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ANALYTICAL QUALITY BY DESIGN (AQBD): NEW PARADIGM FOR ANALYTICAL METHOD DEVELOPMENT

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ABSTRACT

Quality of a finished product is gauged by compliance of certain predetermined specifications. This is ascertained by validated analytical procedures carried out by quality control personnel and laid down by the Quality Assurance (QA) department of a pharmaceutical company. In the present scenario, testing of the finished product alone is not sufficient, but emphasis is on 'Total Quality Management' through in-process testing and analysis. To achieve this goal, Quality by Design (QbD) concept has already been introduced and practised by all countries following guidelines of International Conference on Harmonization (ICH guidelines). Other features like Quality Risk Management, Pharmaceutical Quality System and Process Analytical Technology (PAT) guidelines are also being now introduced and integrated into analytical method development processes. They are very popularly accepted as AQbD (Analytical Quality by Design) concepts by the industry. Though not officially circulated, this new paradigm has attracted appreciation from all concerned and is evident by increasing publications in this field. The day may not be far off when this becomes official. Till then, certain observations and suggestions are compiled and presented through this review paper.

INTRODUCTION

Quality should be built in by design, it cannot be tested in a product, is the main motto of 'Total Quality Management'. To achieve this goal of optimized quality product, the knowledge gained from pharmaceutical development studies and manufacturing provides the scientific background. The method optimization was earlier based on One Factor at a Time (OFAT) approach (Bhoop Bhupinder Singh *et al*., 2013) where a single component was varied with time and its effect studied.

This approach was not much helpful as it neglected the effect caused due to interaction of more than one factors. Now a day, the approach followed is Quality by Design (QbD) which employs Design of Experiments (DoE) as important concept. DoE approach is a systematic, scientifically analysed better understandable approach. The figure 1 highlights the demerits of OVAT leading to use of DOE approach.

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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" (ICH, 2009 and Sangshetti Jaiprakash *et al*., 2014).

Some key definitions as given by ICH Q8 are mentioned below:

Design space: "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."

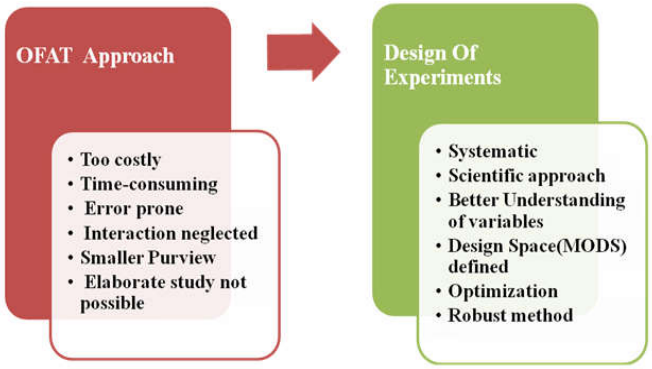

Fig. 1. Showing demerits of OFAT leading to DOE approach

Design of Experiments: "A structured, organized method for determining the relationship between factors affecting a process and the output of that process."

Process Analytical Technology (PAT): "A system for designing, analyzing, and controlling manufacturing through timely measurements (i.e., during processing) of critical quality and performance attributes of raw and in-process materials and processes with the goal of ensuring final product quality."

ICH Q9 guideline considers quality risk management as a valuable component of an effective quality system. Risk is defined as the combination of the probability of occurrence of harm and the severity of that harm. It is important to understand that product quality should be maintained throughout the product lifecycle. This further ensures the high quality of the drug product.

ICH Q10 guideline describes model quality management system for pharmaceutical manufacturing.

QbD Principles for Analytical Method Development

Analytical testing, is a critical step for pharmaceutical development processes like raw material analysis, in-process checking, release testing, stability studies. To ensure the quality product analytical method should also be in unison with the QbD and PAT. Thus, due stress should also be laid on regulatory guidelines for AQbD describing the development of method as per DoE including risk management system and details of quality systems required (Bhoop *et al*., 2010).

Proposed key definitions for AQbD (Tang, Yubing, 2014 and Chatterjee, Sharmista, 2013)

According to ICH Q8, main terminology used in the process optimization are Quality Target Product Profile (QTTP), Design Space (DS) and Design of Experiments (DoE). The analogous terminologies for analytical method development used by quality experts are Analytical Target Profile (ATP), Method Operable Design Region (MODR) and Method Development Strategy (MDS).

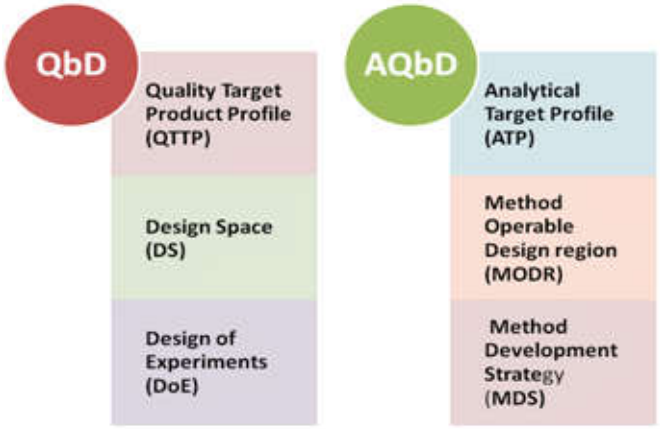

Fig. 2. Comparative terminology for QbD and AQbD

The definition of these terms are given in the figure 3.

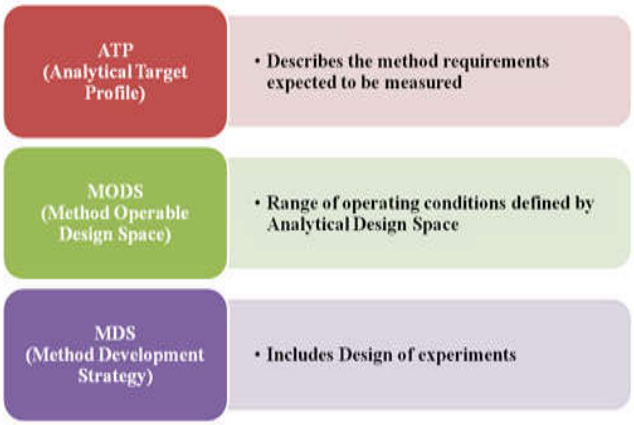

Fig. 3. Key definitions for AQbD

Steps involved in Analytical Method development in unison with QbD (Sangshetti Jaiprakash *et al*., 2014; Candioti Luciana Vera *et al*., 2014; Karmarkar *et al*., 2011 and Debrus *et al*., 2013)

The first step in designing of analytical methods by using the principle of QbD is the selection of the type of analytical method and the various factors affecting the method. These factors can be classified as primary parameters and secondary parameters. This step involves the study of primary parameters. The parameters are then prioritized based on the extent of the effect caused on analysis. This phase is followed by Screening phase which, calculates approximately the effects of secondary parameters on selected responses (like resolution and selectivity in case of HPLC). The model which can be used for this stage are *Two Levels Full Factorial, Two Levels Fractional Factorial, Plackett- Burman*. The next step is response surface generation by using any of the method from *Central Composite Design, Box-Behnken Design, Full Factorial Design at three levels, Doehlert Matrix Design or D- Optimal design.* This stage is followed by the optimization stage which employs the use of computer software as well virtual screening to determine MODS.

This approach when applied to HPLC analytical method development includes four main steps: The first step is to determine primary parameters like screening of column chemistry, organic modifier, pH of buffer and mobile phase. This is followed by next step where the selectivity optimization is confirmed through changes in gradient time and mobile phase temperature. Finally, column geometry optimization to get sufficient resolution and MODS is determined. The optimization process is a continuous process and should be monitored from time to time for efficient outcome. Figure 4 gives the schematic representation of the steps involved in analytical method development.

A simple example is selection of conditions for chromatographic method development on the basis of structure of drug defining physicochemical properties like logP, logD, pKa etc. The advent of computer technology has reduced the time required for calculation and results are more precise with the use of statistical methods for treatment of data. The various statistical methods used can be Multiple Linear Regressions (MLR), Partial Least Square (PLS) or Principal Component Analysis and other tools like Analysis of Variance (ANOVA), student's t-test, Pearson coefficient are also used whenever required.

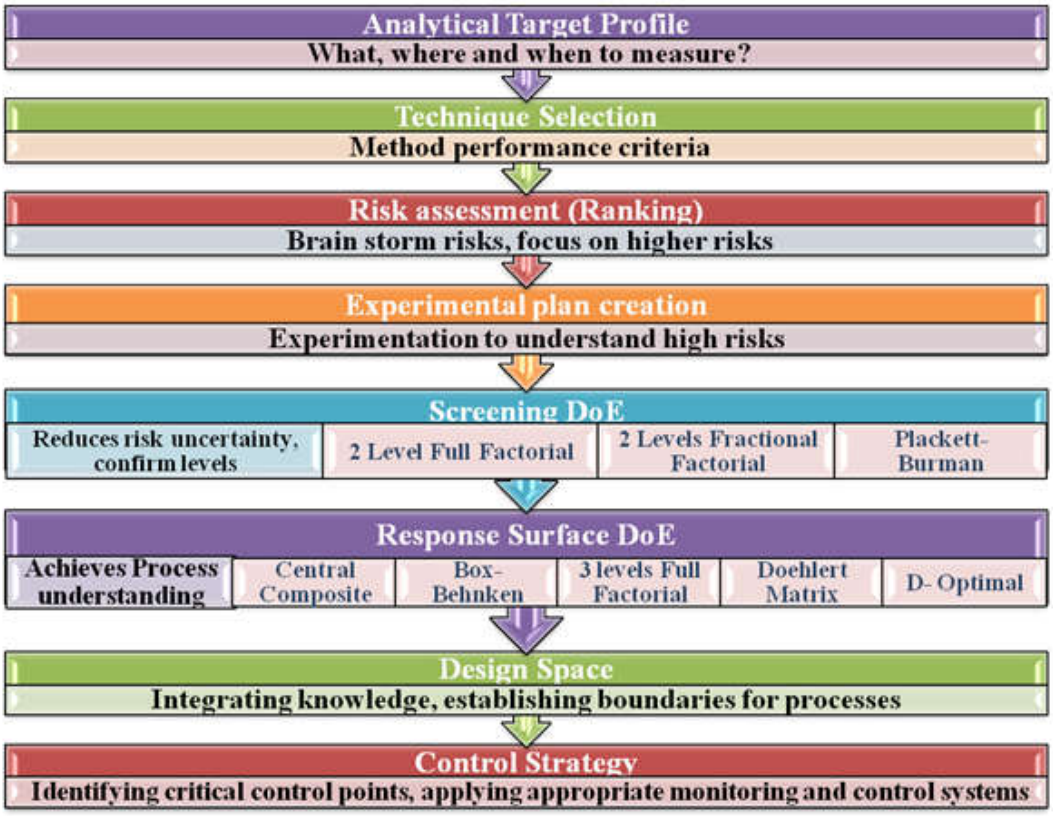

Fig. 4. Showing steps involved in the DOE and designs employed for Screening and Response Surface Steps

Computer softwares used in optimization of parameters and generation of MODS (Bhoop Bhupinder Singh *et al.*, 2013 and Debrus *et al.*, 2013)

The method development based on structure defining physicochemical parameters is in vogue.

Table 1. Computer Softwares used for HPLC and DoE.

Software for Chromatography	Software for DoE
DryLab (Molnár Institute, Germany)	Fusion AE (S-Matrix, United States)
ACD/LC and GC Simulator (ACD/Labs, Canada)	MODDE (Vicenza, Italy)
ChromSword (ChromSword Group, Latvia)	Design Expert (State-Ease Inc., USA)
Osiris (Datalys, Grenoble, France)	Modde (Umetrics,Sweden)
	JMP (SAS Institute Inc.)
	Unscrambler (CAMO, Norway)

This is made much easier by the use of computer based programmes. The given Table 1 shows some of the softwares used for chromatographic and DOE simulations.

Review of some publications for Analytical Methods employing DoE concept

The information from various publications using concept of QbD and PAT including DoE concept for the development of the analytical method for assay and determination of stability has been compiled in Table 2. The main parameters selected for the collation are the screening along with optimization parameter.

These are the two main steps which are foundation of the further decision making. The models or designs used for screening as well as response surface designing are also compiled. The computer software packages, if used are also included as important parameter for designing.

Table 2. Highlighting the various important parameters studied in DoE

S. No.	Name of drug	Class of drug	Type of Analytical method	Stages	Parameter's considered	Design / Model	Software used	Ref.
1.	Amitriptyline and its main impurities	Tricyclic Antidepressant	Solvent-Modified Micellar Electrokinetic Chromatography	▪ Screening phase ▪ Scouting phase	▪ Applied voltage ▪ Concentration and pH of the background electrolyte ▪ Concentration of the surfactant, cosurfactant and organic modifiers ▪ CE operative modes for maximum selectivity	▪ Response surface methodology by Doehlert Design. ▪ DS by Monte-Carlo simulations ▪ Robustness assessment by Plackett–Burman design	▪ Nemrod-W package for knowledge space ▪ MODDE 9.1 package (Vicenza, Italy)	[10]
2.	*Ginkgo biloba L.*	Plant Material	Direct analysis in real time mass spectrometry (DART-MS)	▪ Screening phase ▪ Optimization Phase	▪ Concentration of ginkgolides in the loading solution ▪ Loading flow rate ▪ Adsorption Capacity	2-factor, 3-level full factorial design with two additional replicates on the center point	▪ Design Expert8.0 (State-Ease Inc., USA) ▪ Data analysis by Matlab7.9 software (The Mathworks Inc., USA)	[11]
3.	Divided in different groups	Antibiotics	HPLC UPLC	▪ Screening Phase ▪ Optimization Phase	▪ pH of the aqueous part of the mobile phase ▪ Gradient time ▪ Temperature of chromatographic column ▪ Retention time ▪ Resolution	▪ D-optimal design Design Surface ▪ Bayesian model ▪ Monte-Carlo predictive	▪ HPLC calculator v3.0 (University of Geneva, Switzerland) ▪ Algorithm for DS written in R 2.13 (free-ware) ▪ e-noval® V3.0 software (Arlenda,Belgium)	[12]
4.	▪ Phthalic Acid ▪ Vanillic Acid ▪ Isovanillic Acid ▪ Aspirin ▪ Furosemide Doxepin ▪ Terbinafin ▪ Atorvastatin ▪ Clopidogrel	Model drugs	HPLC		▪ Gradient time ▪ Temperature ▪ pH of the aqueous eluent ▪ Stationary phase	▪ Column design space ▪ Elution design space	▪ ColumnMatch (Molnár-Institute, Germany). ▪ DryLab 2010 (Molnar Institute, Germany)	[13]

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5.	Luliconazole in bulk and cream formulation	Antifungal drug	HPLC	▪ Screening phase	▪ Acid Hydrolysis ▪ Alkali degradation ▪ Oxidative degradation ▪ Dry heat degradation ▪ Wet heat degradation	▪ Factorial design ▪ Multiple Regression equation ▪ 3 variables at two levels ▪ 2 variables at two levels	▪ ColumnMatch (Molnár-Institute, Berlin, Germany) ▪ DryLab 2010 (Molnár-Institute, Germany)	[14]
				▪ Optimization phase				
6.	Hydrolyzed Protamine sulfate peptides	Biotechnological Products	RP-HPLC	▪ Screening Phase	▪ Mobile phase pH ▪ Flow rate ▪ Column temperature ▪ Injection volume ▪ Methanol concentration	▪ Plackett–Burman experimental design ▪ Multivariate regression ▪ Pareto ranking analyses	NA	[15]
				▪ Optimization phase	▪ Peak Resolution ▪ USP tailing	▪ Box–Behnken design		
7.	▪ Histamine ▪ Paroxetine ▪ Cetirizine ▪ Caffeine ▪ Pseudoephedrine ▪ Serotonin ▪ Dopamine ▪ DL-Norepinephrine	Model drugs	Supercritical Fluid Chromatography	▪ Screening	▪ Nature of stationary and mobile phase	▪ 4 factors central composite design ▪ Polynomial equation using multiple linear equation ▪ Monte–Carlo simulations	▪ Chemstation (Agilent) ▪ Empower3(Waters) ▪ HPLC calculator ▪ JMP10.0.0 (SAS Institute)	[16]
				▪ Robust method optimization	▪ Concentration of TFA dissolved in methanol ▪ Temperature			
8.	▪ Acetaminophen ▪ Phenylephrine ▪ Chlorpheniramine	Common-cold pharmaceutical formulation	HPLC	▪ Screening stage	▪ pH of the aqueous part ▪ Gradient time	▪ Plackett and Burman design ▪ Full factorial design ▪ Fractional factorial design	▪ In-house computer software	[17]
				▪ Optimization Designs	▪ Selectivity	▪ D optimal design ▪ Central Composite Designs		
9.	*Spirospermum penduliflorum* Thouars (Menispermaceae)	Vasorelaxantaporphine alkaloids (dicentrine and neolitsine)	HPLC-UV	▪ Screening stage ▪ Validation	▪ Mobile phase pH ▪ Initial proportion of methanol ▪ Gradient slope	▪ Full factorial design of 36 experimental condition ▪ Multiple linear equations		[18]

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10.	API and P4NX99-D, the P4NX99 molecule	Coded drug and impurities	Stability-indicating LC-MS method	▪ Optimization of the method for the determination of impurities and the API ▪ Optimization of the method taking into account the aged matrix	LC factors ▪ Flow rate ▪ Injection volume MS factors ▪ Cone temperature ▪ Capillary temperature ▪ Nebulizer gas ▪ Desolvation gas ▪ Cone voltage ▪ Capillary voltage ▪ Dwell time	▪ Polynomial Regression ▪ Monte Carlo simulations for error propagation ▪ Grid search method	▪ RStudio v 0.96 a Integrated Development Environment (IDE) ▪ e.noval software v3.0 (Arlenda, Belgium)	[19]
11.	Ebastine and its pharmaceutical formulations	Antihistaminic	Stability-indicating UHPLC	▪ Screening Phase ▪ Optimization	▪ Gradient time ▪ Temperature ▪ Ternary composition of the eluent ▪ Flow rate ▪ Start and end concentration of the gradient ▪ Selectivity	▪ 2-D resolution maps ▪ 3-D resolution cube	DryLab (Molnar Institute, Germany)	[20]
12.	Atomoxetine	Treatment of Attention Deficit Hyperactivity Disorder	HPLC impurity method	▪ Screening phase ▪ Optimization phase	▪ pH of mobile phase ▪ Buffer concentration ▪ Organic solvent concentration ▪ Ion-Pair concentration ▪ Column temperature	Five-factor, two-level fractional factorial design with four centerpoints		[21]
13.	Darifenacin and degradation prodcts	M3 selective receptor antagonist	RP-UPLC		▪ Temperature, ▪ % organic ratio ▪ Buffer pH	Central Composite Design	DesignExpert version 8.0.7.1(Stat-Ease, Inc., USA)	[22]
14.		15 Antipsychotic Basic Drugs	RP-LC	▪ Initial screening ▪ Selectivity optimization ▪ Robust optimization	▪ Column chemistry ▪ Mobile phase pH ▪ Organic modifier ▪ Changes in gradient time ▪ Mobile phase temperature ▪ Resolution	▪ Stepwise Regressions ▪ Error propagation by Monte Carlo Simulations	Fusion AE 9.6 (Matrix Softwares)	[23]
15.	Pramipexole	▪ Parkinson's Disease ▪ Restless Legs Syndrome	RP-HPLC		▪ Gradient time ▪ Temperature ▪ pH of aqueous eluent ▪ Flow Rate ▪ Start and end concentration of organic mobile phase	Multi-Factorial Design Space	DryLab (Molnár-Institute, Germany)	[24]

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16.	Furosemide	Diuretic	RP-HPLC	▪ Primary Parameter Selection ▪ Secondary Parameter Screening ▪ Method Optimization	▪ Organic modifier ▪ Buffer pH ▪ Gradient time ▪ Initial hold time ▪ Initial % organic modifier ▪ Final % organic modifier ▪ Flow rate	▪ IV optimal design and cubic model for individual design ▪ Taguchi orthogonal array ▪ Face centred central composite design	DesignExpert version 8.0.7.1(Stat-Ease, Inc., USA) [25]
17.	4-dimethylaminopyridine impurity in glucocorticoids	Genotoxic impurity	LC–MS/MS	▪ Initial screening ▪ Optimization	For HPLC ▪ Flow ▪ Gradient ▪ Injection Volume For MS ▪ Cone Voltage Collision ▪ Energy ▪ Separation of peaks peak prea ▪ Length of analysis signal to noise ratio	▪ Regression Analysis ▪ Fractional Factorial ▪ Quadratic model, Central Composite Face	Modde 9.0.0.0 (Umetrics, Sweden) [26]
18.	API and P4NX99-D		Liquid Chromatography (LC)	▪ Screening phase ▪ Optimization of the method for the determination of impurities and the API ▪ Optimization of the method taking into account the aged matrix	▪ Organic modifier % ▪ pH of mobile phase ▪ Column type ▪ Analyzer resolution ▪ Accuracy ▪ Signal noise ratio ▪ Signal spikes in total ion current	▪ D-optimal mixture design ▪ Polynomial regression response modelling ▪ Monte Carlo simulations for error propagation	▪ RStudio v0.96, Integrated Development Environment (IDE) ▪ e.noval v3.0 (Arlenda, Belgium) [27]
19.	Bovine serum albumin	Biological product	UPLC	▪ Screening Phase ▪ Optimization Phase	▪ Acetonitrile (%) ▪ Formic Acid (%) ▪ Boiling Time ▪ Percentage Bovine Serum Albumin Loss	Multivariate data-analysis	Modde 8.0.2 software (Umetrics, Sweden) [28]
20.	Zileuton racemate in bulk and tablet Formulation	Inhibits 5-Lypoxygenase	RP-HPLC-PDA LC – GC	▪ Screening phase ▪ Optimization phase	▪ Methanol content ▪ Flow rate ▪ Concentration of orthophosphoric acid	▪ Central Composite Design (CCD) and Response Surface Methodology ▪ Multiple Linear Regression (MLR) and ANOVA	Design Expert (Stat-Ease Inc., US) [29]

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21.	Separation of curcumin, arteether, tetra-hydrocurcumin and dihydroar-temisinin	Malaria	HPLC	▪ Screening phase ▪ Optimization phase	▪ Percentage of organic modifier ▪ Flow rate of the mobile phase ▪ Column temperature	▪ Full Factorial Design	▪ Empower2.0 forWindows ▪ e-noval® V3.0 software(Arlenda, Belgium).	[30]
22.	▪ Noradrenergic ▪ Dopaminergic ▪ Serotonergic Compounds from Mouse Brain Tissue	Multiple Neuropsychiatri c Disorders	Reversed-Phased Ion-Pair With Amperometric End-Point Detection	▪ Screening phase ▪ Optimization	▪ Modifier ▪ Methanol concentration ▪ pH of mobile phase ▪ Column temperature ▪ Ion-Pair counter concentration ▪ Voltage of detector ▪ Resolution ▪ Analysis time	▪ Two-Level Fractional Factorial Experimental Design	JMP® 8.0.1 software (SAS Institute Inc.)	[31]
23.	Six organotin compounds	Toxins in water	Headspace-Solid-Phase Micro-Extraction (HS-SPME) combined with Gas chromatography Tandem Mass Spectrometry (GC–MS/MS)	▪ Screening ▪ Optimization	Extraction efficiency ▪ Pre- incubation time ▪ Incubation temperature ▪ Agitator speed ▪ Extraction time ▪ Desorption temperature ▪ Buffer (pH , concentration and volume) ▪ Head space volume ▪ Sample salinity Preparation of Standards ▪ Ultrasonic time ▪ Desorption time in injector GC-IT-MS/MS ▪ Excitation voltage ▪ Excitation time ▪ Ion source temperature ▪ Isolation time ▪ Electron energy	▪ Plackett–Burman design (Screening method) ▪ Central Composite Design (CCD) ▪ Full Factorial Design	MINITAB program.	[32]
24.	BEL097 BEL174	Coded drugs	HPLC with polysaccharide-based stationary phase	▪ Screening phase ▪ Optimization phase	▪ Trifluoroacetic acid (TFA) concentration ▪ n-Hexane concentration ▪ Column temperatures ▪ Resolution or separation criterion	▪ Central Composite Design (CCD) ▪ Monte Carlo simulations	JMP v 8.0.2 (SAS Institute, Tervuren, Belgium)	[33]
25.	▪ Sulfadiazene ▪ Sulfacetamide ▪ Sulfathiazole	Antibiotics	HPLC	▪ Screening phase ▪ Optimization phase	▪ Pump flow rate ▪ Gradient time ▪ Gradient slope ▪ Column oven temperature ▪ Maximise resolution ▪ Minimize retention time	▪ Experimental Error ▪ Transformation ▪ Regression ▪ Outlier ▪ Residuals ▪ Pareto Ranking Analyses	Fusion AE (Matrix software)	[34]

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26.	Vancomycin	Antibiotics	UPLC	▪ Rapid Screening ▪ Optimization	▪ Column chemistry ▪ Buffer pH ▪ Organic mobile phase ▪ Pump flow rate ▪ Gradient time ▪ Final % organic ▪ Column temperature	▪ Rank Response Variable ▪ Monte Carlo Simulation ▪ Process Capability Statistics	▪ Fusion (Matrix) ▪ Empower 2 software	[35]
27.	Linagliptin	Diabetes Type II	Stability indicating HPLC	▪ Screening ▪ Optimization	▪ % Organic component ▪ Column chemistry ▪ Gradient time ▪ Run time ▪ Selectivity Factor ▪ Capacity Factor	Monte Carlo Simulation	▪ Fusion AE (Matrix Software) ▪ Agilent 1200 Infinity Series Method Development Solution	[36]
28.	▪ Coenzyme Q10 ▪ Ascorbic Acid ▪ Folic Acid	Nutraceutical	Microemulsion Electrokinetic Chromatography Method (MEEKC)		Mixture Components ▪ Buffer ▪ Surfactant–Cosurfactant ▪ Oil Process Variables ▪ Voltage ▪ Buffer Concentration ▪ Buffer pH	▪ I-optimality criterion ▪ MPV models ▪ Special-cubic mixture model		[37]
29.	Compound A	Coded Sample	HPLC	▪ Instrumentation and chromatographic Conditions ▪ System suitability test ▪ Intermediate precision study ▪ Robustness study	▪ % Acetonitrile (ACN) ▪ pH of Mobile Phase ▪ Detector Wavelength ▪ Column Temperature ▪ Flow Rate ▪ Buffer Concentration ▪ Column Types	Fractional Factorial Design	JMP® software	[38]
30.	Almotriptan and its main Impurities	Migraine Headaches	Capillary Electrophoresis (CE)	▪ Scouting Phase ▪ Screening Asymmetric Matrix	▪ CE operative modes ▪ Addition of pseudo stationary phases ▪ Additives to the background electrolyte Process Variables (PVs) ▪ Voltage ▪ Temperature ▪ Buffer Concentration Buffer pH Mixture Components (MCs) ▪ Borate Buffer, ▪ n-Heptane as Oil ▪ Sodium Dodecyl Sulphate/N-Butanol As Surfactant/Cosurfactant	▪ Monte-Carlo simulations ▪ MPV D-optimal design	MODDE (Umetrics, Sweden)	[39]

Conclusion

The paradigm shift from OFAT to QbD (DoE) has supported the pharmacy professionals to cater the needs of combative Quality Assurance. Discerning the importance of analytical methods in pharmaceutical formulation development, the same principles should be applied to analytical method development also. The main endeavour of review is to focus on the use of aforementioned Design of Experiment concept in Research and Development and afterwards translation to Quality Assurance Department. The number of research publications reviewed in the paper endorses the fact. The designing increases the confidence in the method developed, as it covers all the aspects and compiles the results categorised under the Design Space. The initial process is costly but ultimately becomes cost effective in case of errors and risks. The benefits of Analytical Quality by Design concept are enormous. The main is during regulatory registration, the changes within the design space for the formulation development do not require refilling. So, to make the process of change in analytical method for registered product unproblematic, regulatory agencies should issue the guidelines pertaining to Analytical Quality by Design. The awareness in the professionals can be ensured by conducting various training programmes, workshops and awareness campaigns. Another important aspect is use of computer software for accurate statistical analysis of data. Cheaper reliable software accessibility will be appreciable. Thus, concluding with the remarks that Analytical Quality by Design is in infancy recently, will grow with regulatory control to its full potential.

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