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Implementation of Quality by Design Approach for Developing Chromatographic Methods with Enhanced Performance: A Mini Review

Abstract

Quality by Design (QbD) is a newer paradigm being widely implemented by pharmaceutical industries for producing robust drug products with consistency in their quality as per the predefined objectives. The QbD approach emphasizes on building quality from the beginning and helps developing products that meets the consumer and regulatory requirements. QbD in pharmaceutical formulation and development is already trending with astounding success. However, the application of QbD in analytical sciences, also refereed as Analytical QbD (AQbD) is yet to receive the acceptance and recognition from the scientific community. AQbD implementation endeavors to facilitate development of quality analytical methods with improved method performance meeting the regulatory flexibility to work within a robust design space in order to avoid failures during method transfer process. It can be effectively applied to diverse areas including analysis of APIs and related substances, forced degradation products, optimization of sample preparation techniques for drug products for their quantification in biological samples. The present mini-review, in this regard, provides an overview of the vital precepts of AQbD, salient features, different stages involved during development of AQbD compliant analytical methods, and highlights of the recent literature instances related to the AQbD applications in pharmaceutical analysis.

Keywords: Quality-by-Design; Analytical method; Robustness; Design of experiments

Mini Review

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Abbreviations: QbD: Quality-by-Design; QbT: Quality-by-Testing; HPLC: High Performance Liquid Chromatography, UFLC: Ultra Fast Liquid Chromatography; UPLC: Ultra Performance Liquid Chromatography; US FDA: United States Food and Drug Administration; ATP: Analytical Target Profile, CAA: Critical Analytical Attribute; CMV: Critical Method Variable; RSM: Response Surface Methodology; QRM: Quality Risk Management; CNX: Control-Noise-Experimentation; FMEA: Failure Mode and Effect Analysis; DoE: Design of Experiments; CCD: Central Composite Design, BBD: Box-Behnken Design, OD: Optimal Design, LC-MS/MS: Liquid Chromatography-Mass Spectrometry/Mass Spectrometry; BSA: Bovine Serum Albumin; FDC: Frenz Dissolution Cell

Introduction

Quality by Design (QbD) is a systematic approach for the development of pharmaceutical products and processes beginning with the predefined objectives and primarily emphasizes on product and process understanding based on the principles of sound science and quality risk management [1]. Since its introduction by ICH and USFDA through series of guidance from Q8-Q10, QbD application is a mandatory requirement for the development of pharmaceutical products [2]. Although implementation of QbD for analytical methods is not a current regulatory requirement; however, the literature reports in the past a few years is a testimony to the real time benefits of QbD for efficient development of diverse analytical methods. Recently implementation of QbD paradigms for development of robust analytical methods has been highly popularized [3]. The QbD approach for analytical method development involves a multi step process. It starts with defining the analytical target profile (ATP) and critical analytical attributes (CAAs), identifying the critical method variables (CMVs) and their subsequent optimization using suitable experimental designs, modelization and optimum search through response surface methodology (RSM) to embark upon the analytical design space, and postulation of control strategy for continuous improvement [4]. The present mini-review highlights the key steps involved in AQbD approach for obtaining the quality analytical methods with enhanced method robustness, performance and reliability.

Discussion

According to USFDA guidance, AQbD approach for analytical methods can be implemented through six steps (Figure 1).

Establishment of analytical target profile (ATP)

Establishment of ATP can be achieved thorough identification of the analytical target, sample condition and setting up the quantification criteria as per the method intent. The selection of an analytical target is based on the method goal. The method goal signifies the final quality that is desirable by regulatory authorities. A thorough survey of literatures and study of chemical properties is vital for selection of a target.

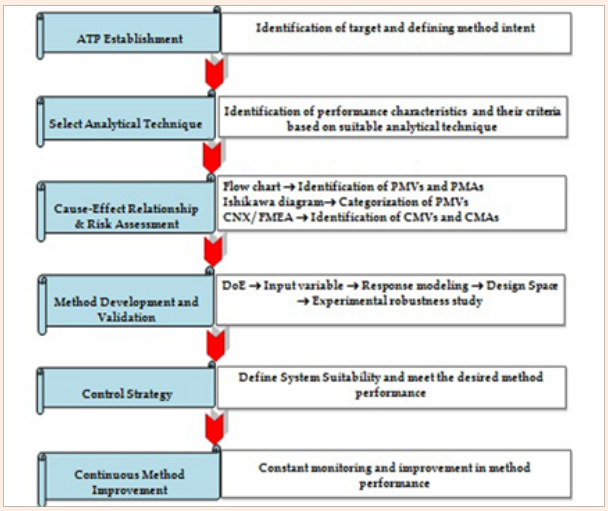

Figure 1: Step-by-step implementation of AQbD approach.

Selection of analytical technique

A suitable analytical technique can be selected based on the need of the method intent and method performance criteria should be set up. The method intent may vary from improved resolution between the drug and its impurities [5-7], enhanced method robustness [8-11], column selectivity [12], bioanalytical quantification of drugs and metabolites [13,14] and analyte recovery [15], and sample treatment [16].

Cause and effect relationship & risk management

The third phase involves assessment of possible risks by quality risk management (QRM) approach to find out the critical method parameters (CMPs) and possible variations in the sample integrity. Risk assessment provides deep insight on the method variables, which requires a scientific investigation followed by defining control strategies. Preparation of an Ishikawa Fish-bone diagram for establishing a cause and effect relationship is the first step in effective risk assessment. Further, a Cause-Effect Risk Assessment Matrix with Control-Noise-Experimentation (CNX)/Failure Mode and Effect Analysis (FMEA) approach enlisting various potential method variables from the Fish-bone diagram may be used to find out the potential method variables affecting selected responses for risk management. For a liquid chromatographic method, the CMPs may include mobile phase composition, pH of buffer, column age, stationary phase, flow rate; sample purity, column oven temperature, detection wavelength etc. and responses can be like peak area, retention time, peak resolution, capacity factor, tailing factor, theoretical plates, etc. can be investigated. The variables with highest score are subjected to systematic optimization using suitable experimental design. In case of a bioanalytical sample preparation factors can be included as extraction time, partition co-efficient of extraction solvent, extraction temperature, centrifugation speed etc. can be considered as CMPs to investigate their effect on extraction of analyte from the biological matrix.

Design of Experiments (DoE)-based method development

A robust and reliable analytical method can be developed utilizing an appropriate experimental design. It is widely used for performing statistically designed experiments to evaluate the method superiority. It provides knowledge for working within the design space for achieving consistent quality for regulatory flexibility. The design space is an experimental safe zone where the method variables have no significant influence on the method robustness and quality. Response surface methods like Central Composite Design (CCD), Box-Behnken Design (BBD) and Optimal design (OD) etc. are used for predicting and optimizing the responses for most of the analytical techniques [17-19]. These designs help the analytical scientists to understand the relationship between different CMPs and their effect on the method responses.

Defining the Control Strategies:

The control strategies are developed in order to meet the desired method performance by defining the control space and system suitability parameters. These parameters include retention time, resolution, theoretical plates, tailing factor, etc [20,21].

Continuous improvement

The final phase of AQbD involves a continuous surveillance of the method performance to gain more knowledge on the design space and updating the process with most recent innovations to further improve the method quality [22, 23].

Vital applications of AQbD

Quantification of drugs and their impurities: Karmarkar et al. [5] developed a QbD-based HPLC method for chromatographic separation of amiodarone and its seven impurities. Effects of CMPs *viz*. organic phase composition, buffer pH, and column oven temperature and column lot were assessed on resolution among all the peaks for the impurities.

In another study, Furlanetto et al. [6] reported a solvent modified micellar electrokinetic chromatography method for better separation of amitriptyline and its impurities. Parameters such as applied voltage, concentration and pH of the background electrolyte, concentration of the surfactant sodium dodecyl sulphate, of the co-surfactant n-butanol and of the organic modifiers acetonitrile and urea were studied for their influence on analysis time and resolution.

Dabigatran and its ten impurities were analyzed by liquid chromatography employing principles of QbD [7]. Gradient time, content of the acetonitrile at the start and end of linear gradient were studied for their impact of retention time of all the peaks. The approach produced an optimum design space for quantification of all the impurities along with dabigatran.

Robust and reliable analytical methods: Panda et al. [8-10] reported two RP-UFLC and a UV spectrophotometric method with assured robustness using the AQbD approach. Two reversed-phase ultrafast liquid chromatographic methods were developed and validated for robust quantification of telaprevir

[8] and paliparidone [9] in pharmaceutical dosage forms. Various CMPs such as organic phase composition, flow rate of mobile phase, pH of buffer solution etc. and their effect were assessed on responses like retention time, theoretical plate number and tailing factor. Similarly, an UV spectrophotometric method was developed and validated for robust estimation of Vilazodone [10] in pharmaceutical dosage forms considering slit width and scan speed as the CMPs and absorbance as the response.

Beg et al. [11] reported an AQbD compliant UPLC method for determination of olmesartan in presence of its degradation products. CMPs like mobile phase ratio and flow rate were optimized based on the responses obtained for responses such as peak area, retention time, theoretical plates and peak tailing.

Stability-indicating Methods: A case study revealing the basic advantages of QbD over QbT (Quality-by-Testing) was reported by Hubert et al [13]. The study highlights a QbD oriented workflow for developing a stability-indicating method for routine analysis of a drug and its unexpected impurities from long-term storage.

Garg et al. [14] reported a stability-indicating HPLC method for simultaneous determination of omeprazole and ketoprofen. The paper describes a unique experimental design approach by examining the controllable factors while blocking the uncontrollable factors like system-to-system variability to obtain better resolution between peaks.

Bioanalysis of Drugs and Biological Sample Preparation: Khurana et al. [15] have reported QbD based development and validation of a bioanalytical UPLC method for analysis of docetaxel in human plasma. Mobile phase ratio and injection volume were found to be the CMPs, which affected the responses *viz.* peak area, retention time, theoretical plates and symmetry factor. The QbD approach presented optimum chromatographic condition for selective quantification of analyte.

Hasnain et al. [16] published a paper describing development and validation of a bioanalytical LC-MS/MS method for quantification of fluoxetine in human plasma. Evaluation of responses such as retention time and peak area for the method variables mobile phase flow rate, pH and mobile phase composition was carried out. Implementation of QbD to this study revealed reduction in the variability due to method variables and helped achieving improved method robustness.

Beg et al. [17] reported a unique approach for implementation of QbD for enhancing liquid-liquid extraction of nevirapine from rat plasma during bioanalytical studies. Extraction parameters such as extraction time, centrifugation speed and temperature were selected as the CMPs for attaining maximal percentage recovery of nevirapine from rat plasma as the response.

Sample treatment: Taevernier et al. [18] have successfully applied AQbD for determination of optimal sample treatment procedure of bovine serum albumin containing Franz diffusion cell solutions producing maximum precipitation of BSA. The study demonstrated that formic acid and acetonitrile content were found to have maximum influence on precipitation of BSA samples.

Chiral Separation of Enantiomeric Impurities

A capillary electrophoresis using QbD domain was developed by Orlandini et al. [24] for chiral separation of levosulpiride and its enantiomeric impurities (R-SUL). Process parameters such as pH, concentration of S-β-cyclodextrin(SCD) and neutral cyclodextrin (NCD) were studied to obtain better resolution and retention time. A design space was identified as multidimensional zone for obtaining optimum enantiomeric resolution and analysis time.

Conclusion

Although the AQbD approach is under very nascent stage with demand of stringent regulatory requirements from the federal agencies, yet the applications are highly diverse. Notwithstanding the utility in chromatographic method development, this can be applied to spectrophotometry, spectrofluorimetry, mass spectrometry, etc. too for attaining the enhanced performance and detailed understanding.

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