

PILOT PLANT SCALE- UP TECHNIQUE

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Lecturer

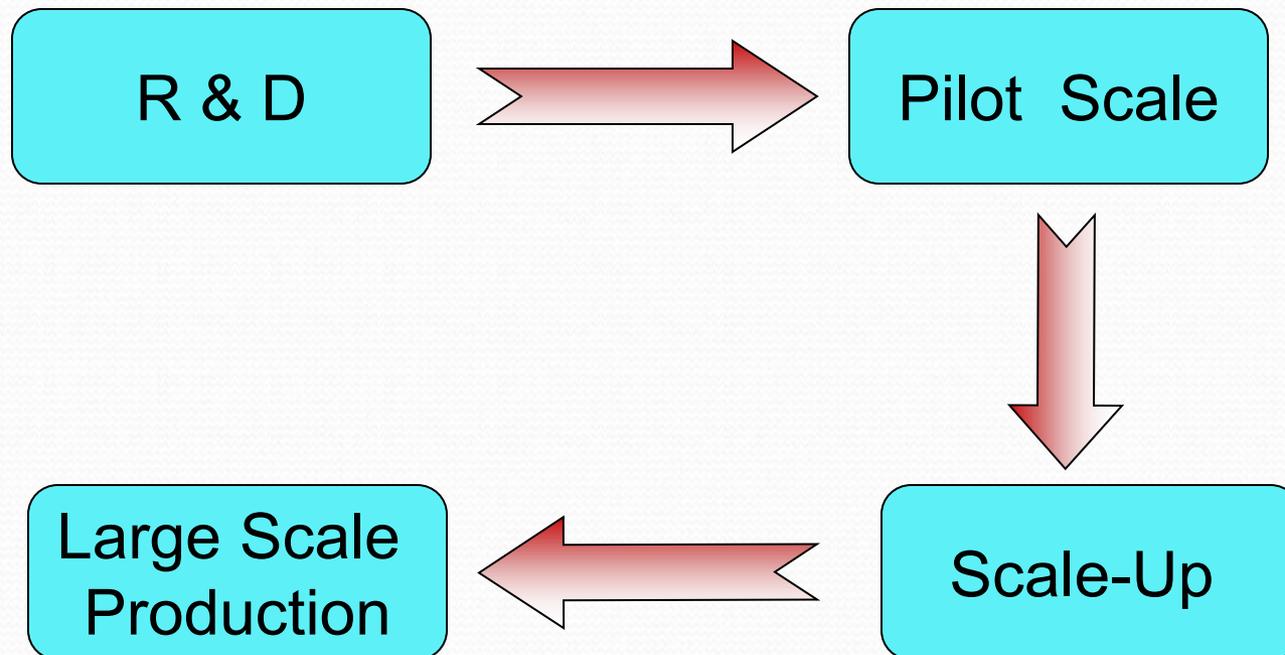
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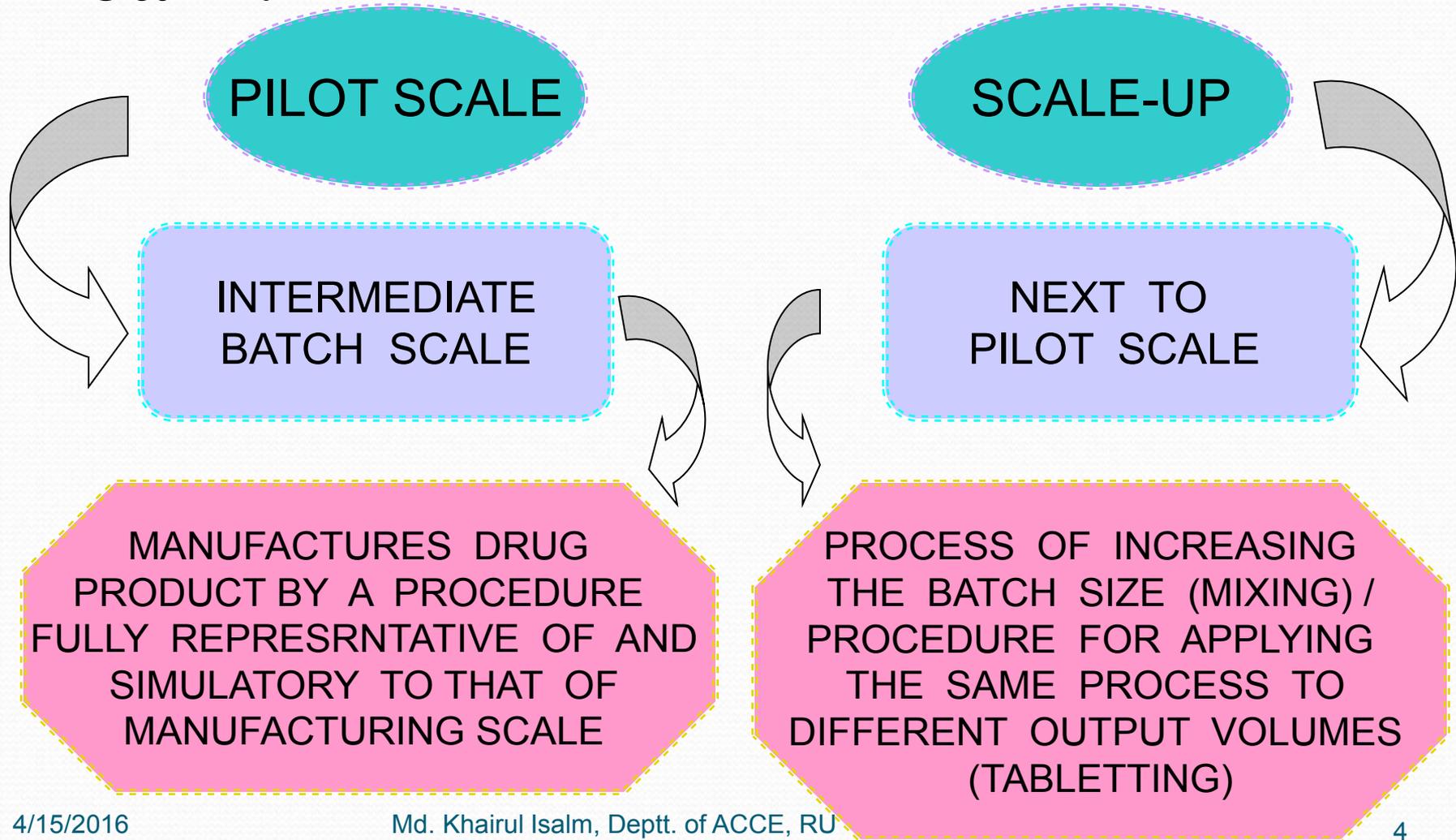
Fundamental Definitions

- **Plant:-** A chemical plant is an industrial process plant that manufactures (or otherwise processes) chemicals, usually on a large scale. It is a place where the 5 M's like money, material, man, method and machine are brought together for the manufacturing of the products.
- **Pilot Plant:-** A pilot plant is a small industrial system which is operated to generate information about the behavior of the system for use in design of larger facilities. Pilot plant is a relative term in the sense that plants are typically smaller than full-scale production plants, but are built in a range of sizes. (A pilot plant is a small scale replica of the full scale final plant that is not yet built to provide design data for the ultimate large one).
- **Model:** A geometrical similar replica of complete prototype on a small scale with equal scale ratios in all direction is termed as a model. Its function is to exhibit the effects of change in shape or operating conditions of a existing plant.
- **Prototype:** A large scale apparatus or full size plant is called prototype.
- **Scale-up:-** The art for designing of prototype using the data obtained from the pilot plant model.

Pilot Scale and Scale-Up



What Do Pilot Scale and Scale-Up Mean ?



Objectives of pilot plant study

[[Commit your blunder on a small scale and make your profit on a large scale]]

- A pilot plant allows investigation of a product and process on an intermediate scale before large amounts of money are committed to full-scale production.
- It is usually not possible to predict the effects of a many-fold increase in scale.
- It is not possible to design a large scale processing plant from laboratory data alone with any degree of success.

Classification of design data

The design data required for each piece of equipment can be classified under six heads-

- Data available from past experience.
- Data given in the laboratory report or which can be derived from the laboratory results.
- Data available in the literature.
- Data which can be approximated sufficiently closely for design purpose by means of thermodynamic relations, the theorem of corresponding states, or some of the many empirical or semi empirical correlations that have appeared in recent year.
- Data which could be obtained by further research in the laboratory.
- Other practical felt to be necessary for design purpose.

Information falling under this head can be determined only in a pilot plant.

Factors affecting the rate equation

- Dimensional and time factors: The dimensional factor indicate the manner in which the total quantity of change per hours depends upon the dimension of the apparatus whether for example, it varies with the length, surface and volume of the vessel. The time factor indicates the manner in which the rate varies with time.
- Operating variables: Operating variables include temperatures, pressures, concentrations, rates of flow and residence time.
- Physical and chemical properties: Physical and chemical properties represent the usual form in which laboratory data are fed into the design calculation. They may be determined in the laboratory, taken from literature or reference handbooks, or approximated by means of theoretical or empirical rule.
- Numerical factor: The numerical factor is a dimensionless factor which s needed to balance the rate equation when the later is expressed in dimensionless form. The numerical factor is actually a shape factor which varies with geometrical shape of the apparatus but is independent of its size.

STEPS IN SCALE UP

Define product economics based on projected market size and competitive selling and provide guidance for allowable manufacturing costs



Conduct laboratory studies and scale-up planning at the same time



Define key rate-controlling steps in the proposed process



Conduct preliminary larger-than-laboratory studies with equipment to be used in rate-controlling step to aid in plant design



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graph TD; A[Design and construct a pilot plant including provisions for process and environmental controls, cleaning and sanitizing systems, packaging and waste handling systems, and meeting regulatory agency requirements] --> B[Evaluate pilot plant results (product and process) including process Economics to make any corrections and a decision on whether or not to proceed with a full scale plant development];
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Design and construct a pilot plant including provisions for process and environmental controls, cleaning and sanitizing systems, packaging and waste handling systems, and meeting regulatory agency requirements

Evaluate pilot plant results (product and process) including process Economics to make any corrections and a decision on whether or not to proceed with a full scale plant development

Why Scale-Up needed.....

A well
defined
process

A perfect
product in
laboratory
and pilot
plant

But May
fail in QA
Tests

Because
process are
scale
dependent

Processes
behave
differently
on a small
scale and a
large scale

Scale up is
necessary
to
determine
the effect
of scale on
product
quality

OBJECTIVES OF SCALE UP....

To produce physically and chemically stable products



Review of the processing equipment



Guidelines for production and process control



Evaluation and Validation



To identify the critical features of the process



To provide master manufacturing formula

Requirements/ considerations for pilot plant and Scale-Up....

- Reporting Responsibility
- Personnel Requirements
- Space Requirements
 - Administration and Information Process
 - Physical Testing Area
 - Standard Pilot-plant Equipment Floor Space
 - Storage Area
- Review of Formula
- Raw materials
- Equipment
- Production rates
- Process Evaluation
- Preparation of Master Manufacturing Procedures
- Product Stability and Uniformity
- GMP Considerations

General considerations

1. Reporting Responsibility

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graph TD; A[1. Reporting Responsibility] --> B[R & D group with separate staffing]; A --> C[The formulator who developed the product can take into the production and can provide support even after transition into production has been completed];
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R & D group
with separate
staffing

The formulator who developed the product can take into the production and can provide support even after transition into production has been completed

General considerations (contd.)

2. Personnel Requirement

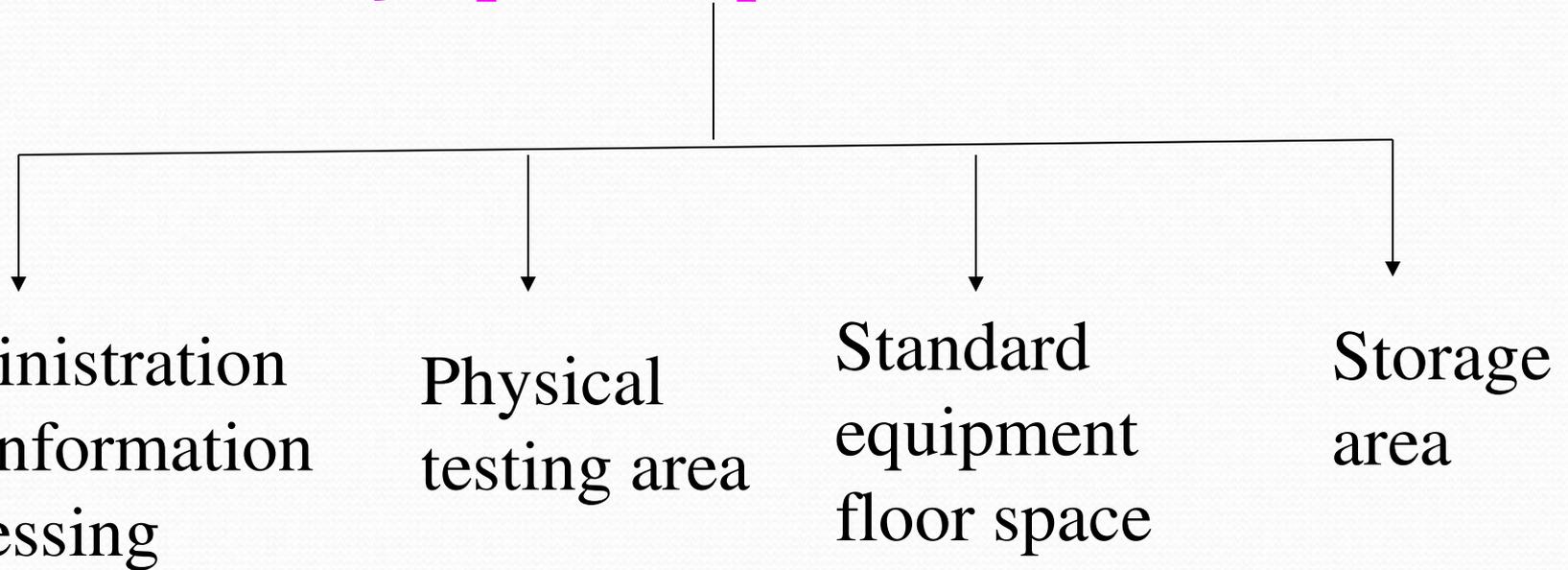
Scientists with experience in pilot plant operations as well as in actual production area are the most preferable. As they have to understand the intent of the formulator as well as understand the perspective of the production personnel.

The group should have some personnel with engineering knowledge as well as scale up also involves engineering principles.



General considerations (contd.)

3. Space Requirements

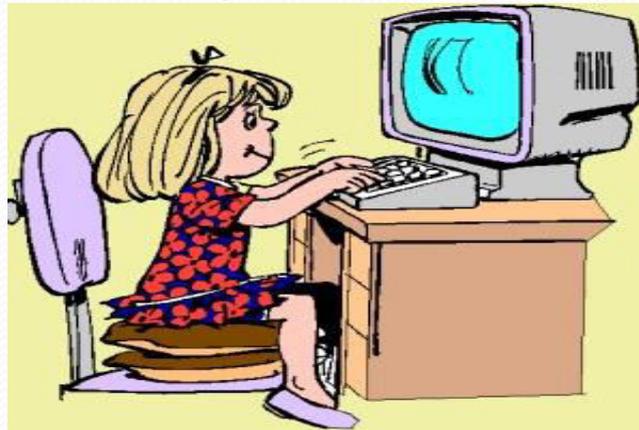


General considerations (contd.)

3.1. Administration and information process:

Adequate office and desk space should be provided for both scientist and technicians.

The space should be adjacent to the working area.



General considerations (contd.)

3.2. Physical testing area:

This area should provide permanent bench top space for routinely used physical- testing equipment.



General considerations (contd.)

3.3. Standard pilot-plant equipment floor space:

Discreet pilot plant space, where the equipment needed for manufacturing all types of dosage form is located.

Intermediate – sized and full scale production equipment is essential in evaluating the effects of scale-up of research formulations and processes.

Equipments used should be made portable where ever possible. So that after use it can be stored in the small store room.

Space for cleaning of the equipment should be also provided.

□ General considerations (contd.)

3.4. Storage Area

It should have two areas divided as approved and unapproved area for active ingredient as well as excipient.

Different areas should be provided for the storage of the in-process materials, finished bulk products from the pilot-plant & materials from the experimental scale-up batches made in the production.

Storage area for the packing material should also be provided.



General considerations (contd.)

4. Review of the formula:

A thorough review of the each aspect of formulation is important.

The purpose of each ingredient and it's contribution to the final product manufactured on the small-scale laboratory equipment should be understood.

Then the effect of scale-up using equipment that may subject the product to stresses of different types and degrees can more readily be predicted, or recognized.

General considerations (contd.)

5. Raw materials:-

One purpose/responsibility of the pilot-plant is the approval & validation of the active ingredient & excipients raw materials.

Why?



Raw materials used in the small scale production cannot necessarily be the representative for the large scale production

General considerations (contd.)

6. Equipment:-

The most economical and the simplest & efficient equipment which are capable of producing product within the proposed specifications are used.

The size of the equipment should be such that the experimental trials run should be relevant to the production sized batches.

If the equipment is too small the process developed will not scale up,

Whereas if equipment is too big then the wastage of the expensive active ingredients.

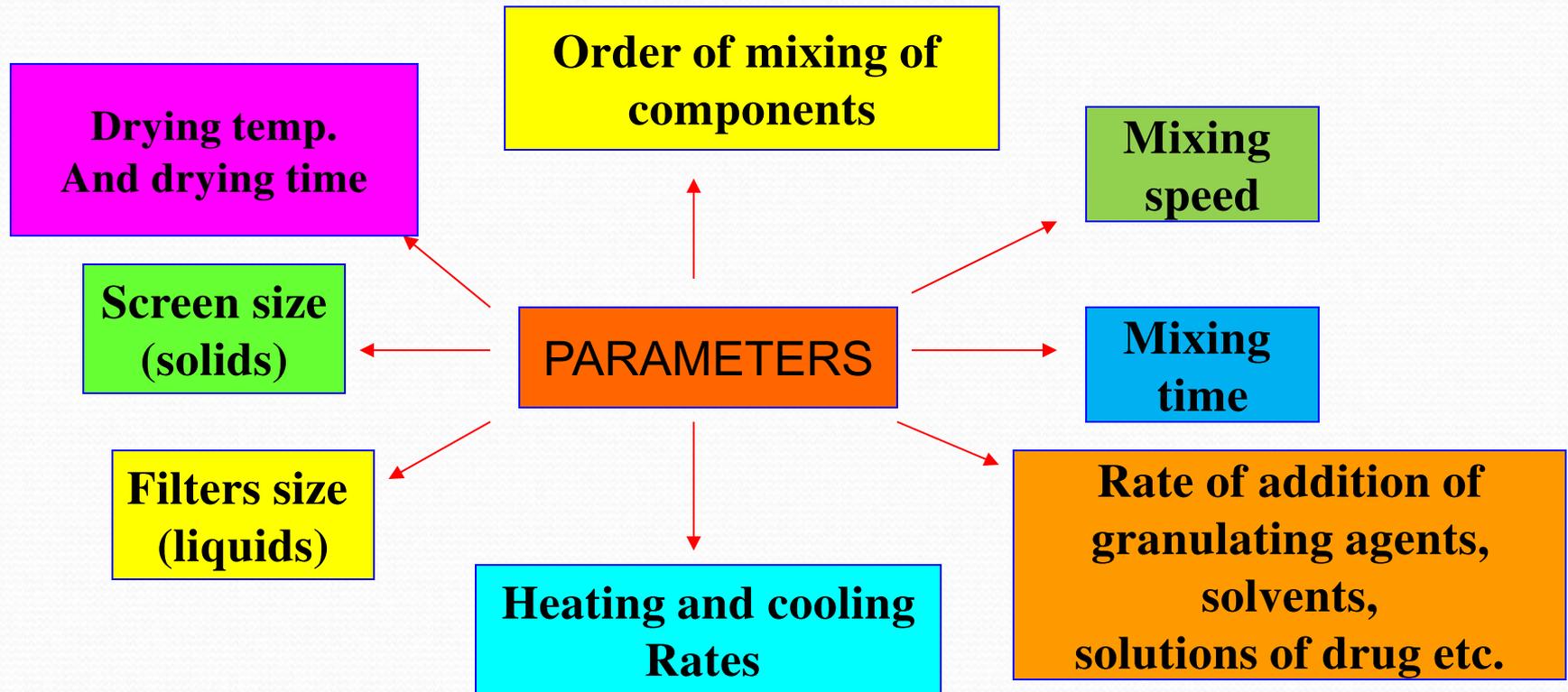
General considerations (contd.)

7. Production Rates:-

The immediate as well as the future market trends/requirements are considered while determining the production rates.

General considerations (contd.)

8. Process Evaluation:-



Why to carry out process evaluation????

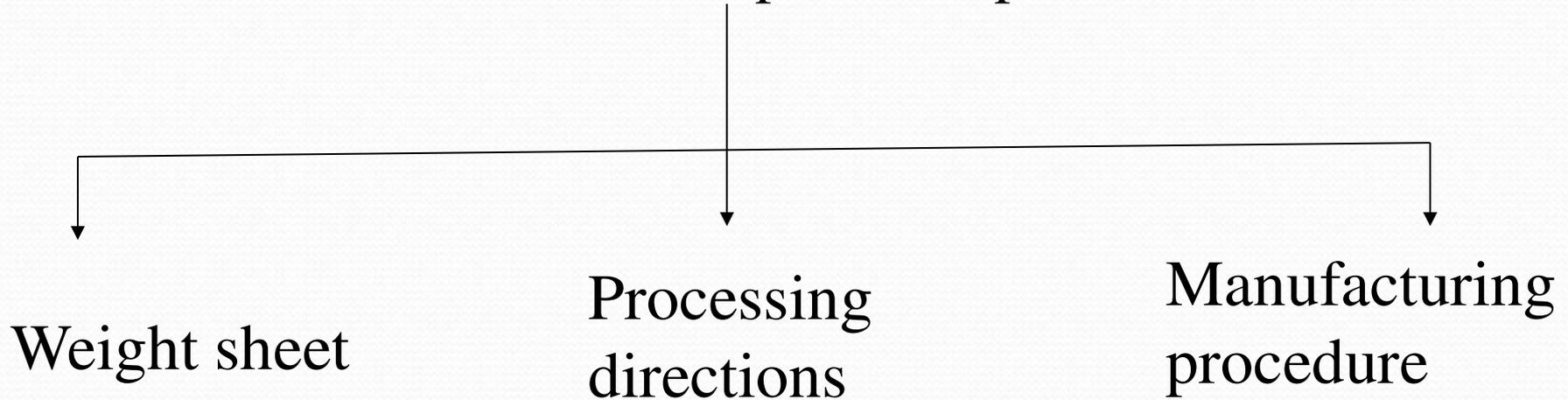
- The knowledge of the effects of various process parameters as few mentioned above form the basis for process optimization and validation.



General considerations (contd.)

9. Master Manufacturing Procedures:-

The three important aspects



General considerations (contd.)

10. Product stability and uniformity:-

The primary objective of the pilot plant is the physical as well as chemical stability of the products.

Hence each pilot batch representing the final formulation and manufacturing procedure should be studied for stability.

Stability studies should be carried out in finished packages as well.

General considerations (contd.)

11. GMP consideration

- Equipment qualification
- Process validation
- Regularly schedule preventative maintenance
- Regularly process review & revalidation
- Relevant written standard operating procedures
- The use of competent technically qualified personnel
- Adequate provision for training of personnel
- A well-defined technology transfer system
- Validated cleaning procedures.
- An orderly arrangement of equipment so as to ease material flow & prevent cross- contamination

Similarity

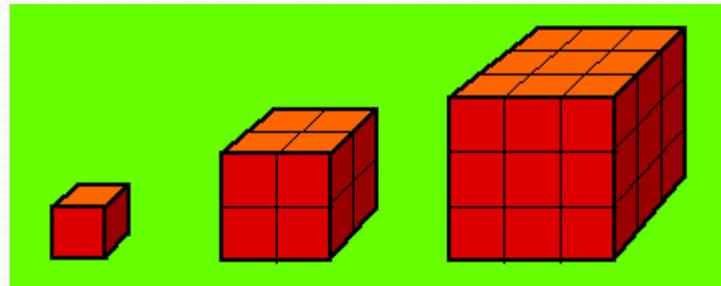
Similarity is concerned with the relations between physical systems of different sizes and it is thus fundamental to the scaling up or down of physical and chemical process. Material objects and physical systems in general are characterized by three qualities: size, shape and composition. All three are independently variable so that the two objects may differ in size while having the same shape and chemical composition or they can be alike in shape only but of different sizes and composed of different materials.

Principle of similarity

- The spatial and temporal configuration of a physical system is determined by ratios of magnitude within the system itself and does not depend upon the size or nature of the units in which these magnitude are measured.
- Four similarity states are important in chemical engineering-
 - a) Geometrical similarity
 - b) Mechanical similarity
 - c) Thermal similarity
 - d) Chemical similarity

Geometrical similarity

- Two bodies are geometrically similar when to every point in the one body there exist a corresponding point in the other.



$$\frac{x'}{x} = \frac{y'}{y} = \frac{z'}{z} = \mathbf{L(\text{constant})}$$

- Prototype: A large scale apparatus or full size plant is called prototype.
- Model: A geometrical similar replica of complete prototype on a small scale with equal scale ratios in all direction is termed as a model. Its function is to exhibit the effects of change in shape or operating conditions of a existing plant.
- Distorted model: A small scale replica of complete prototype with different scale ratios in different direction is called distorted model.
- Model element: Prototype has a multi structure composed of substantially identical element. The small scale apparatus may called an element i.e. a full size replica of one or more cells or unit components of the prototype.
- Distorted model element: a small scale replica of one or more cells or unit components of the prototype with different scale ratios in different direction is called distorted model element.

Mechanical similarity

Mechanical similarity comprises static similarity, kinematic similarity and dynamic similarity-

- Static similarity: Geometrically similar bodies are statically similar when under stress their relative deformations are such that they remain geometrically similar.

$$\frac{F'}{F} = F$$

- Kinematic similarity: Geometrically similar moving systems are kinematically similar when corresponding particles trace out geometrically similar paths in corresponding intervals of time.

- Dynamic similarity: Geometrically similar moving systems are dynamically similar when the ratios of all corresponding forces are equal.

$$\frac{F'_1}{F_1} = \frac{F'_2}{F_2} = \dots \dots \dots = \frac{F'_n}{F_n} = F(\text{constant})$$

Thermal similarity

- Geometrically similar systems are thermally similar when corresponding temperature difference bear a constant ratio to one another and when the systems, if moving are kinematically similar..

$$\frac{H'_r}{H_r} = \frac{H'_c}{H_c} = \frac{H'_v}{H_v} = \frac{H'_f}{H_f} = H(\text{constant})$$

Chemical similarity

- Geometrically and thermally similar systems are chemically similar when corresponding concentration differences bear a constant ratio to one another and when the systems, if moving, are kinematically similar. The intrinsic ratios are-

$$\frac{\text{Rate of chemical formulation}}{\text{Rate of bulk flow}}$$

and

$$\frac{\text{Rate of chemical formulation}}{\text{Rate of molecular diffusion}}$$

Similarity criteria

Mechanical, thermal or chemical similarity between geometrically similar systems can be specified in terms of criteria which are intrinsic ratios of measurement, forces or rates within the system. Since these criteria are dimensionless, there are two general methods of arriving at them.

- Where the differential equations are unknown, but provided we do know all the variables which would enter into the differential equations, it is possible to derive the similarity criteria by means of dimensional analysis.
- Where the differential equations are known but can not be integrated, the similarity criteria can be derived from differential form.
- Where the differential equations are both known and capable of being integrated and solved, there is no need for either similarity criteria or model experiments, since the behaviour of the large scale system should be directly calculable.

Dimensional Analysis

- Dimensional analysis is the analysis of the relationships between different physical quantities by identifying their fundamental dimensions (such as length, mass, time, and electric charge) and units of measure (such as miles vs. kilometers, or pounds vs. kilograms vs. grams) and tracking these dimensions as calculations or comparisons are performed.
- A technique that involves the study of dimensions of physical quantities. Dimensional analysis is used primarily as a tool for obtaining information about physical systems too complicated for full mathematical solutions to be feasible. It enables one to predict the behavior of large systems from a study of small-scale models. It affords a convenient means of checking mathematical equations.
- A method of analysis in which physical quantities are expressed in terms of their fundamental dimensions.

Principle of dimensional homogeneity

- Every complete physical equation is either dimensionally homogeneous or capable of being resolved into two or more separate equations that are dimensionally homogeneous.
- Any equation describing a physical situation will only be true if both sides have the same dimensions. That is it must be dimensionally homogenous.

This property of dimensional homogeneity can be useful for:

- ❖ Checking units of equations;
- ❖ Converting between two sets of units;
- ❖ Defining dimensionless relationships

If we want to find the force on a propeller blade we must first decide what might influence this force. It would be reasonable to assume that the force, F , depends on the following physical properties:

diameter, d ; forward velocity of the propeller (velocity of the plane), u ; fluid density, ρ ; revolutions per second, N ; fluid viscosity, μ .

Before we do any analysis we can write this equation:

$$F = f(d, u, \rho, N, \mu)$$

Or, $\phi = \phi_1(F, d, u, \rho, N, \mu)$ where f and ϕ_1 are unknown functions.

These can be expanded into an infinite series which can itself be reduced to

$$F = K d^m u^p \rho^q N^r \mu^s$$

where K is some constant and m, p, q, r, s are unknown constant powers.

From dimensional analysis we

obtain these powers

form the variables into several dimensionless groups .

The value of K or the functions f and ϕ_1 must be determined from experiment. The knowledge of the dimensionless groups often helps in deciding what experimental measurements should be taken.

Buckingham's theorem of dimensional analysis

It has been shown that every dimensionally homogeneous equation can be expressed as a zero function of a set of dimensionless groups. Buckingham stated further that every such equation can be expressed as zero function of a complete set of dimensionless groups. This important generalization is known as Buckingham theorem and sometimes called Π theorem. It falls into two parts-

1. The solution to every dimensionally homogeneous physical equation has the form $\Phi(\Pi_1, \Pi_2, \dots) = 0$
Where Π_1, Π_2, \dots Represent a complete set of dimensionless groups of variables and dimensional constant in the equation.
2. If an equation contains n separate variables and dimensional constants and these are given dimensional formulas in terms of primary quantities, then the number of dimensionless groups in a complete set is $n-m$.

Dimensionless groups

A dimensionless group is a combination of dimensional or dimensionless quantities having zero overall dimension. In a system of coherent units, it can therefore be represented by a pure number.

The purpose of dimensionless equations are:

- To simplify the equation(s) by reducing the number of variables used.
- To analyze system behavior regardless of the unit used to measure variables.
- To rescale parameters and variables so that all computed quantities are of same order (relatively similar magnitudes).

During dimensional analysis several groups will appear again and again for different problems. Some common non-dimensional numbers (groups) are listed below.

Reynolds number $Re = \frac{\rho u d}{\mu}$ inertial, viscous force ratio

Euler number $Eu = \frac{p}{\rho u^2}$ pressure, inertial force ratio

Froude number $Fr = \frac{u^2}{gd}$ inertial, gravitational force ratio

Weber number $We = \frac{\rho u d}{\sigma}$ inertial, surface tension force ratio

Mach number $Mn = \frac{u}{c}$ Local velocity, local velocity of sound ratio