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APPLICATION OF QUALITY BY DESIGN TO DIFFERENT ASPECTS OF PHARMACEUTICAL TECHNOLOGIES

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ABSTRACT: Quality by Design [QbD] is a science based approach widely used in industry to continually monitor and improve the quality of product. It is a modern risk based strategic framework of all the aspects related to quality. ICH guidelines Q8 to Q11 summarizes all the different perspectives of quality by design system in required depth along with ways to implement it. This review in all focuses on the general terms of QbD its meanings and application along with different wide range applications of the QbD to pharmaceutical fields like Analysis, Formulation, Design and Technology development, Control Strategies etc. Also it includes a short view over the application of Various QbD tools like PAT, CAPA and HACCP in Pharmaceutical industry along with their importance in the Quality aspect of Pharmaceutical products. It also tries to cover the major aspects to be concerned while selecting the wide ranges of designs and statistical tools while employing QbD to a Particular aspect of Pharmaceutical Technology.

INTRODUCTION: Pharmaceutical industry is constantly searching the ways to ensure and enhance product safety, quality and efficacy. However, drug recall, manufacturing failure cost, scale up issues and regulatory burden in recent past produces huge challenge for industry. In traditional, the product quality and performance are predominantly ensured by end product testing, with limited understanding of the process and critical process parameters. Regulatory bodies are therefore focusing on implementing Quality by Design [QbD], a science based approach that improves process understanding by reducing process variation and the enabling process-control strategies.

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In case of QbD, a quality issue can be efficiently analysed and root cause quickly identified. QbD requires identification of all critical formulation attributes and process parameter as well as determining the extent to which any variation can impact the quality of the finished product [1]. Changes in formulation and manufacturing processes during development and lifecycle management should be looked upon as opportunities to gain additional knowledge and further support establishment of the design space. Design space is proposed by the applicant and is subject to regulatory assessment and approval. Working within the design space is not considered as a change. Movement out of the design space is considered to be a change and would normally initiate a regulatory post approval change process.

Regulatory Control Guidelines Emphasising QbD: The QbD approach which is based on scientific and methodical product development was included in the quality guidelines of International Conference on Harmonization [ICH] from 2005

onwards. This approach includes, ICH Q8 [Pharmaceutical Development], Q9 [Quality Risk Management], and Q10 [Pharmaceutical Quality System] guidelines. The pharmaceutical products quality was also emphasised in Process Analytical Technology [PAT] guidelines for new pharmaceutical product development and quality. In 2004, USFDA agreed to include QbD in "Pharmaceutical cGMP 21st Century - A risk based approach."

QbD describes a pharmaceutical development approach referring to formulation design and development and manufacturing process to maintain the prescribed product quality. Guidelines and mathematical models are used to ensure the establishment and use of the knowledge in the subject in an independent and integrated way. In order to initiate a successful QbD program, the first step is to identify those process parameters that are essential to product quality and develop well - validated analytical methodologies to monitor those parameters.

Key Element of QbD:

ICH Q8: Pharmaceutical Development: [1, 2] It discusses the various element of Quality by Design. These in combination with the enabler form the fundamental basis for the QbD approach to development. It involves the following key element during pharmaceutical development:

1. Define the Quality Target Product Profile
2. Identify the Quality Attributes
3. Perform a Risk [Assessment] Analysis
4. Determine the Critical Quality Attributes and Critical Process Parameter
5. Determine the Design Space
6. Identify a Control Strategy

Quality Target Product Profile [QTPP]: According to ICH Q8 [R2], QTPP is "Prospective summary of the quality characteristics of a drug product that ideally will be achieved to ensure the desired quality, taking into account safety and efficacy of the drug product". Basically it is a tool for setting the strategy for drug development. Recently QTPP is widely used in development planning, clinical and commercial decision making, regulatory agency interactions, and risk management. It is the quality characteristics that the drug product should possess in order to reproducibly deliver the therapeutic benefit promised in the label. The QTPP guides formulation scientists to establish formulation strategies and keep the formulation effort focused and efficient.

Quality Attributes: Once QTPP has identified, the next step is to identify the relevant CQAs. A critical quality attribute as defined by ICH Q8 [R2] is 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 generally associated with raw materials [drug substance, excipients], intermediates [in-process materials], and drug product. Drug product CQAs derived from the QTPP is used to guide the product and process development.

Drug product CQAs are the properties that are important for product performance, that is, the desired quality, safety, and efficacy. This indicates that CQAs are subsets of QTPP that has a potential to be altered by the change in the formulation or process variables. For example, QTPP may include additional quality attributes of the drug product such as strength and dosage form, which are not the part of CQA as it will not change during drug development process. However, QTTP attributes such as assay, content uniformity, dissolution, and permeation flux will also be a part of CQA as they may be altered by formulation or process variables. For example, the CQAs of drug substance and drug product are enlisted in **Table 1**. [3]

TABLE 1: TYPICAL CQAS FOR DRUG SUBSTANCE AND DRUG PRODUCTS

For Drug Substance [Chemical]	For Drug Product [Tablet]
Appearance	Appearance
Particle size	Identification
Morphic forms	Hardness
Water content	Uniformity of dosage
Residual solvents	Physical form
Organic impurities	Dissolution
Inorganic impurities	Degradation products
Heavy metals	Water content
Residue on ignition	Assay
Assay	Microbiological limits

ICH Q9: Quality Risk Management [QRM]: [4] Identification of CQAs is done through risk assessment as per the ICH guidance Q9. The FDA

defines a Risk Management as, a strategic safety program designed to decrease product risk by using one or more interventions or tools. It is systematic process for the assessment, control, communication and review of risks to the quality of the drug product across the product lifecycle [6]. (**Fig. 1**).

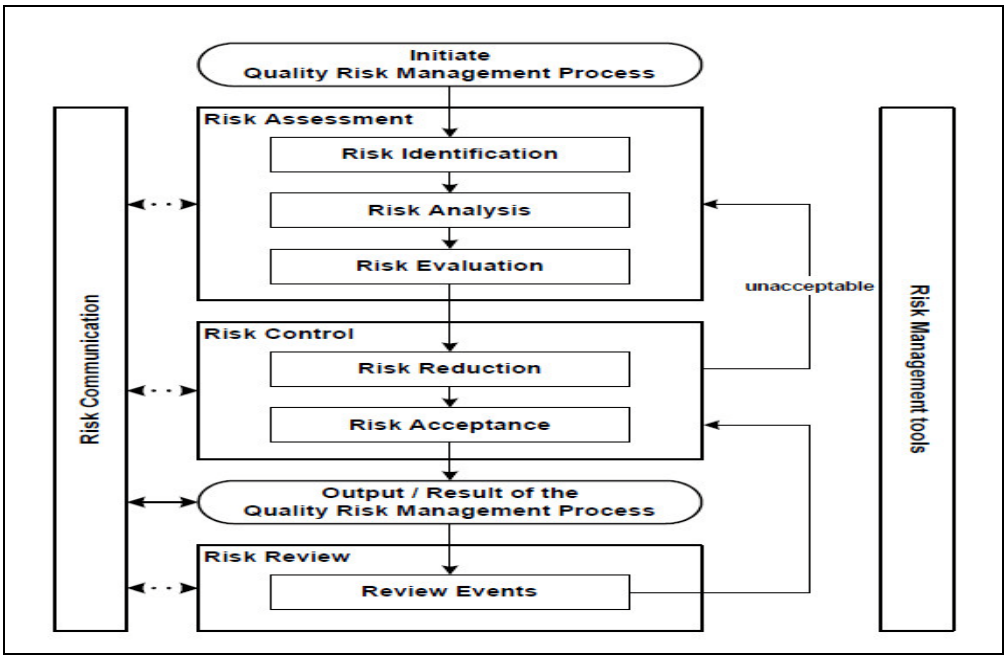


FIG. 1: RISK MANAGEMENT STEPS

Failure Mode Effect Analysis [FMEA]: [1] FMEA is one of the most commonly used risk-assessment tools in the pharmaceutical industry. It is a systematic and proactive method to identify and mitigate the possible failure in the process. Failure modes represent any errors or defects in a process, material, design, or equipment. Once failure modes are established, FMEA tool evaluates the effect of these failures and prioritizes them accordingly. This tool is further advanced with studying criticality of the consequences and providing clear indication of situation. It also includes the use of Ishikawa [Cause and effect / Fishbone] diagram. (**Fig. 2**)

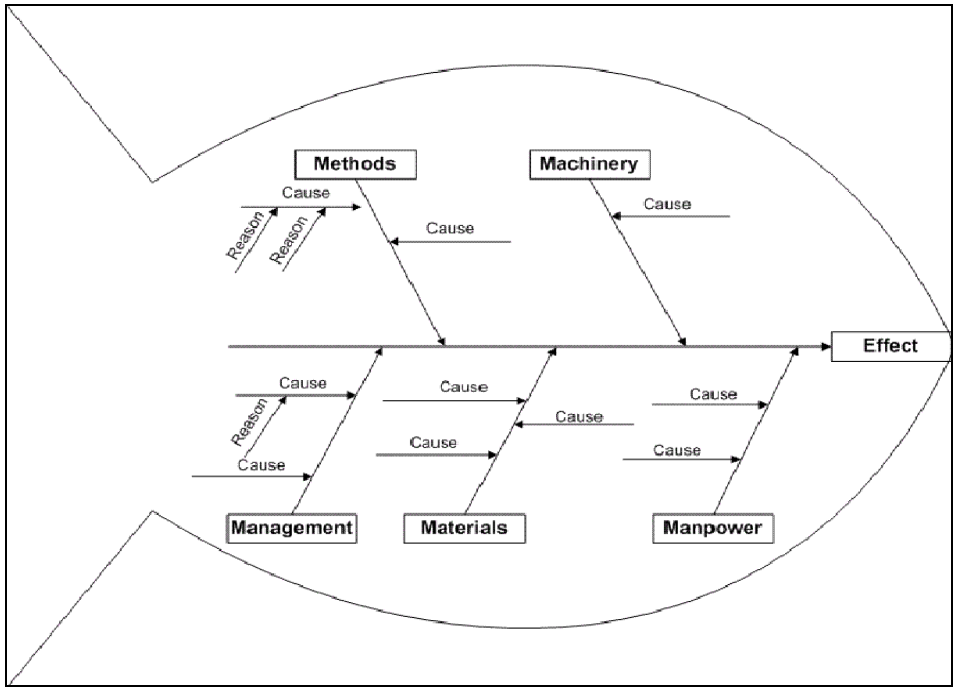


FIG. 2: ISHIKAWA DIAGRAM

Hazard Analysis and Critical Control Points [HACCP]: HACCP provides detailed documentation to show process or product understanding through identifying parameters to control and monitor the hazards and their respective critical points. The definition of hazard includes both safety and quality concern. Examples of hazards within the pharmaceutical environment includes aspects of the facility [environmental conditions, hygiene aspects]; material flow; manufacturing steps; personnel hygiene and technical aspects relating to process design.

1. HACCP consists of the following seven steps:
2. Conduct a hazard analysis and identify preventive measures for each step of the process
3. Determine the critical control points
4. Establish critical limits
5. Establish a system to monitor the critical control points
6. Establish the corrective action to be taken when monitoring indicates that the critical control points are not in a state of control
7. Establish system to verify that the HACCP system is working effectively
8. Establish a record-keeping system. [1, 5, 6]

Determination of Critical Process Parameters: A critical process parameter [CPP] is any measurable input [input material attribute or operating parameter] or output [process state variable or output material attribute] of a process step that must be controlled to achieve the desired product quality and process consistency. A parameter is critical when a realistic change in that parameter can cause the product to fail to meet the QTPP. Thus, whether a parameter is critical or not depends on how large of a change one is willing to consider. Thus the first step in classifying parameters is to define the range of interest which we call the potential operating space [POS]. The POS is the region between the maximum and minimum value of interest for each process parameter. Criteria for identifying critical and non-critical parameters are that a parameter is non-critical when there is no trend to failure within the POS and there is no evidence of interactions within the proven acceptable range [PAR], which is the range of experimental observations that lead to acceptable quality. **Table 2**

TABLE 2: CLASSIFICATION OF PROCESS PARAMETERS

Parameter type	Definition	Sensitivity
Non-critical process parameter [non CPP]	Not critical	• No failure in target product quality profile [TPQP] observed or predicted in the potential operating space [POS], and • No interaction with other parameters in the proven acceptable range [PAR]
Unclassified process parameter [UPP]	Critically unknown	• Not established • The default in the absence of pharmaceutical development
Critical process parameter [CPP]	Critical control needed to ensure quality	• Failure in target product quality profile [TPQP] observed or predicted in the potential operation space [POS], or • Interactions with other parameters in the proven acceptable range [PAR]

Design Space: ICH Q8 [R2] defines 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. Working within the design space is not considered as a change. Movement out of the design space is considered to be a change and would normally initiate a regulatory post approval change process. Design space is proposed by the applicant and is subject to regulatory assessment and approval." Design space may be constructed for a single unit operation, multiple unit operations, or for the entire process. Though according to FDA guideline, defining design space is optional since the product and process understanding can be established without a formal design space, nevertheless, such approach can assist to better understanding and attain overall control of a system.

The Design Space is linked to criticality through the results of risk assessment, which determines the associated CQAs and CPPs. It describes the multivariate functional relationships between CQAs and the CPPs that impact them, and should

include their linkage to or across unit operations. Such relationships are arrived at by iterative application of risk assessment and experimental design, modeling, as well as the use of literature and prior experience.

Methods for Determining Design Space Included: one variable at a time experiments, statistically designed experiments, and modeling approaches. Methods for presenting design space included graphs [surface-response curves and contour plots], linear combination of parameter ranges, equations, and models. Alternatively, the design space can be explained mathematically through equations describing relationships between parameters for successful operation. **Fig. 3** [7, 8, 9]

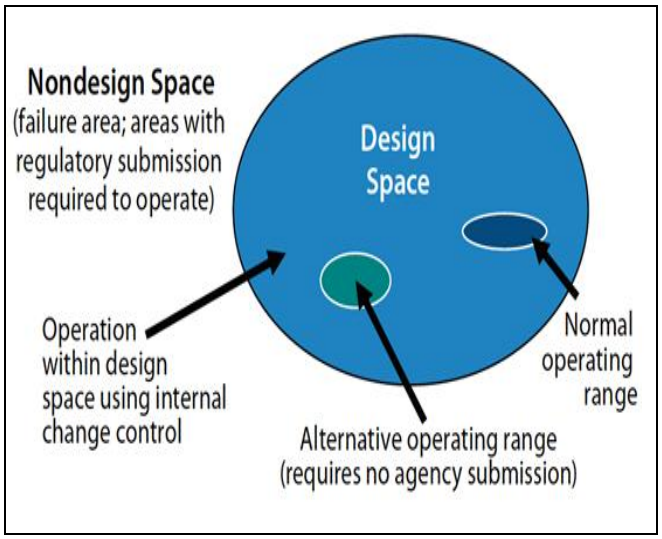


FIG. 3: ESTABLISHING DESIGN SPACE

Design Space May include:

Discovering the Process Design Space: Understanding your processes is the key to defining the design space. Critical process parameters [CPPs] are identified by determining the extent to which any process variation can affect the quality of the product. When you define your design space, you are able to anticipate issues and plan how to control the process. Actual experimental data, product experience, or literature guidance can be used to define the extremes of the parameter sets to be refined.

Understanding the Control Space: Based on the process design space, a well-executed control space can be defined. This enables you to understand your processes in a way that ensures product quality from known variability of the production process. This disciplined approach will keep your complex production processes under control. To illustrate the concept of a control space study, think of a reference product data set with tightly clustered data points that represent the output of a tightly controlled process.

Plotting the output of your process and comparing it to such a reference will give a clear indication of whether your process is in control. One technique to help avoid such a disparity is to conduct a Design of Experiments [DOE] study on your product in the development stage. Considerable wasted effort can be eliminated with such an approach as can any unexpected adverse outcome from the lack of control space understanding.

Targeting the Operating Space: The operating space is the best set of parameters, determined statistically, which enable you to accommodate any natural variability in CPPs and CQAs. For generic products, the operating space should be within the control space and should allow a reference product to be tested with the same set of parameters.

For new products, the operating space should be within the design space and compliant with regulatory guidelines. Innovators can gain a competitive advantage by thoroughly exploring the design space, including testing multiple batches of formulations to truly refine their product.

ICH Q10: Quality System: [10]

Control Strategy: Using a risk assessment approach, it is possible to establish a control strategy for product attributes that assures high quality through process and/or testing control The Attribute Testing Strategy [ATS] tools were designed to identify quality attributes that required process and/or testing controls, or that could be captured in a monitoring system to enable lifecycle management of the control strategy. The ATS is set based on the application of a risk ranking and filtering tool [RRF tool].

This tool takes into account the relevance of the identified critical quality attributes [CQAs] and the process capability and stability for these CQAs with respect to their acceptable ranges. In turn, the acceptable ranges for the CQAs set the frame for the determination of critical process parameter identification and the Design Space.

ICH Q10 defines a control strategy as "a planned set of controls derived from current product and process understanding that assures process performance and product quality. The controls can include parameters and attributes related to drug substance and drug product materials and components, facility and equipment operating conditions, in process controls, finished product specifications and the associated methods and frequency of monitoring and control."

A control strategy normally include input material controls, process controls and monitoring, design space around individual or multiple unit operations, and/or final product specifications used to ensure consistent quality. The finished drug products are tested for quality by assessing if they meet specifications.

Design of Experiment: In case of design of experiment [DOE] approach, variables are first 'screened' to determine which are critical to the outcome. Second step is the 'optimization', where the best suitable and optimal range or working conditions are determined. It involves the use of different experimental designs for changing conditions and exploring how such changes will affect the quality of final product.

Advantages of DOE:

1. Better innovation due to the ability to improve processes.
2. More efficient technology transfer to manufacturing.
3. Less batch failures.
4. Greater regulator confidence of robust products.
5. Risk- based approach and identification.
6. Innovative process validation approaches.
7. For the consumer, greater product consistency[11]

Use of DOE: DOE is used to determine the causes of variation in the response, to find conditions under which the optimal response is obtained. It is also used to compare responses at different levels of controlled variables and to develop a model for predicting response. To predict these results and achieve optimal conditions different experimental designs are used which are elaborated below: **Table 3** and **4** [2, 12-15]

TABLE 3: VARIOUS EXPERIMENTAL DESIGNS

Name of Design	Application
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. It is used to estimate a linear model
Response Screening Design	Response screening design involves just the main effects and interactions or they may also have quadratic and possibly cubic terms to account for curvature model which may be appropriate to described a response
General Factorial Design	Design for 1 to 12 factors where each factor may have a different number of levels
Fractional Factorial Design	Full factorial experiments can require many 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.
2 – level factorial design	Design for 2 to 21 factors where each factor is varied over 2 levels. It is used for estimating main effects and interactions. It may be used for screening many factors to find the significant few
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. It is a design for 2 to 31 factors where each factor is varied over 2 levels. It is useful for ruggedness testing where one can hope to find little effect on response due to interaction of any of the factors
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. Each factor is varied over 3 levels. If categorical factors are added, the Box – Behnken Design will be duplicated for every combination of the categorical fractional levels
D – Optimal Design	A design for categorical factors that is created based on the model which is specified. The design is a subset of all possible combination of factors. It is generated to minimize the error associated with the model coefficients
Taguchi OA Design	These are orthogonal array designs from Taguchi's textbook. In these design, all main effects and no interactions are considered

Simple Lattice Design	It is a mixture design for 2 to 30 components where each component must have the same range and there are no constraints on the design space. The points chosen are the pure components and then enough points between those to estimate the polynomial chosen. It is augmented to include the center point and axial check blends
Historical Data Design	It is a design for importing already existing data. It is necessary to specify maximum and minimum values for each possible factor. The rows must be set equal to number of historical data points one has. Cut and Paste has to be used to import data into the blank design layout

Applications: QbD is applied on a large scale in pharmaceutical industry. Some of the applications are as follows

Application of Pharmaceutical Qbd for Enhancement of the Solubility and Dissolution of Class II BCS Drug Using Polymeric Surfactants and Crystallization Inhibitors: Development of Controlled - Release Tablets: [16] The aim of this research was to develop a Felodipine Solid Mixture [FSM] containing hydrophilic carriers and/or polymeric surfactants. Felodipine was chosen as the BCS Class-II drug. The material attributes of excipients used for preparation of FSMs were identified. For these effect of different hydrophilic carriers and polymeric surfactants on solution of felodipine was studied. The screening of the inhibitory effects of different hydrophilic carriers and polymeric surfactants on crystallization of Felodipine from supersaturated solution was done. The FSMs were prepared using Box-Behnken Design which helped in obtaining results in fewer runs than Central Composite Design.

The FSMs prepared were than evaluated. It was observed that there was no proposed design space if pluronic content was below 45.1 mg. On the other hand, mixture of pluronic and HPMC showed dual action which helped in development of design space. **Table 5** Experimental Design used was Box Behnken Experimental Design. The software used was Design Expert Software.

TABLE 5: PARAMETER AND SENSITIVITY CHART-1

Parameter	Parameter Type	Sensitivity
Amount of polymer HPMC [mg]	Critical Material Attribute	Had stabilizing and inhibitory effect on solubilized drug
Amount of polymeric surfactant, Inutec SPI [mg]	Critical Material Attribute	Increased solubility of Felodipine by surface active mechanism
Amount of Pluronic F127 [mg]	Critical Material Attribute	Increased solubility of Felodipine by surface active mechanism
Preparation Technique	Critical Process Parameter	Increased solubility of Felodipine
Maximum solubility after 30 minutes [µg/ml]	Critical Quality Attribute	Successful Operating Range – $\geq$ 75µg/ml Observed Value – 110.2 µg/ml
Equilibrium Solubility after 24 hours [µg/ml]	Critical Quality Attribute	Successful Operating Range – $\geq$ 45µg/ml Observed Value – 58.7 µg/ml
Dissolution Efficiency [%]	Critical Quality Attribute	Predicted Value – 75 – 95 % Observed Value – 72.4 %

Application of QbD to Development of Analytical Separation Methods: [17-20] The need for application of QbD to be applied to Analytical separation methods was observed since these methods are used for quality control analysis of API and drug products. The methods used for investigation were HPLC and Capillary Electrophoresis [CE] methods. [**Table 6**]

A Qbd Case Study on Enteric Coated Pellets: Screening of critical variables and establishment of design space at laboratory scale [21].

TABLE 6: PARAMETER TYPE AND SENSITIVITY-2

Parameter	Parameter Type	Sensitivity
Separation Criteria [S]	Critical Quality Attribute	It gives difference between retention time
Run Time	Critical Quality Attribute	Time consumption
Efficiency	Critical Quality Attribute	Process
Robustness	Critical Quality Attribute	Important while choosing working point

The aim of the research was to prepare Naproxen enteric coated pellets [NAP-ECPs] by fluid-bed coating using QbD principle. The method used was Failure Mode and Effect Analysis [FMEA].

TABLE 7: PARAMETER TYPE AND SENSITIVITY-3

Parameter	Parameter Type	Sensitivity
Coating Weight Gain	Critical Material Attribute	Uniformity of weight and drug release will change.
Percent of Triethyl Citrate	Critical Material Attribute	Its concemtration decides the acid resistance
Percent of Glyceryl Monostearate	Critical Material Attribute	Its concemtration decides the drug release
Response of acid resistance	Critical Quality Attribute	Efficiency of enteric coating will change
Cumulative drug release	Critical Quality Attribute	Depends on uniform coating

The most important variables affecting enteric coated pellets characteristics were assessed by Plackett-Burman Design. The main, interactive and quadratic effect of above mentioned variables were assessed by Box-Behnken Design. To establish relation between variables and CQAs, Response Surface Method was used. [**Table 7**]

A QbD Case Study on Liposomes Containing Hydrophilic API: Formulation, Processing Design and Risk Assessment: [22] The drug selected was Tenofovir. Tenofovir has high polarity which results in low intracellular absorption. Liposomes of Tenofovir were developed which have high hydrophobicity and which resulted in enhanced intracellular uptake. The drug being anti-retroviral, it was needed to be targeted to Limphatic tissues and macrophage rich regions. The care was taken that there is no leakage of drug until cellular uptake which might lead to toxicity. [**Table 8**]

TABLE 8: PARAMETER TYPE AND SENSITIVITY-4

Parameter	Parameter Type	Sensitivity
Lipid Concentration	Critical Process Parameter	It affects drug encapsulation efficiency. Higher the lipid concentration, higher the encapsulation of drug.
Drug Concentration	Critical Process Parameter	It also affects drug encapsulation efficiency. Decrease in drug concentration lead to higher drug encapsulation of drug
Lipid Chain Length	Critical Material Attribute	It has no effect on drug encapsulation efficiency
Preparation Technique	Critical Process Parameter	Larger particles were broken by sonication and freeze-thaw cycle which increased encapsulation efficiency
Particle Size	Critical Quality Attribute	Lower the particle size, higher the encapsulation efficiency. It was selected between 100-200 nm
Drug Encapsulation Efficiency	Critical Quality Attribute	High percent of drug encapsulation resulted in low manufacturing cost and increased drug concentration in final formulation. This allowed greater flexibility in dosing which resulted in increase in patient compliance

It was concluded that larger particle size and uni-lamellar structure would result in liposome formulation with higher drug encapsulation.

A Qbd Case Study on Liposomes Containing Hydrophilic API: Screening of Critical Variable and Establishment Design Space at Laboratory Scale: [23] This research was the continuation of above mentioned research. Plackett-Burmann Design was used to screen eight high risk variables out of which two variables were found out which had impact on drug encapsulation efficiency *viz.* lipid concentration and drug concentration. The Central Composite Design [CCD] was then used to elucidate relation between lipid concentration, drug concentration and encapsulation efficiency. To fully utilize CCD and to make accurate prediction of further formulations, 3 mathematical models were used *viz.* linear model, quadratic model and linear model with interaction terms. Two software were used in this research as follows: [**Table 9**]

TABLE 9: PARAMETER TYPE AND SENSITIVITY-5

Software	Use
Minitab 15.0 Software	For design and analysis
Mathematica 7.0 Software	For plotting various 3D and Contour graphs

A QbD Approach on Starch-Based Nanocapsules: A Promising Platform for Topical Drug Delivery: [24] The aim of research was to develop novel Starch based Nanoparticulate Carrier System [StNC] for topical delivery of lipophilic bioactive molecules. The method used was emulsification-solvent evaporation method.

Capric/ Caprylic triglycerides were dissolved in cationic surfactant ethanol solution. It was added to aqueous phase containing Tween 80 and hydrated polymer. Constant magnetic stirring was done. Coumarin-6 was incorporated [for the purpose of identification and localization of drug in compound] and the probe was added simultaneously to the lipid component. Particle size analysis and zeta potential measurements were done. The QTPP element were defined in the beginning as follows: **Table 10** and **11**

TABLE 10: RELATION OF QTPP WITH TARGET

Sr. no.	QTPP element	Target
1.	Route of Administration	Topical
2.	Dosage Form	I. Nanoparticle [nanocapsule] < 1µm II. Particle Size Distribution d[10] → 0.1 – 0.3 µm d[50] → 0.2 – 0.5 µm d[90] → 0.3 – 0.9 µm Span → 0.5 – 2 µm
3.	Stability	Zeta Potential > 30 mV At least 12 months shelf life at 5 ± 3 °C
4.	Biological Effects	Non-sensitizing and non-irritant

TABLE 11: PARAMETER TYPE AND SENSITIVITY-6

Parameter	Parameter Type	Sensitivity
Stirring Time	Critical Process Parameter	Longer stirring time lead to smaller nanocapsules with lower span
% of non-ionic surfactant	Critical Process Parameter	Higher the amount of non-ionic surfactant, lower the particle size
Amount of lipid	Critical Process Parameter	Higher the amount of lipid, more the particle size

All StNC formulations had zeta potential of Ca. + 33.6 ± 6.7mV. The positive value indicated interaction of nanocapsules with skin components. The skin components are negatively charged at physiological pH. So, cationic surfactants are expected to have higher skin retention and penetration. Hence, it was proved that StNC is a promising pharmaceutical dosage form for topical application.

Near Infrared and Raman Spectroscopy as Process Analytical Technology Tools for the Manufacturing of Silicone-based Drug Reservoirs: [25] FDA's Process Analytical Technology [PAT] is part of the QbD concept, it focuses on "improving the pharmaceutical development, manufacturing and quality assurance through innovation in product and process development, process analysis and process control". This forced us to add a research on PAT in our review.

Using near infrared [NIR] and Raman spectroscopy as PAT tools, 3 critical quality attributes of a silicone based drug reservoir were studied. First, the Active Pharmaceutical Ingredient [API] homogeneity in the reservoir was evaluated using Raman spectroscopy [mapping]: the API distribution within the industrial drug reservoirs was found to be homogeneous while API aggregates were detected in laboratory scale samples manufactured with a non-optimal mixing process. Second, the cross-linking process of the reservoirs was monitored at different temperatures with NIR spectroscopy.

Conformity tests and Principal Component Analysis [PCA] were performed on the collected data to find out the relation between the temperature and the time necessary to reach the cross-linking end points. An agreement was found between the conformity test results and the PCA results. Third, based on the HPLC reference method, a NIR model able to quantify the API in the drug reservoir was developed and thoroughly validated. Partial Least Squares [PLS] regression on the calibration set was performed to build prediction models of which the ability to quantify accurately was tested with the external validation set. **Table 12**

A Process Analytical Technology [PAT] Approach to Control a New API Manufacturing Process: Development, Validation and Implementation: [26] Quantitative NIR methods are generally applied to detect and determine the analyte as it exists in the sample matrix [*i.e.* without any sample preparation] and require multivariate calibration to link the NIR spectrum with the analytical reference method result. This implies that NIR method is conceptually different from conventional analytical techniques; the design, the development and the validation of such

a method are inextricably linked and must be considered holistically. **Fig.** lists all the steps performed during the calibration and validation phases. To ensure the fit for purpose use of the presented NIR method, calibration and validation designs were built following the QbD framework; including analytical target profile [ATP] risk assessment, design of experiments [DOE] and robustness / ruggedeness evaluation. **Fig.4**

TABLE 12: PARAMETER TYPE AND SENSITIVITY-7

Parameter	Parameter Type	Sensitivity
Evaluating Critical Quality Attributes of Silicone based drug reservoirs by NIR and Raman Spectroscopy	Quality Target Product Profile	It helped to quantify API in drug reservoir
Evaluating the API homogeneity in the reservoir	Critical Quality Attribute	the API distribution within the industrial drug reservoirs was found to be homogeneous while API aggregates were detected in laboratory scale samples manufactured with a non optimal mixing process
Monitoring the cross-linking process of the reservoirs at different temperatures with NIR Spectroscopy	Critical Quality Attribute	It helped in finding out the optimal temperature at which cross-linking takes place [80^0C]
Developing and validating an NIR model able to quantify the API in drug reservoir	Critical Quality Attribute	It clearly showed that the developed NIR method can replace the conventional reference HPLC method

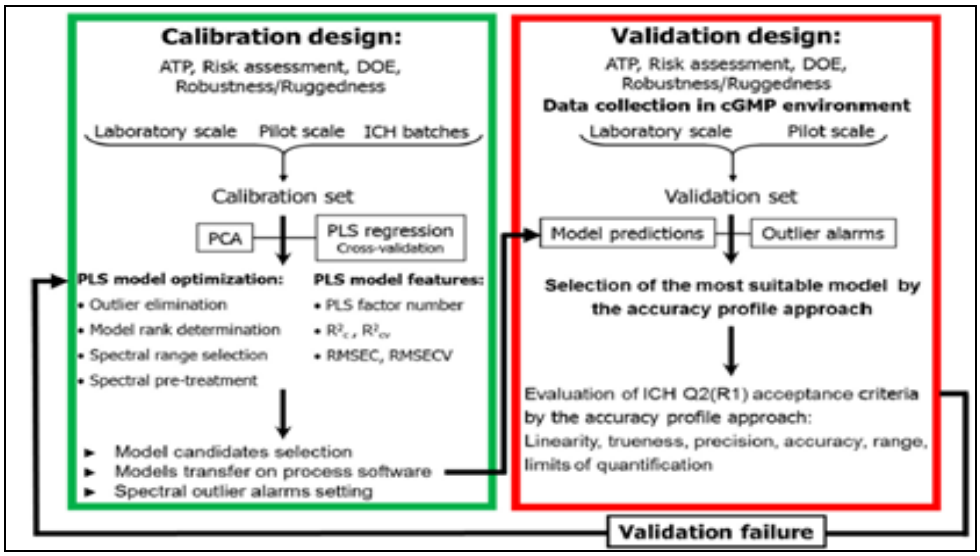


FIG. 4: METHOD DEVELOPMENT AND VALIDATION METHODOLOGY

Quality-by-Design Based Development of a Self-Micro-emulsifying Drug Delivery System [SMEDDS] to Reduce Food Effect of Nelfinavir Mesylate: [27] Nelfinavir Mesylate is a drug having poor aqueous solubility and moderate permeability. So, SMEDDS was developed for Nelfinavir Mesylate. For preparing SMEDDS, D-optimal mixture design was used. Software generated numerically optimized SMEDDS were developed. Maisine 35-1, Tween 80 and Transcutol HP were identified as oil, surfactant and co-surfactant. Ternary phase diagrams were plotted to identify the efficient self-emulsification region. Prepared SMEDDS were found to be thermodynamically stable with droplet size of 121nm, poly-dispersity index [PDI] of 0.198, and emulsification time of < 1 min. There was absence of food effect with no significant difference in dissolution performance in fasted state simulated intestinal fluid and fed state simulated intestinal fluid. There was 4.57 fold enhancement in apparent permeability and 3.5 - 3.6 fold enhancement in oral bioavailability. Development of SMEDDS formulation was found to be best alternative to enhance oral bioavailability of Nelfinavir Mesylate. **Table 13**

TABLE 13: PARAMETER TYPE AND SENSITIVITY-8

Parameter	Parameter Type	Sensitivity
Amount of Maisine 35-1, Tween 80, Transcutol HP	Critical Process Parameters	These were considered as the independent variables while constructing ternary phase diagram
Droplet Size	Critical Quality Attribute	It determines *in-vivo* fate of emulsion. The equation generated between independent variables and PDI suggested a combination of Maisine 35-1, Tween 80 and Transcutol HP strongly contributed to prepare SMEDDS bearing uniform droplet size distribution
Polydispersity Index	Critical Quality Attribute	It gives an estimate of droplet size of formulation. It was found that joint effort of Tween 80 and 393 Transcutol HP was maximum in decreasing PDI
Self Emulsification Time	Critical Quality Attribute	It was found that Transcutol HP predominantly influenced self emulsification time
Viscosity	Critical Quality Attribute	It determines the ability of formulation to be filled in hard or soft gelatin capsules. Transcutol HP was found to decrease viscosity
Firmness	Critical Quality Attribute	It is the measure of the force required to obtain a given deformation or by the amount of deformation under a given force. The enhancement in the firmness of SMEDDS could be obtained by enhancing the Transcutol HP and Tween 80 in the ternary mixture to highest levels

Taking above factors into consideration, mid-levels of amount of Maisine 35-1, Tween 80, Transcutol HP were considered. Development of SMEDDS formulation was found to be best alternative to enhance oral bioavailability of Nelfinavir Mesylate.

Quality by Design Approach for Optimizing the Formulation and Physical Properties of Extemporaneously Prepared Orodispersible Films: [28] The quality by design [QbD] approach was applied for optimizing the formulation of extemporaneously prepared orodispersible films [ODFs]. The starting formulation was based on earlier experiments and contained the film forming agent's hypromellose and carbomer 974P and the plasticizer glycerol. Trometamol and disodium EDTA were added to stabilize the solution.

Quality Target Product Profile, Critical Quality Attributes and Critical Process Parameters were defined which are as mentioned in the table. Response surface methodology [RMS] was used to evaluate the effects of the CPPs on the CQAs of the final product. The main factor affecting tensile strength and Young's modulus was the percentage of glycerol. From the results a design space could be created. **Table 14**.

TABLE 14: PARAMETER TYPE AND SENSITIVITY-9

Parameter	Parameter Type	Sensitivity
Tensile Strength	Critical Quality Attribute	preferred tensile strength was found for ODFs containing a high percentage of HPMC, a low percentage of glycerol and dried at a low drying temperature
Elongation at Break	Critical Quality Attribute	ODFs should have sufficient handling properties. Three combinations of a low percentage glycerol with a high or low percentage of HPMC and different drying temperatures resulted in an elongation of break > 10%
Young's Modulus	Critical Quality Attribute	For ODFs a Young's modulus below 550 N/mm^2 is preferable
Model Justification	Critical Quality Attribute	The normal probability plot of residuals showed for all test that residuals fell approximately along a straight line indicating that the data were normally distributed.
Design Space	Critical Quality Attribute	It gave an range in which further studies were needed to be done

The software used was Design Expert Software

Establishing Control System Using QbD Principles: [29, 30] An integrated set of risk assessments and their related elements developed at Roche/Genentech were designed to provide an overview of product and process knowledge for the production of a recombinant monoclonal antibody. This chapter describes the elements and tools used to establish acceptance criteria and an attribute testing strategy [ATS] for product variants and process related impurities. The acceptable ranges for CQAs are set based on their potential impact on efficacy and safety/immunogenicity. This approach is focused on the management of patient impacts, rather than simply maintaining a consistent analytical profile. The ATS tools were designed to identify quality attributes that required process and/or testing controls or that could be captured in a monitoring system to enable lifecycle management of the control strategy. [**Fig. 5**]

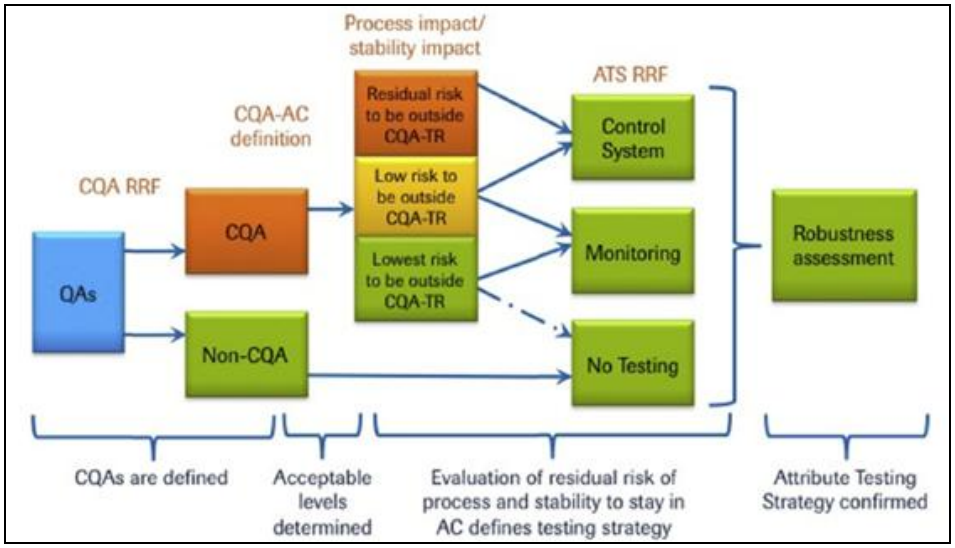
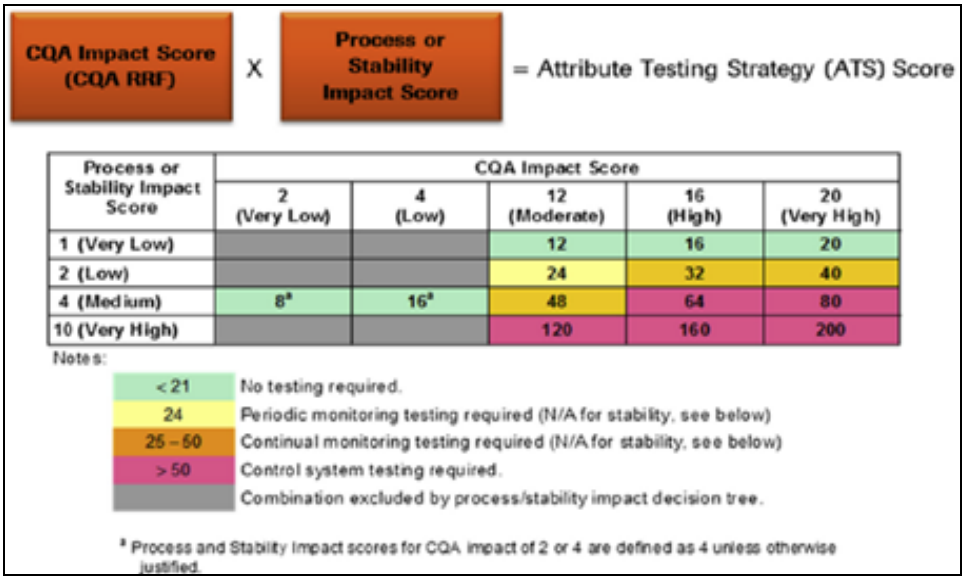


FIG. 5: DEVELOPMENT OF ATTRIBUTE TESTING STRATEGY

The ATS is set based on the application of a risk ranking and filtering tool [RRF tool]. This tool takes into account the relevance of the identified critical quality attributes [CQAs] and the process capability and stability for these CQAs with respect to their acceptable ranges. [**Fig. 6**]



Process or Stability Impact Score	CQA Impact Score				
	2 (Very Low)	4 (Low)	12 (Moderate)	16 (High)	20 (Very High)
1 (Very Low)			12	16	20
2 (Low)			24	32	40
4 (Medium)	8[a]	16[a]	48	64	80
10 (Very High)			120	160	200

Notes:

< 21	No testing required.
24	Periodic monitoring testing required (N/A for stability, see below)
25 – 50	Continual monitoring testing required (N/A for stability, see below)
> 50	Control system testing required.
	Combination excluded by process/stability impact decision tree.

[a] Process and Stability Impact scores for CQA impact of 2 or 4 are defined as 4 unless otherwise justified.

FIG. 6: ATS RISK RANKING FILTER

Understanding Pharmaceutical Quality by Design: [31] This review clarifies the concept of pharmaceutical Quality by Design [QbD]. In this article, they have given process parameters and

quality attributes for pharmaceutical unit operations. This gives us an idea of selection of process parameters and quality attributes for even basic operations used in industry and laboratory. Here, the parameters have been mentioned for Roller compaction/chilsonation and Extrusion-Spheronisation. **Table 15** and **16**

TABLE 15: PROCESS PARAMETERS AND QUALITY ATTRIBUTES FOR ROLLER COMPACTION/ CHILSONATION

Parameter	Parameter Type	Sensitivity
Deaeration	Process parameter	It affects Flow Property
Roll shape	Process parameter	It affects Shape and size of product
Ribbon appearance	Critical Quality Attribute	It affects Uniformity
Ribbon porosity	Critical Quality Attribute	It affects Fine Flow
Ribbon tensile strength	Critical Quality Attribute	It affects Flexibility

TABLE 16: PROCESS PARAMETERS AND QUALITY ATTRIBUTES FOR EXTRUSION-SPHERONIZATION

Parameter	Parameter Type	Sensitivity
Screw Feed [rpm]	Process Parameter	It affects Yield quality
Feeding rate [g/min]	Process Parameter	It affects Final yield of the product
Air flow	Process Parameter	It affects Extrusion ability of product
Residence Time	Process Parameter	It affects Drying and uniformity
Density	Critical Quality Attribute	It affects Proper flow
Moisture Content	Critical Quality Attribute	It affects Uniform extrusion
Pellets after spheronization	Critical Quality Attribute	It affects Final QC aspects of product
Pellets size and distribution	Critical Quality Attribute	It affects Uniformity in content and dose
Brittleness	Critical Quality Attribute	It helps to estimate robustness of product
Elasticity	Critical Quality Attribute	It affects film formation

CONCLUSION: Quality by design is an important tool in today's era as far as pharmaceutical industries are concerned. Considering this ICH has also specified guidelines for using QbD in daily practices of industry. Till date there was no relevant literature available regarding different applications of QbD. An effort was made here to bring together such varied practical applications along with basics of QbD. This article concludes to be useful for studying and understanding all such basics and applications of QbD in different fields relating Pharmaceutical industry.

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