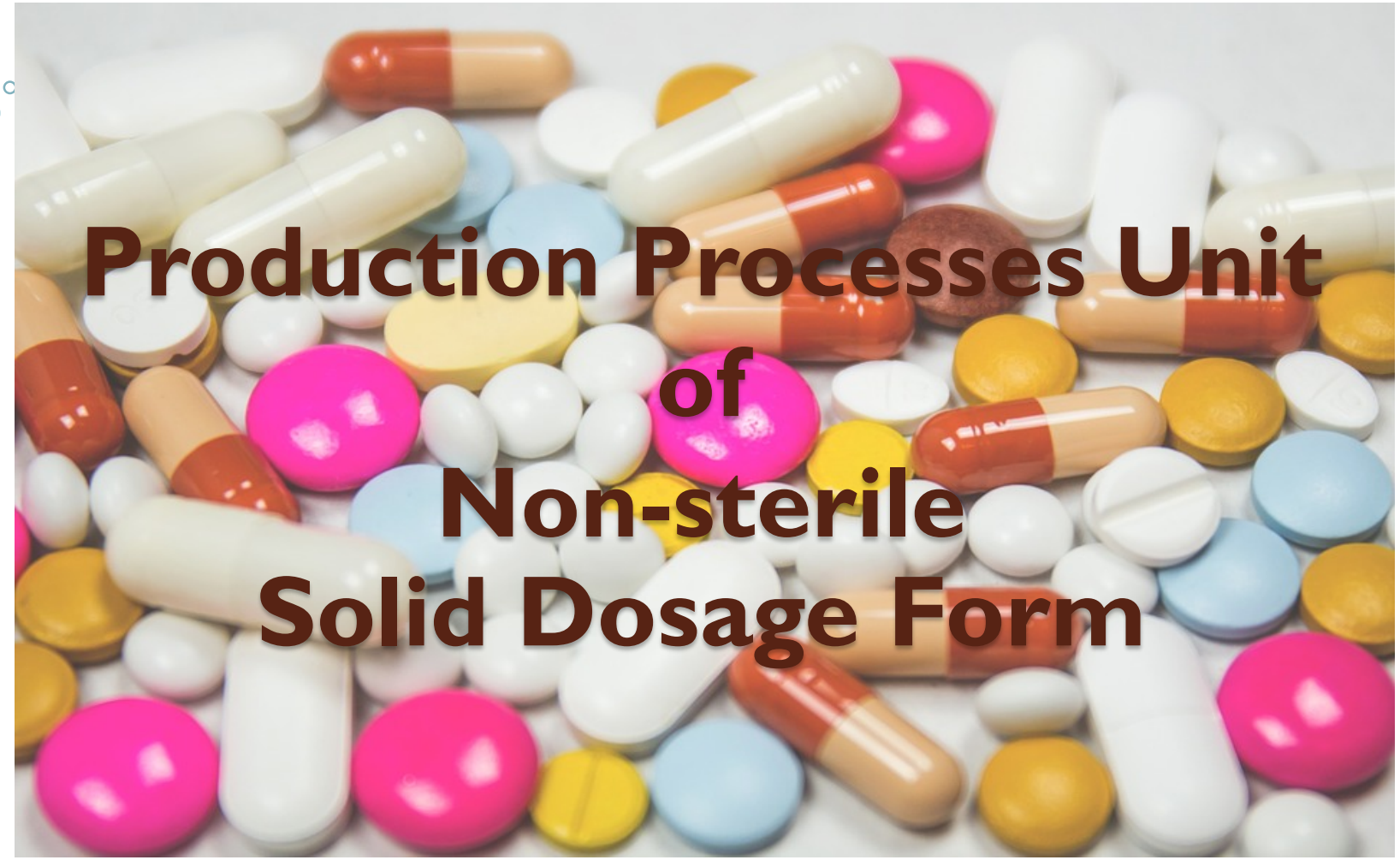

Production Processes Unit of Non-sterile Solid Dosage Form

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Physical dosage form classification

- Liquid dosage form
  - Clear liquid
  - Suspension
  - Emulsion
- Semi-solid dosage form
  - Cream
  - Ointment
  - Gel
- Solid dosage form
  - Powder
  - Tablet
  - Capsule

Production Processes Unit

- Particle Size Reduction
- Weighing
- Granulation
  - Wet Granulation
  - Dry Granulation
- Tablet Compression
- Coating
  - Sugar coating
  - Film coating
  - Microencapsulation
- Capsule filling
  - Hard capsule filling
  - Soft gelatin filling
- Printing
- Packaging

Production Processes

Process unit	Powder	Plain tablet	Coated tablet	Capsule
Raw materials				
Particle size reduction				
Weighing				
Granulation				
Mixing				
Compression				
Coating				
Capsule filling				
Printing				
Packaging				

Particle Size Reduction

Molee Sontichai

Particle Size Reduction in Production Processes

- Raw materials
- Wet granulation process
- Dry granulation process
- Coating process

Particle Size Reduction

- Advantage
  - Content uniformity
  - Improve flowability
  - Effective drying
  - Improve dissolution rate
  - Improve absorption rate
- Disadvantage
  - Drug degradation
  - Decrease stability
  - Contamination

Factors affecting particle size reduction

- Hardness of materials
- Surface of materials
- Abrasiveness
- Softening temperature
- Moisture content
- Stickiness
- Explosive substance

Principle of Size Reduction

- Compression
- Impaction
- Attribution and rubbing
- Cutting and chopping

Equipments use in size reduction

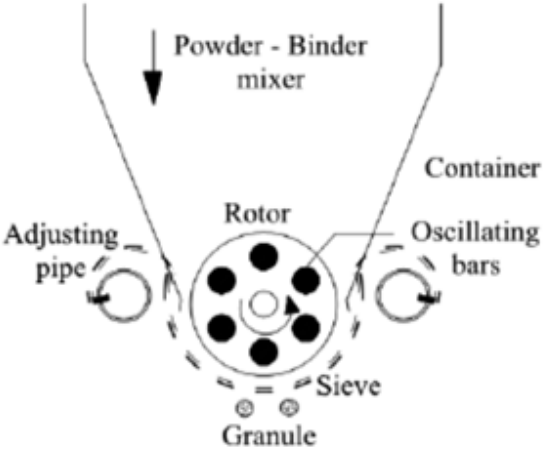
- **Mortar and Pestle**
  - Classical and simplest equipment.
  - It's work on application of attrition and pressure

Mortar and pestle

รางและล้อบดยา

Equipments use in size reduction

- **Oscillating mill**
  - Can use for both wet and dry materials.
  - Particle size 250 μm – 5 mm



(A Review on Techniques for Sago Pearl Granulation and Sizing Process)

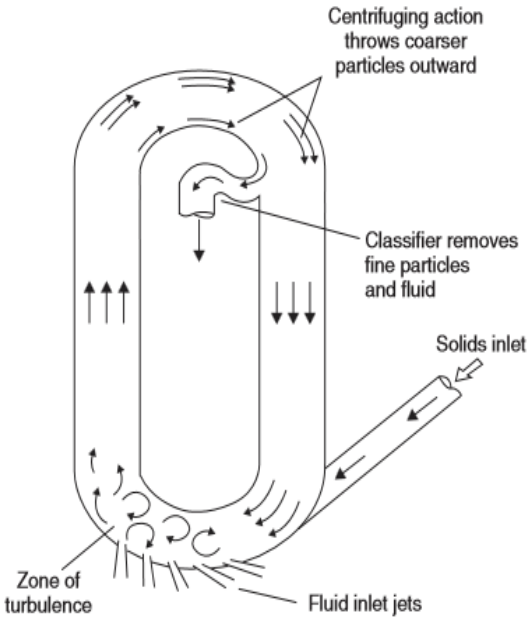
(https://www.dynamicengitech.com/Oscillating-Granulator.html)

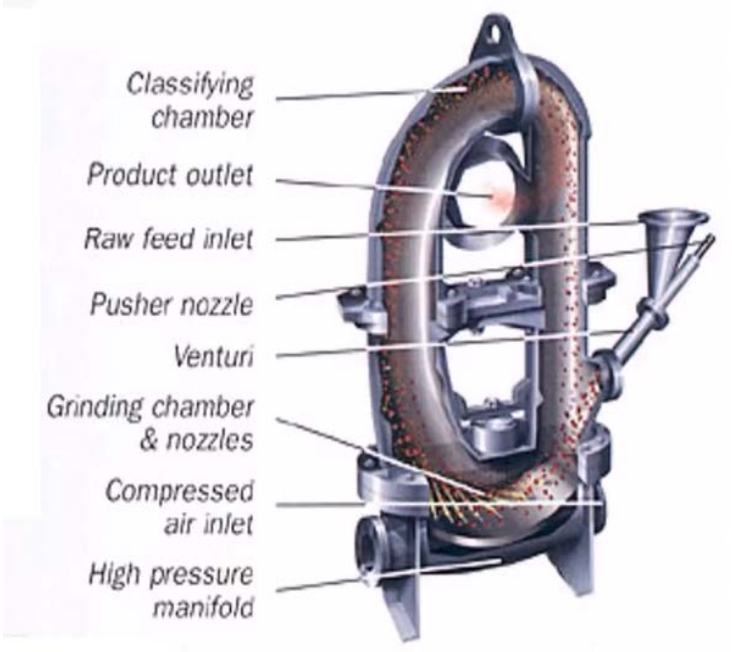
Equipments use in size reduction

- **Fluid energy mill**

  The feed materials is suspended in a high velocity of air steam which will impact and attrition each other.

  - Suitable for medium hard materials
  - Particle size 1 – 20 μm



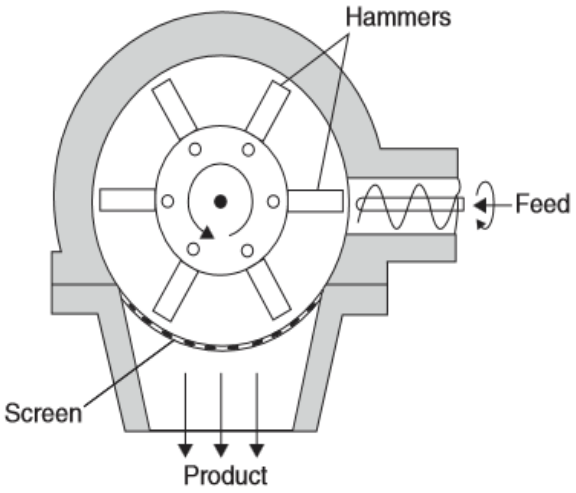


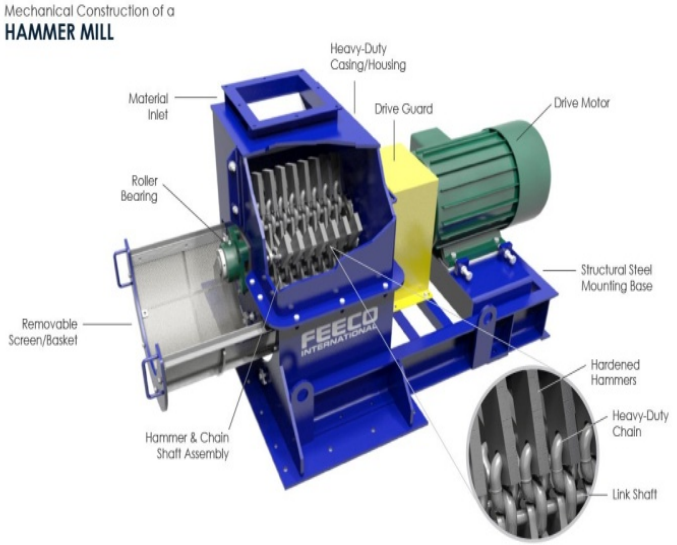
Equipments use in size reduction

- **Hammer mill**

  It operates on the principle of impact between rapidly moving hammer which mounted on a rotor and powder materials.

  - Almost materials can be milled
  - Can change milling blade or hammer for difference materials
  - Can mill many particle size range.



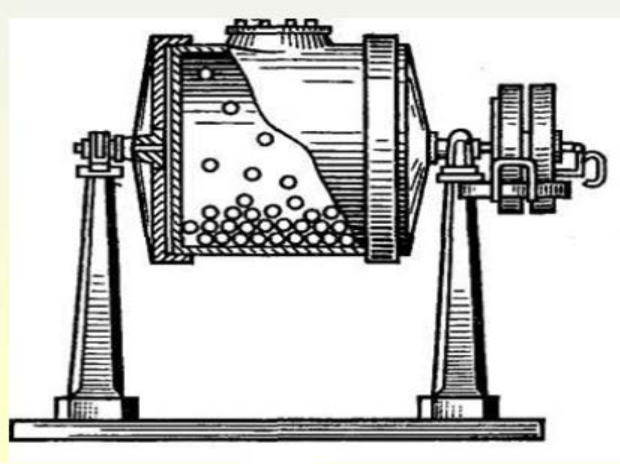


Equipments use in size reduction

- **Ball mill**

  It works on the impact between rapidly moving of ball and powder materials in a hollow cylinder

  - Can mill to fine powder.
  - Can mill in sterile condition.
  - used in Cement Plant, Ceramic plant, Steel Mill, Mining etc.
  - Particle size 0.07 – 0.4 mm

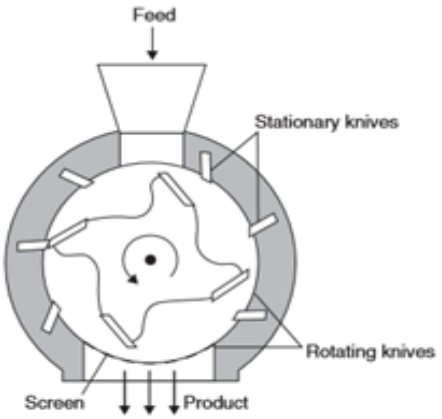


Equipments use in size reduction

- **Cutting mill**

  Size reduction by cutting or shearing the materials with sharp knives.

  - Can use for soft, elastic, medium-hard and fibrous materials.
  - Suitable for crude drug crushing.
  - Screen size 0.25 – 20 mm



(Pharmaceutical Manufacturing Handbook: Production and Processes)

General view

Cutting blade

Equipments use in size reduction

Mill	Action	Particle size	Use
Fluid energy mill	Attribution & impaction	Up to 1 – 20 μ	Moderate hard and friable materials
Hammer mill	Impaction & chopping	Up to 20 – 40 μ	Almost all drugs, wet & dry granulation
Ball mill	Attribution & impaction	Up to 10 μ or less	Brittle drugs, aseptic condition, toxic substances
Cutting mill	Cutting	Up to 20 – 80 mesh	Soft, elastic, fiber materials
Oscillating mill	Attrition	Coarse to moderated fine (250 μ - 5 mm)	Wet & dry granulation

Methods for Particle Size Analysis

- Sieving method
- Optical microscopy method
  - Microscope
  - Electron microscope
- Sedimentation method
  - Gravity method
  - Centrifugal method
- Light scattering
  - Optical particle counter
  - Laser diffraction
  - Dynamic light scatterring

Particle Size Analysis

Method	Principle
Sieve	Sieve analysis utilizes a series or stack, or nest of electro brass or stainless steel sieves that have smaller mesh at the bottom followed by meshes that become progressively coarser toward the top of the series. Useful for measuring particles in size range 10–50,000 µm
Microscopy	Analysis is carried out on two-dimensional images (projected diameter) of particles which are assumed to be randomly oriented in three dimensions. Can measure particles in the size range 1–1000 µm. Electron microscopy is useful for analysis of particles in submicrometer range (0.01–100 µm). It also gives information on surface morphology and shape of the powder.
Sedimentation	Size analysis is based on sedimentation of particles as a function of their size due to gravitational pull or by using a centrifugal force. Can measure particles in the size range 0.01–100 µm.
Light scattering	This is based on the principle of light scattering of particles as a function of their hydrodynamic radius. Commonly used, as it requires a small sample size and is a rapid method for particle size measurement. It can be used to measure particles varying in size from 0.001 to 100 µm.

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Granulation process

Meant:

- is the process to combine powdered particles to form bigger one that called granules. It involves agglomeration of fine particles into larger granules. Typically, pharmaceutical granules have a size range between 0.2 – 4.0 mm, depending on subsequent using.

Granulation process

Purpose of granulation:

1. Improve uniformity of powder components
2. Improve flowability
3. Improve compressibility
4. Decrease segregation of powder components
5. Decrease dusting

Ideal characteristics of granules

1. All ingredients in formulation should be distributed in the granules uniformly.
2. Granules which are different size or density should not be separated in hopper according to vibration of machine.
3. Granules should have good binding, lubrication and disintegrating properties.
4. Granules should have sufficient fines to fill empty spaces between coarse granules for better compression characteristics and appearance of tablet.
5. A tablet granulation should have sufficient physical strength to form strong tablets when compacted

Granulation Processes

There are 2 methods

- Wet granulation method
- Dry granulation method

Wet granulation process

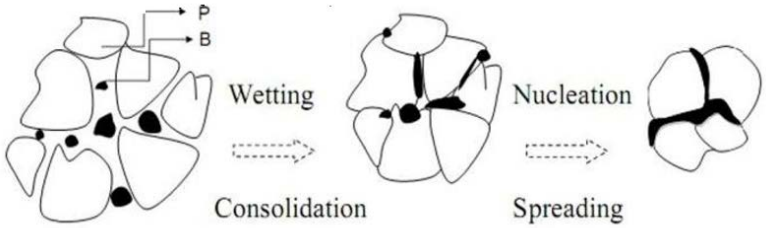
- Blending
- Wet mixing
- Granulating (wet sieving or wet granulating)
- Drying
- Dry sieving (sizing or dry granulating)
- Dry mixing (dry blending or lubricant mixing)

Blending & Wet mixing

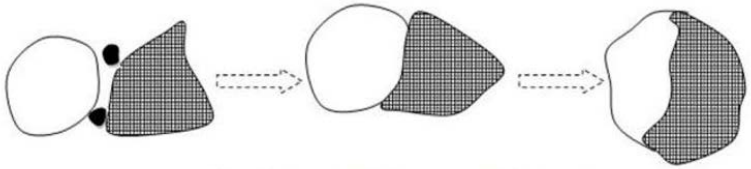
- Blending
  - After weighing materials as formulation
  - Adding the materials which include APIs, diluents, disintegrants, etc.
  - Mixing
- Wet mixing
  - Adding binder paste, etc.
  - Kneading

Wet granulation

- Mechanism of wet granule formation



Nucleation of particles (P – Powder particle, B – Binder)



Coalescence between agglomerates

- Factors influence the granule formation
  - Particle size of powder
  - Type of blinder
  - Volume of blinder
  - Massing time
  - Shearing applied
  - Drying rate

Blending & Wet mixing

- **Mortar & Pestle**

It's the classical pharmaceutical preparation which using for long time for particle size reduction, dry mixing and wet mixing. Shearing force to form wet granules by hand pressing the pestle to the mortar.

- **Advantage and use**
  - Small scale of mixing.
- **Disadvantage**
  - Can not control the uniformity of powder in each time of mixing

Blending & Wet mixing

- **Pony mixer**

  Consists of vertical cylinder bowl which can be rotated.

  The blade is mounted with a rotated shaft at the top of the bowl

  Shear of mixing is applied between moving blade and bowl wall

- **Advantage and use**
  - Speed of rotation can be varies.
  - Low speed are used for dry blending and fast speed for wet mixing.
  - It's useful for wet granulation process
- **Disadvantage**
  - It's not suitable for dry mixing
  - It generates dust, may cause of cross contamination

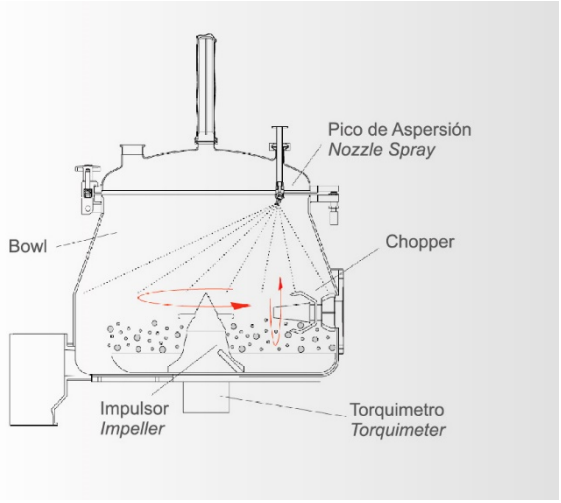
Blending & Wet mixing

- **Sigma Ribbon mixer**
  - Consists of horizontal cylindrical trough, the top can be opened.
  - There are 2 helical blades which mounted on the same shaft through the long axis of the trough.
  - Materials will be loaded from the top of trough

- **Advantage and use**
  - Can be used for mixing fine solid, wet solid mass and plastic solid
  - High shear can be applied.
- **Disadvantage**
  - It's poor mixer.
  - Shearing action is less than pony mixer.
  - It's fixed the speed.
  - The dead spots are observed at the end of blades.

Blending & Wet mixing

- High speed mixer
  - Consists of impeller and chopper for mixing and can be controlled the speed.
  - The end point can be set by measuring the torque of impeller



- Advantage
  - Use less time for wet mixing
  - Can set end point of mixing.
  - Close mixing bowl, can prevent dust spreading

- Disadvantage
  - The particles may be burnt due to high speed of impeller.
  - It take time for cleaning

Wet granulating or Wet sieving

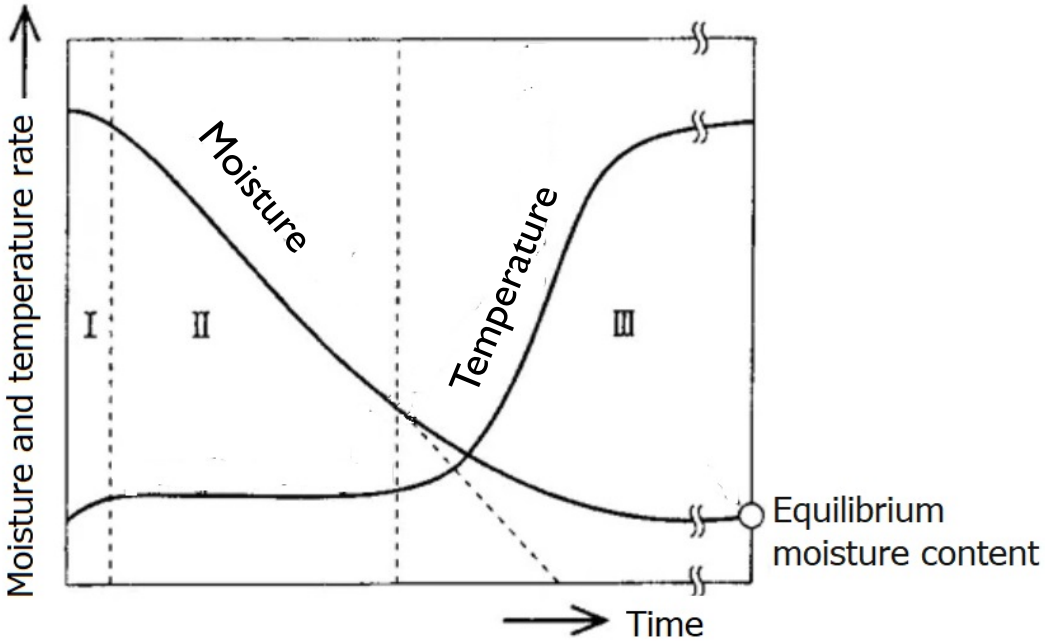
The wet mass is forced through a perforated screen (6 – 12 mesh screen), forming threads of the wet granules.

- Screen
- Fitz mill
- Oscillating mill
- High speed granulator

Drying process

- **Drying process**
  - Removing the moisture from wet granules by oven at temperature about 55°C to the level of moisture that satisfied for subsequent use.
- **Mechanism of hot air on drying**
  - Initial period, moisture dry as constant rate. It is mostly dependent on rate of heat transfer to materials.
  - Next, drying rate become fall down to nearly horizontal at very long time. The moisture from lower part will migrate to the surface of granule. The speed of moisture transferring depends on porosity of granule.
  - Then the moisture content is constant at the "equilibrium moisture content" which is dehydrated form of ingredients.
  - Under drying, the granules will be shrinkage and deformation.

Drying process



- **End point of drying**
  - Normally, LOD of granules is about 1 – 5%.

Drying process

- **Effect on drying**
  - Moisture in granules will effect to the stability of product.
  - Residual moisture in granules will reduce the electrostatic charges on particle.
  - Water soluble color can migrate the surface of granules, become mottled tablet after compression.
  - Small size of granules can reduce the drying time and more uniformity of moisture.

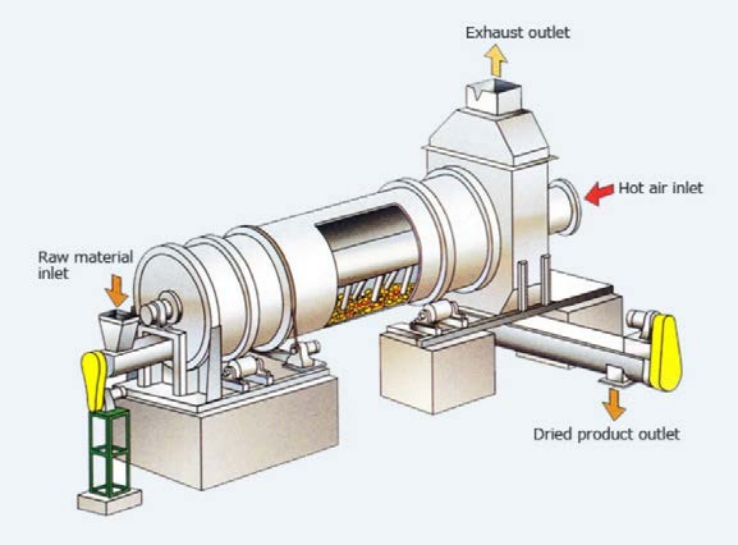
Drying process

- **Tray dryer**
  - Trays on the shelf or in the rack truck
  - Electric heat or gas as the source of heat
  - Should place granules not more than 1 inch thickness

- **Advantage**
  - Use in small scale production or small factory.
  - Easy to operate and maintenance
  - Cheap
- **Disadvantage**
  - Not uniform drying
  - It take long time for drying

Drying process

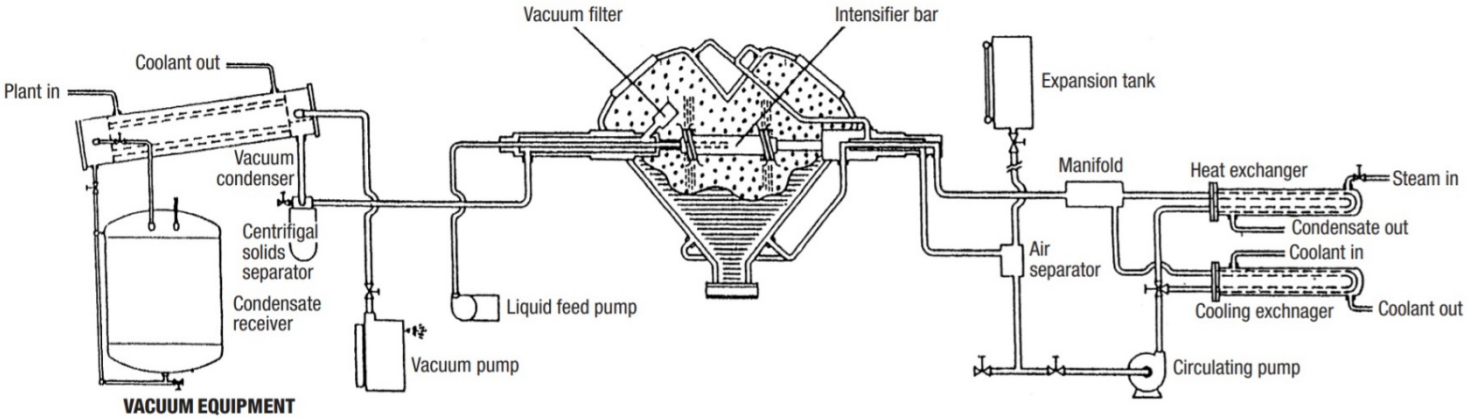
- **Rotary dryer**
  - Long cylinder with baffle inside and it rotates.
  - Direction of product opposite to the direction of hot air flow. The granules cascade down through the air stream.
- **Advantage**
  - Suitable for large volume of production and can be automatic.
  - Low maintenance cost.
- **Disadvantage**
  - Fine particle may be loss, if use high velocity of hot air.



Drying process

- **Vacuum dryer**
  - Have heating unit and vacuum unit
  - Principle
    - Boiling point of water is lower than 100 °C, if pressure is less than atm.

- **Type of vacuum dryer**
  - Tray type
  - Single pot processor (SPP) type



Drying process

- **Advantage**
  - Theoretically, drying more rapid than tray dryer and rotary dryer.
  - Use lower temperature for drying. It's suitable for heat sensitive materials.
  - SPP type can do blending, wet mixing, wet granulating, drying and dry mixing in the same machine.
  - Can reduce dust and energy cost.
- **Disadvantage**
  - More complicated machine
  - More expensive.

Drying process

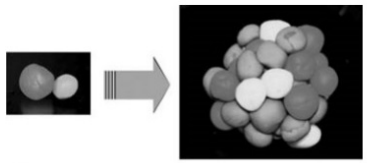
- **Fluidized bed dryer**
  - Normally, use particle size 50 - 5,000 μ, if less or bigger may need to add vibrator for successful fluidization.
  - It need high velocity of hot air which equals the total weight of bed to lift it and add more for the particle separate.
  - Fluidization begin after hot air lift bed up, the hot air will increase the drying rate of particles.
- **Advantage**
  - High drying rate.
  - Reduce contact time of heat for drying
  - Low maintenance cost
- **Disadvantage.**
  - Use high velocity of hot air
  - Particles may develop electrostatic charge.
  - Burning particles in fluid bed dryer may occur.
  - May have more fine particles
  - Outlet filter blockage is common problem. It may be the cause of accident in during operation

Drying process

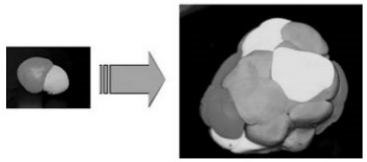
- **Microwave dryer**
  - Microwave drying is a method to dry materials by using electromagnetic radiation.
  - Using microwaves at 915 MHz and 2450MHz frequencies for drying application which it does not interfere with communication frequencies.
  - microwave radiation is able to penetrate the entire granules or bed of granules
  - Rapid heat generation within the granule or the bed and vaporization was generated inside granules or the bed.
- **Advantage**
  - Enhancement of heat transferring process
  - Develop internal vaporization of particles which enhance drying rate.
  - Improve product quality.
  - Can be energy source for other types of dryer such as vacuum dryer, fluid bed dryer
- **Disadvantage**
  - If the vaporization is too rapid or the granule is lack of porosity structure for the vapor, the granule may be broken due to internal pressure build-up

Drying process

Fluid bed granulator



Nucleation of particle by consolidation of fluid bed granulator



Coalescence between agglomerates of high shear mixer ganulator

Drying process

Fluid bed granulator

- **Advantage**
  - Can be automation system for blending, wet granulating, drying
  - Can save labor cost, energy, working time and reduce materials loss
  - Transferring heat of granulator is better than tray dryer 2 – 6 times
  - Uniformity of drying
- **Disadvantage**
  - Low uniformity of density
  - Low density
  - It take time for cleaning time
  - Use more binder solution
  - Filter may be obstructed and become problem for the process
  - Fine particles may develop electrostatic charge and organic solvent may be the cause of explosion.

Dry sieving (Size reduction)

The granules will be reduced the size to around 10 – 20 mesh or smaller, it depends on tablet size.

น้ำหนักเม็ดยา (มก.)	ขนาดของแร่ง		เส้นผ่าศูนย์กลางของสาก (Die) (มม.)
	แร่งเปียก	แร่งแห้ง	
50	16	20	5 – 6.5
100	16	20	7
150	12	16	8
200	12	16	8.5
300	10	12	10.5
500	10	12	12
1000	8	8	16

(ที่มา: แนวทางการพัฒนาผลิตภัณฑ์ยารูปแบบของแข็ง เอกสารอบรมสัมมนาของสำนักงานคณะกรรมการอาหารและยา)

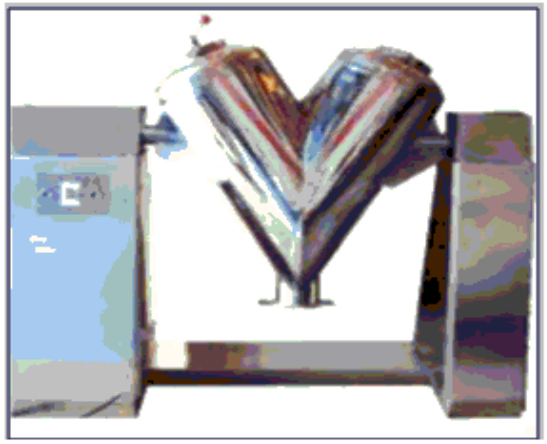
- **Equipements**
  - Manual sieving
  - Fitz mill
  - Oscillating mill

Dry mixing (dry blending)

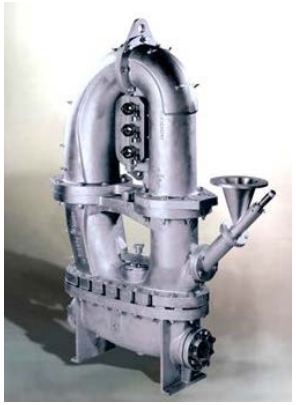
It's the process to add the lubricant to a granulation. The lubricant and granulation are tumbled or mixed gently to distribute the lubricant without coating particle or breaking them to finer particle.

Equipments

- Plastic bag
- Tumbling mixer
  - V-shape
  - Cube shape
  - Cylindrical shape
  - Double cone shape



Wet granulation process



Reduce size

Blending &
wet mass

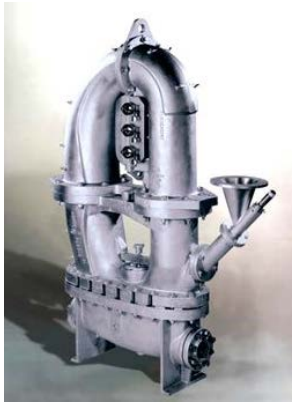
Granulating

Drying

Dry sieving
or Sizing

Dry blending
or mixing

Wet granulation process



Reduce size

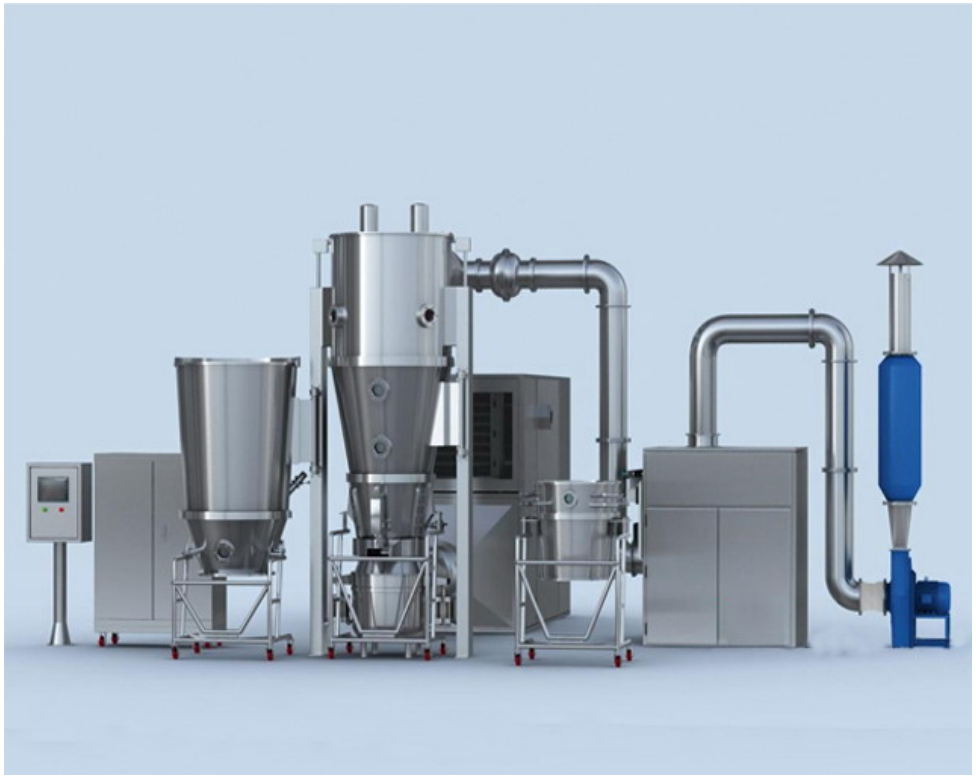
Blending, wet mass & granulating

Fluid bed drying

Dry sieving or Sizing

Dry mixing

Wet granulation process



Fluid bed granulator

Dry mixing

Advantage for wet granulation

- To prevent segregation of powder components during tableting or storage.
- It be better uniformity of components, especially for low-dose drugs.
- Granules are formed more spherical than powder and better flowability.
- Control particle size distribution for tableting to improve appearance of final product and prevent capping.
- The process may improve disintegration rate of poorly soluble drugs by imparting hydrophilic properties to the surface of the granules.
- To reduce the level of dust present during manufacturing process. It means that can be reduced the incidence of cross contamination and risk to workers.
- To improve compactability and the compression characteristics of drug substances. Allow to use lower pressure for compression. It can be reduced machine wear.

Disadvantage of wet granulation

- Wet granulation often requires several processing steps.
- The cost of wet granulation is higher because of the time, labour, energy, equipment and space required for the process.
- The process is not suitable for thermolabile and moisture sensitive materials.
- Migration of soluble dyes may occur during the drying process.
- Incompatibilities between formulation ingredients will be aggravated by the granulating solvent which tends to bring them into close contact.
- There is a possibility of material loss during processing due to the transfer of material from one unit operation to the other.
- Dissolution rate of tablets manufactured by wet granulation may decrease with ageing.

Dry granulation process

When do we select dry granulation method?

- Drug sensitive to the moisture and heat
- Primary powder particles are aggregated under high compress.

Dry granulation process

Dry granulation process

- Slugging technique
- Roller compaction technique
- Direct compression

Dry granulation process

Dry granulation process

- Blending or Mixing
- Compaction : 2 methods
  - Slugging granulation
  - Roller compaction granulation
- Milling or crushing and sieving.
- Lubricant mixing

Direct compression

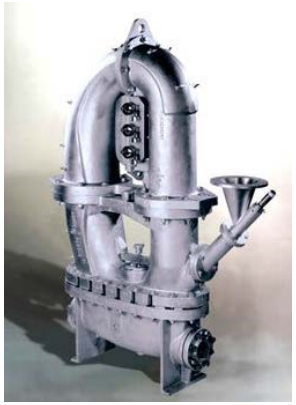
- Blending and lubricant mixing
- Compression

Dry granulation process

Slugging granulation

- Compress primary powder into large flat tablets or pallets by using large heavy duty rotary tableting machine. This step calls "slugging (or precompression)"
- Typically slug size is 25 mm. in diameter and 10 – 15 mm. in thickness.
- Normally, apply high pressure to compress about 15 tons to form granules

Dry granulation by Slugging



Reduce size

Blending

Slugging

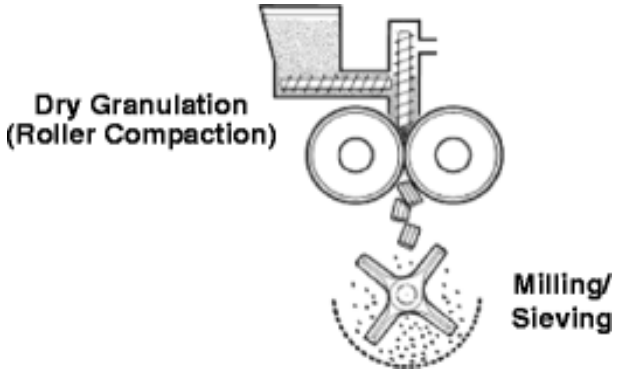
Sieving
or sizing

Blending

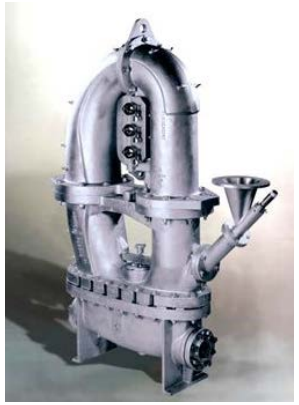
Dry granulation process

Roller compaction machine

- Normally, there are two rollers with equal diameters. It rotates in the direction which powder from the hopper flow.
- The powder is pressed with two rollers with pressure 1 – 6 tons that produce a compacted ribbon or flakes.
- At the below of two rollers, the flake crusher reduces the ribbons or flakes into small sizes

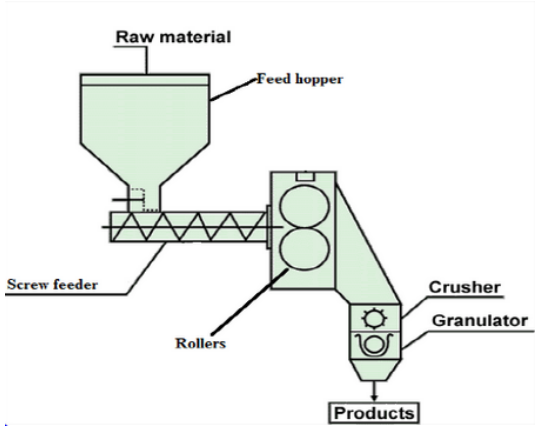


Dry granulation by Roller Compaction



Reduce size

Blending



Roller compaction granulator

Blending

Dry granulation method

Advantage

- Useful for moisture and temperature sensitive materials
- Less machines and space than wet granulation
- Improve disintegration because dry binder used has less adhesive effect.
- This method is valuable for effervescent tablet production.

Dry granulation method

Disadvantage

- Require high heavy duty of slugging and roller compaction machine
- More dust in process which may contaminate to other drug.
- Dose uniformity issue :
  - Segregation of components may occur.
  - Low dose drug
- Flowability may be an issue to consider. It may be the cause of weight variation.
- The tablets manufactured by dry granulation tend to be softer than the tablets manufactured by wet granulation.

Tablet compression process

PHOTO CREDIT: SEJONG PHARMATECH

Molee Sontichai

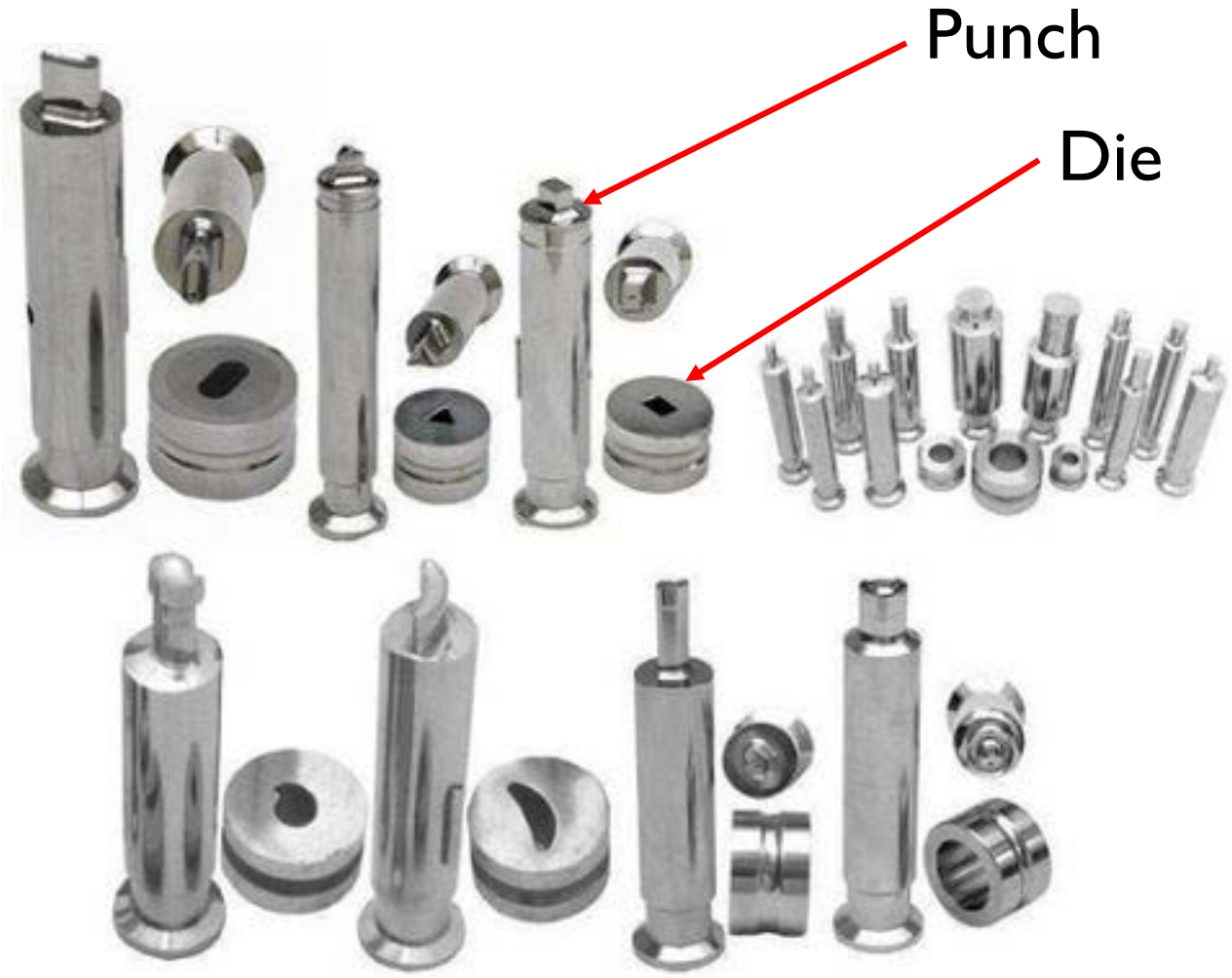
Tablet Compression Process

It's the process to transform powder or granules into tablets which have uniform shape, size and weight as product specification.

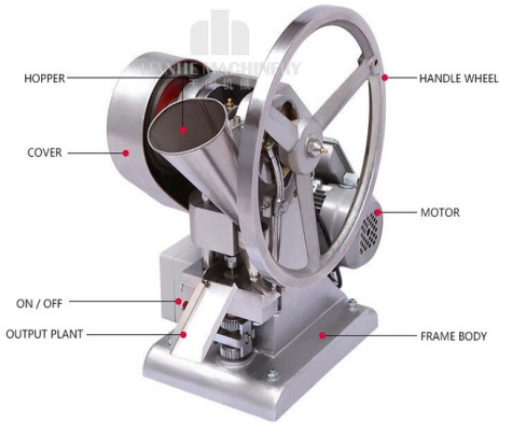
Why are tablets a popular dosage form?

- Accurate dosage
- Good stability
- Easy to mask unpleasant taste
- Attractive appearance
- Easy to handle
- Cheaper cost

Punches and Dies



Tablet press machine



Single – Punch Tablet Machine

Rotary Tablet Machine

High Speed Rotary Tablet Machine

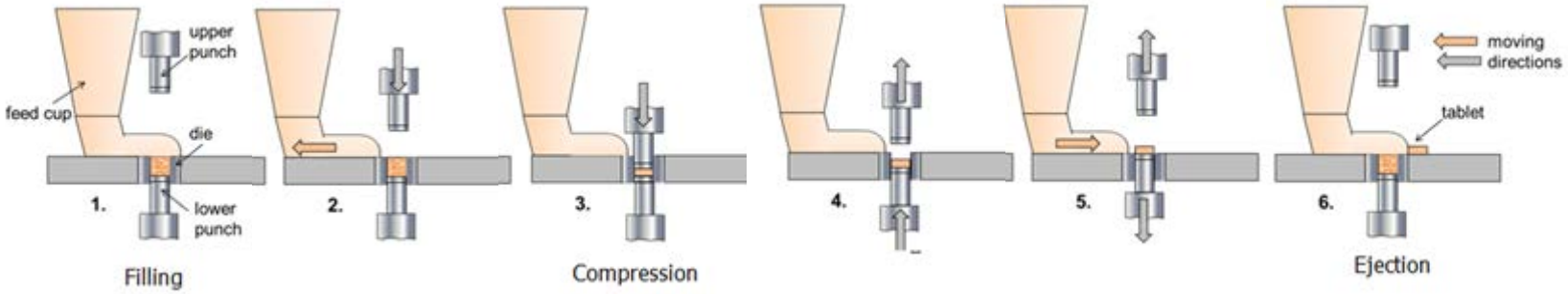
Multilayer Rotary Tablet Machine

Basic operation of tablet press machine

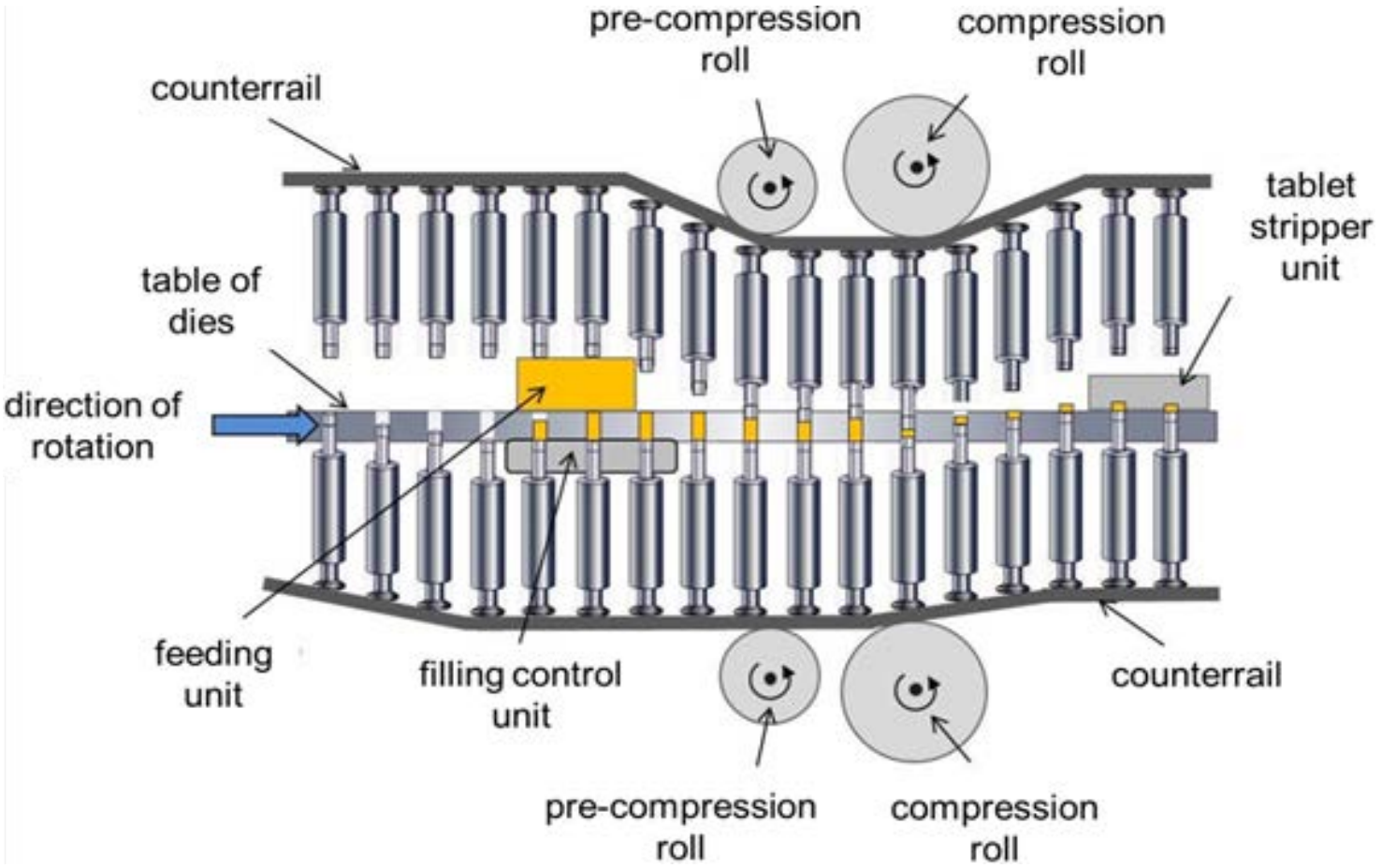
Tablet compression can be divided into 3 steps

- Filling
- Compression
- Ejection

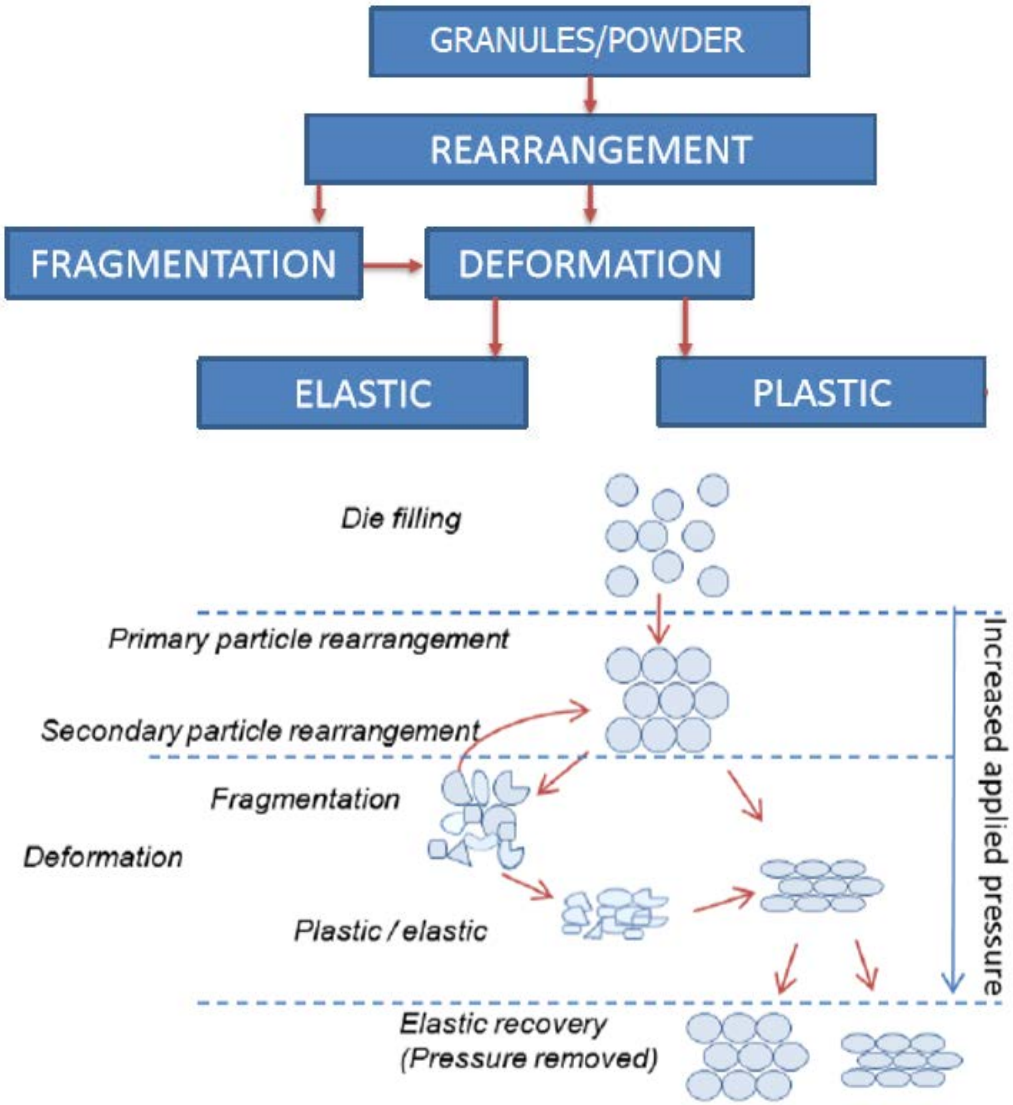
Operation of single-punch Tablet press machine



Operation of a rotary tablet press machine from side view



Mechanical of tablet compression



Mechanical of tablet forming

- Mechanical interlocking
- Intermolecular force
- Solid bridge
- Binder bridge

Coating Process

Molee Sontichai

Coating Process

Objective of tablet coating

- Protecting the sensitive drug from its surrounding environment such as air, moisture or light.
- Mask unpleasant taste, odor, and color of drug.
- Making it easier for the patient to swallow the product.
- Can print name, logo or any symbol on tablet for easy to identify products.
- Easy for handling with high-speed packaging/filling lines, and automated counters in pharmacies and reduce dust contamination
- Reducing the risk of interaction between incompatible components by separating them into core tablet and coating parts.
- Improving product robustness because coated products generally are more resistant to abrasion and attrition.
- Modifying drug release, as in enteric-coated, repeat-action and sustained-release products.

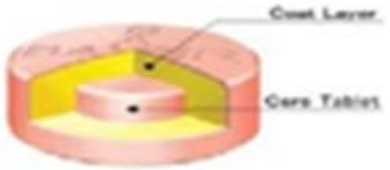
Type of Coating Processes

- Sugar coating
- Film coating
- Microencapsulation
- Compression coating

Sugar coating

Film coating

Encapsulation



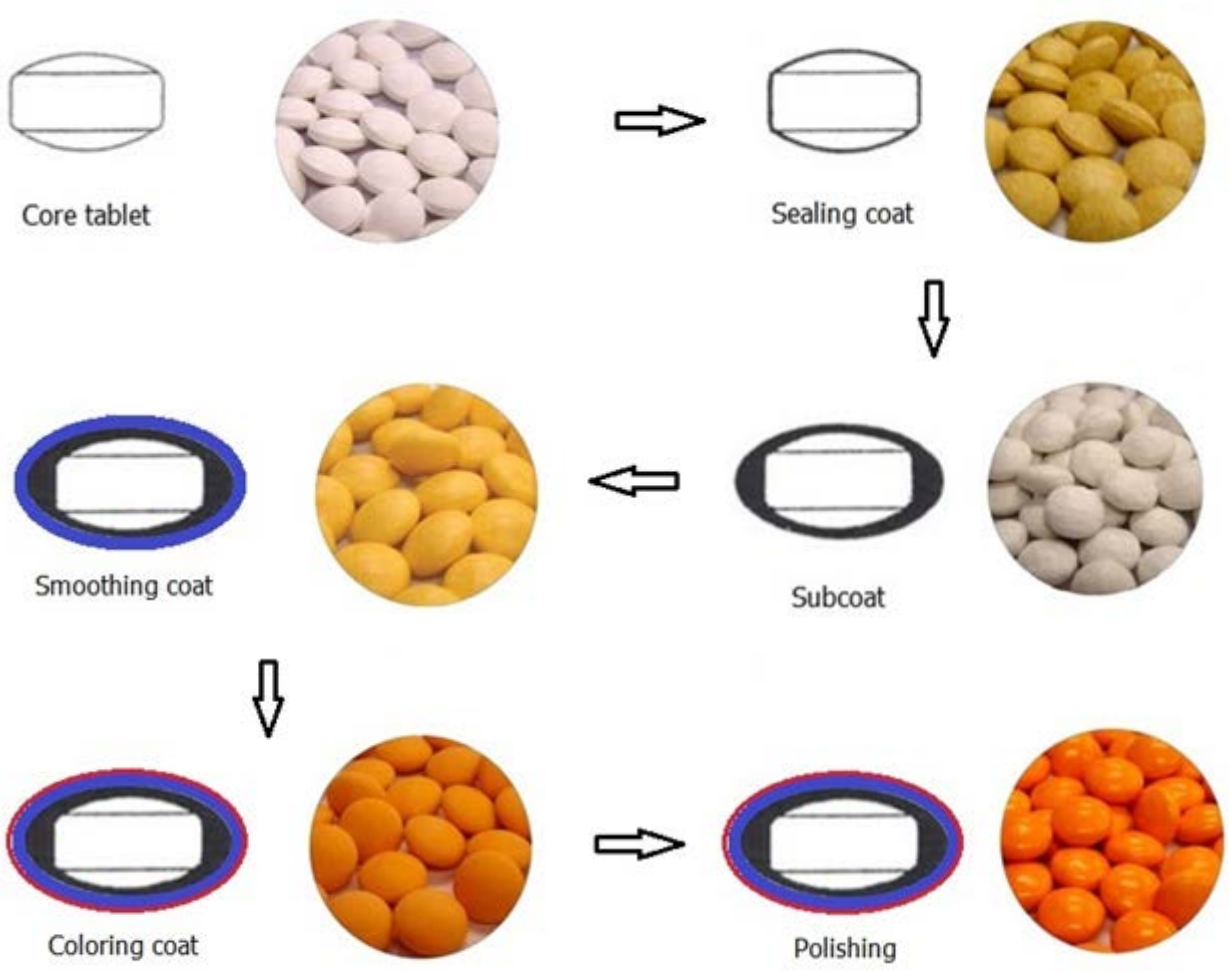
Compression coating

Sugar Coating

Step of sugar coating

- Sealing coat (Protective coat)
- Sub-coating
  - Lamination process
  - Suspension process
- Smooth coating
- Color coating
- Polishing
- (Printing)

Sugar Coating Sample



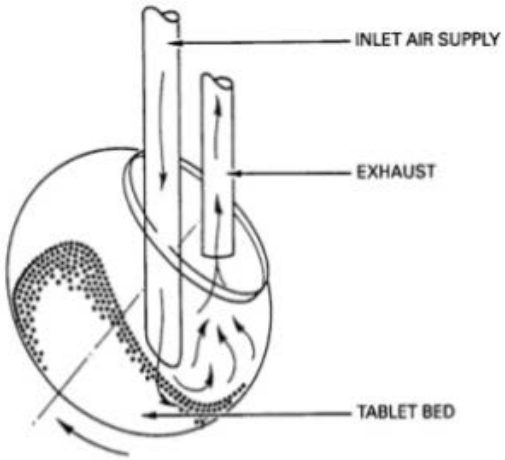
Sugar Coating Equipments

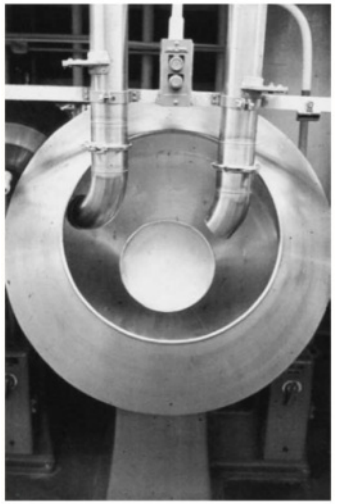
- Coating pan
- Baffle
- Spraying gun
- Hot air system
- Dust collector
- Polishing pan

Sugar Coating Equipments

Coating pan : normally use standard coating pan

- Standard coating pan
  - Circular stainless pan and mounted with rotated axis in horizontal rotation.
  - Heated air is supplied into inside of coating pan.
  - Exhaust air with dust is removed at closing to the opening of coating pan
  - Coating solution are supplied to tablets by handling or spraying
  - Use baffle or hand to distribute coating solution or powder,

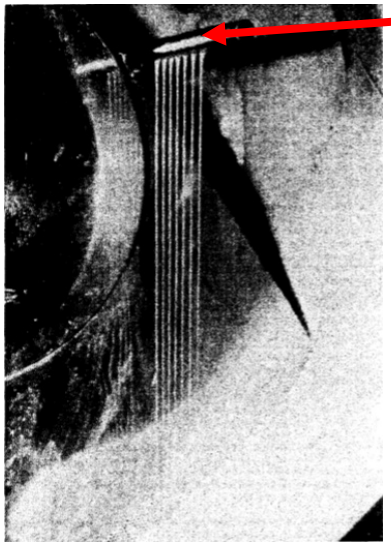




Sugar Coating Equipments

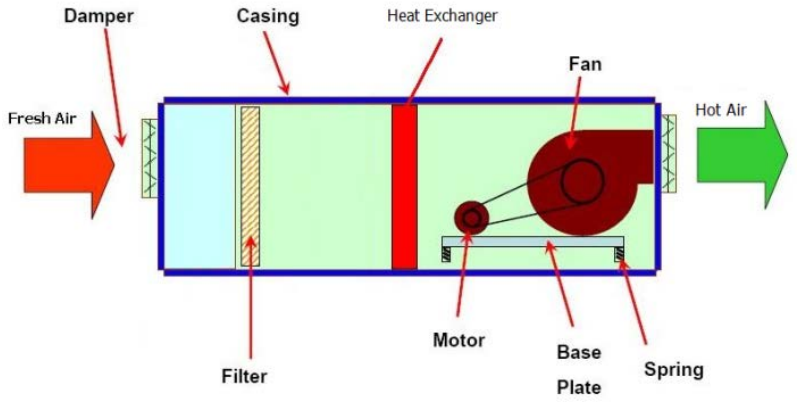
- Baffle

- Spray gun



Sugar Coating Equipments

- Hot air system
  - Heat exchanger
  - Filter



- Dust collector

Sugar Coating Equipments

- Polishing pan

Sugar Coating Process

Advantage

- Sugar coating machine is cheap
- Can be reprocessed
- Require less hardness of core tablet

Disadvantage

- Time consuming for the process
- High weight gain of tablet
- Required special training for coating operator

Film Coating Process

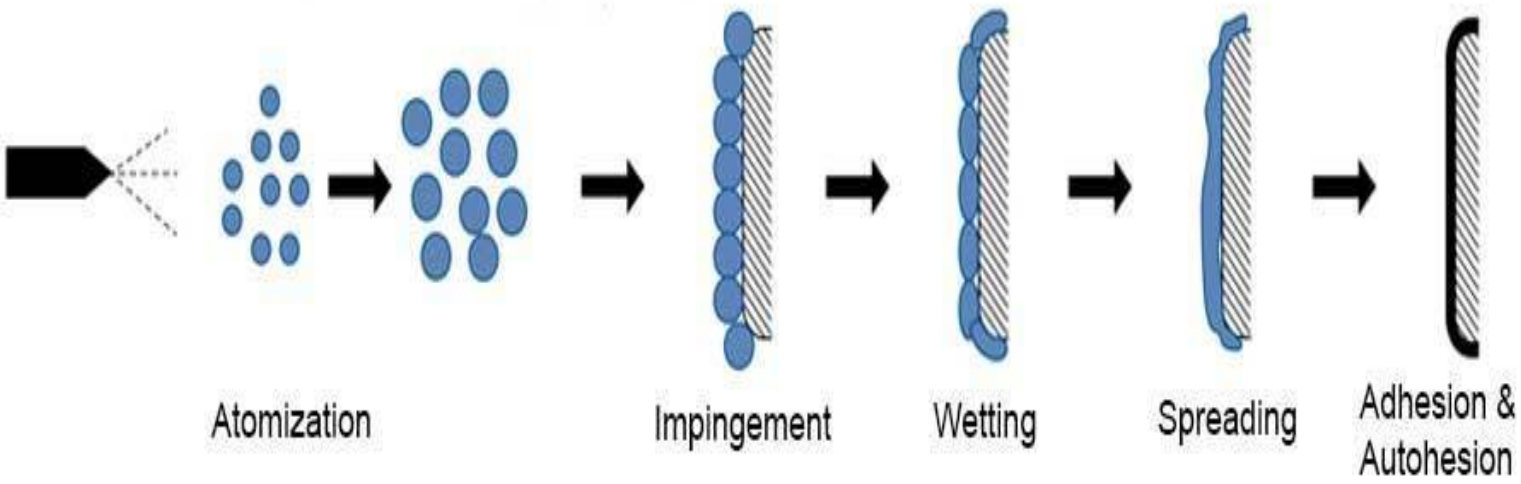
Film coating tablet is a thin polymer - based applied to a tablet. Thickness of a coating is usually about 20 – 200 μ.

The film coating process should consider the following criteria

- Control balancing between coating liquid addition rate and drying process
- Control uniformity of coating liquid distribution on the surface of product.
- Control to optimize the quality of the final coated tablet for both conventional release products and modified release products

Film Coating Process

Step of film coat forming



Film Coating Process

Film coating VS Sugar coating

- Advantage of film coating
  - The weight of film-coated tablets increase less than sugar coated tablets (about 2 – 3% of core tablet weight).
  - Shorter production time than sugar coating and can save the production cost.
  - Generate dust in the process less than sugar coating
  - Many formulation of coating film can be designed, depend on the purpose of coating such as enteric film, sustained release film, control release film, etc.
  - Improved resistance to chipping of the coating

- Disadvantage of film coating
  - Flammability hazards.
  - Toxicity hazards
  - Environment pollution
  - High cost

Film Coating Process

Film coating solution : contains

- Polymers
- Plasticizers
- Colorants
- Solvent

Film Coating Process

Solvent of film coating

- Aqueous film coating
  - Water is used as solvent
- Non aqueous film coating
  - Organic solvents are used as solvent.

Film Coating Process

Aqueous VS non aqueous film coating

Aqueous solvent	Non aqueous solvent
No safety issue for operator	Operator safety issue
Can release to atmosphere without treatment	Expensive cost for treatment before release to atmosphere
No flammable	Flammable and can explode. Required facility and equipment with intrinsically safety
Required more drying time. It may be effected to the stability of product.	Rapid drying time
Can not be used with moisture sensitive product	Can be applied to moisture sensitive product

Film Coating Process

Type of film coating

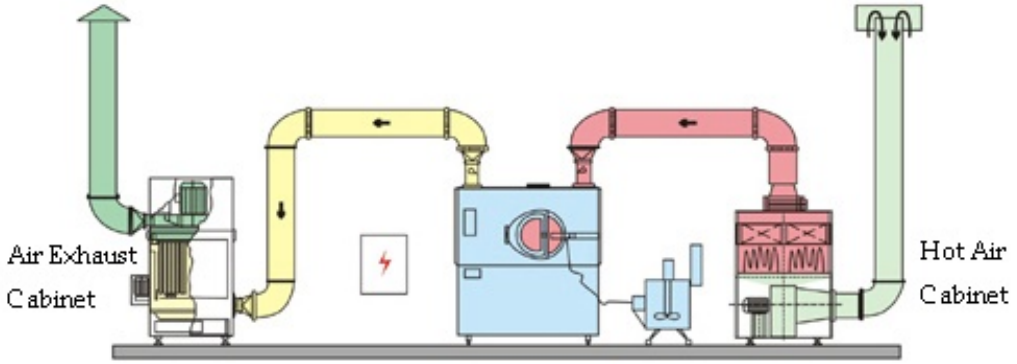
- Conventional film coating or Non functional film coating
- Modified – release film coating or Functional film coating
  - Delayed – release coating : Enteric coating
  - Sustained – release coating : Extended - release coating, Control - release coating

Film Coating Process

Method of film coating

- Pan coating
- Fluidized bed coating
- Electrostatic spray powder coating

Pan Coating System

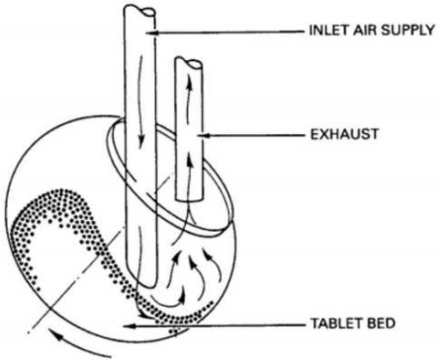


Pan Coating System

- Spray gun

Standard Coating Pan

The common design of standard coating pan

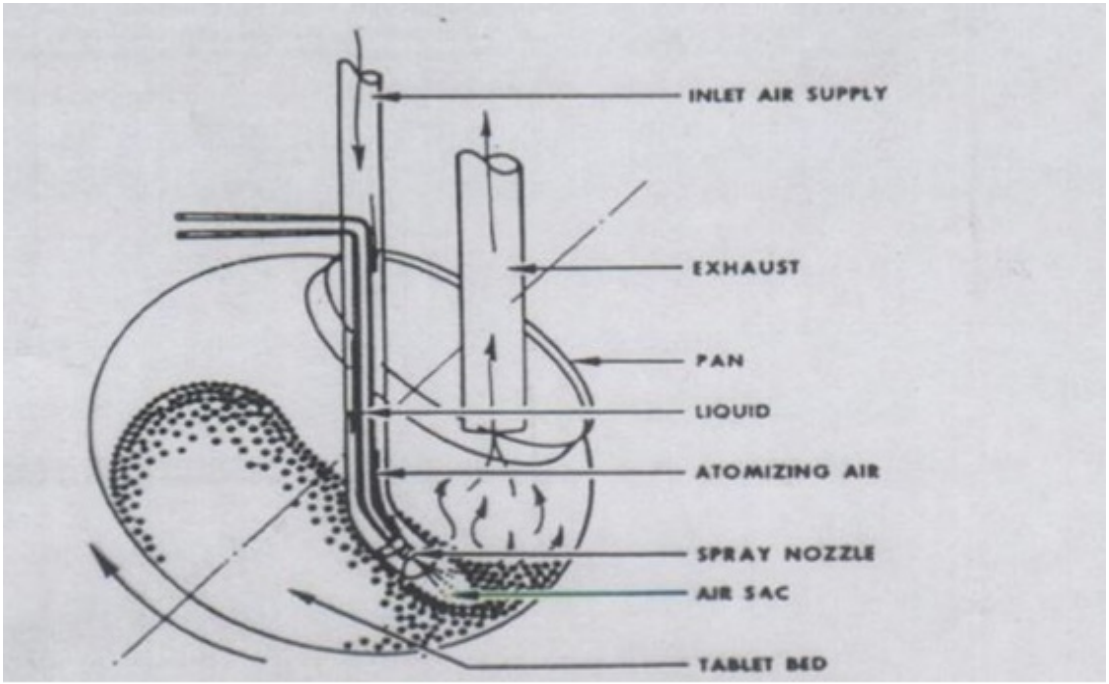


- Hot air flows downward on the surface of tablet bed.
- The exhaust air at the opening of coating pan.
- Diadvantage
  - Low drying efficiency
  - Health hazards for the operator and increased risk of explosion in the case of organic solvent-based film coating

Coating pan

- Standard coating pan
  - Immersion tube system
  - Immersion sword tube system
  - Pellegrini system
- Perforated coating pan
  - Accella-cota system
  - Dria coater pan
  - Hi coater system
  - Glatt coater system

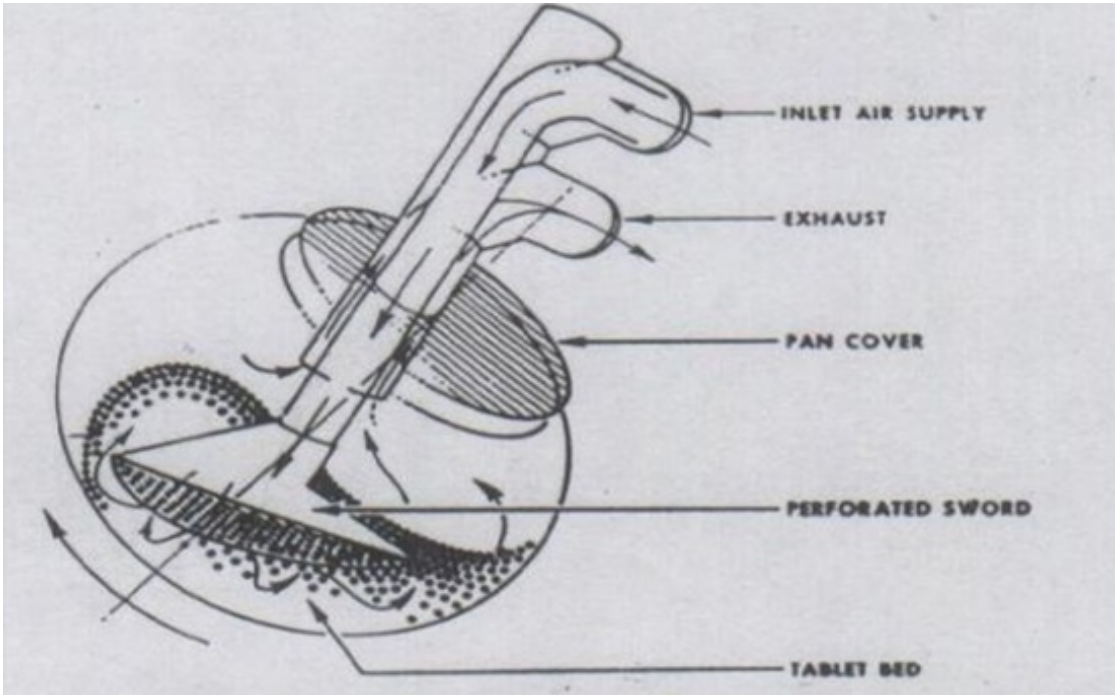
Standard Coating Pan



Immersion tube system

- Hot air flows upward and exhausted by conventional type.
- The tube of supplied air has a spray nozzle that delivers both the hot air and coating solution
- Can be used for both sugar and film coating

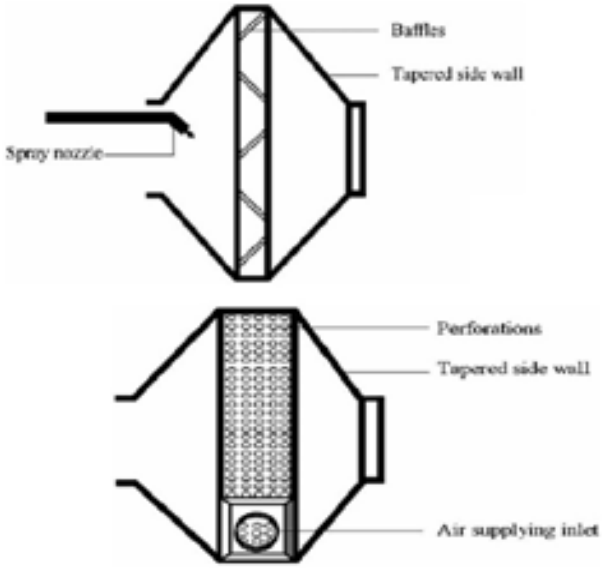
Standard Coating Pan

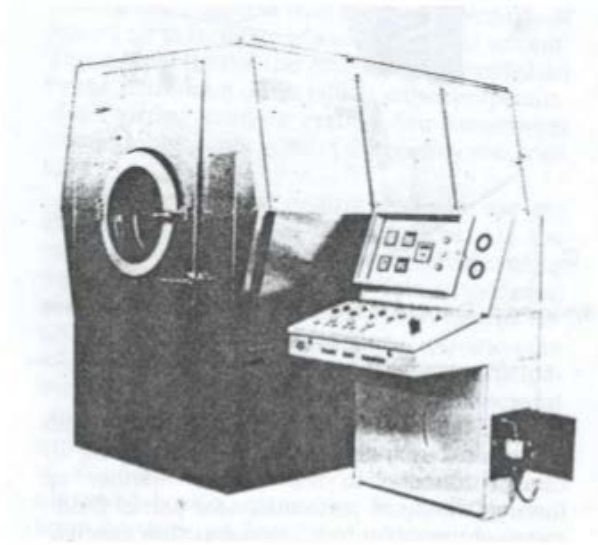


Immersion sword tube system

- The perforated metal sword for supplying hot air immerses in the tablet bed.
- The hot air flows through perforated metal sword then upward through the tablet and exhaust.
- Can be used for both sugar and film coating

Standard Coating Pan

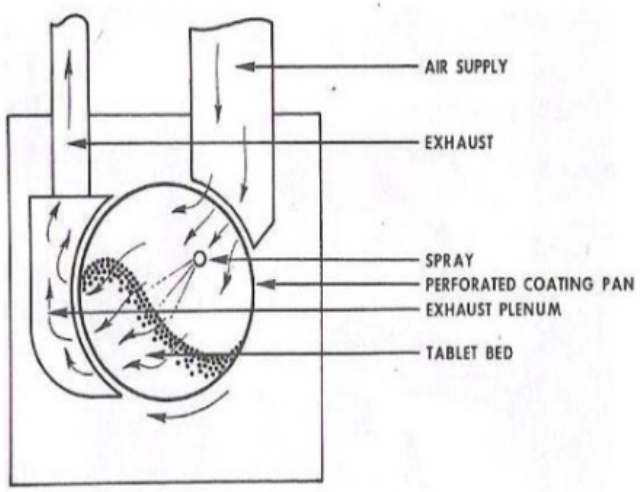




Pellegrini system

- Pan contains baffle and diffuser to supply hot air.
- It's limited drying capacity.
- It's suitable for Sugar coating only.

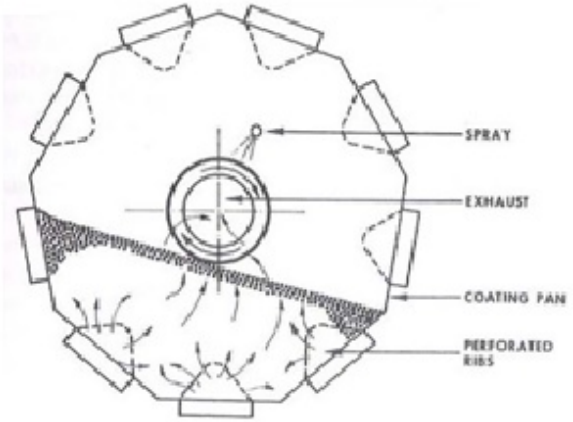
Perforated Coating Pan

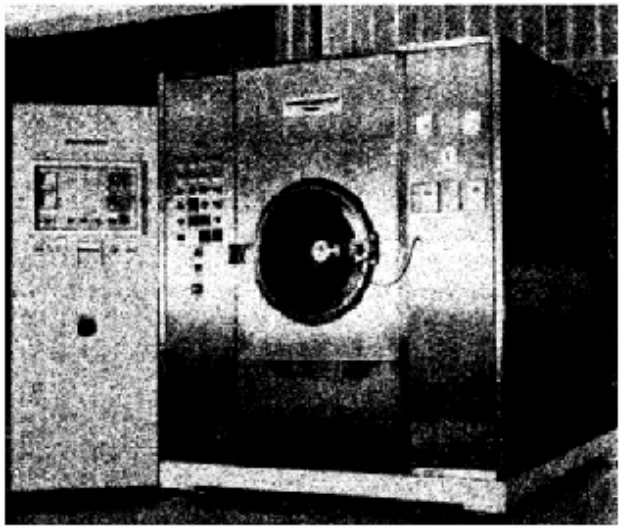


Acella-cota system

- Baffles mix tablet freely in coating pan
- Hot air flows from the upper part of coating pan, passing through tablet bed and leaves the pan through the perforation

Perforated Coating Pan

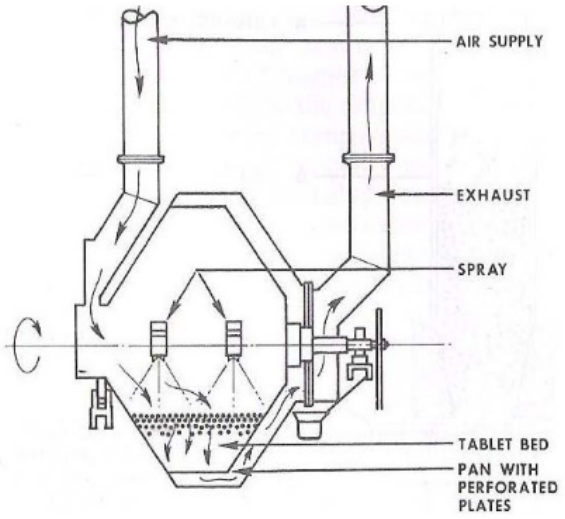




Dria coater pan

- Has nine hollow perforated ribs, which are located on the inside periphery of coating pan
- Hot air flows from perforated ribs below tablets and flow upwards to fluidize the tablet, then exist through back side of coating pan.

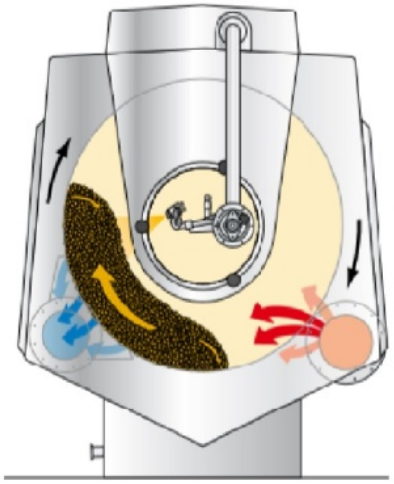
Perforated Coating Pan



Hi coater pan

- Both coating solution and hot air downward
- Hot air leaves the coating pan through the perforation at the below of coating pan.

Perforated Coating Pan



Glatt coater pan (GC smart series)

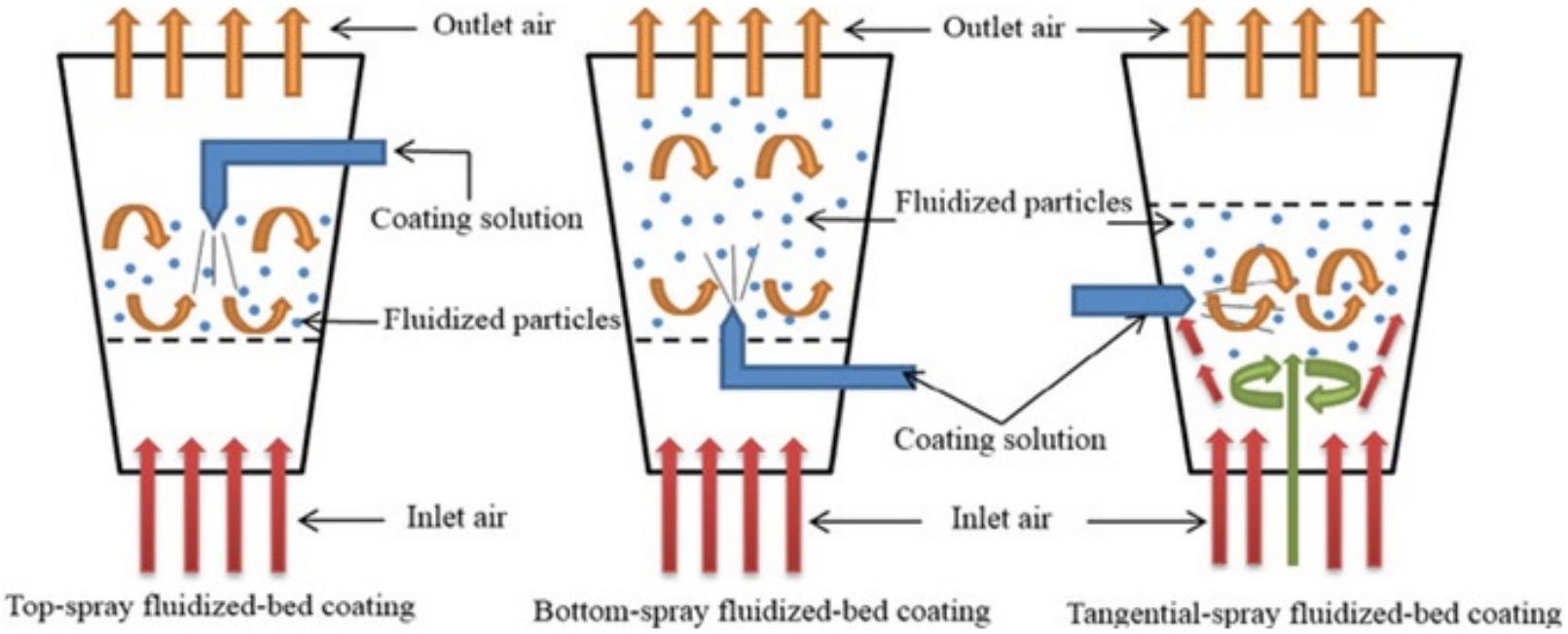
- Similar to Accela-cota
- Hot air plenum located beneath the moving tablet bed. The hot air is exhausted from coating pan through either or both of two sections.
- Hot air current doesn't cause turbulent air around spray gun.

Film Coating Process

- Fluidized Bed Coating

Fluidized Bed Coating

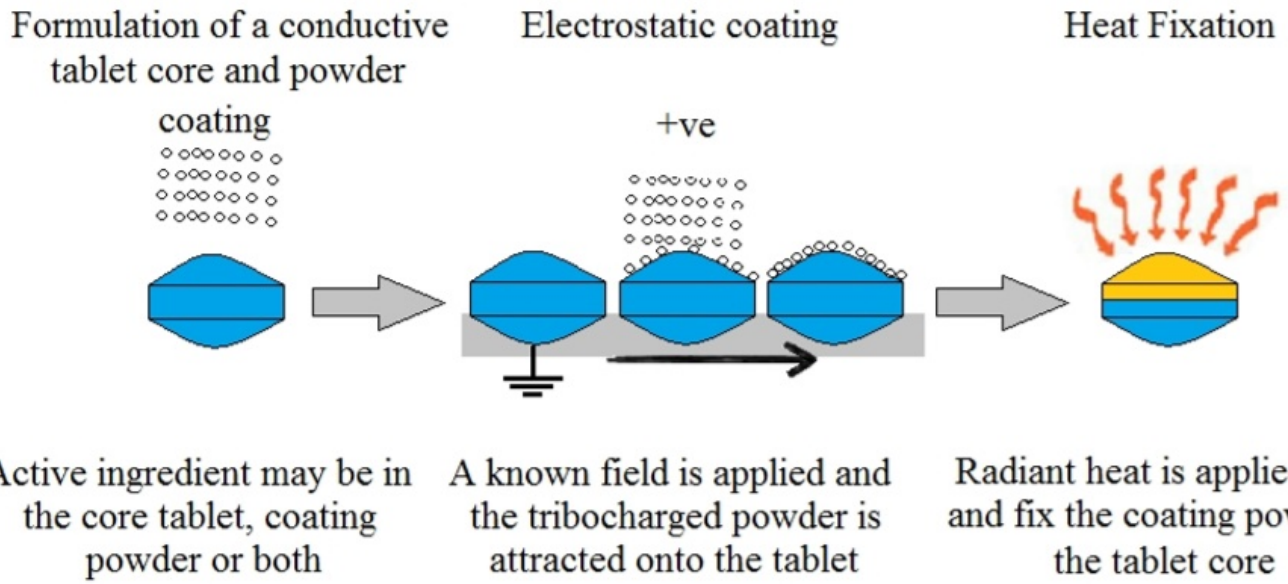
Fluidized bed types



Film Coating Process

Electrostatic spray powder coating

- The concept of electrostatic spray powder coating is spraying of mixture of finely particles and polymers with ion charge onto the earthen charged substrates without the usage of any solvent and then heating the substrate for curing until the powder mixture is fused into film.



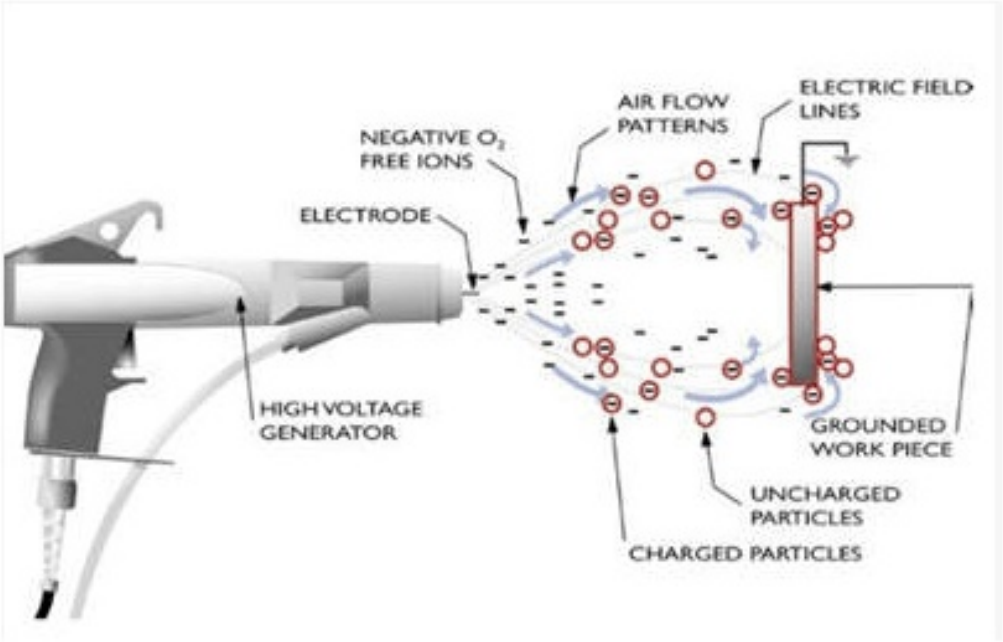
Film Coating Process

Electrostatic spray powder coating

- Coating process
  - Powder dry coating
  - Plasticizer dry coating
- There are two types of spraying gun
  - Corona charging
  - Tribo charging

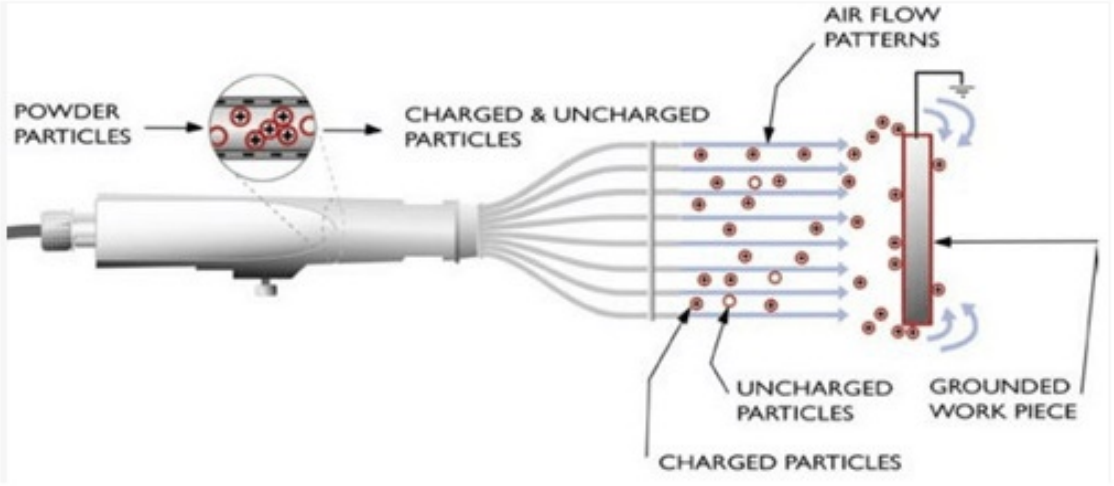
Film Coating Process

- Corona charging
  - It's the spray gun which has high voltage generator. An electrode located in or near the powder stream. An ion field is generated between electrode and the grounded product. The powder passing through this field are bombarded with ions and charged. The charged powder are attracted to the grounded product and the electrostatic is remained long enough for the product pass through a cure oven.



Film Coating Process

- Tribo charging
  - The principle of Tribo charging is friction charging associated with the dielectric properties of solid substances. It's no free ions and electric field is present between the spray gun and ground substrate. The electrical forces are regarded to the repulsive forces among the charged particles. After spraying, charged particles pass through the space adjacent to the substrate and attracting to the ground substrate and the attraction forces between the charged particles and ground substrate make the particle to deposit on the substrate.



Film Coating Process

Advantage of electrostatic spray powder coating

- No solvents are used.
- The coating film is deposited onto the surface of tablets in a much more precise manner than any other existing pharmaceutical coating process.
- Tablet surfaces can be only partially coated, thus facilitating applications involving drug delivery.
- Lower cost than aqueous and non aqueous coating

Disadvantage

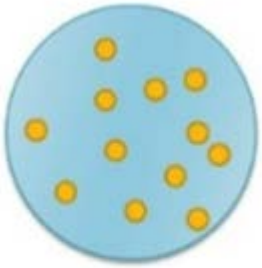
- Use high voltage to generate ions
- Tablets or substrate should have electrical resistivity less than 10^9 Ωm

Microencapsulation Process

- Microencapsules means

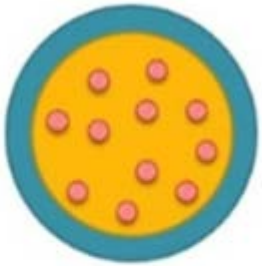
  is the process which small solid particles or droplets of liquid are surrounded or coated with film of polymeric materials. It's the same as a film cover the core to give small capsules that is called as microcapsules.

- Type of microencapsules



microsphere

uni-nuclear microcapsule



Multinuclear microsphere

Microencapsulation Process

Purpose of microencapsules

- Mask unpleasant taste and smell
- Protect sensitive API from environment such as moisture, light
- Change the status from liquid to solid or powder for easy to handling and storage
- Increase flowability
- Slow down the evaporation of volatile oil
- Decrease the irritation of drug
- Control the release of drug action

Microencapsulation Process

Microencapsulation method

- Physical method
  - Pan coating method
  - Fluidized bed technology
  - Multiorifice-centrifugal process
  - Spray drying and Spray congealing
- Chemical method
  - Coacervation-phase separation
  - Solvent evaporation
  - Polymerization

Microencapsulation Process

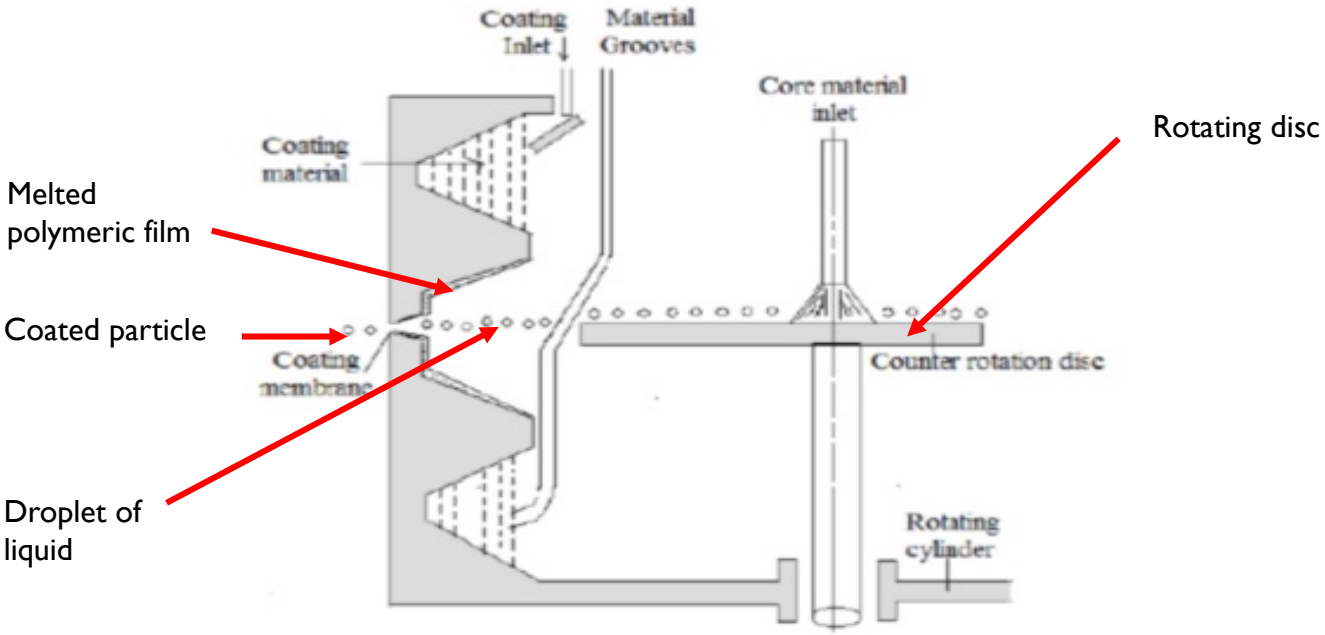
- Physical method
  - Pan coating method
    - Use coating pan
    - Can coat pellet size > 600 μm. It's suitable for larger particle coating
    - Time consuming and high material loss
  - Fluidized bed technology
    - Use Wurster fluidized bed
    - Various coating materials can be used
    - Can coat pellets size 50 μm – 10 mm, may be problem for agglomeration of the particle

Microencapsulation Process

- Physical method
  - Multiorifice-centrifugal process
    - Can coat for both solid and liquid
    - Liquids are encapsulated by a rotating head containing concentric nozzles.
    - In this process, a jet of core liquid is surrounded by a sheath of wall solution or melt
    - This process is excellent for forming particle size 500 – 4000 μm in diameter

Microencapsulation Process

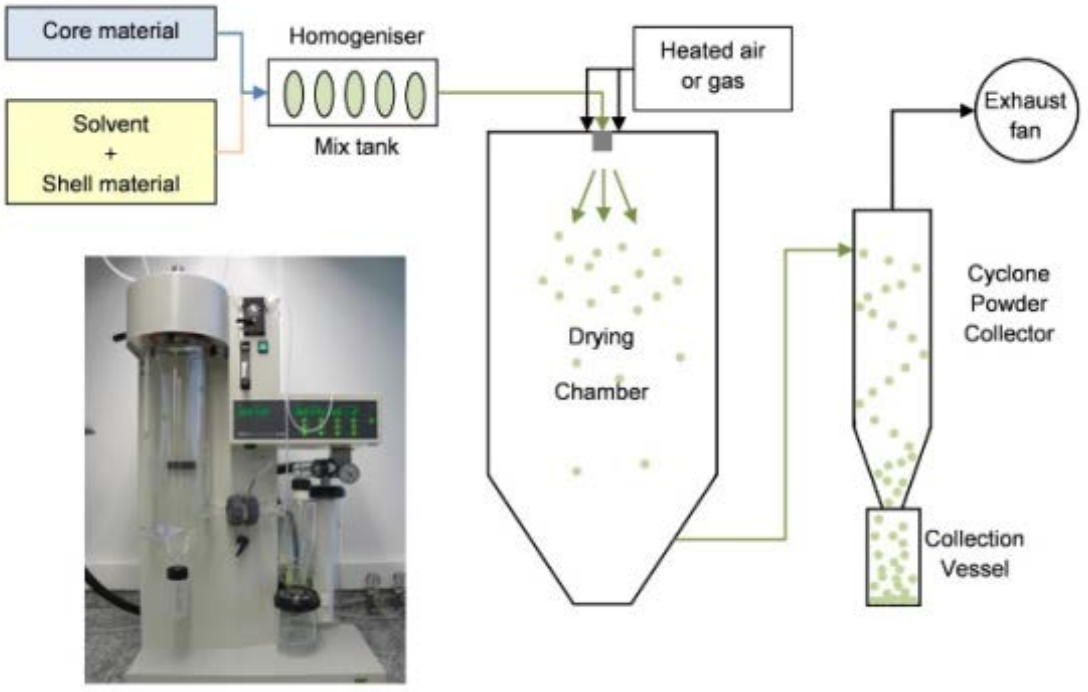
- Physical method
  - Multiorifice-centrifugal process



Multiorifice-centrifugal process

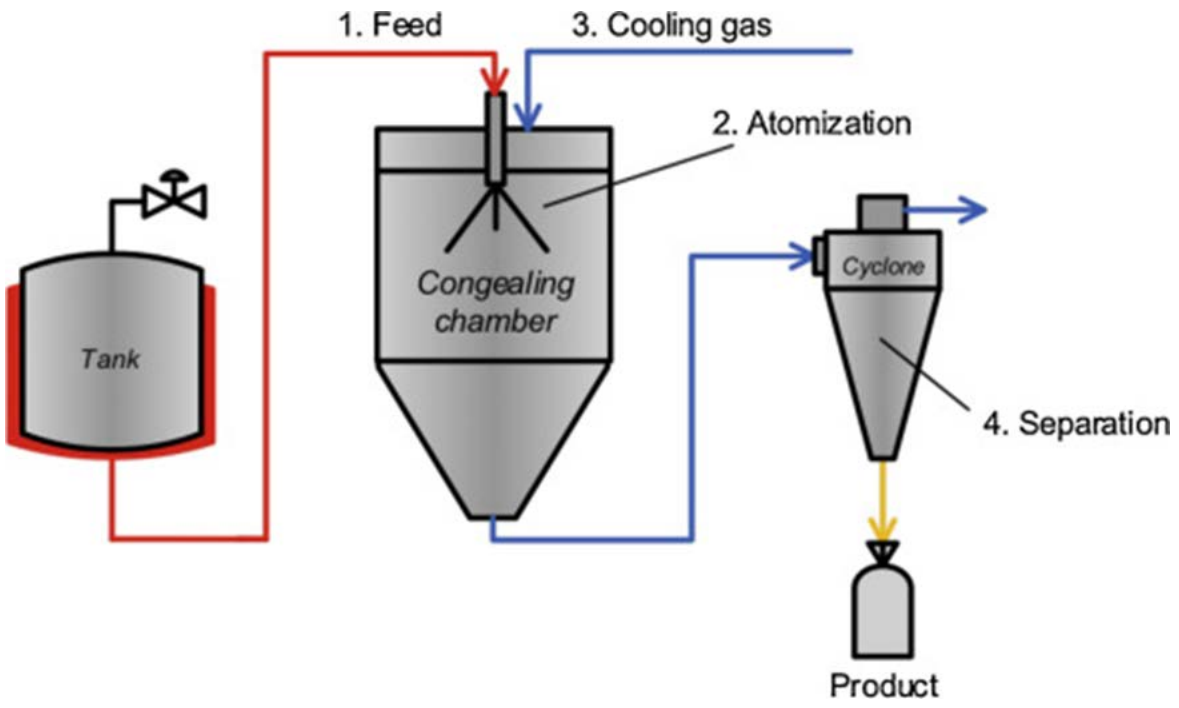
Microencapsulation Process

- Physical method
  - Spray drying
    - Dispersing the core material in liquefied coating substance and spray.
    - Spray drying is effected by rapidly evaporation of a solvent in which the coating material is dissolved.



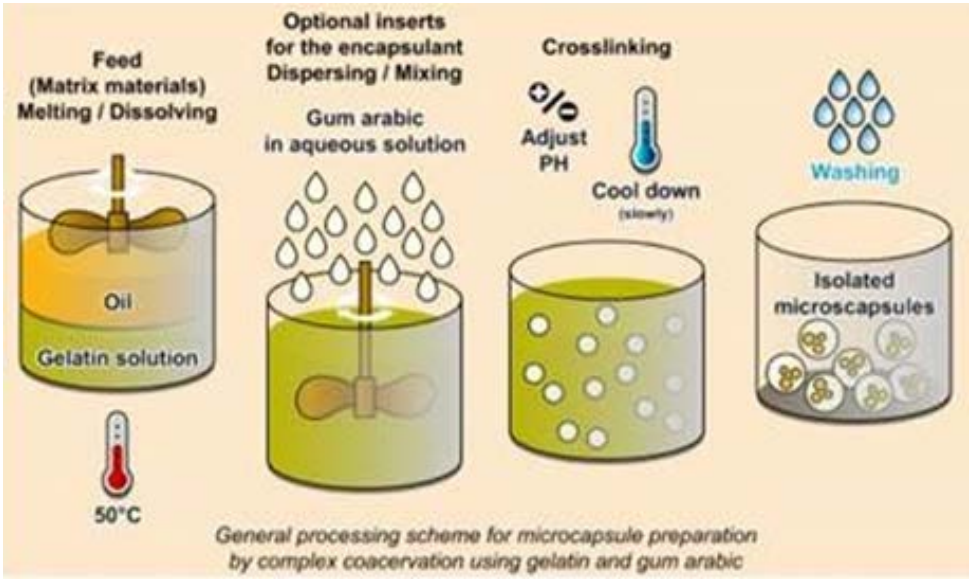
Microencapsulation Process

- Physical method
  - Spray congealing
    - Core material is dispersed in s coating material melt rather than a coating solution.
    - Coating solidification is accomplished by spraying the hot mixture into a cool air stream.



Microencapsulation Process

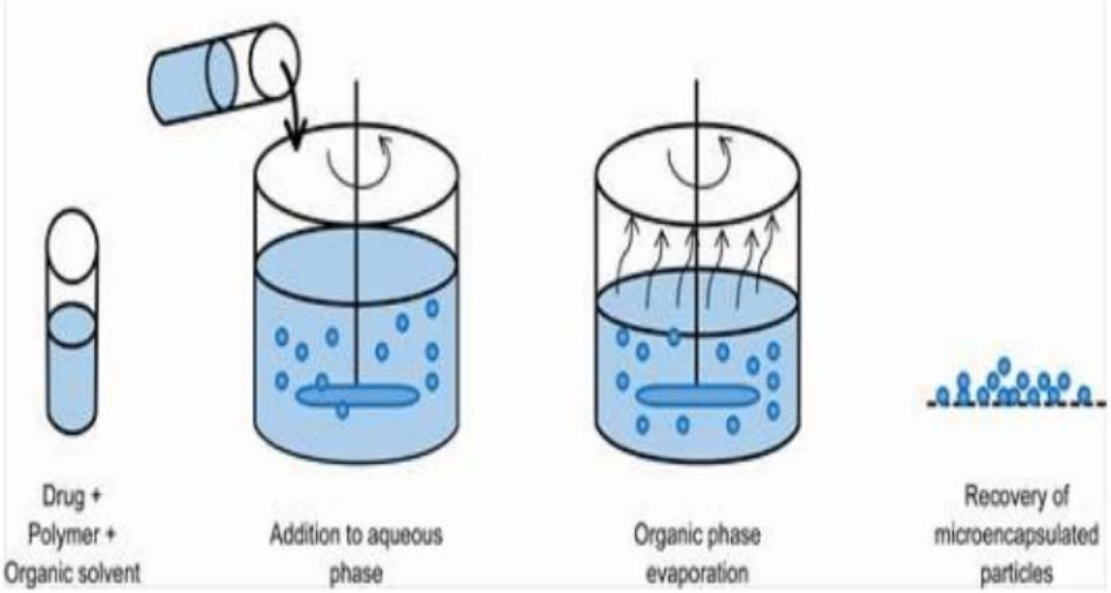
- Chemical method
  - Coacervation-phase separation
    - There are 3 steps under continuous agitation.
      - Coacervation-phase separation or formation of three immiscible phase
      - Deposition of the coating
      - Rigidization of the coating



General processing scheme for microcapsule preparation by complex coacervation using gelatin and gum arabic

Microencapsulation Process

- Chemical method
  - Solvent evaporation
    - There are 2 cases
      - The core material is dispersed in the polymer solution, polymer shrinks around core.
      - The core material is dissolved in the polymer solution.
    - Emulsification of polymer phase into an aqueous phase containing a suitable stabilizer. A matrix or microsphere is formed.
    - Removal of polymer solvent from microcapsule by extraction or evaporation.



Microencapsulation Process

- Chemical method
  - Polymerization
    - Single or double monomer are added to the disperse solution of core material.
    - Add the catalyst to activate the polymerization reaction
    - Form the wall of microcapsule
    - Stabilization of polymer structure, the polymer is consolidated by changing pH or temperature or addition of additives

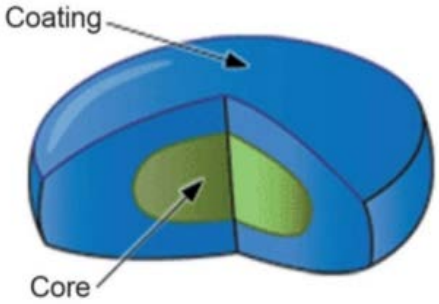
Microencapsulation Process

Final dosage forms of microencapsules

- **Powder**
- **Tablets**
- **Capsules**
- **Injection**

Compression Coating Process

Compression coating



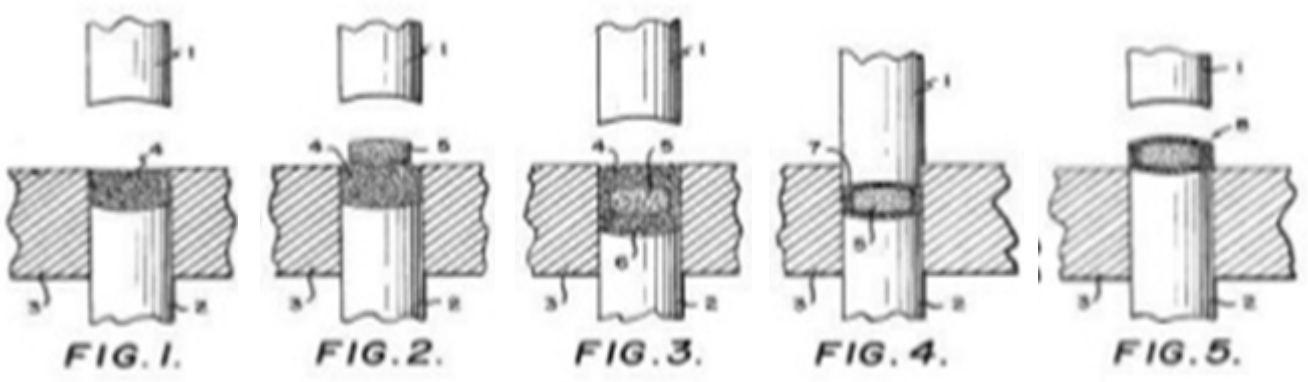
Compression coating:

The compression coating materials around preformed core tablet. It doesn't require any solvent for coating. It's known as solvent-less coating technique or dry coating technique and call the tablet as pressed coated tablet or compression coated tablet.

Compression Coating Process

Compression coating process:

- Core tablet is prepared on one turret in small size and to prepare compression coating of core tablet on another turret with a bigger die cavity.
- Compression coated tablets are prepared by putting half of coating material in die cavity, then place core tablet carefully in the center of die cavity and fill with other half of coating material to cover core tablet and compress the powder with core tablet inside.



Compression Coating

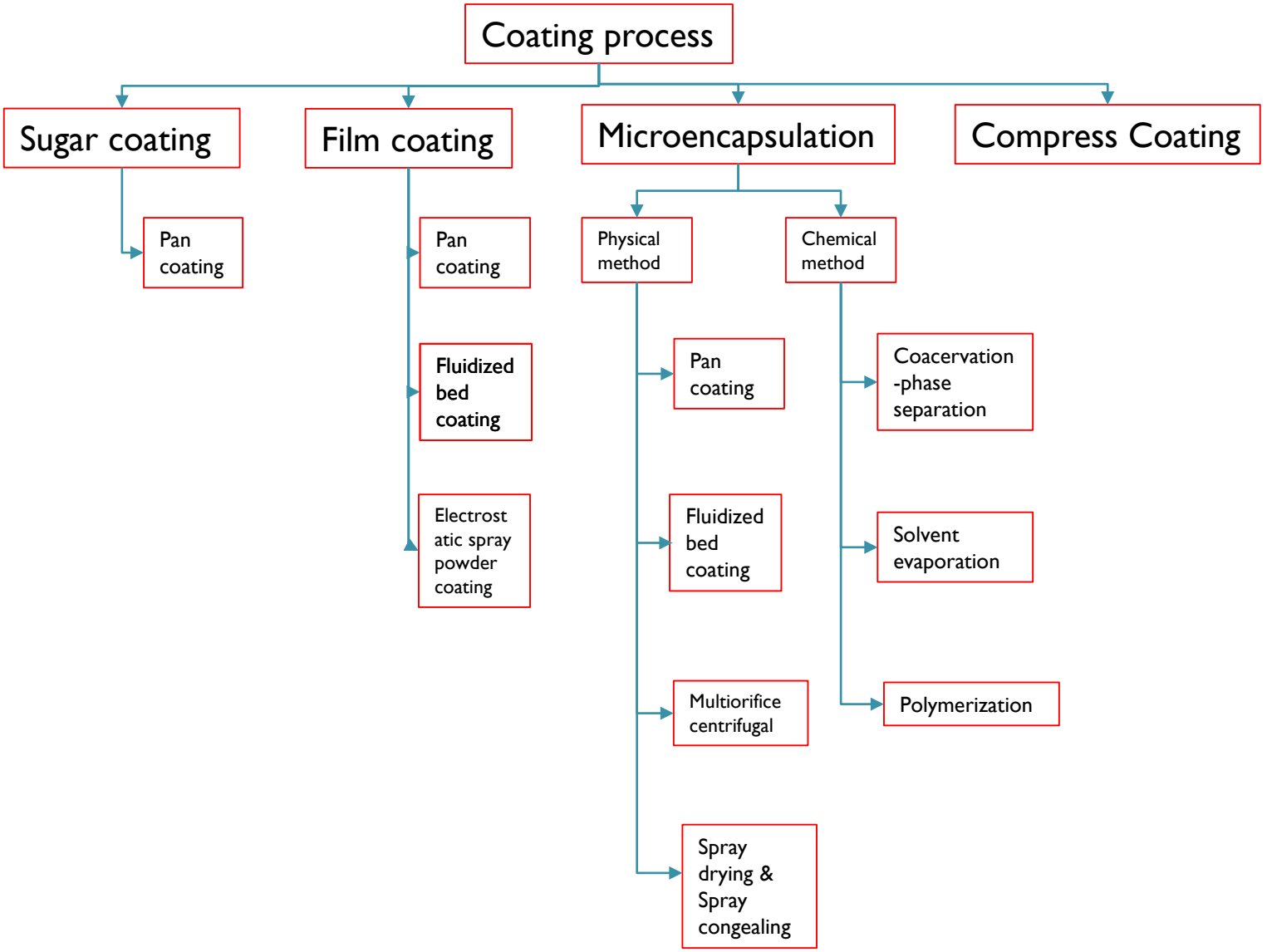
Advantage

- Considered as dry coating without using solvent and heating in process
- Improve the stability of moisture sensitive drug, because no water is used in coating process.
- Fast and more economical manufacturing process than sugar coating.
- Can prevent incompatibility components by separating it in core tablet and coating part.
- Mask unpleasant taste, smell

Disadvantage

- Significant increase the size and weight of core tablet.
- Use special machine, expensive

Coating process



Capsule Filling Process

Molee Sontichai

Capsule Filling Process

Gelatin

A protein product derived from hydrolyzed collagen material

- **Type A gelatin (Acid gelatin)**

  by acid hydrolysis of pork skin

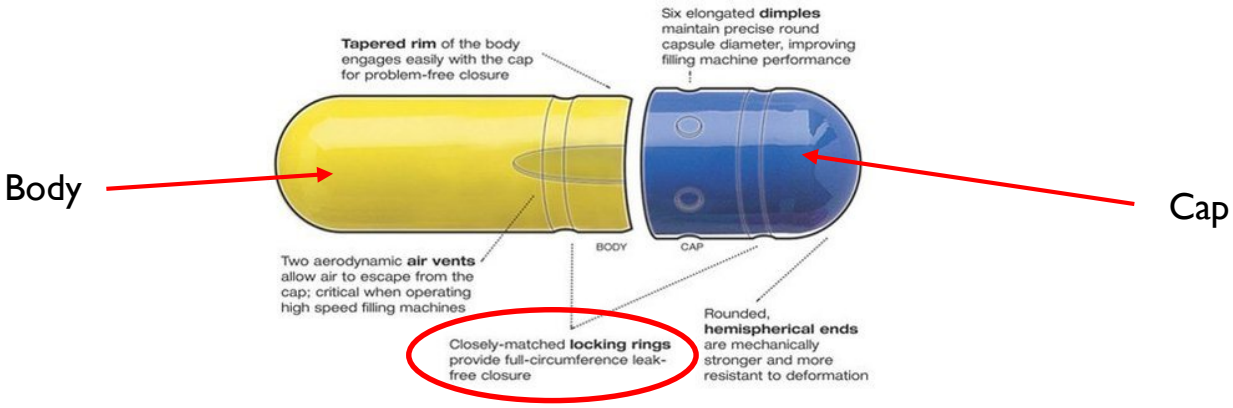
- **Type B gelatin (Alkaline gelatin)**

  by alkaline hydrolysis of bones or cow skin

Capsule Filling Process

Type of capsule

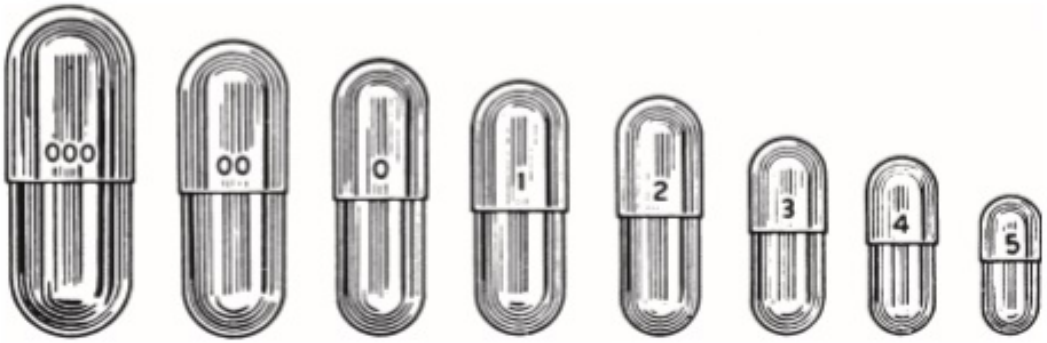
- Hard gelatin capsule



- Soft gelatin capsule

Hard Gelatin Capsule

- Size and shape of hard gelatin capsule



Size	Volume (mL)	Fill weight[a] (g)
000	1.37	1.096
00	0.95	0.760
0	0.68	0.544
1	0.50	0.400
2	0.37	0.296
3	0.30	0.240
4	0.21	0.168
5	0.13	0.104

Source: Adapted from http://capsugel.onlinemore.info/download/BAS192-2002.pdf.

[a]Assumes a powder density of 0.8 g/cm^3.

Hard Gelatin capsule

Hard gelatin capsule filling method

- By hand : Trituration mixing and manual capsule filling
- Small scale : Mixing and semi-automatic filling

Hard Gelatin Capsules

Hard gelatin capsule filling method

- Large scale : Granulation, mixing and automatic capsule filling

Soft-gelatin capsules

Soft-gelatin capsule or softgels

Soft-gelatin capsules

Advantage of soft-gelatin capsule

- Easy to swallow
- Solid, semi-solid and liquid can be filled such as powder, granule, pellet, oil, etc.
- Can make in many size and shape, round, oval, square, droplet shape, etc.
- Can design the releasing action, conventional release, delayed release and controlled release product

Disadvantage

- Use special machine'
- Awareness for the stability of drug
- Limited for additive selection

Soft-gelatin capsules

Soft-gelatin capsule filling method

- Plate process
- Rotary die process
- Reciprocating die process
- Accogel process
- Seamless gelatin capsule

Soft-gelatin capsules

Soft-gelatin capsule filling method

- Plate process
  - Placing a warm gelatin sheet on a die plate which have a numerous die pockets.
  - Pulling down the sheet into the pocket by applying vacuum.
  - Pouring the measured liquid medicament into gel pocket.
  - Placing the second gelatin sheet and putting the top die plate on it.
  - Pressing the die plate to form fill, seal and cut into individual capsule unit.
  - Removing and washing the capsule.

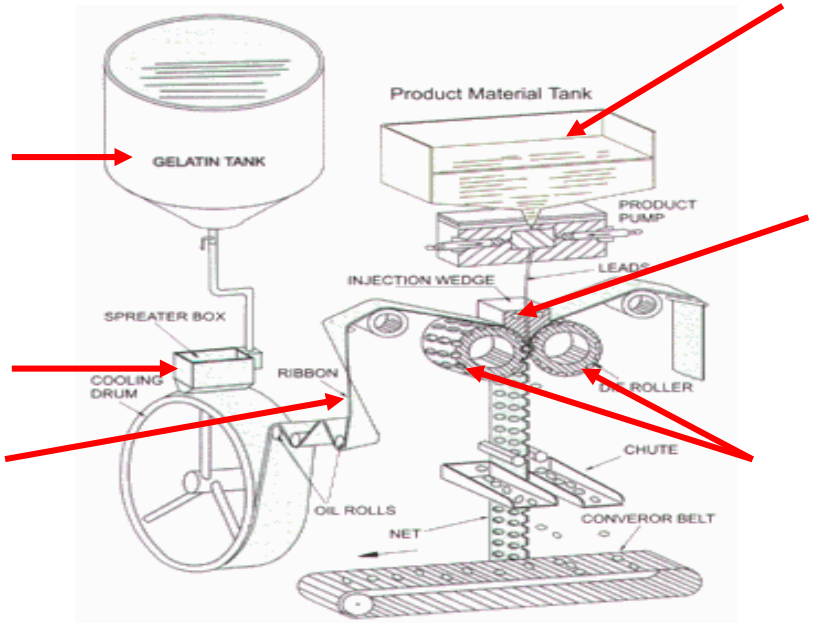
Soft-gelatin capsules

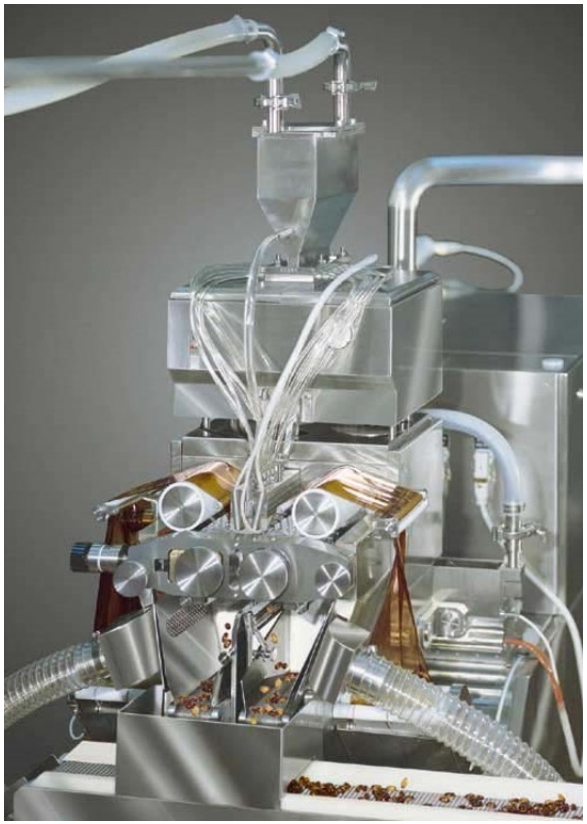
Soft-gelatin capsule filling method

- Rotary die process
- Reciprocating die process
  - Dissolved gelatin in water at about 80 °C
  - Add plasticizer, color, opacifier and preservative.
  - Then maintain the temperature at 57 – 60 °C in melting tank.
  - The hot gel mass transfer to drum and cool down to form two separate gelatin ribbon.
  - Two gel ribbons are fed to twin rotating dies, before opposing roller meet, medicament is filled and then the gel ribbon are pressed immediately to form a capsule..
  - Then cut into individual capsule,

Soft-gelatin capsules

Rotary die process and Reciprocating process





Source: Pharmagel Engineering SPA: Milan, Italy

Soft-gelatin capsules

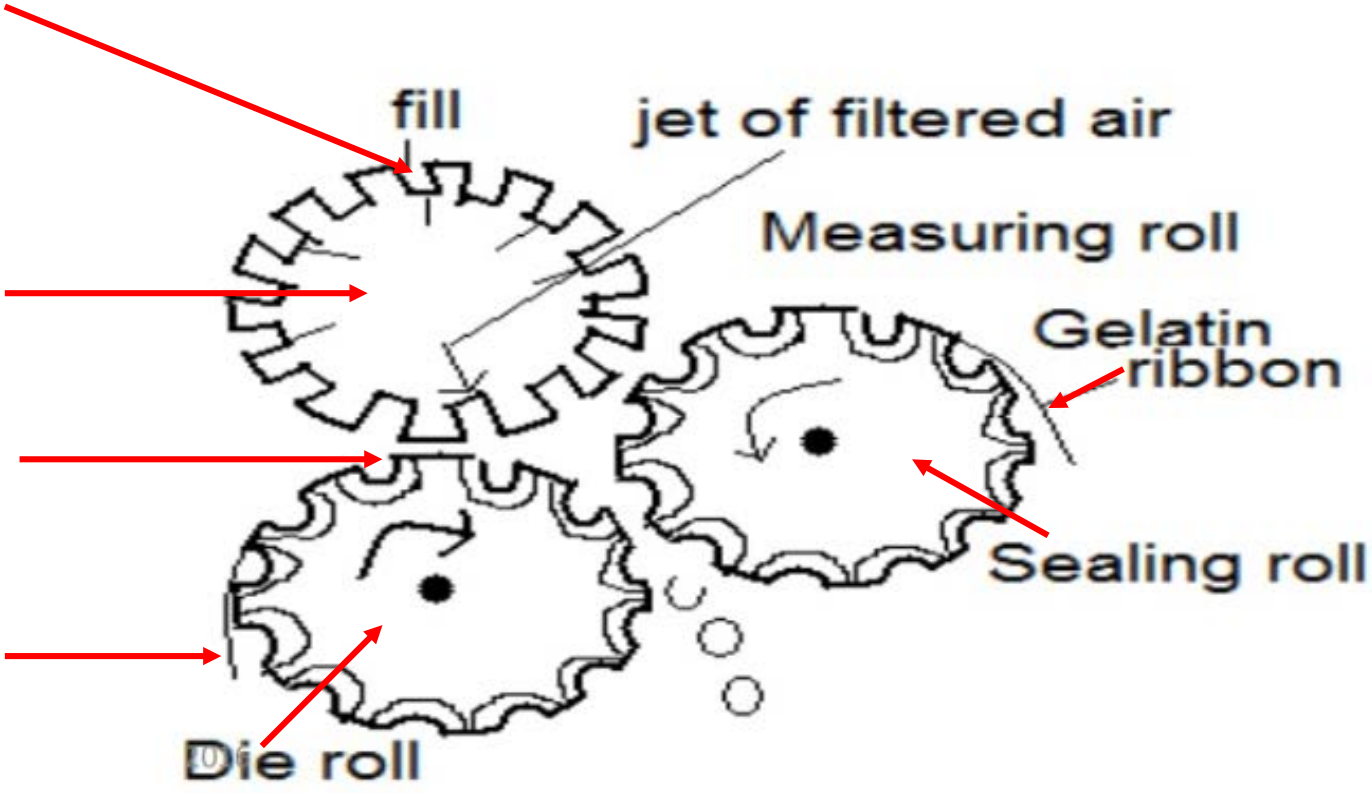
Soft-gelatin capsule filling method

- Accogel process
  - This technique is special process for powder filling in soft gelatin capsule.
  - In general process, there are 3 roller
    - A measurement roller
    - A die roller
    - A sealing roller
  - The measurement roller measure dose of medicament and transferring to the gelatin-linked pocket of the die roller.
  - The die roller continue rotation to the sealing roller where the second gelatin sheet is applied to form the other half of the capsule.
  - Press between the die roller and sealing roller to seal and cut the capsule

Soft-gelatin capsules

Soft-gelatin capsule filling method

- Accogel process



Soft-gelatin capsules

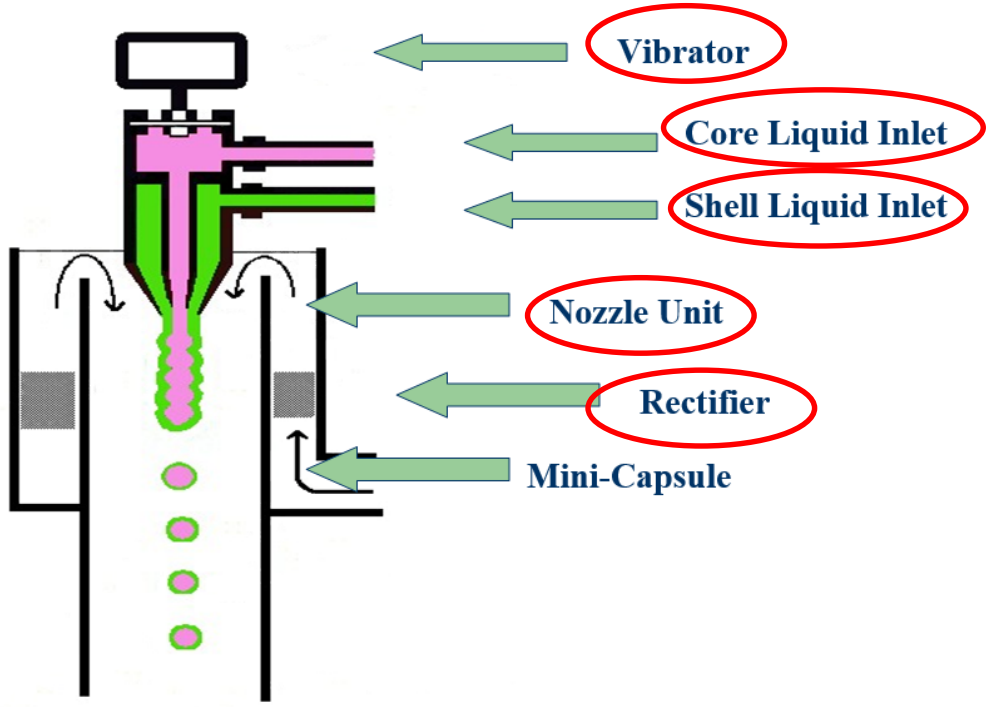
Soft-gelatin capsule filling method

- Seamless gelatin capsule or Bubble method
  - The concentric tube dispenser discharge the molten gelatin as the shell of capsule
  - The medicament liquid was vibrated and pump from the concentric tube as droplets of liquid medicament core within a molten gelatin envelop.
  - The droplets assume a spherical shape under surface tension forces and the gelatin congeals on cooling oil column.
  - Washing to remove oil and drying the softgels.

Soft-gelatin capsules

Soft-gelatin capsule filling method

- Seamless gelatin capsule



Difference between Hard Gelatin and Soft Gelatin Capsules

Hard Gelatin Capsules	Soft Gelatin Capsules
Hard gelatin capsule shell contains of two parts, body and cap	Soft gelatin capsule shell becomes only one part after sealing
Cylindrical shape	Various shapes, round, oval, oblong
Usually in hard gelatin capsule consists of medicaments in form of powder, beads, granules	Usually in soft gelatin capsule consists of liquid, solid dissolved or dispersed, powder, granules, pellets
Hard gelatin capsule prepares from gelatin, plasticizer, titanium dioxide, coloring agent, water	Soft gelatin capsule prepare from gelatin, plasticizer, preservative, water, coloring agent and flavors
Medicaments may leakage out of hard gelatin capsule due to rough handling, if no sealing between cap and body	Soft gelatin capsules are sealed to be one part on machine

QUALITY CONTROL IN SOLID DOSAGE FORMS

- *Molee Sontichai*

Quality control

- In-process Control (IPC)
- In-process Quality Control (IPQC)
- Finished Product Quality Control (FPQC)

Finished Product Quality Control of Tablet

FPQC

Quality control in tablet

- **Quality control in tablet as USP**
  - Universal test for tablet
  - Specific test for tablet
- **Quality control in tablet as Pharmacopoeia**
  - Non-official tests or Non-Pharmacopoeial tests
  - Official tests or Pharmacopoeial tests

Quality control in tablet as USP

- **Universal tests**
  - Description
  - Identification
  - Assay
  - Impurities
- **Specific tests**
  - Volatile content
  - Disintegration test
  - Tablet friability
  - Hardness or Tablet breaking force
  - Uniformity of dosage unit

Quality control in tablet as Pharmacopoeia

- **Non – official tests**
  - Hardness test (Breaking force)
  - Thickness
  - Diameter
  - Friability test
- **Official tests**
  - Uniformity of weight (Weight variation)
  - Uniformity of content
  - Disintegration test
  - Dissolution test
  - Content of Active ingredient

In – process Quality Control of Tablet

IPQC

IPQC in granulation process

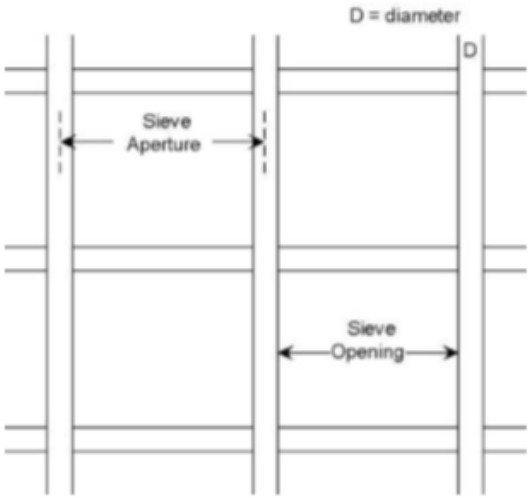
- **Particle size distribution**

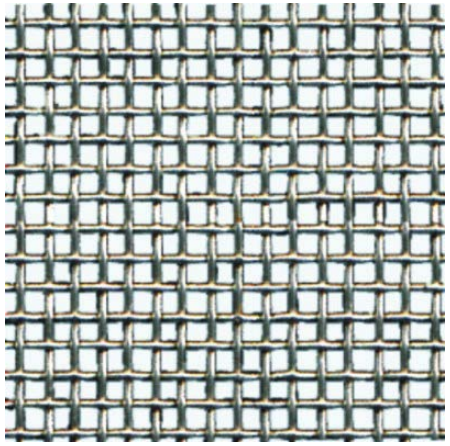
Mesh size

is the mesh number (Tyler Standard Sieve Series), it relates to the four little square openings across one inch of screen. The number of mesh size increase, the size of the openings and particle size captured decrease. Higher mesh number is equal finer particle sizes.

Sieve no.

is US sieve series. They will call sieve no.





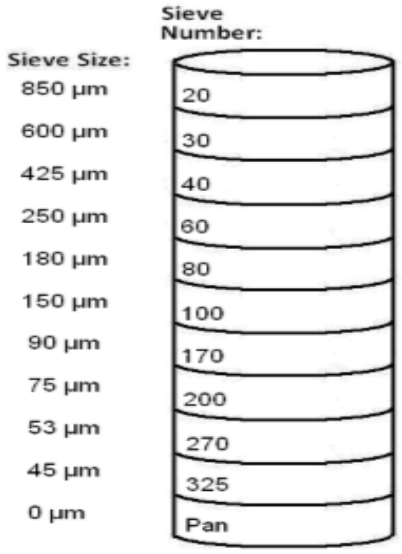
IPQC in granulation process

- **Particle size distribution**

US Sieve Size	Tyler Equivalent	Opening	
		mm	in
No. 4	4 Mesh	4.76	0.187
No. 5	5 Mesh	4.00	0.157
No. 6	6 Mesh	3.36	0.132
No. 7	7 Mesh	2.83	0.111
No. 8	8 Mesh	2.38	0.0937
No.10	9 Mesh	2.00	0.0787
No. 12	10 Mesh	1.68	0.0661
No. 14	12 Mesh	1.41	0.0555
No. 16	14 Mesh	1.19	0.0469
No. 18	16 Mesh	1.00	0.0394
No. 20	20 Mesh	0.841	0.0331

IPQC in granulation process

- **Particle size distribution**
- Measurement method
  1. Obtain the appropriate sieve
  2. Obtain the sample
  3. Perform the test (shake, frequency, strength, time)
  4. Weigh the sample in each sieve
  5. Calculate total percent passed for each sieve
  6. Plot percent passed against sieve size

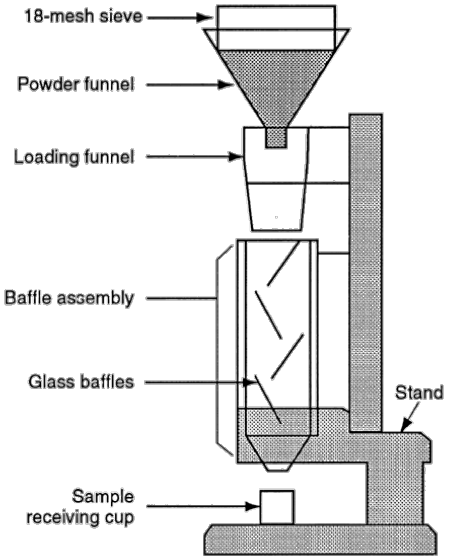


IPQC in granulation process

- **Density**
  - Bulk density

    Bulk density = Mass/Volume

    - Measurement in graduated cylinder
    - Measurement in a Volumeter
    - Measurement in a Vessel
  - Tapped density



IPQC in granulation process

- **Loss on dry**

$$\text{Loss on drying (\%)} = \frac{\text{initial weight of sample - weight of sample after drying x 100}}{\text{Initial weight of sample}}$$

➢USP <731> Loss on drying

- Weighing bottle → heat → cool in desiccator→ weigh
- Weigh sample → put in weighing bottle → heat
- Cool in desiccator→ weigh
- Calculate % weight loss

➢ Moisture analyzer

IPQC in tablet compression process

- Tablet Breaking Force or Tablet Hardness
- Tablet Diameter
- Tablet Thickness
- Tablet Weight
- Tablet Friability Test
- Tablet Disintegration or Dissolution Rate

IPQC in tablet compression process

- **Tablet Breaking Force or Tablet Hardness**
  - **Sample 10 tablets**
  - **Tablet breaking force measurement by applying force in horizontal of tablet diameter**

Monsanto Hardness Tester

Strong - cobb Tester

PharmaTest Type: PTB 302

IPQC in tablet compression process

- **Tablet Diameter**
- **Tablet Thickness**

IPQC in tablet compression process

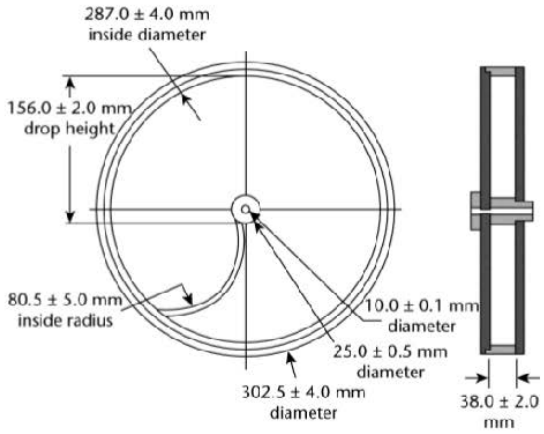
- **Tablet Weight**
  - **Average weight**
    - Sample 20 tablets
    - Weigh and average the weight
  - **Uniformity of weight**
    - Sample 20 tablets or Sample all punch & die or one round of tableting station
    - Individual weigh

USP Standards	Max. % Difference Allowed	BP/ IP Standards
130 mg or less	10 %	84 mg or Less
130 mg – 324 mg	7.5 %	84 mg – 250 mg
More than 325 mg	5 %	More than 250 mg

IPQC in tablet compression process

- **Tablet Friability Test**
  - **Sample 20 tablets**
  - **Friability test and calculate the % of Friability loss, should be loss than 1%**

$$\text{Friability loss (\%)} = \frac{\text{Initial weight} - \text{Final weight}}{\text{Initial weight}} \times 100$$



IPQC in tablet compression process

- **Tablet Disintegration**
  - **Sample 6 tablets**
  - **Temperature of solution 37± 2 °C**
  - **Check disintegrating time**

Tablet Disintegration Time Test

USP Standard for Disintegration Time Test			
Type of Tablet	Medium	Temperature	Limit
Uncoated Tablets	Water / specific medium as specified in the individual monograph	37° ± 2 °C	As specified in the individual monograph
Coated Tablets	Water / specific medium as specified in the individual monograph	37° ± 2 °C	As specified in the individual monograph
Delayed-Release /Enteric-Coated Tablet	1. Simulated Gastric Fluid TS	37° ± 2 °C	After 1 hour, no evidence of disintegration, cracking. softening
	2. Simulated Intestinal Fluid TS	37° ± 2 °C	As specified in the individual monograph
Buccal Tablets	Water / specific medium as specified in the individual monograph	37° ± 2 °C	After 4 hours
Sublingual Tablet	Water / specific medium as specified in the individual monograph	37° ± 2 °C	As specified in the individual monograph
Hard Gelatin Capsule	Water / specific medium as specified in the individual monograph	37° ± 2 °C	As specified in the individual monograph
Soft Gelatin Capsule	Water / specific medium as specified in the individual monograph	37° ± 2 °C	As specified in the individual monograph

Note

Capsule: Attach a removable wire cloth, which has a plan square weave with 1.8 – 2.2 mm mesg apertures and with a wire diameter of 0.60 – 0.655 mm, to the surface of the upper plater of the basket-rack assembly

Result: If 1 or 2 tablets fail to disintegrated completely, repeat the test on 12 additional tablets. The requirement is met if not fewer than 16 tablets of the total of 18 tablets tested are disintegrated completely.

Tablet Disintegration Time Test

BP Standards for Disintegration Time Test				
S/N	Type of Tablet	Medium	Temperature	Limit
1.	Normal Release Tablets (Uncoated Tablets)	Water/ Buffer	37° ± 2°C	15 minutes/ as specified in the individual monograph
2.	Sugar Coated Tablets	Water/ 0.1 N HCl	37° ± 2°C	60 minutes/ as specified in the individual monograph
3.	Film Coated Tablets	Water	37° ± 2°C	30 minutes/ as specified in the individual monograph
4.	Dispersible Tablets	Water	15° – 25°C	03 minutes/ as specified in the individual monograph
5.	Effervescence Tablets	200 ml of non-agitated water	15° – 25°C	05 minutes/ as specified in the individual monograph
6.	Modified-Release/ Enteric-Coated Tablets	i. 0.1 M HCl/ as specified in the individual monograph	37° ± 2°C	No evidence of disintegration after 2- 3 hour
		ii. Phosphate buffer solution pH 6.8	37° ± 2°C	60 minutes
6.	Orodispersible Tablets	Water/ as specified in the individual monograph	37° ± 2°C	03 minutes
7.	Soluble Tablets	Water	15° – 25°C	03 minutes
8.	Oral Lyophilisates	200 ml of non-agitated water	15 – 25°C	03 minutes

IPQC in tablet compression process

- **Dissolution Rate**
  - **Sample 6 tablets**
  - **Temperature of solution** 37 ± 0.5 **°C**
  - **Sampling solution 3 interval times and test in QC by spectrophotometer**
  - **Except extended or delayed release**

Dissolution Apparatus

Dissolution Apparatuses Commonly Used to Test Dosage Forms			
USP Apparatus	**Description of the Apparatus**	**Rotation Speed**	**Dosage Forms to be Tested**
I	Basket	50 - 120 rpm (revolutions per minute)	Immediate-release tablets Delayed-release tablets Extended-release tablets
II	Paddle	25 - 50 rpm	Immediate-release tablets Delayed-release tablets Extended-release tablets
III	Reciprocating cylinder	635 dpm (dips per minute)	Immediate-release tablets Extended-release tablets
IV	Flow-through cells	N/A	Extended-release tablets Poorly soluble drug
V	Paddle over disk	25 - 50 rpm	Transdermal
VI	Cylinder	N/A	Transdermal
VII	Reciprocating disk	30 rpm	Extended-release tablets

IPQC in Capsule Filling Process

Hard gelatin capsule

- Visual inspection
- Weight
  - Weight variation
  - Uniformity of weight
- Content uniformity
- Disintegration test

IPQC in Capsule Filling Process

Soft gelatin capsule

- Gelatin ribbon thickness and uniformity across the ribbon
- Visual inspection
- Weight
  - Weight variation
  - Uniformity of weight
- Content uniformity
- Disintegration test