Manufacture of Granulations Part 4

Industrial pharmacy

5th class

1st semester

Dry manufacturing methods

The manufacture of granulations for tablet compression may follow one or a combination of three established methods:

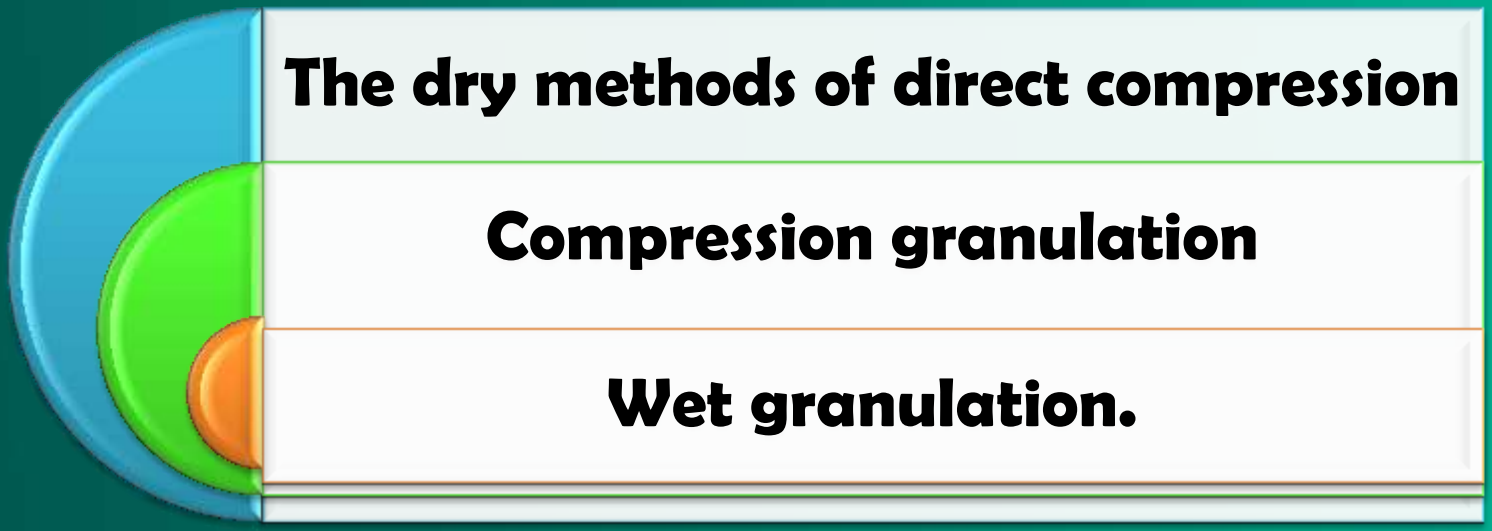

Table 11-3. processing steps commonly required in the various tablet granulation preparation techniques

Processing step	Wet	Dry	Direct
Raw material	x	x	x
weigh	x	x	x
Screen	x	x	X
Mix	x	x	
Compression (slug)		x	
Wet mass	x		
Mill	x		
Dry	x		
Mill	x	x	
Mix	x	x	
compression	x	x	x

1. Direct compression

There are a few crystalline substances, such as sodium chloride, that may be compressed directly.

Note: 1- The vast majority of medicinal agents are rarely so easy to tablet

2- Compression of single substance may produce tablets that do not disintegrate.

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Other components are needed

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Interfere with the compressibility of the active ingredient

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Minimize the usefulness of the method.

- **Most large-dose drugs do not lend themselves to direct compression?**

Most materials possess relatively weak intermolecular attraction or are covered with films of adsorbed gases that hinder compaction.

- **Direct compression is impractical with drugs having small-doses?**

Uniform blends of the drug and coarser direct compression diluents cannot be achieved.

- **What is most streamlined method of tablet manufacture in direct compression?**

Use of compressible diluents with

i. **A direct compressible diluent** (1- inert substance that may be compacted with little difficulty, 2- compress even when quantities of drugs are mixed with it).

ii. **Compression capacity is still maintained** when other tablet materials necessary for flow, disintegration, are blended in.

iii. **Direct compression materials, must be in a good flow compressibility, inert, tasteless, reworkable, able to disintegrate, and inexpensive.**

Advantages of direct compression

1. Low labor input
2. Dry process
3. Fewer processing steps

Limitations of direct compression.

1. Difference in particle size and bulk density between the drug and diluent may lead to stratification with the granulation. problems are of special concern with low-dose drugs.

Poor content uniformity of the drug in the compressed tablet

2. A large-dose drug may present problems with direct compression if it is not easily compressible by itself. To facilitate compression, it requires an amount of diluent so large that the resultant tablet is costly and difficult to swallow.

3. In direct compression the diluent may interact with the drug. A good example of such a reaction is that which occurs between amine compounds and spray-dried lactose, as evidenced by a yellow discoloration.

4. Because of the dry nature of direct compression, static charge builup can occur on the drug during routine screening and mixing,

prevent a uniform distribution of drug in the granulation.

2. Compression granulation

Used for many years, and is a valuable technique in situations where:

The effective dose of a drug is too high for direct compaction, and the drug is sensitive to heat, moisture, or both, which precludes wet granulation.

Ex: Many aspirin and vitamin formulations are prepared for tabletting by compression granulation.

Mechanism of compression granulation

1. When the initial blend of powders is forced into the dies of a large-capacity tablet press and is compacted masses are called slugs, **and the process is referred to as "slugging",** thus the compaction of the components of a tablet formulation by means of a tablet press or specially designed machinery.
2. The slugs are then screened or milled to produce a granular form of tabletting material, which now flows more uniformly than the original powder mixture.
3. When a single slugging process is insufficient to confer the desired granular properties to the material, slugs are sometimes screened, slugging again, and screened once more.
4. Final compression into a tablet.

Why we make slugging?

Slugging is just an elaborate method of subjecting a material to increased compression time.

The act of slugging followed by screening and subsequent compression of the particles is roughly equivalent to an extended dwell time during compression in a tablet machine.

1. The two or more times that the material is subjected to compaction pressures causes a strengthening of the bonds that hold the tablet together.

2. The resultant granules also increase the fluidity of these powder mixtures, which themselves do not flow well enough to fill the dies satisfactorily.

Advantages of compression granulation method:

1. Requires less equipment and space than other methods,
2. Eliminates the addition of moisture and the application of heat, as found in the wet massing and drying steps of the wet granulation method.

Large scale production of compression granulation

It can be performed on a specially designed machine called a roller compactor.

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Roller compactors are capable of producing as much as 500 kg per hour or more of compacted ribbon-like material

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Then screened or milled into a granulation suitable for compression into tablets.

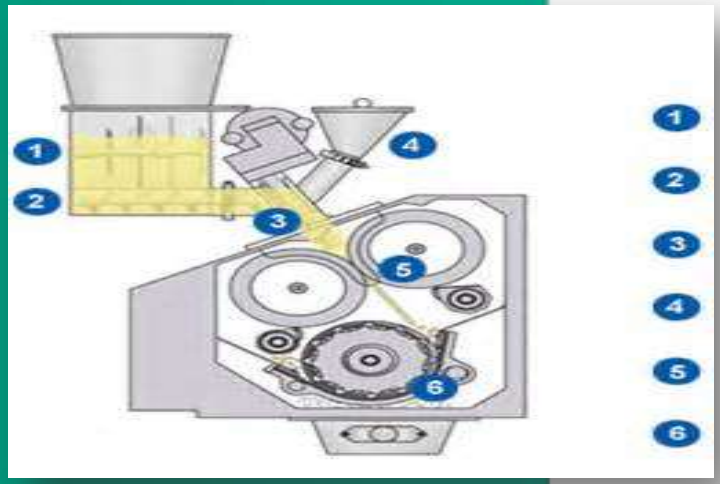
Mechanism of roller compaction

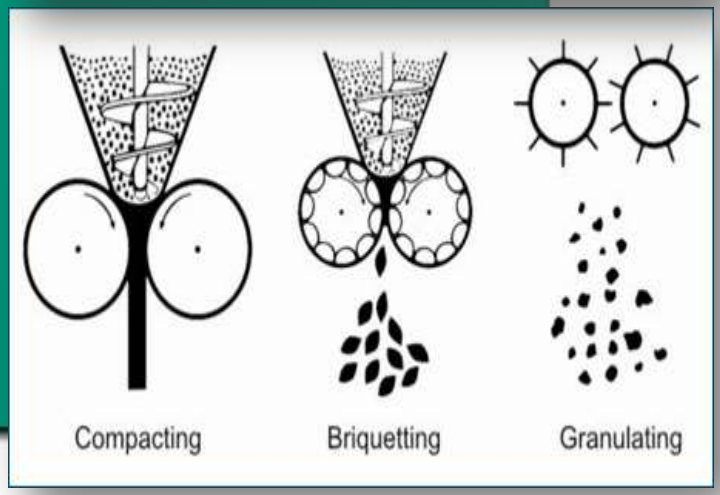
1. Roller compactors, utilize two rollers that revolve toward each other. By means of hydraulic ram forcing one of the rollers against the other, the machine is capable of exerting known fixed pressures on any powdered material that flows between the rollers by a screw conveyor system.

2. After passing through the rollers, the compacted mass resembles a thin wide ribbon that has fallen apart into large segments.

Note: These are equivalent to the slugs produced by the slugging process.

3. The segments are then screened or milled for the production of granules.





3. Wet granulation

- The wet granulation technique uses the same preparatory and finishing steps (screening or milling, and mixing) as the two previously discussed granulation techniques.

The unique portions of wet granulation process involve the **wet massing of the powders, wet sizing or milling, and drying.**

Methods

Wet granulation forms the granules by binding the powders together with an adhesive, instead of by compaction.

Employs a solution, suspension, or slurry containing a binder, which is usually added to the powder mixture

Or the binder may be incorporated dry into the powder mix, and the liquid may be added by itself.

The method of introducing the binder depends on:

1. its solubility (since the solution should be fluid enough to disperse readily in the mass).
2. components of the mixture (when small amount is permissible, the binder is blended with the dry powder initially; when a large quantity is required , the binder is usually dissolved in liquid).

The mass should merely be moist rather than wet or pasty, there is a limit to the amount of solvent that may be employed.

Important notes:

The liquid plays a key role in the granulation process.

1. **Liquid bridges are developed between particles**

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As the amount of liquid added is increased → tensile strength of these bonds increases.

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These surface tension forces and capillary pressure are primarily responsible for initial granule formation and strength.

Mechanism: Once the granulation liquid has been added, mixing continues until a uniform dispersion is attained and all the binder has been activated.

2. During granulation, particles and agglomerates are subjected to consolidating forces by action of machine parts and of interparticulate forces.

3. Granulation in large blenders requires 15 min to an hour. The length of time depends on:
   a. Wetting properties of the powder mixture
   b. Granulating fluid
   c. Efficiency of the mixture.

4. A rough way of determining the end point is to press a portion of the mass in the palm of the hand; if the ball crumbles under moderate pressure, the mixture is ready for the next stage in processing, which is wet screening.

Wet screening process:

Converting the moist mass into coarse, granular aggregates **by passage through a hammer mill or oscillating granulator, equipped with screens having large perforations.**

The purpose of wet screening:

1. Consolidate granules
2. Increase particle contact point
3. Increase S.A. to facilitate drying.

Notes: **1- Overly wet material dries slowly and forms hard aggregates, which tend to turn to powder during subsequent dry milling.**

2- There are many instances in which wet milling may be omitted, with a considerable saving of time.

Drying process:

Required in all wet granulation procedures

During drying, interparticulate bonds result from fusion or recrystallization and curing of the binding agent, with van der Waals forces playing a significant role.

Purpose of drying:

1. Remove the solvent that was used in forming the aggregates
2. Reduce the moisture content to an optimum level of concentration within the granules.

After drying, the granulation is screened again.

The size of the screen depends upon:

1. Grinding equipment used
2. Size of the tablet to be made.

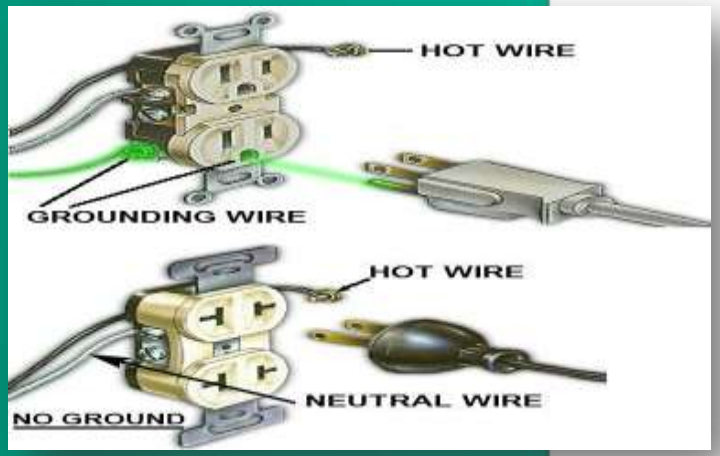
Important note: The use of volatile or inflammable solvents for wet granulation creates other problems:

1. Safety considerations demand that at a minimum, the work areas be well-ventilated:

a. **Reduce direct toxic effects**

b. **Keep the solvent vapor concentration below explosion limits.**

2. All equipment should be electrically grounded to prevent sparks that could initiate explosions.



Equipment

When traditional equipment is used in the conventional wet granulation

Entire process is labor-intensive and time-consuming.

The equipment used for granulation is not highly effective for dry mixing.

A different mixer is used for dry mixing prior to granulation (Examples are sigma blade and planetary mixers).

Problem: Granulation mixers are:

1. Slow
2. Require care for even addition of granulating liquids.
3. Considerable time is needed to distribute the binder properly through the mass.

Solution: newer equipment has been developed that can accomplish both dry mixing and wet granulation efficiently and in much less time.**(Ex:high-speed mixer/granulators).**