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A MINI-REVIEW ON RECENT ADVANCEMENT ON OPTIMIZATION OF ANALYTICAL METHODS BY QUALITY BY DESIGN

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ABSTRACT

Quality-by-design (QbD) approach has been applied to optimize the analytical methods. The principle of QbD for the development of analytical methods is known as Analytical Quality by Design (AQbD). In most cases, a variety of input elements can have an impact on the quality of products. Design of Experiments (DoE) has recently been popular as a way to better understand the impacts of multivariate and interrelated input variables on the output responses of pharmaceutical goods and analytical methods. QbD implementation for analytical method development is covered in ICH guidelines Q8 to Q10,this article addresses the definition of Analytical Quality by Design (AQbD), a Quality by Design (QbD) extension. Due to the lack of informative reviews, this article has been shared to address the optimization of analytical procedures through the adoption of QbD in the pharmaceutical quality system, as well as to correspond with product quality by design and pharmaceutical analytical technology (PAT).Identification of ATP (Analytical Target Profile), CQA (Critical Quality Attributes) with risk assessment, Method Optimization, and Development using DoE, MODR(method operable design region) are all essential AQbDtools.This review addresses the concepts and applications of QbD for the optimization of analytical methods such as HPLC, RP-HPLC, Gas chromatography, GC-MS, LC-MS, reporting successful optimized analytical methods published in the last few years.

INTRODUCTION

In the pharmaceutical industry, quality by design (QbD) has been a significant conceptual model meanwhile its implementation by the US Food and Drug Administration.The International Conference on Harmonization (ICH) describes QbD as a strategic drug manufacturing approach that begins with set goals.[1]present review paper summarizes the recent advancement on optimisation of analytical methods by QbD.

Quality is actually designed by QbD into the process, thus countering the conventional quality by testing (QbT) model that measures the product's quality by evaluating it at the end of the production process. QbD leads to the development of design space (DS), described as the complex combinations and corelations of product parameters and process variables shown to guarantee the quality assurance.[2]

Quality by Design is the modern approach for quality of pharmaceuticals. It describes use of Quality byDesign to ensure quality of Pharmaceuticals. The aim of the pharmaceutical development is to design a quality product and its

manufacturing process to consistently deliver the intended performance of the product.

pharmaceutical Quality by Design (QbD) is a systematic method to development that starts with defined aims and prioritizes product and process understanding and control, all while adhering to solid science and quality risk management. The literature is rich in reviews that demonstrate the benefits of QbD in the fields of chemistry and pharmaceuticals. However in such review articles, a commercially focused pipeline study detailing QbD tools and methodologies that are currently being applied in the industry is often lacking. Therefore, we intend to provide a better perception of current QbD implementation and pharmaceutical industry's position, optimization of analytical methods in this review and provide valuable information on QbD methodologies and techniques that are currently being more intensively implemented to achieve various objectives. We also point out existing gaps and possible opportunities that we have identified from the critical review of the bibliographic corpus that could be considered in the future to increase and enhance the acceptance of QbD in the Pharma Companies.[3]

QBD PRINCIPLES

A comprehension approach, beginning with set targets and applying science expertise and managing risk, as demonstrated by drug production using the QbD principles. The FDA Regulatory Authority expressed the significance of quality by providing PAT as a framework for novel pharmaceutical production and assurance of quality (pharmaceutical products). ICH Q8-pharmaceutical development, Q9-quality risk management, Q10-pharmaceutical quality system set down QbD that is scientific and probability of new product development, management of risk and quality police. fig 3[4]

ELEMENTS OF QBD

AQbD begins with a target analytical profile, which is an analogue of QTPP. Analytical Target Profiling specifies the purpose of the analytical technique implementation procedure, comparing the outcome of QTPP approach to accomplish. ATP is a simple declaration that defines the intent of the mechanism used to direct the choice and pattern of method. In AQbD, ATP is a main variables that promotes enhanced creation and choice of analytical methods once the regulatory authorities have approved them."[5]

Quality Target Product Profile (QTPP), which determines the drug product's CQAs. Design and perception of goods, including the recognition of essential material characteristics Design and understanding of processes, involving the determination of critical process parameters (CPPs) and a detailed insight of the concepts of Scaling-up, connecting CMAs and CPPs with CQAs.

A strategy, which involves requirements for the substance(s) of the prescription, the excipient(s) and the drug product

CRITICAL QUALITY ATTRIBUTES

The important quality features, such as purity, potency, and substitution for bioavailability criticality, must be determinedIt is determined by the quality attribute's impact on the product's protection, efficacy, and consistency. Establish a connection among CPP & CQAs: Detection of attributes that can be used as a substitute for clinical safety and effectiveness[7]

Quality Target Product Profile defining the drug substance critical Quality Attributes.QTPP is a potential description of the consistency properties of a drug substance that can be better done, taking into consideration of the reliability, efficiency of drug product, to guarantee optimal quality. QTPP forms the foundation of product development design. Following considerations for encompassing in the QTPP have included:(3)

- purpose for the usage of drug, route of drug administration, type of drug delivery system and dosage form
- Strength of Dose
- container and its closures
- Release of medicinal moiety and attributes that affect pharmacokinetic characteristics suitable to the type of drug substance dosage being established
- Quality requirements for the drug product suitable for the expected product placed on the market [7]

PROCESS ANALYTICAL TECHNOLOGY (PAT)

In order to make sure the quality of final product, process analytical technology (PAT) has been identified as a method for the timely planning, review and control of production with quick and efficient assessment of essential content and production characteristics of input and in process products and procedures.[8]

METHOD OPERABLE DESIGN REGION

Design Space is a multifaceted configuration as well as activity of process variables that have been evaluated to ensure quality assurance, consequently, protection and effectiveness (CMA and CPP). A transition subject to notice that ensures regulatory flexibility is not regarded to be a change of input factors within the design space domains. Additionally, quantitative approaches for desirability functions can be measured for multi response optimization. Different parameters, such as optimizing, minimizing, reducing, Optimization of the output responses and the target[9]

DESIGN OF EXPERIMENTS (DOE'S) AND RESPONSE MODELLING

DOE's provide an accurate, excellent method for assessing the effects of variables and their interactions collectively modelling and predicting relation between these variables and CQAs. Assessment of experimental errors and evaluation of the validity model should be allowed. The two main types are 1. Screening designs 2. Response surface designs

Screening designs:

Examples of screening designs are i) Plackett design ii) Burman designs

These are well known and that results in the study of factors at two levels.

response surface designs:

These DOEs include i) Full factorial design ii) Central composite design iii) Box-Benkhen and Doehlert designs that results in the study of factors at three level. DOE relates to designs and estimate and optimise the results.[10]

selection of doe tools:

In order to achieve a statistical relationship, several methods can be used during optimisation. On the basis of response variables, control parameter knowledge and scientific comprehension between result and variable, the assessment on the choice of tool for doe must be made. Especially in comparison to factorial design, the Taguchi method can be used for a lesser number of trials (50 percent, 25 percent, etc) but complicated interactions need to be determined. The plackett-Burman methods should be used when a large number of input parameters are to be examined without interference effects. The table shows a standard range of techniques.

Means - Design and development of formulations and production processes to assure a predefined quality

Need to - Understand how the variables of the formulation and production processes impact product quality

Ensures – Quality of substance with successful monitoring strategy

Fig 1: What is Quality by Design

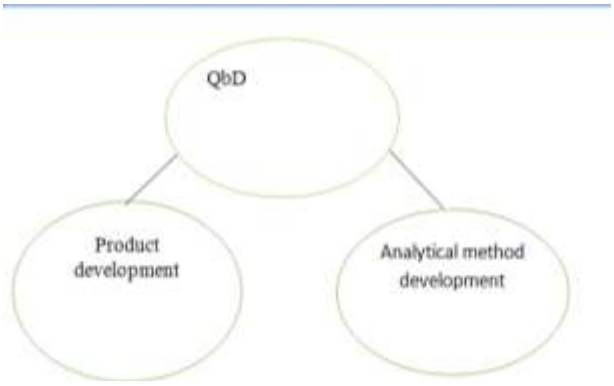

Fig 2: Qbd In Pharmaceutical Industry

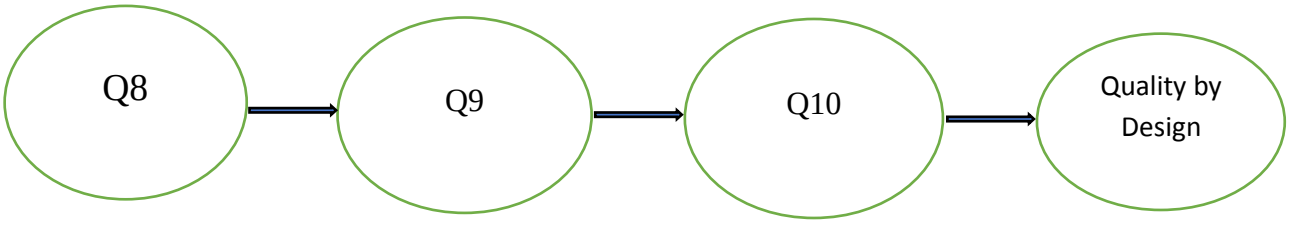

Fig. 3QbD principles

Table 1: Difference between regulatory perspective of QbD and AQbD(6)

Product Quality by Design	Analytical Quality by Design (AQbD)
Quality Target Product Profile (QTPP)	Analytical Target Profile (ATP)
Critical Quality Attributes (CQA)	Critical Performance Attributes (CPA)
Impact evaluation of sensitive material attributes and criteria for critical processing	Critical Process Characteristics and Critical Method Parameters risk evaluation
Designing of Experiments Development of Design Space (DS)	Designing of Experiments Development of Method Operable Design Region-MODR
Manufacturing Process Validation	Analytical Method Validation
Implementation of Control Strategy	Implementation of Control Strategy
Continual Process Improvement	Continual Method Improvement

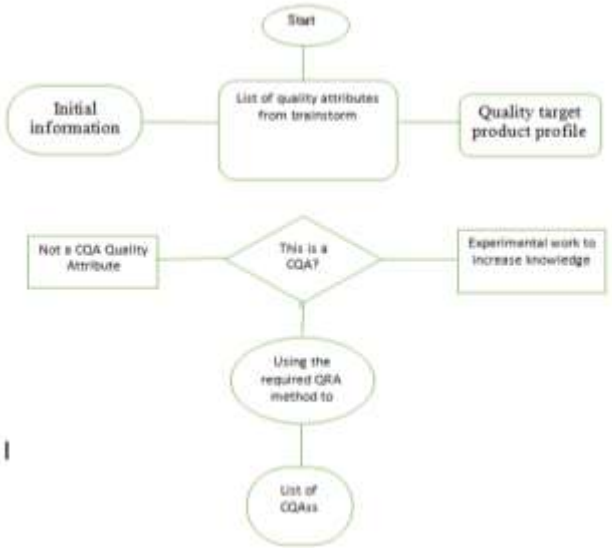

Fig 4: Decision tree to decide CQAS[7]

Table 2: Selection of DOE tools

Name of the design	No of variables	Benefit	Drawback
Full factorial design	Optimization variables 2-5	Without any confusion, assessing the Central and Primary Contact Effect	If the number of variables increases, experimental runs increase.
Taguchi method	Variables for optimization and screening	Minimal number of experimental runs	It is a difficult task to assess the confounding impact of interactions
Plackett-Burman Method	Identifying a few critical variables from a large number of variables	For large numbers of variables, you need very smaller runs	Does not report an interaction impact

QBD HAS MANY BENEFITS

An assumption that can be gained from reading the literature is that QbD is similar with the design of QbD experiments, enabling process information to be created that is appropriate for technology transfer, design space and performance maintenance, process control and improvement systems, and risk mitigation is very significant.[11]

Effective, scalable, agile scheme
Increase the quality of production, minimize costs project rejection
Inclusion of risk assessment
Remove failures of batch
Mitigate deviations and expensive inquiries
Prevent troubles of regulatory enforcement
Organizational learning is a potential investment
Better decisions on

Table 3: Advancement of QbD in optimisation of various Analytical methods

Risk assessment	Technique	Critical method Variables	DOE	Design space	Application	Target method	Reference
The interaction between CMPs and CAAs of the ATP is depicted using an Ishikawa fishbone cause-effect diagram.	RP-HPLC	Mobile phase and Flow rate	Taguchi design	MODR-Monte Carlo simulations	Quantification of Ferulic acid	C18 column acetonitrile: water (47:53 % v/v) pH - 3.0 0.8 mL/min flow rate λmax - 322 nm	(12)
An analytical target profile (ATP)and critical quality attributes (CQAs) were first defined in a standard analytical quality by design approach.	HPLC	Resolution between critical-pairs of peaks.	central composite design with four factors (pH, temperature, flow rate, and acetonitrile %).	4D design space	robust stability indicating method of azilsartanmedoxomil using QbD	C8 column 0.025 M phosphate buffer (pH 2.7) and acetonitrile (52.5: 47.5%) 1.5 mL/min flow rate λmax - 225 nm	(13)
Study of Failure Mode Effect Analysis (FMEA) helped to choose important	RP-HPLC	mobile phase ratio flow rate	face-centred cubic design	MODR	In the presence of stress-induced degradation conditions, a quantitative study of sorafenib	C18 column acetonitrile and water in the ratio	(14)

process parameter					Tosylate	of (65:35 v/v) 0.8 mL/min flow rate UV Detection - 265 nm	
The basis for the difference in CAAs with different inputs was extended by Ishikawa fish-bone diagram.	RP-HPLC	pH, Flow rate, Injection volume, Buffer type	seven factor and eight run Taguchi screening design	response surface analysis	systematic design of the high sensitivity liquid chromatographic process for FA assessment in medicinal products using AQbD	C18column methanol: acetonitrile (5: 95, v/v) and an aqueous phase with (pH of 2.8) (60: 40 v/v) λmax - 235 nm	(15)
Ishikawa fish-bone diagram	HPLC	Ratio of Mobile phase, Flow rate, volume of injection, Wavelength	Taguchi experimental design	CCD of response surface methodology	Utility of QbD to optimize chromatographic conditions for the implementation of a highly sensitive liquid chromatography condition for ketoprofen	C18 column phosphate buffer: methanol (50: 50v/v) pH (6.8) 1.0 mL/min flow rate λmax - 258 nm.	(16)
Fish-bone diagram of Ishikawa reflecting the impactof possible main MPs and PPs	RP-HPLC	Mobile phase ratio Flow rate	seven-factor eight-run Taguchi design	The face-centered cubic design	Estimation of Olmesartan Medoxomil Using QbD by Liquid Chromatographic approach	C18 column acetonitrile and water containing 0.1% orthophosphoric acid, (pH 3.5) 40:60	(17)

						(v/v) 1.0 mL/min flow rate UV Detection - 243 nm	
Experimental design facilitated understanding of the critical method variables	RP-HPLC	Ratio of mobile phase, pH , flow rate	Taguchi design	Box–Behnken design	The use of analytical QbD optimized the chromatographic isolation of nevirapine (rat plasma).	C18 column 68:9:23 % v/v elution of methanol, acetonitrile and water 1.0 mL/min flow rate UV Detection - 230 nm	(18)
Stationary phase, Gradient time, Column temperature, pH of the eluentA, were identified as critical parameters for design of experiments	UHPLC - UV detection combined with 2D-UHPLC -MS method	Mobile phase composition or column temperature flow rate pH	Dry Lab chromatography modelling software package	The aim of the QbD approach is to create a "digital Design Space" where the process is robust	In order to implement the assessment of identified isoflavonoids in routine dietary supplement evaluation, a UHPLC-UV method was developed.	C18 column (2D-UHPLC -MS) run time-2.0 min Detector -two diode array detectors	(19)
Critical method attributes (CMAs) are monitored according to AQbD approach, since they indicate the responses that show the output of the method.	UHPLC	buffer molarity, buffer pH, column temperature	full factorial design (2^6)	central composite face centered response-surface design	The initial effective tool for precise monitoring of ropinirole hydrochloride process-related impurities.	C8 column Acidicbuffer (A) and acetonitrile/methanol (B) 70:30% (v/v) UV Detectio	(20)

						n - 250 nm	
The critical method parameter was investigated using a central composite face response-surface model.	RP-HPLC	Mobile phase Flow rate Column temperature	central composite face response-surface design	MODR-The Monte Carlo simulation	The new approach is sufficient for the identification of seven Celecoxib process-related impurities.	immobilized chiral Pak IA-3 column ratio of acetonitrile 44.918 % (45%) 0.795 mL/min flow rate	(21)
The essential parameters should be defined in an early risk assessment.	UHPLC	gradient time, temperature, ratio of mobile phase	chromatography modelling software Dry Lab	the Monte-Carlo simulation	stability UHPLC method for ebastine using QbD	C18 column 50 mm × 2.1 mm, 1.7 m acetate buffer pH 6.2 and mixture of acetonitrile and 2-propanol (1:1)	(22)
To identify the critical factors Taguchi screening method was used	RP-HPLC	Theoretical Plates, % Assay, Tailing Factor	Box-Behnken Design	Surface response design	robust RP-HPLC method was implemented and optimised evaluation of methotrexate based on Quality by Design (QbD)	C18column different ratio composed of buffer, ACN and MeOH (pH 3.0) 0.6 ml/min flow rate UV Detection wavelen	(23)

						gth - 302 nm	
Risk assessment was conducted Using factorial fractional design (FFD)	RP-HPLC	Flow rate Ratio of mobile phase	Fractional Factorial Design (FFD)	central composite design (CCD)	Estimation of RLX in bulk drugs and marketed formulations	methanol and sodium acetate buffer (pH 4) 50:50 (v/v) 1ml/min flow rate λmax - 287nm.	(24)
A three factorial design to identify the critical characteristics of quality	RP-HPLC	PH of the buffer Flow rate and % of acetonitrile	three factorial design	central composite design	For the assessment of PES and related impurities in the pharmaceutical industry.	buffer and acetonitrile (95:5 v/v) 1.3 mL/min flow rate (pH 3.0) λmax - 210nm	(25)
Risk evaluation experiments have been used to analyse the effects of variables impacting the quality profile of the target system.	RP-HPLC	mobile phase composition flow rate UV-wavelength (nm C)	Box–Behnken statistical design (BBD)	To access the analytical design space, use response surface methodology.	The bioanalytical method based on the QbD approach is ideal for in-vitro and in-vivo DFG estimation.	C18 column acetonitrile and water in the ratio of 50:50 % (v/v) 0.5 mL/min flow rate λmax - 235nm	(26)
fractional factorial design revealed has significant influence on method CAAs	HPLC	Flow rate, Injection volume, Column temperature, Buffer strength,	Box-Behnken design	The optimal chromatographic conditions were defined using response surface mapping, computational optimizatio	estimation of quercetin dihydrate using AQbD	C18 column acetonitrile and ammonium acetate buffer 35:65 % (v/v) 0.7 mL/min flow	(27)

				n, anda desirability function.		rate λmax - 237nm.	
The essential parameters should be defined in an early risk analysis.	LC-MS	mobile phase composition, Buffer pH, Flow rate	3-factor 3-level BBD	Box-Behnken design factor–response relationship and plausible interaction among them	LC–MS approach for Fluoxetine quantification using QbD	C18 column ammonium formate and acetonitrile solution (5:95 ratio) 0.8 mL/min flow rate injection volume - 10 µL	(28)
Risk assessment is done to identify the critical analytical attributes	HPLC	mobile phase composition, buffer concentration, flow rate and wavelength	24–1 fractional factorial design (FFD)	response surface methodology	Using experimental design, simultaneous assessment of rifampicin and ofloxacin was done successfully	C18 column mixture of 0.03M Potassium dihydrogen phosphate buffer pH 3.0 as mobile phase A and Acetonitrile as B (55:45) UV detector - 230 nm	(29)
Other experimental designs are assessed against at least three dependent variables and multiple responses.	RP-HPLC	Mobile phase composition Flow rate pH Peak Area Retention Time	32 - factorial design	box-Behnken experimental design	Estimation of amoxicillin trihydrate using Box-Behnken experimental design	0.02 M potassium dihydrogen orthophosphate (A) methanol (B)	(30)

						(ratio 50:50 %v/v) 1 mL/min flow rate λmax - 229 nm	
An Ishikawa fish-bone cause-effect	RP-HPLC	Flow rate and mobile phase ratio	fractional factorial design (FFD	central composite design (CCD)	quantification of MTX	solvents like acetonitrile and ammonium acetate buffer (pH 6) (ratio 25:75 v/v) 0.8 mL/min flow rate λmax - 257nm.	(31)
For crticalfactors, the Box-Behnken design was optimised.	LC/MS/MS	composition of mobile phase, flow rate and pH	experiment optimized by BBD	Box-Behnken design	Quantificationof Paracetamol and Diclofenac using QbD	C8 column solution A and B in the ratio of 20:80 0.4 ml/min flow rate Injection volume - 7µl	(32)

DISCUSSION

This article list out the analytical methods optimised by using QbD. The analytical methods like HPLC, UHPLC, RP-HPLC, LC-MS, LC/MS/MS are optimised and are tabulated in this review including risk assessment, technique involved, critical method variables, design of experiments, design space, applications of the analytical method and target method. This information is collected from research and review articles.

There are only a few publications in the literature that illustrate how systematic QbD activities can be used effectively in analytical sciences. This article is the authors' humble attempt to raise awareness about AQbD paradigms and provide the requisite impetus for their successful implementation in the Indian pharmaceutical scenario.

CONCLUSION

Quality by Design (QbD) performs a pivotal role in maintaining the quality of products in the pharmaceutical sector. To improve quality, scientists can easily identify the risk initially. This follows the development of a quality control or routine testing analytical system which is developed by measuring the efficiency of the method over time to ensure that the method remained by the specified ATP parameters. It designs quality into the method. The present review paper explains the analytical methods developed by using AQbD methodology are highly robust, as well as cost and time efficient, since method implementation requires less scientific investigation. It can be inferred that this review paper gives a quick review of several analytical methods optimised by using QbD which are collected from research and review articles published in last few years. As a result of the implementation of the latest ICH Guideline for Analytical method Development (Q14), the pharmaceutical industry will be compelled to follow the AQbD methodology.

CONFLICTS OF INTEREST: None

CONSENT FOR PUBLICATION: Not applicable

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