GRANULATION
Definition

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

- Pharmaceutical granules typically have a size range between 0.2 and 4.0 mm, depending on their subsequent use.

- In the majority of cases this will be in the production of tablets or capsules, when granules will be made as an intermediate product and have a typical size range between 0.2 and 0.5 mm, but larger form in their own right.
• Granulation normally commences after initial dry mixing of the necessary powdered ingredients so that a uniform distribution of each ingredient through the mix is achieved.

• After granulation the granules will either be packed (when used as a dosage form), or they may be mixed with other excipients prior to tablet compaction or capsule filling.
Reasons for granulation

• Primary reasons:
  1. To prevent segregation of the constituents of the powder mix
  2. To improve the flow properties of the mix
  3. To improve the compaction characteristics of the mix
Granulation to prevent powder segregation
• Segregation is due primarily to differences in the size or density of the components of the mixture.

• An ideal granulation will contain all the constituents of the mix in the correct proportion in each granule, and segregation of the ingredients will not occur.

• It is also important to control the particle size distribution of the granules because, although the individual components may not segregate, if there is a wide size distribution the granules themselves may segregate.
To improve the flow properties of the mix

• Many powders, because of their small size, irregular shape or surface characteristics, are cohesive and do not flow well.

• Poor flow will often result in a wide weight variation within the final product owing to variable fill of tablet dies etc.

• Granules produced from such a cohesive system will be larger and more isodiametric, both factors contributing to improved flow properties.
To improve the compaction characteristics of the mix

- Some powders are difficult to compact even if a readily compactable adhesive is included in the mix, but granules of the same formulation are often more easily compacted and produce stronger tablets.

- This is associated with the distribution of the adhesive within the granule and is a function of the method employed to produce the granule.

- Often solute migration occurring during the post granulation drying stage results in a binder-rich outer layer to the granules. This in turn leads to direct binder-binder bonding, which assists the consolidation of weakly bonding materials.
• Other reason:

1. The granulation of toxic materials will reduce the hazard associated with the generation of toxic dust that may arise when handling powders. Thus granules should be non-friable and have a suitable mechanical strength.

2. Materials which are slightly hygroscopic may adhere and form a cake if stored as a powder.

3. Granules, being denser than the parent powder mix, occupy less volume per unit weight. They are therefore more convenient for storage or shipment.
Methods of Granulation

• **Dry granulation**
• **Wet granulation (involving wet massing)**

• In a suitable formulation a number of different excipients will be needed in addition to the drug.

• The common types used are **diluents**, to produce a unit dose weight of suitable size, and **disintegrating agents**, which are added to aid the break-up of the granule when it reaches a liquid medium, e.g. on ingestion by the patient. **Adhesives** in the form of a dry powder may also be added, particularly if dry granulation is employed.

• **These ingredients will be mixed before granulation.**
Dry granulation

• the primary powder particles are aggregated under high pressure.

• used for drugs that do not compress well after wet granulation, or those which are sensitive to moisture.

• There are two main processes.
  1. Slugging: a large tablet (known as a 'slug') is produced in a heavy-duty tabletting press

  2. Roller compaction: the powder is squeezed between two rollers to produce a sheet of material
Granulation

ADVANTAGES:

- Improve flow properties of the mix
- Improve compression properties of the mix
- Prevent segregation of components in powder mix
- Better distribution of color and soluble drug if added in the binding solution
- Reduce production of toxic dust
- Reduce possibility of 'cake' formation
- Increase convenience of transport

Fig. 25.13  Roller compaction: (a) Alexanderwerk and (b) Hutt types.
• In both cases these intermediate products are broken using a suitable **milling technique** to produce granular material, which is usually **sieved** to separate the desired size fraction.

• The unused fine material may be reworked to avoid waste.
Wet granulation (involving wet massing)

- involves the massing of a mix of dry primary powder particles using a granulating fluid.

- The fluid contains a solvent which must be volatile so that it can be removed by drying, and be non-toxic.

- Typical liquids include water, ethanol and isopropanol, either alone or in combination.

- The granulation liquid may be used alone or, more usually, as a solvent containing a dissolved adhesive (also referred to as a binder or binding agent) which is used to ensure particle adhesion once the granule is dry.
Water

• commonly used for economical and ecological reasons. The primary advantage of water is that it is non-flammable, which means that expensive safety precautions such as the use of flameproof equipment need not be taken.

• Its disadvantages as a solvent are that
  1. it may adversely affect drug stability, causing hydrolysis of susceptible products,
  2. it needs a longer drying time than do organic solvents. This increases the length of the process and again may affect stability because of the extended exposure to heat.
• Organic solvents are used when water-sensitive drugs are processed, as an alternative to dry granulation, or when a rapid drying time is required.
• In the traditional wet granulation method **the wet mass is forced through a sieve** to produce wet granules which are then dried.

• A subsequent screening stage breaks agglomerates of granules and removes the fine material, which can than be recycled.

• Variations of this traditional method depend on the equipment used, but the general principle of initial particle aggregation using a liquid remains in all of the processes.
GRANULATION MECHANISMS

Particle-bonding mechanisms

1. Adhesion and cohesion forces in the immobile liquid films between individual primary powder particles
2. Interfacial forces in mobile liquid films within the granules
3. The formation of solid bridges after solvent evaporation
4. Attractive forces between solid particles
5. Mechanical interlocking.
Adhesion and cohesion forces in immobile films

• If sufficient liquid is present in a powder to form a very thin, immobile layer, there will be an effective decrease in interparticulate distance and an increase in contact area between the particles.

• The bond strength between the particles will be increased because of this, as the van der Waals forces of attraction are proportional to the particle diameter and inversely proportional to the square of the distance of separation.
• **adsorbed moisture accounts for the cohesion of slightly damp powders.** Although such films may be present as residual liquid after granules prepared by wet granulation have been dried, it is unlikely that they contribute significantly to the final granule strength.

• **In dry granulation,** however, the pressures used will increase the contact area between the adsorption layers and decrease the interparticulate distance, and this will contribute to the final granule strength.

• **Thin, immobile layers may also be formed by highly viscous solutions of adhesives,** and so the bond strength will be greater than that produced by the mobile films discussed below. The use of starch mucilage in pharmaceutical granulations may produce this type of film.
Interfacial forces in mobile liquid films

- During wet granulation liquid is added to the powder mix and will be distributed as films around and between the particles.

- Sufficient liquid is usually added to exceed that necessary for an immobile layer and to produce a mobile film.

- There are three states of water distribution between particles,
Moist granule tensile strength increases about three times between the pendular and the capillary state.
• At low moisture levels, termed the **pendular state, the particles are held together by lens-shaped rings of liquid**.

• These cause adhesion because of the surface tension forces of the liquid/air interface and the hydrostatic suction pressure in the liquid bridge.

• When all the air has been displaced from between the particles the **capillary state is reached, and the particles are held by capillary suction at the liquid/air interface**, which is now only at the granule surface.

• The **funicular state represents an intermediate** stage between the pendular and capillary states.

• **Moist granule tensile strength increases about three times between the pendular and the capillary state.**
Water distribution between particles of a granule during formation and drying.

Low moisture levels:
- Dry state prior to granulation
- Adding granulating fluid
- Drying

Higher moisture levels:
- Liquid bridges (G)
- Solid bridges (D)
- Pendular
- Funicular
- Capillary
- Suspension

Not required, undesirable:

G → D

X → Not required, undesirable
• It may appear that the state of the powder bed is dependent upon the total moisture content of the wetted powders, but the capillary state may also be reached by decreasing the separation of the particles.

• In the massing process during wet granulation, continued kneading/mixing of material originally in the pendular state will densify the wet mass, decreasing the pore volume occupied by air and eventually producing the funicular or capillary state without further liquid addition.
• In addition to these three states, a further state,
• the droplet, is important in the process of granulation by spray drying of a suspension.
• In this state,
• the strength of the droplet is dependent upon the surface tension of the liquid used.

• These wet bridges are only temporary structures in wet granulation because the moist granules will be dried.
• They are, however, a prerequisite for the formation of solid bridges formed by adhesives present in the liquid, or by materials that dissolve in the granulating liquid
Solid bridges

- Formed by:
  1. partial melting
  2. hardening binders
  3. crystallization of dissolved substances
• *Partial melting*: 

• *not considered to be a predominant mechanism in pharmaceutical materials.*

• it is possible that the pressures used in dry granulation methods may cause melting of low melting-point materials where the particles touch and high pressures are developed.

• When the pressure is relieved, crystallization will take place and bind the particles together.
• **Hardening binders:**

• *This is the common mechanism* in pharmaceutical wet granulations when an **adhesive is included in the granulating solvent.**

• The liquid will form liquid bridges and the adhesive will harden or crystallize on drying to form solid bridges to bind the particles.

• Adhesives such as polyvinylpyrrolidone, the cellulose derivatives (such as carboxymethylcellulose) and pregelatinized starch function in this way.
• **Crystallization of dissolved substances:**

• *The solvent* used to mass the powder during wet granulation may partially dissolve one of the powdered ingredients.

• When the granules are dried, crystallization of this material will take place and the dissolved substance then acts as a hardening binder.

• Any material soluble in the granulating liquid will function in this manner, e.g. lactose incorporated into dry powders granulated with water.
• The size of the crystals produced in the bridge will be influenced by the rate of drying of the granules.

• the slower the drying time, the larger the particle size.

• It is therefore important that the drug does not dissolve in the granulating liquid and recrystallize, because it may adversely affect the dissolution rate of the drug if crystals larger than that of the starting material are produced.
Attractive forces between solid particles

- In the absence of liquids and solid bridges formed by binding agents, there are two types of attractive force that can operate between particles.

1. **Electrostatic forces** may be important in causing powder cohesion and the initial formation of agglomerates, e.g. during mixing. In general they do not contribute significantly to the final strength of the granule.

2. **Van der Waals forces** are about four orders of magnitude greater than electrostatic forces and contribute significantly to the strength of granules produced by dry granulation. The magnitude of these forces will increase as the distance between adjacent surfaces decreases, and in dry granulation this is achieved by using pressure to force the particles together.
Mechanical Interlocking:

- The mechanical interlocking theory of adhesion states that good adhesion occurs only when an adhesive penetrates into the pores, holes and crevices and other irregularities of the adhered surface of a substrate, and locks mechanically to the substrate. The adhesive must not only wet the substrate, but also have the right rheological properties to penetrate pores and openings in a reasonable time.
Mechanisms of granule formation

• The proposed granulation mechanism can be divided into three stages:
  1. Nucleation
  2. Transition
  3. Ball growth
Nucleation

- Granulation starts with particle-particle contact and adhesion due to liquid bridges.

- A number of particles will join to form the pendular state.

- Further agitation densities the pendular bodies to form the capillary state and these bodies act as nuclei.
Transition

- Nuclei can grow in two possible ways:
  1. single particles can be added to the nuclei by pendular bridges
  2. two or more nuclei may combine.

- This stage is characterized by the presence of a large number of small granule distribution. This is a suitable end-point for granules used in capsule and tablet manufacture.
Ball growth

• Further granule growth produces large, spherical granules and the mean particle size of the granulating system will increase with time.

• If agitation is continued produce an unusable, overmassed system, although this is dependent upon the amount of liquid added and the properties of the material being granulated.

• Although ball growth produces granules that may be too large for pharmaceutical purposes, some degree of ball growth will occur in planetary mixers.
mechanisms of ball growth

1. **Coalescence**: Two or more granules join to form a larger granule.

2. **Breakage**: Granules break into fragments which adhere to other granules, forming a layer of material over the surviving granule.

3. **Abrasion transfer**: Agitation of the granule bed leads to the attrition of material from granules. This abraded material adheres to other granules, increasing their size.

4. **Layering**: When a second batch of powder mix is added to a bed of granules the powder will adhere to the granules, forming a layer over the surface and increasing the granule size. This mechanism is only relevant to the production of layered granules using spheronizing equipment.
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PHARMACEUTICAL GRANULATION EQUIPMENT

- Wet granulators:
  - Shear granulators
  - High-speed mixer/granulators
  - Fluidized-bed granulators
  - Spray-driers
  - Spheronizers/pelletizers
  - Extrusion/spheronization
  - Rotor granulation
- Dry granulators
  - Sluggers
  - Roller compactors
Shear granulators

- In the traditional granulation process a planetary mixer is often used for wet massing of the powders, e.g. Hobart, Collette, Beken

1. **Powder mixing** usually has to be performed as a separate operation using suitable mixing equipment. With some formulations, such as those **containing two or three ingredients in approximately equal quantities**, however, it may be possible to **achieve a suitable mix in the planetary mixer without a separate stage.**
2. The mixed powders are fed into the bowl of the planetary mixer and **granulating liquid is added as the paddle of the mixer agitates the powders.** The planetary action of the blade when mixing is similar to that of a household mixer.

3. The moist mass has then to be transferred to a **granulator**, such as an **oscillating granulator**
• The rotor bars of the granulator oscillate and force the moist mass through the sieve screen, the size of which determines the granule size.

• The mass should be sufficiently moist to form discrete granules when sieved.

  Why?

• If excess liquid is added, strings (cords) of material will be formed and

• if the mix is too dry the mass will be sieved to powder and granules will not be formed.
4. The granules can be collected on trays and transferred to a drying oven. (Disadvantages?)
   1. The drying time is long.
   2. Intragranular solute migration
   3. Granules may aggregate owing to bridge formation at the points of contact of the granules.

An alternative method is to dry the granules using a fluidized-bed drier.

   → This is quicker and,
   → it keeps the individual granules separated during drying,
   → it reduces the problems of aggregation and intragranular solute migration,
   → thereby reducing the need for a sieving stage after drying.

5. To deaggregate the granules and remix them, a sieving stage is necessary after drying.
Planetary mixer

Oscillating granulator
Shear granulators

- The **disadvantages** of this traditional granulation process are:
  1. its long duration,
  2. the need for several pieces of equipment,
  3. the high material losses that can be incurred because of the transfer stages.

- **Advantages** are:
  1. the process is not very sensitive to changes in the characteristics of the granule ingredients (e.g. surface area variations in different batches of an excipient),
  2. the end-point of the massing process can often be determined by inspection.
High-speed mixer/granulators

• This type of granulator (e.g. Diosna, Fielder) is used extensively in pharmaceutics.

• The machines have a stainless steel mixing bowl containing

• a three-bladed main impeller, which revolves in the horizontal plane, and

• a three-bladed auxiliary chopper (breaker blade) which revolves either in the vertical or the horizontal plane
1. The unmixed **dry powders** are placed in the bowl and **mixed** by the rotating impeller for a few minutes.

2. **Granulating liquid is then added** via a port in the lid of the granulator while the impeller is turning.

3. **The granulating fluid is mixed into the powders by the impeller.**

4. The chopper is usually switched on when the moist mass is formed, as its function is to break up the wet mass to produce a bed of granular material.

5. Once a **satisfactory granule has been produced**, the granular product is discharged, **passing through a wire mesh which breaks up any large aggregates**, into the bowl of a **fluidized-bed drier**.
• The **advantage of the process** is that mixing, massing and granulation are **all performed within a few minutes in the same piece of equipment**.

• **The process needs to be controlled with care as the granulation progresses so rapidly** that a usable granule can be transformed very **quickly** into an unusable, **over-massed system**.

• Thus it is often necessary to **use a suitable monitoring system** to indicate the end of the granulation process, i.e. when a granule of the desired properties has been attained.

• The **process is also sensitive to variations in raw materials**, but this may be minimized by using a suitable end-point monitor.
**Fluidized-bed granulators**

- **Fluidized-bed granulators** (e.g. Aeromatic, Glatt) have a similar design and operation to **fluidized-bed driers**, i.e. the powder particles are fluidized in a stream of air.

- but in addition granulation fluid is sprayed from a nozzle on to the bed of powders.
1. Heated and filtered air is blown or sucked through the bed of unmixed powders to fluidize the particles and mix the powders; fluidization is actually a very efficient mixing process.

2. Granulating fluid is pumped from a reservoir through a spray nozzle positioned over the bed of particles.

3. The fluid causes the primary powder particles to adhere when the droplets and powders collide.

4. Escape of material from the granulation chamber is prevented by exhaust filters, which are periodically agitated to reintroduce the collected material into the fluidized bed.

5. Sufficient liquid is sprayed to produce granules of the required size, at which point the spray is turned off but the fluidizing air continued.

6. The wet granules are then dried in the heated fluidizing airstream.
• **Advantages of fluidized-bed** granulation over conventional wet massing:

• **All the granulation processes**, which require separate equipment in the conventional method, are performed in one unit, saving labour costs, transfer losses and time.

• the process can be automated once the conditions affecting the granulation have been optimized.
• **Disadvantages of fluidized-bed granulation**

1. the equipment is initially **expensive**

2. There are numerous **apparatus, process and product** parameters that **affect the quality** of the final granule.

• **optimization** of process (and product) parameters affecting granulation **needs extensive development work**, not only **during initial formulation work** but also **during scale-up from development to production**.

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<th>Table 25.1 Apparatus, process and product variables influencing fluidized-bed granulation</th>
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Spray-driers

a dry, granular product is made from a solution or a suspension rather than initially dry primary powder particles.

The solution or suspension may be of drug alone, a single excipient or a complete formulation.

- The resultant granules are free-flowing hollow spheres and the distribution of the binder in such granules (at the periphery following solute migration during drying) results in good compaction properties.
• This process can be used to make tablet granules, only when suitable granules cannot be produced by the other methods.

• Spray-drying can convert hard elastic materials into more ductile (spongy) ones.

• Spray-dried lactose is the classic example, it has advantages over α-lactose monohydrate crystals when compacted.

• The primary advantages of the process are the short drying time and the minimal exposure of the product to heat owing to the short residence time in the drying chamber.

• This means that little deterioration of heat-sensitive materials takes place, and it may be the only process suitable for this type of product.
Spheronizers/pelletizers

• For some applications it may be desirable to have a dense, spherical pellet.
• Such pellets are used for controlled drug release products following coating with a suitable polymer coat and filling into hard gelatin capsules.

• A commonly used process involves the separate processes of wet massing, followed by extrusion of this wet mass into rod-shaped granules and subsequent spheronization of these granules.

• This process is used so frequently to produce modified release multiparticulates
Extrusion/spheronization

• a multistep process used to make uniformly sized spherical particles.

• It is used primarily to produce multiparticulates for controlled drug release applications.

• The major advantage over other methods of producing drug loaded spheres or pellets is the ability to incorporate high levels of active ingredients without producing excessively large particles (i.e. minimal excipients are necessary).
The main steps of the process

1. *Dry mixing of ingredients to achieve a* homogenous powder dispersion. This uses normal powder-mixing equipment.

2. *Wet massing to produce a sufficiently plastic* wet mass; employs normal equipment and processes as used in wet granulation

3. *Extrusion to form rod-shaped particles of* uniform diameter; The wet mass is forced through dies and shaped into small cylindrical particles with uniform diameter.
4. **Spheronization to round off these rods into spherical particles**; The working part consists of a bowl with fixed side walls and a rapidly rotating bottom plate or disc. The bottom disc has a grooved surface.

5. **Drying to achieve the desired final moisture content**; in tray dryers and fluidized-bed driers.

6. **Screening (optional) to achieve the desired narrow size distribution**. Normal sieves are used.
Wet product spheronizing during toroidal motion

Spinning friction wheel

(a) Cylinder
(b) Cylinder with rounded ends
(c) Dumbbell
(d) Ellipsoid
(e) Sphere

Spheronization time →
Applications of extrusion/spheronization

- **Controlled drug release:** Both immediate-release and controlled-release pellets can be formed.
- These pellets can either be filled into hard gelatin capsule shells or compacted into tablets to form unit dosage forms.
- Pellets can contain two or more ingredients in the same individual unit, or incompatible ingredients can be manufactured in separate pellets.
- Pellets can be coated in sub-batches to give, say, rapid-, intermediate- and slow-release pellets in the same capsule shell.
- Dense multiparticulates disperse evenly within the GI tract and have less variable gastric emptying and intestinal transit times than do single units, such as coated monolithic tablets.
• **Processing:**
  • to increase the bulk density,
  • improve flow properties
  • reduce the problems of dust usually encountered with low-density, finely divided active and excipient powders.

• Extrusion/spheronization is a more labour intensive process than other forms of granulation and should therefore only be considered when other methods are either not satisfactory for that particular formulation or are inappropriate (i.e. when spheres are required).
Rotor granulation

1. allows the direct manufacture of spheres from dry powder.
2. In the Freund granulator, the powder mix is added to the bowl and wetted with granulating liquid from a spray.
3. The base plate rotates at high speed and centrifugal force keeps the moist mass at the edges of the rotor.
4. Here, the velocity difference between the rotor and the static walls, combined with the upward flow of air around the rotor plate, causes the mass to move in a toroidal motion, resulting in the formation of discrete spherical pellets.
5. These spheres (actually wet granules) are dried by the heated inlet air from the air chamber.
Freund granulator
• it is possible to continue process and coat the pellets by subsequently spraying coating solution on to the rotating dried pellets.

• layered pellets can be produced by using the uncoated pellets as nuclei in a second granulation with a powder mix of a second ingredient.
Dry granulators

- Dry granulation converts primary powder particles into granules using the application of pressure without the intermediate use of a liquid.

- It therefore avoids heat-temperature combinations that might cause degradation of the product.

- Two pieces of equipment are necessary for dry granulation: first, a machine for compressing the dry powders into compacts or flakes, and secondly a mill for breaking up these intermediate products into granules.
**Sluggers**

- The dry powders can be compressed using a conventional tablet machine or, more usually, a large heavy duty rotary press can be used.

- This process is often known as 'slugging', the compact made in the process (typically 25 mm diameter by about 10-15 mm thick) being termed a 'slug'.

- A hammer mill is suitable for breaking the compacts.
• **Roller compactors**
  
  - Roller compaction is an alternative gentler method,

  - the powder mix being squeezed between two rollers to form a compressed sheet.

  - The sheet normally is weak and brittle and breaks immediately into flakes.

  - These flakes need gentler treatment to break them into granules, and this can usually be achieved by screening alone.
Fig. 25.13 Roller compaction: (a) Alexanderwerk and (b) Hutt types.
Effect of granulation method on granule structure

• Pre-compressed granules, consisting of compressed drug and binder particles, are held together by simple bonding during compaction.

• Granules prepared by wet massing consist of intact drug particles held together in a sponge-like matrix of binder.

• Fluidized-bed granules are similar to those prepared by the wet massing process, but possess greater porosity and the granule surface is covered by a film of binding agent.

• With spray-dried systems the granules consist of spherical particles composed of an outer shell and an inner core of particles.