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B. Pharm
Semester-VII

Subject Name: Industrial Pharmacy-II
Subject Code: BP702TT

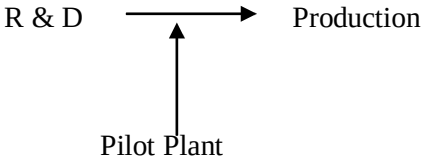
UNIT-1
PILOT PLANT SCALE UP TECHNIQUES

CONTENTS:

[1] INTRODUCTION

What is Pilot plant :

"Defined as a part of the pharmaceutical industry where a lab scale formula is transformed into a viable product by the development of liable practical procedure for manufacture."



Why conduct Pilot Plant Studies?

- 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 complex food processing plant from laboratory data alone with any degree of success

A pilot plant can be used for

- Evaluating the results of laboratory studies and making product and process corrections and improvements
- Producing small quantities of product for sensory, chemical, microbiological evaluations, limited market testing or furnishing samples to potential customers, shelf-live and storage stability studies
- Determining possible salable by-products or waste stream requiring treatment before discharge
- Providing data that can be used in making a decision on whether or not to proceed to a full-scale production process; and in the case of a positive decision, designing and constructing a full-size plant or modifying an existing plant

Considerations in pilot plant development

- Kind and size – depends on goals; evaluating product and process; producing samples of product for evaluation; market testing or furnishing to potential customers
- Location: near R&D facility? At an existing plant? Close liaison between R&D and pilot plant staff is essential
- Labor requirements and costs: engineering staff, skilled operations and maintenance staff-pilot plant costs may exceed those of usual plant production costs. The pilot plant may be used for training personnel for a full- scale plant

Objective of scale up

"Find mistakes on small scale and make profit on large scale."

- To produce physically and chemically stable therapeutic dosage forms.
- Review of the processing equipment.
- Guidelines for productions and process control.
- Evaluation and validation.
- To identify the critical features of the process.
- To provide master manufacturing formula.

▶ Pilot plant studies include the close examination of the formula to determine :

- Its ability to withstand batch scale .Process
- modification .
- Compatibility of the equipment with the formulation .
- Cost factor .
- Availability of raw materials meeting the specifications required to produce the product .
- Market requirement .
- Physical space required and the layout of the related functions .

▶ Thus , during the scale up efforts in the pilot plant :

- Production and process controls are evaluated , validated and finalized .Product
- reprocessing procedures are developed and validated .
- Appropriate records and reports are issued to support cGMP .

▶ In short , all critical features of a process must be identified so that as the process is scaled up , it can be adequately monitored to provide assurance that the process is under control and that the product produced at each level of the scale up maintains the specified attributes originally intended.

PILOT PLANT DESIGN

▶ A pilot plant design should support three key strategic objectives :

- Formulation and process development .
- Clinical supply manufacture .
- Technology evaluation , scale up and transfer .

▶ Attributes playing a key role in achieving the above objectives are :

- cGMP Compliance .
- A flexible highly trained staff .
- Equipment to support multiple dosage form development .
- Equipment at multiple scales based on similar operating principles to those in production .

- The pilot plant design should be according to cGMP norms . The layout should be according to the need for flexibility (portable equipment installed , use of multipurpose rooms) , restricted access , personnel flow and material flow. The facility and equipment should be able to capture critical process information . Intermediate sized and Full scale production equipment should be available in order to evaluate the effects of scale up of research formulations . Adequate space required to carry out each function smoothly (eg., cleaning of pilot plant equipments) . The final design should result in a facility that support the key strategic objectives and should have low maintenance and operating costs .

- Although the pilot plant design must simulate the manufacturing environment in which the new product will ultimately be produced , there are many differences in operation because of the specific objectives of the two types of facilities i.e. the pilot plant facilitates product development activities , whereas the manufacturing plant routinely fabricates products for the market place .

PILOT PLANT OPERATION

- **Operational Aspects** of Pilot Plant includes :

Validation

Training

Engineering Support

Maintenance

Calibration

Material Control

Inventory

Orders

Labeling

Process and Manufacturing Activities

Quality Assurance and Quality Control

- **VALIDATION :** A validation master plan should be develop that addresses-- The design specifications
  - Installation qualification
  - Operational qualification
  - Performance qualification

of all major utility systems , process equipment , and computer control systems . A fully validated pilot plant should ensure compliance with cGMP and should meet current FDA standards .

- **TRAINING :** Training in four major area required –-

  - Compliance with quality standards such as cGMP
  - Safety and environmental responsibilities
  - Compliance with SOPs
  - Technical skills and knowledge

- **ENGINEERING SUPPORT :** It is required for –-

  - Design , construction , commissioning and validation of the pilot plant facility
  - Co-ordination , scheduling and direction of ongoing operations

- **MAINTENANCE :** It is required

  to –- Meet cGMP norms
  - To ensure data integrity and equipment reliability during the development process.

The maintenance program should be documented and written procedures established.

- **CALIBRATION :** Calibration of critical instruments/equipments is required

  for–- Compliance with cGMP
  - Maintaining the integrity of data generated during the development process

Calibration should be performed by well trained and expert staff .

- **MATERIAL CONTROL :** More flexible and efficient computer based system isrequired for material control in pilot plant .

- **INVENTORY :** Inventory should be maintained in a Computer Based Inventory-Ordering-Dispensing System .

- **ORDERS** : All orders must be placed through the computer system . For placement of the order , First In First Out (FIFO) criteria is followed .

- **LABELING :** Labels should comply with GMP-GLP requirements . Computer systemmust be used for labeling .

- **PROCESS AND MANUFACTURING ACTIVITIES** : It includes –

  - Formulation and Process Development Studies

- Clinical supply manufacture
- Technology evaluation , scale up and transfer

Precise documentation of each trials have to be made .

- **QUALITY ASSURANCE & QUALITY CONTROL :**

QA Activities –-

- Auditing pilot plant
- Auditing and approval of component suppliers
- Reviewing , approving and maintaining batch records for clinical supplies
- Sampling and release of raw materials and components required for clinical supplies
- Release of clinical supplies
- Maintaining and distributing facility and operating procedures (SOPs)
- Review and approval of validation and engineering documentation .

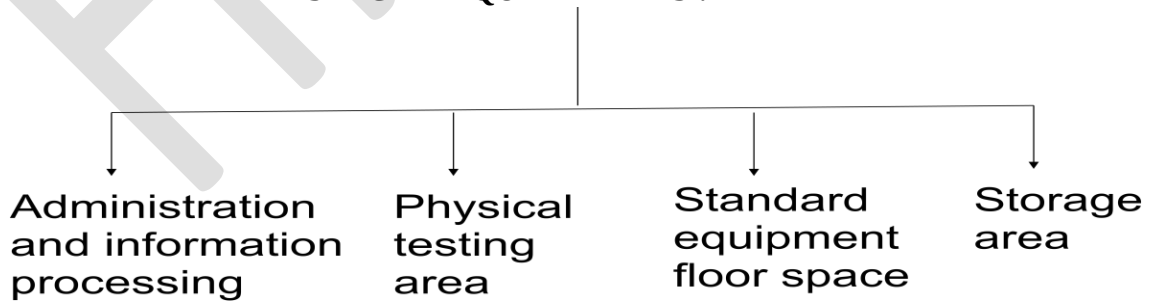
QC Activities –-

- Release testing of finished products
- Physical , chemical , and microbiological testing of finished clinical products, components and raw materials
- Testing for validation and revalidation programs
- QC in-process testing during development , scale up , and technology transfer activities

[2] GENERAL CONSIDERATIONS

- **PERSONNEL REQUIREMENTS :** Personnel should have –-
  - 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

SPACE REQUIREMENTS :



- Separate provisions for API and excipients further segregated into approved and unapproved areas according to GMP .
- Storage area for in process materials , finished bulk products , retained samples , experimental production batches , packaging materials (segregated into approved and unapproved areas) .
- Controlled environment space allocated for storage of stability samples

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.

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 forthe large scale production

RELEVANT PROCESSING 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.

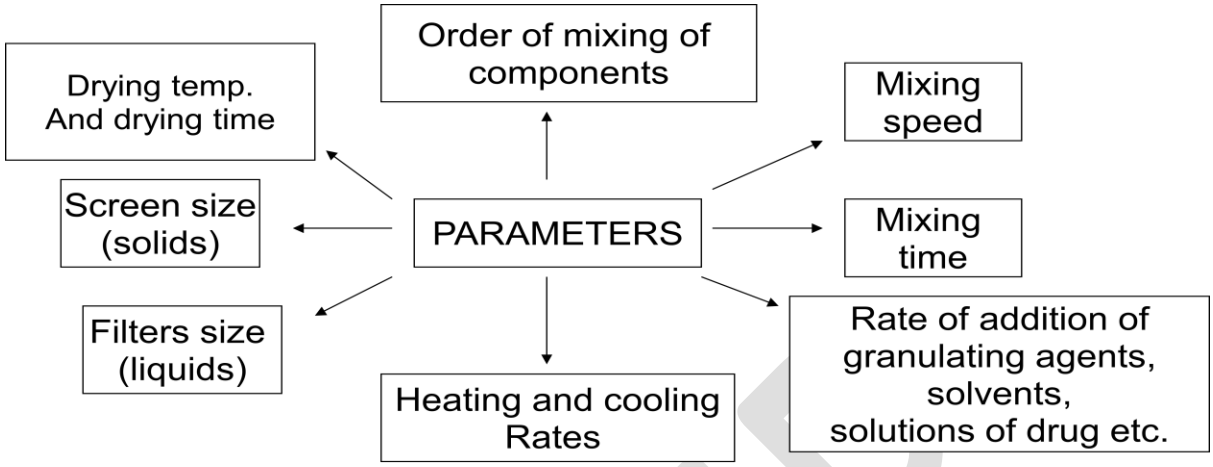
PRODUCTION RATES :

It can be determined by the immediate future market requirements.

Equipment and the process should be chosen on the basis of production of a batchat a frequency that takes into consideration :

1. Product loss in the equipment during manufacture .
2. The time required to clean the equipment between batches .
3. The number of batches that will need to be tested for release .

- **PROCESS EVALUATION :**



- It is the basis of process validation Documentation of process is to be done . Process is validated only if there are no changes in the formula , quality of the ingredients , orthe equipment configuration .
- Revalidation needs to be done to ensure that changes have not take place .

- **PREPARATION OF MASTER MANUFACTURING PROCEDURES**: It includes-

- The chemical weigh sheet. It should clearly identify the chemicals required in a batch and present the quantities and the order in which they will be used .
- The sampling directions
- In-process and finished product specifications
- Manufacturing directions should be in a language understandable by the operator termed as SOP's .
- Batch Record Directions should include specifications for addition rates , mixing times , mixing speeds , heating and cooling rates , temperature .
- Proper documentation should be carried out.

- **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

- **GMP CONSIDERATIONS :**

GMP items that should be a part of scale up are –-

- 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

TRANSFER OF ANALYTICAL METHODS TO QUALITY ASSURANCE :

- Analytical methods developed in research must be transferred to QA department .

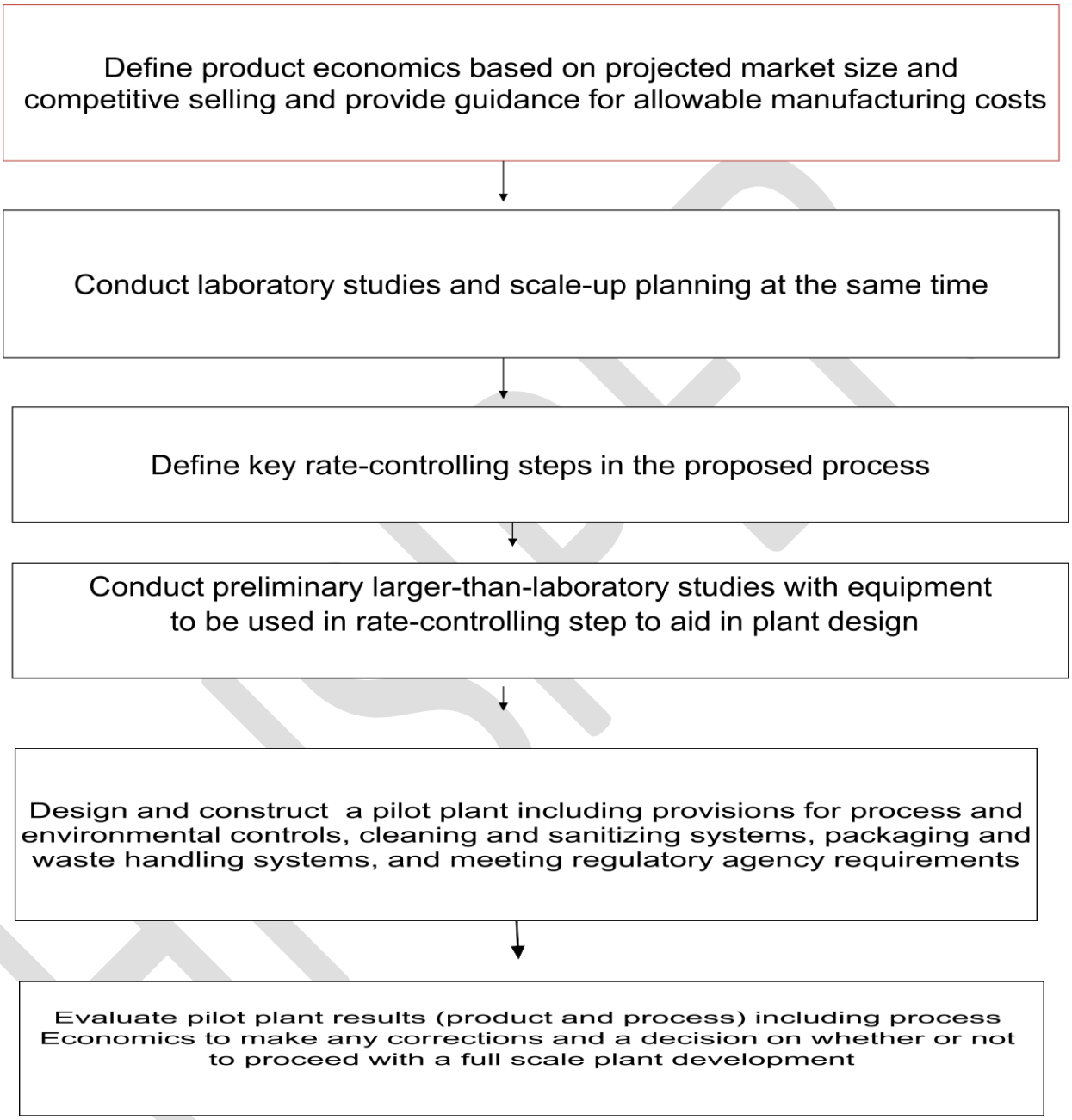
Transfer process includes –-

1. Review the process to make sure that proper analytical instrument is available .
2. Personnel should be trained to perform the test .
3. Reliability of the test should be checked .
4. At last assay procedure should be reviewed before transfer .

[3] SCALE – UP TECHNIQUES

- **Scale-up**:- The art for designing of prototype using the data obtained from the pilot plant model.

STEPS IN SCALE UP



[4] Pilot Plant design for Tablets

- The primary responsibility of the pilot plant staff is to ensure that the newly formulated tablets developed by product development personnel will prove to be efficiently, economically, and consistently reproducible on a production scale.
- The design and construction of the pharmaceutical pilot plant for tablet development should incorporate features necessary to facilitate maintenance and cleanliness.
- If possible, it should be located on the ground floor to expedite the delivery and shipment of supplies.
- Extraneous and microbiological contamination must be guarded against by incorporating the following features in the pilot plant design:
- Fluorescent lighting fixtures should be the ceiling flush type.
- The various operating areas should have floor drains to simplify cleaning.
- The area should be air-conditioned and humidity controlled.
- High -density concrete floors should be installed.
- The walls in the processing and packaging areas should be enamel cement finish onconcrete.
- Equipment in the pharmaceutical pilot plant should be similar to that used by production division- manufacture of tablets.

1)Material handling system

- In the laboratory, materials are simply scooped or poured by hand, but in intermediate- or large-scale operations, handling of this materials often become necessary.
- If a system is used to transfer materials for more than one product steps must betaken to prevent cross contamination.
- Any material handling system must deliver the accurate amount of the ingredient to the destination.
- The type of system selected also depends on the characteristics of the materials.
- More sophisticated methods of handling materials such as vacuum loading systems, metering pumps, screw feed system.

2) Dry Blending

- Powders to be used for encapsulation or to be granulated must be well blended to ensure good drug distribution.
- Inadequate blending at this stage could result in discrete portion of the batch being either high or low in potency.
- Steps should also be taken to ensure that all the ingredients are free of lumps and agglomerates.

- For these reasons, screening and/or milling of the ingredients usually makes the process more reliable and reproducible.
- **The equipment used for blending are:**

V- blender
Double cone blender
Ribbon blender
Slant cone blender
Bin blender
Orbiting screw blenders vertical and horizontal high intensity mixers.

- **SCALE UP CONSIDERATIONS**

  - **Time of blending .**
  - **Blender loading.**
  - **Size of blender.**

3) Granulation

- **The most common reasons given to justify granulating are:**

1. To impart good flow properties to the material,
2. To increase the apparent density of the powders,
3. To change the particle size distribution,
4. Uniform dispersion of active ingredient.

- **Traditionally, wet granulation has been carried out using,**

✓ Sigma blade mixer,
✓ Heavy-duty planetary mixer.

- Wet granulation can also be prepared using tumble blenders equipped with high-speed chopper blades.
- More recently, the use of multifunctional "processors" that are capable of performing all functions required to prepare a finished granulation, such as dry blending, wet granulation, drying, sizing and lubrication in a continuous process in a single equipment.

Fluidized Bed Granulations :

1. Process Inlet Air Temperature
2. Atomization Air Pressure
3. Air Volume
4. Liquid Spray Rate
5. Nozzle Position and Number of Spray Heads
6. Product and Exhaust Air Temperature
7. Filter Porosity

8. Cleaning Frequency
9. Bowl Capacity

4) Binders:

- Used in tablet formulations to make powders more compressible and to produce tablets that are more resistant to breakage during handling.
- In some instances the binding agent imparts viscosity to the granulating solution so that transfer of fluid becomes difficult.
- This problem can be overcome by adding some or all binding agents in the dry powder prior to granulation.
- Some granulation, when prepared in production sized equipment, take on a dough-like consistency and may have to be subdivided to a more granular and porous mass to facilitate drying.
- This can be accomplished by passing the wet mass through an oscillating type granulator with a suitably large screen or a hammer mill with either a suitably large screen or no screen at all.

5) Drying

- The most common conventional method of drying a granulation continues to be the circulating hot air oven, which is heated by either steam or electricity.
- The important factor to consider as part of scale-up of an oven drying operation are airflow, air temperature, and the depth of the granulation on the trays.
- If the granulation bed is too deep or too dense, the drying process will be inefficient, and if soluble dyes are involved, migration of the dye to the surface of the granules.
- Drying times at specified temperatures and airflow rates must be established for each product, and for each particular oven load.
- Fluidized bed dryers are an attractive alternative to the circulating hot air ovens.
- The important factor considered as part of scale up fluidized bed dryer are optimum loads, rate of airflow, inlet air temperature and humidity.

Tray Dryer-- Parameters to be considered for scale up are :

1. Air flow
2. Air temperature
3. Depth of the granulation on the trays
4. Monitoring of the drying process by the use of moisture and temperatureprobes
5. Drying times at specified temperatures and air flow rates for each product

Fluidized Bed Dryer : Parameters to be considered for scale up are :

1. Optimum Load

2. Air Flow Rate
3. Inlet Air Temperature
4. Humidity of the Incoming Air

6) Reduction of Particle size

- Compression factors that may be affected by the particle size distribution are flowability, compressibility, uniformity of tablet weight, content uniformity, tablet hardness, and tablet color uniformity.
- First step in this process is to determine the particle size distribution of granulation using a series of "stacked" sieves of decreasing mesh openings.
- Particle size reduction of the dried granulation of production size batches can be carried out by passing all the material through an oscillating granulator, a hammer mill, a mechanical sieving device, or in some cases, a screening device.
- As part of the scale-up of a milling or sieving operation, the lubricants and glidants, which in the laboratory are usually added directly to the final blend, are usually added to the dried granulation during the sizing operation.
- This is done because some of these additives, especially magnesium stearate, tendto agglomerate when added in large quantities to the granulation in a blender.

7) Blending

- Type of blending equipment often differs from that using in laboratory.
- In any blending operation, both segregation and mixing occur simultaneously are a function of particle size, shape, hardness, and density, and of the dynamics of the mixing action.
- Particle abrasion is more likely to occur when high-shear mixers with spiral screws or blades are used.
- When a low dose active ingredient is to be blended it may be sandwiched between two portions of directly compressible excipients to avoid loss to the surface of the blender.

In scale up of blending , following parameters should be considered -

1. Blender loads ,
2. Blender size ,
3. Mixing speeds ,
4. Mixing times ,
5. Bulk density of the raw material (must be considered in selecting blender andin determining optimum blender load)
6. Characteristics of the material

8) Specialized Granulation procedures:

Slugging (Dry Granulation)

- A dry powder blend that cannot be directly compressed because of poor flow orcompression properties.
- This is done on a tablet press designed for slugging, which operates at pressures of about 15 tons, compared with a normal tablet press, which operates at pressure of 4tons or less.
- Slugs range in diameter from 1 inch, for the more easily slugged material, to ¾ inch in diameter for materials that are more difficult to compress and require more pressure per unit area to yield satisfactory compacts.
- If an excessive amount of fine powder is generated during the milling operation the material must be screened & fines recycled through the slugging operation.

Dry Compaction

- Granulation by dry compaction can also be achieved by passing powders between two rollers that compact the material at pressure of up to 10 tons per linear inch.
- Materials of very low density require roller compaction to achieve a bulk density sufficient to allow encapsulation or compression.
- One of the best examples of this process is the densification of aluminum hydroxide.
- Pilot plant personnel should determine whether the final drug blend or the active ingredient could be more efficiently processed in this manner than by conventional processing in order to produce a granulation with the required tabletting or encapsulation properties.

Compression

- The ultimate test of a tablet formulation and granulation process is whether the granulation can be compressed on a high-speed tablet press.
- During compression, the tablet press performs the following functions:

1. Filling of empty die cavity with granulation.
2. Precompression of granulation (optional).
3. Compression of granules.

Ejection of the tablet from the die cavity and take-off of compressed tablet.

- When evaluating the compression characteristics of a particular formulation, prolonged trial runs at press speeds equal to that to be used in normal production should be tried.
- Only then are potential problems such as sticking to the punch surface, tablet hardness, capping, and weight variation detected.
- High-speed tablet compression depends on the ability of the press to interact with granulation.

- Following are the parameters to be considered while choosing speed of press.

1. Granulation feed rate.
2. Delivery system should not change the particle size distribution.
3. System should not cause segregation of coarse and fine particles, nor it should induce static charges.

- The die feed system must be able to fill the die cavities adequately in the short period of time that the die is passing under the feed frame.
- The smaller the tablet , the more difficult it is to get a uniform fill a high press speeds.
- For high-speed machines, induced die feed systems is necessary.
- These are available with a variety of feed paddles and with variable speed capabilities.
- So that optimum feed for every granulation can be obtained.
- After the die cavities are filled ,the excess is removed by the feed frame to the center of the die table.
- Compression of the granulation usually occurs as a single event as the heads of the punches pass over the lower and under the upper pressure rollers.
- This cause the punches to the penetrate the die to a preset depth, compacting the granulation to the thickness of the gap set between the punches.
- The rapidity and dwell time in between this press event occurs is determined by the speed at which the press is rotating and by the size of compression rollers.
- Larger the compressions roller, the more gradually compression force is applied and released.
- Slowing down the press speed or using larger compression rollers can often reduce capping in a formulation.
- The final event is ejection of compressed tablets from die cavity.
- During compression, the granulation is compacted to form tablet, bonds within compressible material must be formed which results in sticking.
- High level of lubricant or over blending can result in a soft tablet, decrease in wettability of the powder and an extension of the dissolution time.
- Binding to die walls can also be overcome by designing the die to be 0.001 to 0.005 inch wider at the upper portion than at the center in order to relieve pressure during ejection.

Tablet Coating

- Sugar coating is carried out in conventional coating pans, has undergone many changes because of new developments in coating technology and changes in safety and environmental regulations.
- The conventional sugar coating pan has given way to perforated pans or fluidized-bed coating columns.

- The development of new polymeric materials has resulted in a change from aqueous sugar coating and more recently, to aqueous film coating.
- The tablets must be sufficiently hard to withstand the tumbling to which they are subjected in either the coating pan or the coating column.
- Some tablet core materials are naturally hydrophobic, and in these cases, film coating with an aqueous system may require special formulation of the tablet core and/or the coating solution.
- A film coating solution may have been found to work well with a particular tablet in small lab coating pan but may be totally unacceptable on a production scale.
- This is because of increased pressure & abrasion to which tablets are subjected when batch size is large & different in temperature and humidity to which tablets are exposed while coating and drying process.

[5] Scale-up for parenterals

Injectables

- The majority of the parenteral solutions are solutions requiring a variety of tankage, piping and ancillary equipment for liquid mixing, filteration, transfer and related activities.
- The majority of the equipments are composed of 300 series austenitic stainless steel, with tantalum or glass lined vessels employed for preparation of formulations sensitive to iron and other metal ions.
- The vessels can be equipped with external jackets for heating and/or cooling and various types of agitators, depending upon the mixing requirements of the individual formulation**.**

Working area of a parenteral pilot plant

- Incoming goods are stored in special areas for Quarantine, Released and Rejected status.
- A cold room is available for storage of temperature-sensitive products. Entrance into the warehouse and production areas is restricted to authorized personnel.
- Sampling and weighing of the raw material is performed in a dedicated sampling area and a central weighing suite, respectively.
- The route for final products is separated from the incoming goods; storage of final products is done in designated areas in the warehouse while they are awaiting shipment.
- Several clothing and cleaning procedures in the controlled transport zone and production area ensure full quality compliance.

- In addition, a technical area is located in between the production zone and the area for formulation development.
- Here, the water for injection equipment is located, as well as the technical installation of the lyophilizer.

Facility Design

To provide the control of microbial, pyrogen and particles controls over the production environment are essential.

Warehousing:

All samples should be aseptically taken, which mandates unidirectional airflow and full operator gowning.

These measures reduce the potential for contamination ingress into materials that are yet to receive any processing at any site.

Preparation Area:

The materials utilized for the production of the sterile products move toward the preparation area through a series of progressively cleaner environments.

First the materials are passed through class 100,000 i.e. grade D environment for presterilization.

↓

Transfer of materials are carried out in air-locks to avoid cross contamination

↓

The preparation areas are supplied with HEPA filters. There should be more than 20 air changes per hour

↓

The preparation place is Class 100 area.

Compounding area:

The manufacture of parenterals is carried out in class 10,000 (Grade C) controlled environments in which class 100 unidirectional flow hoods are utilized to provide greater environmental control during material addition.

These areas are designed to minimize the microbial, pyrogen, and particulate contamination to the formulation prior to sterilization.

Aseptic filling rooms:

The filling of the formulations is performed in a Class 100 environment.

- Capping and Crimp sealing areas:
  The air supply in the capping line should be of Class 100
- Corridors:
  They serve to interconnect the various rooms. Fill rooms, air locks and gowning rooms are assessed from the corridor.
- Aseptic storage rooms.
- Air-locks and pass-throughs:
  Air locks serve as a transition points between one environment and another.
  They are fitted with the UltraViolet lights, spray systems, or other devices that may be effectively utilized for decontamination of materials.

Formulation aspects

Solvent:

The most widely used solvent used for parenteral production is water for injection. WFI is prepared by by distillation or reverse osmosis. Sterile water for injection is used as a vehicle for reconstitution of sterile solid products before administration and is terminally sterilized by autoclaving

Solubilizers:

They are used to enhance and maintain the aqueous solubility of poorly water-soluble drugs.

Solubilizing agents used in sterile products include:

1. co-solvents: glycerine, ethanol, sorbitol, etc.

2. Surface active agents: polysorbate 80, polysorbate 20, lecithin**.**

3. Complexing agents: cyclodextrins etc

They act by reducing the dielectric constant properties of the solvent system, thereby reducing the electrical, conductance capabilities of the solvent and thus increase the solubility.

- **Antimicrobial preservative agents:**

- **Buffers:**

They are used to maintain the pH level of a solution in the range that provides either maximum stability of the drug against hydrolytic degradation or maximum or optimal solubility of the drug in solution.

- **Antioxidants:**

Antioxidants function by reacting prefentially with molecular oxygen and minimizingor terminating the free the free radical auto-oxidation reaction. **Examples phenol (0.065-0.5%), m-cresol (0.16-0.3%) etc.**

[6] Scale up for Liquid orals

- The physical form of a drug product that is pourable displays Newtonian or pseudoplastic flow behaviour and conforms to it's container at room temperature.
- Liquid dosage forms may be dispersed systems or solutions.
- In dispersed systems there are two or more phases, where one phase is distributedin another.
- A solution refers two or more substances mixed homogeneously.

Steps of liquid manufacturing process

1. Planning of material requirements:
2. Liquid preparation:
3. Filling and Packing:
4. Quality assurance:

Critical aspects of liquid manufacturing

- Physical Plant:

- Heating, ventilation and air controlling system:

The effect of long processing times at suboptimal temperatures should be considered in terms of consequences on the physical or chemical stability of ingredients as well as product.

SOLUTION :

Parameters to be considered are –-

1. Tank size (diameter)
2. Impeller type
3. Impeller diameter
4. Rotational speed of the impeller
5. Number of impellers
6. Number of baffles
7. Mixing capability of impeller
8. Clearance between Impeller Blades and wall of the mixing tank
9. Height of the filled volume in the tank
10. Filteration equipment (should not remove active or adjuvant ingredients)
11. Transfer system
12. Passivation of SS (prereacting the SS with acetic acid or nitric acid solution to remove the surface alkalinity of the SS)

SUSPENSION :

Parameters to be considered are –-

1. Addition and dispersion of suspending agents (Lab scale – sprinkling method & Production scale – vibrating feed system)
2. Hydration/Wetting of suspending agent
3. Time and temperature required for hydration of suspending agent
4. Mixing speeds (High speed leads to air entrapment)
5. Selection of the equipment according to batch size
6. Versator (to avoid air entrapment)
7. Mesh size (the one which is chosen must be capable of removing the unwanted foreign particulates but should not filter out any of the active ingredients . Such a sieve can only be selected based on production batch size trials.)

EMULSION :

Parameters to be considered are –-

1. Temperature
2. Mixing equipment

3. Homogenizing equipment
4. Inprocess or final product filters
5. Screens , pumps and filling equipment
6. Phase volumes
7. Phase viscosities
8. Phase densities

Formulation aspects of oral liquids

Solutions:

Protecting the API	**Buffers, antioxidants, preservatives**
Maintaining theappearance	**Colorings, stabilizers, co-solvents, antimicrobial preservatives**
Taste/smell masking	**Sweetners, flavorings.**

Suspensions:

Purpose	Agent
Facilitating the connection between API andvehicle	**-wetting agents Salt formation ingredients**
Protecting the API	**- Buffering-systems, polymers, antioxidants**
Maintaining the suspension appearance	**Colorings, suspending agent, flocculating agent.**
Masking the unpleasant taste/smell	**Sweeteners, flavorings**

Emulsions:

Purpose	Agent
Particle Size	**Solid particles, Droplet particles**
Protecting the API	**Buffering-systems, antioxidants, polymers**
Maintaining the appearance	**Colorings, Emulsifying agents, Penetrationenhancers, gelling agents**
Taste/smell masking	**Sweetners, flavorings**

[7] SCALE UP FOR SEMISOLID PRODUCTS

The following parameters are to be considered during the scale up of semisolid products :

1. Mixing equipment (should effectively move semisolid mass from outside wallsto the center and from bottom to top of the kettle)
2. Motors (used to drive mixing system and must be sized to handle the productat its most viscous stage.)
3. Mixing speed
4. Component homogenization
5. Heating and cooling process
6. Addition of active ingredients
7. Product transfer
8. Working temperature range (critical to the quality of the final product)
9. Shear during handling and transfer from manufacturing to holding tank tofilling lines
10. Transfer pumps (must be able to move viscous material without applyingexcessive shear and without incorporating air)
11. While choosing the size and type of pump ,
    a. Product viscosity
    b. Pumping rate
    c. Product compactibility with the pump surface
    d. Pumping pressure required should be considered.

[8] SCALE UP FOR BIOTECHNOLOGY-DERIVED PRODUCTS

- The design and scale up of biological processes is very challenging (due to complexity of biological systems and the physical and biochemical characteristics of the protein products) .
- **The following parameters are to be considered for scale up of biotechnological products –-**

BIOREACTOR OPERATION : Usually stirred tank bioreactor is used

Mixing efficiency given by –

1. Impeller rate
2. Aeration rate
3. Hydrostatic pressure
4. Agitation rate
5. Mixing time

FILTERATION OPERATION : The key process parameters for filteratio nscale up are -

1. Transmembrane pressure
2. Volume
3. Operating time
4. Temperature
5. Flux rate
6. Protein concentration
7. Solution viscosity
8. Retentate flow rate

9. Permeate flux

The fluid dynamic variables used in the scale up work are –

1. The length of the fibers (L , per stage)
2. The fiber diameter (D)
3. The number of fibres per catridge (n)
4. The density of the culture (□)
5. The viscosity of the culture (□)

From these variables , scale up parameters such as wall shear rate and its effecton flux are derived .

- **CENTRIFUGATION :**

  At laboratory scale – batch centrifuge is used .

  At production scale – continuous centrifuge is used .

  Low shear centrifuge used to minimize the shear sensitivity of animal cells .

- **CHROMATOGRAPHY :**

  Key parameters for chromatography scale up are-

1. Gel capacity
2. Linear velocity
3. Buffer volume
4. Bed height
5. Temperature
6. Cleanability
7. Gel lifetime
8. pH of the elution buffer
9. conductivity of the elution buffer

- **VIRAL CLEARANCE** : Viral inactivation and/or removal steps are critical part of the process design for biotechnology products derived from mammalian cell culture system .

[9] PRINCIPLES OF SIMILARITY

Equipments selected for pilot plant studies should preferably be similar in all respects to those actually used in commercial production . If similarity exists then it helps in effective process translation as well as in production of good quality product . In actuality , approximations of similarity are often necessary due to departures from ideality (e.g., differences in surface roughness , variations in temperature gradients , changes in mechanism) . Stress should be given on four types of similarity :

A. **Geometric Similarity :** Similarity with respect to shape , height , thickness , breadth etc., Small scale model equipments and large scale equipments must be inthe scale ratio of 1:2 , 1:5 , 1:20 etc.

B. **Mechanical Similarity :** Mechanical similarity (the application of force to a stationary or moving system) can be described in terms of Static , Kinematic or Dynamic similarity .

Static Similarity –- It is the deformation under constant stress of one body or structure to that of another . It exists when geometric similarity is maintained .

Kinematic Similarity -- Geometrically similar moving systems will exhibit kinematic similarity when corresponding particle takes geometrical similar path in the corresponding time interval .

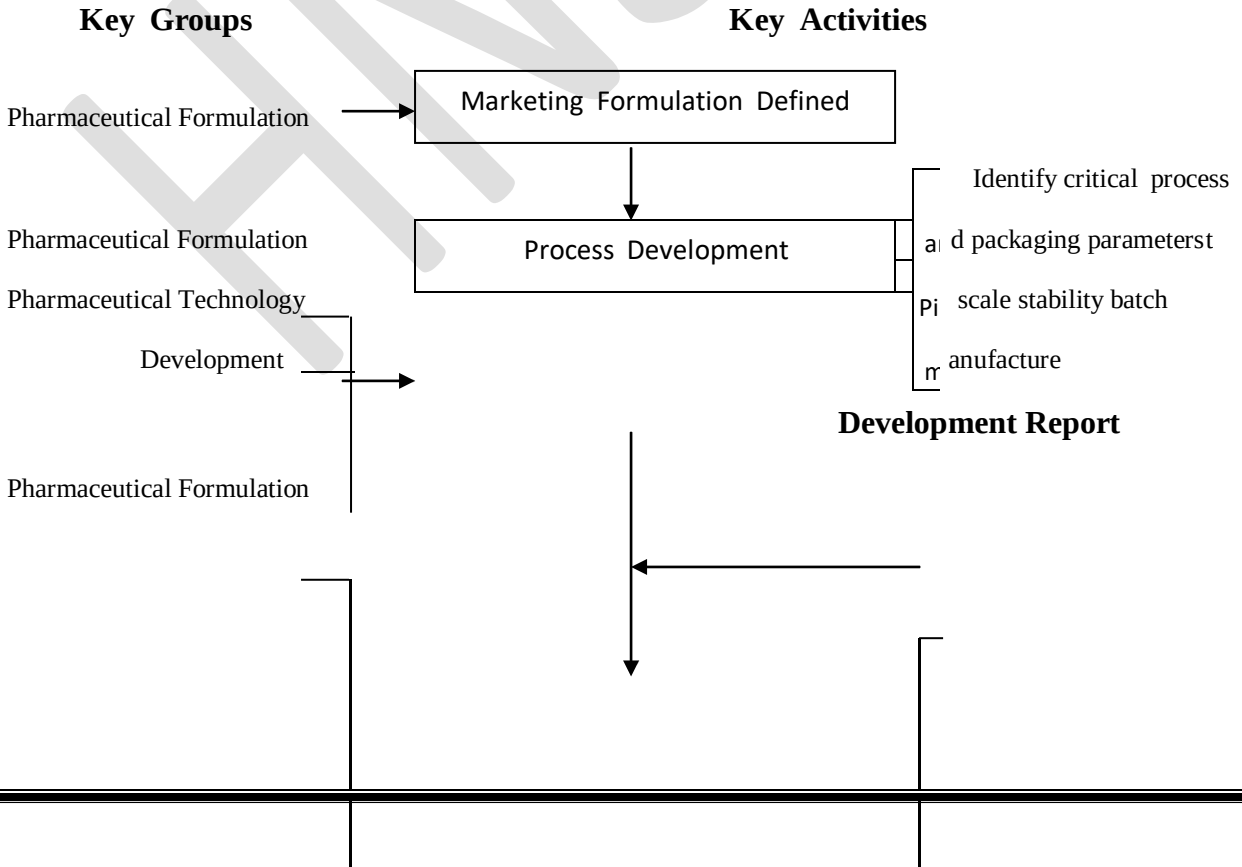
Dynamic Similarity -- Forces (gravitational , centrifugal , pressure) which accelerate or retard the motion of materials . Geometrically similar moving systems are dynamically similar when the ratio of all forces is equal . It is useful in the prediction of pressure drops , power consumption.

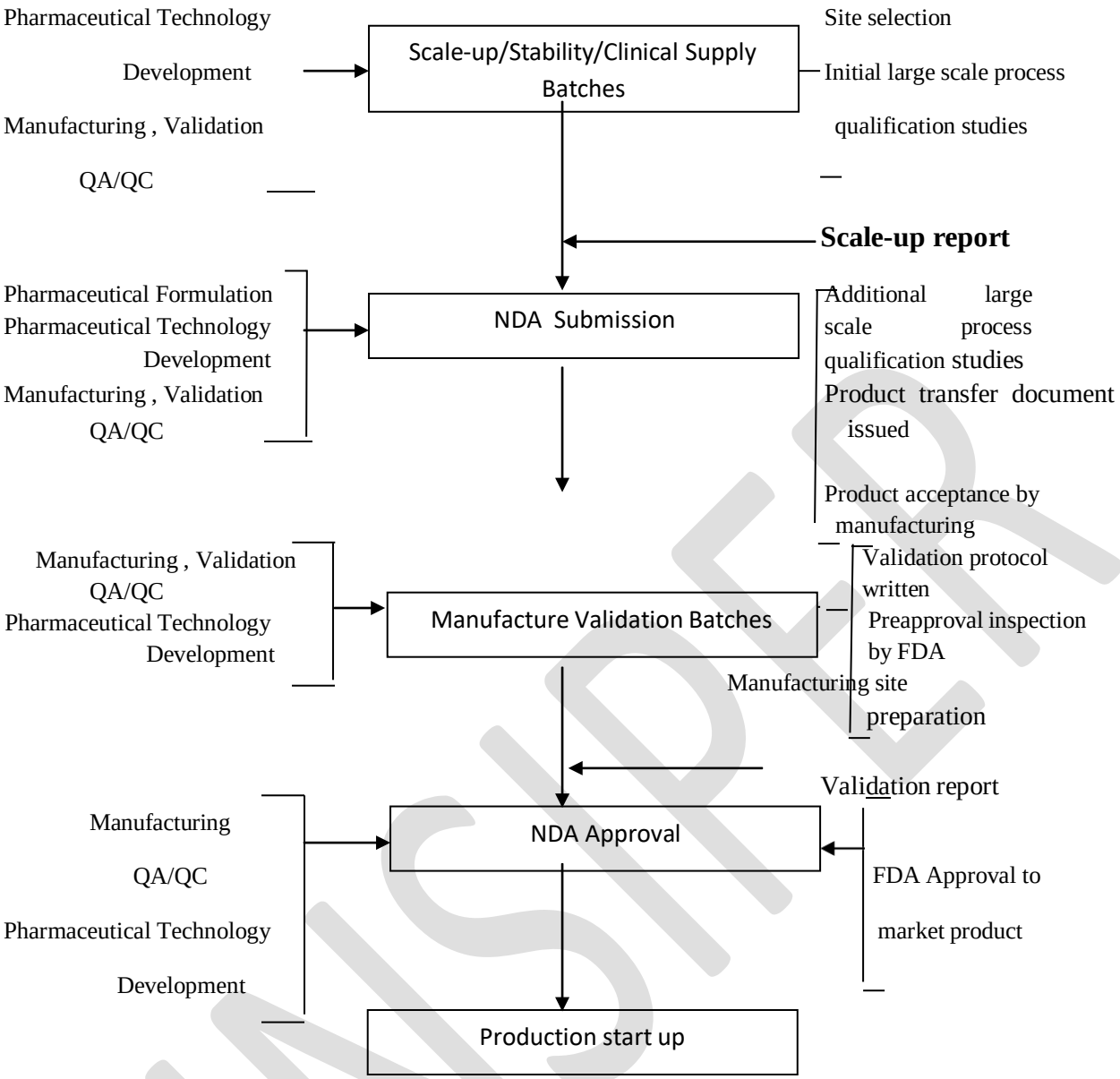
C. **Thermal Similarity :** It is concerned with flow of heat (by radiation , conduction , convection , or the bulk transfer of material) . Geometrically similar systems are thermally similar when temperature difference bears constant ratio and in moving systems it must have kinematic similarity .

D. **Chemical Similarity :** It is the similarity concerned with the variation in chemical composition from point to point as a function of time . It is related to the existence of comparable concentration gradients . It is dependent upon both thermal and kinemtatic similarity .

■ The relationship of key groups , key activities and development milestones typically experienced during the transfer of formulation and process technology from the pilot plant to the production facility is shown below :

DEVELOPMENT MILESTONES





[10] HOW TO SCALE-UP SCIENTIFICALLY ?

- A rational approach to scale-up is Dimensional Analysis which is a proven method of developing functional relationships that describe any given process in a dimensionless form to facilitate modeling and scale-up or scale-down .

- Dimensionless Analysis is a method for producing dimensionless numbers and deriving functional relationships among them that completely characterize the process . It was first systematically applied to fluid flow 90 years ago by Lord Rayleigh on the basis of the principle of similitude referred to by Newton in one of his early works .

- Dimensionless Numbers :

  Basic Dimensional Quantities : Length (L), Mass (M), Time (T) .

  Dimensional Numbers have no dimensions . Such numbers are frequently used to describe the ratios of various physical quantities .

  Newton (Ne) = $P/(\square n^3$

  d^5)Froude (Fr) = n^2d/g

  Reynolds (Re) = $d^2n\square/\square$

  in which P is power consumption (ML^2/T^3)

  $\square$ is specific density of particles

  (M/L^3)n is the impeller speed (T^{-1})

  d is the impeller diameter (L)

  g is the gravitational constant (L/T^2)

  $\square$ is the dynamic viscosity (M/LT)

- Ne is a measure of the power required to overcome friction in fluid flow in a stirredreactor. In mixer granulation applications, this number can be calculated from the power consumption of the impeller .

  Fr is described for powder blending and was suggested as a criterion for dynamic similarity as well as scale-up parameter in wet granulation .

  Re relates the inertial force to the viscous force, is used to describe mixing processes .

[11] SCALE-UP OF LIQUID AND SEMISOLIDMANUFACTURING PROCESSES

- In mixing and semisolid manufacturing, mixing is an important unit operation .
- Flow regimes in pharmaceutical system undergoing mixing process may range from laminar to turbulent to transitional flow . The flow regime in the vicinity of an impeller is often turbulent while the flow regime elsewhere in the system can be laminar or transitional .

  For turbulent flow regime, power is $\square N^3D^2$ ($\square$ = density ; N = rotational speed ; D = Diameter of impeller) .

  For laminar flow regime, power is $\square N^2$ ($\square$ = viscosity)

- **Scale-up of solutions** : Three methods can be applied .

1. Power Law Approach :-

$$N_2 = N_1 (1 \square R)^n$$

n is power law exponent

N_1 & N_2 are rotational speed of impeller

R is geometric scaling factor such as : D_1T_1 or D_2T_2 (D = impeller diameter and Tis mixing tank diameter) ; Z_1T_1 or Z_2T_2 (Z = height of liquid in the mixing tank)

2. Dimensionless Numbers :-

Reynolds Number (the ratio of inertial to viscous forces in a flow)

$$Re = (D^2 \square N \square \square)$$

Froude Number (the ratio of inertial stress to the gravitational force per unitarea in a liquid)

$$Fr = (DN^2 \square g)$$

It is a means of correlating process characteristics at various production scales .

D = Diameter of impeller ; N = Rotational speed of impeller ;

$\square$ = Viscosity ; $\square$ = density ; g = acceleration gravity

3. Scale of agitation approach :-

Applicable only if system show Newtonian flow and Geometric similarity . The rheological behaviour of shear-thinning (pseudoplastic) systems may be described by the ostawald-de Waele equation between the shear rate extremescorresponding to the zero shear viscosity, $\square_0$ and to the infinite shear viscosity, $\square_\square$

$$T = K\square^a$$

In which T is the shear stress , $\square$ is the rate of shear and K and a are constants .

The ratio of $\square:\square_0$ corresponding to the ratio of $T:T_0$ would then be used to facilitate scaling .

[12] SCALE-UP OF POWDER BLENDING OPERATIONS

- Regarding scale-up requirements, blending processes can be classified into two fundamentally different groups i.e. for Free flowing and cohesive materials . Their blending requirements vary .

- Free Flowing Materials :- They are powders and granulations in which interparticle cohesive forces are small enough for particles to move individually .
  Both inter and intra shell mixing processes can be described by similar equation such as : $\sigma^2 = Ae^{-kN}$ where

  σ^2 is mixture variance
  N is number of revolutions
  A is unspecified constant
  K is rate constant .

  The Froude Number : $\mathbf{Fr = [\omega^2 R/g]}$ where

  ω is rotation rate
  R is vessel radius
  g is acceleration from gravity
  is suggested for tumbling blender scale-up .

- Cohesive Powders :- The effect of cohesion on powder flow and scale-up in particular for blending operations is a problem . A cohesive powder can be defined as a material in which the adhesive forces between particles exceed the particle weight by at least an order of magnitude .

  1. The cohesive effects are much stronger in smaller vessels and tend to disappear in large vessels . This is because as the blender scale increases gravitational and convective force increase, thereby overwhelming cohesive force .

  2. As the blender size increases, the chunk to blender size ratio shrinks.

  Both arguments can be mathematically expressed in terms of dimensionless cohesion number σ_c

  $$\sigma_c = \sigma/\rho gR = (\sigma/\rho g)/R = S/R$$

  in which σ = effective cohesive stress (under actual conditions)
  ρ = powder density under flow conditions
  g = acceleration of gravity
  R = Vessel Volume
  S = $\sigma/\rho g$ is the chunk size which can be defined as the internal length scale of flow driven by material properties .

  As R increases , σ_c decreases

- Mixing rate for radially (top-bottom) segregated loading , is independent and constant regardless of mixture cohesion and mixer size .

  Mixing rate for axially (left-right) segregated loading , the scale-up factors is depended on cohesion , indicating that scale-up is a mixture dependent problem (but this is at small scale) .

  The conclusion from these result is that laboratory scale experiments for cohesive powders are of questionable validity for predicting full-scale behaviour . Behaviour at small scales is likely to be strongly affected by cohesive effects that are of much less intensity in the large scale .

The most common scale-up criterion for the application of shear via impellers and bars is to match the linear speed of the moving element .

[13] IMPROVING THE LIKELYHOOD OF SCALABILITY

- Identifying the physical and chemical phenomena involved in pharmaceutical manufacturing process .
- Understanding whether and how these phenomena are affected by a change inscale (i.e. Are they dependent on volume , area or length ?)
- Identifying the predominant or controlling process mechanism .
- Identifying the critical process variables that affect scalability .
- Identifying or determining the physicochemical properties (eg: density , particle size , viscosity) of the formulation components and the products relevant to scalability .
- Using dimensional analysis to reduce the number of variables required tocharacterize a process as the manufacturing scale changes .
- Using software that enables the estimation of equipment performance andmaterial characteristics .

[14] CONCLUSION

In order to scale up and transfer a process successfully from laboratory scale to pilot scale and multiple commercial manufacturing scales, a thorough understanding of the integration of scale factors , facility design , equipment design and process performance is necessary .

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