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RSM: A CHEMOMETRIC APPROACH FOR ANALYTICL METHOD DEVELOPMENT

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ABSTRACT

The application of response surface methodology (RSM) in the optimization of analytical methods is discussed in this paper. To introduce readers to this multivariate statistical technique, the theoretical concepts of RSM and steps for its implementation are defined. Response Surface Methodology (RSM) is an optimization technique used in experiment/research studies to define interrelationships between variables. This paper addresses an optimization strategy based on response surface methodology and the Box-Behnken process. RSM aids in the selection of the most appropriate experimental design for determining the relationship between variables. RSM is a methodology that is used to create analytical methods for specific drugs in order to classify and measure the active content while reducing sources of variability. The use of multivariate statistical techniques for chromatographic and spectroscopic device optimization. As compared to the one-factor-at-a-time (OFAT) approach, analytical methods developed using the RSM approach are more robust, easy to verify, have shorter run times, and can determine a greater number of analytes in a single run.

KEYWORDS

QbD, Response surface methodology, Box-Behnken design and Analytical method development.

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INTRODUCTION

As evidenced by numerous implementations in industry quality control and research and development (R and D) laboratories, the quality by design (QbD) methodology has been widely used in the development of pharmaceutical products. As compared to quality by testing (QbT), QbD increases comprehension of processes and goods by establishing predetermined targets based on statistical, mathematical, chemistry, and quality risk management.

QbD processes are divided into four stages.

Analytical target profile (ATP)

The objective of an analytical method and its necessary performance criteria (critical quality attributes-CQAs) are included in the analytical target profile.

Risk assessment

This move focuses on data processing and is related to sample preparation for further analytes determination. Then, additional possible variables such as noise variables can be detected, and measurement method analysis methods can be used to test them, as well as instrumental parameters, which can be evaluated using design of experiment (DoE) strategies (a critical part)

The design space (DS) is calculated using the DoE data. DS depicts the analytical chemistry conditions under which an analytical process or manufacturing technique will operate without jeopardizing the final result. The establishment of reliable methods for use in analytical chemistry laboratories is part of this component.

Several analytical figures of merit, such as accuracy and precision expressed as relative standard deviation (RSD) and coefficient of determination (R2), are observed as part of the control strategy and validation[1-4].

Analytical methods are one of the most important aspects of drug product creation and manufacturing. Throughout the life cycle of a drug product, they play an important role in supporting other growth and manufacturing processes. An analytical method must be precise, accurate, and dependable in order to be useful for its intended purpose[5,6].

The isolation of the analytes present in the sample is usually the key working concept of an analytical process. The most popular LC techniques used are high-performance liquid chromatography (HPLC) and ultra performance liquid chromatography (UPLC), which are mostly used in reversed-phase mode with UV absorbance detection. The number, significance, and relationship of analytes that must be calculated determine the objective of analysis. The most widely used analytical methods are those for assaying an active pharmaceutical ingredient (API) or determining its associated substances and degradation products[6].

It takes a long time to develop a precise and reliable stability-indicating LC method for determining related substances and degradation products. To provide stressed samples containing the analyte and its degradation products, it involves the deliberate forced degradation of a drug substance and/or a drug product under various stress conditions, such as hydrolytic, oxidative, photolytic, or thermal conditions. The stress conditions are more extreme than the ICH-recommended accelerated and long-term stability conditions for stability testing. The method for the assay should be capable of detecting any decrease in the drug substance's content during its shelf life, and the analytical method for determining degradation products should be capable of detecting their increase during the product's shelf life. Such methods are stability indicating[6-11].

HPLC methods are often developed by trial-and-error or one-factor-at-a-time (OFAT) methods, in which one chromatographic parameter is varied in successive experiments until an appropriate resolution between chromatographic peaks is achieved. If there are several parameters influencing the separation, this greatly increases the number of experiments. The identification of important process parameters based on the analyst's expertise and experience is missing in this approach. As a result, it can be time-consuming, especially when looking at less important method operating parameters that have little impact on separation. Furthermore, interactions between parameters, which may be important, are rarely investigated. As a result, using the OFAT approach to design a system often results in a non optimized method with a lack of understanding of multi parameter interaction effects, resulting in a method with a non robust working efficiency[5,6,12].

In most cases, method development and validation take place in one lab, while routine analyses take place in another. Because of the many variables involved (different LC systems, different column and/or solvent batches, uncertainty attributed to analysts, etc.), inconsistent process output can make the method transfer phase crucial. These variables

could have a major impact on how the approach works in practice, resulting in out-of-trend (OOT) or out-of-specification (OOS) performance[12]. Even if system transfer is effective, it is only a one-time experiment, confirming that the method works as expected at the time and location of the transfer, but not demonstrating its long-term reliability[10]. Changes in method parameters are often required because methods built using the OFAT approach have a high risk of failure. A revalidation procedure is required in this situation, and the change must be submitted to regulatory agencies. These modifications have a negative effect on cost, time, and energy[5,13].

Regulatory aspects

The United States Food and Drug Administration (FDA) introduced the idea of Quality by Design (QbD) in 2004 as an important method for creating innovative drug products and processes[14]. The main goal is to scientifically design consistency directly into the drug product via codependent pharmaceutical processes[5,13]. The International Conference on Harmonisation (ICH) accepted QbD in 2005, defining it as "a structured approach to growth that starts with predefined goals and emphasizes product and process understanding based on sound science and quality risk management," according to the ICH Q8(R2) guideline[15]. The ICH Q9 guideline[16] was published the same year, and the ICH Q10 guideline[13] was added in 2008. They include an overview of scientific concepts and basic quality risk control techniques that can be used to incorporate quality into a pharmaceutical product at various stages of its lifecycle, and ICH Q10 also emphasizes creativity and continuous improvement in the production and manufacture of pharmaceutical products. In addition, the ICH Q11 guideline[17], which focuses on scientific concepts and approaches to developing and producing drug substances, was published in 2012. Although the ICH Q8(R2) guideline calls for a QbD approach as part of pharmaceutical production lifecycle management, the QbD approach can also be applied to analytical procedure lifecycle management, including activities such as analytical method development, validation, transition, and continuous improvement.

Theory and steps for RSM application

Box and collaborators developed response surface methodology in the 1950s[18,19]. This term was coined to describe the graphical perspective created after a mathematical model was found to be fit, and it has since become widely used in chemometrics texts. RSM is a collection of mathematical and statistical techniques focused on fitting empirical models to experimental data obtained in the context of experimental design. To achieve this aim, linear or square polynomial functions are used to characterize the system under investigation and, as a result, to explore (modeling and displacing) experimental conditions until it is optimized[20]. The following are several steps in the implementation of RSM as an optimization technique: 1. According to the study's goal and the researcher's experience, the collection of independent variables with significant effects on the method through screening studies and the delimitation of the experimental region; (2) The choice of the experimental design and carrying out the experiments according to the chosen experimental matrix; (3) The mathematic–statistical treatment of the obtained experimental data through the fit of a polynomial function; (4) The evaluation of the model's fitness; (5) Verifying the necessity and feasibility of conducting a displacement in direction to the optimal region; and(6) obtaining the optimum values for each studied variable[21].

Symmetrical second-order experimental designs and their applications in analytical chemistry

Full three-level factorial designs

When the factor number is greater than 2, the full three-level factorial design has limited use in RSM because the number of experiments needed for this design (calculated by expression N= 3k, where N is the experiment number and k is the factor number) is very large, reducing its efficiency in the modeling of quadratic functions. Since a full three-level factorial design with more than two variables necessitates more experimental runs than can normally be accommodated in practice, designs with less experimental points, such as the Box-Behnken, central composite, and Doehlert designs,

are more commonly used. For two variables, however, the performance is equivalent to central composite designs[22,23]. The majority of three-level factorial designs are used in the chromatography sector.

Box–Behnken

Higher order response surfaces are produced using Box-Behnken designs, which require fewer runs than a traditional factorial technique. In order to keep the higher order surface description, this and the central composite techniques effectively suppress selected runs. To suit a 2nd order equation, the Box-Behnken design uses twelve middle edge nodes and three center nodes. The central composite plus Box-Behnken becomes a full factorial with three extra samples taken at the centre. Points are placed on the midpoints of the edges of the cubical design area, as well as in the middle, in Box-Behnken designs[24].

Box-Behnken designs

Experiments using the Box–Behnken design include response surface modeling. There are no absolute or fractional factorial designs in these designs. The design points are located in the center of the dimensionk-1 subareas. For example, in the case of three variables, the points are in the middle of the experimental domain's edges.

There are three levels per factor in these designs. For three reasons, the Box–Behnken design fails to meet the iso-variance per rotation criterion. If center points are applied to the designs above with more than three variables, they will follow the iso-variance criterion. The orthogonality criterion can also be met with these designs.

The Box–Behnken designs allow the impact of the different design factors to be studied sequentially if the other factors are kept constant while the first factors are being studied[19].

Application of QbD in analytical methods of measurement

QbD does not imply a reduction in scientific testing; rather, it refers to the right study at the right time, based on research and risk evaluation. Implementing QbD aids in the creation of a rugged and stable system that complies with ICH guidelines, which is why pharmaceutical companies are embracing this concept. In the development of the analytical method in the QbD setting, factors that improve robustness are taken into account. This method's quality improvement is made easier with this approach. In the literature, there are parallel possibilities for applying QbD to analytical methods and manufacturing processes. It implies that methods such as target profile, design space, and risk assessment can also be applied to the analytical process. While not all pharmaceutical companies use it, it has a bright future because regulatory bodies will make it mandatory. Because of the numerous benefits and ease of compliance with regulatory authorities, industries can choose to follow this definition voluntarily. The Pharmaceutical Research and Manufacturers of America (PhRMA), the Analytical Technical Group (ATG), and the European Federation of Pharmaceutical Industries and Associations (EFPIA) have all expressed strong opinions on the parallel application of QbD to analytical methods[25-28].

Application QbD or elements of QbD to analytical method

In development of HPLC method for drug products/substances:

A new approach to developing high-pressure reversed phase liquid chromatography (HPLC) methods using quality by design (QbD) concepts. Gradient time, temperature, aqueous eluentpH, and stationary phase are four typical critical parameters in HPLC that are evaluated using computer modeling software and a column database within the quality by design system.

In stability studies

The development of a stability indicating HPLC method for a complex pain relief drug product containing drug material, two preservatives, and their degradants is defined using quality by design (QbD) concepts. The initial approach lacked resolution in oxidative degradant peaks for drug degradants and preservatives, as well as peaks for preservatives and another drug degradant. Fusion AETM software was used to optimize the process using a DOE approach. Within the operating space, the QbD-based method creation allowed the

development of a design space and an operating space with specifics of all method performance characteristics and limitations, as well as method robustness.

In UHPLC

Rapid high-performance liquid chromatography with high prediction accuracy and design space computer modeling, demonstrating the accuracy of retention time prediction at high pressure (enhanced flow-rate) and demonstrating that computer-assisted simulation can be used with sufficient precision for UHPLC applications.

Benefits of AQbD (Analytical Quality by design)

1. The development of a reliable process. 2. Variable sources can be better regulated.3. Increased regulatory flexibility-Changes within the "Analytical Design Room" are not considered a process reform. The company avoids this high expense. 4. Method Transfer success is greater when a method is transferred from research level to quality control department. 5. It creates an environment conducive to the development of new techniques by continuous improvement over the lifecycle.6. Gained a better understanding of the information domain

QbD can be applied for various analytical methods which include

1. HPLC and other chromatographic techniques (For stability studies, method development, and determination of impurities in pharmaceuticals), 2. Advanced techniques such as mass spectroscopy, ultra-high-performance liquid chromatography, and capillary electrophoresis. 3. Karl Fischer titration for determination of moisture content 4. Vibrational spectroscopy, such as the UV process, is used to identify and quantify compounds.

CONCLUSION

Response surface methodology is widely used in the optimization of analytical procedures today, owing to its advantages over traditional one-variable-at-a-time optimization, such as the ability to generate large quantities of data from a limited number of experiments and the ability to evaluate the interaction effect between the variables of response. To apply this approach to experimental optimization, you must first select an experimental design, fit an appropriate mathematical function, and evaluate the quality and accuracy of the fitted model before making predictions based on the experimental data.

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CONFLICT OF INTEREST

We declare that we have no conflict of interest.

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