Granulation

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Granulation

Granulation is the process in which the primary powder particles are made to adhere to form larger, multiparticulate entities called granules.

Granules are either used in their own right as a dosage form or as an intermediate product in the production of tablets or capsules.

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Granulation

Reasons for granulation

The main aims of granulation are:

1. To prevent segregation and thereby improve homogeneity.
2. Improve the flowability of mix to ensure complete and uniform filling of tablet dies, capsules etc. This lead to less weight and dose variations.
   - Granules produced from cohesive materials will be larger and more isodiametric
3. Improve the compactability of powder.
   - Some materials have bad flow and compression properties so that they can not be formed by direct compression and therefore need granulation.

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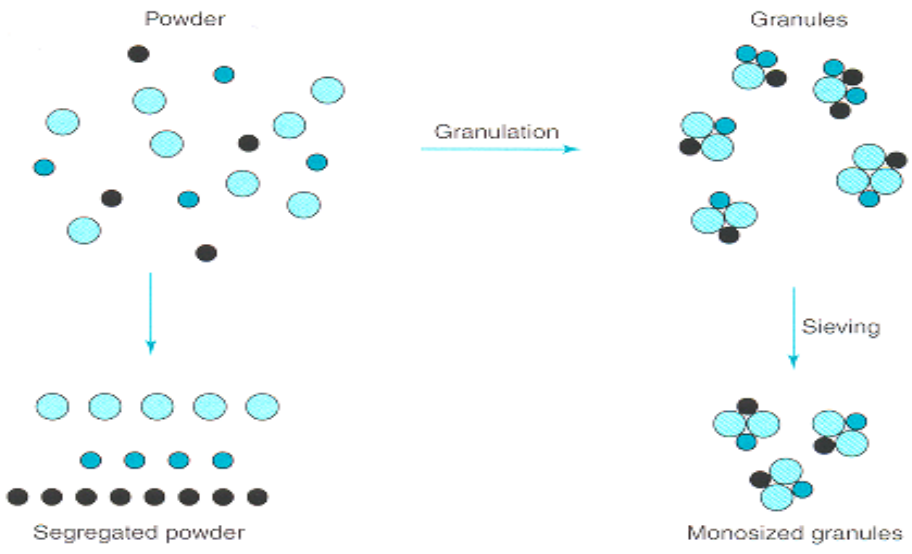

ıtic diagram to illustrate how granulation can prevent powder segregation.

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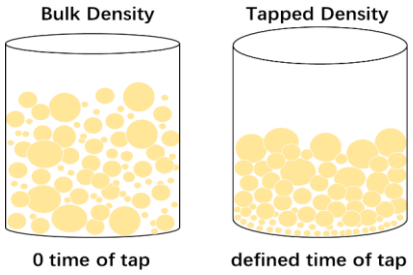
Granulation

Reasons for granulation

4. Eliminate problems due to dust (e.g. toxic materials).
5. To reduce the problem of caking of hygroscopic materials.
6. Increase bulk density of the powder mixture making them more convenient for storage or shipment.



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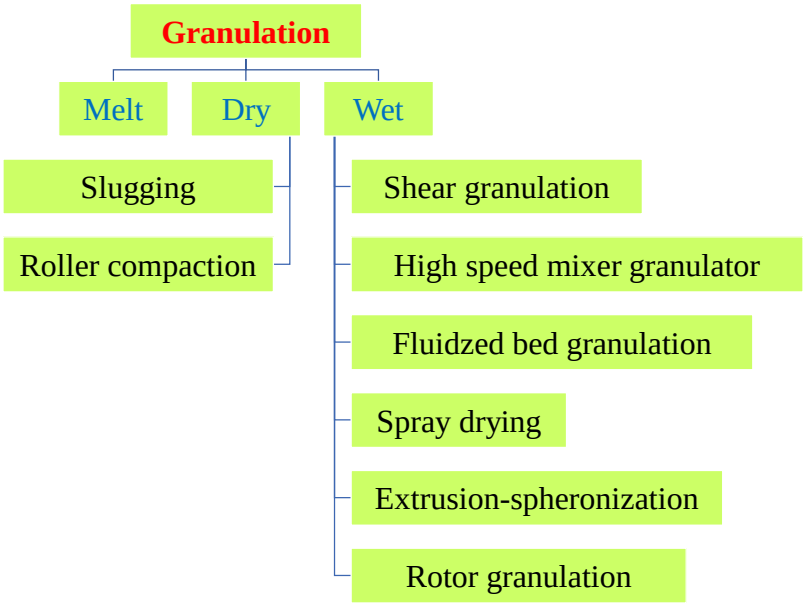

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Granulation methods

Dry granulation

- Other term used to describe the process is compression granulation.
- It converts the powders into granules by application of pressure without the intermediate use of liquid.
- This method is used mainly with heat and moisture sensitive materials like aspirin and many vitamins.
- There are two main processes of dry granulation: **Slugging & Roller compaction**

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Dry granulation methods

Slugging

Procedure:

- Powders (drug and additives like diluent, binder and disintegrant) are mixed and compressed on high capacity tableting machine.
- The compacted masses (slugs) are subsequently comminuted and screened into smaller granules.

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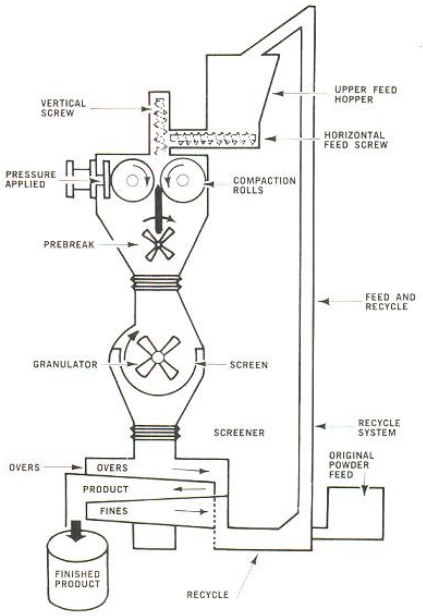
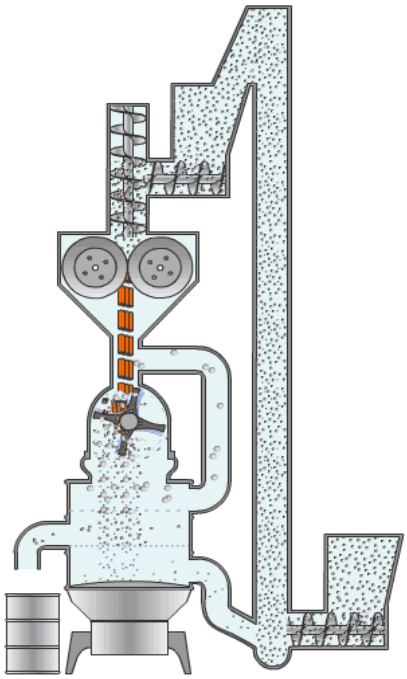


FIG. 11-13. *Schematic diagram of a Chilsonator roller compactor in a granulation production system. (Courtesy of the Fitzpatrick Company, Elmhurst, IL.)*



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Dry granulation methods

Roller compaction

- On large scale, dry granulation can be performed on a specially designed machine called roller compactor.
- The powder is squeezed between two rollers to produce a sheet of material which is then comminuted and screened to small granules.

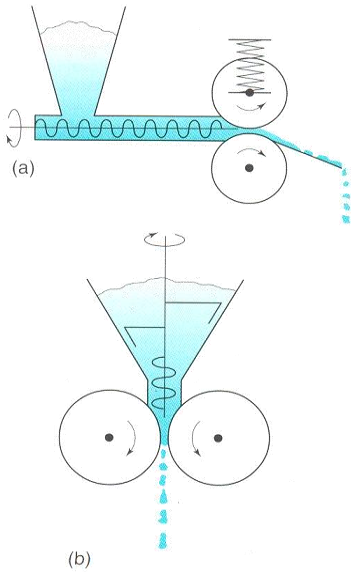

Fig. 29.12 Roller compaction: (a) Alexanderwerk and (b) Protec types.

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Dry granulation methods

Advantages of the roller compaction process:

1. The process is economical.
2. There are relatively low investment costs compared with alternative granulation processes using multiple, and more expensive equipment.
3. It can cope with a wide range of materials, particle size, bulk density and flowability (But not all materials)
4. The process is easily scaled up.
5. The product has uniform properties with respect to its mechanical strength.
6. Additionally, the more gentle ‘squeeze’ of roller compactors leaves the resulting granules capable of further compaction into tablets without the work-hardening problems encountered with slugging.

Dry granulation methods

Advantages of dry granulation:

- Utilizes less equipment and space than wet granulation.
- Eliminates the need for binder solution and drying process.

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Granulation methods

Wet granulation

- This is the main method for preparation of pharmaceutical granulation and the granules prepared are of good quality.

Disadvantages

A. High cost
B. Long operation procedure
C. The use of binding liquid and heat creates problem for heat and moisture sensitive drugs. Sometimes alcohol is used in binding liquid instead of water if the drug is sensitive to moisture.

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Granulation methods

Procedure

1. The ingredients to be granulated are mixed to achieve good homogeneity.

2. In addition to the active drug, the mixture may contain a diluent, disintegrant, binder.

3. The binder (adhesive) is either mixed with powders or dissolved in the granulation liquid.

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Granulation methods

4. Granulation liquid is prepared (Volatile solvents are used such as water, ethanol and isopropanol, so that they can be removed by drying).
5. The granulation liquid is added to the powder mixture and mixing continues until uniform dispersion (wet mass) is obtained. This process is termed ***wet massing***.
6. The wet mass is screened to obtain the desired coarse particle size and the particles are then tray -dried. Alternatively fluid-bed drying is applied.
7. Size reduction of granules may be done using a hammer mill.

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Granulation mechanisms

Particle bonding mechanisms

There are five primary bonding mechanisms between particles:

1) Adhesion and cohesion forces in the immobile liquid films between individual primary powder particles.
   - An immobile layer (thin film) around particles will increase the diameter and decrease interparticulate distance, therefore it increases van der Waals forces.

2) Interfacial forces in mobile liquid films within the granule.
   - During wet granulation, sufficient liquid is added to produce a mobile film.
   - There are different states of liquid distribution between particles according to moisture content:
     - Pendular
     - Funicular
     - Capillary
     - Droplet (Suspension)

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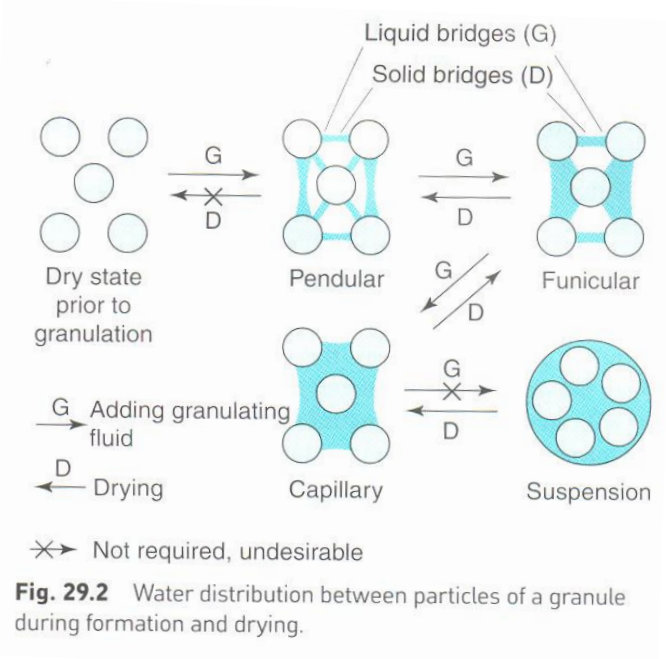

Fig. 29.2 Water distribution between particles of a granule during formation and drying.

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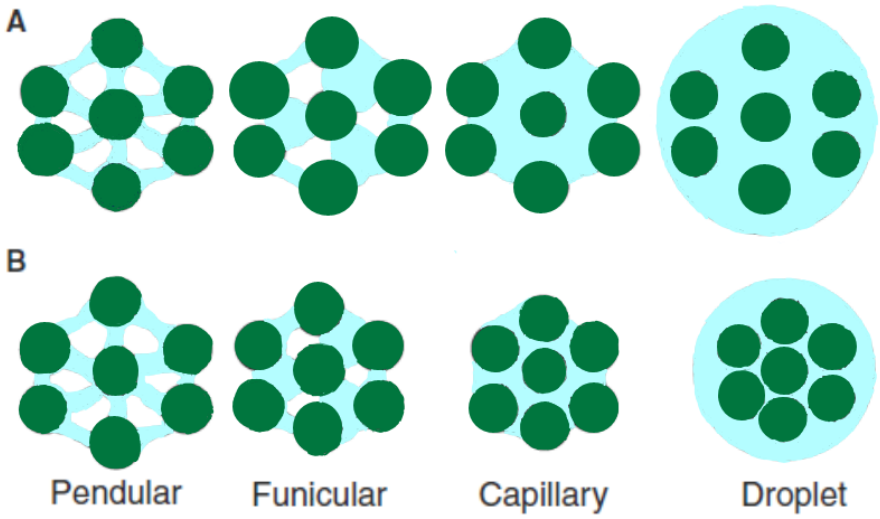

Fig. 2 Liquid-bridging state of agglomerates undergoing (A) binding liquid addition and (B) densification.

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Particle bonding mechanisms

3) The formation of solid bridges after solvent evaporation(drying). These can be formed by:
- Partial melting
- Hardening binders
- Crystallization of dissolved substances

4) Attractive forces between solid particles
- Electrostatic forces
- Van der Waal forces

5) Mechanical interlocking

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Pharmaceutical granulation equipment

Wet granulators

1) Shear granulators

- This is a traditional method of granulation
- It often uses a ***planetary mixer*** for wet massing of the powders.
- Mixing of powders is either done in a separate mixers or in the same planetary mixer.
- The liquid is added as the paddles of mixer agitates the powder.
- The moist mass is then transferred to a granulator (such as ***oscillating granulator***)

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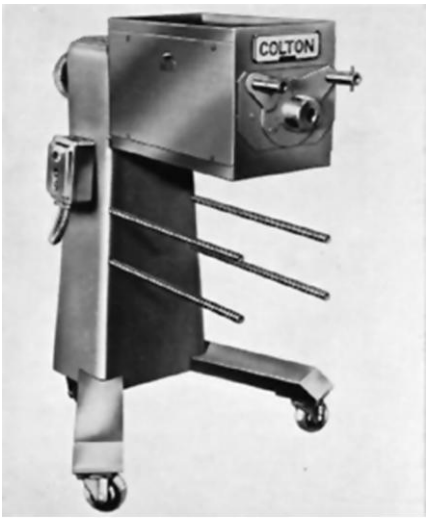
Pharmaceutical granulation equipment

- The rotor bars of this granulator oscillate and force the moist mass through the sieve screen.
- The mass should be sufficiently moist to form discrete granules:
  - If excess liquid → strings of material will be formed
  - If too dry → the mass will be sieved to powders and not granules
- The granules can then be collected on trays and transferred to a drying oven or dried using fluidized-bed drier.



Oscillating granulator

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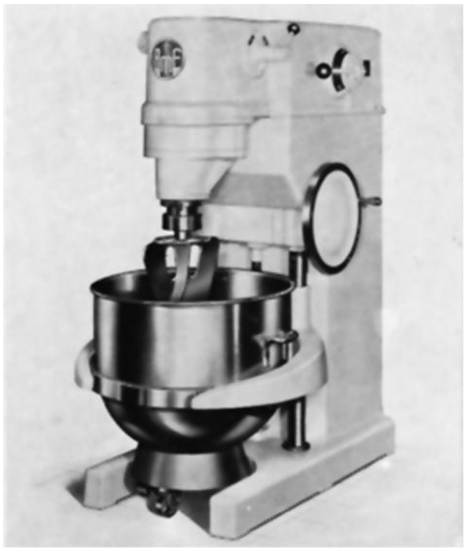
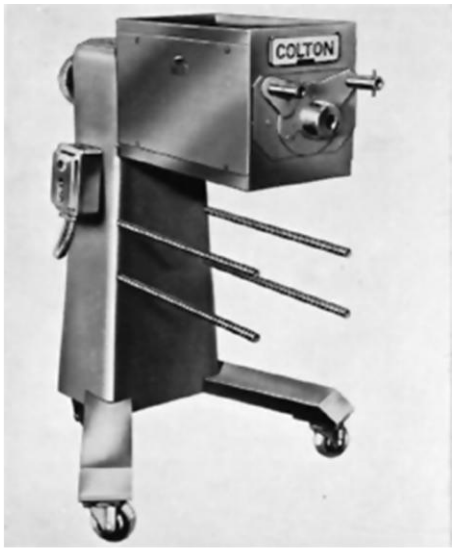


planetary mixer



oscillating granulator

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If excess liquid → strings of material will be formed
If too dry → the mass will be sieved to powders and not granules

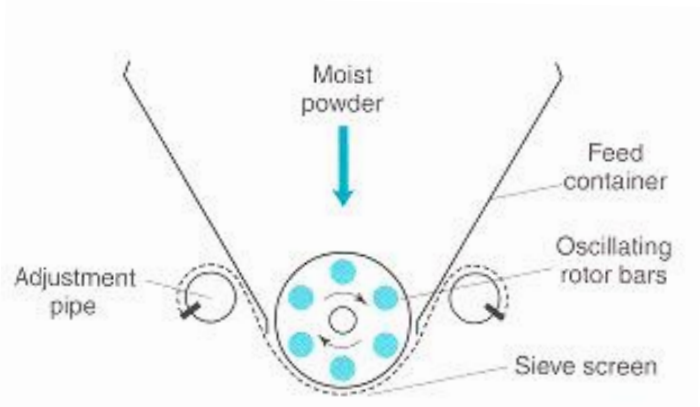

Fig. 29.6 Oscillating granulator.

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***Disadvantages of tray drying*:**

- The drying time is long
- Dissolved material may migrate to the upper surface of the bed on the tray
- Granules may aggregate due to bridge formation at the points of contact of granules

➢To deaggregate the granules and remix them a **sieving** stage is necessary after drying

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Advantages of the traditional method (shear granulation)

1. The process is not very sensitive to changes in the characteristics of the granule ingredients
2. The end-point can often be determined by inspection

Disadvantages of traditional granulation

1. Too long duration
2. The need for several pieces of equipment
3. High material loss because of the transfer stages

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Pharmaceutical granulation equipment

2) High-speed mixer/granulators (High shear granulators)

- This machine have a three-bladed main impeller, which revolves in the horizontal plane, and a three–bladed auxillary chopper which either revolves in the vertical or horizontal plane.
- The unmixed dry powders are placed in the bowl and mixed by the rotating impeller for a few minutes.
- The granulating liquid is then added via a port in the lid of the granulator while the impeller is turning.
- The chopper is usually switched on when the wet mass is formed to break up the wet mass to produce a bed of granular material.

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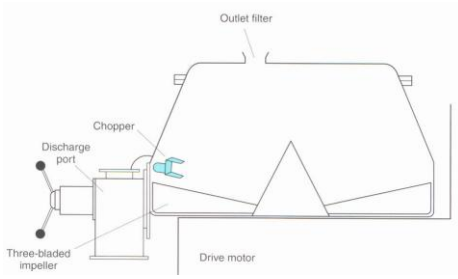
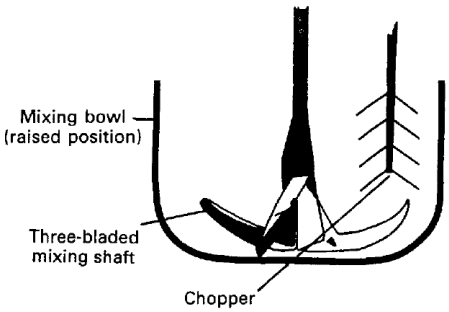
Bottom-driven



Top-driven



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Bottom-driven high shear granulators

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Top-driven high shear granulators

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High-speed mixer/granulators

- Once a satisfactory granules has been produced, the granular product is discharged , passing through a wire mesh that breaks up any large aggregates, into the bowl of a fluidized-bed drier.
- Granulation proceeds rapidly and controlling with care is necessary as granules can proceed very rapidly to unusable, overmassed system.
- The process is sensitive to variations in raw material.
- ***Advantage***: Mixing, wet massing and granulation are done in few minutes.

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Pharmaceutical granulation equipment

3) Fluidized-bed granulators

- Fluid-bed granulators are similar in design and operation to fluid bed dryers, but in addition fluid is sprayed from a nozzle on to the bed of powder.
- Heated and filtered air is blown through the bed of unmixed powders to fluidize the particles and mix the powder.
- Exhaust filters allow the prevent the escape of powders.
- Granulating fluid is pumped over the bed of powder which cause particles to adhere and form granules.
- After formation of granules, the spraying is stopped and the fluidizing hot air continues to dry them.

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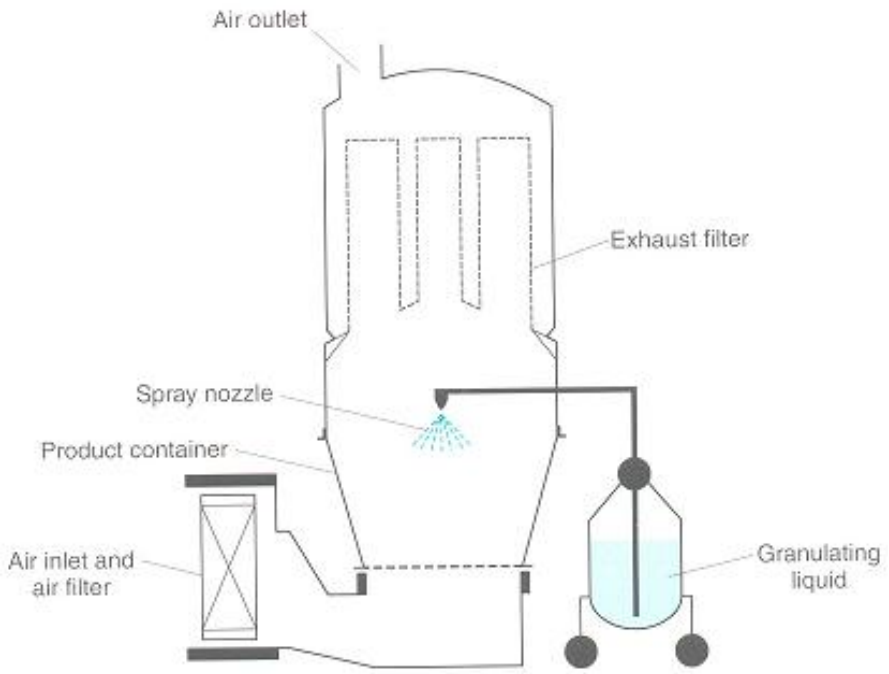
Air outlet
Exhaust filter
Spray nozzle
Product container
Air inlet and
air filter
Granulating
liquid

33


ARIA 600


Glatt
Spraying
Uniform coating process
make a gif.com

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Fluidized-bed granulators

Advantages

1. The performance of many steps (mixing, granulation and drying) in one equipment.
2. The Process can be automated once the conditions affecting the granulation have been optimized.

Disadvantages

A. Expensive instrument

B. Optimization needs extensive work

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Apparatus, process and product variables influencing fluidized-bed granulation

Apparatus parameters	Process parameters	Product parameters
Air distribution place	Bed load	Type of binder
Shape of granulator body	Fluidizing air flow rate	Quantity of binder
Nozzle height	Fluidizing air temperature	Binder solvent
Positive or negative pressure operation	Fluidizing air humidity	Concentration of granulating solution
	Atomization • Nozzle type • Spray angle • Spraying regime • Liquid flow rate • Atomizing air flow rate • Atomizing air pressure • Droplet size	Temperature of granulating solution
		Starting materials • Fluidization • Powder hydrophobicity

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Pharmaceutical granulation equipment

4) Spray driers

- This differs from other methods of granulation in that granules are formed from a solution or a suspension rather than initially dry powder particles.
- The components (drug, diluent) are suspended in a liquid that may contain a dissolved binder.
- The solid percentage should be relatively high.
- The suspension is pumped under continuous agitation in a stream of hot air.
- The liquid evaporates leaving the solid in form of free-flowing hollow spherical granules with uniform size.

❖Used mainly for the preparation of direct compression diluents.

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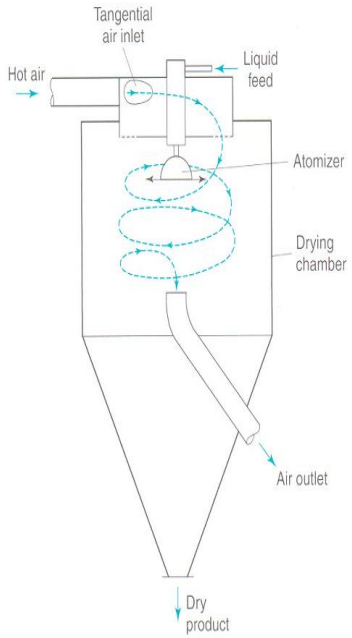
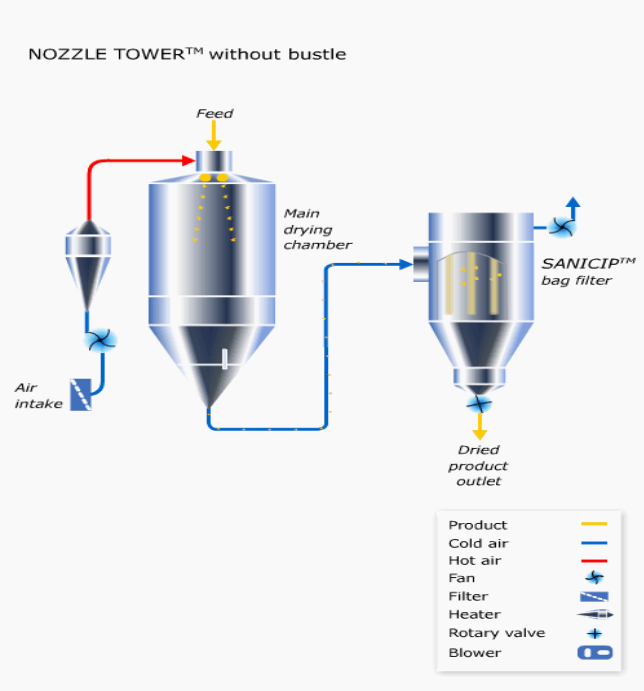


Fig. 30.7 Spray dryer.



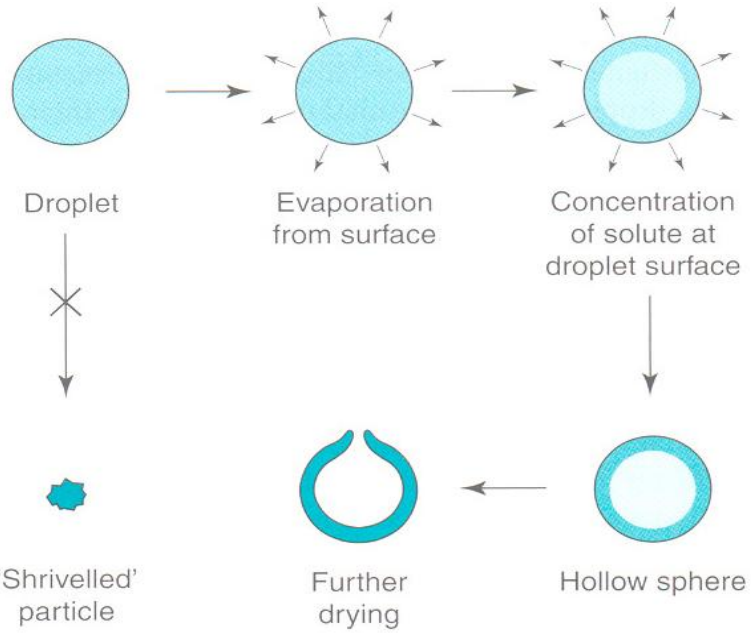


Fig. 30.9 Formation of product in spray drying.

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Spray driers

Advantages

A. Short drying time
B. Minimal exposure of the product to heat → little deterioration of heat-sensitive materials.
C. The characteristic particles have large surface area and so rapid dissolution.
D. The powder has a uniform and controllable particle size.
E. The product formed has excellent flow and compaction properties.
F. Labor costs are low.

Disadvantages

A. It is costly process and the machine is expensive.
B. The overall thermal efficiency is low.

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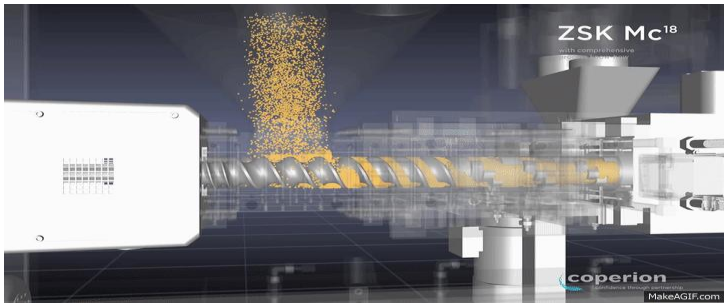
Pharmaceutical granulation equipment

5) Extruders/Spheronizers

- Extrusion/spheronization is a multistep process used to make uniformly sized spherical particles.

- It is used mainly to produce multiparticulates for controlled drug release applications.



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Extruders/Spheronizers

- The main steps of the process are:

1. Dry mixing of ingredients

2. Wet massing

- More amount of liquid is used than other methods.
- Uniform dispersion of liquid is necessary

3. Extrusion

- The wet mass is forced through dies to form rod-shaped particles of uniform diameter.

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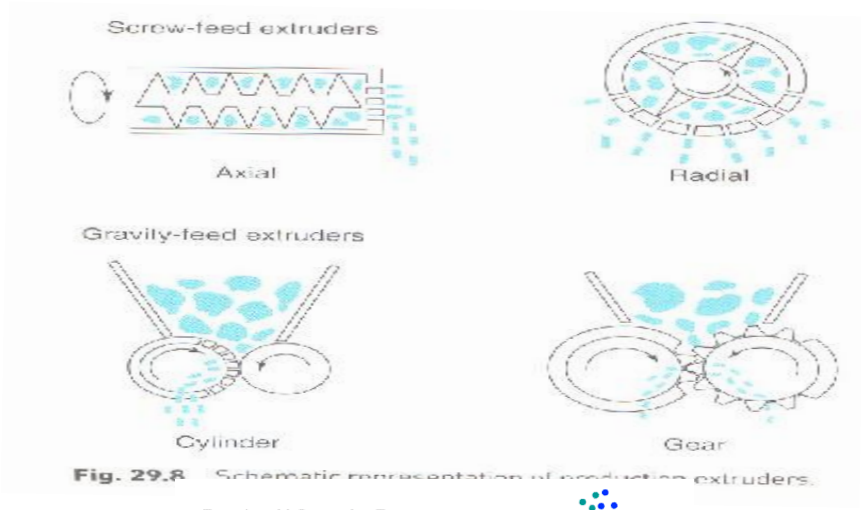
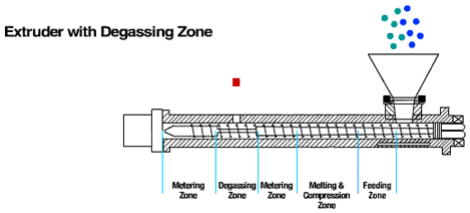


Fig. 29.8 Schematic representation of production extruders.



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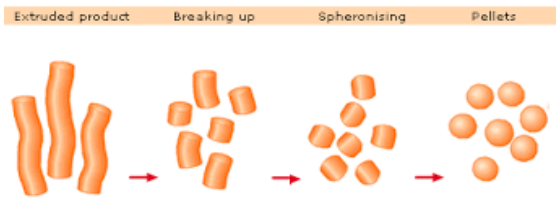
4. Spheronization

- To round off the rods into spherical particles
- This is done in a simple apparatus with fixed side walls and rapidly rotating bottom plate with grooved surface.
- The rounding is done by particle-particle and particle-surface frictions.



5. Drying: Either fluidized-bed or tray drying.

6. Screening: To obtain suitable narrow particle size

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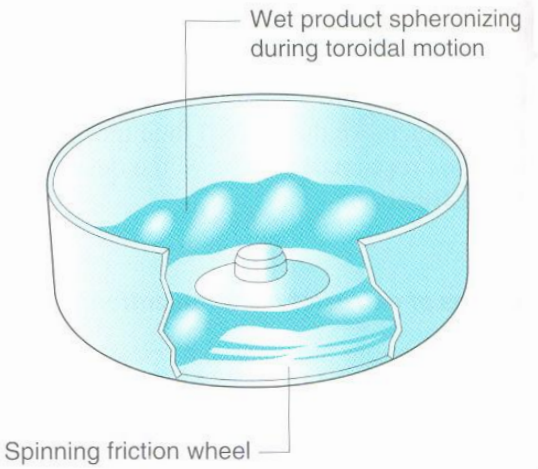

Fig. 29.9 A spheronizer showing the characteristic toroidal (rope-like) movement of the forming pellets in the spheronizer bowl during operation.

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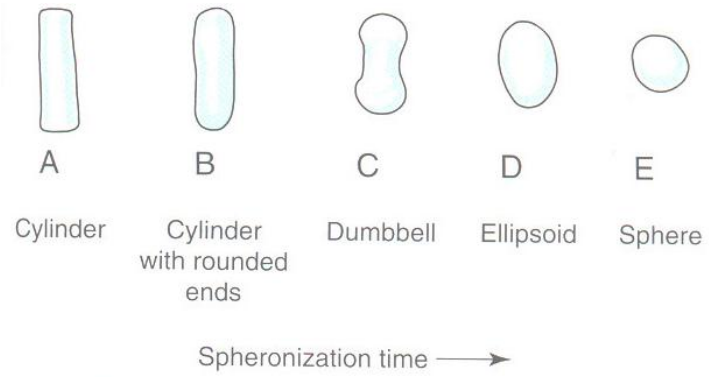

Fig. 29.10 Representation of a mechanism of spheronization. The diagram shows a transition from cylindrical particles (a) into cylindrical particles with rounded edges (b), then dumbbells (c), to ellipsoids (d) and finally spheres (e).

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Pharmaceutical granulation equipment

6) Rotor granulation

- This process allows the direct manufacture of spheres from dry powder.
- In the Freund granulator, the powder mix is added to the bowl and wetted with granulation liquid from a spray.
- The baseplate rotates at high speed and centrifugal force keeps the moist mass at the edges of the rotor.
- The velocity difference between the rotor and the static walls, combined with the upward flow of air around rotor plate, causes the mass to move in a toroidal motion, resulting in the formation of discrete spherical pellets.

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Pharmaceutical granulation equipment

6) Rotor granulation

- These spheres are dried by the heated inlet air from the air chamber, which acts also as a positive pressure seal during granulation.
- Using this technique, it is possible to continue the process and coat the pellets by subsequently spraying coating solution on the rotating dried pellets.
- In addition, layered pellets can be formed by using uncoated pellets as nuclei in a second granulation with a powder mix of a second ingredient.

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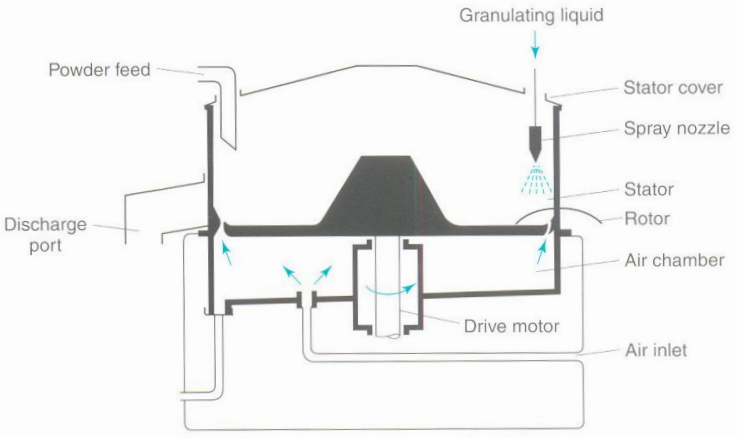

Fig. 29.11 Rotorgranulator.

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Melt granulation

- Melt granulation and melt pelletization processes that have gathered increasing interest in the pharmaceutical industry.
- Unlike the conventional use of aqueous or organic solutions of binders, a molten liquid which remains as a constituent of the formulation is utilized as a binder.
- However, the basic principles in melt granulation processes are relatively similar to those of wet granulation processes with solvents except that the interpretation of the melt agglomeration processes is not complicated by an evaporation of the molten binding liquid.

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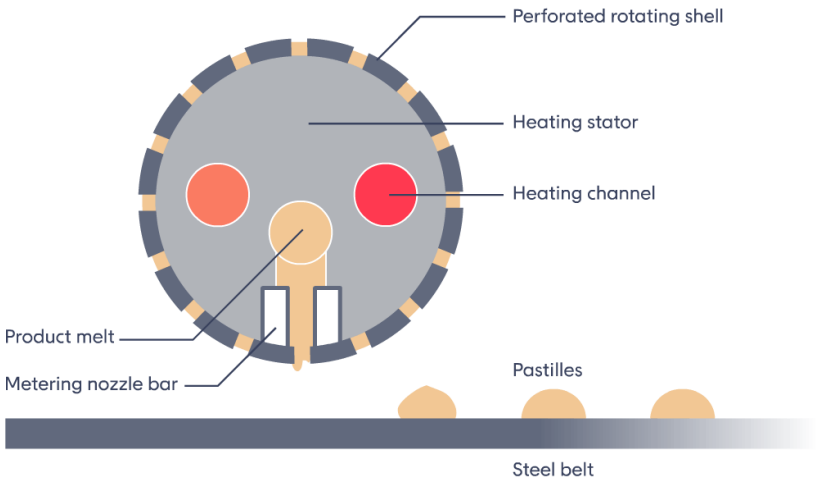
Melt granulation and melt pelletization



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Melt granulation

Hot melt binders

- Hydrophilic:
  - Polyethylene glycols (PEGs): Grades between 2000 - 6000
- Hydrophobic (water insoluble)
  - Carnauba wax
  - Hydrogenated castor oil
  - Hydrogenated cotton-seed oil
  - Stearic acid
  - Fatty acids derivatives (glyceryl behanate, glyceryl monostaearate, glyceryl trilaurate, glyceryl tripalmitate, glyceryl tristearate, hexadecyl palmitate)

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Melt granulation

Hot melt processes

- The following methods (machines) have been adapted for melt granulation:
  1. Shear granulation
  2. High speed mixer granulators
  3. Spray drying
  4. Spray congealing is similar to spray drying. However a molten sample is sprayed and subjected to cold air for congealing.
  5. Fluidized bed granulation
  6. Extrusion/spheronization

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Powders and granules

- The term 'powder' when used to describe a dosage form describes a formulation in which a drug powder has been mixed with other powdered excipients to produce the final product.
- The function of the added excipients depends upon the intended use of the product (ex. Colors, flavors, sweetening agents may be added to powders for oral use).
- Granules which are used as a dosage form consist of powder particles that have been aggregated to form a large particle, which is usually 2 – 4 mm in diameter.

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Powders and granules

- Powders and granulated dosage forms are traditionally dispensed as:
  a. Bulk powders or granules for internal use
  b. Divided powders or granules (i. e. single preparation) for internal use
  c. Dusting powders for external use.
  d. Insufflations for administration to ear , nose or throat
  e. Antibiotic syrups to be reconstituted before use
  f. Powders for reconstitution into injections
  g. Dry powder inhalers.


Powders and granules

Advantages of powders and granules as a dosage form

1. Solid preparations are more chemically stable than liquid ones.
2. Powders and granules are a convenient form in which to dispense drugs with a large dose (ex. Mg trisilicate oral powder dose is 1 – 5 g).
3. Orally administered powders and granules of soluble medicament have a faster dissolution rate than tablets and capsules.

Powders and granules

Disadvantages of powders and granules

1. They are less convenient to carry than a small container of capsules and tablets (except laminated sachets).
2. The masking of unpleasant taste may be a problem.
3. They are not suitable for administration of potent drugs with a low dose.
4. They are not suitable for the administration of drugs which are inactivated in, or cause damage, to the stomach.

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Powders and granules

Dispensed preparations:

Bulk powders

- The mixed ingredients are packed into a suitable b container, such as wide-mouthed glass jar.
- The constituents are usually relatively non-to medicaments with a large dose.

Divided powders

- Divided powders are similar formulations to bulk powders but individual doses are separately wrapped.
- Modern packaging materials of foil and plastic laminates have replaced paper wrapping.

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Powders and granules

Bulk granules

- Segregation, If present in bulk powders, can be prevented by granulation.
- Bulk granules contain similar medicaments to powders (I.e. those with low-toxicity, high dose drugs).

Divided granules

- These are granulated products in which amount sufficient for one dose is individually wrapped.
- Effervescent granules can be presented in this manner

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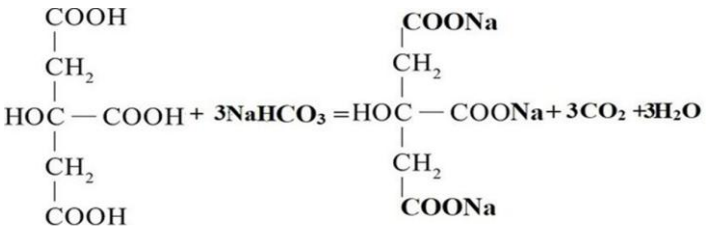
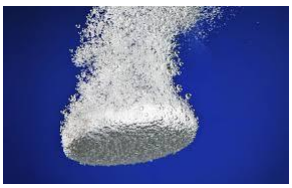
Effervescent granules

- Effervescent pharmaceutical preparations generally contain acid substances and a source of CO_2 (carbonates or bicarbonates salts of sodium, potassium and calcium).

- Traditional acid materials are the citric and tartaric acid. However, ascorbic acid, fumaric acid and acetylsalicylic acid may be used.



Citric acid **Sodium citrate**



60

Preparation of effervescent granules

Wet Granulation Methods

- The acid and carbonate parts of the effervescent formulation can be granulated either separately or as a mixture with water (crystal water of citric acid, liquid water, or water vapor), ethanol (possibly diluted with water), isopropanol, or other solvents.

Dry Granulation

- Granulation by slugging or roller compaction is suitable for active ingredients that cannot be wet granulated.

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Powders and granules

Dusting powders

- Dusting powders contain ingredients used for therapeutic, prophylactic, or lubricant purposes and are intended for external use.
- Only sterile dusting powders should be applied to open wounds.
- Dusting powders for lubricant purposes or superficial skin conditions need not be sterile but they should be free from pathogenic organisms.
- Containers: glass, plastic or metal containers with a perforated lid.
- The powder must flow well from such a container, so that they can be dusted over the affected area.
- The active ingredients must therefore be diluted with materials having reasonably good flow properties, e.g. purified talc or maize starch.

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Powders and granules

Insufflations

- Insufflations are medicated powders which are blown into regions such as the ear, nose and throat using an insufflator.
- The use of traditional insufflations had declined because:
  - They are not very acceptable
  - Dose non-uniformity (if the drug has systemic activity)
- Some potent drugs are now presented in this way because they are rapidly absorbed when administered a fine powder via the nose.

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Powders and granules

Dry powder inhalers

- The use of dry-powder systems for pulmonary drug delivery is now extensive.
- This dosage form has developed into one of the most effective methods of delivering active ingredients to the lung for the treatment of asthma and chronic obstructive pulmonary disease.

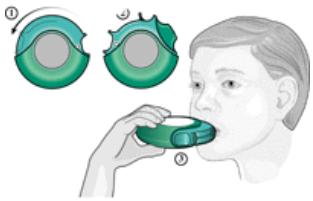

Figure 1: Diskus

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Powders and granules

Oral antibiotic syrups

- For patients who have difficulty in taking capsules and tablets, e.g. young children, a liquid preparation of a drug offers a suitable alternative.
- However many drugs, e.g. antibiotics, are physically or chemically unstable when formulated as a solution or suspension.
- The method used to overcome this instability problem is to manufacture the dry ingredients of the intended liquid preparation in a suitable container in the form of a powder or granules.
- When pharmacist dispenses the product, a given quantity of water is added to reconstitute.
- Shelf life of reconstituted syrup is 1-2 weeks.

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Powders and granules

Powders for injection

- Injections of medicaments that are unstable in solution must be made immediately prior to use and are presented as sterile powders in ampoules.
- Sufficient diluent, e.g. sterile water for injection, is added from a second ampoule to produce the required drug concentration.

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