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- CONCEPT OF OPTIMIZATION
- OPTIMIZATION PARAMETERS
- CLASSICAL OPTIMIZATION
- STATISTICAL DESIGN
- DESIGN OF EXPERIMENT
- OPTIMIZATION METHODS

INTRODUCTION

- The term Optimize is defined as “to make perfect”.
- It is used in pharmacy relative to formulation and processing
- Involved in formulating drug products in various forms
- It is the process of finding the best way of using the existing resources while taking in to the account of all the factors that influences decisions in any experiment

INTRODUCTION

- Final product not only meets the requirements from the bio-availability but also from the practical mass production criteria
- Pharmaceutical scientist- to understand theoretical formulation.
- Target processing parameters – ranges for each excipients & processing factors

INTRODUCTION

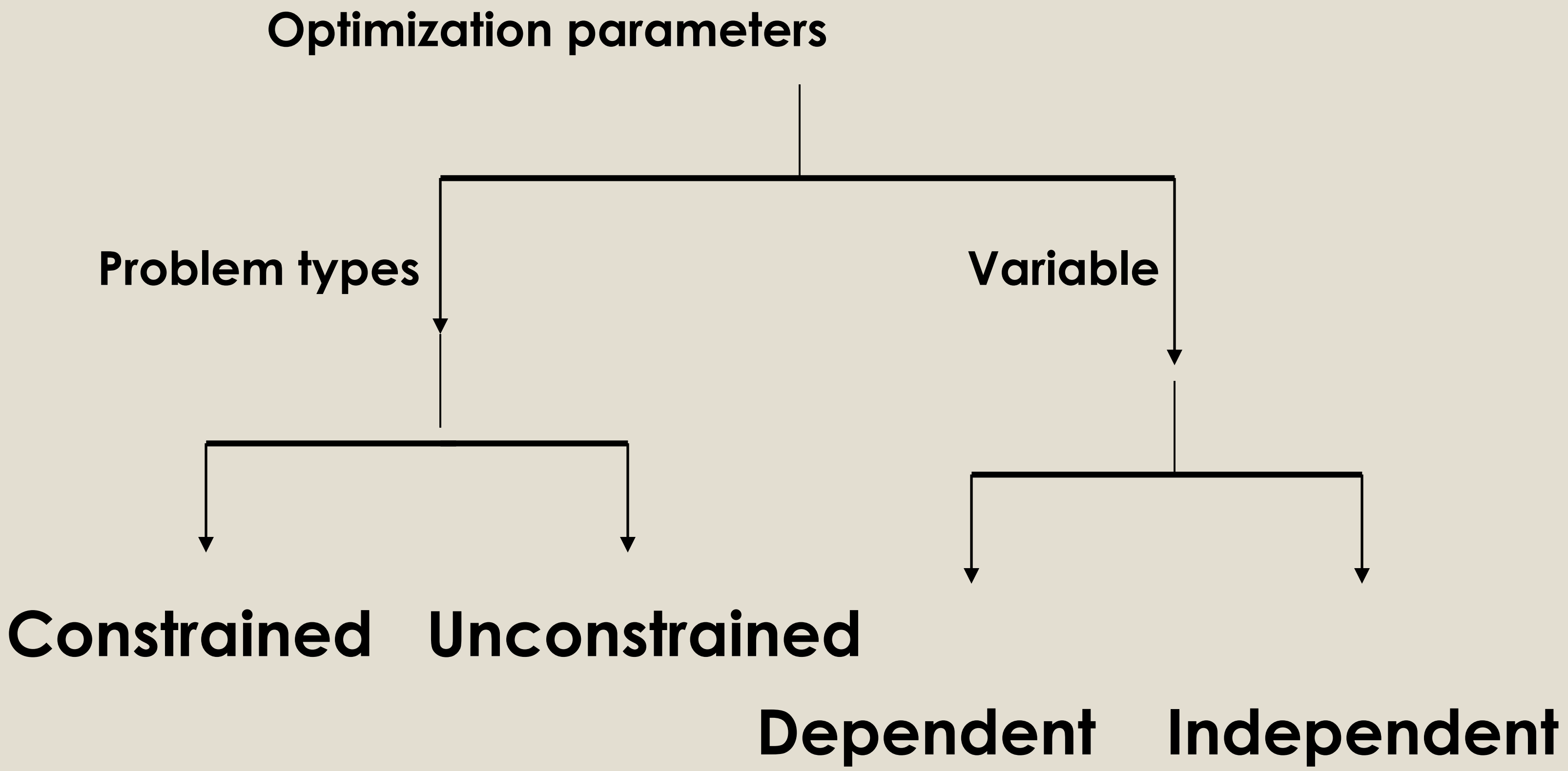
- In development projects , one generally experiments by a series of logical steps, carefully controlling the variables & changing one at a time, until a satisfactory system is obtained
- It is not a screening technique.

Optimization

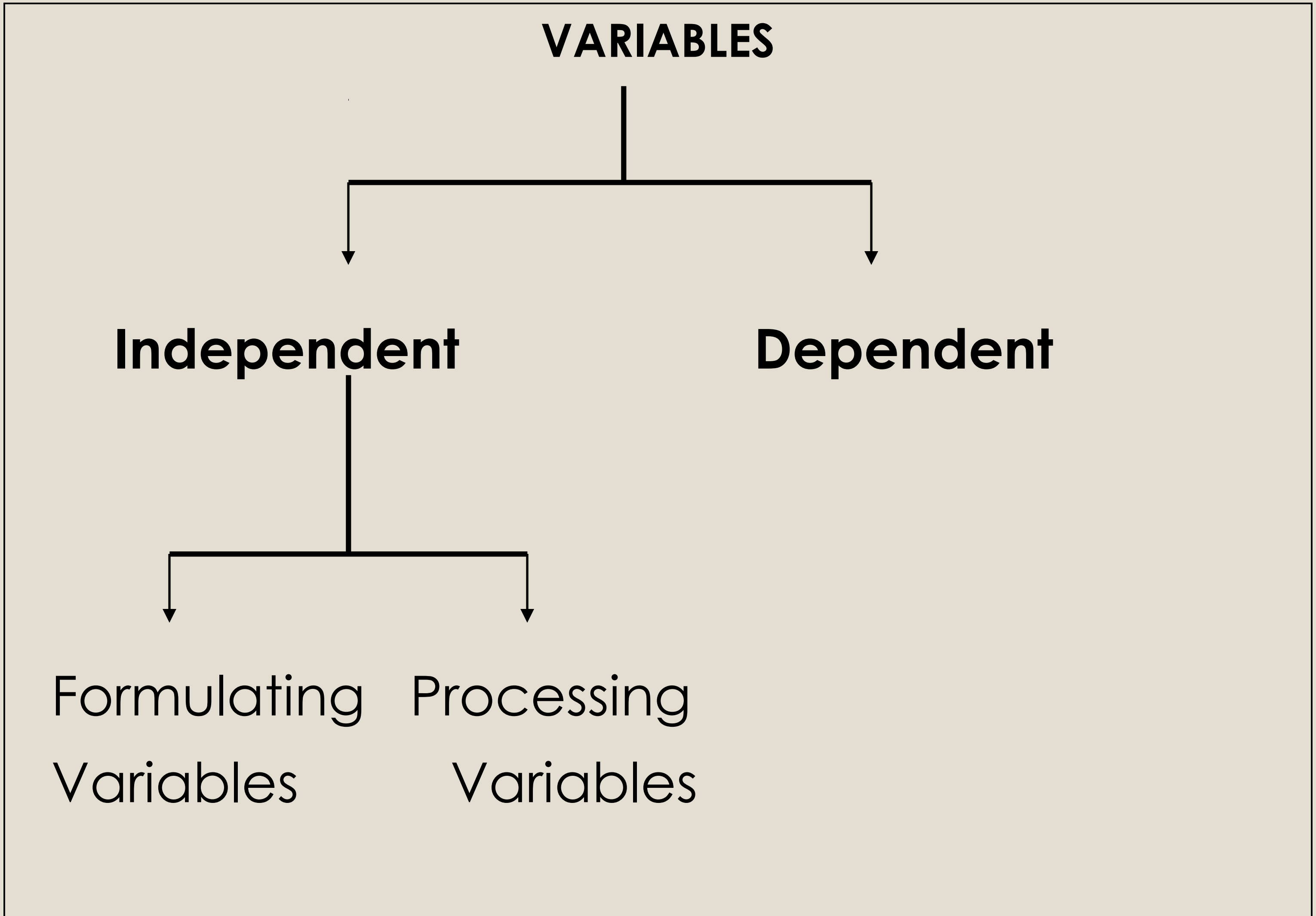
It is necessary because,

1. It reduces the cost.
2. It provides safety and reduces the error.
3. It provides innovation and efficacy.
4. It saves the time.

Optimization parameters



Optimization parameters



Optimization parameters

- **Independent variables or primary variables** :Formulations and process variables directly under control of the formulator. These includes ingredients , Mixing time

- **Dependent or secondary variables** : These are the responses of the in progress material or the resulting drug delivery system. It is the result of independent variables .
- If greater the variables in a given system, then greater will be the complicated job of optimization.
- But regardless of the no.of variables, there will be relationship between a given response and independent variables. Once we know this relationship for a given response, then will able to define a response surface

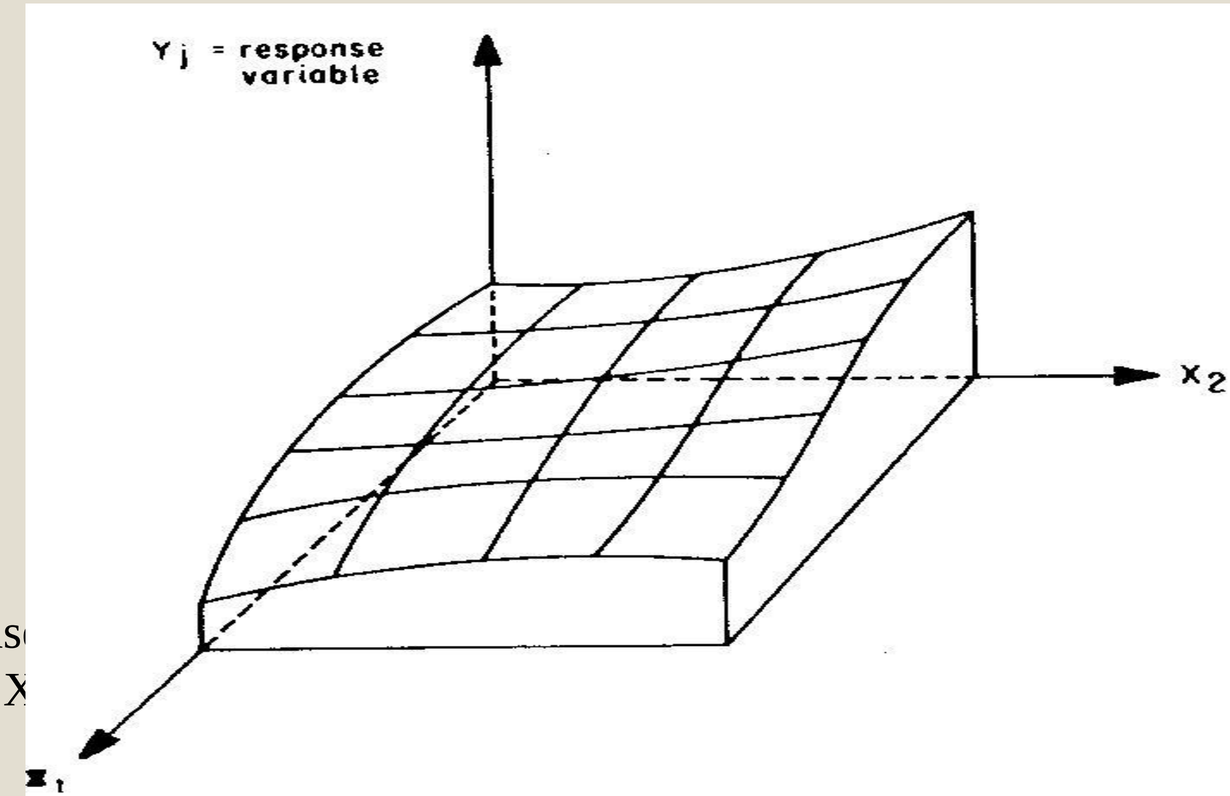
Optimization parameters

- Relationship between independent variables and response defines response surface

- Representing >2 becomes graphically impossible

- Higher the variables , higher are the complications hence it is to optimize each & everyone.

Optimization parameters



- Respons … ent variables X_1 and X

Classic optimization

- It involves application of calculus to basic problem for maximum/minimum function.

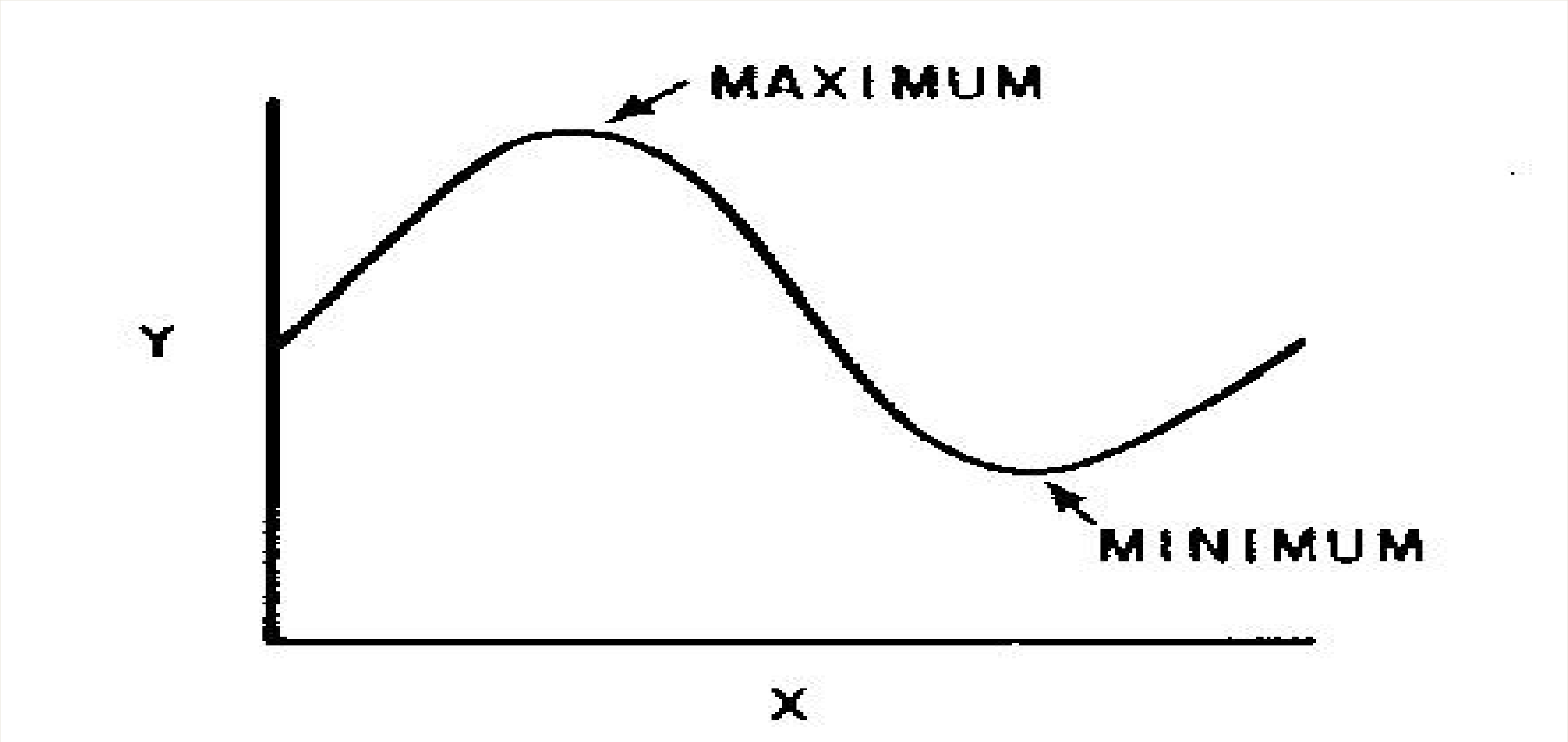
- Limited applications

  i. Problems that are not too complex

  ii. They do not involve more than two variables

- ❑For more than two variables graphical representation is impossible
- ❑It is possible mathematically

Graph Representing The Relation Between The Response Variable And Independent Variable



Classic optimization

- Using calculus the graph obtained can be solved.

$$Y = f(x)$$

- When the relation for the response y is given as the function of two independent variables, x_1 & X_2

$$Y = f(X_1, X_2)$$

The above function is represented by contour plots on which the axes represents the independent variables x_1 & x_2

Overall Plan of Optimization

Statistical design

- Techniques used divided in to two types.

- Experimentation continues as optimization proceeds

  It is represented by

1. **Evolutionary operations(EVOP)**
2. **Simplex methods.**

- Experimentation is completed before optimization takes place. It is represented by

1. **Classic mathematical**
2. **Search methods.**

Evolutionary operations

- It is the one of the most widely used methods of **experimental optimization** in fields other than pharmaceutical technology is the evolutionary operation(EVOP),
- It is well suited to production situation.
- The basic idea is that the production procedure(formulation and process) is allowed to evolve to the optimum by careful planning and constant repetition.

Evolutionary operations

Method: This process is run in a such a way that

A. It produces a product that meets all specifications.

B. Simultaneously, it generates information on product improvement.

Experimenter makes a very small change in the formulation or process but makes it so many times i.e., repeates the experiment so many times.

Then he or she can be able to determine statistically whether the product has improved.

And the experimenter makes further any other change in the same direction, many times and notes the results

Evolutionary operations

- This continues until further changes do not improve the product or perhaps become detrimental.
- Applications:

1. It was applied to tablets by Rubinstein.
2. It has also been applied to an inspection system for parenteral products.

Drawbacks:

1. It is impractical and expensive to use.
2. It is not a substitute for good laboratory scale investigation.

Simplex method:

- It is most widely applied technique.
- It was proposed by Spendley et.al.
- This technique has even wider appeal in areas other than formulation and processing.
- A good example to explain its principle is the application to the development of an analytical method i.e., a continuous flow anlayzer, it was predicted by Deming and king.
- Simplex method is a **geometric figure that has one or more point than the number of factors.**
- If two factors or any independent variables are there, then simplex is represented triangle.
- Once the shape of a simplex has been determined, the method can employ a simplex of fixed size or of variable sizes that are determined by comparing the magnitude of the responses after each successive calculation.

Statistical design

- For second type it is necessary that the relation between any dependent variable and one or more independent variable is known.

- There are two possible approaches for this

- Theoretical approach- If theoretical equation is known , no experimentation is necessary.
- Empirical or experimental approach – With single independent variable formulator experiments at several levels.

Statistical design

- The relationship with **single independent** variable can be obtained by

  Simple regression analysis or

  Least squares method.

- The relationship with **more than one** important variable can be obtained by

  Statistical design of experiment and

  Multi linear regression analysis.

- Most widely used experimental plan is **factorial design**

TERMS USED

- FACTOR: It is an assigned variable such as concentration , Temperature etc..,
  - *Quantitative*: Numerical factor assigned to it

    Ex; Concentration- 1%, 2%,3% etc..
  - *Qualitative*: Which are not numerical

    Ex; Polymer grade, humidity condition etc
- LEVELS: Levels of a factor are the values or designations assigned to the factor

FACTOR	LEVELS
Temperature	30^0 , 50^0
Concentration	1%, 2%

TERMS USED

- RESPONSE: It is an outcome of the experiment.
  - It is the effect to evaluate.
  - Ex: Disintegration time etc..,
- EFFECT: It is the change in response caused by varying the levels
  - It gives the relationship between various factors & levels
- INTERACTION: It gives the overall effect of two or more variables

  Ex: Combined effect of lubricant and glidant on hardness of the tablet

TERMS USED

- Optimization by means of an experimental design may **be helpful in shortening the experimenting time**.
- The **design of experiments** is a structured , organised method used to determine the relationship between the factors affecting a process and the output of that process.
- Statistical DOE refers to the process of planning the experiment in such a way that appropriate data can be collected and analysed statistically.

TYPES OF EXPERIMENTAL DESIGN

- Completely randomised designs
- Randomised block designs
- Factorial designs
  - Full
  - Fractional
- Response surface designs
  - Central composite designs
  - Box-Behnken designs
- Adding centre points
- Three level full factorial designs

TYPES OF EXPERIMENTAL DESIGN

❑Completely randomised Designs

- These experiment **compares the values** of a response variable based on different levels of that primary factor.
- For example ,if there are 3 levels of the primary factor with each level to be run 2 times then there are 6 factorial possible run sequences.

❑Randomised block designs

- For this there is **one factor** or variable that is of primary interest.
- To control non-significant factors,an important technique called **blocking** can be used to reduce or eliminate the contribition of these factors to experimental error.

TYPES OF EXPERIMENTAL DESIGN

- Factorial design
  - Full
    - Used for **small set** of factors
  - Fractional
    - It is used to examine **multiple factors** efficiently **with fewer runs** than corresponding full factorial design
  - Types of fractional factorial designs
    - Homogenous fractional
    - Mixed level fractional
    - Box-Hunter
    - Plackett-Burman
    - Taguchi
    - Latin square

TYPES OF EXPERIMENTAL DESIGN

- Homogenous fractional
  - Useful when **large number of factors** must be screened
- Mixed level fractional
  - Useful when **variety of factors** need to be evaluated for main effects and higher level interactions can be assumed to be negligible.
- Box-hunter
  - Fractional designs with factors of more than two levels can be specified as homogenous fractional or mixed level fractional

TYPES OF EXPERIMENTAL DESIGN

Plackett-Burman

- It is a popular class of screening design.
- These designs are very efficient screening designs when only the **main effects are of interest**.
- These are useful for detecting large main effects economically ,assuming all interactions are negligible when compared with important main effects
- Used to investigate **n-1 variables** in **n experiments** proposing experimental designs for more than seven factors and especially for n*4 experiments.

TYPES OF EXPERIMENTAL DESIGN

❑Taguchi

- It is similar to PBDs.
- It allows estimation of **main effects** while minimizing variance.

❑Latin square

- They are special case of fractional factorial design where there is one treatment **factor of interest** and **two or more blocking factors**

Response surface designs

- This model has quadratic form

$$\gamma = \beta_0 + \beta_1 X_1 + \beta_2 X_2 + \ldots . \beta_{11} X_1^{2} + \beta 22 X_2^{2}$$

- Designs for fitting these types of models are known as response surface designs.

- If defects and yield are the ouputs and the goal is to minimise defects and maximise yield

Three-level full factorial designs

- It is written as 3^k factorial design.
- It means that **k factors** are considered each at 3 levels.
- These are usually referred to as low, intermediate & high values.

- These values are usually expressed as 0, 1 & 2
- The third level for a continuous factor facilitates investigation of a **quadratic relationship between the response** and **each of the factors**

FACTORIAL DESIGN

- These are the designs of choice for **simultaneous determination of the effects of several factors & their interactions.**

- Used in experiments where the effects of different factors or conditions on experimental results are to be elucidated.

- Two types
  - *Full factorial*- Used for small set of factors
  - *Fractional factorial*- Used for optimizing **more number of factors**

LEVELS OF FACTORS IN THIS FACTORIAL DESIGN

FACTOR	LOWLEVEL(mg)	HIGH LEVEL(mg)
A:stearate	0.5	1.5
B:Drug	60.0	120.0
C:starch	30.0	50.0

EXAMPLE OF FULL FACTORIAL EXPERIMENT

Factor combination	**Stearate**	**Drug**	**Starch**	**Response Thickness Cm*10^3**
(1)	_	_	_	475
a	+	_	_	487
b	_	+	_	421
ab	+	+	_	426
c	_	_	+	525
ac	+	_	+	546
bc	_	+	+	472
abc	+	+	+	522

EXAMPLE OF FULL FACTORIAL EXPERIMENT

- Calculation of main effect of A (stearate)

- The main effect for factor A is

- $$\frac{\{-(1)+a-b+ab-c+ac-bc+abc] \times 10^{-3}}{4}$$

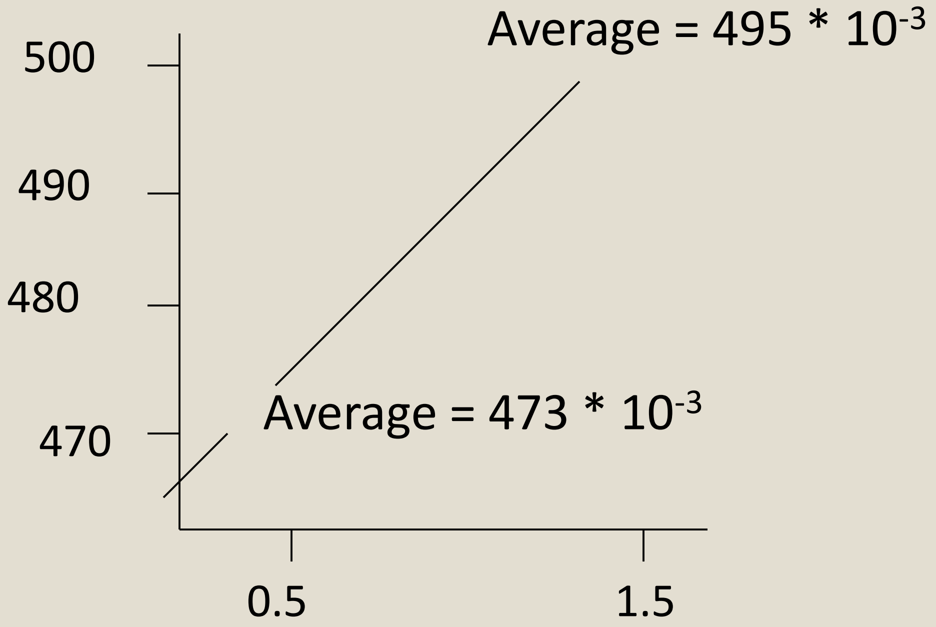
- Main effect of A =

$$= \frac{a + ab + ac + abc}{4} - \frac{(1) + b + c + bc}{4}$$

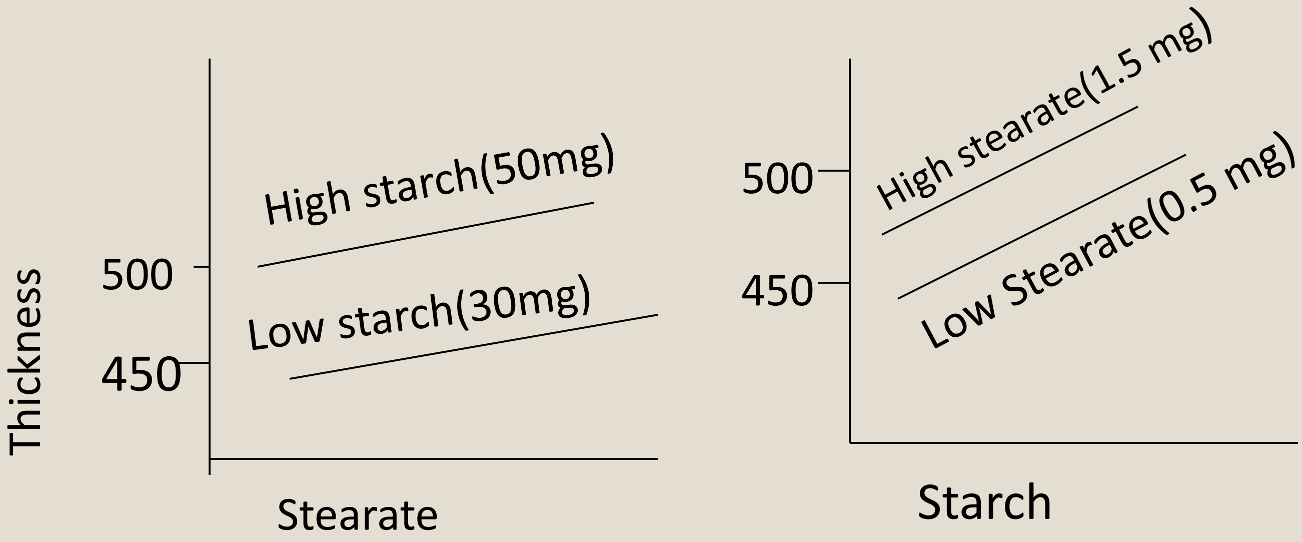
$$= \frac{[487 + 426 + 456 + 522 - (475 + 421 + 525 + 472)] \times 10^{-3}}{4}$$

= 0.022 cm

EFFECT OF THE FACTOR STEARATE



STARCH X STEARATE INTERACTION



General optimization

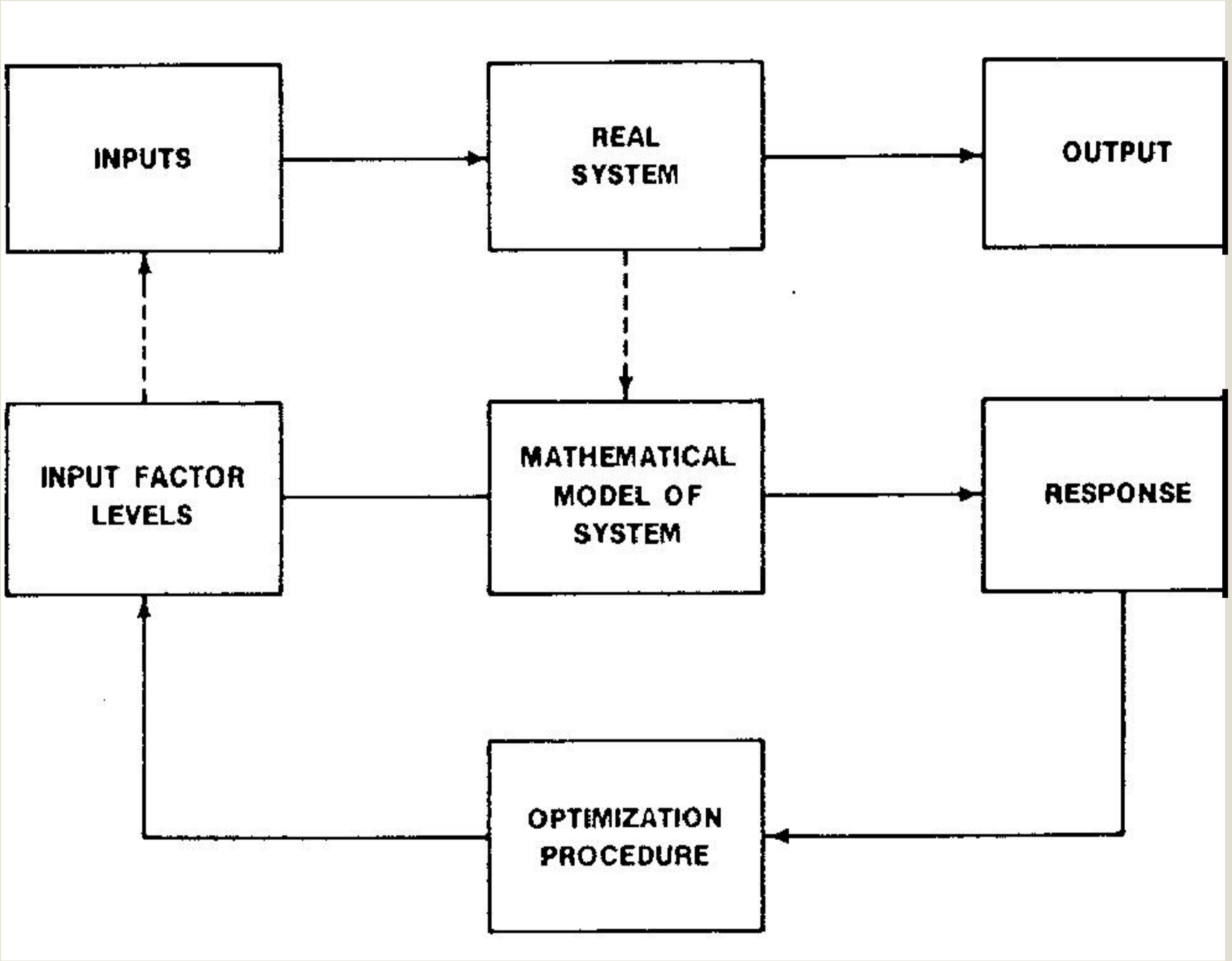
- By MRA the relationships are generated from experimental data , **resulting equations are on the basis of optimization.**

- These equation **defines response surface** for the system under investigation

- After collection of all the runs and calculated responses ,calculation of **regression coefficient** is initiated.

- Analysis of variance (ANOVA) presents the sum of the squares used to estimate the factor main effects.

FLOW CHART FOR OPTIMIZATION



Applied optimization methods

- ❑Evolutionary operations
- ❑Simplex method
- ❑Lagrangian method
- ❑Search method
- ❑Canonical analysis

Evolutionary operations (evop)

- It is a method of experimental optimization.
- Technique is well suited to **production situations**.
- 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

Evolutionary operations (evop)

- Applied mostly to TABLETS.

- Production procedure is optimized by careful planning and constant repetition

- It is impractical and expensive to use.

- It is not a substitute for good laboratory scale investigation

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

Graph representing the simplex movements to the optimum conditions

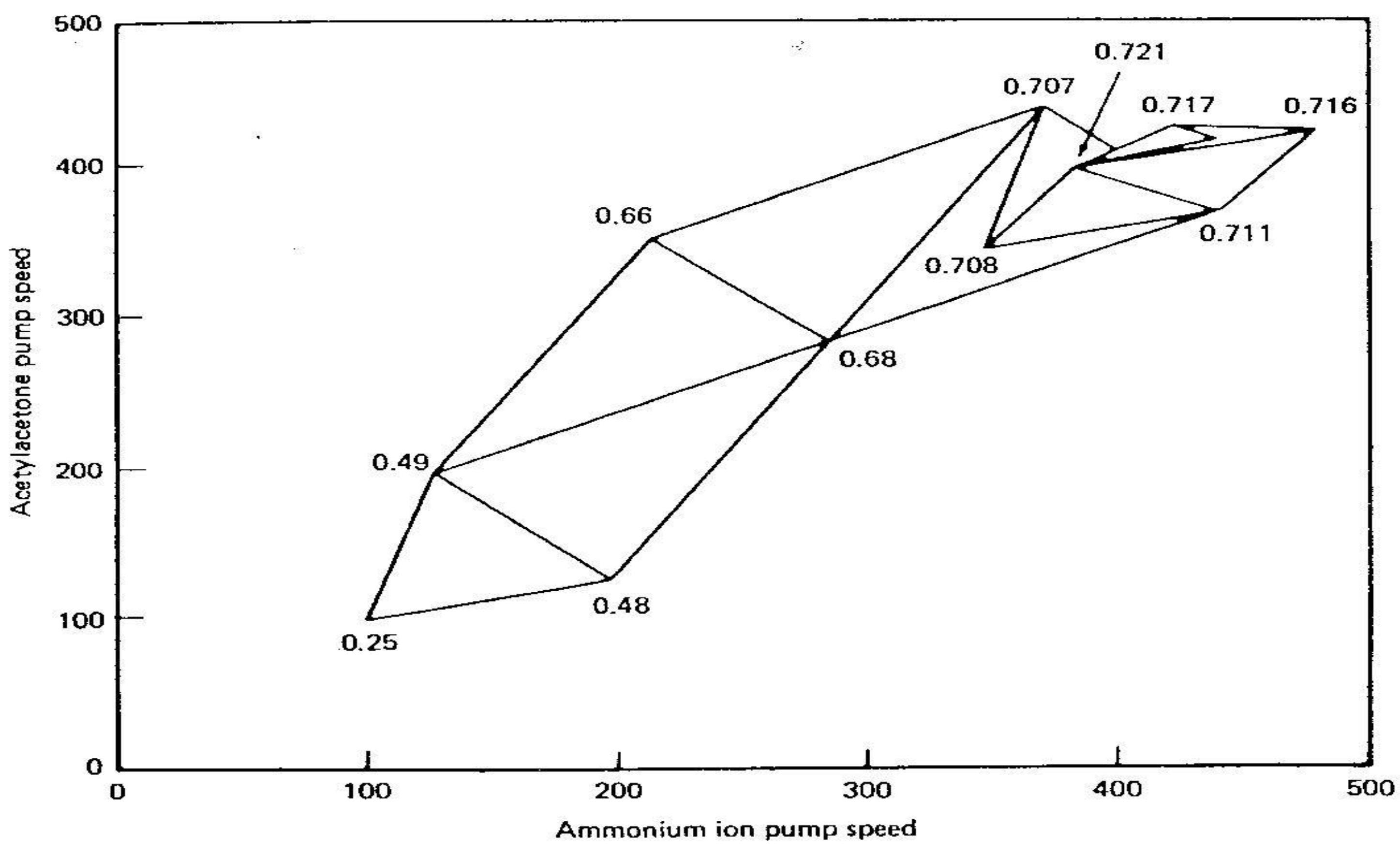


Fig. 5 The simplex approach to optimization. Response is spectrophotometric reading at a given wavelength. (From Ref. 6.)

Simplex method

- The two independent variables show pump speeds for the two reagents required in the analysis reaction.

- Initial simplex is represented by lowest triangle.
- The vertices represents spectrophotometric response.

- The strategy is to move towards a better response by moving away from worst response.
- Applied to optimize CAPSULES, DIRECT COMPRESSION TABLET (acetaminophen), liquid systems (physical stability)

Lagrangian method

- It represents **mathematical** techniques.
- It is an extension of classic method.
- It is applied to a pharmaceutical formulation and processing.
- This technique follows the second type of statistical design
- Limited to 2 variables - disadvantage

Steps involved

- Determine objective formulation
- Determine constraints.
- Change inequality constraints to equality constraints.
- Form the Lagrange function F:
- Partially differentiate the lagrange function for each variable & set derivatives equal to zero.
- Solve the set of simultaneous equations.
- Substitute the resulting values in objective functions

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, invitro release rate e.t.c..,

Example

- Polynomial models relating the response variables to independents were generated by a backward stepwise regression analysis program.

- $Y= B_0+B_1X_1+B_2X_2+B_3\ X_1^2 +B_4\ X_2^2 +B+_5\ X_1\ X_2 +B_6\ X_1X_2$

$+ B_7X_1^2+B_8X_1^2X_2^2$

Y – Response

B_i – Regression coefficient for various terms containing the levels of the independent variables.

X – Independent variables

Tablet formulations

Formulation no,.	Drug	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%)

Tablet formulations

- Constrained optimization problem is to locate the levels of stearic acid(x_1) and starch(x_2).

- This minimize the time of invitro release(y_2),average tablet volume(y_4), average friability(y_3)

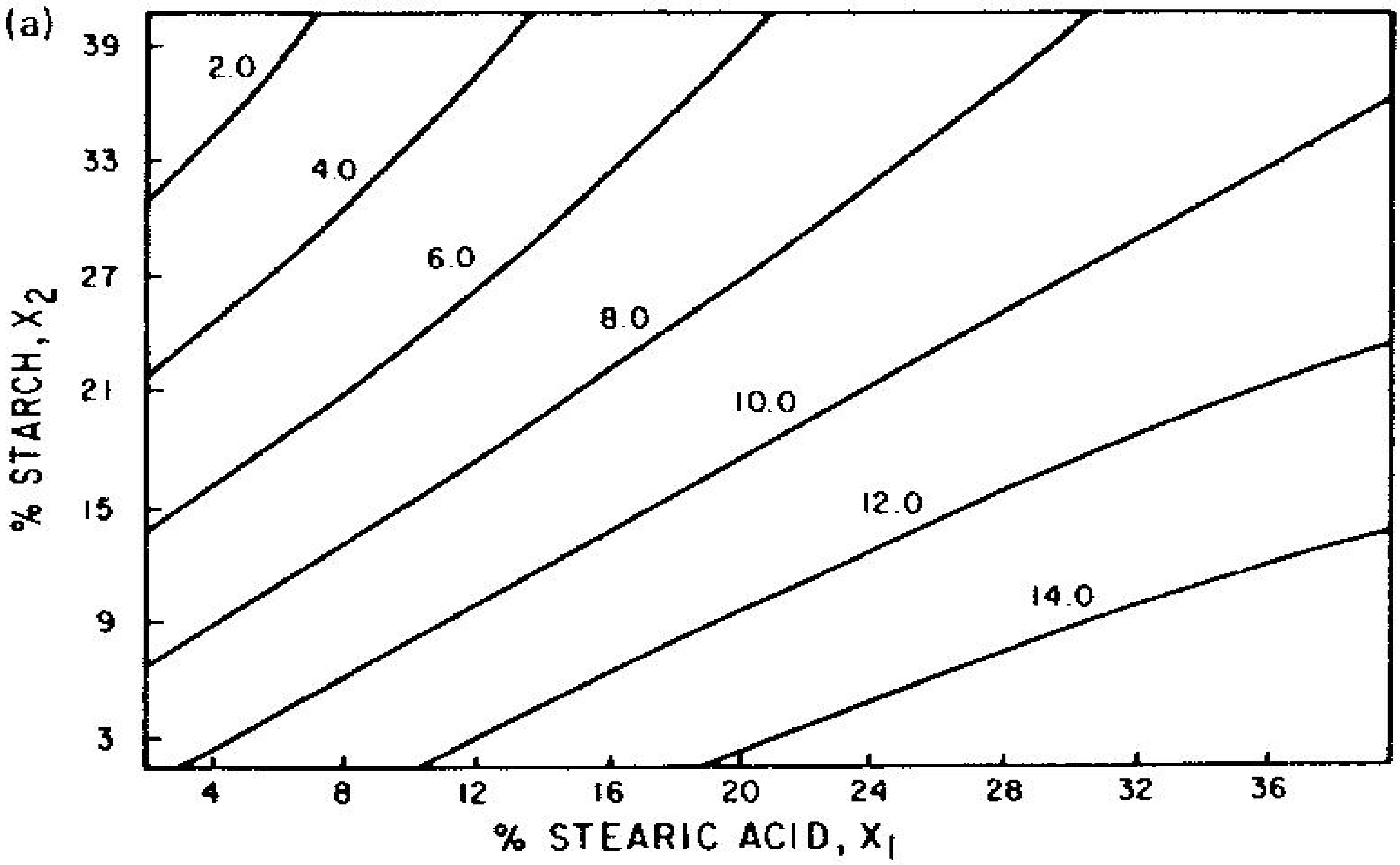
- To apply the lagrangian method, problem must be expressed mathematically as follows

$$Y_2 = f_2(X_1,X_2)\text{-invitro release}$$

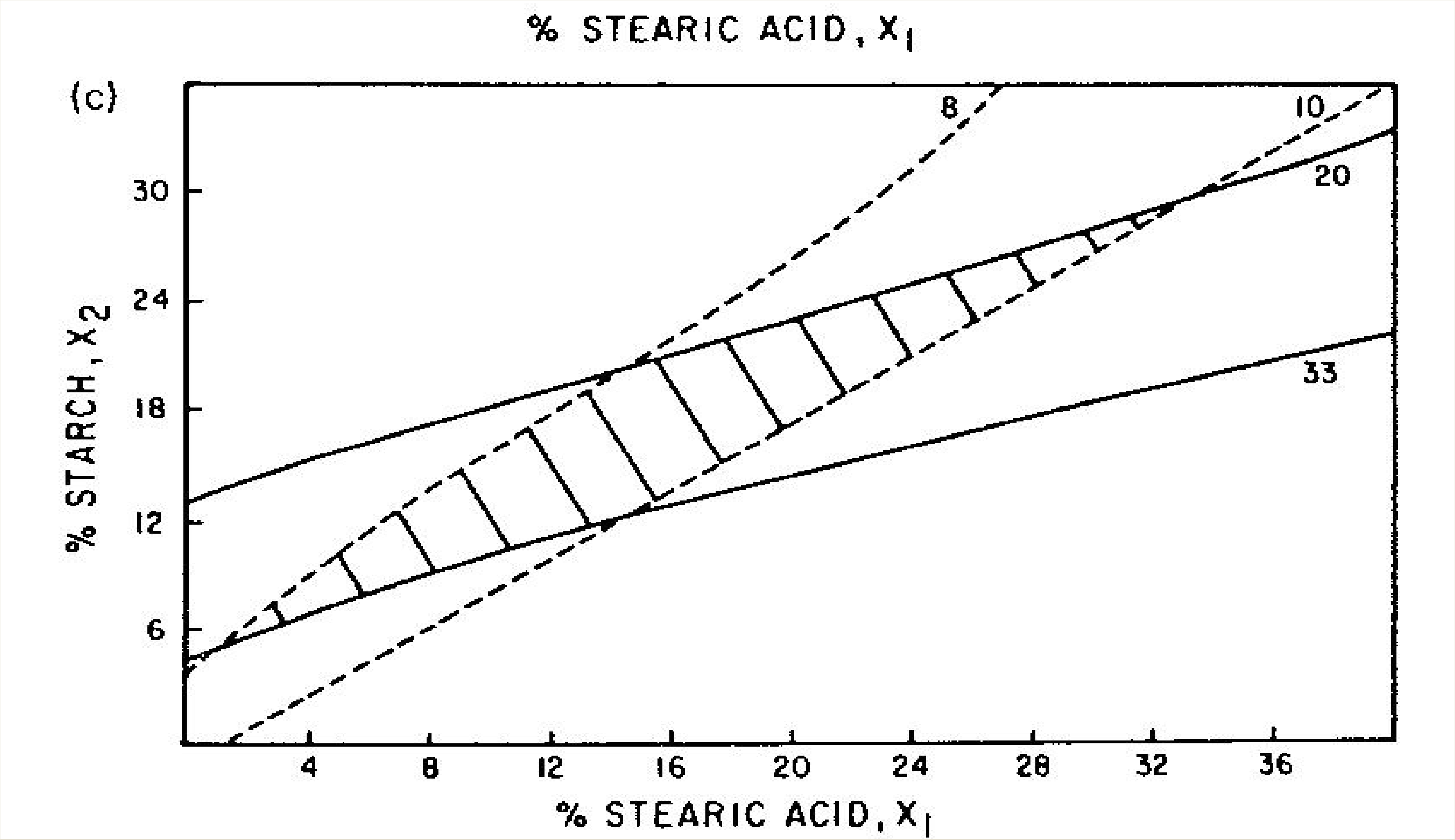
$$Y_3 = f_3(X_1,X_2)<2.72\text{-Friability}$$

$$Y_4 = f_4(x_1,x_2) <0.422\text{-avg tab.vol}$$

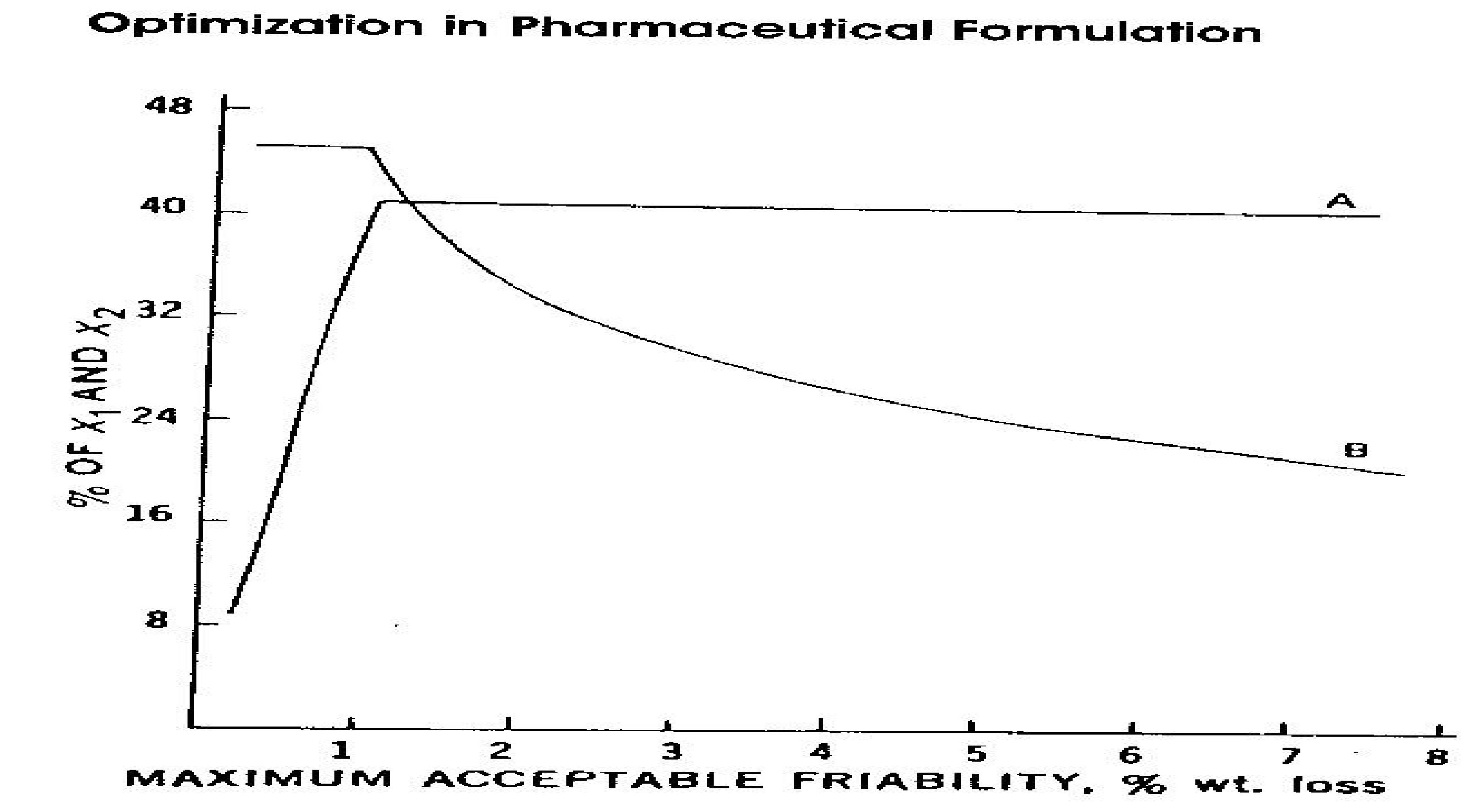
CONTOUR PLOT FOR TABLET HARDNESS



GRAPH OBTAINED BY SUPER IMPOSITION OF TABLET HARDNESS & DISSOLUTION



Tablet formulations



Search method

- It is defined by appropriate equations.
- It do not require continuity or differentiability of function.
- It is applied to pharmaceutical system
- For optimization 2 major steps are used

- Feasibility search-used to locate set of response constraints that are just at the limit of possibility.
- Grid search – experimental range is divided in to grid of specific size & methodically searched

Steps involved in search method

- ❑Select a system
- ❑Select variables
- ❑Perform experiments and test product
- ❑Submit data for statistical and regression analysis
- ❑Set specifications for feasibility program
- ❑Select constraints for grid search
- ❑Evaluate grid search printout

Example

Tablet formulation

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

Example

- Five independent variables dictates total of 32 experiments.

- This design is known as five-factor, orthagonal, central,composite, second order design.

- First 16 formulations represent a half-factorial design for five factors at two levels .

- The two levels represented by +1 & -1, analogous to high & low values in any two level factorial.

Translation of statistical design in to physical units

Experimental conditions

Factor	-1.54eu	-1 eu	Base0	+1 eu	+1.547eu
X_1= ca.phos/lactose	24.5/55.5	30/50	40/40	50/30	55.5/24.5
X_2= compression pressure(0.5 ton)	0.25	0.5	1	1.5	1.75
X_3 = corn starch disintegrant	2.5	3	4	5	5.5
X_4 = Granulating gelatin(0.5mg)	0.2	0.5	1	1.5	1.8
X_5 = mg.stearate (0.5mg)	0.2	0.5	1	1.5	1.8

Translation of statistical design in to physical units

- Again formulations were prepared and are measured.
- Then the data is subjected to statistical analysis followed by multiple regression analysis.
- The equation used in this design is second order polynomial.
- $y = {}_1a_0+a_1x_1+\ldots+a_5x_5+a_{11}x_1{}^2+\ldots+a_{55}x^2{}_5+a_{12}x_1x_2$

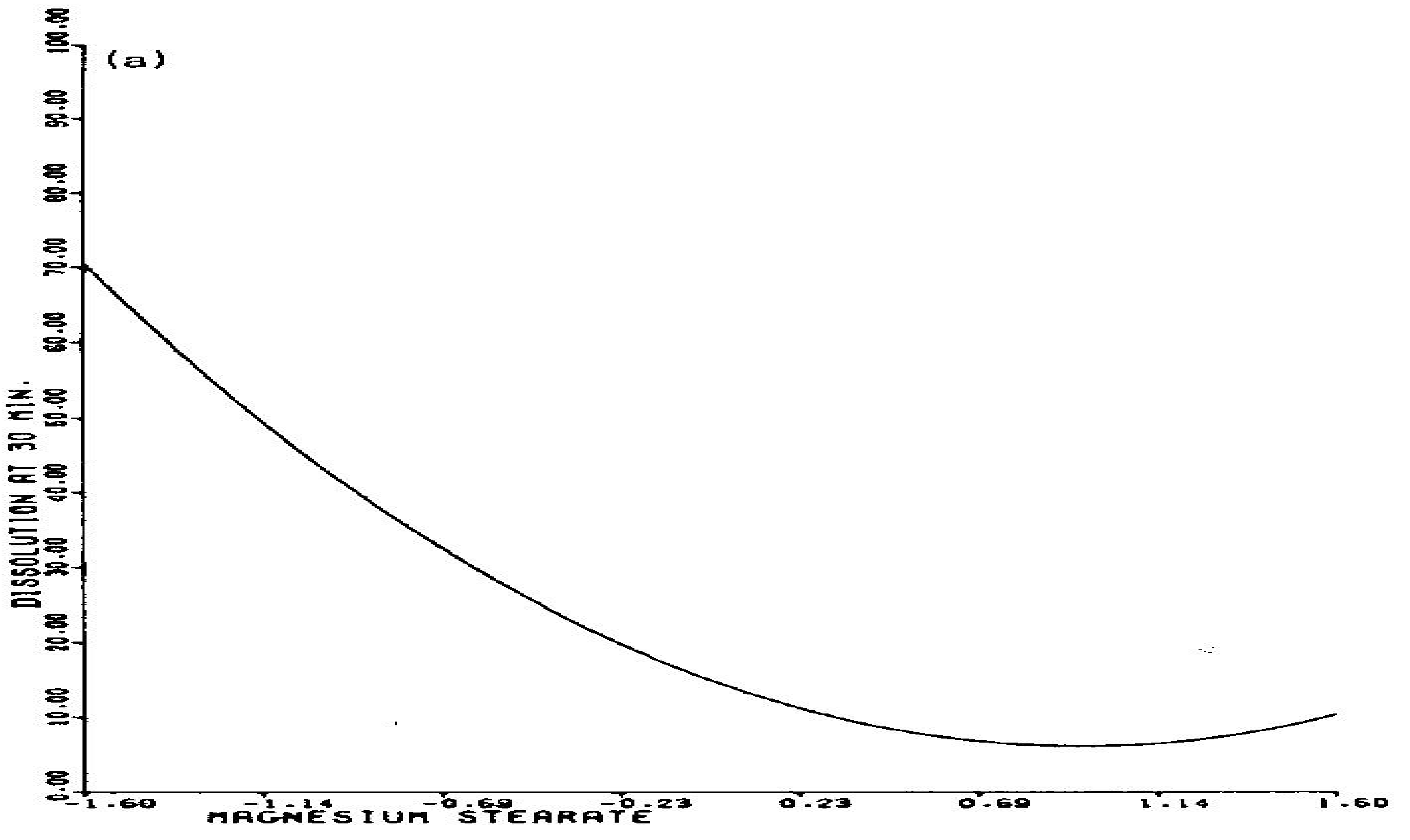
  $+a_{13}x_1x_3+a_{45}\ x_4x_5$

Translation of statistical design in to physical units

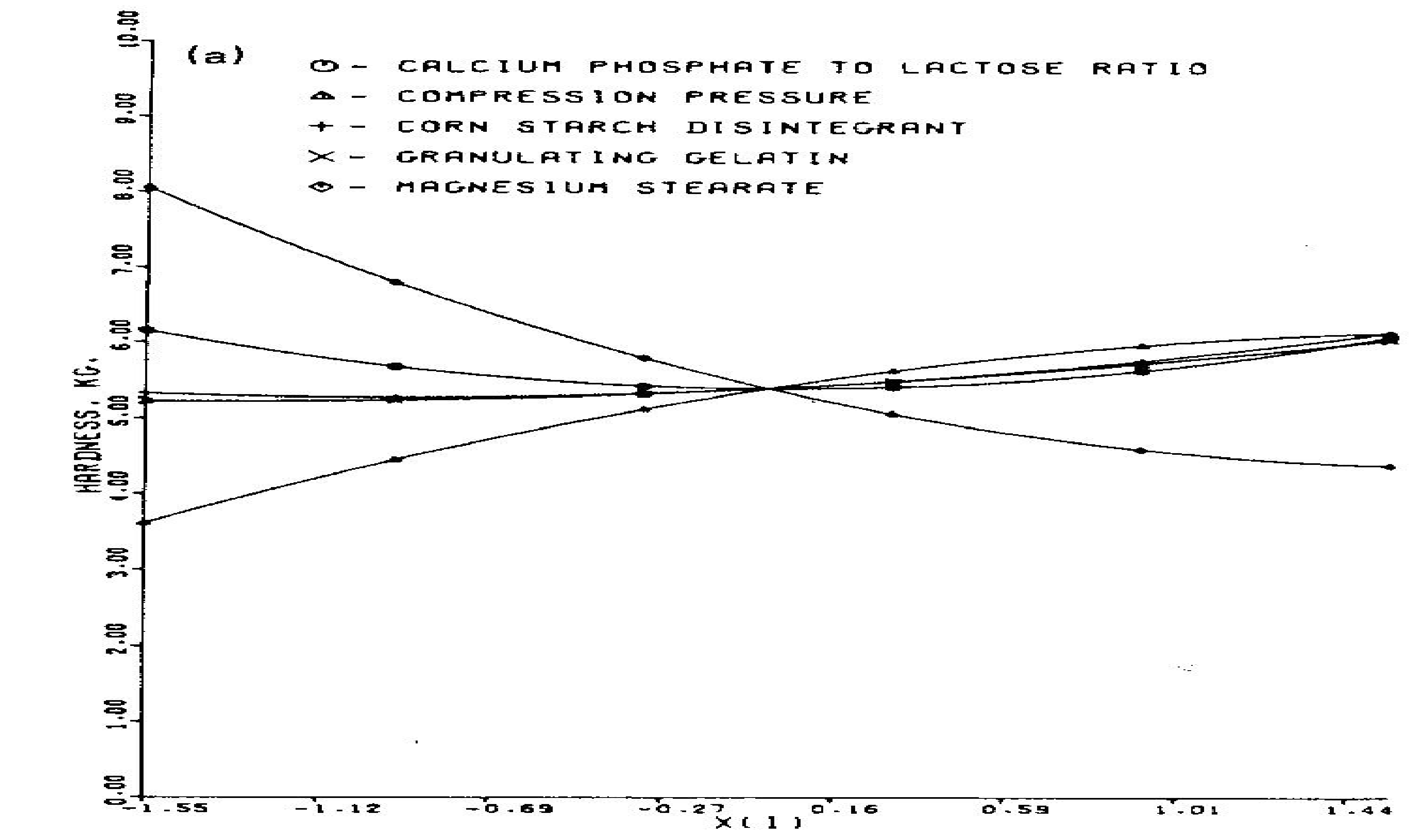
- A multivariant statistical technique called principle component analysis (PCA) is used to select the best formulation.

- PCA utilizes variance-covariance matrix for the responses involved to determine their interrelationship.

PLOT FOR A SINGLE VARIABLE



PLOT OF FIVE VARIABLES



PLOT OF FIVE VARIABLES

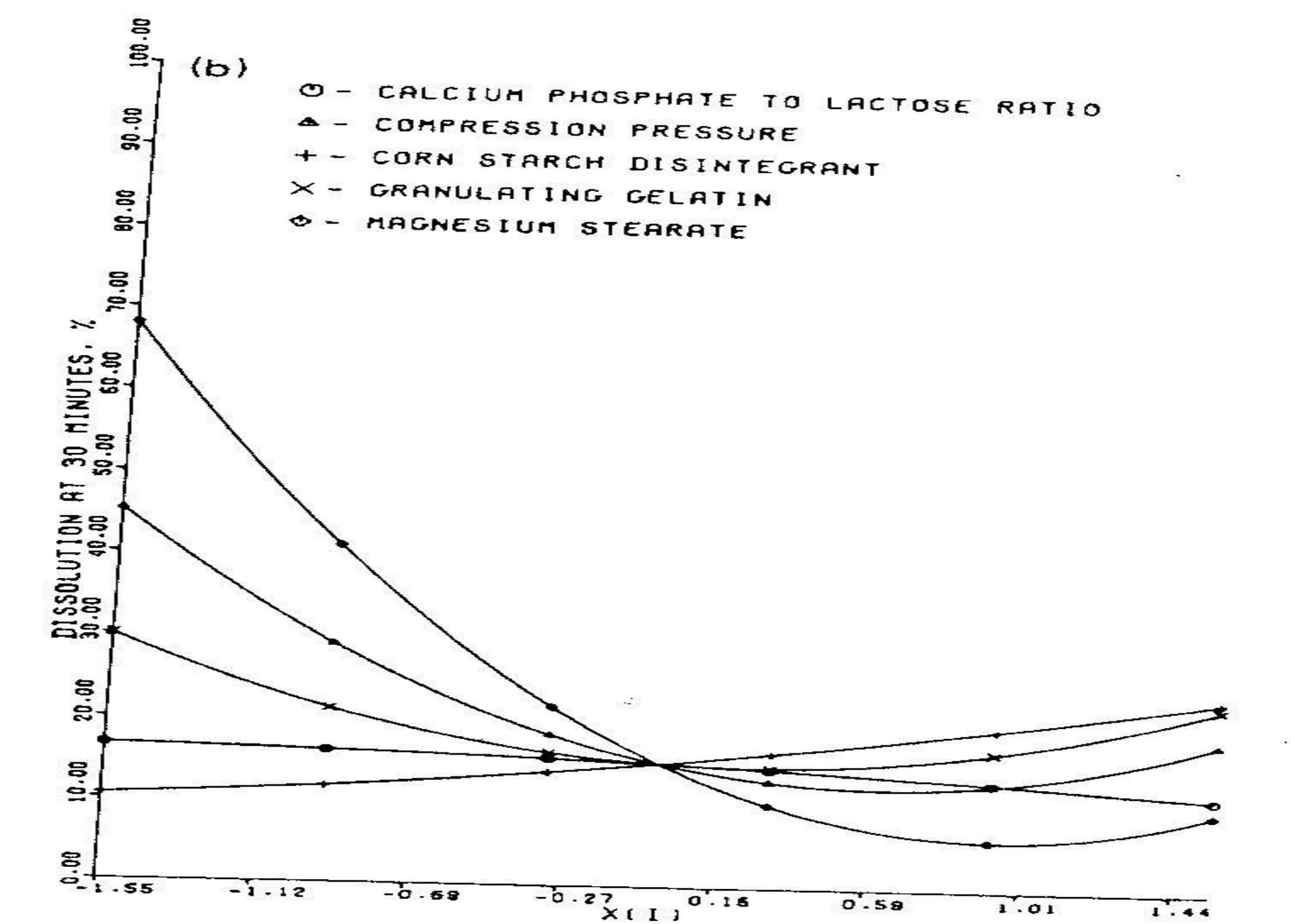


Fig. 12 Continued.

ADVANTAGES OF SEARCH METHOD

- It takes five independent variables in to account.

- Persons **unfamiliar with mathematics of optimization & with no previous computer experience could carryout an optimization study.**

Important Questions

- Classic optimization
- Define optimization and optimization methods
- Optimization using factorial design
- Concept of optimization and its parameters
- Importance of optimization techniques in pharmaceutical processing & formulation
- Importance of statistical design

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