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# Experimental design - basic considerations

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## Abstract

Experimental design is a critically important tool for improving the performance of a manufacturing process. It has also extensive application in the development of new processes. It is important to investigate all factors that may be of importance and to not be overly influenced by past experience, particularly when we are in the early stages of experimentation or when the process is not very mature.

**Key words:** experimental design, experimentation, fluidized bed

## Introduction

The focus of many experiments in pharmaceutical technology is on experiments in physico-chemical characterisation of active substances and excipients, technological process, drug stability and analysis, new product design, manufacturing process development, and process improvement. Planning and conducting of the experiments and analysing the resulting data has its purpose in obtaining the valid and objective conclusions. In many cases, the objective may be to develop a robust process, that is, a process affected minimally by external sources of variability.

## Experimental process

The overall experimental process can be divided into a number of stages:

### (1) statement of the problem

- what is experiment supposed to achieve; what is its objective?

### (2) the choice of factors to be investigated, and the levels of those factors which are to be used;

### (3) the selection of suitable response

- we must be sure that the measurement of the chosen response will really contribute to achievement of the objective
- the accuracy of the proposed methods of measuring the response must also be considered

### (4) the choice of the experimental design

- this is often a balance between cost and statistical validity

- the more an experiment is replicated, the greater is the reliability of the results
- replication increases cost and the experimenter must therefore consider the acceptable degree of uncertainty;
- inextricably linked with this stage is selection of the method to be used to analyze the data

### (5) performance of the experiment

- the data collection process
- this will follow the experimental design laid down earlier

### (6) data analysis

- using methods defined earlier

### (7) conclusions and recommendations

Too often, the objective of the experiment is imperfectly defined. It is then discovered that the experimental design is deficient and has provided insufficient and/or inappropriate data for the most effective form of analysis to be carried out. Thus the term "experimental design" must include not only the proposed experimental methodology but also the methods whereby the data from the experiments are to be analysed. The importance of considering both parts of this definition together cannot be overemphasized.

## Examples

The most important variables for the possible granulation process in a fluidized bed are given in this article. As we already know, the granulation process in a fluidized bed is a complex process. There are many process variables (spray rate, inlet airflow rate, inlet temperature, inlet air humidity, nozzle air pressure, nozzle height) (1) that can influence the granule properties. These variables have been studied extensively (2,3,4)

The most widely studied granule properties in the literature are: geometric mean granule size, granule size distribution, loose and tap density (Hausner index), granule flow rate, and loss of drying. (5, 6, 7, 8, 9).

In the experiments on a small scale (10) were shown that the inlet temperature, the inlet airflow rate, the spray rate and the nozzle air pressure were the key process variables determining the granule size.

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An increase in inlet temperature, airflow rate or nozzle air pressure reduced granule size whilst the spray rate increased it. The effect of the inlet air humidity on the granule size has not been investigated much yet. One expects that an increase of the inlet air humidity will increase the granule size, because it decreases the water evaporation capacity of the inlet air and increases the powder bed moisture content. The latter depends on the equilibrium between liquid supplied by the spray rate and the inlet air humidity and the evaporation of liquid by the inlet airflow rate and the inlet air temperature. Some authors (7,8,9) showed that the granule size depends on the powder bed moisture content. If too much liquid is added or the evaporation of the liquid is not adequate than this results in an increase of the powder bed moisture content. Above a certain powder bed moisture content the powder bed becomes overwetted and defluidizes (11).

At an increased inlet airflow rate, the powder bed defluidizes at higher moisture content due to the increased deformation force on the agglomerated granules exercised by the airflow.

When the evaporation of the liquid is excessive because of high inlet flow rate and/or high inlet air temperature or low supply of liquid by the spray rate, the powder bed moisture content will be low and a spray dry process will be obtained where the granule size depends essentially on the droplet size of the binder (12).

The droplet size is mainly dependent on the nozzle air pressure and the spray rate. Therefore, the granule size is affected by the following fundamental variables: powder bed moisture content, droplet size of the binder solution and the deformation force exercised by the airflow. These variables must be controlled between certain ranges in order to produce granules of a desirable size.

According to the disposed scientific references, the following variables should be investigated in the design:

- spray rate,
- inlet airflow rate,
- inlet air temperature
- the nozzle air pressure,
- the droplet size of the binder solution
- granule size distribution,
- angle of repose,
- loose and tap density (Hausner index),
- angle of repose,
- and loss on drying

Because of the complexity of the granulation process, experimental design is an appropriate way to investigate it. Experimental designs are widely used in pharmaceutical science. Experimental designs dealing with the granulation process have been applied in the studies (13,14)

## Conclusion

Experimental design have found broad application in many disciplines. In fact, we can view experimentation as part of the scientific process and as one of the ways we learn about how systems or process work. Generally, we learn through a series of activities in which we make about a process, perform experiments to generate data from process, and then use the information from the experiment to establish new conjectures, which lead to new experiment.

Experimental design is a critically important tool for improving the performance of a manufacturing process. It has also extensive application in the development of new processes. The application of experimental design techniques early in process development can result in:

- improved process yields
- reduced variability and closer conformance to nominal or target requirements
- reduced development time
- reduced overall costs

The experimenter must choose the factors to be varied in the experiment, the ranges over which these factors will be varied, and the specific levels at which runs will be made. Thought must also be given to how these factors are to be controlled at the desired values and how they are to be measured. It is necessary to choose the region of interest for each variable (that is, the range over which each factor will be varied) and on how many levels of each variable to use. Process knowledge is required to do this.

This process knowledge is usually a combination of practical experience and theoretical understanding. It is important to investigate all factors that may be of importance and to not be overly influenced by past experience, particularly when we are in the early stages of experimentation or when the process is not very mature.

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