if 2 factors are considered, the design will be 2^2, and for 3 factors, the design will be 2^3 and so on. In full factorial design, if there are a large number of influencing factors, the increasing number of runs can make the experiment very difficult to undertake. It may cause consumption of time and resources. Inorder to reduce the number of runs fractional factorial design (2^{k-p}) can be performed. These designs require the selection of p independent generators. Considering a 2^k design, if p=1 only half of runs would be required (2^{3-1} would have four runs instead of eight runs of a 2^3 design).

Response surface designs

These are designs which are used to examine the effects of the most significant factors that are recognised by screening studies. The number of factors in this design is usually 2 or 3 and these factors are varied on at least three levels. The main goal of response surface design is optimization.[6]

They consist of complex designs that aim to provide information about how the examined factors influence the responses, how they interact and above all, to find the optimum values of each factor that allow the desired responses to be obtained. Factorial designs are used to determine which are the independent factors that mostly contribute to the response. While RSD use mathematical and statistical techniques to optimize the responses and to understand how they are influenced by a set of independent factors. Here the responses are analysed by factorial and ANOVA methods to determine a truthful approximation of the real relationship between the responses and independent factors. A fist order model is applied if a linear function is appropriated to describe the relation. Polynomial function is applied if the relation creates a curvature. For example, quadratic function.[5]

The qualitative (discrete) factors cannot be used in these designs. A visual representation of the factors influence on the studied response is included in the response surface designs. As a result, it is possible to show the influence of two factors on the studied response in a graphically comprehensive manner. For more than two factors, only fractions of the entire response surface are visualised.[6] Based on the experimental goal and number of independent factors considered, the design type is selected. The most commonly employed response surface designs are the central composite design (CCD) and the Box-Behnken design (BBD) where three or five independent factors are investigated.[5]

Central composite design

The central composite design model is an integral part of response surface methodology. The greatest advantage of this type of optimization model is that it is more accurate and there is no need for building a second order quadratic model. After excising the CCD model within an experiment, a linear regression model has been used to construct the model and coadded values have been used. The CCD model is also called as Box Wilson central composite design.[7]

The central composite design is one of the most popular designs and it consist of a combination of 2^k full factorial and fractional factorial designs. This design examines the influence of the independent variables on the dependent variables. There are total of five levels: three levels (low, medium, and high) and two-star points (-α, +α). The axial points represent the extremes of low values and high values. They allow the design to fit in a second order model, admitting the estimation of a curvature and thus, being reliable in the predicted responses.[5]

Box Behnken design

BBD is likely to be the second most popular response surface design and has been suggested as a good substitute for CCD. In this design, three levels for each factor (low, center, and high) are defined and the corners of the design space are not considered; the focus depends on different combinations of the center and middle points. They are used to generate high resolution response surfaces following a smaller number of trials. It uses 3 center nodes and 12 central edge nodes to get fitted on a second-order equation. Though, BBD is not grounded on FD or FFD and needs at least three levels per factor. In the case of three factors, for instance, the points are located in the middle of the edges of the experimental domain. These designs are useful when the researcher does not consider important extreme responses (i.e. the corners of the cube). The corner level omission results in a simpler design with a small number of runs, when compared to the CCD. This design is described for a minimum of three factors and contains $N= (2f(f-1)) + C_0$ experiments, of which C_0 is the number of center points.[5]

Table 2: Popular optimization experimental designs with their Merits and Demerits.

S. no.	Optimization designs	Merits	Demerits	References
	Screening designs			
1.	Plackettt-Burman design	Efficiently screen many variables; effective for robustness testing; appropriate for very large number of factors, where even FFDs need a large number of experimental runs	Stagnant designs in which experimental runs are preset and limited to ≤ 16 trials. Effects confounded as appropriate for only two levels.	[8]
2.	Fractional factorial design (FFD)	Efficiently screen dominant factors	Screening of many factors	[9]

		from various potential factors; assess the interactions between factors	leads to increase in number of experimental runs; effects cannot be accurately estimated as there remains confusion with interaction terms.	
3.	Taguchi design	Accessible for huge number of factors and levels; effective for robustness testing of products or processes.	It is very complex and requires large number experimental runs; rarely apply in the pharmaceutical industry and modern analysis techniques.	[10]
	Response surface designs			
4.	Full factorial design	Competently evaluate main effects and interactions; maximum usage of data.	Cannot be recommended for five or more factors, reflection of curvature is not probable for two level designs; predication beyond the region is insensible.	[11]
5.	Central composite designs (CCD)	Applicable for sequential experiments; lesser number of trials needed as compared to three-level full factorial designs	CCD generally have axial points outside the cube	[12]
6.	Box -Behnken design (BBD)	BBD permits effective assessment of the first and second order coefficients, economical than	They are not suitable for sequential experiments; they cannot include runs	[13]

		CCD as it needs a fewer number of experimental runs provided same number of factors	from factorial experiments.	
7.	Optimal designs	Beneficial when resources restricted or there are constraints on factor settings; can be applied even if experimental domain is irregular in shape; can be used to create a good design for fitting a linear, quadratic or cubic model.	Design steps are slightly complex	[14]
8.	Mixture designs	Employed for factor optimization study; standard mixture designs and constrained mixture designs	Each factor cannot be adjusted independently of the others	[10]

3. Designing and Implementation of control Strategy/Policy

A control strategy is required to ensure that both material and processes remain within the anticipated range of lower and upper limits. Parameters and materials are regularly monitored during production to ensure consistency. Scale up typically involves a trial-and-error approach, where process parameters may differ but attributes which influence the quality remains the same. Hence control strategy is required.[4]

4. Continuous improvement throughout product life cycle

Product quality can be enhanced through the product life cycle, offering companies opportunities to employ innovative methods for quality improvement. Monitoring the process performance ensures consistency in product quality. Routine manufacturing provides valuable experience and knowledge that aids in refining methods and processes. Periodic maintenance can be conducted internally within a company's quality system, ensuring the design space remains unchanged. Quality by Design (QbD) facilitates continuous improvement throughout the product's lifecycle.[4]

Application of statistical tools of quality by design for novel drug delivery formulations

Novel drug delivery formulations especially nanostructured lipid carriers (NLCs), liposomes, niosomes, polymeric lipid carriers, microemulsion, nanoemulsion, metallic nanoparticles and solid lipid nanoparticles employs DoE for organized formulation development. The application of finest principles of QbD in association with thorough scientific knowledge is perfect to formulate quality products with high reliability and reproducibility.[2]

Table 3: Doe based optimization of various novel drug delivery carriers.

S. no.	Novel carriers	Bioactive/ drug	Design	Dependent variables	Independent variables	References
1	**Nanostructured lipid carriers**	Silymarin	Central composite rotatable design (CCRD)	Lipid concentration and concentration of Smix (surfactant and cosurfactant mix), combination of lipid and Smix concentration	Particle size, zeta potential, and entrapment efficiency	[15]
		Curcumin	Central composite design (CCD)	Vitamin E, tocopheryl polyethylene glycol succinate (TPGS), and poloxamer 188	Homogenizer speed and sonication time	[16]
		Resveratrol	Two-level, three-factor full factorial design	The amount of drug, surfactant, and solubilizer	Particle size, drug loading, and entrapment efficiency	[17]
		Natamycin	Four-factor, three-level Box-Behnken design	Content of lipids (castor oil and Precirol ATO 5), concentration of Span 80, high-pressure homogenization.	Particle size, polydispersity index, % drug entrapment, and % drug loading	[18]
2	**Solid lipid nanoparticles (SLNs)**	Curcumin	Three-variable, three-factors Box-Behnken design	Drug to lipid ratio surfactant concentration and speed of homogenization	Particle size, PDI, and entrapment efficiency	[19]
		Etoposide	Three-factor, three-level	Lipid mix concentration	Particle size, polydispersity	[20]

			Box-Behnken experimental design	(3:1%, w/v), surfactant concentration (%), and sonication time (min)	index, and entrapment efficiency	
		Luliconazole	Three-factor, three-level Box-Behnken experimental design.	surfactant concentration, lipid amount, and solvent volume.	Particle size and entrapment efficiency.	[21]
3	**Polymeric nanoparticles**	Resveratrol	Box-Behnken design	Amount of resveratrol amount, amount of poly- (lactic-co-glycolic) acid (PLGA), and amount of poly(-caprolactone)-poly(ethylene glycol) (PCL-PEG)	Particle size, polydispersity index, zeta potential, encapsulation efficiency, and ratio between NP size before and after freeze-drying (Sf/Si)	[22]
		Cinacalcet hydrochloride	Three factor three level Box - Behnken design	Drug: PLGA ratio, Poloxamer -188 concentration and stirring speed	QT 24%, Particle size, zetapotential and PDI.	[23]
4	**Liposomes**	Diacerein	Three-factor, three-level Box-Behnken experimental design	Amount of Span 60, amount of cholesterol, and hydration time	Particle size, entrapment efficiency, and polydispersity index	[24]
		Tranexamic acid	Three-factor, three-level Box-Behnken design	Lipid: cholesterol ratio, RPM of magnetic stirrer and number of cycles of probe sonication	Encapsulation efficiency and mean particle size	[25]
		Cefoperazone sodium	Box-Behnken design	drug: lipid ratio, hydration time and Sonication time	particle size and entrapment efficiency	[26]
		Azacitidine	Box Behnken design	Lipid concentration, cholesterol	particle size and drug entrapment efficiency	[27]

				concentration, sonication time		
5	**Microemulsion**	Itraconazole	D optimal mixture experimental design	Concentration of benzyl alcohol, Cremophor® EL and Transcutol® P	Globule size, pH value, viscosity	[28]
		Lidocaine and prilocaine	D-optimal mixture design	Concentration of oil, Smix and water	Globule size, skin retention, cumulative permeation and skin permeation flux.	[29]
6	**Nanoemulsion**	Agomelatine	Three-factor three-level central composite design.	% oil, $\%S_{mix}$ and sonication time	Hydrodynamic diameter (nm), % transmittance and % CDR	[30]
		Quercetin	3-factor 3-level Box–Behnken design	% surfactant and cosurfactant mixture (Smix), % amplitude and sonication time.	droplet size, polydispersibility index, % entrapment efficiency.	[4]

CONCLUSION

The objective of implementing Quality by Design (QbD) in pharmaceuticals are to minimize the product variability and defects, thereby improving the product development and manufacturing efficiencies. The key elements of QbD include defining the Quality Target Product Profile (QTPP), understanding and designing of the product and process, scaling up, developing a control strategy and continuous improvement. The QbD implementation is facilitated by tools such as prior knowledge, risk assessment, DoE and PAT. The application of QbD based statistical software in the formulation and optimization of drug delivery systems might result into high quality and cost-effective products with desirable features. This approach will provide maximum information with fewer trials and greater reproducibility. QbD is regarded as a crucial approach for ensuring product quality through well organized and effective experimental trails, and there by improving product and process performance.

ACKNOWLEDGEMENT

The authors are thankful to college of Pharmaceutical Sciences, Govt. Medical College, Kannur for the support and encouragement.

CONFLICTS OF INTEREST

The authors declare that they have no conflict of interest.

ABBREVIATIONS

QbD - Quality by design
QTPP - Quality target product profile
CQA - Critical quality attributes
CMA - Critical material attributes
CPP - Critical process parameters
DoE - Design of experiment
FD - Factorial design
CCD - Central composite design
BBD - Box Behnken design

REFERENCES

1. Yu LX, Amidon G, Khan MA, Hoag SW, Polli J, Raju GK, et al. Understanding pharmaceutical quality by design. AAPS J, 2014; 16(4): 771–83.
2. Pradhan M, Parihar AK, Singh D, Singh MR. Quality by design and formulation optimization using statistical tools for safe and efficient bioactive loading. InAdvances and Avenues in the Development of Novel Carriers for Bioactives and Biological Agents, 2020; 1: 555-594.
3. Abraham J. International conference on harmonisation of technical requirements for registration of pharmaceuticals for human use. InHandbook of transnational economic governance regimes, 2010; 1: 1041-1053.
4. Sangshetti JN, Deshpande M, Zaheer Z, Shinde DB, Arote R. Quality by design approach: Regulatory need. Arab J Chem, 2017; 1, 10: S3412–25.
5. Correia AC, Moreira JN, Sousa Lobo JM, Silva AC. Design of experiment (DoE) as a quality by design (QbD) tool to optimise formulations of lipid nanoparticles for nose-to-brain drug delivery. Expert Opin Drug Deliv, 2023; 2, 20(12): 1731–48.
6. Djuris J, Ibric S, Đurić Z. Quality by design in the pharmaceutical development. In Computer-aided applications in pharmaceutical technology, 2024; 1: 1-21.

7. Bhattacharya S. Central composite design for response surface methodology and its application in pharmacy. InResponse surface methodology in engineering science, 2021; 28. IntechOpen.
8. Plackett RL, Burman JP. The Design of Optimum Multifactorial Experiments. Biometrika, 1946; 33(4): 305–25.
9. Jacyna J, Kordalewska M, Markuszewski MJ. Design of Experiments in metabolomics-related studies: An overview. J Pharm Biomed Anal, 2019; 5, 164: 598–606.
10. N Politis S, Colombo P, Colombo G, M Rekkas D. Design of experiments (DoE) in pharmaceutical development. Drug Dev Ind Pharm, 2017; 43(6): 889–901.
11. Singh B, Dahiya M, Saharan V, Ahuja N. Optimizing drug delivery systems using systematic "design of experiments." Part II: retrospect and prospects. Crit Rev Ther Drug Carrier Syst, 2005; 22(3): 215–94.
12. Ladani RK, Patel MJ, Rakesh PP, Bhatt T. Modern optimization techniques in field of pharmacy. Res J Pharm Biol Chem Sci, 2010; 1(2): 148.
13. Hibbert DB. Experimental design in chromatography: a tutorial review. J Chromatogr B Analyt Technol Biomed Life Sci, 2012; 1, 910: 2–13.
14. Swarbrick J, Boylan JC. Encyclopedia of Pharmaceutical Technology: Volume 20 - Supplement 3. CRC Press, 2000; 342.
15. Iqbal B, Ali J, Baboota S. Silymarin loaded nanostructured lipid carrier: From design and dermatokinetic study to mechanistic analysis of epidermal drug deposition enhancement. J Mol Liq, 2018; 1, 255: 513–29.
16. Lakhani P, Patil A, Taskar P, Ashour E, Majumdar S. Curcumin-loaded nanostructured lipid carriers for ocular drug delivery: design optimization and characterization. Journal of drug delivery science and technology, 2018; 1, 47: 159-66.
17. Rajput AP, Butani SB. Resveratrol anchored nanostructured lipid carrier loaded *in situ* gel via nasal route: Formulation, optimization and *in vivo* characterization. J Drug Deliv Sci Technol, 2019; 1, 51: 214–23.
18. Patil A, Lakhani P, Taskar P, Wu KW, Sweeney C, Avula B, et al. Formulation Development, Optimization, and In Vitro-In Vivo Characterization of Natamycin-Loaded PEGylated Nano-Lipid Carriers for Ocular Applications. J Pharm Sci, 2018; 107(8): 2160–71.
19. Rompicharla SVK, Bhatt H, Shah A, Komanduri N, Vijayasarathy D, Ghosh B, et al. Formulation optimization, characterization, and evaluation of *in vitro* cytotoxic potential

of curcumin loaded solid lipid nanoparticles for improved anticancer activity. Chem Phys Lipids, 2017; 1, 208: 10–8.

20. Ahmad I, Pandit J, Sultana Y, Mishra AK, Hazari PP, Aqil M. Optimization by design of etoposide loaded solid lipid nanoparticles for ocular delivery: Characterization, pharmacokinetic and deposition study. Mater Sci Eng C Mater Biol Appl, 2019; 100: 959–70.
21. Khurana G, Sharma VV, Arora D. QbD-Driven Development and Characterization of Solid Lipid Nanoparticles (SLNs)–Based Nanogel of Luliconazole for the Effective Management of Dermal Fungal Infection. J Pharm Innov, 2023; 1, 18(4): 2249–64.
22. Musazzi UM, Youm I, Murowchick JB, Ezoulin MJ, Youan BBC. Resveratrol-loaded nanocarriers: Formulation, optimization, characterization and *in vitro* toxicity on cochlear cells. Colloids Surf B Biointerfaces, 2014; 1, 118: 234–42.
23. Ghose D, Patra CN, Ravikumar BVV, Swain S, Jena BR, Choudhury P, et al. QbD-based Formulation Optimization and Characterization of Polymeric Nanoparticles of Cinacalcet Hydrochloride with Improved Biopharmaceutical Attributes. Turk J Pharm Sci, 2021; 18(4): 452–64.
24. Moghddam SRM, Ahad A, Aqil M, Imam SS, Sultana Y. Formulation and optimization of niosomes for topical diacerein delivery using 3-factor, 3-level Box-Behnken design for the management of psoriasis. Mater Sci Eng C Mater Biol Appl, 2016; 1, 69: 789–97.
25. Verma P, Yadav KS. Quality by Design (QbD) enabled and Box-Behnken design assisted approach for formulation of tranexamic acid loaded stratum corneum lipid liposomes. J Drug Deliv Sci Technol, 2023; 1, 86: 104571.
26. Ghodake V, Vishwakarma J, Vavilala SL, Patravale V. Cefoperazone sodium liposomal formulation to mitigate *P. aeruginosa* biofilm in Cystic fibrosis infection: A QbD approach. Int J Pharm, 2020; 25, 587: 119696.
27. Kesharwani P, Md S, Alhakamy NA, Hosny KM, Haque A. QbD Enabled Azacitidine Loaded Liposomal Nanoformulation and Its In Vitro Evaluation. Polymers, 2021; 13, 13(2): 250.
28. Choi DH, Kim YS, Kim DD, Jeong SH. QbD based development and evaluation of topical microemulsion-based hydrogel against superficial fungal infections. Journal of Pharmaceutical Investigation, 2019; 15, 49: 87-103.
29. Negi P, Singh B, Sharma G, Beg S, Raza K, Katare OP. Phospholipid microemulsion-based hydrogel for enhanced topical delivery of lidocaine and prilocaine: QbD-based development and evaluation. Drug Deliv, 2016; 23, 23(3): 941–57.

30. Ahmed S, Gull A, Alam M, Aqil Mohd, Sultana Y. Ultrasonically tailored, chemically engineered and “QbD” enabled fabrication of agomelatine nanoemulsion; optimization, characterization, *ex-vivo* permeation and stability study. Ultrason Sonochem, 2018; 1, 41: 213–26.