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APLICAREA PROIECTĂRII EXPERIMENTELOR ÎN ANALIZA FARMACEUTICĂ | APPLICATION OF DESIGN OF EXPERIMENTS IN PHARMACEUTICAL ANALYSIS

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Rezumat. Scopul studiului a fost determinarea principiilor de implementare a modelelor experimentale: screening-ul și optimizarea în elaborarea metodelor de analiză farmaceutică. Cele mai cunoscute modele de screening sunt: factorial cu două niveluri, factorial fracționat și Placket-Burman, fiind de obicei utilizate pentru a selecta cei mai importanți factori care afectează răspunsurile și pentru a-i elimina pe cei nesemnificativi. Cele mai cunoscute modele de optimizare sunt: factorial cu trei niveluri, compozit central și Box-Behnken. Modelele de screening permit modelarea doar de ordinul întâi, în timp ce modelele de optimizare permit o suprafață de răspuns de ordinul doi. Modelul ar trebui să fie selectat pe baza Analizei variației, care compară variabilitatea datorată nivelului factorilor cu variabilitatea datorată erorii reziduale. Astfel, proiectarea experimentului ajută la identificarea modului în care variabilele independente afectează caracteristicile de performanță ale unei metode de analiză.
Cuvinte-cheie: proiectarea experimentelor, analiză farmaceutică, design factorial, variabila dependentă, variabilă independentă, analiza variației.
Abstract. The objective of the study was determination of principles of implementation of experimental models: screening and optimization in development of methods of pharmaceutical analysis. The most well-known screening designs are: two-level full factorial, fractionate factorial and Placket-Burman, being usually used to select the most important factors that affect the responses and to remove the insignificant ones. The most well-known optimization designs are: three-level full factorial, central composite and Box-Behnken. The screening designs allow modeling only first order response surface, while optimization designs allow a second order response surface. The model should be selected based on the application of Analysis of Variance, which compares the variability due to the level of factors with the variability due to residual error. Therefore, the design of experiment contributes to identify how the independent variables affect the analytical method performance characteristics.
Keywords: design of experiments, pharmaceutical analysis, factorial design, dependent variable, independent variable, Analysis of Variance.

INTRODUCTION

The notion of quality by design in pharmaceutical analysis has been inserted to ensure the quality of medicines. ICH Q8 (R1) guideline defines quality by design 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 [1, 2]". Quality by design concepts is also defined in ICH Q9 (quality risk management) and Q10 (pharmaceutical quality system) [2, 3].

In recent years, quality by design is applied more often to analytical methods, which contributes to development of robust and cost-effective analytical methods [2, 4-7]. Therefore, the concepts of analytical quality by design contribute for understanding drug excipient interactions and for the measure of

critical quality attributes during experiment, process, control and also continuous process verification [2, 8-11].

Traditionally, the development and optimization of analytical methods have been carried out by analyzing one factor at time. In addition to demanding a high number of experiments, design of experiments may provide better results with few numbers of experiments. Design of experiments is a set of statistical tools which include screening designs; and optimization designs [2, 12-14].

Design of experiments is the main component of analytical quality by design. Thus, the present paper provides theoretical considerations for implementation of design of experiments in analytical quality by design.

MATERIALS AND METHODS

To identify relevant studies, it was used the following academic search engines: Medline, PubMed, the Cochrane Methodology Register, Scopus, IET Digital Library (search by titles and abstracts), Google Scholar and Science Direct (full-text search). The last search was march 2021. It was also used supplementary search techniques and sources (`similar articles" function in PubMed, conference abstracts and reference lists).

The general search pattern was as follows: „quality by design", „pharmaceutical analysis", „factorial design", „dependent variable", „independent variable", „Analysis of Variance".

The search yielded 112 articles, which were further filtered manually. All selecting bibliographic sources were summarized in a structured, narrative way.

RESULTS AND DISCUSSIONS

Design of experiments is a structured and organized method for determining the relationships between input factors affecting one or more output responses. Experimental designs may be divided into two types: screening designs and optimization designs [2, 7].

Screening designs are often used in the first step of design of experiments in order to select the most important input factors and discard the insignifcant ones. Two-level full factorial designs, fractionate factorial designs and Placket-Burman designs allow one to study a wide number of input factors with reduced numbers of experiments, however, they also have some limitations. The main limitations of two-level full factorial designs rely on the large number of experiments required, when compared to fractionate factorial designs and Plackett-Burman designs. The number of experiments required for two-level full factorial designs may be calculated as 2^k, where k is the number of input factors to be studied [2, 4-7].

Fractionate factorial designs can be determined by using a 2^{k-p} design, where p is the number of generators chosen to fractionate the design. Thus, fractionate factorial designs may not be suitable for assessing the interactions among factors. Plackett-Burman designs are special types of two-level fractionate factorial designs (resolution III), which allow one to study up to N-1 input factors with N experiments, which should be multiple of 4 [2, 4-11].

Three-level full factorial designs, central composite designs, and Box-Behnken designs are the most used optimization designs because they allow modeling complex response surface. One of the most important limitations of screening designs rely on the fact that they only allow modeling 1st order (linear) response surface, because they have only two level for each input factor. Optimization designs uses 3 to 5 levels of each input factors, which allow modeling 2nd order (quadratic) response surface [2, 12-14].

Three-level full factorial design are often used only when two or three input factors need to be study, because an increased number of experiments is required. The number of experiments required may be calculated as 3^k, where k is the number of input factors to be studied [2, 12-14].

Central composite designs are one of the most used optimization designs because they use 5 level of each input factor with a reduced number of experiments required, when compared to three-level full factorial design [2, 12-14].

Box-Behnken design are special types of three-level fractionate factorial designs, which allows modeling 1st and 2nd order response surfaces. These designs are more cost-effective than three-level full factorial designs, particularly for large number of input factors [2, 12-14].

Mathematical model should be selected based on the application of Analysis of Variance (ANOVA). The main idea of ANOVA is to compare the variability due to treatment (varying the level of input factors) with the variability due to residual error. Based on ANOVA, we can decide to include or to exclude the coefficients of linear terms, interaction terms and quadratic terms. This decision is based on p-values for each coefficient regression term. When the regression coefficient term is not different from 0 (p-value > 0.05), it indicates that the output response is not affect by varying the input factor levels. Thus, this coefficient regression term may be excluded from the regression model [2, 12-14].

Recently, design of experiment has been used in the rational development and optimization of analytical methods. Culture media composition, mobile phase composition, flow rate, time of incubation are examples of input factors (independent variables) that may the screened and optimized using design of experiment. Several output responses (dependent variables), such as retention time, resolution between peaks, microbial growth, among other responses were found in literature [2, 12-14] (table 1).

Table 1. Some applications of design of experiments in pharmaceutical analysis

Object of study	Type of design	Application of design	Reference
Central composite design	Oral Drug Delivery	To identify critical factors, their interactions and ideal process conditions that accomplishes the targeted responses	[15]
Full factorial design	Pharmaceutical processes	Optimization of instrumental parameters for spray drying of riseridone nanosuspension	[16]
Factorial design	Oral Drug Delivery	Implementation of quality by design approach in formulation development	[17]
Box-Behnken design	Transdermal Drug Delivery	Optimization of micro-emulsion formulation	[18]
Response surface methodology	Analytical method development	Optimization, sensitivity analysis and robustness study of analytical method	[19]
Factorial factorial design and Box-Behnken design	Analytical study	Screening and optimization of factors	[20]

CONCLUSIONS

Design of experiment's tools help to identify and explain how critical analytical parameters (independent variables) affects the analytical method performance characteristics (dependent variables) and therefore, the analytical target profle. Implementation of design of experiment's tools provides robust analytical methods, which plays significant role in drug product development.

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