Marwadi University
Marwadi Chandarana Group

NAAC A+

B.Pharm, Sem 7
Industrial Pharmacy II
(13PH0702)

Unit 1: Pilot Plant Scale Up Techniques

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Definitions

- **Plant:** A place where the 5 M's (money, material, man, method and machine) are bought together for the manufacturing of the products.

- **Pilot plant:** The part of the pharmaceutical industry where a lab scale formula is transformed into a viable product by development of liable and practical procedure of manufacture.

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

Pilot plan scale up

Commercial manufacturing

Pilot plant & scale up study

Laboratory

Why conduct pilot plant studies ?

- It is usually not possible to predict the effects of a many-fold increase in 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.

Pilot plant can be used for

- Evaluation of the results of laboratory studies
- Product and process corrections & improvements.
- Determination of possible salable by-products and waste which requiring treatment before discharge.
- Obtaining 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.
- Production of small quantities of product for

  - sensory, chemical, microbiological evaluations,
  - limited market testing,
  - furnishing samples to potential customers,
  - shelf-live and storage stability studies

Significance / importance of pilot plant

- Examination of formulae
- Production rate adjustment
- Idea about physical space required
- Appropriate record & reports to supports GMP
- Review of range of relevant processing equipments
- Identification of critical features to maintain quality

Objectives of pilot plant

- 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 for process and equipment.
- To identify the critical features of the process.
- To provide master manufacturing formula.

Steps in scale - up

1) Define product economics (based on projected market size, competitive selling) & provide guidance for allowable manufacturing costs.

2) Conduct laboratory studies & scale – up planning at the same time.

3) Define key rate – controlling steps in the proposed process.

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

5) Design and construct a pilot plant (including provisions for process & en
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6) Evaluate pilot plant results (product & process) including process economics to make any corrections and to make a decision on whether or not to proceed with a full scale plant development.

General considerations

1) Reporting Responsibility
2) Personnel Requirements
3) Space Requirements
4) Review of Formula
5) Raw materials
6) Equipment
7) Production rates
8) Process Evaluation
9) Preparation of Master Manufacturing Procedures
10) Product Stability and Uniformity
11) GMP Considerations

General considerations
1) Reporting responsibility

- 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
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 scale up also involves engineering principles.

General considerations
2) Personnel requirement

➢ The qualifications required for a position in a pilot plant organization:

- a blend of good theoretic knowledge of phamaceutics and some practical experience in the pharmaceutical industry.
- the ability to communicate well, both in speaking and in writing.
- Pharmaceutically trained scientists contribute fundamental strength to the function in their ability to assimilate the complex inter relationship between pharmaceutical processes and the potential impact on chemical, physical, biochemical, and medical attributes of dosage forms.

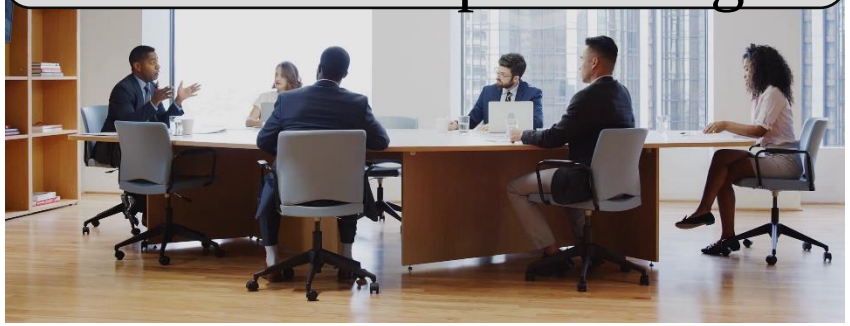
General considerations
2) Personnel requirement

- The number of people in a pilot plant group depends on the number of products being supported and on the level of support required.

- An experienced scientist with a knowledgeable technician should be able to handle one or two major projects simultaneously depending on their complexity, while at the same time providing technical support for an additional group of marketed products.

General considerations
3) Space requirements

3a) Administration and information processing



3b) Physical testing area

3c) Standard pilot plant equipment floor space

3d) Storage area

General considerations
3) Space requirements

3a) Administration and information processing

- Adequate office and desk space should be provided for both scientist and technicians.
- The space should be adjacent to the working area.

- There is the link between research, operations, and other disciplines,

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members of the group frequently meet with people from other departments

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should have an area available where three to four people can meet and discuss subjects of mutual concern.

General considerations
3) Space requirements

3a) Administration and information processing

- There should also be space for a computer terminal

for convenient data entry and retrieval as well as archives for stability data protocols and historical files.

General considerations
3) Space requirements

3b) Physical testing area

- An adequate working area

in which samples can be laid out and examined and where physical tests on these samples can be performed.

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

General considerations
3) Space requirements

3c) Standard pilot-plant equipment floor space

is discrete plant space where equipment needed for manufacturing all types of pharmaceutical dosage forms is located.

- The equipment should be available in a variety of sizes known to be representative of production capability.
- Intermediate-sized and full-scale production equipment is essential in evaluating the effects of scale-up of research formulations and processes.
- Utilization of the area is most efficient when it is subdivided into areas for solid dosage forms, semisolid products, liquid preparations, and sterile products.

General considerations
3) Space requirements

3c) Standard pilot-plant equipment floor space

- Further subdivision of the areas should allow multiple operations to be conducted simultaneously without raising GMP concerns.

- Because the utilization of pilot plant equipment is sporadic and dependent on project as segments, equipment should be made portable, where possible.

- The provision of adequate space for cleaning of pilot plant equipment should be there.
- While some equipment can be cleaned in place, most equipment is better handled in a dedicated cleaning area.

  - stored in a relatively small area & brought out into suitable work areas for use.
  - relieve some of the congestion often found in pilot plant operations
  - provides more working space around equipment that is in use.

General considerations
3) Space requirements

3d) Storage area

- **2 areas:**
  - Approved area
  - Unapproved area

  for active ingredient as well as excipient.

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

General considerations
4) Review of 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
5) Raw materials

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

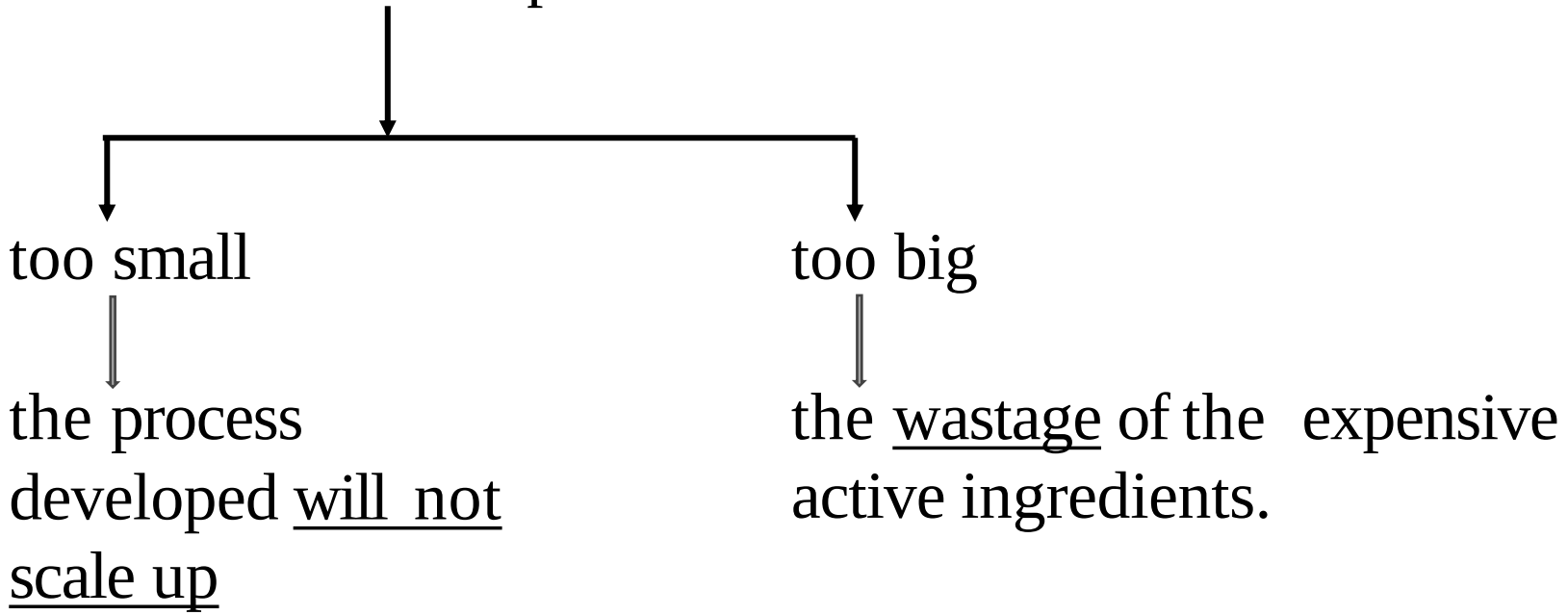
therefore

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

General considerations
6) Equipments

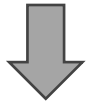
- The most economical, the simplest & efficient equipment which are capable of producing product within the proposed specifications are used.

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



General considerations
7) Production rates

- While determining the production rates



The immediate as well as the future market trends/ requirements are considered

General considerations
8) Process evaluation parameters

Rate of addition of granulating agents, solvents, solution of drugs etc.

Screen size (for solids)

Filter size (for liquids)

Heating & cooling rate

Process evaluation parameters

Order of mixing of components

Mixing speed

Mixing time

Drying temperature, Drying time

General considerations
8) Process evaluation parameters

- The knowledge of the effects of various process parameters (as few mentioned above)

⇓

Form the basis for process optimization & validation

- The process validation

⇓ confirms that

the selected manufacturing procedure assure the quality of the product at various critical stages in the process & finished form.

General considerations

9) Master manufacturing procedures

3 aspects

a) Weighing sheets

Clearly identify the chemicals required in a batch

b) Processing directions

Precise

&

explicit

c) Manufacturing procedure

Written by the actual operator

General considerations

9) Master manufacturing procedures

3 aspects

a) Weighing sheets

Clearly identify the chemicals required in a batch

b) Processing directions

Precise

&

explicit

c) Manufacturing procedure

Written by the actual operator

General considerations
10) Product stability & uniformity

- The primary objective of the pilot plant is the physical & 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 consideration

- Equipment qualification
- Process validation
- Regularly schedule preventative maintenance
- Regularly process review & revalidation
- Relevant written standard operating procedures (SOPs)
- 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

PILOT PLANT SCALE-UP FOR SOLID DOSAGE FORMS

Pilot plant scale-up for solid dosage forms (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.

Pilot plant scale-up for solid dosage forms (Tablets)

- Features for prevention of extraneous and microbiological contamination in the pilot plant design:

1. Fluorescent lighting fixtures should be the ceiling flush type.
2. The various operating areas should have floor drains to simplify cleaning.
3. The area should be air-conditioned and humidity controlled.
4. High -density concrete floors should be installed.
5. The walls in the processing and packaging areas should be enamel cement finish on concrete.
6. Equipment in the pharmaceutical pilot plant should be similar to that used by production division- manufacture of tablets.

Pilot plant scale-up for solid dosage forms (Tablets)

❖Unit operations involved in production of tablets

1) Material handling
2) Dry blending
3) Granulation
4) Drying
5) Reduction ofparticle size
6) Special Granulation techniques
   a) Dry blending
   b) Direct compression
   c) Slugging (dry granulation)

Pilot plant scale-up for solid dosage forms (Tablets)

❖Unit operations involved in production of tablets

1) Material handling

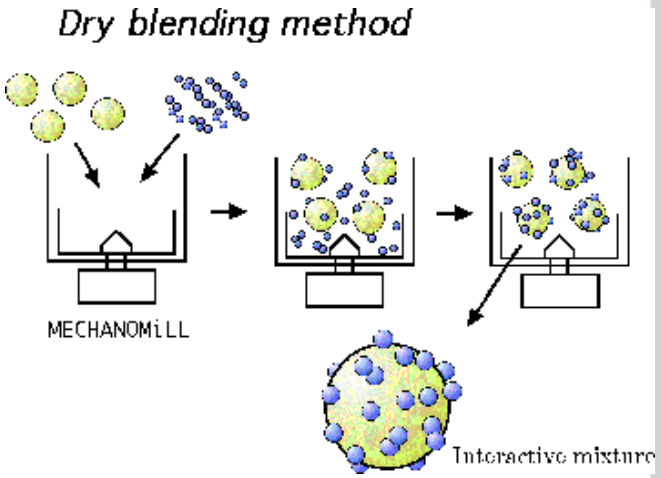
- In the laboratory, materials are simply scooped or poured by hand, but in intermediate- or large-scale operations, handling of this materials often become necessary.
- If a system is used to transfer materials for more than one product steps must be taken to prevent cross contamination.
- Any material 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 can be used.
- There is no or minimal loss of material.

Pilot plant scale-up for solid dosage forms (Tablets)

❖Unit operations involved in production of tablets

2) Dry blending

- Dry blending process uses a binary cohesive-powder mixture which contains two different sizes.
- It is well known that finer particles adhere preferentially on the surface of the coarse particles.
- This type mixture has been called an interactive mixture.
- The blending of fine and coarse particles breaks down the agglomerates of fine and coarse powders, and produces an electric charge by contact and collision between particles.



Pilot plant scale-up for solid dosage forms (Tablets)

❖Unit operations involved in production of tablets

2) Dry blending

- Powders to be used for encapsulation are 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.

Pilot plant scale-up for solid dosage forms (Tablets)

❖Unit operations involved in production of tablets

2) Dry blending

- 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.

- **Scale-up considerations:**
  - Time of blending
  - Size of blender
  - Blender loading

- **Improper blending cause following issues:**
  - Content variation (no content uniformity)
  - Flow problems
  - Non-reproducible compression

Pilot plant scale-up for solid dosage forms (Tablets)

❖Unit operations involved in production of tablets

2) Dry blending

- **Equipments used:**

- V-Blender
- Double cone Blender
- Ribbon Blender
- Slant cone Blender
- Bin Blender
- Orbiting Screw Blenders vertical & horizontal high intensity mixers

Pilot plant scale-up for solid dosage forms (Tablets)

❖Unit operations involved in production of tablets

2) Dry blending

Slant Cone Blender

Bin Blender

Double Cone Blender

Ribbon Blender

Pilot plant scale-up for solid dosage forms (Tablets)

❖Unit operations involved in production of tablets

3) Granulation

"process whereby small particles are gathered into larger, permanent masses in which the original particles can still be identified"

- **Granulation**

↓

- impart good flow properties to the material,
- increase the apparent density of the powders,
- change the particle size distribution,
- uniform dispersion of active ingredient.

Pilot plant scale-up for solid dosage forms (Tablets)

❖Unit operations involved in production of tablets

3) Granulation

➢ **Wet granulation** → utilize some form of liquid to bind the primary particles

- Equipment Used: →
  - Sigma blade mixer
  - Heavy duty planetary mixer

- Efficient and reproducible process

- In wet-granulation process, **binders** promote size enlargement to produce granules and thus improve flowability of the blend during the manufacturing process.

- **Natural Polymers:** Starch, Pregelatinized Starch
- **Synthetic polymers:** PVP, Methyl cellulose, HPMC

Pilot plant scale-up for solid dosage forms (Tablets)

❖Unit operations involved in production of tablets

3) Granulation

➢ **Wet granulation**

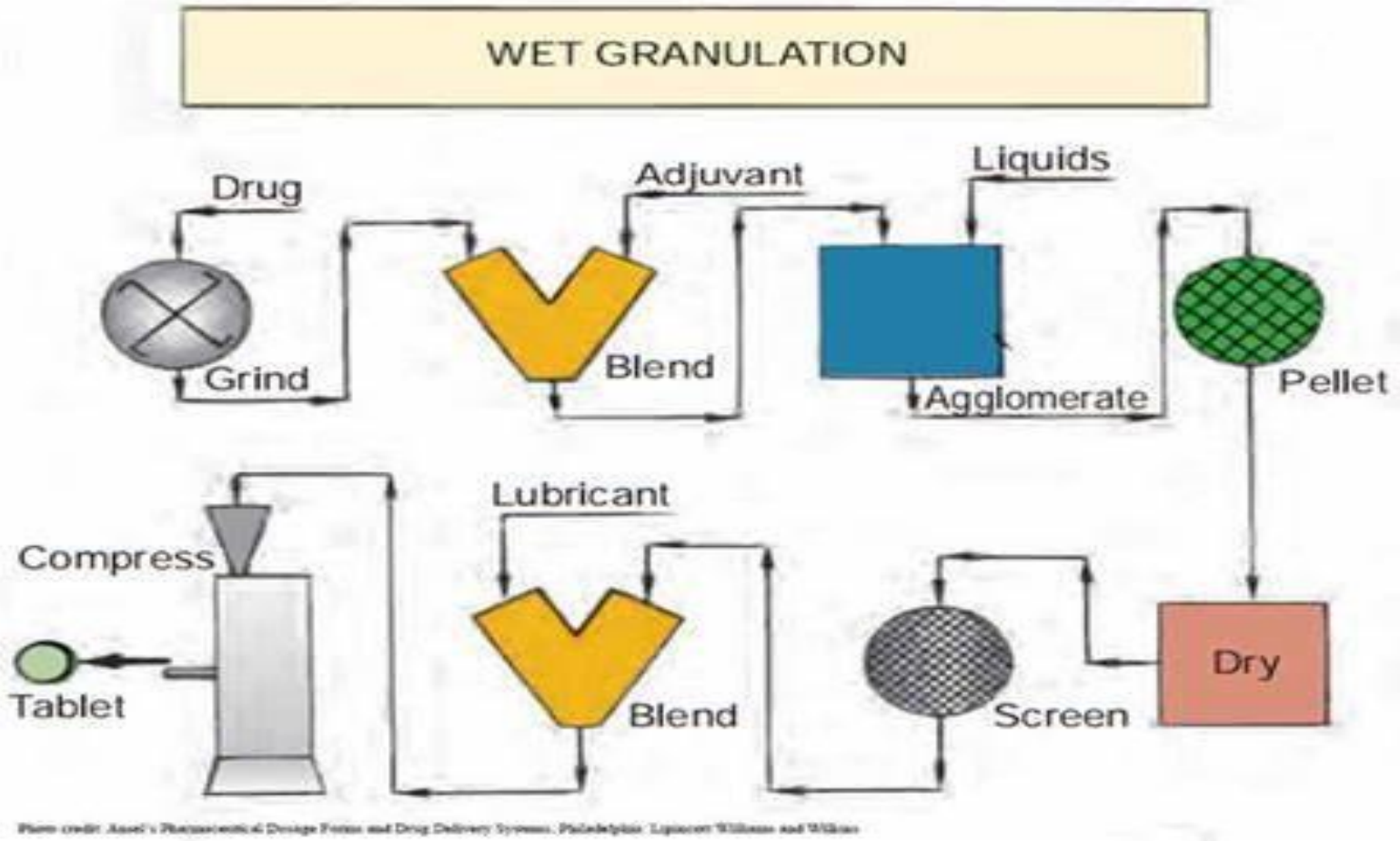
Sigma Blade Mixer

Planetary Mixer

Pilot plant scale-up for solid dosage forms (Tablets)

❖Unit operations involved in production of tablets

3) Granulation



Pilot plant scale-up for solid dosage forms (Tablets)

❖Unit operations involved in production of tablets

3) Granulation

➢ **Wet granulation**

"Multifunctional processors"

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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.

Pilot plant scale-up for solid dosage forms (Tablets)

❖Unit operations involved in production of tablets

3) Granulation

➢ Dry granulation (slugging)

- There are a number of drug substances which are moisture sensitive

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can not be directly compressed.

- A dry powder blend that cannot be directly compressed because of poor flow or compression properties.
- Equipment: Roller compactor

Pilot plant scale-up for solid dosage forms (Tablets)

❖Unit operations involved in production of tablets

3) Granulation

➢ **Fluidized bed granulation** → a process by which granules are produced in single equipment by spraying a binder solution onto a fluidized powder bed.

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finer, free flowing & homogenous material

- Equipment: Fluidized bed granulator

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- The system involves the heating of air and then directing it through the material to be processed .
- Later the same air exists through the voids of the product.

PHOTO CREDIT: GLATT GROUP

Pilot plant scale-up for solid dosage forms (Tablets)

❖Unit operations involved in production of tablets

3) Granulation

- **Scale-up considerations:**

• Process air temperature
(Selected to achieve desired product temperature)
(Adjusted with process air volume)

• Process air volume
(Produce fluidization pattern)
(Delivers heat to the product)

Pilot plant scale-up for solid dosage forms (Tablets)

❖Unit operations involved in production of tablets

3) Granulation

- **Application of granulation:**

  - to reduce dust
  - to densify the material
  - to facilitate metering or volumetric dispensing
  - to enhance the flow rates & rates uniformity

Pilot plant scale-up for solid dosage forms (Tablets)

❖Unit operations involved in production of tablets

4) 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.

- If granulation bed is too deep or too dense
  ↓
  the drying process will be inefficient

- If soluble dyes are involved → migration of the dye to the surface of the granules

Pilot plant scale-up for solid dosage forms (Tablets)

❖Unit operations involved in production of tablets

4) Drying

- **Scale-up considerations:**

- Air flow
- Air temperature
- Depth of the granulation bed

Pilot plant scale-up for solid dosage forms (Tablets)

❖Unit operations involved in production of tablets

4) Drying

➢ 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 temperature probes
5. Drying rates at specified temperatures and air flow rates for each product

Pilot plant scale-up for solid dosage forms (Tablets)

❖Unit operations involved in production of tablets

4) Drying

➢ **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

Pilot plant scale-up for solid dosage forms (Tablets)

❖Unit operations involved in production of tablets

5) Reduction of particle size

- Flowability
- Compressibility
- Uniformity of tablet weight
- Content uniformity
- Tablet color uniformity
- Tablet hardness

Compression factors

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affected by particle size distribution

- First step in this process is to determine the particle size distribution of granulation using a series of "stacked" sieves of decreasing mesh openings.

Pilot plant scale-up for solid dosage forms (Tablets)

❖Unit operations involved in production of tablets

5) Reduction of particle size

- **Equipments used for particle size reduction of dried granulation:**

- Oscillating granulator
- Hammer mill
- Mechanical sieving device
- Screening device

Pilot plant scale-up for solid dosage forms (Tablets)

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❖Unit operations involved in production of tablets

5) Reduction of particle size

- 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.

- In Lab : Added to the final blend
- Scale Up : Added to the dry granulation during size reduction

- This is done because additives like magnesium stearate, agglomerate when added in large quantities to the granulation in a blender.

- Over mixing or under mixing should be avoided.

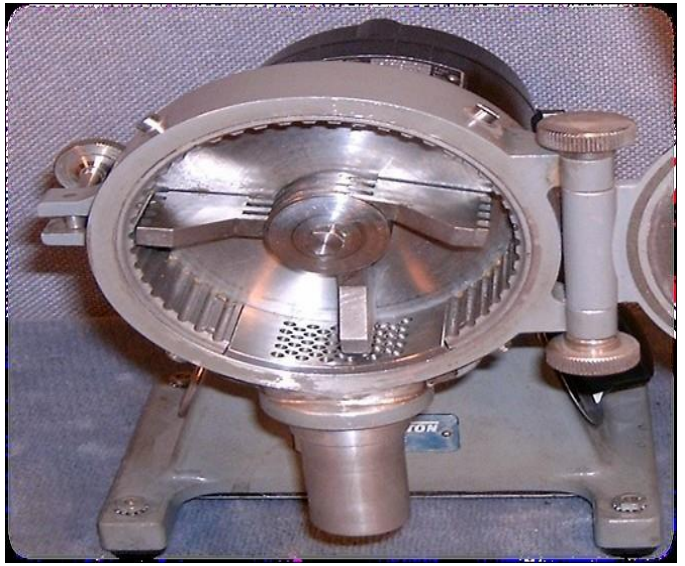
Pilot plant scale-up for solid dosage forms (Tablets)

❖Unit operations involved in production of tablets

5) Reduction of particle size

Oscillating Granulator

Mechanical Sieving



Hammer Mill

Pilot plant scale-up for solid dosage forms (Tablets)

❖Unit operations involved in production of tablets

5) Reduction of particle size

- **Control factors:**

- Speed of mill
- Rate of material feed
- Equipment type

Pilot plant scale-up for solid dosage forms (Tablets)

❖Unit operations involved in production of tablets

6) Blending

- Type of blending equipment often differs from that using in laboratory.
- In any blending operation, both segregation and mixing occur simultaneously as 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.

Pilot plant scale-up for solid dosage forms (Tablets)

❖Unit operations involved in production of tablets

6) Blending

- **Scale-up considerations:**

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 and in determining optimum blender load)
6. Characteristics of the material

- **Control factors:**

1. Blender loads
2. Mixing speeds
3. Mixing times
4. Design

Pilot plant scale-up for solid dosage forms (Tablets)

❖Unit operations involved in production of tablets

6) Blending

➢ Characteristic of material

- Fragile particles or agglomerates → more readily abbraided → more fines
  - Improper mixing,
  - Flow problems,
  - Filling problems,
  - Content uniformity problems
- When high-shear mixing with spiral screws or blades are used → More particle abbraision
- Tumble blenders: for prolonged mixing
- Excessive granulation: poor content uniformity, poor lubrication & improper color dispersion.
- Bulk density of raw materials considered in selection of the blender & determining optimum blender load.

Pilot plant scale-up for solid dosage forms (Tablets)

❖Unit operations involved in production of tablets

7) Compression

➢ **Functions of a tablet press:**

- Filling of empty die cavity with granulation.
- Pre compression of granulation (optional).
- Compression of granules.
- Ejection of the tablet from the die cavity and take- off of compressed tablet.

➢ **Potential problems** such as sticking to the punch surface, tablet hardness, capping, and weight variation detected.

Pilot plant scale-up for solid dosage forms (Tablets)

❖Unit operations involved in production of tablets

7) Compression

Control factors while selecting the speed of the press:

1. Granulation feed rate.
2. Delivery system should not change particle size distribution.
3. System should not cause segregation of coarse & 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 at high press speeds.

Pilot plant scale-up for solid dosage forms (Tablets)

❖Unit operations involved in production of tablets

7) Compression

- Slowing down the press speed or using larger compression rollers → reduce capping in a formulation
- High level of lubricant or over blending →
  - result in a soft tablet
  - decrease in wettability of the powder
  - 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.

Pilot plant scale-up for solid dosage forms (Tablets)

❖Unit operations involved in production of tablets

7) Compression

Single Rotary Press

Double Rotary Press

Pilot plant scale-up for solid dosage forms (Tablets)

❖Unit operations involved in production of tablets

7) Compression

➢ **Different types of punches**

Pilot plant scale-up for solid dosage forms (Tablets)

❖Unit operations involved in production of tablets

8) Tablet coating

- There are mainly 3 types of coating:
  i. Sugar Coating
  ii. Film Coating
  iii. Enteric Coating

- Scale up considerations:
  - The tablet loading of the coating pan
  - Spray rate of the coating solution
  - Quantity of solution required
  - Volume of air used during coating

Pilot plant scale-up for solid dosage forms (Tablets)

❖Unit operations involved in production of tablets

8) Tablet coating

➢ **Equipments Used**

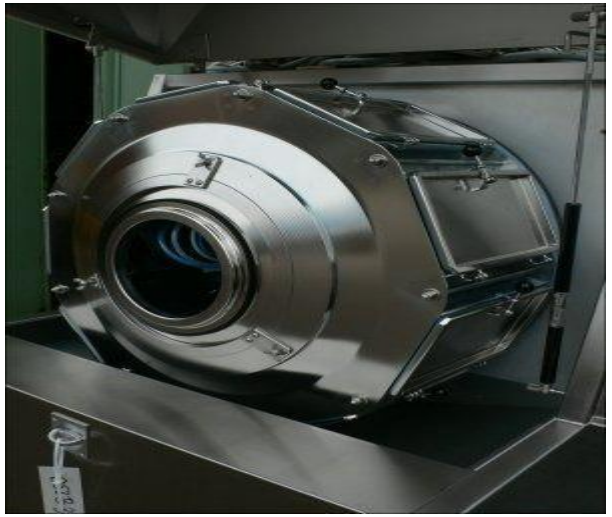
- The standard coating pan
- The perforated coating pan
- Accela cota system
- Hi-coater system
- Dria coater
- Glatt coater
- Fluidized bed (air suspension) coater

Pilot plant scale-up for solid dosage forms (Tablets)

❖Unit operations involved in production of tablets

8) Tablet coating

Coating Pans



Dria Coater

Accela Coata

Fluidized Bed Coating

Pilot plant scale-up for solid dosage forms (Capsules)

- To produce capsules on high-speed equipment, the powder blend must have,
  - uniform particle size distribution
  - bulk density
  - formation of compact of the right size and of sufficient cohesiveness to be filled into capsule shells.

- **Equipments :-**
  - Zanasi or Mertalli – Dosator(hollow tube)
  - Hoflinger – Karg – Tamping pins

Weight variation problem can be encountered with these two methods.

- Overly lubricated granules – delaying disintegration.

Pilot plant scale-up for solid dosage forms (Capsules)

- Humidity affect moisture content of granulation
  on the empty gelatin capsules

- At high humidity → capsule swells,
  make separation of the capsule parts,
  difficult to interfere with the transport of the capsule through the process.

- At low humidity → capsule brittle,
  increased static charge,
  interfere with the encapsulation operation.

- Empty gelatin capsules have a recommended storage condition of 15-25 °C temperature & humidity 35-65 % RH.

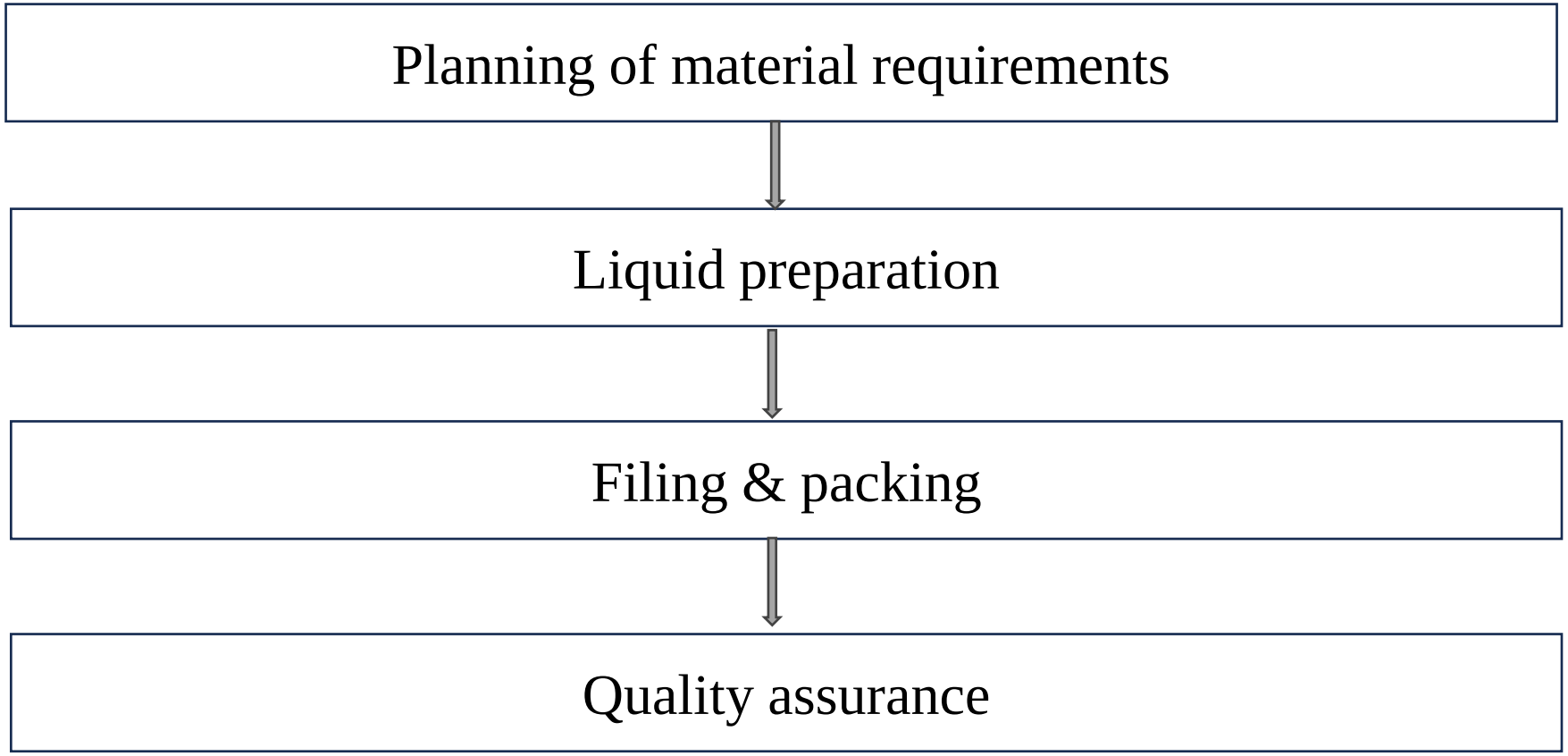
PILOT PLANT SCALE-UP FOR LIQUID ORALS

Pilot plant scale-up for liquid orals

- The physical form of a drug product that is pourable displays Newtonian or pseudoplastic flow behavior 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 distributed in another.
- A solution refers two or more substances mixed homogeneously.

Pilot plant scale-up for liquid orals

❖ Steps of liquid manufacturing process



Pilot plant scale-up for liquid orals

❖ Critical aspects of liquid manufacturing

➢ Physical Plant:

- Heating, ventilation and air controlling system (HVAC)
- 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.

Pilot plant scale-up for liquid orals

❖ **Solutions**

➢ Formulation aspects:

Purpose	Agents
1) Protecting the API	• Buffers • Antioxidants • Preservatives
2) Maintaining the appearance	• Colorings • Stabilizers • Co-solvents • Antimicrobial preservatives
3) Unpleasant taste or smell masking	• Sweeteners • Flavorings

Pilot plant scale-up for liquid orals

❖ Solutions

➢ **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

Pilot plant scale-up for liquid orals

❖ Solutions

➢ **Parameters to be considered are –**

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) Filtration equipment (should not remove active or adjuvant ingredients)

11) Transfer system

12) Passivation of stainless steel (SS) (pretreating the SS with acetic acid or nitric acid solution to remove the surface alkalinity of the SS)

Pilot plant scale-up for liquid orals

❖ Suspensions

➢ Formulation aspects:

Purpose	Agents
1) Facilitating the connection between API & vehicle	• Wetting agents • Salt formation agents
2) Protecting the API	• Buffers • Antioxidants • Polymers
3) Maintaining the suspension appearance	• Suspending agent • Flocculating agent • Colorings
4) Unpleasant taste or smell masking	• Sweeteners • Flavorings

Pilot plant scale-up for liquid orals

❖ Suspensions

➢ **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)

Pilot plant scale-up for liquid orals

❖ Suspensions

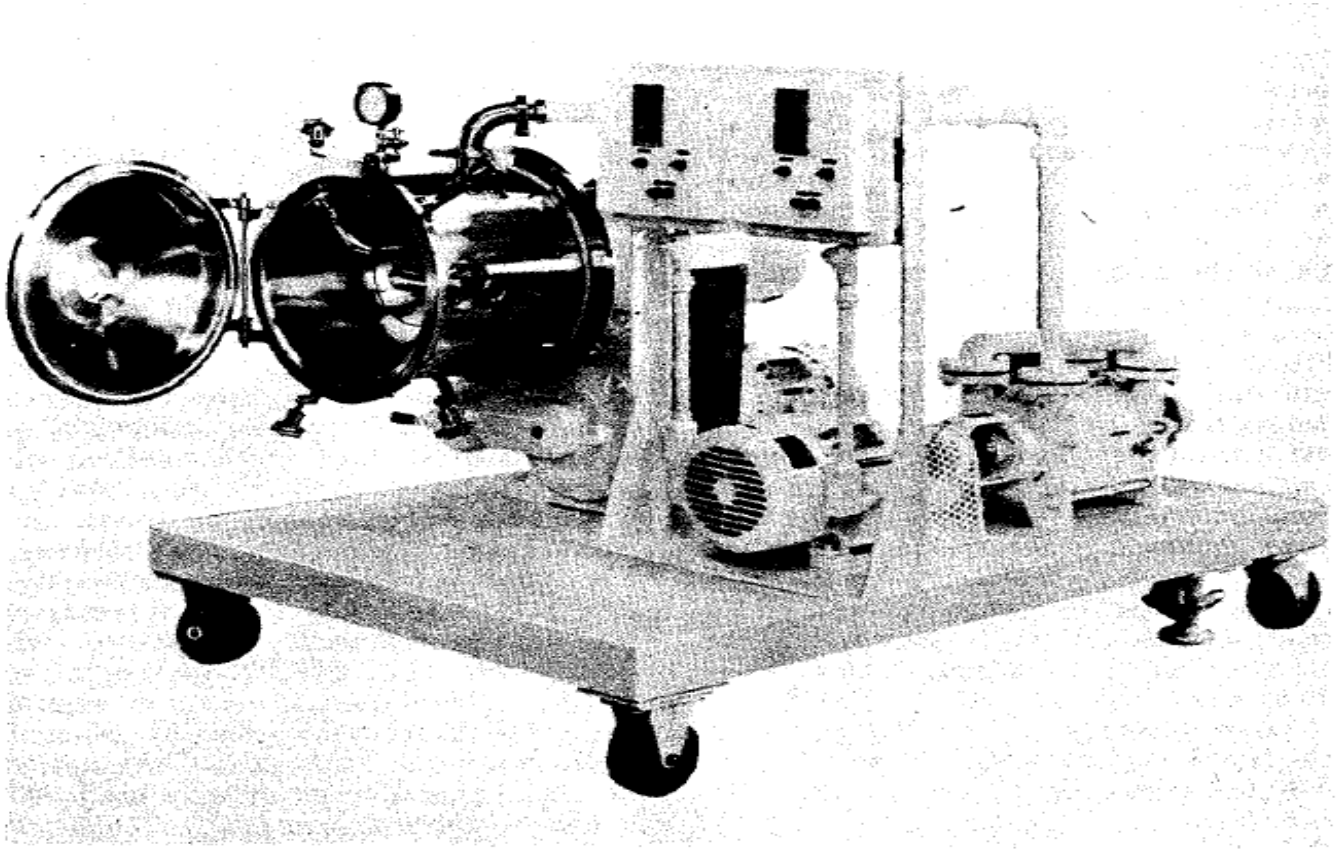


FIG. . *The Versator consists of a vacuum chamber and a high-speed revolving disc. During operation, material is spread into a thin film by the centrifugal force of the disc, and deaeration is achieved under vacuum. If desired, the unit can be pressurized to create entrainment of gas. (Courtesy of the Cornell Machine Co.)*

Pilot plant scale-up for liquid orals

❖ Emulsions

➢ Formulation aspects:

Purpose	Agents
1) Particle size	• Solid particles • Droplet particles
2) Protecting the API	• Buffers • Antioxidants • Polymers
3) Maintaining the appearance	• Emulsifying agents • Penetration enhancers • Gelling agents • Colorings
4) Unpleasant taste or smell masking	• Sweeteners • Flavorings

Pilot plant scale-up for liquid orals

❖ Emulsions

➢ **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

PILOT PLANT SCALE-UP FOR SEMISOLID

Pilot plant scale-up for semisolid dosage forms

- Pastes, gels, ointments and creams are closely related to suspensions, liquids and emulsion except that they are products with **higher viscosities.**

➢ **<u>The following parameters are to be considered during the scale up of semisolid products :</u>**

1) Mixing equipment (should effectively move semisolid mass from outside walls to the center and from bottom to top of the kettle)
2) Motors (used to drive mixing system and must be sized to handle the product at its most viscous stage.)
3) Working temperature range (critical to the quality of the final product)
4) Mixing speed
5) Component homogenization
6) Heating and cooling process
7) Addition of active ingredients
8) Product transfer

Pilot plant scale-up for semisolid dosage forms

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

9) Shear during handling and transfer from manufacturing to holding tank to filling lines

10) Transfer pumps (must be able to move viscous material without applying excessive shear and without incorporating air)

11) While choosing the size and type of pump ,
    - Product viscosity
    - Pumping rate
    - Product compactibility with the pump surface
    - Pumping pressure required should be considered

Pilot plant scale-up for semisolid dosage forms

❖ Suppositories

➢ The manufacturing of suppositories on a laboratory scale usually involves the following steps:

- the preparation of a molten mass
- the dispersion of drug in the molten base
- casting of suppositories in a suitable mold
- cooling of the mold
- opened & remove the suppositories
- More no. of molds & large size Pan for melting of drug & base.

Pilot plant scale-up for semisolid dosage forms

❖ Suppositories

- The manufacturing and packaging processes for suppositories have recently been simplified to a one stage operation.
- This new technology eliminates many of the troublesome molding, cooling & unmolding steps of the older technology.
- The basic improvement of the newer processing equipment is that the molten suppository mass is filled into formed PVC or foil shells, which serve both as the mold and finished package.
- Such a process eliminates many of the problems encountered during the removal of the suppository from the two-piece molds in which they were formed on the older equipment.

Pilot plant scale-up for semisolid dosage forms

❖ Suppositories

- The extra work and equipment required to complete the off-line packing operation of wrapping or blistering are also eliminated.

- The manufacture of suppositories using modern equipment can be divided into several operations involving first the manufacture of the molten suppository mass and then the molding and packaging of the suppository.