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# Response surface methodology: An important tool in optimization

**Meenu Bhan**

Department of Pharmaceutical Sciences, Maharshi Dayanand University, Rohtak, Haryana, India

**Abstract**
Optimization measures the performance of a sytem or process. It comprises of different designs in which experiments are performed to know the significance of the proposed model. There are limits or levels in which experiments are performed. Response surface methodology is the collection of statistical and mathematical techniques. By the use of these techniques the best possible ways are found out to perform. So, it helps the performer to perform best with significant data results and saves time and other resources.

**Keywords:** optimization, designs, response surface methodology, statistical, techniques

## 1. Introduction

### Optimization

Optimization means finding the best possible value of a dependent variable by varying certain independent variables. Several optimization techniques are discussed and their applications in pharmaceutical technology, analysis, clinical chemistry and medicinal chemistry are critically evaluated (Doornbos, 1981) [9].

Optimizing refers to improving the performance of a system, a process, or a product in order to obtain the maximum benefit from it. The term *optimization* has been commonly used in analytical chemistry as a means of discovering conditions at which to apply a procedure that produces the best possible response.

### Response surface methodology

Response surface methodology is a collection of mathematical and statistical techniques based on the fit of a polynomial equation to the experimental data, for empirical model building. An experiment is a series of tests, called runs, in which changes are made in the input variables in order to identify the reasons for changes in the output response. It must describe the behavior of a data set with the objective of making statistical previsions. It can be well applied when a response or a set of responses of interest are influenced by several variables. The objective is to simultaneously optimize the levels of these variables to attain the best system performance (Bas, 2007) [4].

There are some important terms which describes the response surface methodology to a greater extent are the following (Schwartz, 1981) [10].

1. Experimental domain is the experimental field that must be investigated. It is defined by the minimum and maximum limits of the experimental variables studied.
2. Experimental design is a specific set of experiments defined by a matrix composed by the different level combinations of the variables studied.
3. Factors or independent variables are experimental variables that can be changed independently of each other. Typical independent variables comprise the pH, temperature, reagents concentration, microwave irradiation time, flow rate, atomization temperature, and elution strength, among others.
4. Levels of a variable are different values of a variable at which the experiments must be carried out. The variable pH, for example, can be investigated at five levels: 4, 5, 6, 7 and 8 in the optimization of a spectrophotometric method.
5. Responses or dependent variables are the measured values of the results from experiments. Typical responses are the analytical signal (absorbance, net emission intensity, and electrical signal), recovery of an analyte, resolution among chromatographic peaks, percentage of residual carbon, and final acidity, among others.
6. Residual is the difference between the calculated and experimental result for a determinate set of conditions. A good mathematical model fitted to experimental datamust present low residuals values.

The procedure for optimizing the formulation and process for a drug product, or a cosmetic product, is generally the process of making it as perfect as possible within a given set of restrictions or constraints. Physical, chemical, and biological properties must all be given due consideration in the selection of components and processing steps for that dosage form or product.

## 2. Optimization problem

There are two general types of optimization problems—the constrained and the unconstrained. Constraints are those restrictions placed upon the system due to physical limitations or perhaps simple practicality (e.g., economic considerations). In unconstrained optimization problems, there are no restrictions for a given formulation one might say: make the hardest tablet possible, or make lotion with the lowest degree of caking. The constrained problem, on the other hand, would be stated: make the hardest tablet possible, but it must disintegrate in less than fifteen minutes, or the lotion must have minimum caking but it must be pourable (Anthony, 1996) [1].

We must keep in mind that not only the restrictions are competing, but also that an ingredient processing step which may have beneficial effects on one property is very often

detrimental of another; and we must balance these effects.
An additional complication in the pharmaceutical and cosmetic fields is that formulations are not usually simple systems. They often contain many ingredients and variables which may interact with one another to produce unexpected, if not unexplainable, results.
The development of a solid, semisolid, or liquid formulation and the associated process usually involve a number of variables. Mathematically, they can be divided into two groups-independent and dependent.
The independent variable set the formulation and process variables directly under the control of the formulator. These might include the level of a given ingredients or the mixing time for a given process step. The dependent variables are the responses or the characteristics of the resulting product. These are a direct result of any change made in the formulation or process. To study formulations in a rational manner, we must be able to distinguish between the two (Baba, 1991) [1].

**3. The steps involved in this type of optimization procedure are listed below**

1. Select variables (independent, dependent)
2. Perform set of statistically designed experiments
3. Measure properties of interest (dependent variables)
4. Generate predictor equation (statistical model)
5. Optimize (with or without constraints)
   A. Mathematical Calculations
   B. Graphical Observation
   C. Searches
6. The evaluation of the model's fitness.
7. The verification of the necessity and possibility of performing a displacement in direction to the optimal region
8. Obtaining the optimum values for each studied variable.

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

**Full three-level factorial designs**

Full three-level factorial design is an experimental matrix that has limited application in RSM when the factor number is higher than 2 because the number of experiments required for this design (calculated by expression $N=3k$, where $N$ is experiment number and $k$ is factor number) is very large, thereby losing its efficiency in the modeling of quadratic functions. Because a complete threelevel factorial design for more than two variables requires more experimental runs than can usually be accommodated in practice, designs that present a smaller number of experimental points, such as the Box–Behnken, central composite, and Doehlert designs, are more often used. However, for two variables, the efficiency is comparable with designs such as central composite (Bezerraa, 2008) [5].

**Box–Behnken designs**

Box and Behnken suggested how to select points from the three-level factorial arrangement, which allows the efficient estimation of the first- and second-order coefficients of the mathematical model. These designs are, in this way, more efficient and economical then their corresponding 3$k$ designs, mainly for a large number of variables. In Box–Behnken designs, the experimental points are located on a hypersphere equidistant from the central point. Its principal characteristics are:
(1) requires an experiment number according to $N= 2k(k-1) + cp$, where $k$ is the number of factors and ($cp$) is the number of the central points;
(2) all factor levels have to be adjusted only at three levels ($-1$, 0, $+1$) with equally spaced intervals between these levels (Bohidar, 1975).

**Central composite design**

The central composite design was presented by Box and Wilson. This design consists of the following parts: (1) a full factorial or fractional factorial design; (2) an additional design, often a star design in which experimental points are at a distance, fromits center; and (3) a central point. Full uniformly routable central composite designs present the following characteristics:

1) Require an experiment number according to $N= k2 +2k+cp$, where $k$ is the factor number and ($cp$) is the replicate number of the central point;
2) ¸-values depend on the number of variables and can be calculated by ¸=2($k-p$)/4. For two, three, and four variables, they are, respectively, 1.41, 1.68, and 2.00;
3) All factors are studied in five levels ($-¸$,$-1$, 0, $+1$, $+¸$) (Bolton, 1997).

**Doehlert design**

Developed by Doehlert [17], the design is a practical and economical alternative in relation to other second-order experimental matrices. This design describes a circular domain for two variables, spherical for three variables, and hyperspherical for more than three variables, which accents the uniformity of the studied variables in the experimental domain. Although its matrices are not routable as previous designs, it presents some advantages, such as requiring few experimental points for its application and high efficiency. Other characteristics are presented below:

1) Requires an experiment number according to $N= k2 + k + cp$, where $k$ is the factor number and ($cp$) is the replicate number of the central point;
2) Each variable is studied at a different number of levels, a particularly important characteristic when some variables are subject to restrictions such as cost and/or instrumental constraints or when it is interesting to study a variable at a major or minor number of levels;
3) The intervals between its levels present a uniform distribution;
4) Displacement of the experimental matrix to another experimental region can be achieved using previous adjacent points (Schwartz, 1981) [10].

It is important to improve the performance of the systems and to increase the yield of the processes without increasing the cost. The method used for this purpose is called optimization. There is a parameter change in the general practice of determining the optimal operating conditions while keeping the others at a constant level. This is called one-variable-at-a-time technique. The major disadvantage of this technique is that it does not include interactive effects among the variables and, eventually, it does not depict the complete effects of the parameters on the process.

In order to overcome this problem, optimization studies can be carried out using response surface methodology (RSM). RSM is a collection of statistical and mathematical techniques useful for developing, improving, and optimizing processes in which a response of interest is influenced by several variables and the objective is to optimize this response. RSM has important application in the design, development and formulation of new products, as well as in the improvement of existing product design. It defines the effect of the independent variables, alone or in combination, on the processes. In addition to analyzing the effects of the independent variables, this experimental methodology generates a mathematical model which describes the chemical or biochemical processes. RSM consists of a group of mathematical and statistical techniques that can be used to define the relationships between the response and the independent variables (Sharma, 2011).

RSM defines the effect of the independent variables, alone or in combination, on the processes. In addition to analyzing the effects of the independent variables, this experimental methodology also generates a mathematical model. The graphical perspective of the mathematical model has led to the term Response Surface Methodology.

**5. Advantages and disadvantages of RSM**

RSM has several advantages compared to the classical experimental or optimization methods in which one variable at a time technique is used. Firstly, RSM offers a large amount of information from a small number of experiments. Indeed, classical methods are time consuming and a large number of experiments are needed to explain the behavior of a system. Secondly, in RSM it is possible to observe the interaction effect of the independent parameters on the response. Especially in biochemical processes, the interaction effect of the parameters would be more critical such as synergism, antagonism, and addition. The model equation easily clarifies these effects for binary combination of the independent parameters. In addition, the empirical model that related the response to the independent variables is used to obtain information about the process. With respect to these, we can say that RSM is a useful tool for the optimization of chemical and biochemical process (Takayama, 1999).

**6. Future Prospectives**

The scope of optimization technique is intended to support innovation and efficiency in pharmaceutical industry. The framework is founded on understanding to facilitate innovation and production. Pharmaceutical companies need to adopt new technologies, processes and collaborations (Baba Y *et al.* 1989) [2].

**7. Conclusions**

Application of response surface methodology in the optimization of analytical procedures is today largely diffused and consolidated principally because of its advantages to classical one-variable-a-time optimization, such as the generation of large amounts of information from a small number of experiments and the possibility of evaluating the interaction effect between the variables on the response. In order to employ this methodology in experimental optimization, it is necessary to choose an experimental design, to fit an adequate mathematical function, and to evaluate the quality of the fitted model and its accuracy to make previsions in relation to the experimental data obtained.

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