Pharmaceutical industrial technology

Theme:
Granulation. Granulation methods. Influence of the granulation type on the bioavailability of the drug in the tablets.
Technological flow for the manufacturing of the tablets

1. Raw material preparation
2. Weighting
3. Grinding
4. Sieving
5. Mixing

Wet granulation
6. Wetting, mixing
7. Granulation
8. Drying
9. Powdering, mixing
10. Pressing

Dry granulation
6. Granulation
7. Grinding
8. Sieving
9. Powdering, mixing
10. Pressing

Direct pressing
6. Pressing
Granulation

**Definition**

Granulation is the operation by which fine powders are converted into larger particles in order to increase their mobility, sliding properties and at the same time to increase the compressive strength of the compressed substances.

**Advantages**

- Good flowing
- Uniform filling of the die
- The energy required for compression is much lower
- Prevention of stratification of drug substances in tablet masses containing several ingredients.
Requirements for the granulates

- To be mobile, slippery;
- To have uniform dimensions and size, spherical shape being more advantageous than the cylindrical shape;
- To not contain significant amounts of powder resulting from breakage of granules.
- To have the appropriate mechanical strength;
- To not be wet, but also to be not dry - wet granules adhere to die and pounches, and those too dry have low cohesion;
- To assure a good disaggregation of the tablets.
Granulation types

- Wet granulation
- Dry granulation
- Special types of granulation
Wet granulation

It is achieved by wetting the drug mixture with agglutination agent and dispersing the obtained mass through a perforated sieve or plates, or granular machines.

Working phases:

• Preparation of ingredients (grinding, sieving, mixing);
• Wetting with binder excipients (agglutinants);
• Granulation itself
• Drying of the granules
• Uniformization of granulates and their processing
Drums with sigma-shaped blades (universal mixer)
Mixing

Process parameters:

✓ Combining the mixing and wetting phase of the powder mixture
✓ Different speed of the blades (front: 17-24 rpm, rear: 8-11 rpm)
✓ Mixing time: 15 min - 1 oră
✓ Agglutinant quantity
✓ Unloading the mixer by tipping over
Granulation

It consists of moving the wet mass through a sieve usually made of special steel grades with a well-defined mesh diameter.

The machines through which wet mass passes through the sieve are called granulators.

Wet granulation processes:
1. Pressing
2. Agitation
3. Cutting
Granulation by pressing
Universal granulatoror
Cutting granulation. Granulator with 2 rolls

The quality of granules depends on the granulation type
Drying of the granulates

It will be done taking into account the physico-chemical properties of the active principles. During the drying process the following factors will be taken into account:

- Optimal moisture of the material (0.5-6%)
- Drying temperature 40-45°C
- Avoiding prolonged drying (the complete removal of moisture leads to friable granules)

**Drying granules with low humidity (processes):**

- Using infrared rays
- Drying in silica gel columns
- Dryers with high frequency currents
Drying by "suspension in air"

Scheme of SP-30 for drying by air-suspension.

Advantages:

• High process intensity
• Complete process automation
• Reduce specific energy expenditure
• Preserving granular flow capacity
Drying granulator
Dry granulation ("briquetting")

Is used:

✓ For substances that are destroyed when wetted
✓ For substances that do not resist to a thermal treatment
✓ For plant powders that have low cohesion.

Phases of the "briquetting" process:

✓ Compressing the mixture of active and auxiliary substances into high volume tablets (briquettes) with special compressing machines. No agglutinants are added to the briquettes. In special cases, a solid agglutinant (lactose, sugar, calcium carbonate, PEG - 4000 and 6000) is added
✓ Grinding of the briquettes with the mills
✓ Sieving
Dry granulation. Press-granulator
Dry granulation. The compactor
Uniformization of granules. Schema marmerizer.
Uniformization of granules.

Working parameters:

- Rotation speed: 400-1600 rpm
- Spheronization time: 2 min
- Productivity: 20,000 kg / hr
- To prevent adhesion and the formation of conglomerates, microcrystalline cellulose, starch or talc are added.
Modern granulation processes

- Granulation by fluidization (suspension in air, pseudo-liquefaction)
- Granulation in the boiler for dragee manufacturing
- Spray granulation
The method combines the mixing, granulation and drying phase into a single machine. The method is based on the formation of granules by spraying the agglutinants over the granular powder, held in suspension by a hot air stream.
Granulation by fluidization

Advantages

• Shortens the production cycle (lasts for 25-45 minutes instead of 11-30 hours)
• The number of machines used decrease (from 5 to 2)
• The production area is reduced by 50%
• Labor costs are reduced as many manual operations are decaying.
• The granules obtained are more homogeneous regarding to the fractional composition. Most granules (60-80%) range from 0.25-1.5 mm
Granulation in boilers for dragee production
Drying of the liquids.
Disc nebulizer drying scheme
Spray granulation

The method is rational when it is desirable to have short term contact with the heat agent.

There are 2 variations:

- Spraying of the suspension of diluents (eg. lactose, calcium sulphate) with the addition of agglutinants and disintegrating excipients. The percentage of the solid phase in suspension may be 50-60%.

- Spraying of the solution or suspension made up of the active and auxiliary substances.

The method has not been widely applied due to the relatively massive apparatus, large air expenses, the complexity of small particle retention, and large economic costs.
Determination of the physico-chemical and technological properties of granules

- Determination of the shape and size of granules
- Determination of flow capacity
- Determination of moisture
- Determination of porosity
- Determination of filling factor
Adding lubricants and disintegrants to granules

- These are added to the granules if they have not been added prior to granulation.
- Generally, disaggregation of the tablets is better if the disintegrant excipient is added after granulation.
- The best situation is when a part of the disintegrant excipient is mixed with the compressed powders prior to granulation and another part is added to the dried granules.
- Lubricants and disintegrants are incorporated by powdering the granules, the operation takes place in the mixer or in an airborne dryer (for 1-5 min).