Optimization

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Definition:

- The term Optimize is **"to make perfect".**
- It is defined as follows: choosing the **best element** from some set of available alternatives.
- An art, process, or methodology of making something (a design, system, or decision) as perfect, as functional, as effective as possible.

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Terms:

- Factor
- Levels
- Response
- Effects
- Interaction

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Why Optimization is Necessary?

- Reduce the cost
- Save the time
- Safety and reduce the error
- Reproducibility
- Innovation and efficacy

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Advantages:

- Yield the **"best solution"** within the domain of study.
- Require **fewer experiments** to achieve an **optimum formulation.**
- Can trace and rectify **"problem"** in a remarkably **easier** manner.

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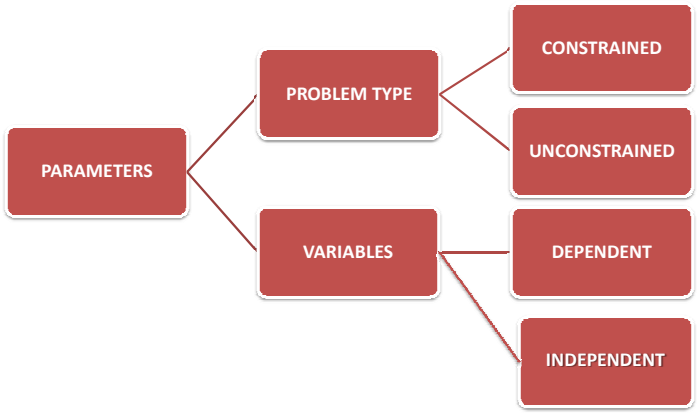
Optimization Parameters:



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Problem Type:

Unconstrained:

- In unconstrained optimization problems there are no restrictions.
- For a given pharmaceutical system one might wish to make the hardest tablet possible.
- The making of the hardest tablet is the unconstrained optimization problem.

Constrained:

- The constrained problem involved in it, is to make the hardest tablet possible, but it must disintegrate in less than 15 minutes.

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Variables:

Independent Variables:

- The independent variables are under the control of the formulator. These might include the compression force or the die cavity filling or the mixing time.

Dependent Variables:

- The dependent variables are the responses or the characteristics that are developed due to the independent variables. The more the variables that are present in the system the more the complications that are involved in the optimization.

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Independent variables	Dependent variables
X1 Diluent ratio	Y1 Disintegration time
X2 compressional force	Y2 Hardness
X3 Disintegrant level	Y3 Dissolution
X4 Binder level	Y4 Friability
X5 Lubricant level	Y5 weight uniformity

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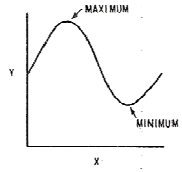
Classical Optimization:

- Classical optimization is done by using the calculus to basic problem to find the **maximum** and the **minimum** of a function.
- The curve in the fig represents the relationship between the response Y and the single independent variable X and we can obtain the maximum and the minimum. By using the calculus the graphical represented can be avoided. If the relationship, the equation

for Y as a function of X, is available [Eq]

Y = *f*(X)



Graphic location of optimum (maximum or minimum)

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Drawback:

- Applicable only to the problems that are not **too complex.**
- They do not involve **more than two variables.**
- For more than two variables graphical representation is **impossible.**

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Applied Optimization Methods:

- **Evolutionary Operation**
- **Simplex Method**
- **Search Method**
- **Lagrangian Method**
- **Canonical Analysis**

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Evolutionary Operation:

- It is the method of experimental optimization.
- Small changes in the formulation or process are made (i.e. repeats the experiment so many times) & statistically analyzed whether it is improved.
- It continues until no further changes takes place i.e., it has reached optimum-the peak.
- The result of changes are statistically analysed.

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- This technique is especially well suited to A production situation.
- Applied mostly to **TABLETS.**

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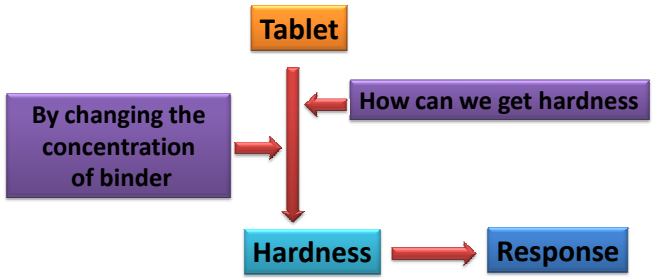
Example:



- **In this example, A formulator can changes the concentration of binder and get the desired hardness.**

Advantages:

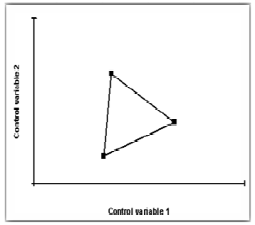
- Generates information on product development.
- Predict the direction of improvement.
- Help formulator to decide optimum conditions for the formulation and process.

Limitation:

- More repetition is required
- Time consuming
- Not efficient to finding true optimum
- Expensive to use.

Simplex Method:

- It is an **experimental method** applied for pharmaceutical systems
- Technique has wider appeal in **analytical method** other than formulation and processing
- Simplex is a **geometric figure** that has one more point than the number of factors.
- It is represented by **triangle**.
- It is determined by comparing the **magnitude** of the responses after each successive calculation.



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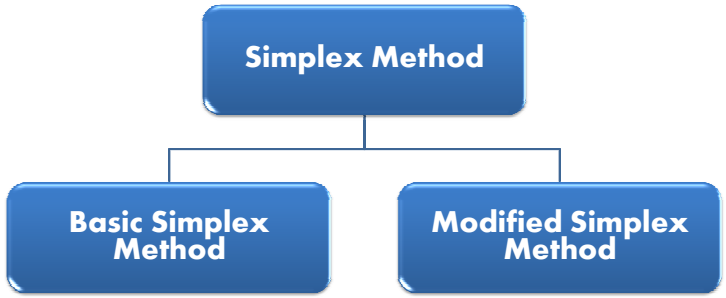
Types of Simplex Method:

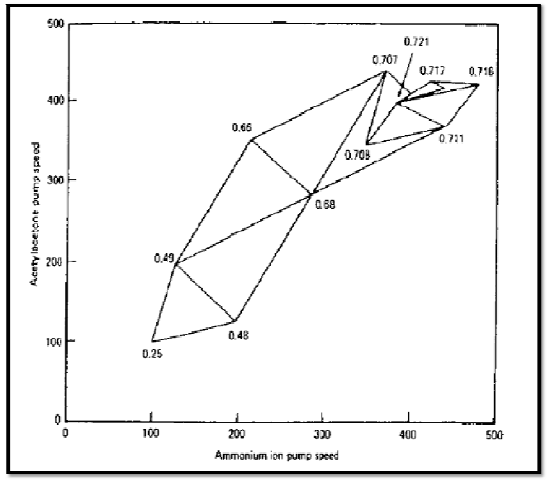


Advantages:

- This method will find the true optimum of a response with fewer trials than the non-systematic approaches or the one-variable-at-a-time method.

Disadvantages:

- There are sets of rules for the selection of the sequential vertices in the procedure.
- Require mathematical knowledge.



Lagrangian Method:

- It represents mathematical techniques.
- It is an extension of classic method.
- It is applied to a pharmaceutical formulation and processing.

Steps involved:

1. Determine the objective function.
2. Determine the constraints.
3. Change inequality constraints to equality constraints.
4. Form the Lagrange function F.
5. Partially differentiate the Lagrange function for each variable and set derivatives equal to zero Solve the set of simultaneous equations.
6. Substitute the resulting values into objective function.

Advantages:

- Lagrangian method was able to handle several responses or dependent variables.

Disadvantages

- Although the lagrangian method was able to handle several responses or dependent variables, it was generally limited to **two independent variables.**

Example

- Optimization of a tablet.
  - Phenyl propranolol (active ingredient) -kept constant.
  - X1 – disintegrate (corn starch).
  - X2 – lubricant (stearic acid).
  - X1 & X2 are independent variables.
  - Dependent variables include tablet hardness, friability volume, in vitro release rate etc..,
  - It is full 3^2 factorial experimental design.
  - Nine formulations were prepared.

Formulation no	Drug (phenylpropanolamine)	Dicalcium phosphate	Starch	Stearic acid
1	50	326	4(1%)	20(5%)
2	50	246	84(21%)	20
3	50	166	164(41%)	20
4	50	246	4	100(25%)
5	50	166	84	100
6	50	86	164	100
7	50	166	4	180(45%)
8	50	86	84	180
9	50	6	164	180

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$Y_2 = f_2 (X_1, X_2)$ -in vitro release

$Y_3 = f_3(X_1,X_2)$<2.72 %-Friability

$Y_4 = f_4 (x_1, x_2)$ <0.422 cm^3 average tablet volume

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Search Method:

- It is defined by appropriate equations.
- It do not require continuity or differentiability of function.
- It is applied to pharmaceutical system.
- The response surface is searched by various methods to find the combination of independent variables yielding an optimum.
- It takes five independent variables into account and is computer-assisted.

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Steps Involved in Search Method:

1. Select a system
2. Select variables
   a. Independent
   b. Dependent
3. Perform experiments and test product.
4. Submit data for statistical and regression analysis.
5. Set specifications for feasibility program.
6. Select constraints for grid search.
7. Evaluate grid search printout.
8. Request and evaluate

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❖For the optimization itself, two major steps were used:

- **The feasibility search**
- **The grid search**

1. The feasibility search :

Variable	Constraint	Experimental range[a]
Disintegration time (min)	1(1)[b]	1.33–30.87
	3(2)	
	5(3)	
Hardness (kg)	12(1)[b]	3.82–11.60
	10(2)	
	8(3)	
Dissolution (% at 50 min)	100(1)[b]	13.30–89.10
	90(2)	
	80(3)	

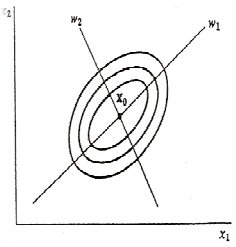
[a]It is possible to request values for a response that are more desirable than any data obtained in the set of 27 experiments.
[b](1) = first choice

Canonical Analysis:

- Canonical analysis, or canonical reduction, is a technique used to reduce a second-order regression equation, to an equation consisting of a constant and squared terms, as follows:

✓ $Y = Y_0+\lambda_1 W_1^2+\lambda_2 W_2^2+.....$

- In canonical analysis or canonical reduction, second-order regression equations are reduced to a simpler form by a rigid rotation and translation of the response surface axes in multidimensional space, as shown in fig for a two dimension system.



ig. 14 Two-dimensional representation of the rigid rota- on and translation involved in canonical analysis.

Other Applications:

- Formulation and processing
- Clinical chemistry
- Medicinal chemistry
- High performance liquid chromatographic analysis
- Formulation of culture medium in virological studies
- Study of pharmacokinetic parameters

Best of Luck!