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Implementing Quality by Design-A methodical approach in the RP-HPLC method development process

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Abstract

The concept of quality by design (QbD) has recently been adopted for the development of pharmaceutical processes to ensure a predefined product quality. Focus on applying the QbD concept to analytical methods has increased as it is fully integrated within pharmaceutical processes and especially in the process control strategy. Quality by design (QbD) refers to the achievement of certain predictable quality with desired and predetermined specifications. The QbD based method development helps in generating a design space and operating space with knowledge of all method performance characteristics and limitations and successful method robustness within the operating space. A very useful component of QbD is the understanding of factors and their interaction effects by a desired set of experiments. For the purpose of QbD for HPLC methods, robustness and ruggedness should be verified early in the method development stage to ensure method performance over the lifetime of the product. Quality-by-Design principles are applied to build in a more scientific and risk-based multi-factorial approach to the development and validation of analytical methods using HPLC.

Keywords: Quality by design, design space, method development

1. Introduction

Analytical method development, validation and transfer are key elements of any pharmaceuticals discovery, developmental program and manufacturing. Analytical techniques and tools require to define the quality of their products and to retain their qualification. The analytical tools include chemical, physico-chemical, instrumental, biological techniques and also the combination of different instrumental methods (hyphenated techniques) for developing qualitative and quantitative determination. Analytical testing also plays a prominent role in pharmaceutical development, risk assessment, process monitoring and control and continuous quality assessment throughout the product life cycle.[1] The development and use of analytical methods evolve from generating information about a manufacturing process and product to using the methods for monitoring and controlling parameters that are critical to a drug's quality. The major challenge in analytical method development is HPLC method development for the analysis of drug substances. In the past, the common practice to develop an analytical method in liquid chromatography was performed by a trial and-error approach, for example by varying one-factor-at-a-time (OFAT) and examine the resolution of peaks until the best method was found. This approach was time-consuming and required a large amount of manual data interpretation. It often resulted in a non-robust performance when transferred into another lab because interactions between factors were not considered. [2] This problem has been now overcome by applying a Quality by Design (QbD) approach to the analytical method development. QbD is defined as "a systematic approach to development that begins with predefined objectives and emphasizes product and process understanding and process control, based on sound science and quality risk management". QbD has been attracting increased attention in the development of analytical separation methods, because these are intended to be used for quality control and analysis of API and drug products, to ensure product quality and thus patient safety. [3]

2. Regulatory aspects of QbD[4]

2.1. ICH guideline: International conference on harmonization in its Q8 pharmaceutical development, Q9 quality risk assessment and Q10 pharmaceutical quality system gives stringent requirements regarding quality of product. The underlying principles of QbD i.e. science- and risk-based product development, risk assessment, lifecycle approach and method design are explained in the quality guidelines of international conference on harmonization i.e. ICH Q8 Pharmaceutical Development, ICHQ9 Quality Risk Management, and ICH Q10 Pharmaceutical Quality System.

2.2. FDA Perspective: FDA's view of QbD is "QbD is a systematic approach to product and process design and development," This concept was accepted by FDA in 2004 and detail description was given in 'pharmaceutical cGMPs for 21st century – a risk based approach'. FDA also states importance of quality of pharmaceutical products by giving Process Analytical Technology (PAT) which is a Framework for Innovative Pharmaceutical Development, Manufacturing and Quality Assurance.

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2. 3. Regulatory Challenges and inspection: In a QbD concept, the regulatory burden is less because there are wider ranges and limits based on product and process understanding. Changes within these ranges and limits do not require prior approval. Traditionally, inspections have been conducted using the FDA systems-based approach and in accordance with CDER's Compliance Program 7356.002M. During prelicense or preapproval inspections under a QbD concept, the FDA inspection team assesses the implementation and effectiveness of the process design as described in the application and whether knowledge and risk management have been transferred successfully from development to manufacturing. The inspection evaluates the quality system and its effectiveness regarding consistent product quality, change control procedures, process improvements, deviation management, and knowledge and risk management during the product lifecycle. But, design, testing, and monitoring programs that demonstrate robustness and consistency would be highlighted.

2.4 QbD principles in method development process: The application of QbD principles to analytical method development is focused on the concept of building quality into the method during development, instead of testing methods for quality after development[5]. A very useful component of QbD is the understanding of factors and their interaction effects by a desired set of experiments. For the purpose of QbD for HPLC methods, robustness and ruggedness should be verified early in the method development stage to ensure method performance over the lifetime of the product.

Two key concepts in implementation and understanding of QbD are:

a. Design space
b. Control strategy

The knowledge obtained during development helps to justify the establishment of the design space and (process) controls.[6]

a. Design space (DS): It is a key component of the development of analytical procedure using QbD. In ICH pharmaceutical-development guideline Q8, DS is defined 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''. Therefore, the multidimensional combination and interaction of input variable corresponds to a subspace, so-called the DS, where assurance of quality has been proved. ''Working within the design space is not considered as a change''.[7] The first step is to define the intended purpose of the analytical method. This has been called the Analytical Target Profile (ATP). The method under development will then follow a risk assessment.[8] The purpose of the risk assessment for LC methods is to develop high confidence that the method will meet all performance criteria under all conditions of use as it progresses through its lifecycle. A systematic approach is used for identifying all the potential method factors that may need to be controlled to ensure method performance.[6] This systematic approach classifies risks in groups related to instrumentation, materials, methods, chemicals and reagents, measurements, human factors, environmental issues (e.g., laboratory temperature, relative humidity, and light).[8]

b. Control strategy: Nonetheless, the development of QbD analytical methods does not end with the DS. A control strategy of the method has to be implemented to assure that the method will perform as intended on a routine basis.[8] The control strategy is obtained from the process understanding gained from modeling the design space. An analytical adaptation of control strategy is defined as the controls on input factors to a method that ensure the method meets both traditional system suitability criteria and wider performance-related goals.[5] Here, elements from the DS can be used to select responses that have to be monitored at each analytical run. These responses that will be implemented in the control strategy are known as system-suitability tests or validity tests. They can be the definition of a minimum resolution value between a critical pair, the acceptable value for tailing peaks, the maximum acceptable value expressed in RSD for the repeated analysis of a standard solution, the minimum value of the determination coefficient (R2) of a standard curve, and so on. [9] The QbD paradigm is employed to obtain better understanding of the effect of these factors on product stability in order to ensure the product stability throughout the expiry date.

3. Implementing QbD-Practical approach

a.Define the Design Space of analytical methods: The starting point is to gather and review all historical information available on the analytical method under development, previously developed methods that are closely related, and the literature and scientific information available on the subject.[8]

b. Define the Analytical target profile and Critical quality attributes: The analytical target profile (ATP) is a set of criteria that define what will be measured (e.g. the level of a specified impurity, % degradation in the sample) and the performance criteria to be achieved by the measurement (e.g. accuracy, precision and range).[10] On the basis of ATP, different analytical methods and/or techniques are evaluated in a preliminary investigation to approach the method objective, in general with the purpose of achieving maximum selectivity with adequate efficiency, and improving the reproducibility and repeatability of measurements. After these preliminary experiments, the QbD workflow can start by defining quality target product profile (QTPP) and critical quality attributes (CQAs) [9].QTPP is defined as a "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". This definition to analytical methods means that, the separation objectives should be well defined. For e.g. Separation of API from the impurities/ degradation

product while meeting method performance criteria based on regulatory requirements. [10]

CQAs are defined as ‘‘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’’. The performance criteria can be called Critical Quality Attributes (CQAs) of the analytical method. These CQAs are the responses that are measured to judge the quality of the developed analytical methods. For separative analytical methods like chromatography, the CQAs can be related to the method selectivity e.g., the resolution (RS). Additional CQAs can be the run time of the analysis, the precision of the analytical method, the lower limit of quantification or the dosing range of the analytical method. Sometimes these CQAs can be directly modeled through a multivariate (non-)linear model. However in some situations, the modeled (primary) responses may differ from the CQAs. The CQAs are obtained after the modeling of these primary responses. For chromatographic methods, the usual key CQA is resolution of the critical pair. However, resolution depends upon the retention factor of the two chromatographic peaks involved, so several authors have proposed to model the retention factors instead of the resolution as the primary response. The resolution can subsequently be computed from these modeled responses.

a.Set the Experimental factors, ranges and levels: To obtain the Design space of analytical methods, the choice of the experimental factors and their respective range is essential. From the whole experimental design region, the factors and the ranges that will affect the responses must be chosen. Depending on the knowledge space, formal designs of experiments must be performed. This investigated knowledge space is a multidimensional space that needs to be large enough to create response variations. Generally, if no prior information about the response variation is known, preliminary experiments should be carried out to estimate the range and the magnitude of variation of each factor. [8]

b.Use of Design of Experiments (DoEs) and response modeling: Conventionally experiments were performed by considering one factor- at-a-time (OFAT) to gain knowledge about a process or to optimize it. OFAT generally requires a higher number of experiments to estimate the factors effect with good precision and their interactions can rarely be estimated. Application of statistical design of experiments is currently encouraged by the regulatory agencies, sometimes together with the use of chromatographic, modeling and optimization software. For automated method development, it is possible to use optimization softwares dedicated to RPLC. Some of these softwares are based on the famous linear solvent strength (LSS) theory including DryLab (Molnár Institute, Berlin, Germany), ACD/LC and GC Simulator (ACD/Labs, Toronto, Canada), ChromSword (ChromSword Group, Riga, Latvia), Osiris (Datalys, Grenoble, France) and Fusion AE (S -Matrix, Eureka, CA, United States) [9]. Tyteca *et al*. introduced an innovative strategy, also based on LSS theory. They proposed a new algorithm able to automatically focus on the most promising areas of the solution space by shifting and stretching the elution window over different parts of the time-axis thanks to the information on the retention properties of the first and last peaks of the chromatogram.[11]

Design Expert.[9] DoEs provide an effective, efficient approach to evaluate simultaneously the effects of factors and their interactions and to model and to predict the relationship between these factors and the CQAs or responses. In recent years, it has proved to be a good alternative to automated softwares based on LSS for chromatographic method development. The selected DoE needs to have good statistical properties (e.g., orthogonality and/or rotatability), and should maintain the number of experiments as low as possible. It should also allow estimation of the experimental error and assessment of the validity of the model tested. Alexander & Molnar*[2]* have developed a stability indicating UHPLC method for ebastine by using the chromatography modeling software DryLab®4 which allowed the visualization of a “Design Space”. The robustness of the developed method was studied by varying the six parameters: gradient time, temperature, ternary composition of the eluent, flow rate and start and end concentration of the gradient at 3 levels (+1, 0, −1). The resulting 729 experiments were performed *in silico* from the previously constructed model for Design Space and showed that the required resolution of 2.0 can be reached in all experiments.

DoE can be split up into two main categories: screening designs and response-surface designs[8]

i. Screening designs: Screening designs estimate the effects of factors on selected responses. When too many factors (four or more) seem to affect the responses and have been revealed by the FMEA prioritization, these designs can be used to select those having the largest effects on the responses. The remaining significant factors are studied in a subsequent DoE [e.g., method optimization]. In the screening category of designs, well known are the Plackett and Burman designs that study factors at two levels. In liquid chromatography (LC), Plackett and Burman designs are also used to estimate the robustness of an optimal separation. Other types of screening designs are fractional factorial designs, which generally do not allow understanding of a process under investigation if it may include interactions and higher order effect terms. However they are very useful in selecting the most important factors that influence the selected responses of the analytical method under investigation.[8]

ii. Response-surface designs. The second category of DoE corresponds to designs used to predict and to optimize the responses. These DoEs are full factorial designs, central composite designs and Box-Benkhen and Doehlert designs. D-optimal designs can also be

selected in order to answer particular requirements (e.g., constraints on the levels of factors, or specific models). These designs are aimed at understanding the process under investigation. It involves understanding the relationship between the factors to assess the behavior of the response, and the effects on the response. These designs are used to find the combination of factors that predict the optimal response with good precision. More than two levels of each factor are usually required in order to fit quadratic or higher order terms {e.g., when pH is a factor in LC, it may be required to study pH up to the third-order term: pH+pH2+pH3}. Response-surface designs are key tools to define the DS of analytical methods. They study a large experimental domain, understanding the behavior of the responses and the CQAs with respect to the studied factors, and they provide a model to predict the value of the CQAs within the range of these levels of factors.[8]

Sonawane and Gide[12] have developed and validated a stability indicating HPLC method for the determination of rebamipide wherein they employed 2^3 full factorial design during forced degradation to determine significant factors responsible for degradation and to obtain optimal degradation conditions. On the basis of preliminary experiments three independent factors; strength of acid/alkali (Normality), irradiation time (min) and microwave power (Watt), each at two levels, were chosen as input (factors) and % degradation as output (response).

In another example, Bianchini *et al*[13] developed and validated a HPLC method for the determination of process realted impurities in pridinol mesylate wherein they optimized the composition of the mobile phase with the aid of a 3^2 full factorial experimental design, prepared with nine chromatographic runs under different conditions, which included the pH of the aqueous phase and the percentage of organic phase as the independent variables (factors), each at three levels. Four responses, including the effects of both factors on the retention time of the first eluting peak, the resolution between each impurity and API, the length of the chromatography, at a flow rate of 1.0 mL min^{-1} and employing a C_{18} column, were studied.

iii. Response modeling: The modeling of the responses can be realized in two main ways. The first involves a theoretical or mechanistic model that connects some of the factors to the responses {e.g., realized with software available to optimize chromatographic methods using the solvophobic theory or linear solvent-strength theory. However, most of the time, there are no theoretical models that include all the factors that may influence the responses and the analytical CQAs. In this case, empirical models can be fitted on the data obtained to link the responses and the factors studied. This is usually performed by fitting multiple linear equations of adequate polynomial degree, related to the number of factors selected. In some situations, it may also be required to fit non-linear models[8]

Table 1: Examples of the RP-HPLC method development approaches based on the QbD paradigm.

Analytical methods	Name of drug	QbD tool used	Authors	Ref. No.
Stability indicating assay	Eletriptan hydrobromide	Optimization using response surface methodology	B. Jocic, M. Zecevic, L. Zivanovic, A. Protic, M. Jadranin, V. Vajs	14
	Complex pain management drug product	Optimization using Fusion AE software	S. Karmarkar, R. Garber, Y. Genchanok, S. george, X. Yang, R. Hammond	15
	Luliconazole	Experimental design-optimization using Full Factorial design	Sandeep sonawane, Paraag Gide	16
	Eberconazole nitrate	Optimization using response surface methodology	M. Vamsi Krishna , Rajendra N. Dash, B. Jalachandra Reddy, P. Venugopal, P. Sandeep, G. Madhavi	17
Impurity profiling	Nimodipine	Optimization using response surface methodology	P. Barmpalexis, F. I. Kanaze, E. Georgarakis	18
	Pazopanib HCl	Impurity fate mapping	Ming-Ling Sun, David Q. Liu, Alireza S. Kord	19
	Atomoxetine HCl	Experimental design-optimization using Fractional Factorial design	Peter F. Gavin , Bemard A. Olsen	20
	Ropinirole	Face-centered central composite design (CCD) with 2^3 full factorial design, ±1 star design	B. Jancic-Stojanovic, A. Malenovic, D. Ivanovic, T. Rakic, M. Medenica	21
LC method	Model- Examplain HCl	Chromatographic simulation for routine RP-HPLC method development	Phil Borman, John Roberts, Chris Jones, Melissa Hanna -Brown, Roman Szucs, Simon Bale	22
Method development and assay using RP-HPLC	Glipizide	Optimization using Fusion Design Expert software	Cijo M. Xavier, Kanakapura Basavaiah, K. B. Vinay, N. Swamy	23
	Screening of 19 anti-malarial drugs	Combined use of Design of experiments (DoE), independent component analysis (ICA) and design space (DS)	B. Debrus, P. Lebrun, J. Mbinze Kindenge, F. Lecomte, A. Ceccato, G. Caliaro, J. Mavar Tayey Mbay, B. Boulanger, R.D. Marini, E. Rozet, Ph. Hubert	24
Method development using HPTLC & UV spectroscopy	**Propafenone Hydrochloride**	Assessment of Critical parameters	Monika L. Jadhav and Santosh R. Tambe	25

2. Conclusion

RP-HPLC method development by quality by design approach is a very useful approach. It reduces the time required for method development and the method which we obtain by applying this approach is robust. It reduces the number of trials. The knowledge built up during the development of complex methods (such as impurity profiling, stability indicating assay) is used to select methods that meet pre-defined, stringent performance criteria and goals.[5]

The potential benefits of using a QbD approach rather than using traditional ‘‘one factor at a time’’ experimentation leads to a better understanding of the factor influencing chromatographic separation and hence the potential for simultaneous development of multiple methods. A few merits of the QbD approach are summarized as:

- Greater confidence in the ability of the method to meet their intended purposes.
- Improved process capability
- Reduced process variability
- Reduced manufacturing costs
- Reduced process design and development time
- Increased understanding of the relationship between process inputs and output(s)

When dealing with a relatively high number of analytes (i.e. higher that 10), the development of specific and robust methods in reversed-phase liquid chromatography (RPLC) generally requires substantial time and effort, even for the most experienced chromatographers. In this context, QbD is preferred as an innovative and comprehensive approach to speed up and automate the method development process. Nonetheless, no current regulatory document provides adequate guidelines for a complete evaluation of the obtained DS quality as well as specific requirements for the robustness validation. Hence assessment of the complete method validation with an important degree of confidence according to QbD method development is the need of the hour.

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