Jijamata Education Society's
College of Pharmacy, Nandurbar.
At Post: Waghoda Shivar, Tal. & Dist: Nandurbar 425412

SUPAC

Scale Up

Increase in batch size i.e From Pilot to Manufacturing Scale

Post Approval Changes

Making changes in already approved and validated process

What is SUPAC

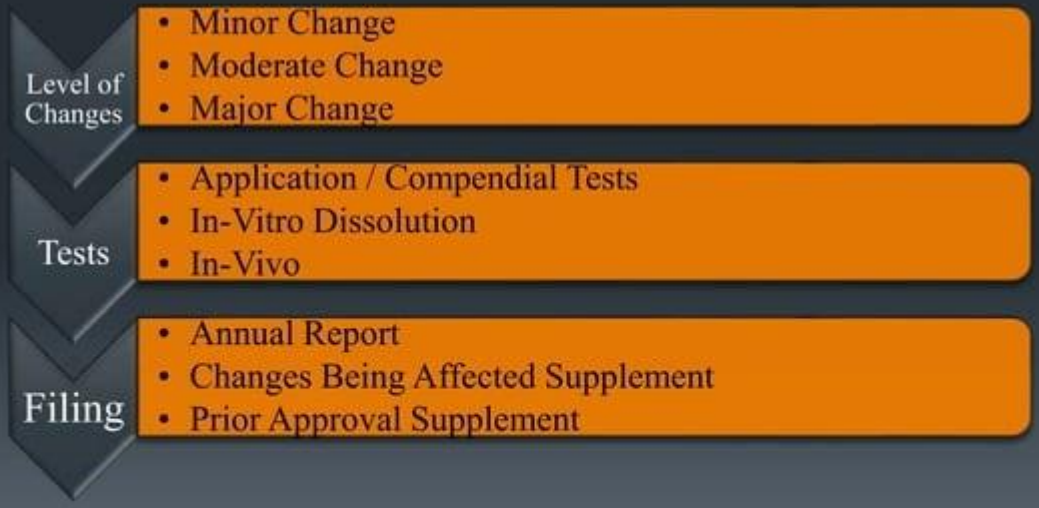
- SUPAC was established by the Centre for Drug Evaluation and Research (CDER), Chemistry, Manufacturing and Controls Coordinating Committee to develop guidance on scale up and other post approval changes.

- It refers to the FDA recommended testing and filing actions to be taken by a pharmaceutical firm when it changes the manufacturing process of a drug product that has been approved via a New Drug Application (NDA), Abbreviated New Drug Application (ANDA) or Abbreviated Antibiotic Drug Application (AADA).

FDA has issued various guidance for SUPAC changes designated as

- SUPAC-IR(For Immediate release solid dosage form)-Focus on changes in the amount of excipients in the drug product.
- SUPAC-MR(For Modified release solid oral dosage form)-Focus on excipients critical or non critical to the drug release.
- SUPAC-SS(For Non Sterile Semisolid Dosage Form including creams ,ointments , gels and lotions)-Focus on changes in preservatives.

SUPAC GUIDELINES DEFINE



I. Site Changes

Site changes consist of changes in location of the site of manufacture for both company owned and contract manufacturing facilities and do not include any scale-up changes, changes in manufacturing (including process and/or equipment), or changes in components or composition. New manufacturing locations should have a satisfactory current Good Manufacturing Practice (CGMP) inspection.

A. Level 1 Changes

Definition: Level 1 changes consist of site changes within a single facility where the same equipment, standard operating procedures (SOP's), environmental conditions (e.g temperature and humidity) and controls, and personnel common to both manufacturing sites are used, and where no changes are made to the manufacturing batch records, except for administrative information and the location of the facility.

Test Documentation

A. Chemistry Documentation: None beyond application/ compendial release requirements.

B. Dissolution Documentation: None beyond application/ compendial release requirements.

C. In Vivo Bioequivalence Documentation- None

Filing Documentation- Annual Report.

B. Level 2 Changes

- Definition: ***Level 2 changes consist of site changes within a contiguous campus, or between facilities in adjacent city blocks, where the same equipment, SOP's, environmental conditions*** (e.g., temperature and humidity) and controls, and personnel common to both manufacturing sites are used, and where no changes are made to the manufacturing batch records, except for administrative information and the location of the facility.
- Test Documentation

A. Chemistry Documentation Location of new site and updated batch records. None beyond application/ compendial release requirements.One batch on long-term stability data reported in annual report.

B. Dissolution Documentation None beyond application /compendial release requirements.

C. In Vivo Bioequivalence Documentation-None.

Filing Documentation- Changes being effected supplement; annual report (long term stability test data).

C. Level 3 Changes

Definition: Level 3 changes consist of a change in manufacturing site to a different campus. A different campus is defined as one that is not on the same original contiguous site or where the

facilities are not in adjacent city blocks. To qualify as a Level 3 change, the same equipment, SOP's, environmental conditions,

and controls should be used in the manufacturing process at the new site, and no changes may be made to the manufacturing

batch records except for administrative information, location and language translation where needed.

Test Documentation

- Chemistry Documentation Location of new site and updated batch records. Application/compendial release requirements.
- Stability: Significant body of data available: One batch with three months accelerated stability data reported in supplement; one batch on long-term stability data reported in annual report. Significant body of data not available: Up to three batches with three months accelerated stability data reported in supplement; up to three batches on long term stability data reported in annual report.
- Dissolution Documentation Case B: Multipoint dissolution profile should be performed in the application/compendia medium at 15, 30, 45, 60 and 120 minutes or until an asymptote is reached. The dissolution profile of the drug product at the current and proposed site should be similar.
- In Vivo Bioequivalence Documentation- None
- Filing Documentation- Changes being effected supplement; annual report (long-term stability data).

Change in batch size

(scale up of manufacture)

Post	Post approval changes in the size of a batch from the pivotal/pilot scale biobatch material to larger or smaller production.
Scale down	Scale down below 1,00,000 dosage units is not covered by this guideline.
Scale up	Scale up changes should be properly validated and if needed, inspected by appropriate agency personnel.

A. Level 1 Changes

- Definition of Level: Change in batch size, up to and including a factor of 10 times the size of the Pilot/ Bio batch, where:
- The equipment used to produce the test batch is of the same design and operating principles;
- The batch is manufactured in full compliance with CGMP's;
- The same standard operating procedures(SOP's) and controls, as well as the same formulation and manufacturing procedures, are used on the test batch and on the full-scale production batch.

Test Documentation

- Chemistry Documentation Application/compendial release requirements. Notification of change and submission of updated batch records in annual report. One batch on long-term stability reported in annual report.
- Dissolution Documentation None beyond application/ compendial release requirements.
- In Vivo Bioequivalence-None.
- Filing Documentation-Annual report (long term stability data).

B. Level 2 Changes

- Definition of Level: Changes in batch size beyond a factor of ten times the size of the pilot/ bio batch, where:

1) The equipment used to produce the test batch is of the same design and operating principles.

2) The batch is manufactured in full compliance with CGMP'S.

3) The same SOP's and controls as well as the same formulation and manufacturing procedures are used on the test batch and on the full-scale production batch.

Test Documentation

A. Chemistry Documentation Application/ compendial release requirements. Notification

of change and submission of updated batch records. Stability testing: One batch with three

months accelerated stability data and one batch on long-term stability.

B. Dissolution Documentation-Case B testing.

C. In Vivo Bioequivalence-None.

Filing Documentation: Changes being effected supplement; annual report (long-term stability data).

III. Manufacturing

- Manufacturing changes may affect both equipment used in the manufacturing process and the process itself.
- A. Equipment 1. Level 1 Changes
- Definition of Change This category consists of:

1) Change from non-automated or non mechanical equipment to automated or mechanical equipment to move ingredients.

2) Change to alternative equipment of the same design and operating principles of the same or of a different capacity.

- Test Documentation: Chemistry documentation application/compendial release requirements. Notification of change and submission of updated batch records. Stability testing: One batch on long term stability.

ii. Dissolution Documentation None beyond application/ compendial release requirements.

iii. In Vivo Bioequivalence Documentation-None

- Filing Documentation-Annual report (long term stability data).

Level 2 Changes

- Definition of Level- Change in equipment to a different design and different operating principles.
- Test Documentation- Chemistry Documentation application/compendial release requirements. Notification of change and submission of updated batch records. Stability testing: Significant body of data available: One batch with three months accelerated stability data reported in supplement; one batch on long-term stability data reported in annual report. Significant body of data not available: Up to three batches with three months accelerated stability data reported in supplement; up to three batches on long-term stability data reported in annual report.
- Dissolution Documentation- Case C dissolution profile.
- In Vivo Bioequivalence Documentation- None.
- Filing Documentation- Prior approval supplement with justification for change; annual report (long-term stability data).

MANUFACTURING CHANGES (PROCESS)

LEVEL	CLASSIFICATION	TEST DOCUMENTATION	FILING DOCUMENTATION
1)	➢ Adjustment of equipment operating conditions (operating speeds, mixing times) ➢ Within approved application ranges	▪ Updated batch records ▪ application/compendial requirements ▪ Stability	Annual report

LEVEL 2

2)	➢ Adjustment of equipment operating conditions (operating speeds, mixing times) ➢ Beyond approved application ranges ➢ SUPAC - SS Change in the process of combining two phases	➢ -Updated batch records - application/compendial requirements ➢ Stability ➢ SUPAC-IR Multi-point dissolution profile. ➢ SUPAC-MR -Multi-point dissolution profiles in multiple medias (e.g., USP buffer media at pH 4.5-7.5 for extended release) three other media (e.g., Water, 0.1N HCl, and USP buffer media at Ph 4.5 And 6.8 for delayed release). ➢ SUPAC-SS In vitro release test Documentation.	➢ Annual report ➢ Changes being Effected Supplement

LEVEL 3

3)	➢ Changes in the type of process used (e.g. wet granulation to direct compression	➢ Updated batch records - application/compendial requirements -Stability - Biostudy or IVIVC. ➢ SUPAC-IR Multi-point dissolution profile. ➢ SUPAC-MR Multi-point dissolution profiles in multiple medias (e.g., USP buffer media at pH 4.5-7.5 for extended release) three other media (e.g., Water, 0.1N HCl, and USP buffer media at Ph 4.5 And 6.8 for delayed release)	✓ Prior approval supplement ✓ Annual report

Limitations of SUPAC

- SUPAC has not been updated since 1995/1997 for main guidelines.
- Does not cover modified equipment.
- Does not discuss multiple changes.

Advantages

- Reducing operating overhead & maintenance expenses.
- More rapid implementation of process and equipment changes.
- Improved yield & reduce failure investigations.
- More rapid implementation of batch size increases.
- Production of fewer unmarketable stability batches.
- Reduce stability testing/costs.

Reference

- https://www.researchgate.net/publication/316021703_SCALE_UP_AND_POSTAPPROVAL_CHANGES_SUPAC_GUIDANCE_FOR_INDUSTRY_A_REGULATORY_NOTE.
- https://www.slideshare.net/sayedasalma/supac-87129226
- http://m.authorstream.com/presentation/jeevithakanapart-1905484-supac/

thank you!

Topic –
Unit I Pilot Plant Scale Up

Presented By
Mr. Vishal V. Kalal
Ass. Prof.

JES'S College Of Pharmacy Nandurbar.

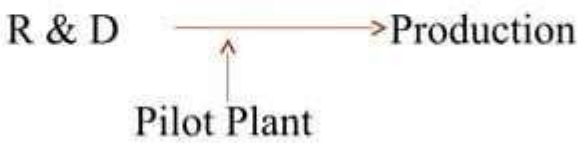
Contents

Definitions

- **Plant**:- It is a place were the 5 M's like money, material, man, method and machine are brought together for the manufacturing of the products.

- **Pilot Plant**:- It is 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.



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 equipments.
- To identify the critical features of the process.
- To provide master manufacturing formula.

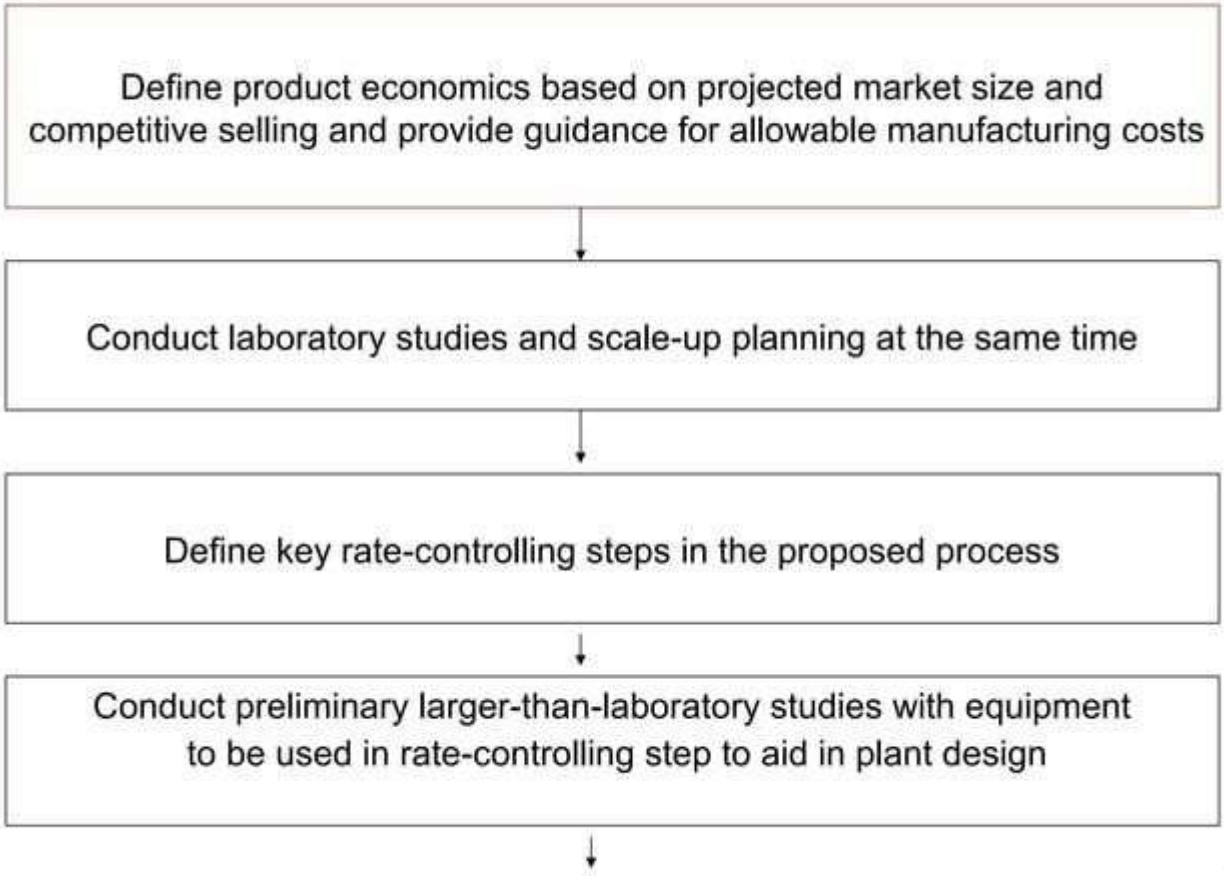
- To try the process on a model of proposed plant before committing large sum of money on a production unit.
- Examination of the formula to determine it's ability to withstand Batch-scale and process modification.
- To avoid the scale-up problems.

SIGNIFICANCE OF PILOT PLANT/ Importance of Pilot Plant

- Examination of formulae.
- Review of range of relevant processing equipments.
- production rate adjustment.
- Idea about physical space required.
- Appropriate records and reports to support GMP.
- Identification of critical features to maintain quality.

Pilot Plant can be used for

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

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 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 scale 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-life and storage stability studies.
- 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

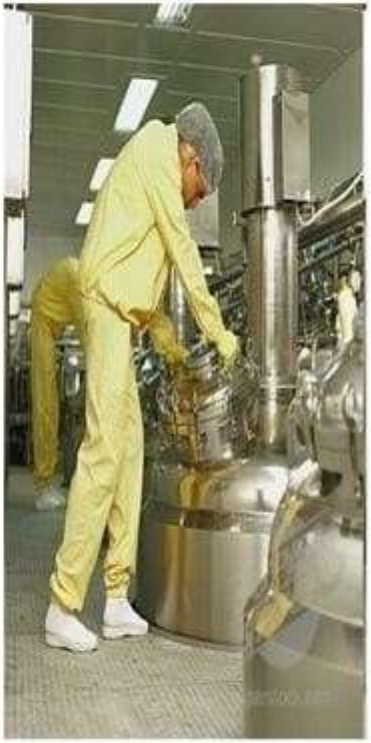
General considerations /Group Responsibilities

1. **Reporting Responsibility**

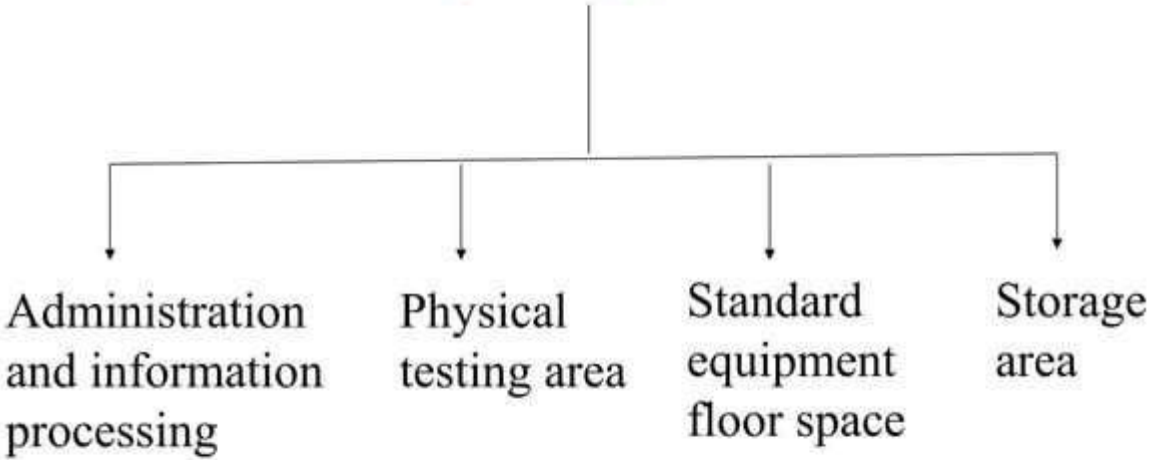
- R & D group with separate staffing
- The formulator who developed the product can take into the production and can provide support even after transition into production has been completed

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.
- Knowledge of computers & electronics



3. Space Requirements



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.
  - Computers.

- **Physical testing area:-**

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

❑ 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.

❑ Storage Area

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

Different areas should 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.

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.

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.

Ingredients may change in particle size, shape or morphology which result in differences in bulk density, static charges, rate of solubility, flow properties, color, etc.

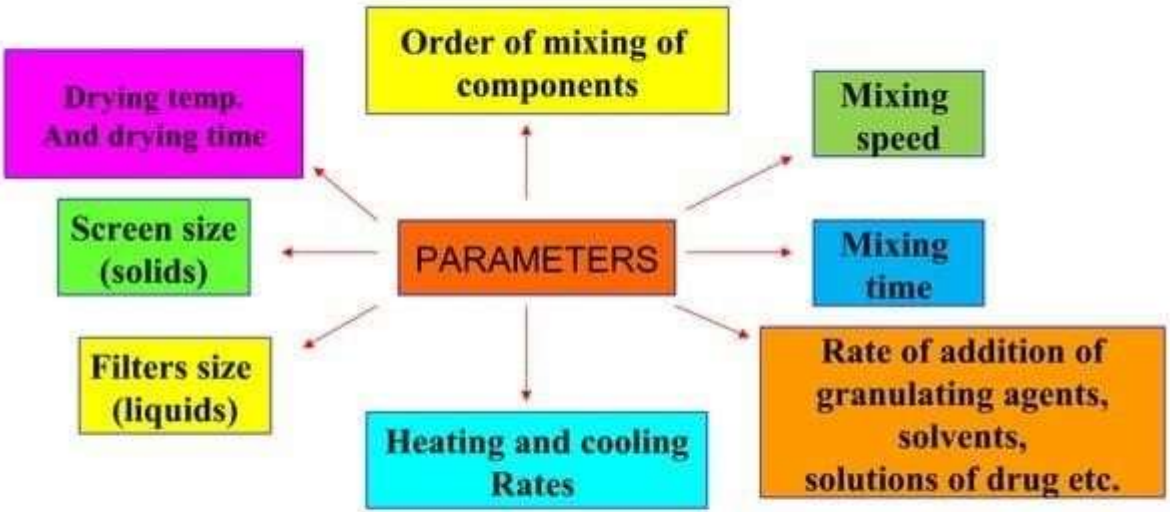
6. Equipment:-

- 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.
- Ease of cleaning
- Time of cleaning

7. Production Rates:-

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

8. Process Evaluation:-



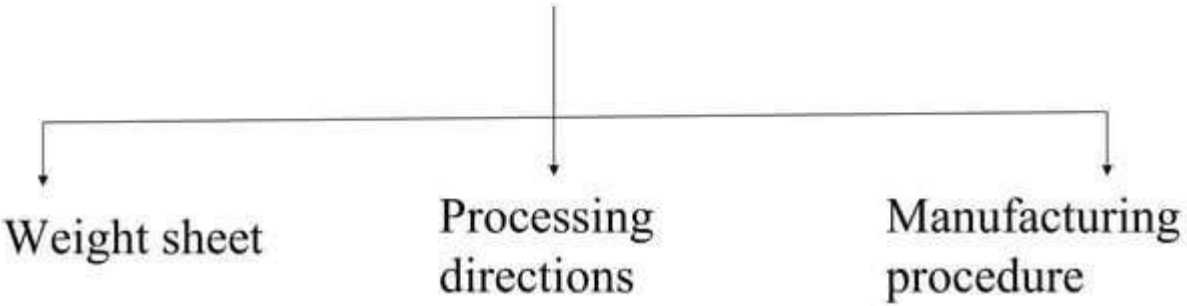
Why to carry out process evaluation????

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

- The purpose of process validation is to confirm that the selected manufacturing procedure assure the quality of the product at various critical stages in the process and in finished form.

9. Master Manufacturing Procedures:-

The three important aspects



Master Manufacturing Procedures

- The weight sheet should clearly identify the chemicals required In a batch. To prevent confusion the names and identifying nos. for the ingredients should be used on batch records.
- The process directions should be precise and explicit.
- A manufacturing procedure should be written by the actual operator.
- Various specifications like addition rates, mixing time, mixing speed, heating, and cooling rates, temperature, storing of the finished product samples should be mentioned in the batch record directions.

Transfer of Analytical Method to Quality Assurance

- During the scale-up of a new product, the analytic test methods developed in research must be transferred to the quality assurance department.

- Early in the transfer process, the quality assurance staff should review the process to make sure that the proper analytic instrumentation is available and that personnel are trained to perform the tests.

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.

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

Advantages

- Members of the production and quality control divisions can readily observe scale up runs.
- Supplies of excipients & drugs, cleared by the quality control division, can be drawn from the more spacious areas provided to the production division.
- Access to engineering department personnel is provided for equipment installation, maintenance and repair.

Disadvantages

- The frequency of direct interaction of the formulator with the production personnel in the manufacturing area will be reduced.

- Any problem in manufacturing will be directed towards it's own pilot-plant personnel's.

Pilot Plant Scale Up Of Tablets Design

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.

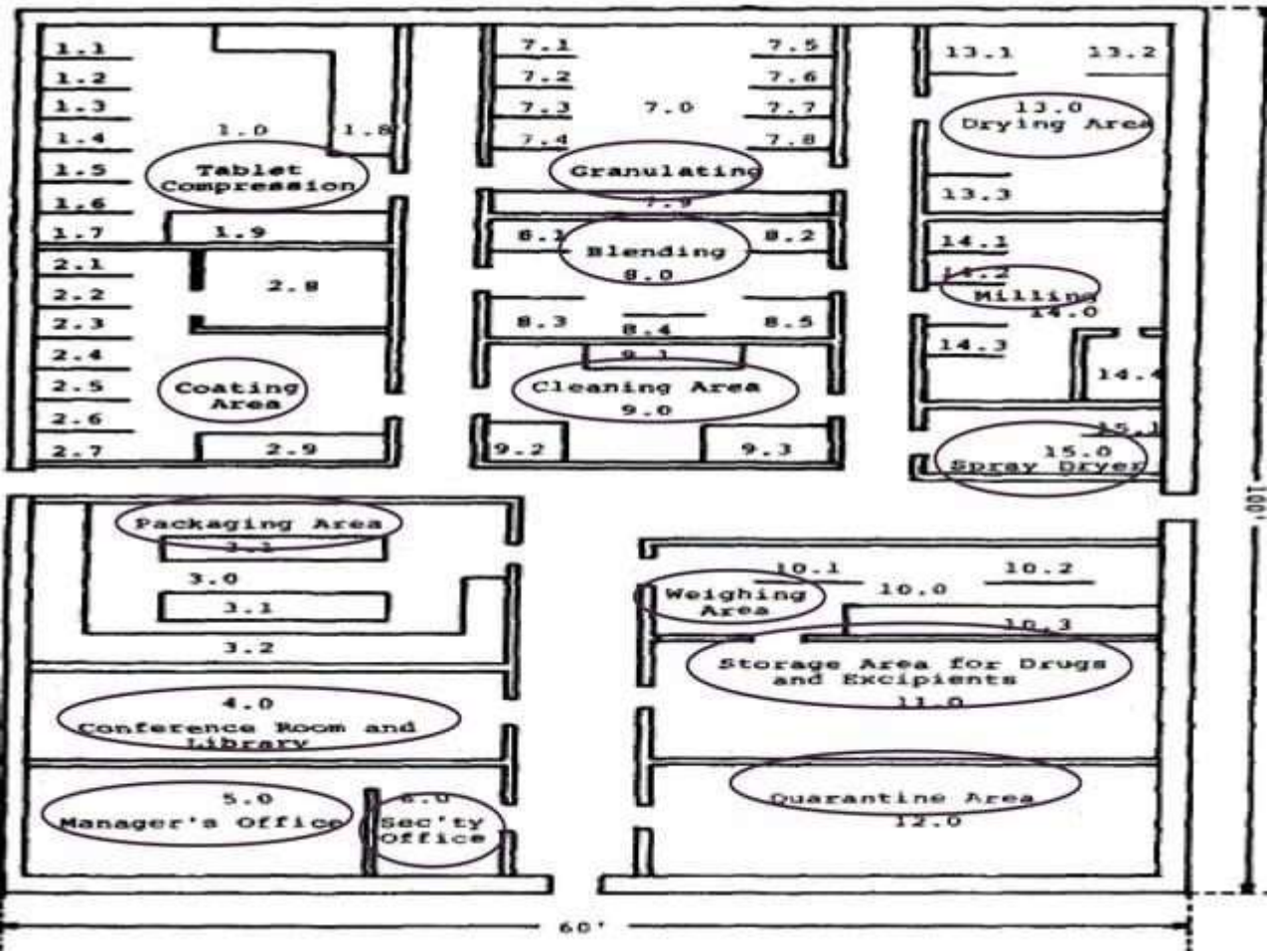
The design and construction of the pharmaceutical pilot plant for tablet development should incorporate features necessary to facilitate maintenance and cleanliness.

If possible, it should be located on the ground floor to expedite the delivery and shipment of supplies.

Pilot Plant Scale Up Of Tablets Design Continued....

Microbial Contamination can be Avoided by the following ways:

- 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 on concrete.
- Equipment in the pharmaceutical pilot plant should be similar to that used by production division- manufacture of tablets.


1.1
1.2
1.3
1.4
1.5
1.6
1.7
1.0
1.8
Tablet Compression
1.9
2.1
2.2
2.3
2.4
2.5
2.6
2.7
2.8
Coating Area
2.9
7.1
7.2
7.3
7.4
7.0
7.5
7.6
7.7
7.8
Granulating
7.9
8.1
Blending
8.0
8.2
8.3
8.4
8.5
9.1
Cleaning Area
9.0
9.2
9.3
13.1
13.2
13.0
Drying Area
13.3
14.1
14.2
Milling
14.0
14.3
14.4
15.1
15.0
Spray Dryer
Packaging Area
3.3
3.0
3.1
3.2
4.0
Conference Room and Library
5.0
Manager's Office
6.0
Sec'ty Office
10.1
10.2
Weighing Area
10.0
10.3
Storage Area for Drugs and Excipients
11.0
Quarantine Area
12.0
100'
60'

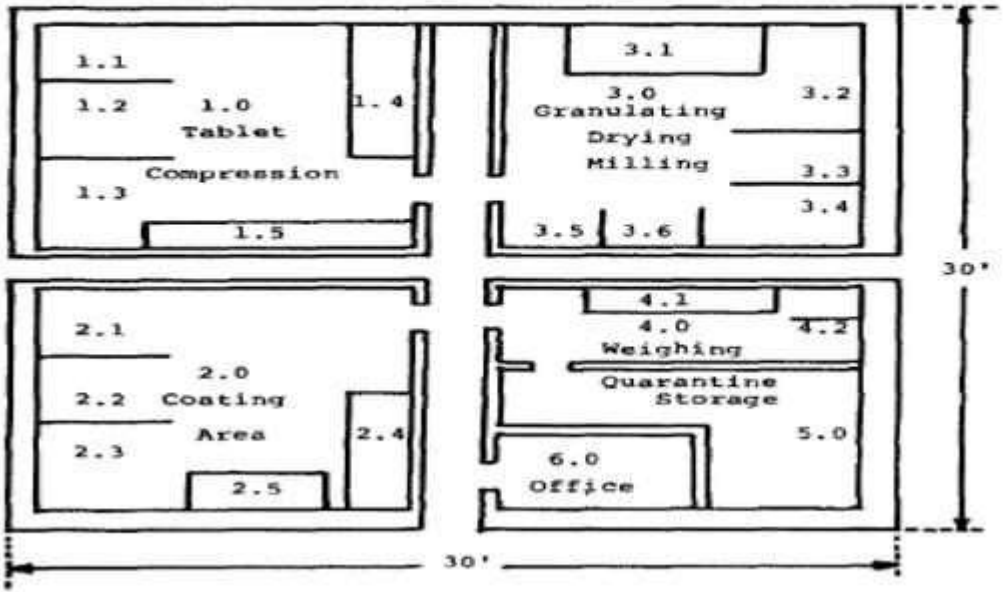
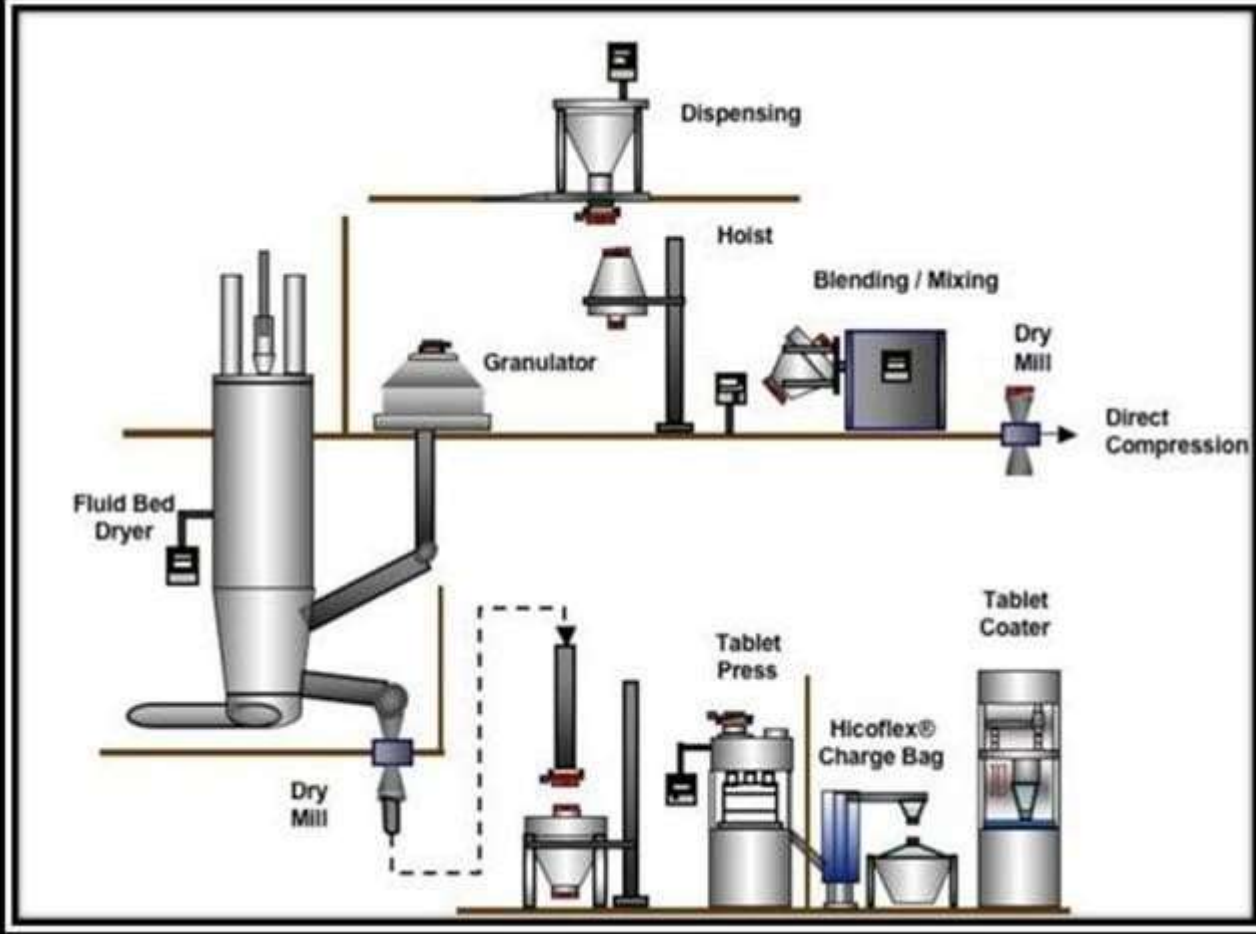


Figure 5 Floor plan for a small pilot plant for tablet development.


Dispensing
Hoist
Blending / Mixing
Granulator
Dry
Mill
Direct
Compression
Fluid Bed
Dryer
Tablet
Coater
Tablet
Press
Hicoflex®
Charge Bag
Dry
Mill

Stages Of Production Of Tablets

- Material handling
- Dry blending
- Granulation
- Drying
- Reduction of particle size
- Special Granulation techn
  - Dry blending
  - Direct compression
  - Slugging (dry granulation

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.
- There is no or minimal loss of material .

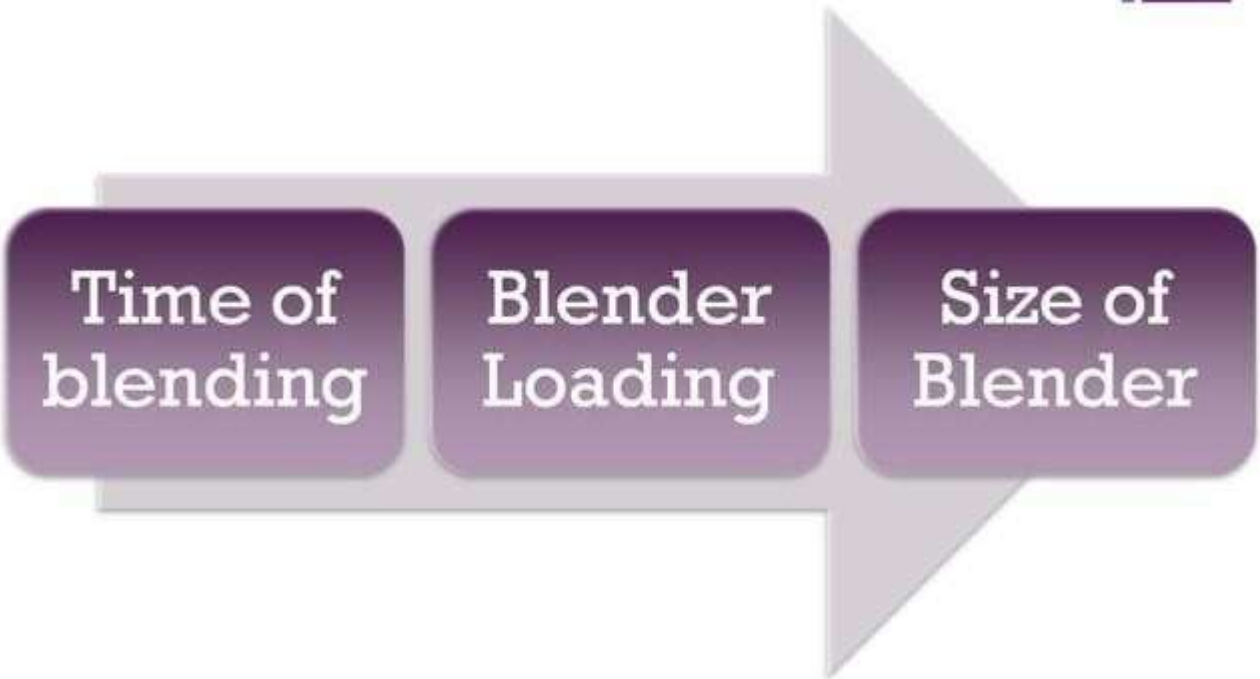
Dry Blending

- 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.

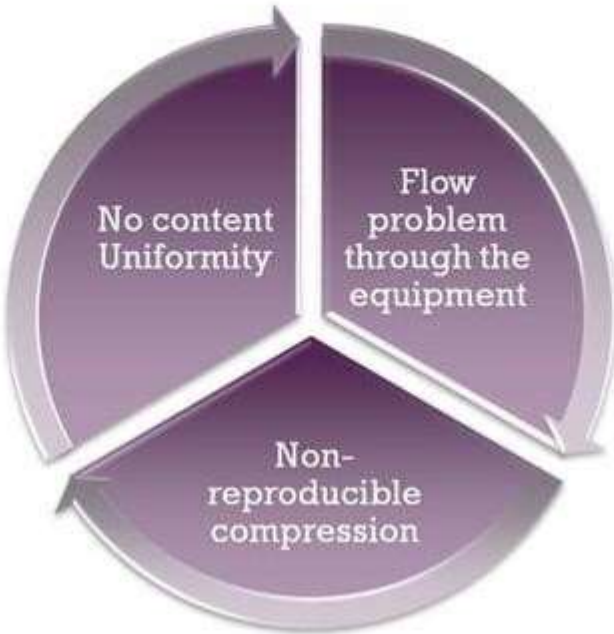
Dry Blending Continued

- Powders to be used for encapsulation are to be granulated and 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.

Scale Up Considerations



Problems Of Improper Blending



Equipment Used

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

Slant Cone Blender

Bin Blender

Double Cone Blender

Ribbon Blender

Granulation

- Granulation is defined as a "process whereby small particles are gathered into larger, permanent masses in which the original particles can still be identified"

The most common reasons to justify granulating are :

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

Scale Up Considerations

Two process are considered similar if they are Geometrically, Kinetically and Kinematically similar :

Two systems are called geometrically similar if they have same ratio of characteristic linear dimensions

Two geometrically similar systems are called kinetically similar if they have same ratio of velocities between corresponding system points

Two kinematically similar systems are dynamically similar when they have forces between corresponding points

Types of Granulation

- Wet methods which utilize some form of liquid to bind the primary particles.

Equipment Used :

1. Sigma blade mixer
2. Heavy duty planetary mixer

- Dry methods which do Granulation Minimizes the technical risks.

Equipment Used :

1. Roller Compaction mill
2. Shear mill

- Fluidized Granulation

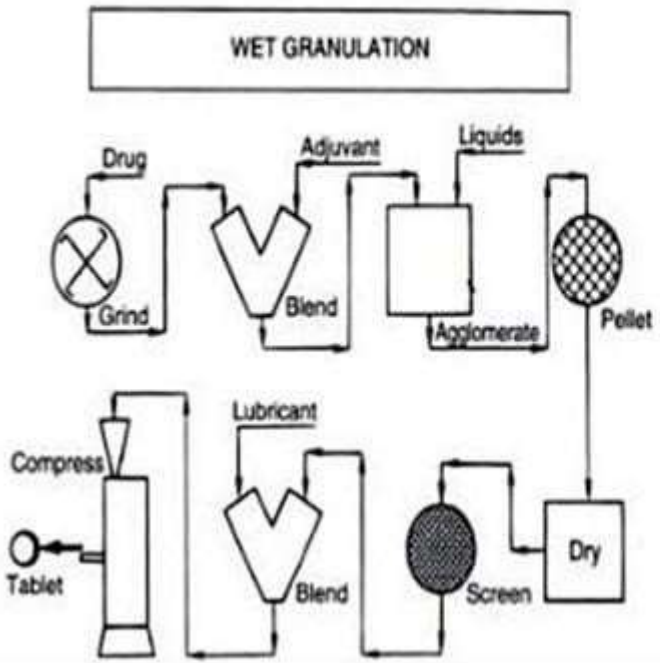
Wet Granulation

- It is employed low-shear mixers or the mixers/blenders normally used for dry blending such as ribbon mixers.
- There are a number of products currently manufactured using these low-shear granulators.
- Efficient and reproducible

Binders Used

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
- **New Natural and Synthetic binders**: Khaya gum, Leucaena leucocephala seed gum, Anacardium occidentale gum, Gellan gum, Combination of detarium gum and veegum.
- **New synthetic binders:** Maltrodextrins, Chitosan derivatives


WET GRANULATION
Drug
Adjuvant
Liquids
Grind
Blend
Agglomerate
Pellet
Lubricant
Compress
Tablet
Blend
Screen
Dry

" Multifunctional processors" are used 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.

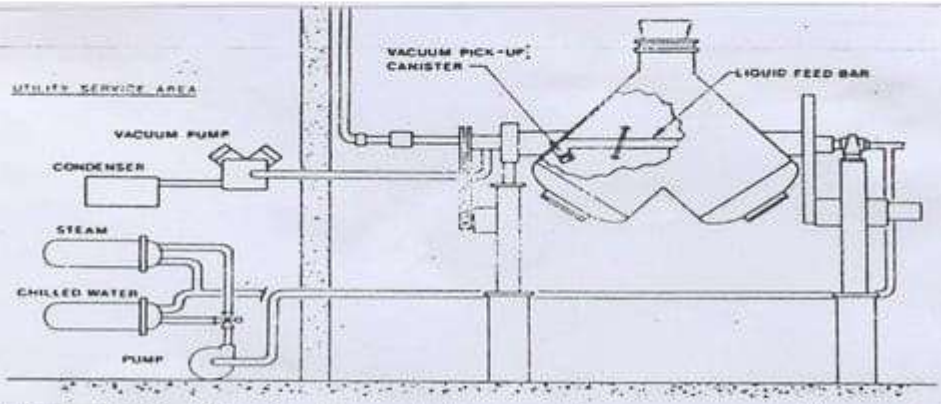
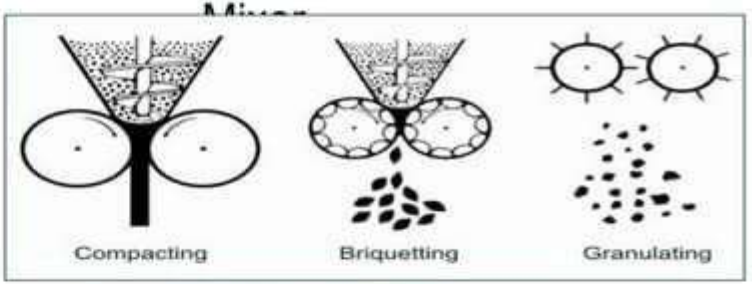


FIG. 23-7. *Schematic of a multifunction pharmaceutical processor. The system contains a solids mixing shell, which includes a liquid dispersion bar. This unit is jacketed to allow heating and cooling. Material can be dried within the unit by use of the vacuum canister and condenser. (Courtesy of Ortho Pharmaceutical Corporation.)*

Sigma Blade Mixer

Planetary Mixer



Roller Mill

Rotary Shear

Dry Method

- Dry compaction technique like roller compaction is commonly used in the Pharmaceutical industry. There are a number of drug substances which are moisture sensitive and cannot be directly compressed

Fluidized Bed Granulations

- Fluid Bed Granulation is a process by which granules are produced in single equipment by spraying a binder solution onto a fluidized powder bed. The material processed by fluid bed granulation are finer, free flowing and homogenous. 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.

FLUIDIZED BED GRANULATIONS

- Process Inlet Air Temperature
- Atomization Air Pressure
- Air Volume
- Liquid Spray Rate
- Nozzle Position and Number of Spray Heads
- Product and Exhaust Air Temperature
- Filter Porosity

Scale Up Considerations

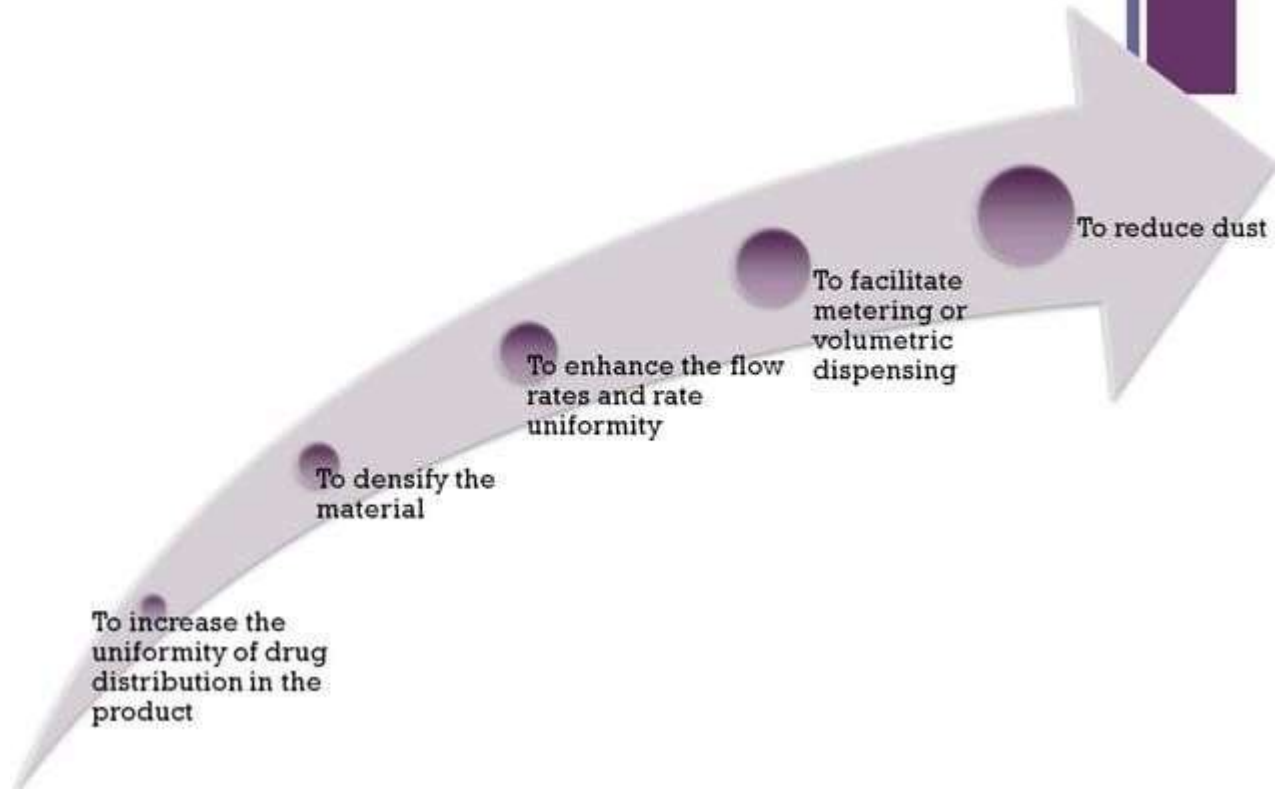
Process air temperature :

1.Selected to achieve desired product temperature.
2. Adjusted with process air volume

Process Air Volume :

1.Produces fluidization pattern.
2.Delivers heat to the product
3.Changes should be at the same time and magnitude (batch to batch)

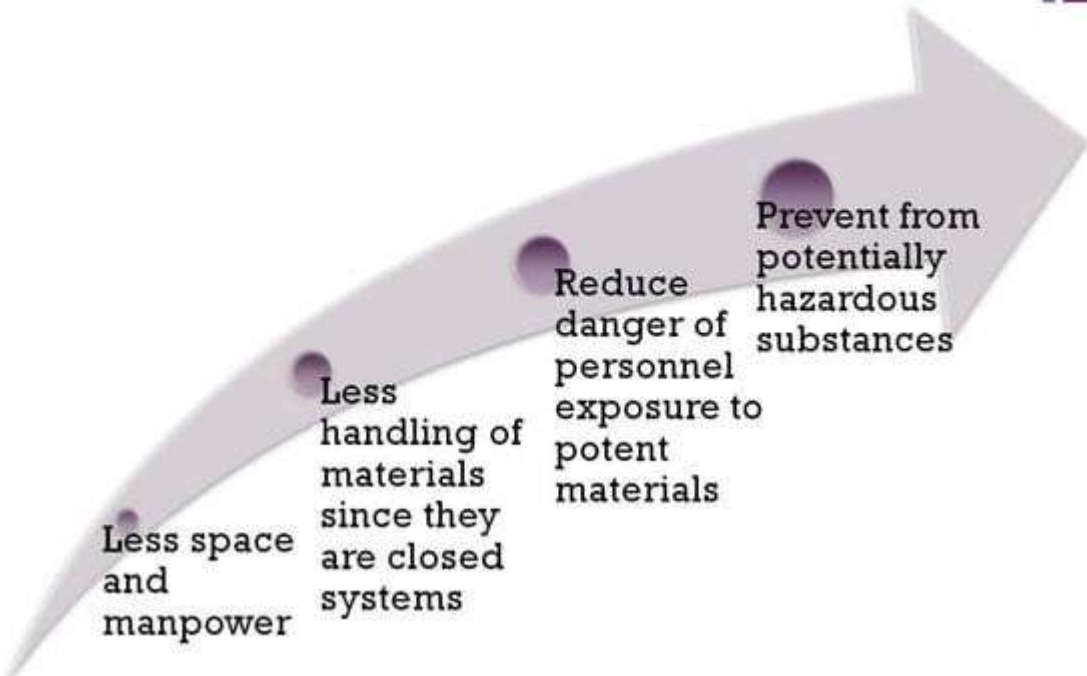
Applications of Granulation



Varying Drying Techniques for Granulation

Sr.No.	Granulation Technique	Drying Technique
1	Wet Granulation	a. Tray or Fluid Bed Dryer b. Vaccum /Gas c. Stripping/microwave d. Spray dryer e. Extrusion/ spheronization / pelletization
2.	Dry Granulation	a. Dry compaction

Advantages


Less space and manpower
Less handling of materials since they are closed systems
Reduce danger of personnel exposure to potent materials
Prevent from potentially hazardous substances

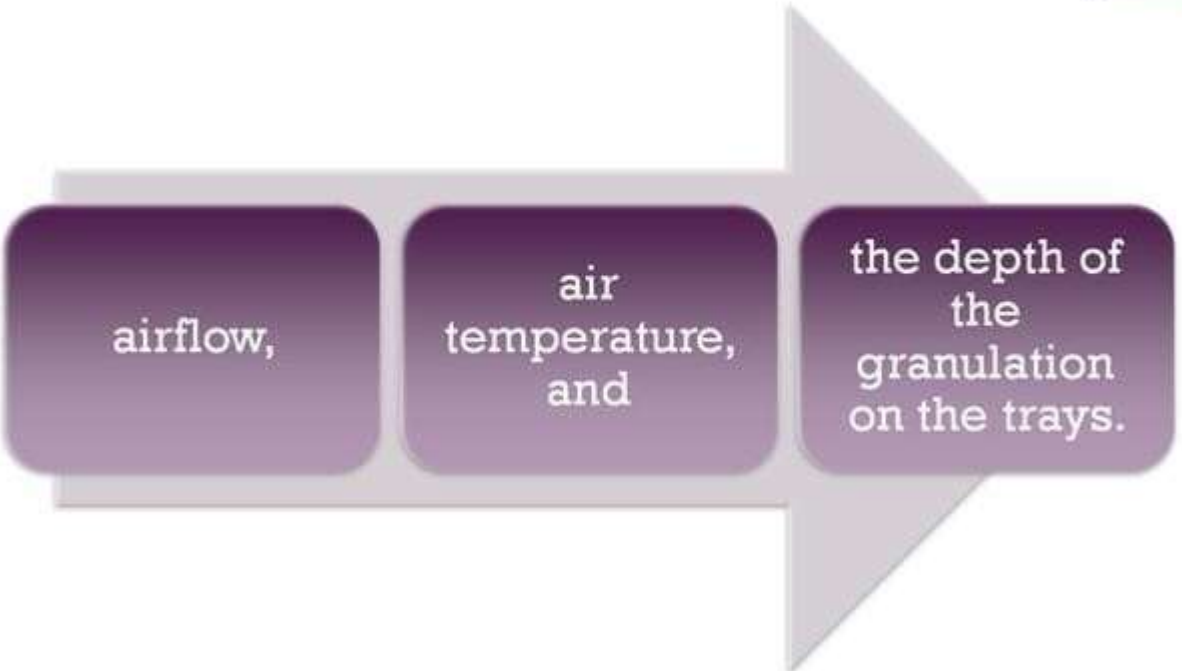
Drying

- 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.

Drying Continued

- 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.

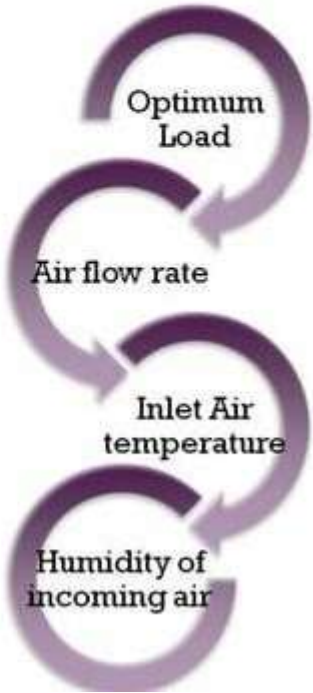
Scale Up Considerations



Tray dryer

- Air Flow
- Air Temperature
- Depth of Granulation Trays
- Monitoring drying process by use of moisture and temperature probes
- Drying times at specified temperatures and air flow rates for each product

Fluidized Bed Dryer



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.

Reduction of Particle Size Continued

- 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 glidents, 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, tend to agglomerate when added in large quantities to the granulation in a blender.

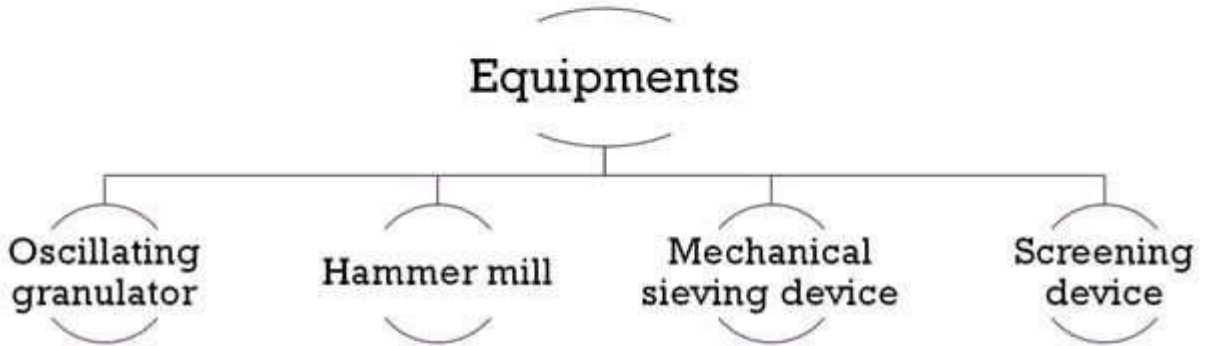
Problems Due to Improper Particle Size

Large particle size- Insufficient filling of die cavity- weight variation

For colored Granulation- coarser the granulation-mottling

Too many fines – Flowabiity problems – wt variation

Capping (occurs if speed of press is increased)


Equipments
Oscillating granulator
Hammer mill
Mechanical sieving device
Screening device

Hammer Mill

Mechanical Sieving

Oscillating
Granulator

Control Factors

Use Of Lubricants and Glidants

In Lab : Added to the final blend

Scale Up : Added to the dry granulation during size reduction

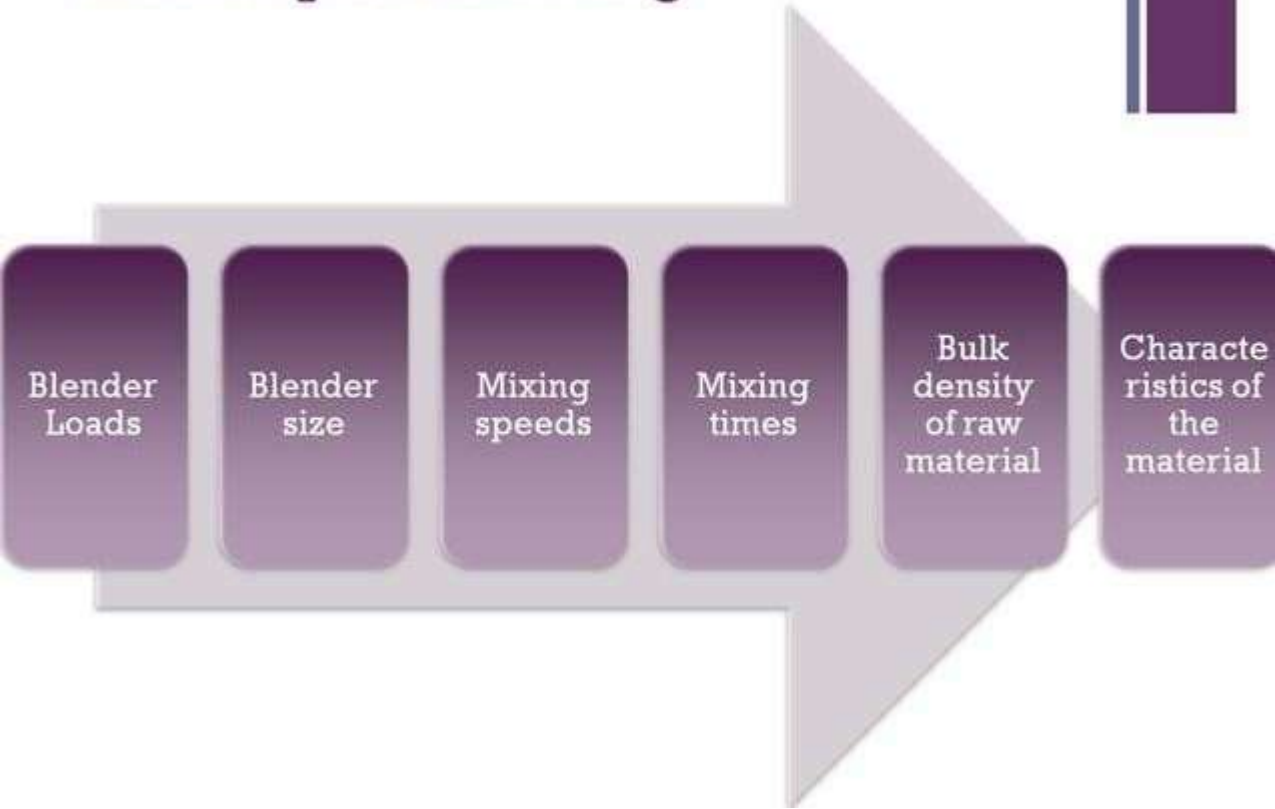
This is done because additives like magnesium stearate ,agglomerate when added in large quantities to the granulation in a blender

Over mixing or under mixing should be avoided

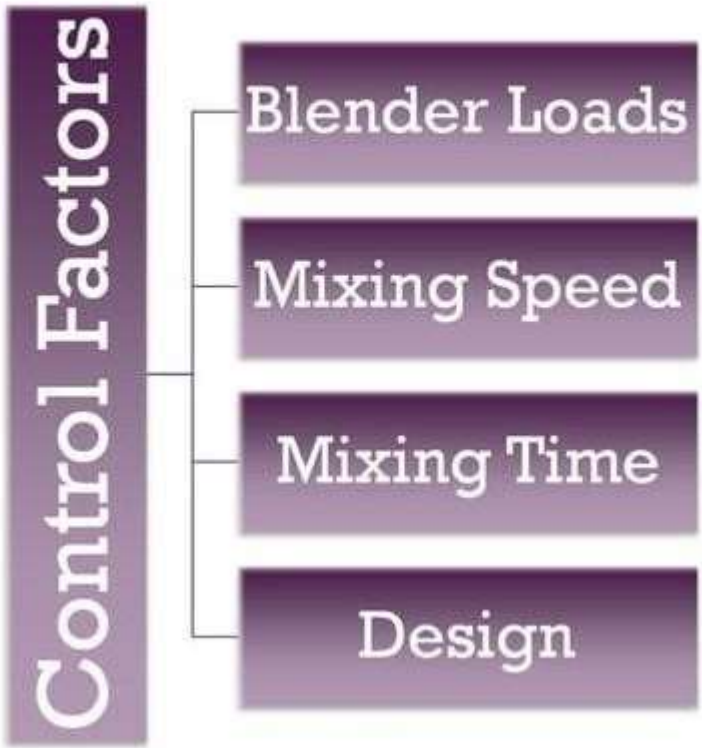
Blending

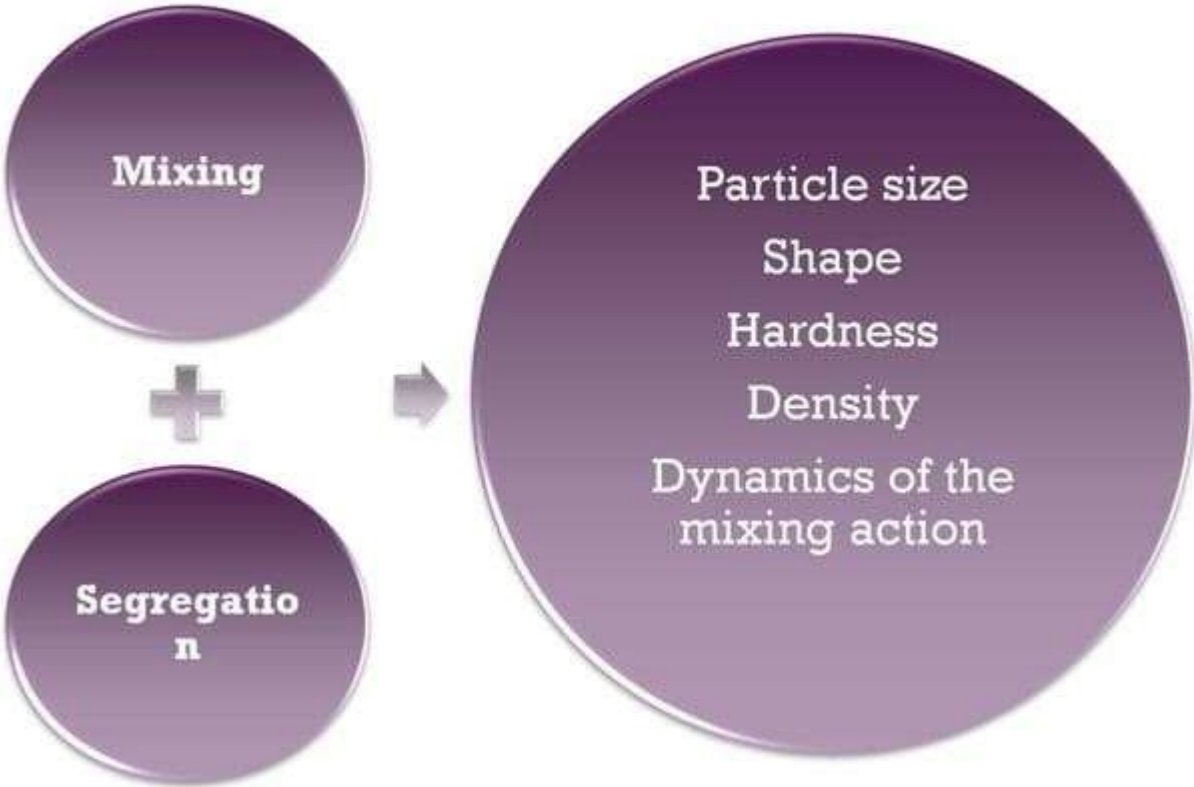
- Type of blending equipment often differs from that using in laboratory.
- In any blending operation, both segregation and mixing occur simultaneously are a function of particle size, shape, hardness, and density, and of the dynamics of the mixing action.
- Particle abrasion is more likely to occur 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.

Scale Up of Blending



Blending


Control Factors
Blender Loads
Mixing Speed
Mixing Time
Design


Mixing
Segregation
Particle size
Shape
Hardness
Density
Dynamics of the mixing action

Characteristics of the material

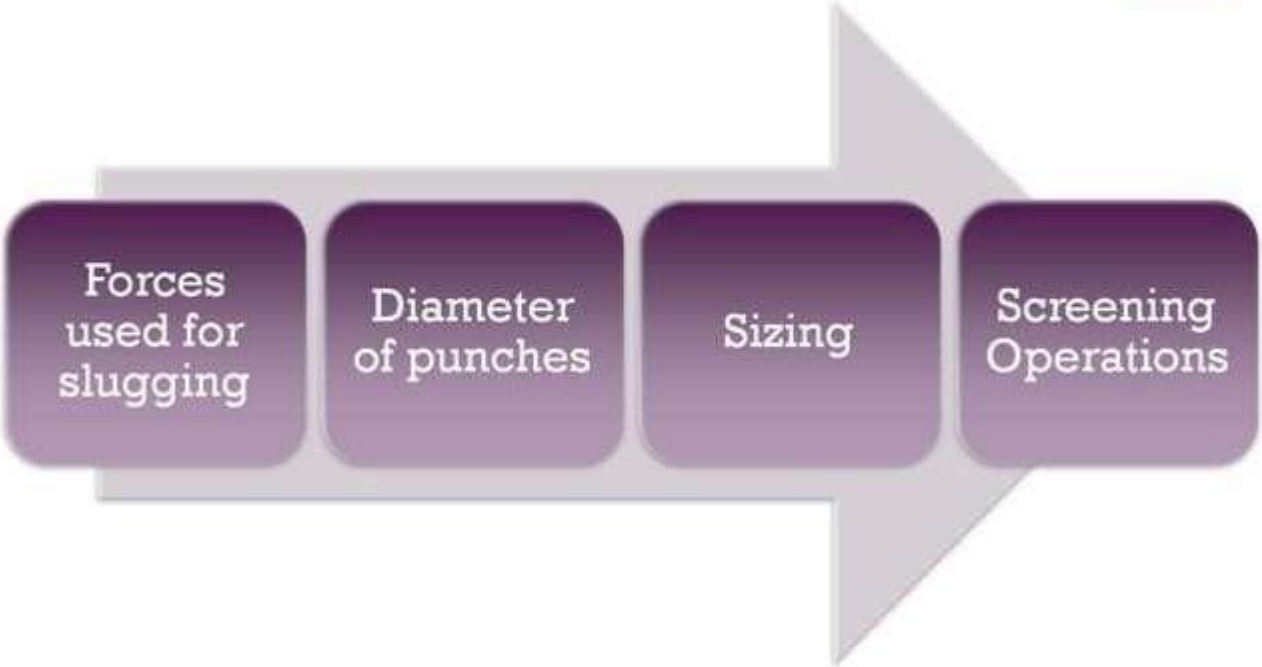
- Fragile particles or agglomerates: more readily abbraided → more fines → improper mixing → flow problems, fill problems, content uniformity problems.
- Particle abbraision is more when high-shear mixing with spiral screws or blades are used.
- Tumble blenders: for prolonged mixing
- Bulk density of raw materials considered in selection of the blender and determining optimum blender load.
- Excessive granulation: poor content uniformity, poor lubrication & improper color dispersion.

Specialized Granulation Techiques

Dry Granulation (or Slugging)

- A dry powder blend that cannot be directly compressed because of poor flow or compression 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 4 tons or less.
- Slugs range in diameter from 1 inch, for the more easily slugged material, to . 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.

Scale Up Considerations



Granulation Handling Feed System

- Handling of finished granulation
- Scale up studies determine effect of handling system on content uniformity and particle size distribution
- Segregation effects tablet weight , thickness and hardness
- Cleaning procedure should be well documented and validated

Direct 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.

Direct 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.

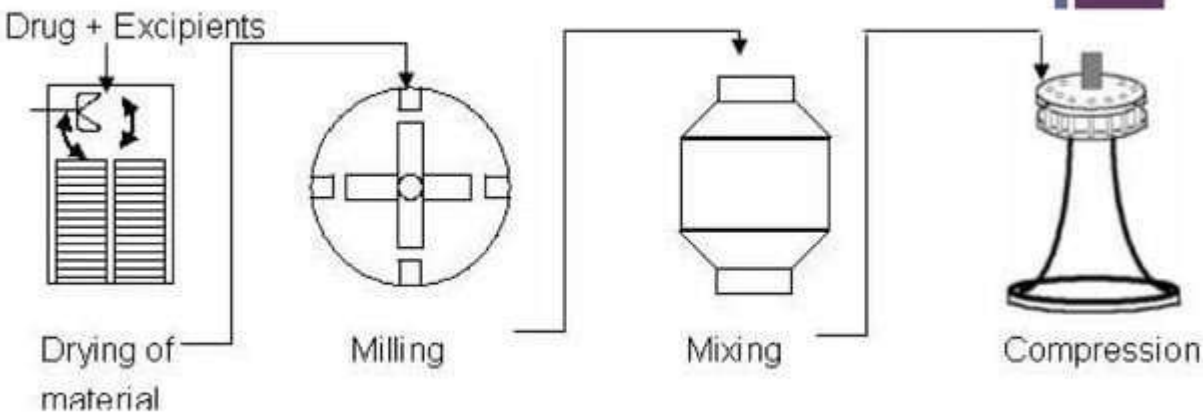
2. Pre compression of granulation (optional).

3. Compression of granules.

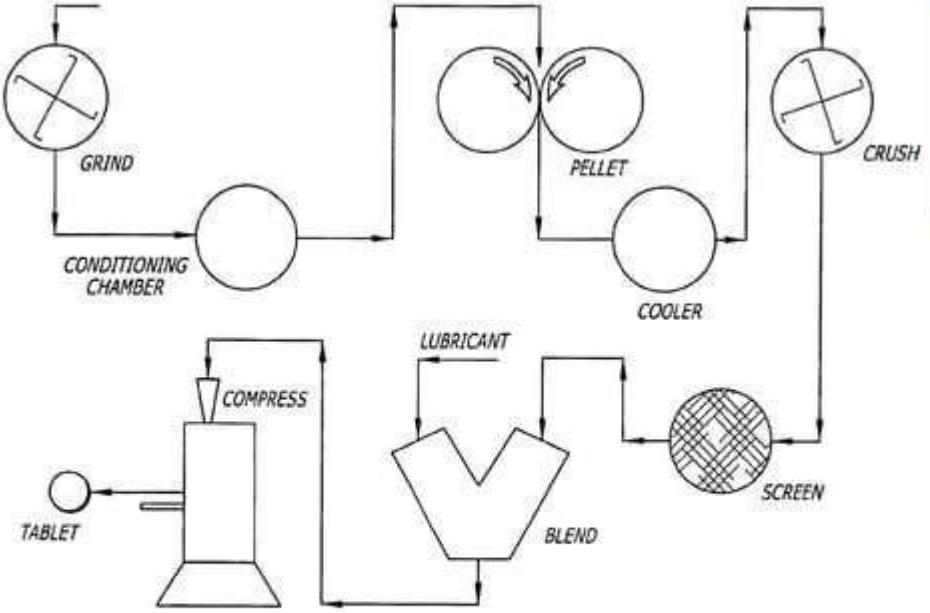
Ejection of the tablet from the die cavity and take - off of compressed tablet.

Scale Up Considerations

- Components of Blender
- Mixing speed
- Mixing Time
- Mixing Action
- Blender Load (overload retards free flow of granules and decreases efficiency of blender , if less load powder simply slides off without mixing)



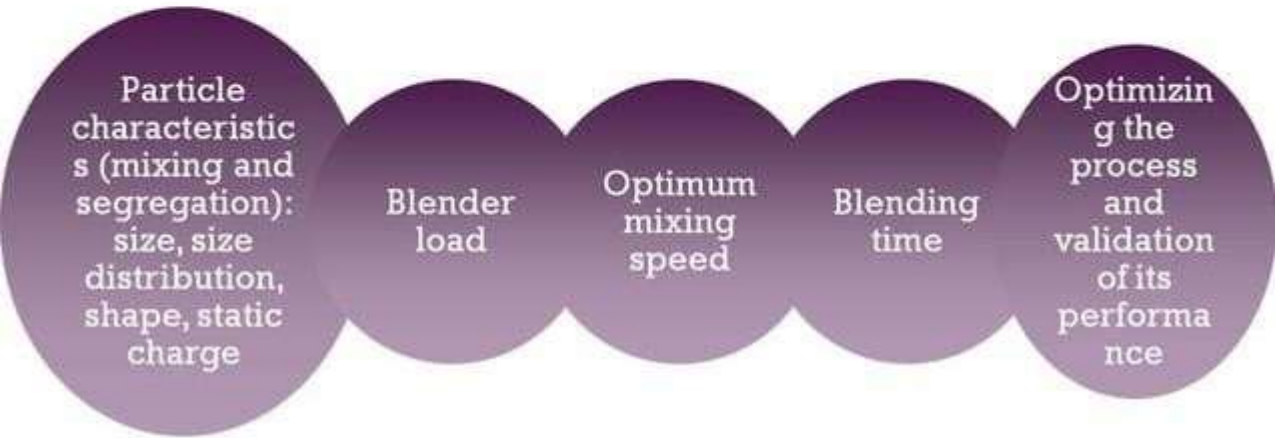
Manufacturing steps for direct compression



Stepwise process for direct compression

Manufacturing steps for Direct Compression

Control Factors :-



Aspects for Optimization

- Order of addition of components to the blender
- Mixing speed: can be varied with the original direction as necessary
- Mixing time: excessive mixing may fracture the fragile excipients and ruin their compressibility
- Use of auxiliary dispersion material within the mixer (chopper blade within a twin shell mixer):
- a) Increase efficiency

  b) Reduce agglomerates

Mixing action:

Determined by the mechanics of the mixer.

Changed by converting from one blender to the other or by modifying the blender through addition of baffles or plates, which would alter the mixing characteristics.

Blender load: affects efficiency

Overload: reduced free flow of granules and reduced efficiency

Localized concentration: content uniformity

Small load: sliding and rolling of powders in the blender, no proper mixing & increased time for mixing.

- Suitable for thermolabile and moisture sensitive API's
- Chances of batch-to-batch variation are negligible, because the unit operations required for manufacturing processes is fewer.
- Particle size uniformity

Demerits

Excipient Related

1. Problems in the uniform distribution of low dose drugs.
2. High dose drugs having high bulk volume, poor compressibility and poor flowability are not suitable for direct compression. For example, Aluminium Hydroxide, Magnesium Hydroxide
3. Direct compression diluents and binders must possess both good compressibility and good flowability.
4. Many active ingredients are not compressible either in crystalline or amorphous forms.
5. May lead to unblending because of difference in particle size or density of drug and excipients. Similarly the lack of moisture may give rise to static charges, which may lead to unblending.
6. Non-uniform distribution of colour, especially in tablets of deep colours.

Demerits

- Process Related

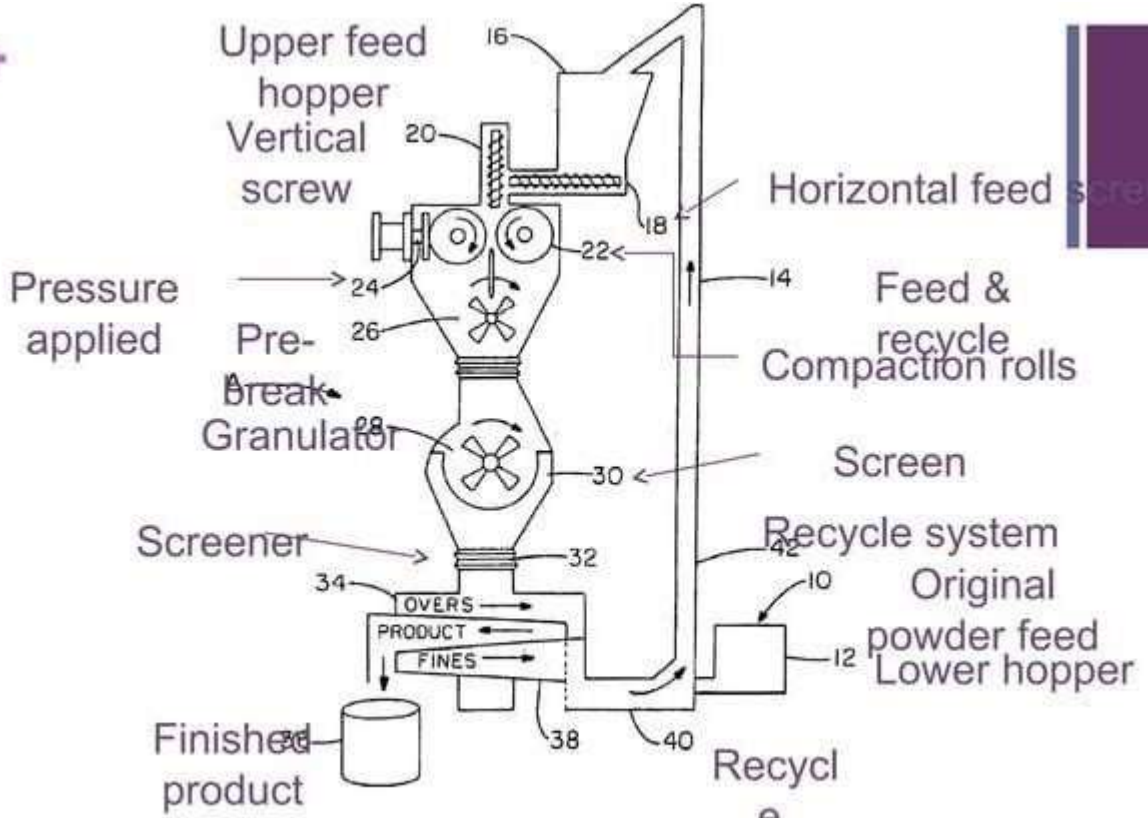
i) Capping, lamination, splitting, or layering of tablets related to air entrapment during direct compression. When air is trapped, the resulting tablets expand when the pressure of tablet is released, resulting in splits or layers in the tablet.

ii) In some cases require greater sophistication in blending and compression equipment.

iii) Expensive equipment

Slugging (Dry Granulation)

- For dry powder blend that cannot be directly compressed because of poor flow or compression properties.
- Done on a tablet press designed for slugging.
- Pressure of 15 tons; normal: 4 tons or less
- Speed is slow since poorly flowable powders require more time to be compressed.
- Diameter of slugs:
  - 1 inch for more easily slugged material
  - ¾ inch for materials difficult to compress



Schematic of slugging operation (lab)

- Materials of very low density require roller compaction to achieve a bulk density sufficient to allow encapsulation or compression. E.g.- densification of aluminium hydroxide

Granulation handling & Feed Systems

- Additional handling can affect content uniformity of the drug and the particle size distribution.
- Segregation due to static charges may lead to flow problems through tablet press hoppers and feed frames.
- This affects tablet weight, thickness and hardness. Finally poor content uniformity.
- More sophisticated equipment → cleaning problem.
- Equipment to be engineered for efficient and total cleaning.
- Well written, documented and validated cleaning procedures are essential for such systems.

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.

- Control factors while selecting the speed of the 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.

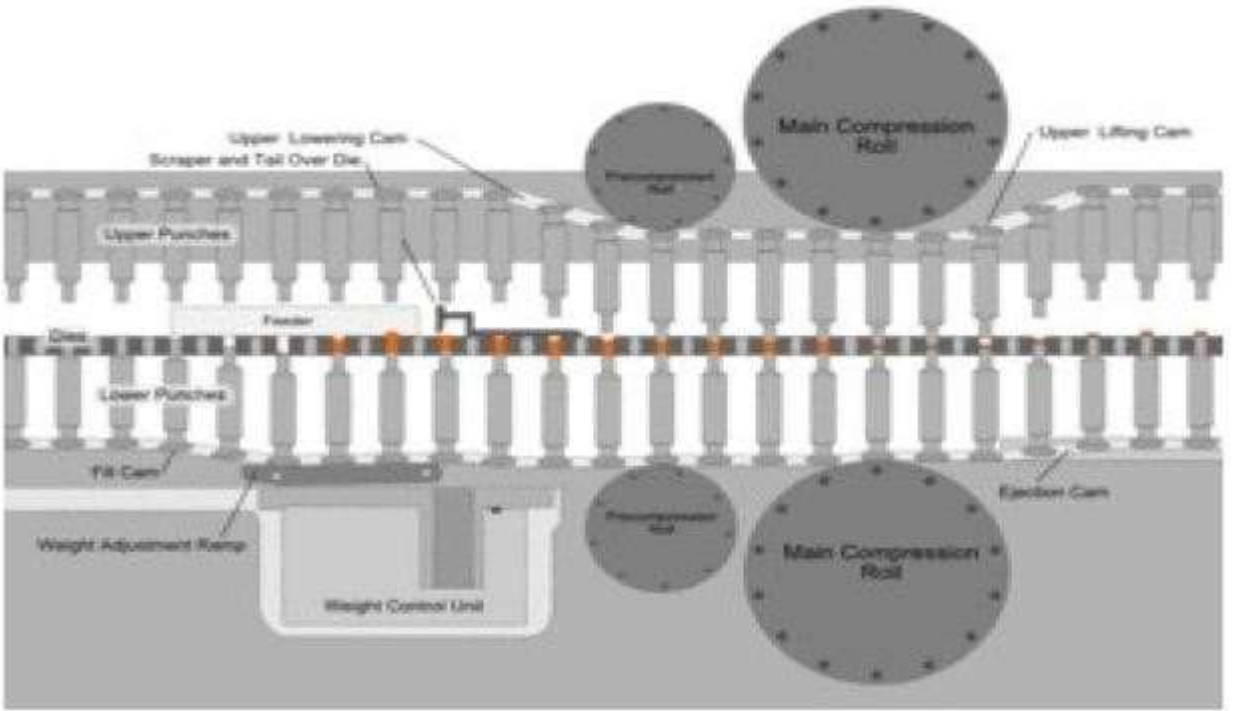
- The die feed system must be able to fill the die cavities adequately in the short period of time that the die is passing under the feed frame.

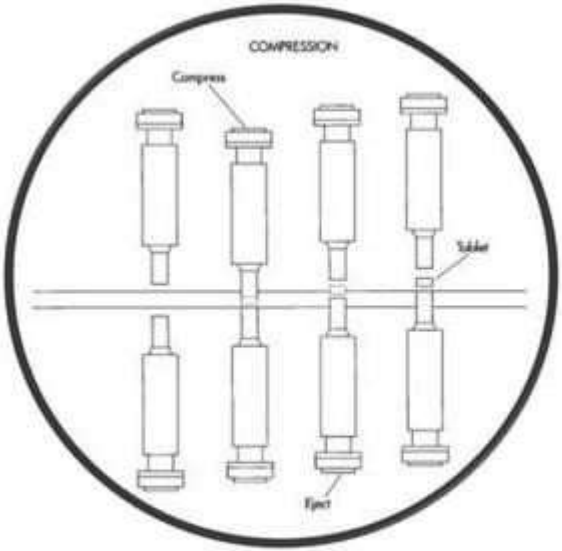
- The smaller the tablet , the more difficult it is to get a uniform fill at high press speeds.

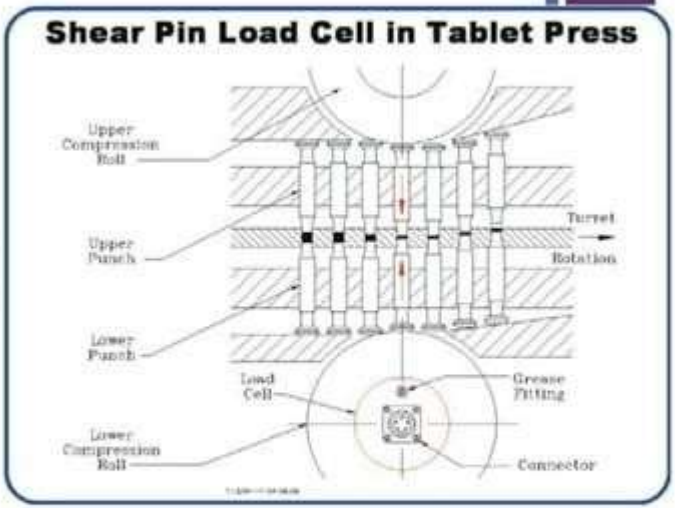
- Slowing down the press speed or using larger compression rollers can often reduce capping in a formulation.
- High level of lubricant or over blending can result in a soft tablet, decrease in wettability of the powder and an extension of the dissolution time.
- Binding to die walls can also be overcome 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.

Single Rotary Press

Double Rotary Press

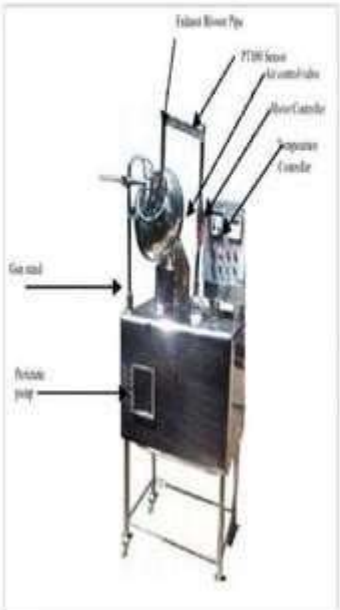

Upper Lowering Cam
Scraper and Tail Over Die
Main Compression Roll
Upper Lifting Cam
Upper Punches
Feeder
Dies
Lower Punches
Fill Cam
Ejection Cam
Weight Adjustment Ramp
Weight Control Unit
Main Compression Roll


COMPRESSION
Compress
Tablet
Eject


Shear Pin Load Cell in Tablet Press
Upper Compression Roll
Upper Punch
Lower Punch
Load Cell
Lower Compression Roll
Turret
Rotation
Grease Fitting
Connector

Different types of punches

Tablet Coating

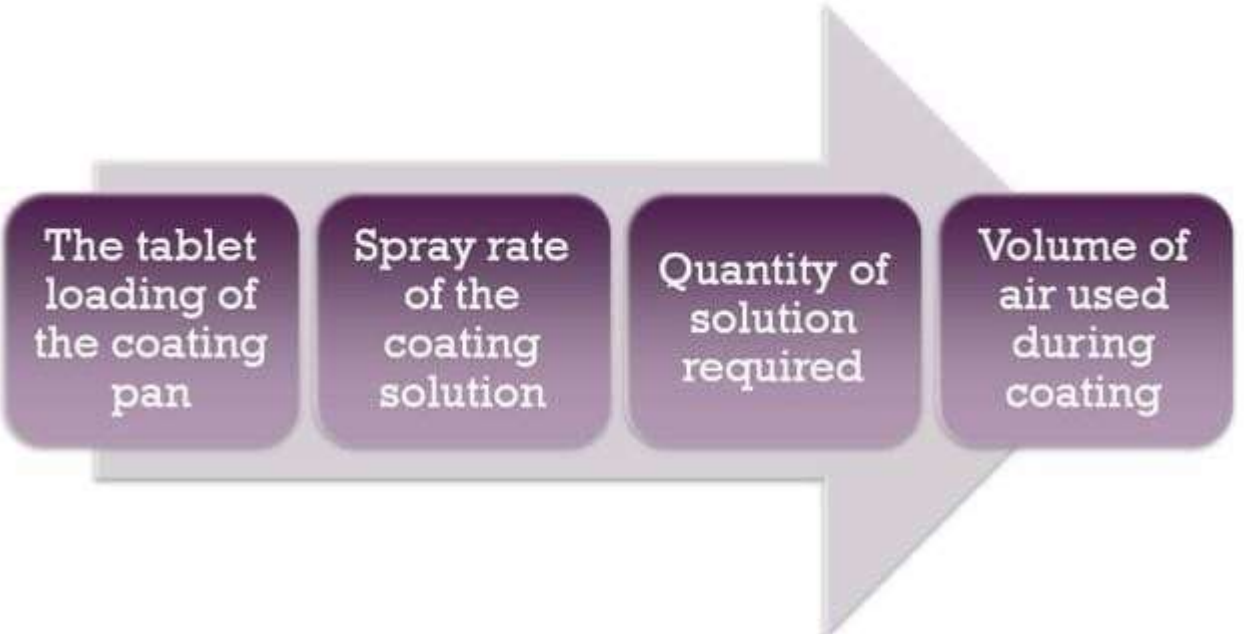


- Tablet coating, which at one time consisted of sugar coating in conventional coating pans, has undergone many changes because of new developments in coating technology and changes in safety and environmental regulations.

There are mainly 3 important techniques involved in coating . They are :

- Sugar Coating
- Film Coating
- Enteric Coating

Scale Up Considerations



Equipments Used

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

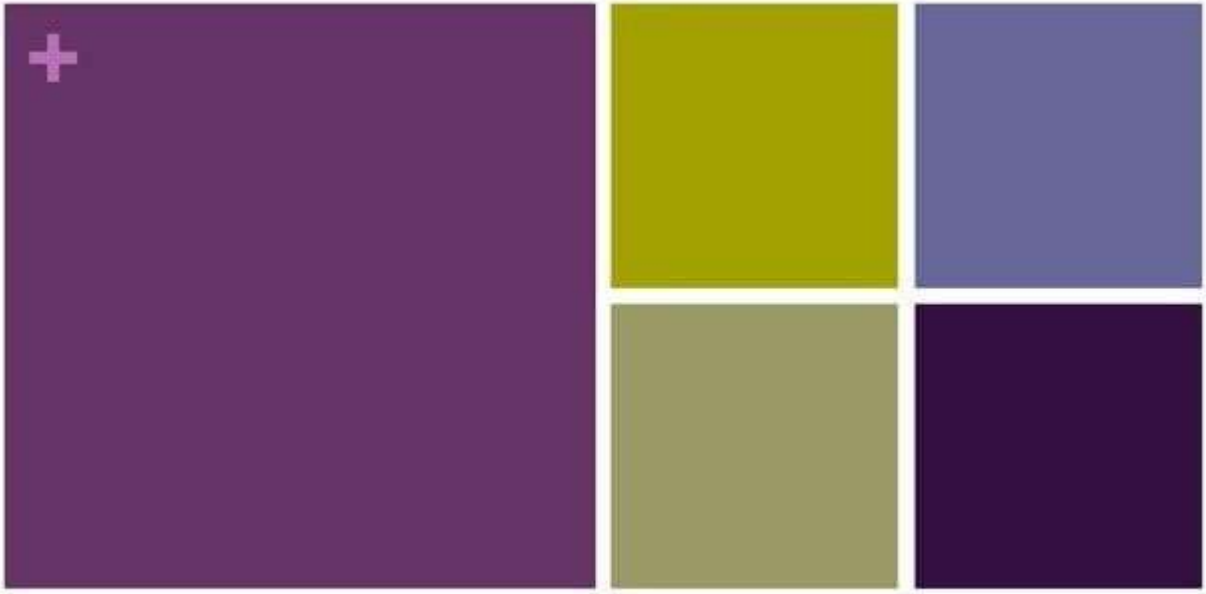
Coating Pans

Accela Coata

Dria Coater

Fluidized Bed Coating


on of the Tableting
as well as wet
Luminarc



Scale up of liquid orals

Liquid orals

- The physical form of a drug product that is pourable displays Newtonian or pseudo plastic 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.

Steps of liquid manufacturing process

- Planning of material requirements:
- Liquid preparation:
- Filling and Packing:
- 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.

Formulation aspects of oral liquids

Suspensions:

Purpose	Agent
Facilitating the connection between API and vehicle	-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

Formulation aspects of oral liquids

Emulsions:

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

Formulation aspects of oral liquids

Solutions:

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

Layout of the pilot plant

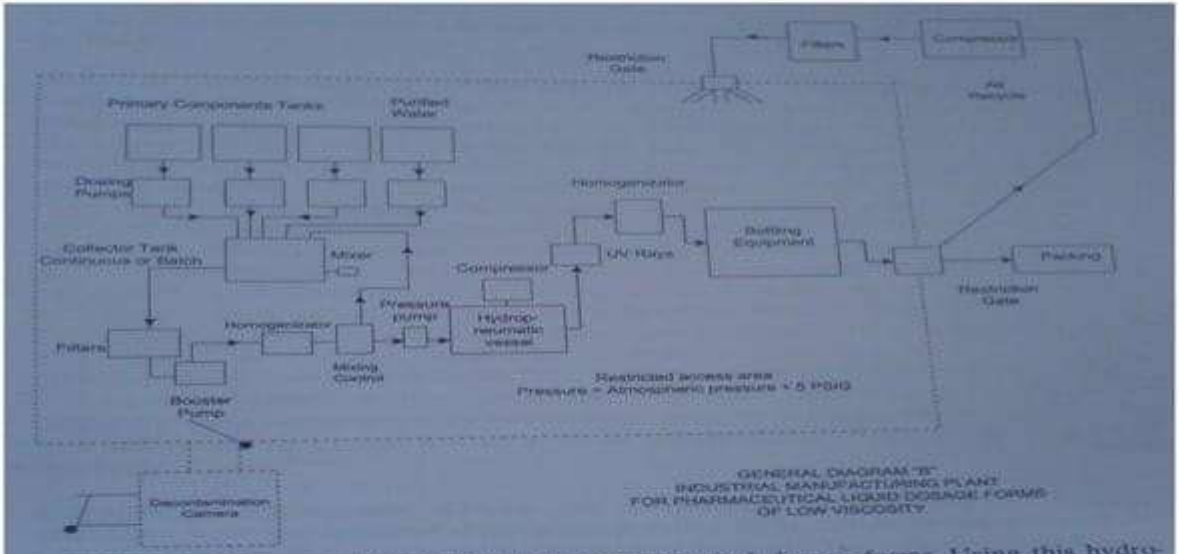
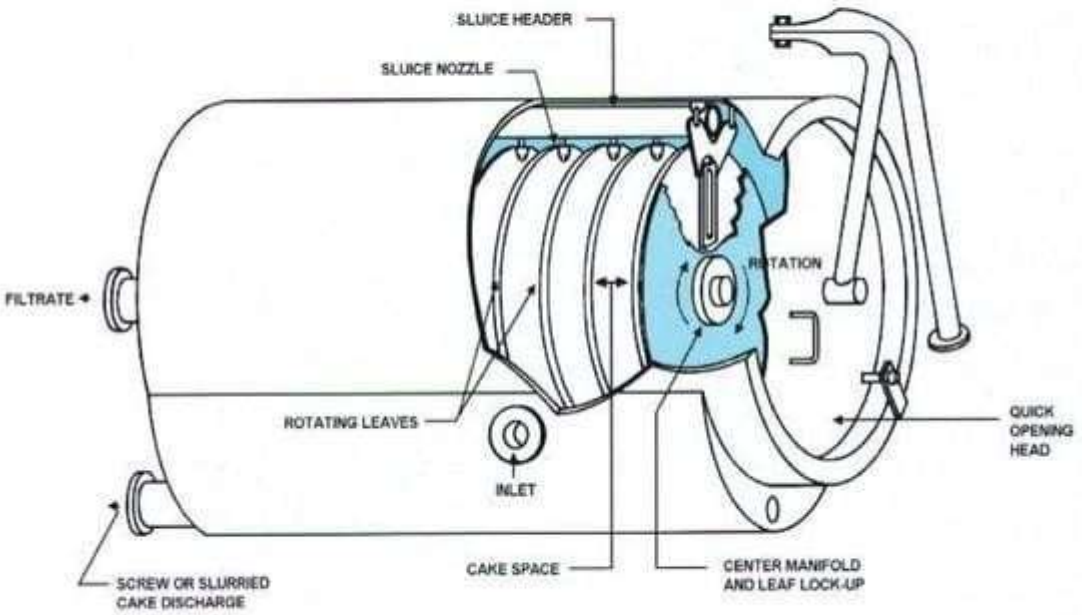


FIGURE 2 Mixing and filling lines for pharmaceutical dosage forms. Using this hydropneumatic system, instead of the mechanical system in Figure 1, the liquid moves by the pressure generated in a compressed air tank.

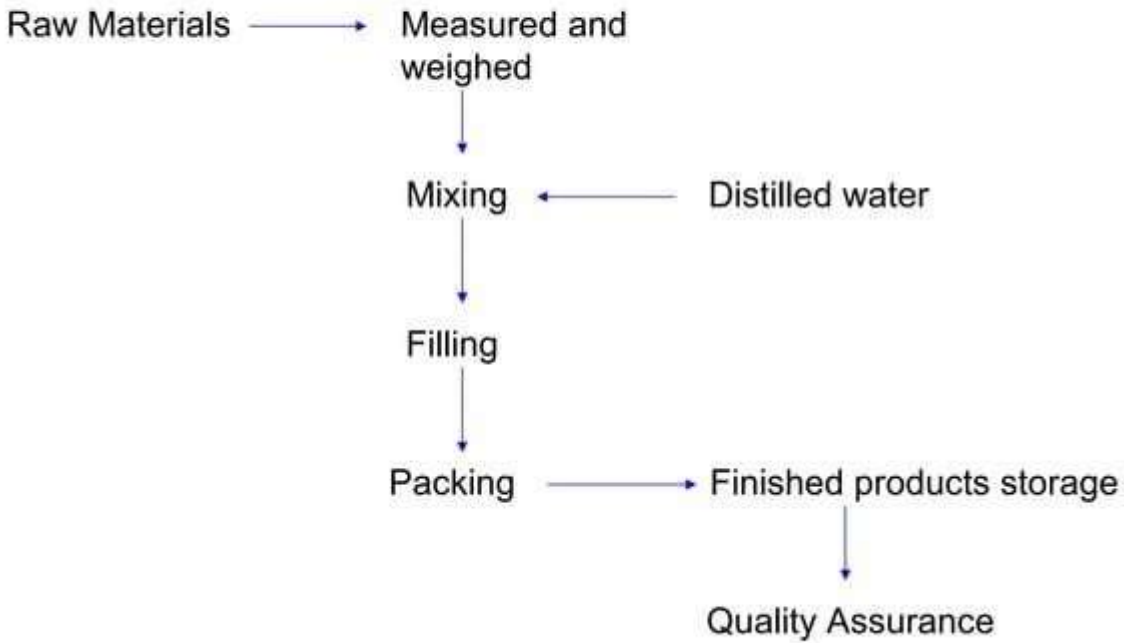
Equipments

- Mixer
- Homogenizer
- Filteration assembly
- Bottling assembly

Filtration assembly



General flow chart



Quality assurance

- Dissolution of drugs in solution
- Potency of drugs in suspension
- Temperature uniformity in emulsions
- Microbiological control
- Product uniformity
- Final volume
- Stability

Scale-up of semisolid dosage forms

Semisolid dosage forms

- In general, semisolid dosage forms are complex formulations having complex structural elements.
- Often they are composed of two phases (oil and water), one of which is a continuous (external) phase, and the other of which is a dispersed (internal) phase.
- The active ingredient is often dissolved in one phase, although occasionally the drug is not fully soluble in the system and is dispersed in one or both phases, thus creating a three-phase system.

Semisolid dosage forms

- The physical properties of the dosage form depend upon various factors, including the size of the dispersed particles, the interfacial tension between the phases, the partition coefficient of the active ingredient between the phases, and the product rheology.

- These factors combine to determine the release characteristics of the drug, as well as other characteristics, such as viscosity.

SUPPOSITORIES

- The manufacturing of suppositories on a laboratory scale usually involves,
  - * 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 moulds & large size Pan for melting of drug & base.

parameters

- For a true solution, the order in which solutes are added to the solvent is usually unimportant.
- The same cannot be said for dispersed formulations, however, because dispersed matter can distribute differently depending on to which phase a particulate substance is added.
- In a typical manufacturing process, the critical points are generally the initial separation of a one-phase system into two phases and the point at which the active ingredient is added.

parameters

- Because the solubility of each added ingredient is important for determining whether a mixture is visually a single homogeneous phase, such data, possibly supported by optical microscopy, should usually be available for review.

- This is particularly important for solutes added to the formulation at a concentration near or exceeding that of their solubility at any temperature to which the product may be exposed.

parameters

- Variations in the manufacturing procedure that occur after either of these events are likely to be critical to the characteristics of the finished product.

- This is especially true of any process intended to increase the degree of dispersion through reducing droplet or particle size (e.g., homogenization).

- Aging of the finished bulk formulation prior to packaging is critical and should be specifically addressed in process validation studies.

General stability consideration

- The effect that SUPAC changes may have on the stability of the drug product should be evaluated. For general guidance on conducting stability studies, see the FDA *Guideline for Submitting Documentation for the Stability of Human Drugs and Biologics.*

General stability consideration

- For SUPAC submissions, the following points should also be considered:

1. In most cases, except those involving scale-up, stability data from pilot scale batches will be acceptable to support the proposed change.

2. Where stability data show a trend towards potency loss or degradant increase under accelerated conditions, it is recommended that historical accelerated stability data from a representative prechange batch be submitted for comparison.

General stability consideration

- It is also recommended that under these circumstances, all available long-term data on test batches from ongoing studies be provided in the supplement.

- Submission of historical accelerated and available long-term data would facilitate review and approval of the supplement.

General stability consideration

3. A commitment should be included to conduct long-term stability studies through the expiration dating period, according to the approved protocol, on either the first or first three (see section III-VI for details) production batches, and to report the results in subsequent annual reports.

The Role of In Vitro Release Testing

- The key parameter for any drug product is its efficacy as demonstrated in controlled clinical trials.
- The time and expense associated with such trials make them unsuitable as routine quality control methods.
- Therefore, in vitro surrogate tests are often used to assure that product quality and performance are maintained over time and in the presence of change.

The Role of In Vitro Release Testing

- A variety of physical and chemical tests commonly performed on semisolid products and their components (e.g., solubility, particle size and crystalline form of the active component, viscosity, and homogeneity of the product) have historically provided reasonable evidence of consistent performance.

- More recently, in vitro release testing has shown promise as a means to comprehensively assure consistent delivery of the active component(s) from semisolid products.

The Role of In Vitro Release Testing

- An in vitro release rate can reflect the combined effect of several physical and chemical parameters, including solubility and particle size of the active ingredient and rheological properties of the dosage form. In most cases, in vitro release rate is a useful test to assess product sameness between prechange and postchange products.

The Role of In Vitro Release Testing

- However, there may be instances where it is not suitable for this purpose. In such cases, other physical and chemical tests to be used as measures of sameness should be proposed and discussed with the Agency.

- With any test, the metrics and statistical approaches to documentation of "sameness" in quality attributes should be considered

The Role of In Vitro Release Testing

- The evidence available at this time for the in vitro-in vivo correlation of release tests for semisolid dosage forms is not as convincing as that for in vitro dissolution as a surrogate for in vivo bioavailability of solid oral dosage forms.

- Therefore, the Center's current position concerning in vitro release testing is as follows:

The Role of In Vitro Release Testing

1. In vitro release testing is a useful test to assess product "sameness" under certain scale-up and postapproval changes for semisolid products.

2. The development and validation of an in vitro release test are not required for approval of an NDA, ANDA or AADA nor is the in vitro release test required as a routine batch-to-batch quality control test.

The Role of In Vitro Release Testing

3. In vitro release testing, alone, is not a surrogate test for in vivo bioavailability or bioequivalence.

4. The in vitro release rate should not be used for comparing different formulations across manufacturers.

Contract manufacturing

Definition of contract manufacturing

- Production of goods by one firm, under the label or brand of another firm. Contract manufacturers provide such service to several (even competing) firms based on their own or the customers' designs, formulas, and/or specifications. Also called private label manufacturing.

Contract manufacturing

- Contract manufacturing is a process that established a working agreement between two companies.
- As part of the agreement, one company will custom produce parts or other materials on behalf of their client.
- In most cases, the manufacturer will also handle the ordering and shipment processes for the client.
- As a result, the client does not have to maintain manufacturing facilities, purchase raw materials, or hire labour in order to produce the finished goods.

Contract manufacturing.

- The basic working model used by contract manufacturers translates well into many different industries.

- Since the process is essentially outsourcing production to a partner who will privately brand the end product, there are a number of different business ventures that can make use of a contract manufacturing arrangement.

- There are a number of examples of pharmaceutical contract manufacturing currently functioning today, as well as similar arrangements in food manufacturing, the creation of computer components and other forms of electronic contract manufacturing.

Contract manufacturing

- Even industries like personal care and hygiene products, automotive parts, and medical supplies are often created under the terms of a contract manufacture agreement.

- In order to secure contract manufacturing jobs, the contract manufacturer usually initiates discussions with the potential client.

- The task is to convince the prospective customer that the manufacturer can use their facilities to produce quality goods that will meet or exceed the expectations of the customer.

Contract manufacturing

- At the same time, the manufacturer will demonstrate how the overall unit cost of production to the customer will be less than any current production strategies in use, thus increasing the amount of profit that will be earned from each unit sold

- There are several advantages to a contract manufacturing arrangement.

- For the manufacturer, there is the guarantee of steady work.

- Having contracts in place that commit to certain levels of production for one, two and even five year periods makes it much easier to forecast the future financial stability of the company.

Contract manufacturing

- For the client, there is no need to purchase or rent production facilities, buy equipment, purchase raw materials, or hire and train employees to produce the goods.

- There are also no headaches from dealing with employees who fail to report to work, equipment that breaks down, or any of the other minor details that any manufacturing company must face daily.

Contract manufacturing

- All the client has to do is generate sales, forward orders to the manufacturer, and keep accurate records of all income and expenses associated with the business venture.

- The general concept of contract manufacturing is not limited to the production of goods. Services such as telecommunications, Internet access, and cellular services can also be supplied by a central vendor and private branded for other customers who wish to sell those services.

- Doing so allows the customer to establish a buy rate from the vendor, then resell the services at a profit to their own client base

Scopes of contract manufacturing

- The scope of the *Contract Manufacturing Procurement* business scenario outlined in this documentation only concerns the customer side (OED -The Office of Enterprise Development).

- This business scenario does not cover how an ERP (Enterprise Relationship Management) system on the supplier's side (that is, the contract manufacturer's side) receives messages sent by the customer, and how it deals with the additional information (for example, components) submitted with these messages.

Scopes of contract manufacturing

- Mappings are only provided for A2A communication (between the OED's ERP system and SAP* SNC*) from IDoc to XML and vice versa.

- This business scenario does not cover the tracking of the manufacturing process (production phases) that takes place at the contract manufacturer's site - it does not take into account the current production phase at the contract manufacturer' site.

- Consequently, the OED planner cannot predict the supply situation of finished goods.

* SAP- Supply Network Planning
* SNC- Supply Network Collaboration

Limits of contract manufacturing

- The *Contract Manufacturing Procurement* business scenario has the following limitations:
  - Once a schedule line in the ERP purchase order is changed, the date and quantity data originally requested are lost. Even if the information is stored in SAP SNC, it is not possible to send this information to the CM.
  - The Contract Manufacturing Procurement business scenario is based on functions introduced in SAP ERP 6.0. For lower releases, you need to develop a customer modification.

Limits of contract manufacturing

- No data import control functions are provided for messages sent from the CM to SAP SNC.
- The bill of material (BOM) is not available in SAP SNC.
- New purchase order items cannot be created in SAP SNC.
- Product substitution is not supported.
- Scheduling agreements for the subcontracted material are not allowed.

Limits of contract manufacturing

- A supplier should be able to update the component consumption in SAP SNC until a good receipt has been posted in the customer ERP back-end system.

- The subcontracting scenario of the Rosetta Network Order Management Program as described in the PIPs* 7B5 (Notify of Manufacturing Work Order), 7B6 (Notify of Manufacturing Work Order Reply), and 7B1 (Work In Process Notification) is not included in the scope of SAP SCM*.

* PIP- Partner Interface Process

* SCM- Supply Chain Management

Reference

- The theory & practice of industrial pharmacy by Leon Lachman, Herbert A. Lieberman, Joseph L. kenig, 3rd edition, published by Varghese Publishing house.

- Lachman L. The Theory and practice of industrial pharmacy. 3rd Edition. Varghese publication house.

- www.google.com

Thank You