DESGIN OF EXPERIMENT

INTRODUCTION

- Design of Experiments (DOE) mathematical methodology used for planning and conducting experiments as well as analyzing and interpreting data obtained from the experiments.
- Simply means to make as Perfect, Effective, or Functional as possible.
- The design of experiments ensures
    I. Formulation quality,
    II. Saves time,
    III. Labor
    IV. And money

Evolution of DOE

1. Trial and error method	• Depends on one's knowledge and experience • Depends on one's luck
2. One factor at a time	• Does not examine all permutations and combinations • Can not examine interactions
3. Design of experiments	• Can predict the results of experiments not yet performed • Can predict the best conditions to meet multiple goals

DOE: Why to use it ?

- Reduce time to design/develop new products & processes
- Improve performance of existing processes
- Improve reliability and performance of products
- Achieve product & process robustness
- Perform evaluation of materials, design alternatives, setting component & system tolerances

DOE: How to use it ?

VARIABLE / FACTOR

1. Independent Variables

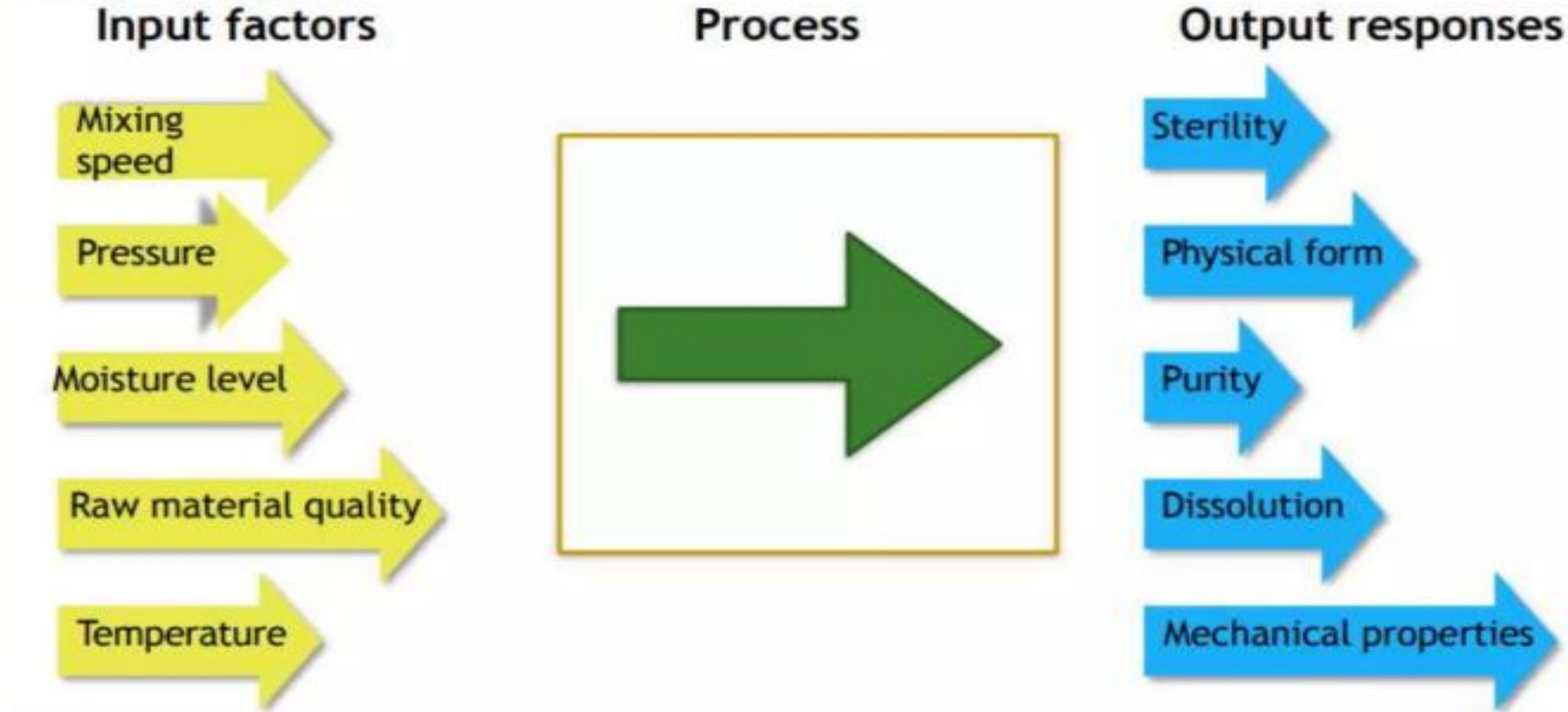
A. **Quantitative :** Numeric values and continuous. e.g. Time, Temperature, Amount of polymer, Plasticizer, Superdisintegrants etc. such as 1%, 2%, 3% concentration

B. **Qualitative :** (also known as categorical variables) e.g. Type of polymer, component or machine.

2. Dependent Variables :

- Characteristics of the finished drug product are Dependent Variables Or Response Variables. e.g. Drug release profile, Percent drug entrapment, Pellet size distribution, Moisture uptake etc.

The properties of products and processes are affected by many factors:



General practical steps and guidelines for planning and conducting DOE are listed below

Examples of DoE application in medicinal product development and pharmaceutical processes.

AREA	APPLICATION	Applied DoE TYPE
Oral Drug Delivery	Dispersible tablets development	Several factorial experiments at 2-3 factors, 2-3 levels
	Immediate release tablet platform	fractional factorial design
	Fast dissolving pellets	2^{5-1} fractional factorial design, 5 factors
	Gastroretentive dosage form	3-level-3-factor, box-behnken design
Inhalation Drug Delivery	Powder for inhalation (formulation and process development)	Half-fractional factorial design with 5 factors at two levels

Table- 1: Examples of DoE application

Examples of DoE application in medicinal product development and pharmaceutical processes.

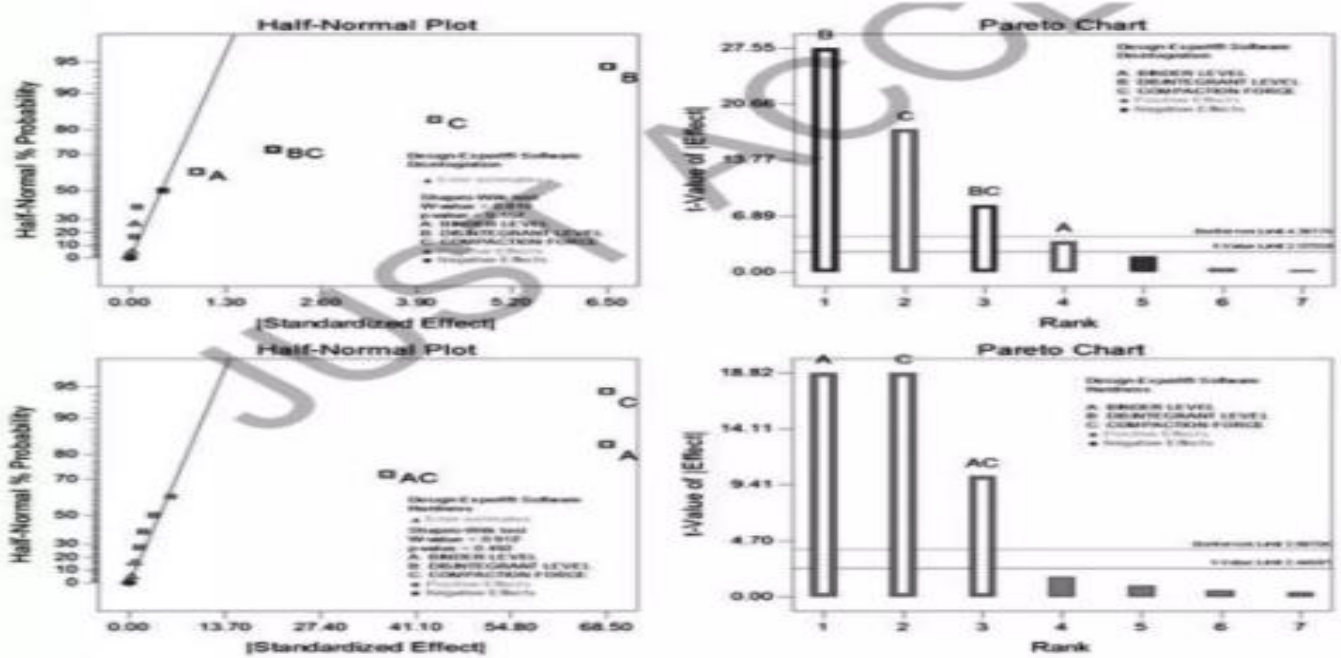
Injections	Formulation for parenteral nutrition (development)	Mixture design
Nanopharmaceutics	Solid Lipid Nanoparticles for Inhalation (process development)	Two level full factorial design

Table- 2: Examples of DoE application

DOE Software

1. Design Expert Software

- The analysis of the designs is carried out using Design Expert Software (Statease, version 9.0.1, Minneapolis, US).



➢Starting from the analysis of the full two level factorial with center points, graphical tools such as half normal and Pareto plots are helpful in identifying the most influential effects

2. Analysis of Variance (ANOVA)

- The formal statistical analysis is carried using ANOVA and the relevant data for the two responses are shown in Tables. 8

Table 8: ANOVA table for disintegration time (Factorial design example)

Source	Sum of Squares	df	Mean Square	Value F	p-value Prob > F	Conclusion
Model	128.17	4	32.04	287.81	< 0.0001	significant
A-BINDER LEVEL	1.62	1	1.62	14.55	0.0124	significant
B-DISINTEGRANT LEVEL	84.50	1	84.50	758.98	< 0.0001	significant
C-COMPACTION FORCE	34.45	1	34.45	309.39	< 0.0001	significant
BC	7.61	1	7.61	68.31	0.0004	significant
Curvature	4.38	1	4.38	39.33	0.0015	significant
Residual	0.56	5	0.11			
Lack of Fit	0.43	3	0.14	2.26	0.3211	not significant
Pure Error	0.13	2	0.06			
Cor Total	133.11	10				

Uses of DOE

It is a multipurpose tool that can be used in various situations for identification of important input factors (input variable) and outputs (response variable).

1. **Comparison:** This is one factor among multiple comparisons to select the best option that uses t–test, Z–test, or F–test.
2. **Variable screening:** These are usually two-level factorial designs intended to select important factors (variables) among many that affect performances of a system, process, or product.

Uses of DoE

3. **Transfer function identification:** if important input variables are identified, the relationship between the input variables and output variable can be used for further performance exploration of the system, process or product via transfer function.
4. **System Optimization:** the transfer function can be used for optimization by moving the experiment to optimum setting of the variables. On this way performances of the system, process or product can be improved.
5. **Robust design:** Deals with reduction of variation in the system, process or product without elimination of its causes.

Advantages of DOE

- Maximize process knowledge, with the minimum us of resources.
- Provide accurate information, in the most efficient way possible.
- Identify factor interactions.
- Characterize the relative significance of each factor.
- Allow for the prediction of the process behavior within the design space.
- Establish a solid cause and effect relationship between CPPs and CQAs.
- Allow for multiple response optimization. As pharmaceutical products exhibit several CQAs, the latter require simultaneous optimization.
- Make the product or process more robust