GRANULES & GRANULATION

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GRANULES & GRANULATION

- **Granules** consist of particles formed by the progressive enlargement of primary particles until their original identity is no longer visible

- **Granulation** refers to the act or process in which primary powder particles are made to adhere to form larger, multi-particle entities called granules.

- **Granulation** is the process of collecting particles together by creating bonds between them. Bonds are formed by compression or by using a binding agent.

• Pharmaceutical granules typically have a size range between 0.2 and 4.0 mm, depending on the subsequent use of the granules.

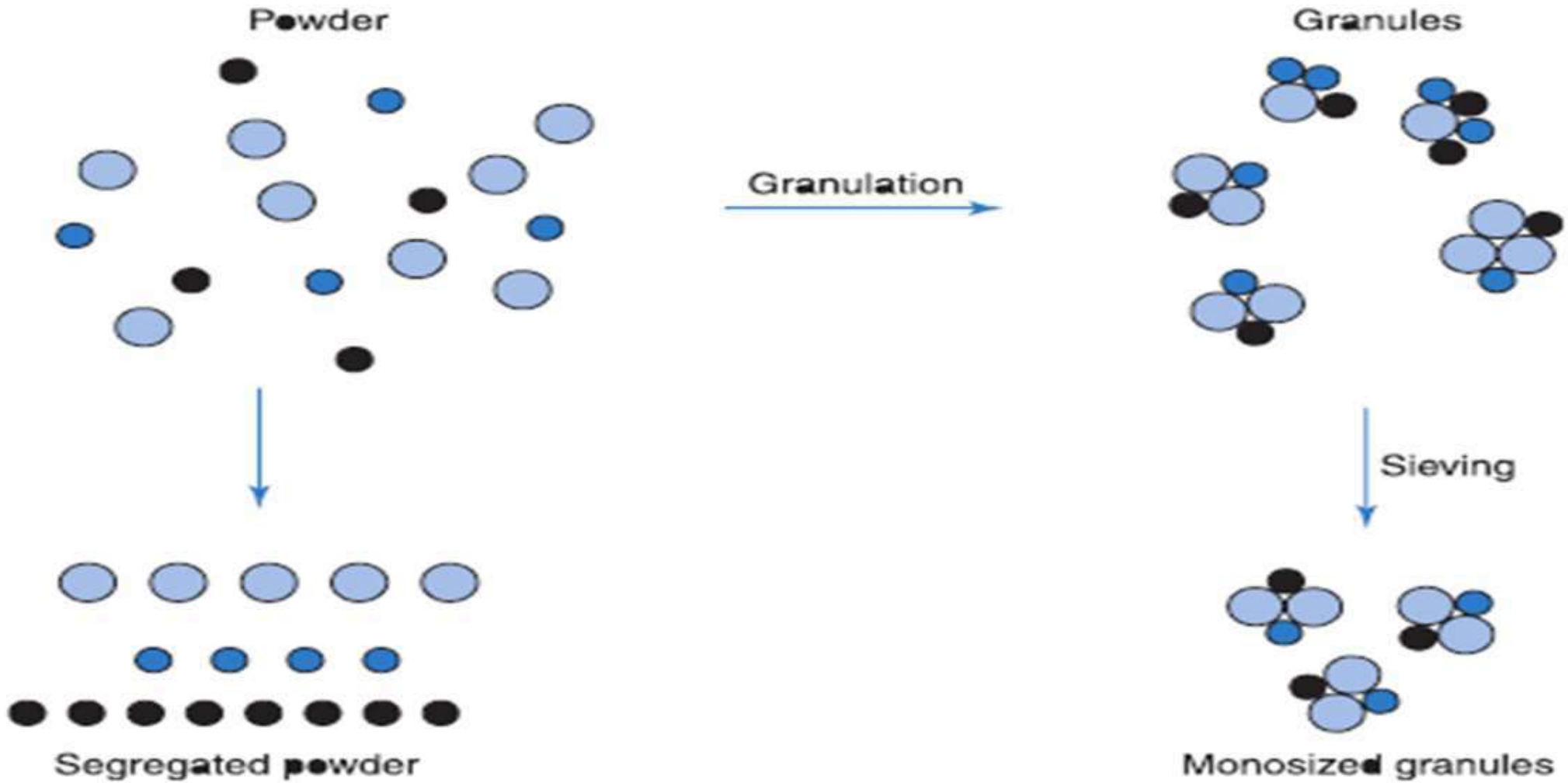
➢ In the majority of cases, when granules will be made as **an intermediate product**, they have a size range towards the lower end of this spectrum – typical between 0.2 and 0.5 mm.

When prepared for use as **a dosage form i**n their own right, they are usually much larger (typically 1–4 mm).

REASONS FOR GRANULATION

1- To prevent segregation of the constituents of the powder mix

Segregation is due to differences in the size or density of the component of the mix. Normally, the smaller and/or denser particles tend to concentrate at the base of the container with the larger and/or less dense ones on the top. An ideal granulation will contain all the constituents of the mix in the correct proportion in each granule and segregation of granules will not occur.



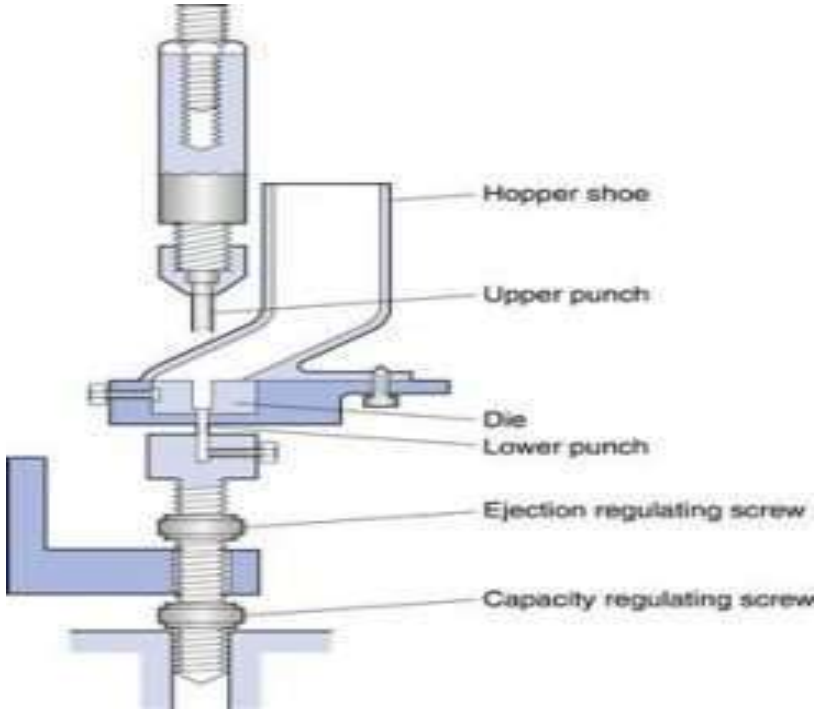
- Schematic diagram to illustrate how granulation can prevent powder segregation.

2- 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 powder flow will also often result in a wide weight variation within the final product due to variable fill of tablet dies, etc.
- The resulting granules produced from irregular particles

will be larger and more isodiametric, both factors

contributing to improved flow properties



3- To improve the compaction characteristics of the mix:

Some primary powder particles are difficult to compact into tablets. Granules of the same formulation are often more easily compacted and produce stronger tablets.

4- The granulation of powdered toxic materials will reduce the hazard associated with the generation of toxic dust that may arise during handling.

5- Materials which are slightly hygroscopic may adhere and form a cake if stored as a powder. Granulation may reduce this hazard as the granules will be able to absorb some moisture and yet retain their flowability because of their size.

6- Granules, having a greater bulk denser than the parent powder mix, occupy less volume per unit weight. They are therefore more convenient for storage or shipment.

MECHANISM OF GRANULE FORMATION

The granulation mechanism can be divided into three stages:

1- 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 densifies the pendular bodies to form the capillary state, and these bodies act as nuclei for further granule growth.

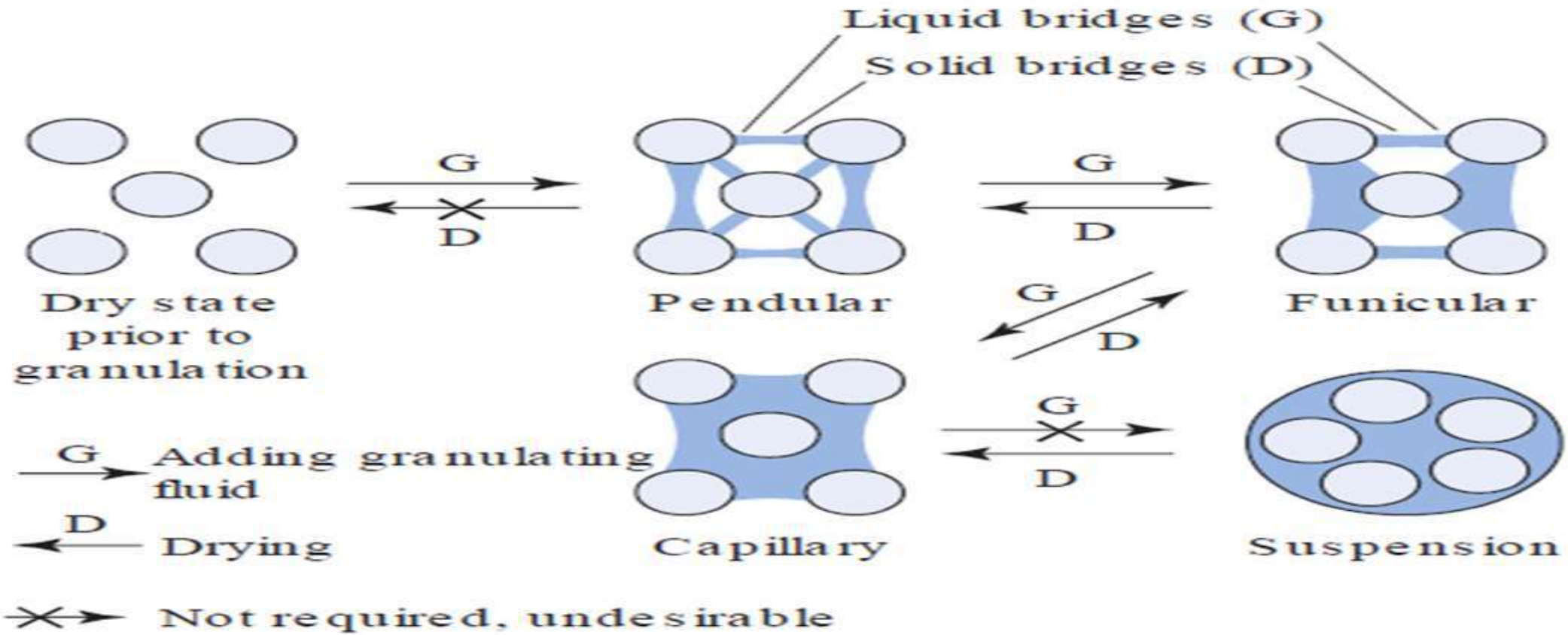


Fig. 28.2 • Water distribution between particles of a granule during formation and drying.

2- Transition:

Nuclei can grow by two possible mechanisms:

1- Single particles can be added to the nuclei by pendular bridges.

2- or two or more nuclei may combine.

The combined nuclei will be reshaped by the agitation of the bed.

This stage is characterized by the presence of a large number of small granules with a fairly wide size distribution.

This point represents a suitable endpoint for granules used in capsule and tablet manufacture as relatively small granules will produce a uniform tablet die or capsule fill.

Larger granules may give rise to problems in small-diameter dies due to bridging across the die and uneven fill.

3- Ball growth:

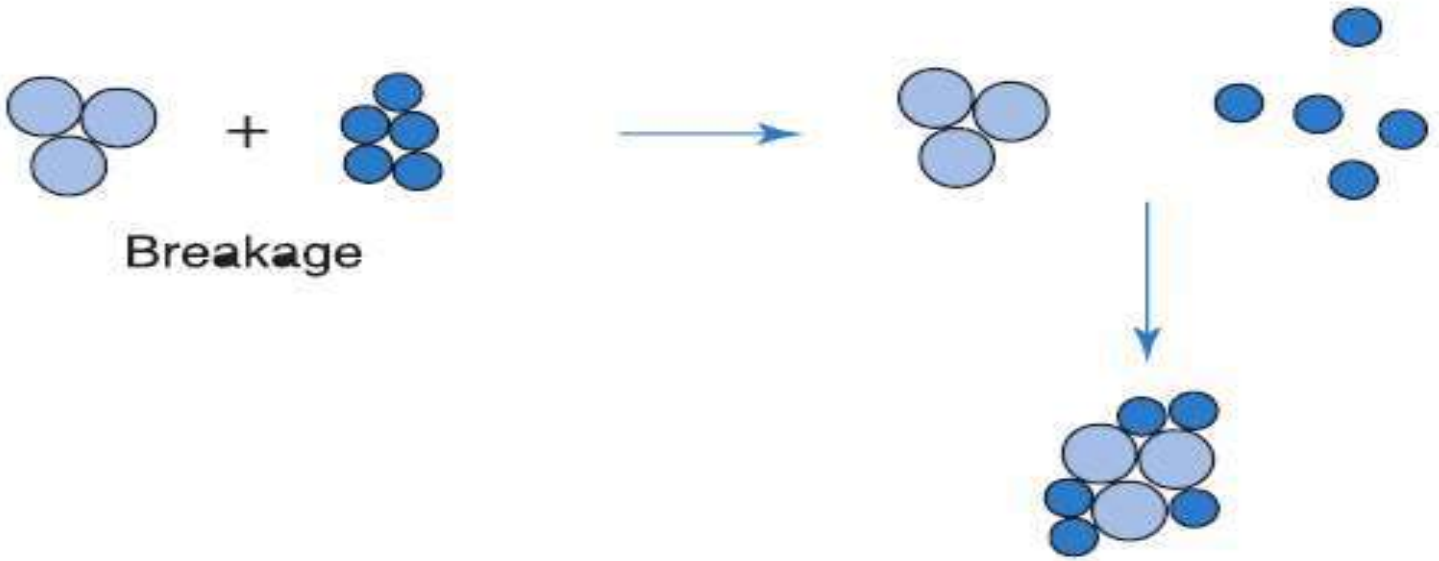
Further granule growth produces large, spherical granules and the mean particle size of the granulating system will increase with time.

If agitation is continued, granule coalescence will continue and produce an unusable, over-massed system, although this is dependent upon the amount of liquid added and the properties of the material being granulated.

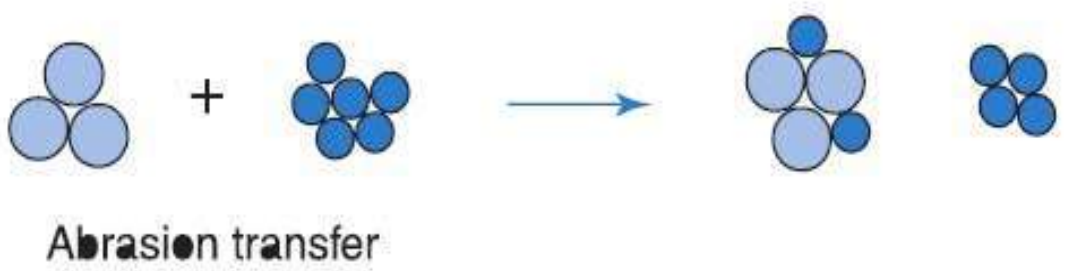
- **There are four possible mechanisms of ball growth:**

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

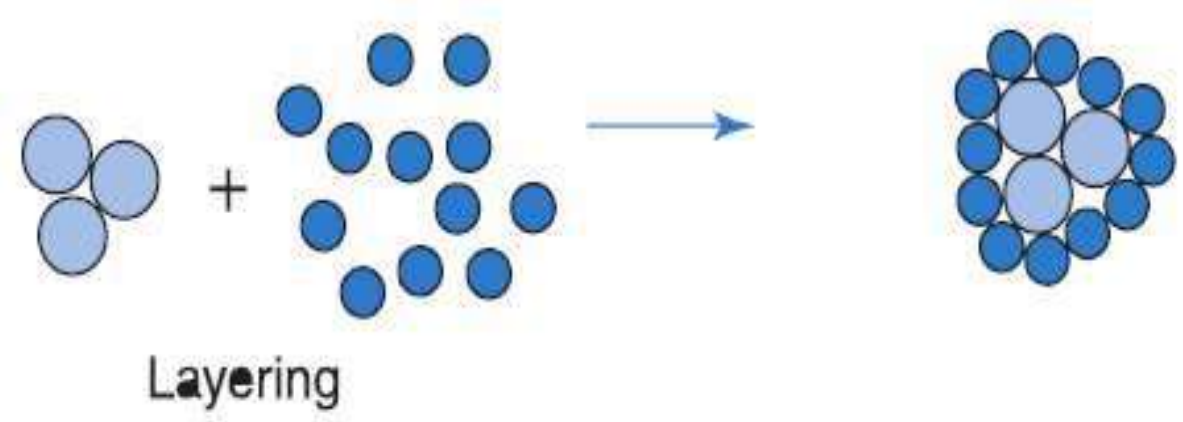
2- Breakage: Granules break into fragments which adhere to other granules, forming a layer of material over the surviving granule.



3- Abrasion Transfer.: Agitation of the granule bed leads to the attrition of material from granules. This abraded material adheres to other granules.



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.



Pharmaceutical Granulation Processes

Granulation methods can be divided into two types:

- **Dry methods**
- **Wet granulation methods.**

DRY GRANULATION

- In the dry methods of granulation, the primary powder particles are aggregated at high pressure.
- There are two main intermediate processes:

Either the production of a large tablet (known as a ‘slug‘ in a heavy-duty tableting press (a process known a slugging) or the powder is squeezed between two rollers to produce a sheet or flakes of material (roller compaction).

- In both cases, the intermediate product is broken using a suitable milling technique to produce granular material which is usually sieved to separate the desired size fraction. The unused ne material may be reworked to avoid waste.
- This dry method may be used for drugs which do not compress well after wet granulation or those which are sensitive to moisture.

Advantages of dry Granulation:

1- It uses lesser equipments and space than wet granulation..

2- It eliminates the need for binder solution.

3- It eliminates the need for heavy mixing equipment.

4- Lower cost than wet granulation.

5- Less time consuming (eliminate the drying step required for wet granulation).

6- Slugging can be advantages for moisture and heat sensitive materials.

7- Improved disintegration since powder particles are not bonded together by a binder.

Disadvantages of dry granulation:

1- It requires a specialized heavy-duty tablet press to form slug.

2- It does not permit uniform color distribution as can be achieved with wet granulation where the dye can be incorporated into binder liquid.

3- The process tends to create more dust than wet granulation, increasing the potential contamination.

Dry granulation equipments

(Dry granulators)

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

❑ Slugging (Old method)

- The dry powders can be compacted 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 compacts made in the process (typically 25 mm diameter by about 10–15 mm thick) being termed slugs.

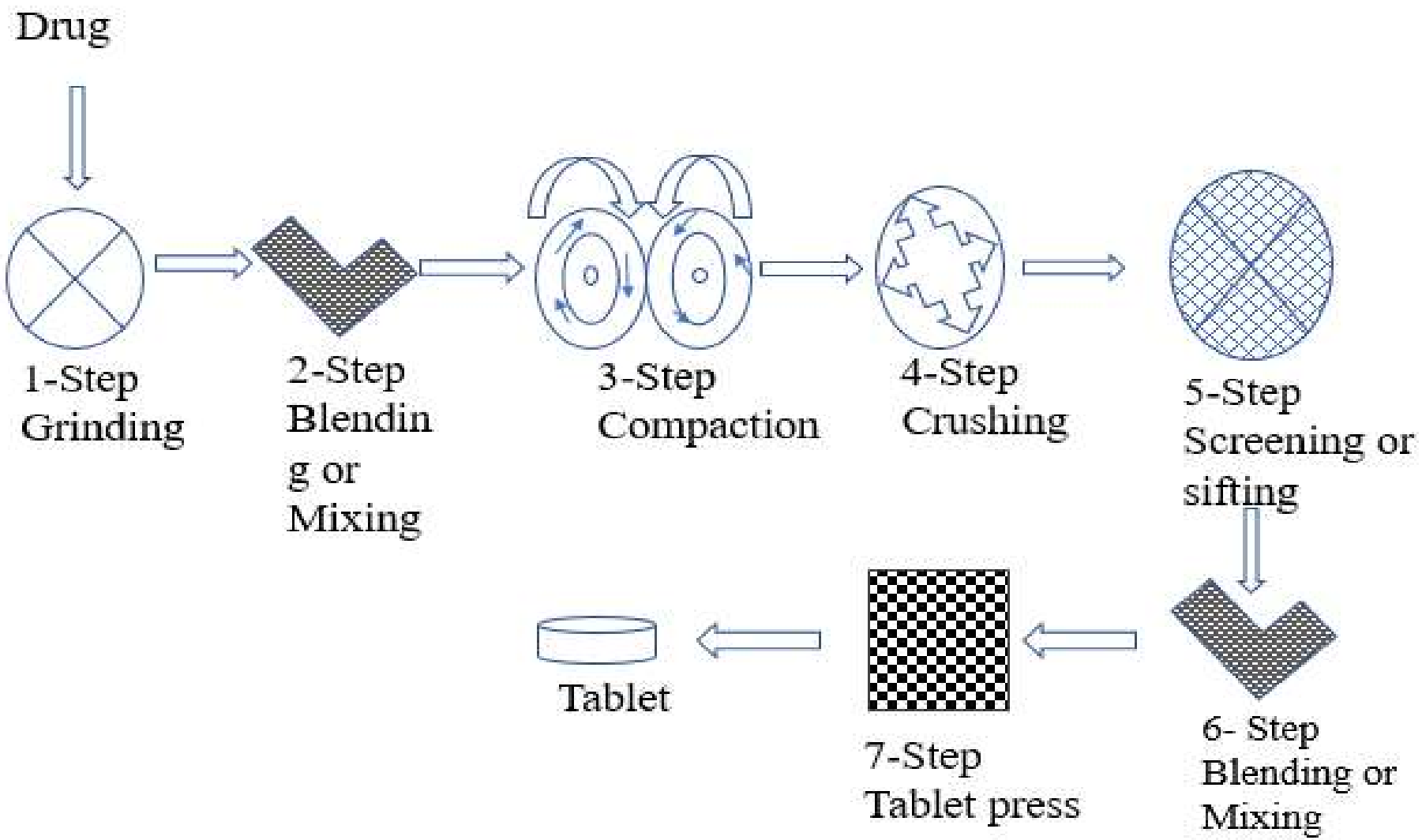
A hammer mill is suitable for breaking the slugs and passed through a screen of desired mesh for sizing.

- Example, Aspirin, which is hydrolyzed on exposure to moisture, may be prepared into tablets after slugging.
- This is an old process that is being replaced by the more modern, and better, roller compaction process.

❑ Roller compaction

Roller compaction is an alternative gentler method, the powder mix being squeezed between two counter-rotating rollers to form a compressed sheet

The sheet formed is normally weak and brittle and breaks immediately into flakes. These flakes need gentler treatment to break them into granules. An oscillating granulator can be used with care, but often the conversion of these flakes to granules can be achieved by screening alone.


Drug
1-Step
Grinding
2-Step
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g or
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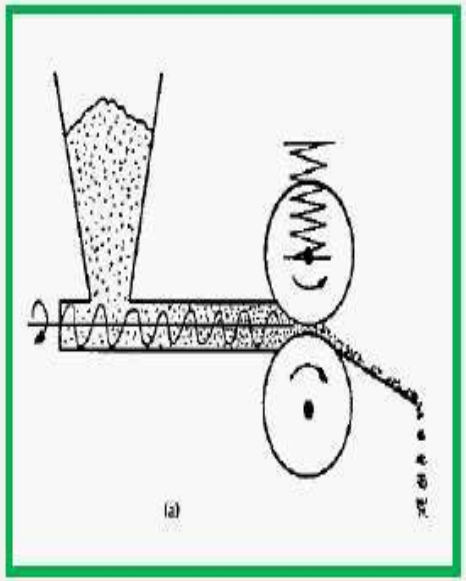
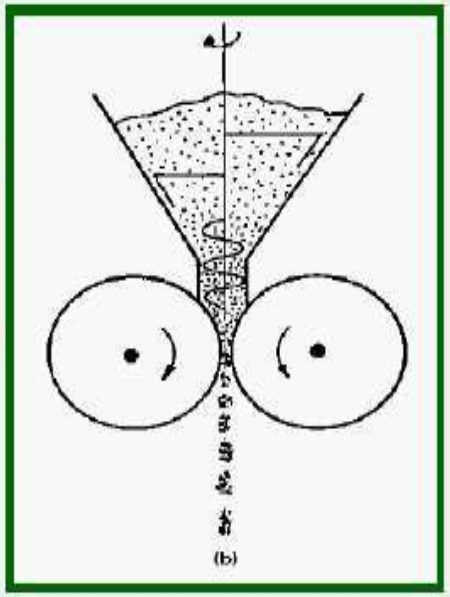
3-Step
Compaction
4-Step
Crushing
5-Step
Screening or
sifting
6- Step
Blending or
Mixing
7-Step
Tablet press
Tablet

Roller Compactors

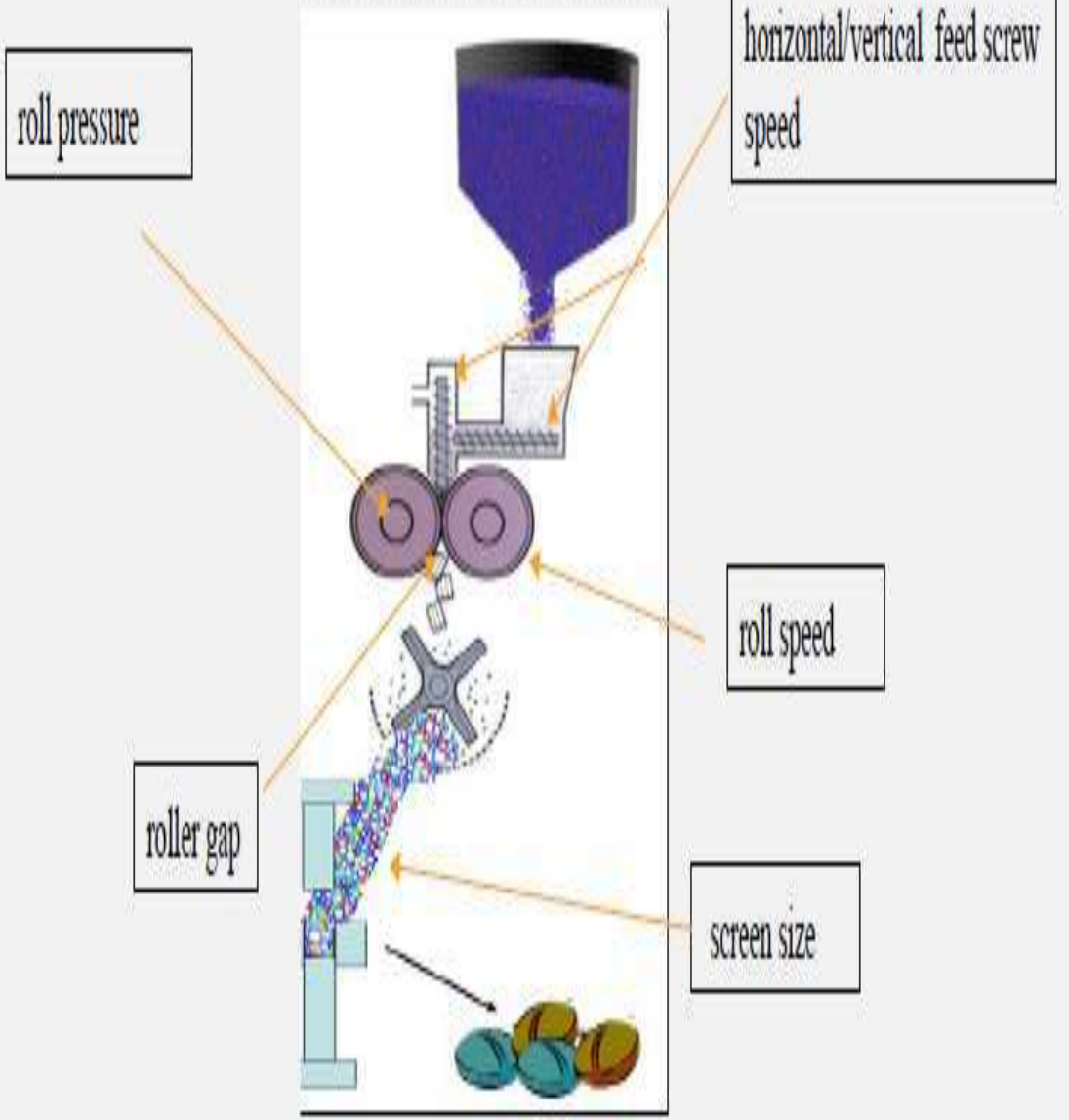


Alexanderwerk Roller compactor

Hutt Roller compactor



Variables of Roller Compaction



WET GRANULATION

- Wet granulation involves the massing of a mix of dry primary powder particles using a granulating fluid.
- The granulating fluid contains a solvent that must be volatile, so that it can be removed by drying, and is non-toxic.
- Typical suitable liquids include water, ethanol and isopropanol either alone or in combination.

- The disadvantages of water as a solvent are that it may adversely affect drug stability, causing hydrolysis of susceptible products, and it needs a longer drying time than organic solvents.

This long drying time increases the duration of the process and again may affect chemical stability of the drug(s) because of the extended exposure to heat.

- The primary advantage of water is that it is non-flammable, which means that expensive safety precautions such as the use of flame-proof equipment need not be taken.
- Organic solvents are used as an alternative to dry granulation when water sensitive drugs are processed, or when a rapid drying time is required.

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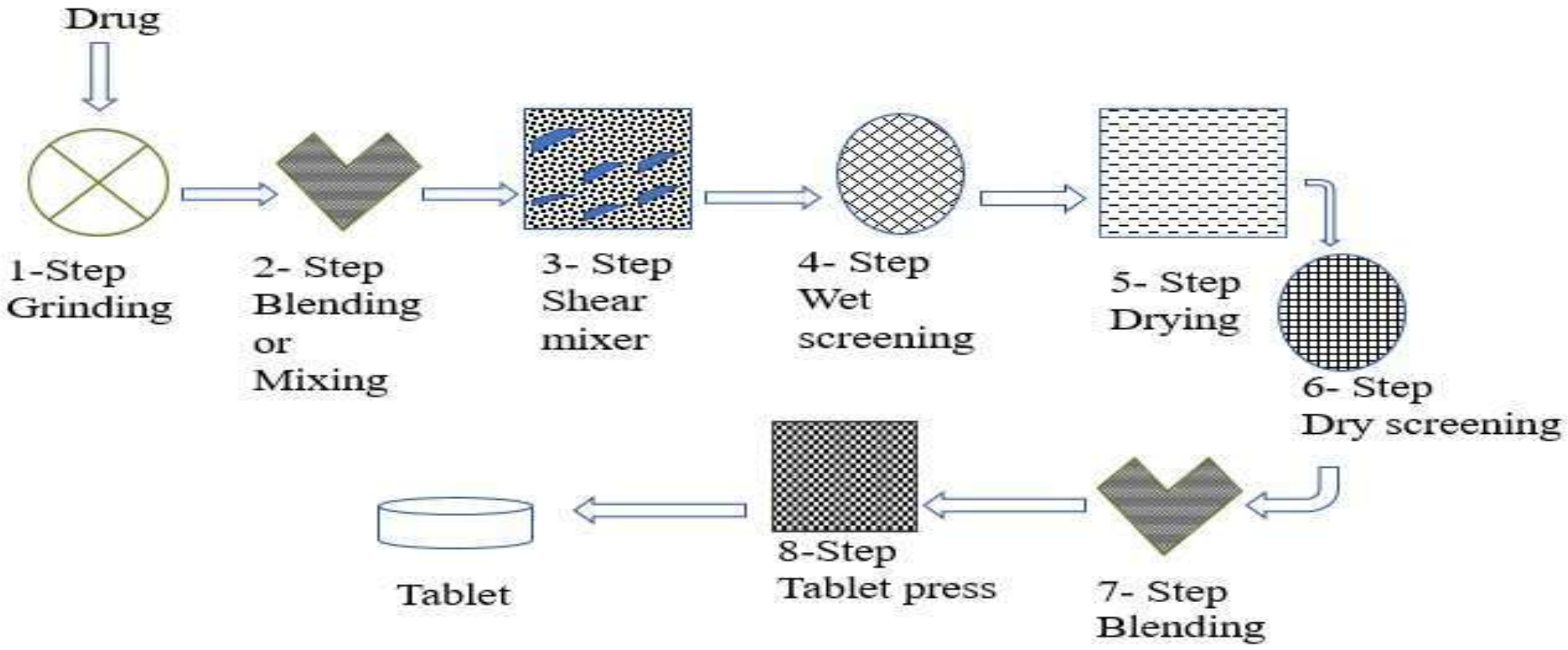
- The granulation liquid may be used alone or, more usually, as a solvent containing a dissolved adhesive (also referred to as a binder or binding agent) which is used to ensure particle adhesion once the granule is dry.

- **Binders** are adhesives that are added to solid dosage formulations. The primary role of binders is to provide the cohesiveness essential for the bonding of the solid particles under compaction to form a tablet. Binders may also improve the hardness of the tablets by enhancing intragranular as well as intergranular forces.
- In a wet-granulation process, binders promote size enlargement to produce granules and thus improve flowability of the blend during the manufacturing process.

Examples:

Natural Polymers: Starch, pregelatinized starch
Synthetic polymers: PVP, methylcellulose, HPMC
New Natural and Synthetic binders: Khaya gum, leucocephala seed gum, anacardium occidentale gum, gellan gum, combination of detarium gum and veegum.
New synthetic binders: Maltrodextrins, chitosan derivatives

- 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 be recycled.



Limitations of wet granulation:

1- The greatest disadvantage of wet granulation is its cost.

It is an expensive process because of labor, time, equipment, energy and space requirements.

2- Loss of material during various stages of processing.

3- Stability may be major concern for moisture sensitive or thermo-labile drugs

Wet granulation equipments
(Wet granulators)

1- Shear granulators.

The older shear granulators have largely disappeared and have been replaced by the much more efficient high-speed mixer/granulators.

2- High speed mixer/granulators.

3- Fluidized-bed granulators.

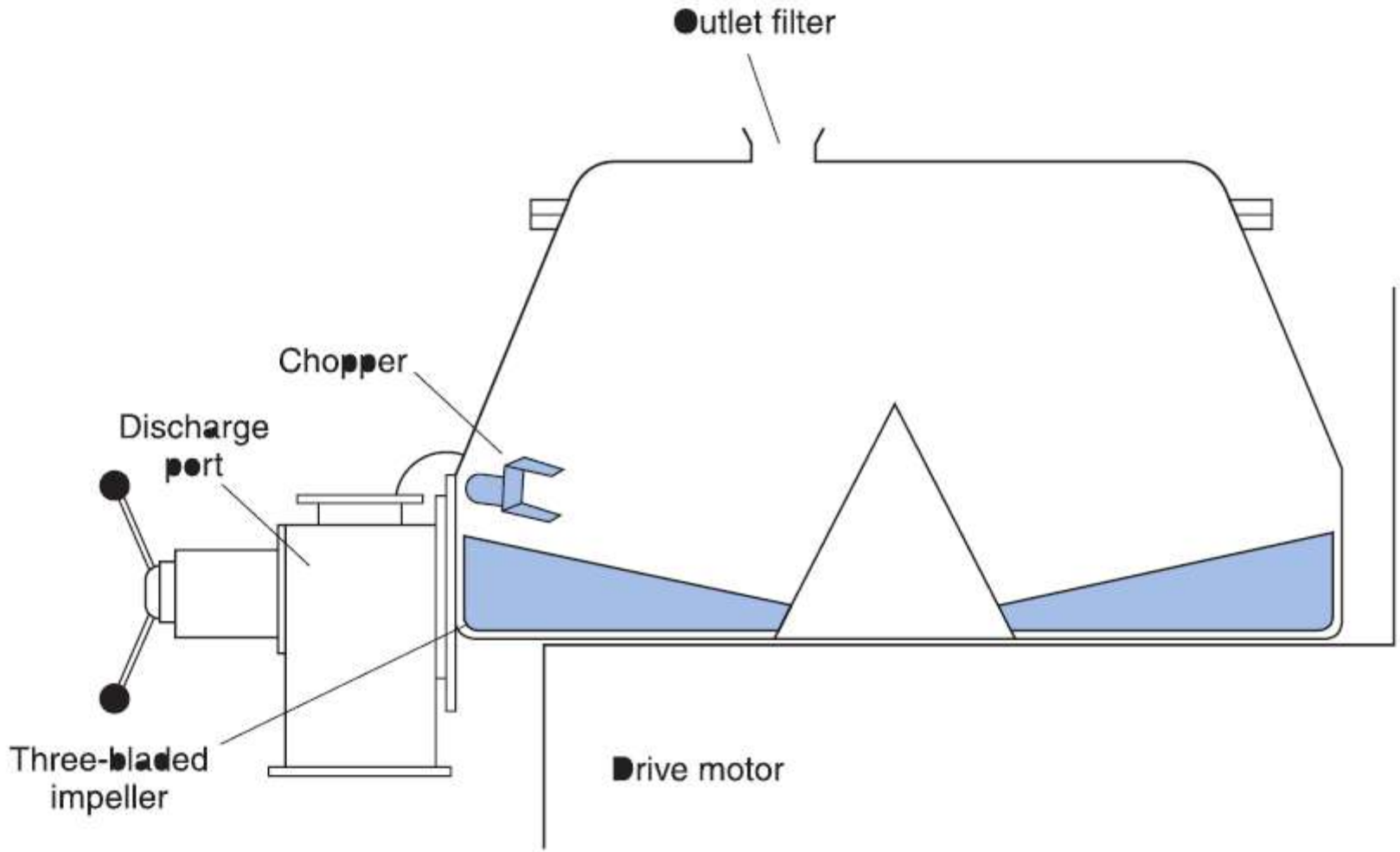
4- Spray driers.

5- Spheronizers /pelletizers

2- High Speed Mixer/Granulators

- High shear mixture has been widely used in pharmaceutical industries for blending and granulation.
- In this type of equipment, the particles are set into movement by an impeller rotating at a high speed (50- 100 rpm).
- Equipment also contains a chopper which rotates at around 1500-4000 rpm. The primary function of chopper is to cut large lumps into smaller fragments thus increases the binder distribution into the blend.
- The binder liquid is added by pouring, pumping or spraying from the top.

High shear mixture granulation



28.4 • High-speed mixer/granulator.

Rapid mixer granulator

Advantages:

1. Short processing time

2. Lesser amount of liquid binders required compared with fluidized bed granulation.

3. Highly cohesive material can be granulated.

Disadvantages:

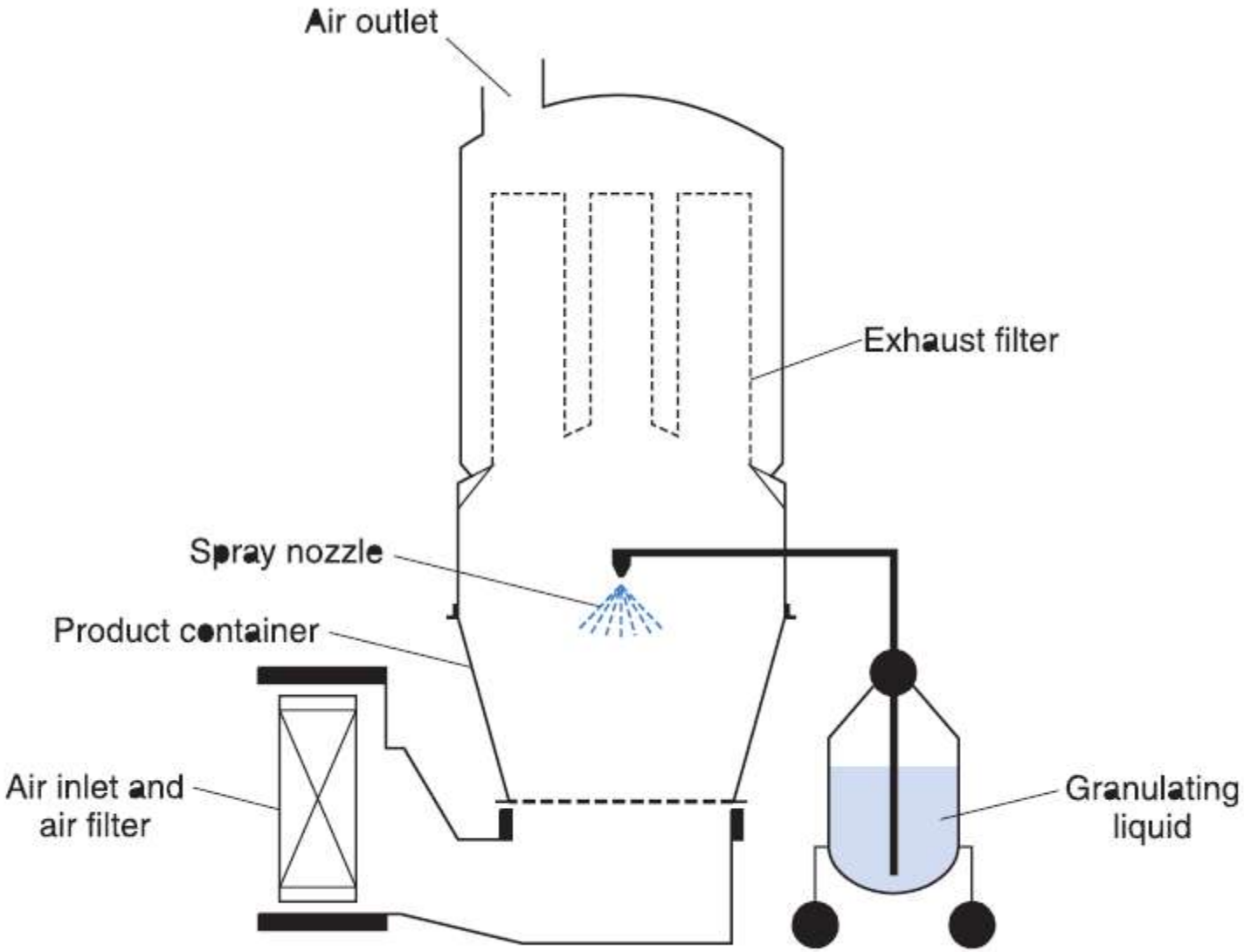
1 Mechanical degradation could take place in case of fragile particles.

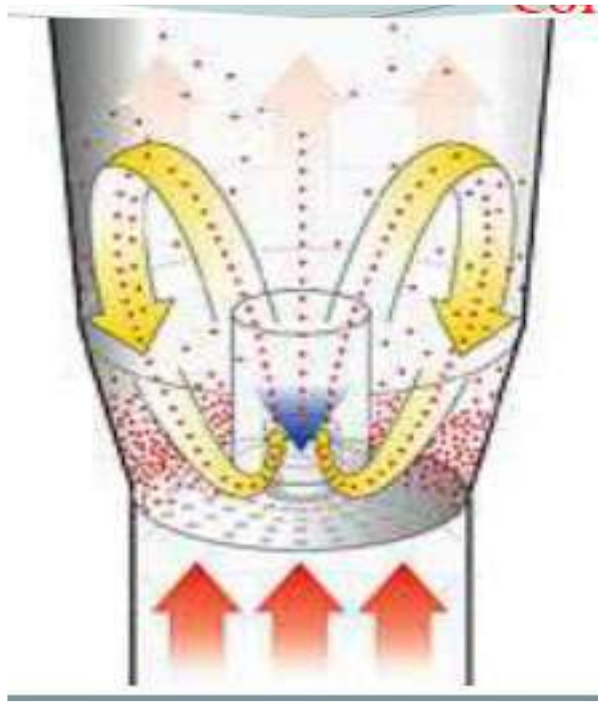
2 Due to increase in temperature chemical degradation of thermolabile material could be resulted.

3 Over wetting of granules may leads to large size lumps formation.

3- Fluidized-bed Granulators

- Fluidization is the operation by which fine solids are transformed into a fluid like state through contact with a gas.
- At certain gas velocity, the fluid will support the particles giving them free mobility without entrapment.
- Fluid bed granulation is a process by which granules are produced in single equipment by spraying a binder solution onto a fluidized powder bed.
- The material processed by fluid bed granulation are finer, free flowing and homogeneous.
- The system involves the heating of air and then directing it through the material to be processed. Later, the same air exit through the voids of the product.





Fluidized-bed granulator.

Advantages:

1- It reduces dust formation during processing.

2- It reduces product loss.

3- It improves worker safety.

Disadvantages:

1-The Fluid Bed cleaning is labor-intensive and time consuming

2- Difficulty of assuring reproducibility

4- Spray Driers

These differ from the other method in that a dry, granular product is made from a solution or a suspension rather than from dry primary powder particles.

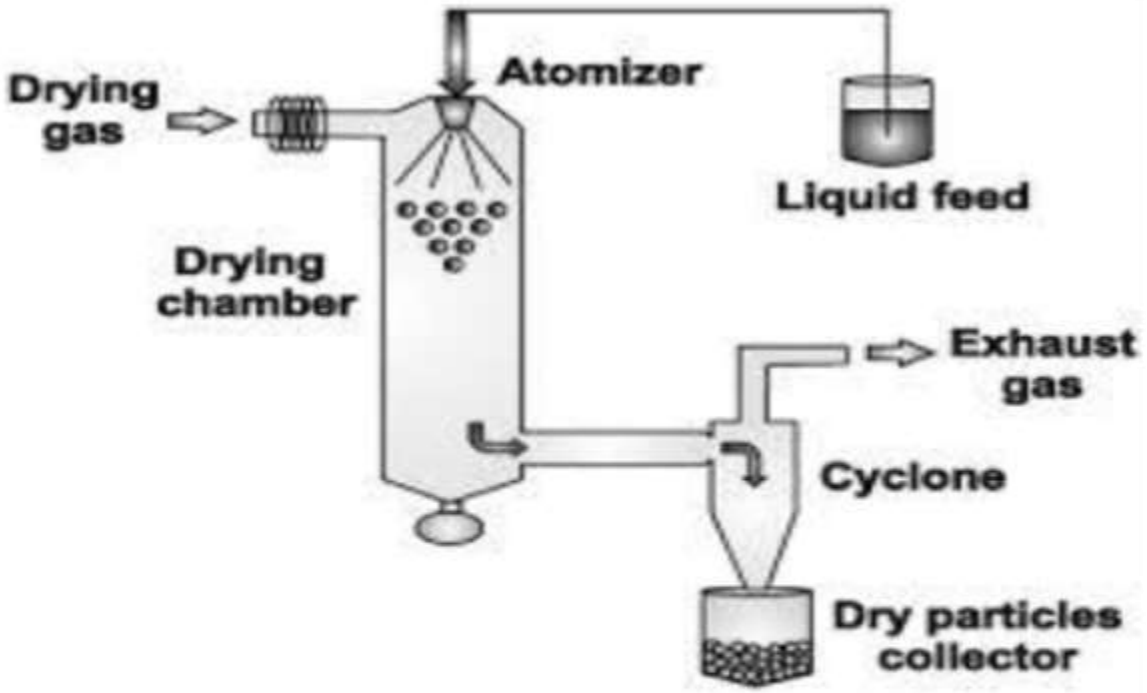
The solution or suspension may be of drug alone, a single excipient or a complete formulation.

Advantages:

1- Rapid and continuous process.

2- Reduces overall cost by avoiding labor intensive drying and granulation steps.

3- Offers minimal product handling and operator exposure to dust.



Schematic drawing of spray dryer.

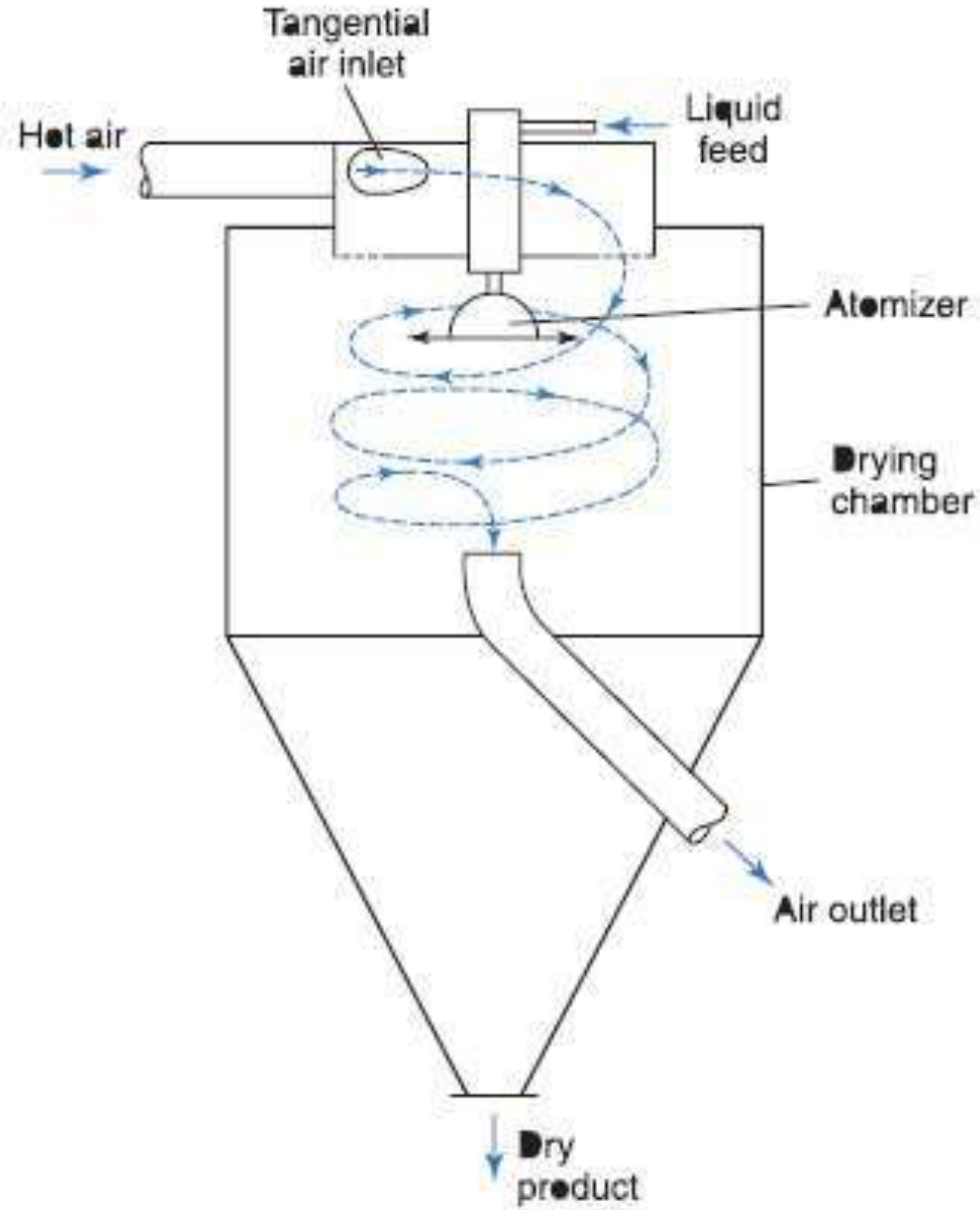


Fig. 29.7 • Spray dryer.

5- Spheronizers /pelletizers:

- For some applications it may be desirable to have a dense, spherical pellet of the type difficult to produce with the equipment described above.
- Such pellets are used for controlled drug release products following coating with a suitable polymer coat and filling into hard gelatin capsules.
- Capsule filling with a mixture of coated and non-coated drug-containing pellets would give some degree of programmed drug release after the capsule shell dissolves.
- 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

The main steps of the process are:

1- Dry mixing of ingredients to achieve a homogeneous powder dispersion

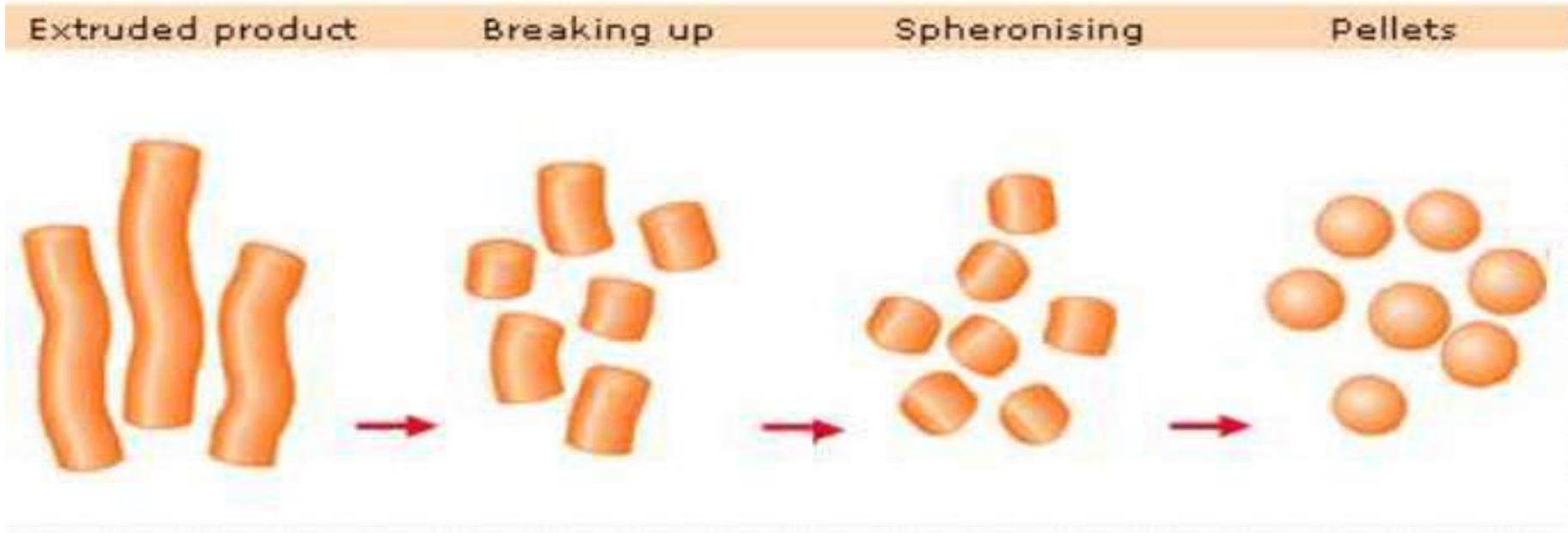
2- Wet massing to produce a sufficiently plastic wet mass

3- Extrusion to form rod-shaped particles of uniform diameter

4- Spheronization to round off these rods into spherical particles

5- Drying to achieve the desired final moisture content

6- Screening (optional) to achieve the desired narrow size distribution


Extruded product
Breaking up
Spheronising
Pellets

Melt Granulation

Melt granulation or thermoplastic granulation: is a technique that facilitates the agglomeration of powder particles using meltable binders, which melts or softens at relatively low temperature (50–90 °C).

- Melt granulation is a size enlargement process in which a thermosetting material (*hot-melt binder*) is used to bind the primary powder particles into granules.

It is a water-free alternative to wet granulation.

- The binder/granulating agent is a semi-solid or solid hydrophilic polymer or a hydrophobic wax.

There are two variants to the technique:

1- The hot-melt binder is added as a solid powder to the drug-excipient powder mix at room temperature and mixed while the temperature of the mix is raised to above the melting point of the binder (ideally at the low end of the range 50 and 90 °C)

2- The hot-melt binder is heated and melted then sprayed on to the powder in a fluidized bed granulator or high-speed mixer granulator.

❑ **Hot-melt binders:**

- Hot-melt binders can be either hydrophilic/water soluble or hydrophobic/water insoluble.
- The most commonly used hydrophilic water-soluble binders are the polyethylene glycols (PEGs).

Polyethylene glycol is the ideal hot-melt binder for granules intended for immediate release products. Grades between PEG 2000 and PEG 6000 can be used with PEG 3000 being well suited (melting point 48–54 °C).

- Hydrophobic water-insoluble binders are particularly useful in producing controlled-release dosage forms.

Many different hydrophobic waxes have been found to be suitable. These include: carnauba wax, hydrogenated castor oil, hydrogenated cottonseed oil, stearic acid and a wide variety of fatty acid derivatives (as glyceryl monostearate, glyceryl trilaurate, glyceryl and sorbitan monostearate).

Most of these are miscible when molten and can be used in combination.

- Melt granulation is an appropriate alternative to other wet granulation techniques which are used for water sensitive materials. Moreover, in comparison with the conventional wet granulation process, it proposes several **advantages**.
- Generally, organic or aqueous solvents are not demanded for the melt granulation process, hence the environmental requirements of organic solvent capture and recycling are eliminated, while the absence of water excludes the wetting and drying phases, making the entire process less energy- and time-consuming

- **Disadvantages of melt granulation:**

1-Heat sensitive materials are poor candidates.

2- Lower-melting-point binder may melt/ soften during handling and storage.

3- Higher-melting-point binders require high melting temperature and can contribute instability problems for heat-labile materials.