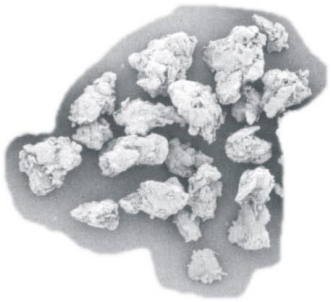


Granules and Pellets

Prof. emer. Dr. Hódi Klára

Granules

as dosage form

Ph. Eur

- Granule is an oral dosage form, which is aggregate of solid powder particles. They could be swallowed or chewed, or dispersible in water or in other suitable solvent.

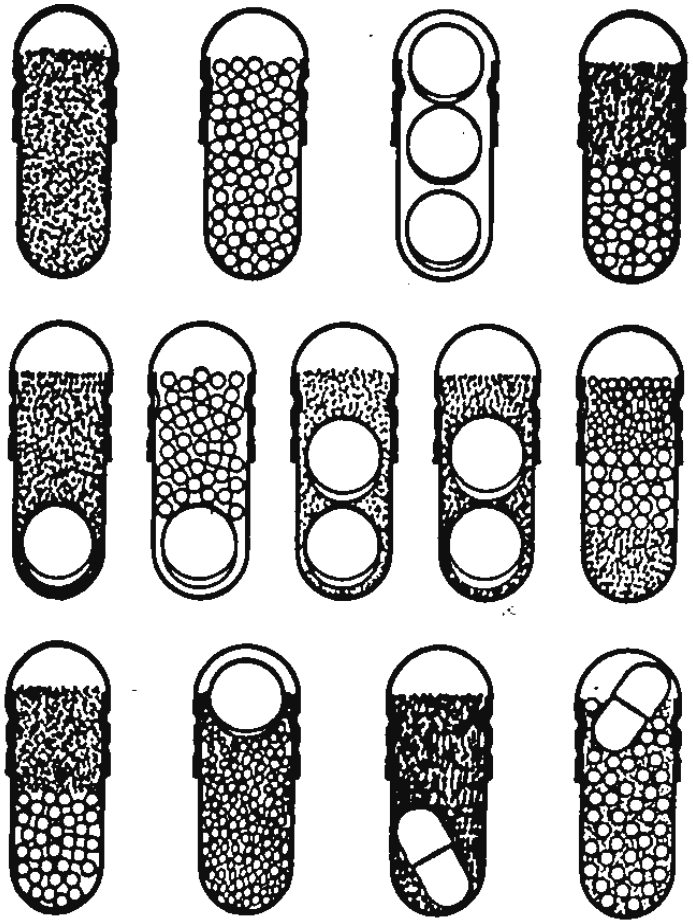
- API(s) + excipient(s) + coloring agents + flavoring agents
- Sachets or dispensing spoon
- Packaging and storage

Single or multi unit dosage form

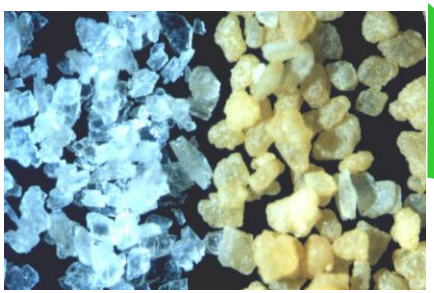
Granules as dosage form

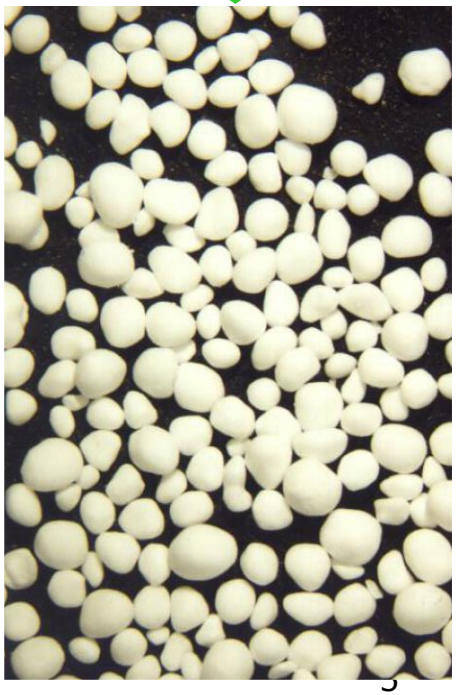
- Coated granules
- Gastroresistant granules
- Modified release granules
- Effervescent granules
- Instant granules

Granules as intermediets



Aims of granulation

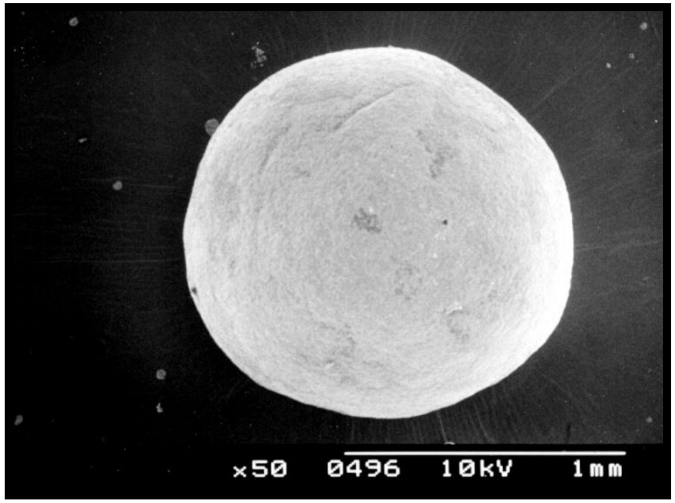


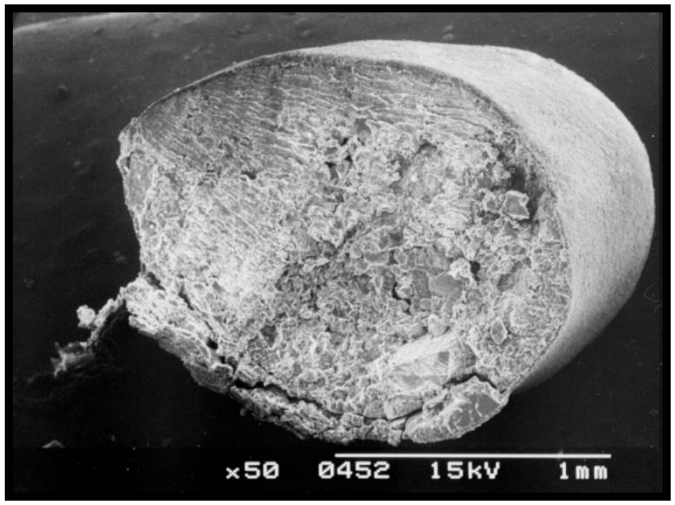


- Decrease of adhesion
- Easy administering
- Taste masking
- Increasing of flow
- Decrease of specific surface
- Decrease the electrostatic charges
- Specific coating
  (intestinosolvens, retard, etc.)

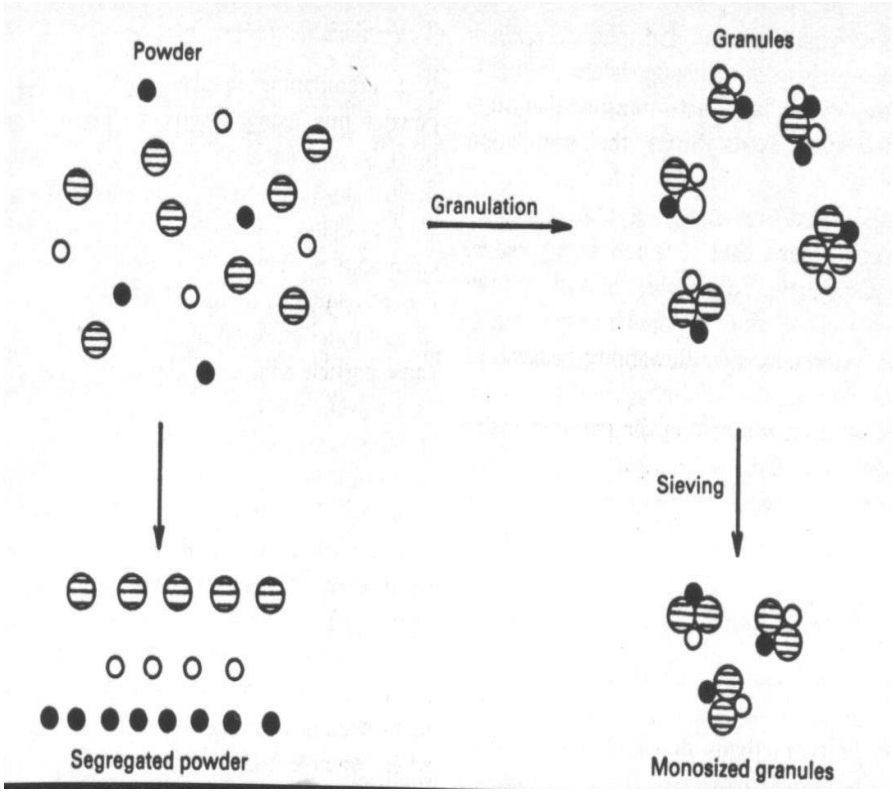
Granules
asymmetric aggregations

Pellets
symmetric aggregations





Granulation is integrating process



API **Excipient**

mixing (homogenization)

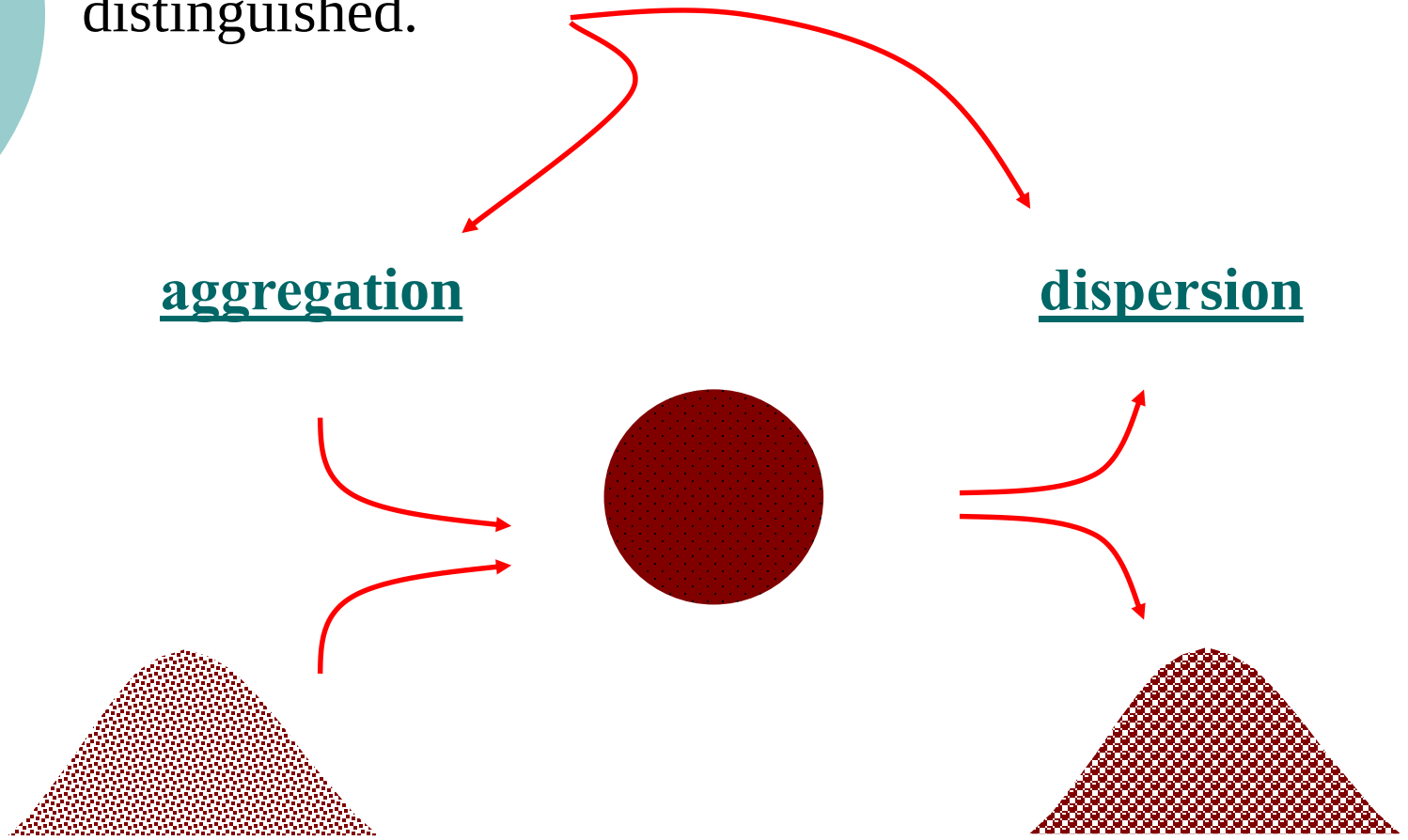
aggregation (kneading)

dispersion (making particles)

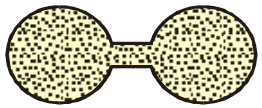
packaging

Preparation of granules

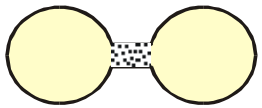
During the production of granules two processes can be distinguished.



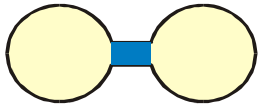
Important binding types with material



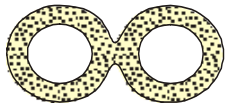
- **Solid bridges**



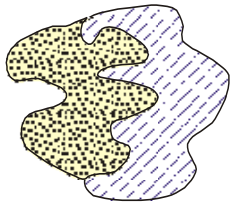
- **Solid bridges with other material**



- **Liquid bridges**

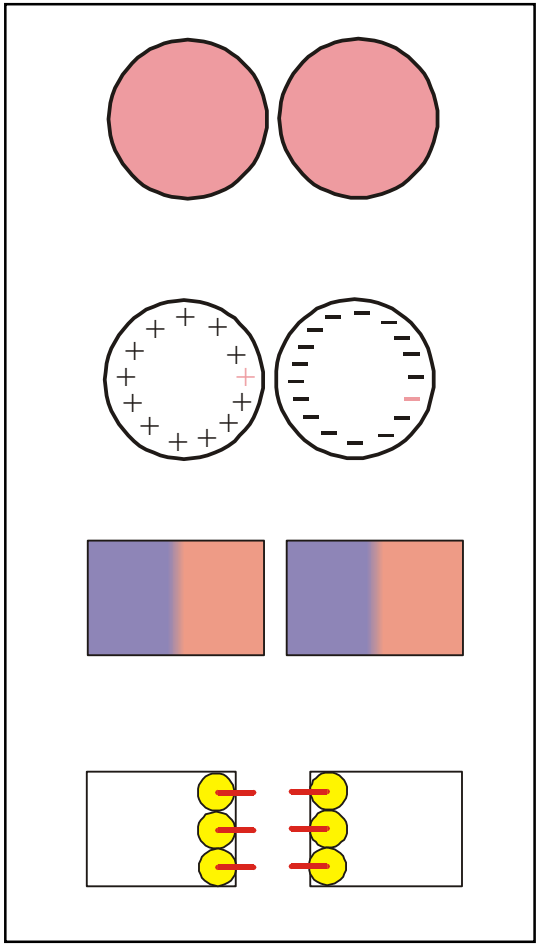


- **Adsorption layer**



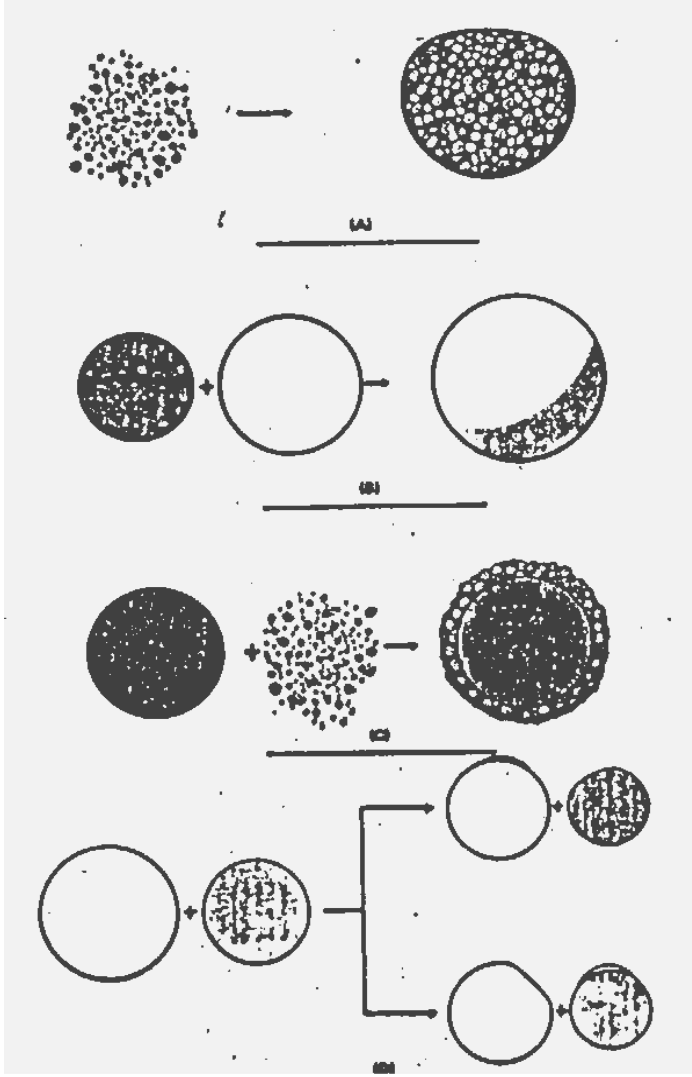
- **Shape binding**

Other important binding types without material



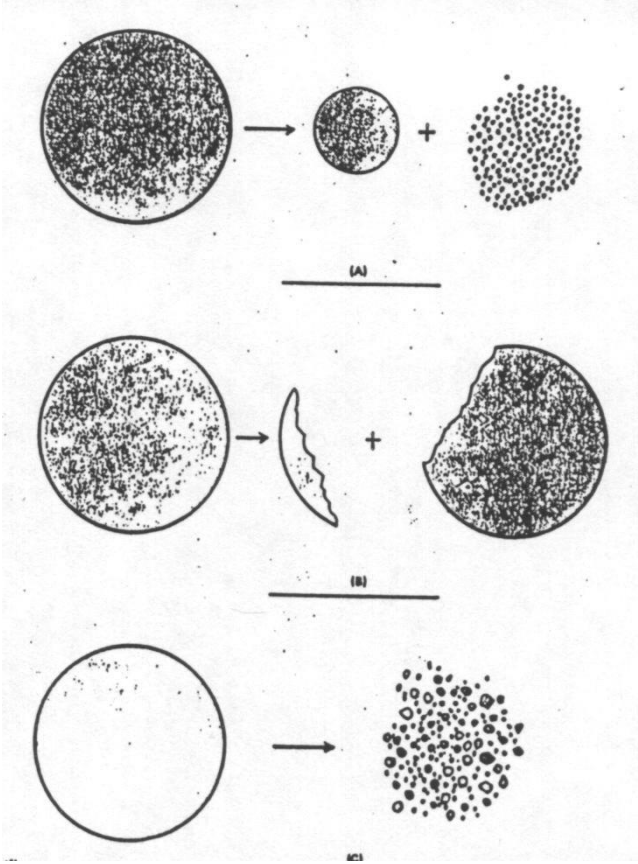
- **van der Waals forces:** it can be formed, when between two particles or surfaces the distance is smaller the 100 nm.
- **Electrostatic forces**
- **Magnetic forces**
- **Free chemical bonds**

Mechanism of particle growth



- Nucleation
- Coalescence
- Layering
- Abrasion transfer

Mechanisms of particle reduction



- **Attrition**
- **Breakage**
- **Shatter**

Aggregation

Wet granulation → **with binder solution** — *sticked granules*

Wet granulation → **with solvent** — *crust granules*

Dry granulation → **compression or compaction**

Melting granulation → ***Sinter*** *granules*

Extrudation and spheronization → **Wet or melt method** — *Pelletization*

Dispersion

Dispersion is the granulation of the aggragted material however the degree of dispersity of the product produced in this way is smaller than the initial value of the powder or the powder mixture.

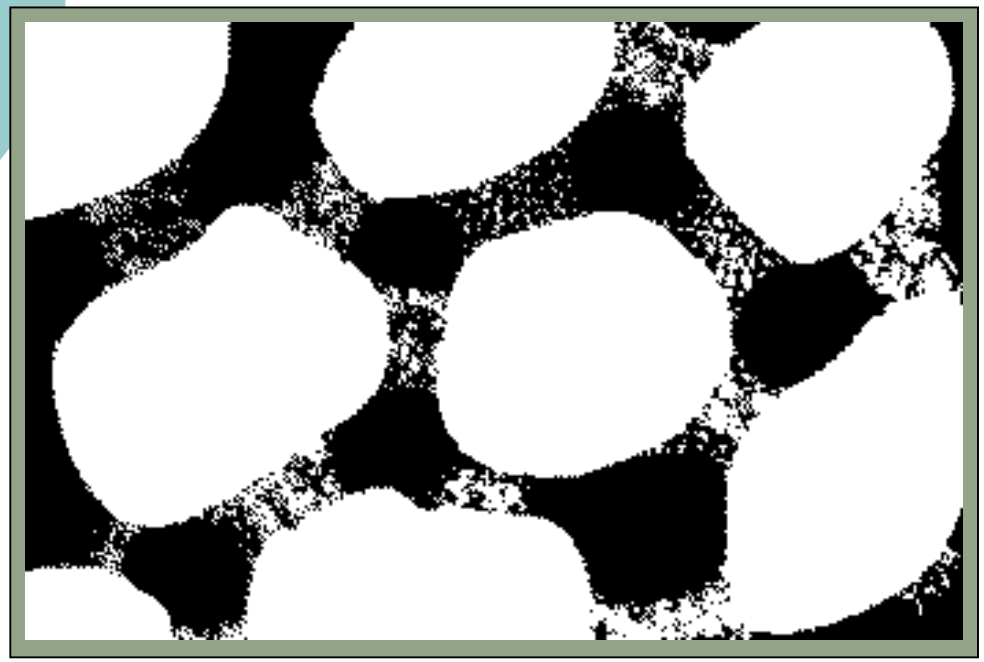
- Pressing through a sieve
- Application of a disc granulator
- Application of an oscillating granulator

Wet granulation

Type of granulation	Granulating solution
Solvent granulation *(crust granules)*	water water-alcohol mixture
Binder granulation *(sticked granules)*	macromolecular colloidal solution i.e.: starch, gelatine, polividon, cellulose ethers (MC, HEC, HPMC, etc.)

Aggregation with binder liquid

sticked granules



Solidified binding agent

binder:

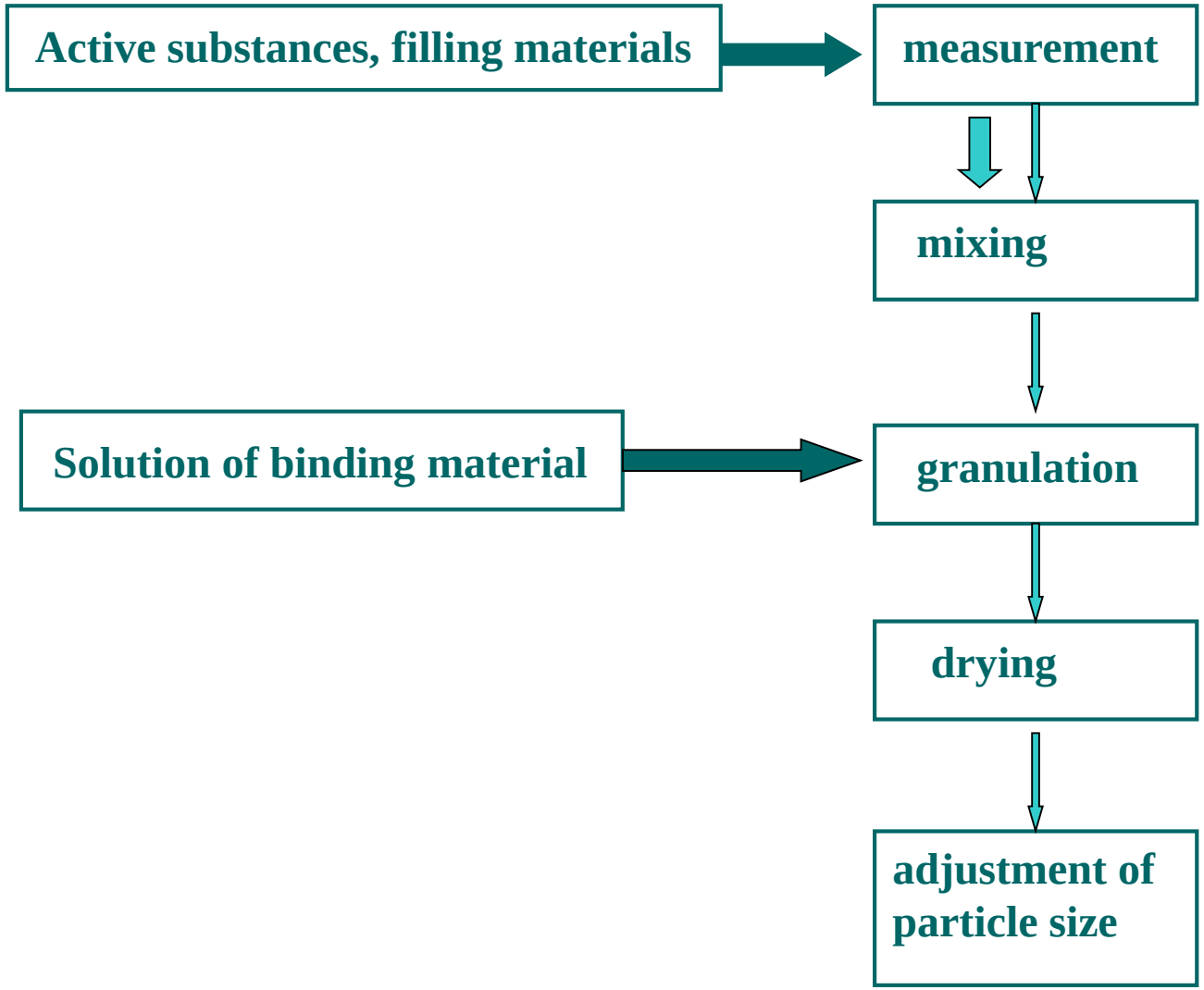
- starch
- gelatine
- PVP, etc.

Aggregation with solvent

crust granules

Partial dissolution of moistened powder material.
The applied moistening solution dissolves one or more component of powder material. Recrystallized solid bridges formed after drying.

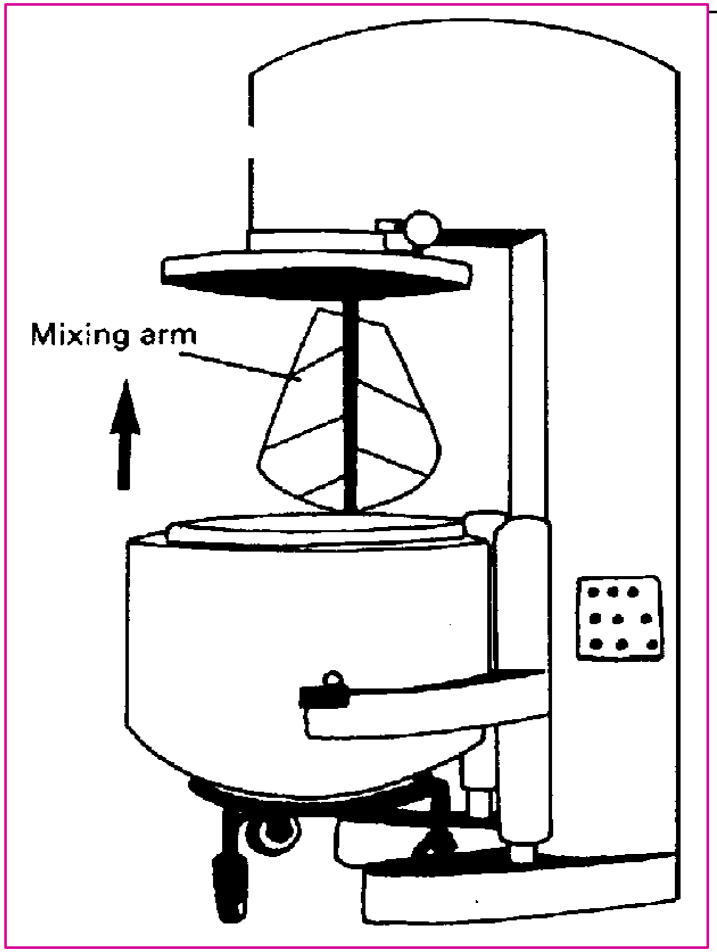
Flow chart of wet granulation



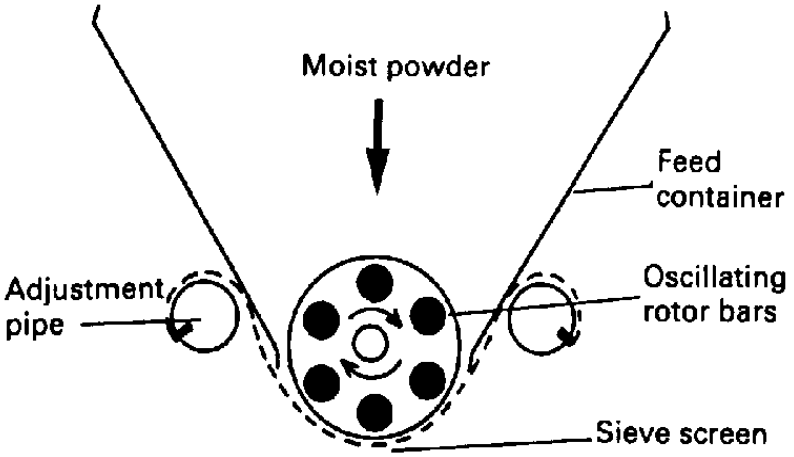
Traditional granule preparation

- Aggregation:
  - (by hands)
  - by machines
- Dispersion:
  - press through sieves

Treaditional granule preparation– by machines



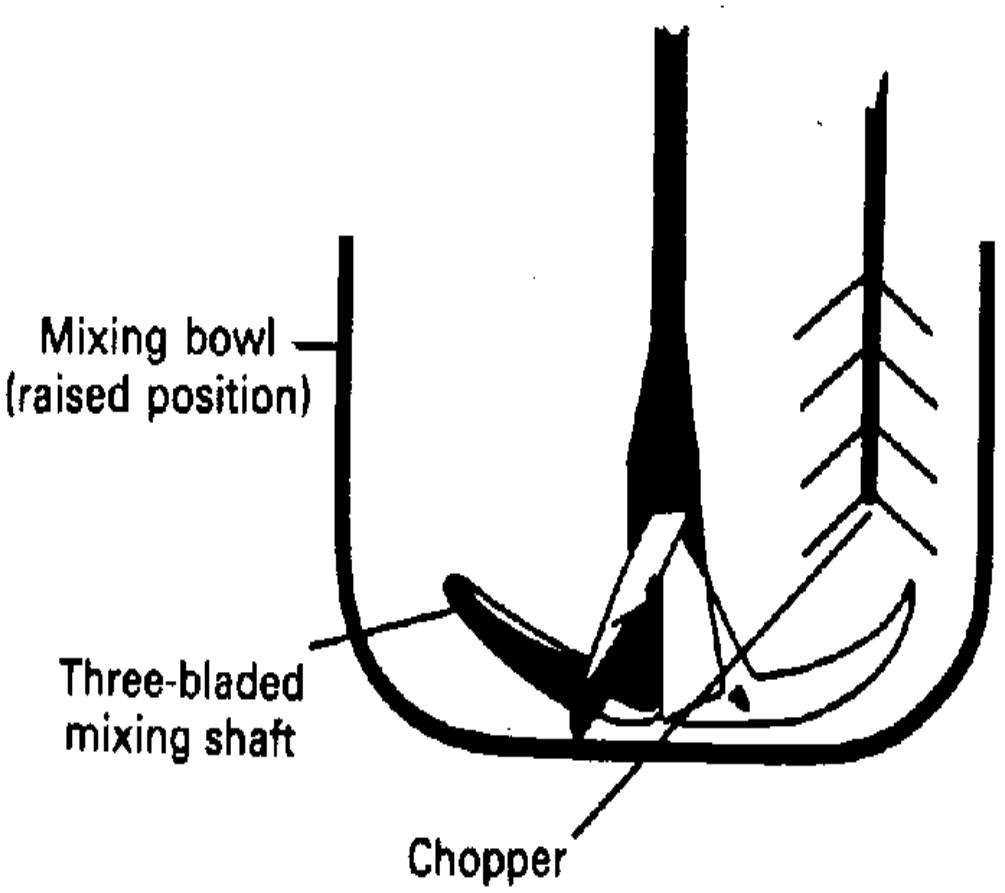
Planetar mixer



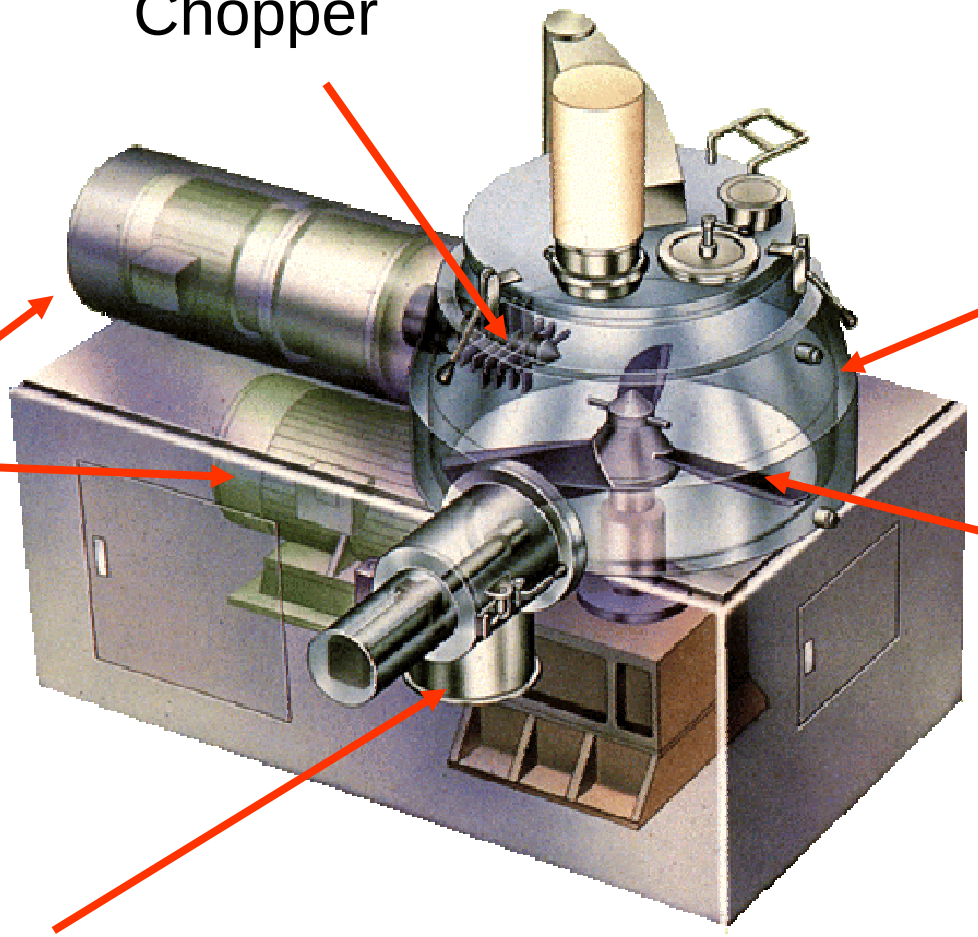
Oscillation granulator

Build-up granulation– high shear mixer

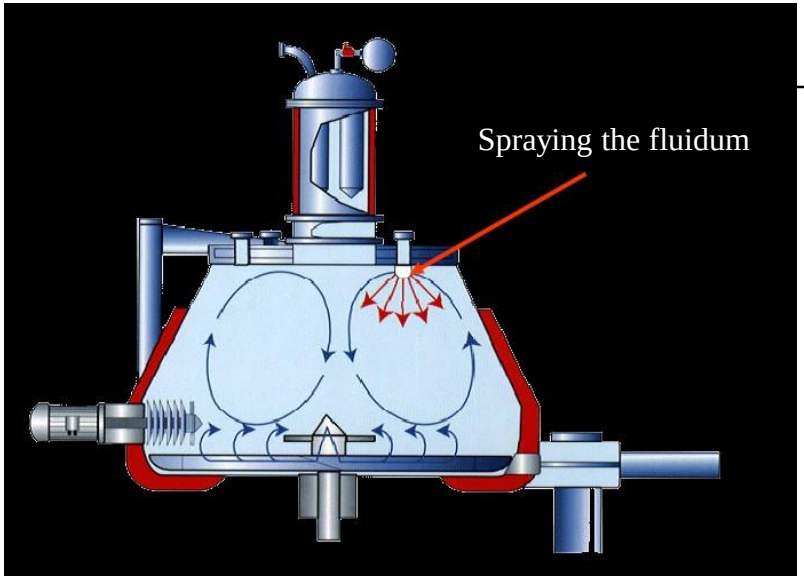
Collette-Gral granulator: mixing shafts and bowl

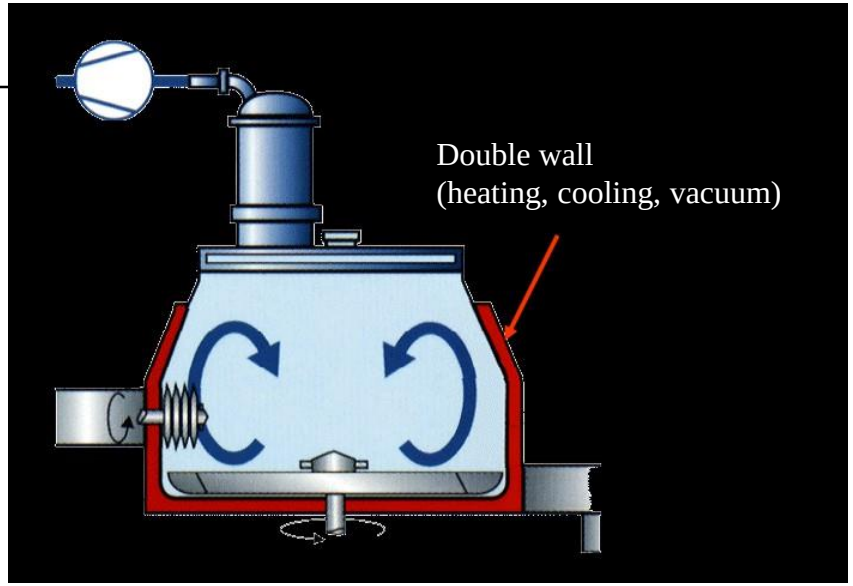


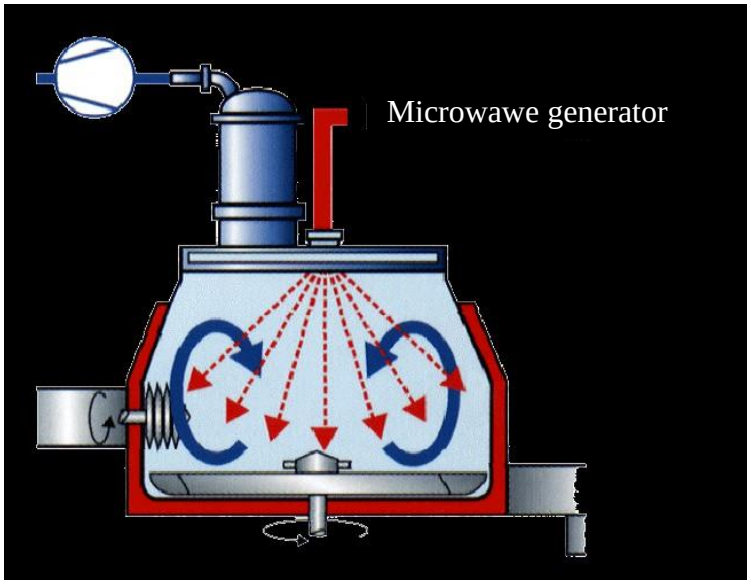
„High shear” granulators



Special equipments







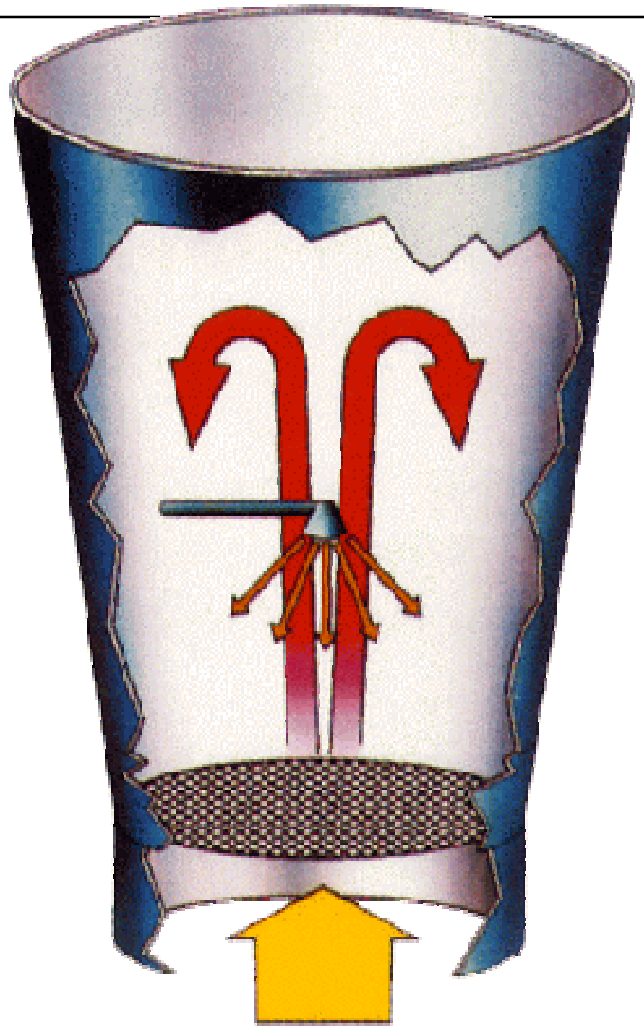
High shear mixer with vacuum dryer

Collette Ultima Pro 600

Critical parameters

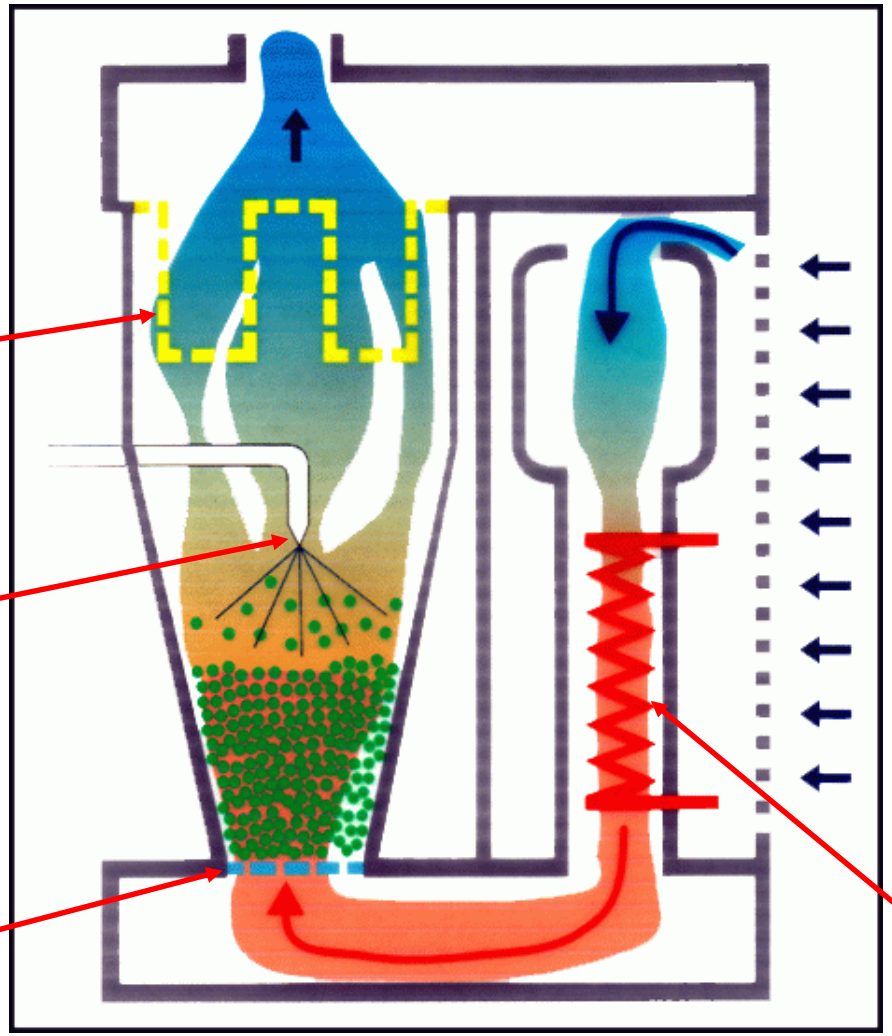
- Impeller speed
  - Determines homogenity of wetting and the mechanical load of the material
- Chopper speed
  - Determines the size of the particles
- Speed of liquid addition
- Temperature
  - Their ratio determines the kinetic of the particle growth

Fluidization systems



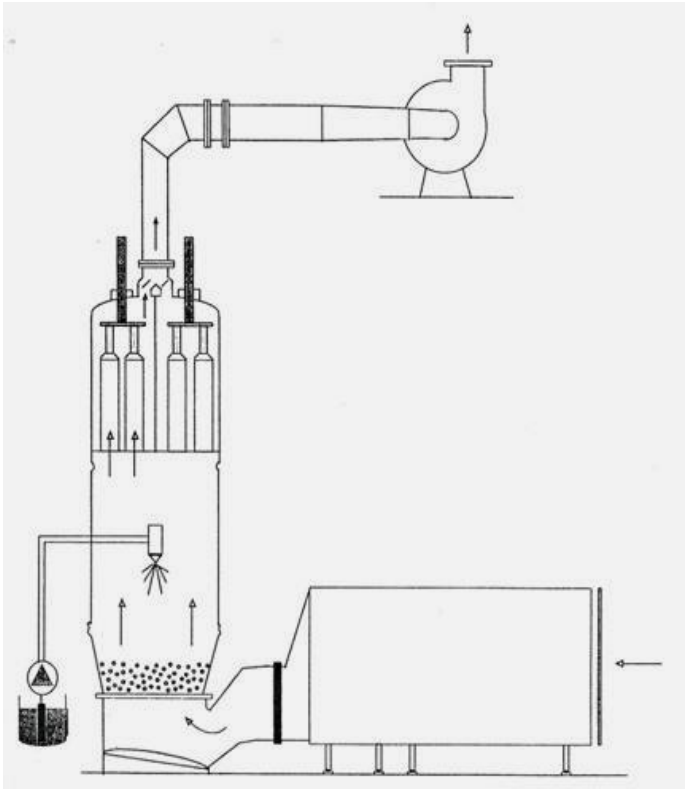
Fluid bed granulator

Strea-1

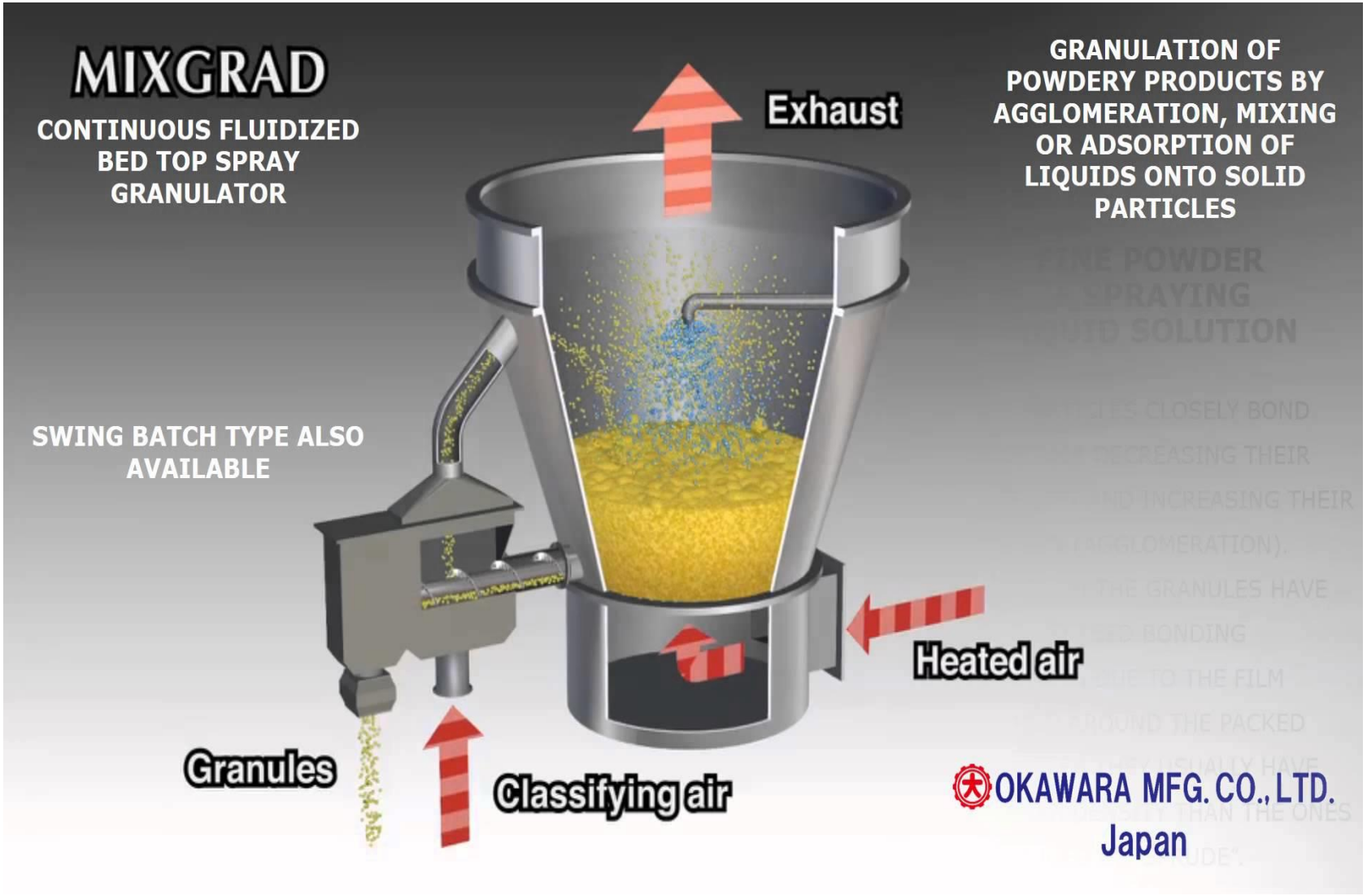


Fluidization process

Glatt WSG 200

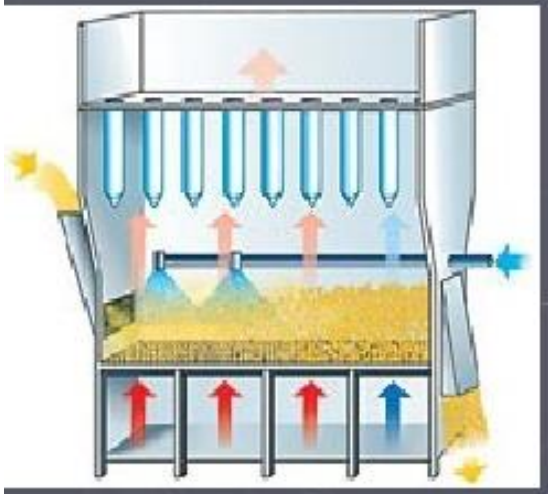


Continous fluid bed granulation

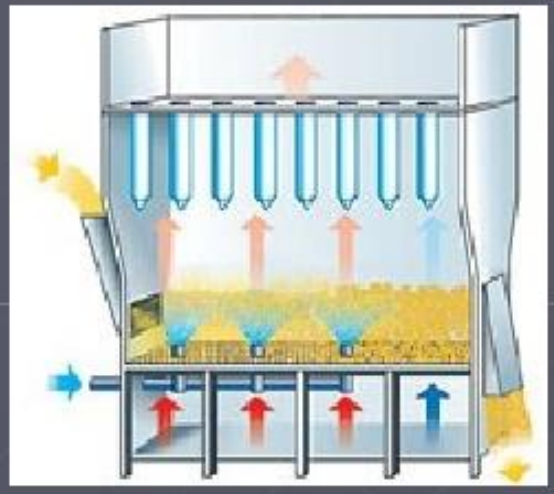


Continous fluid bed granulation

Continuous granulators are sub-divided into several granulation zones, which are operated at different speeds and temperatures, e.g. Granulation in the first and second sections, drying in the third and cooling at the end of the process chamber.



Principle:
Continuous fluid bed granulation,
Top Spray



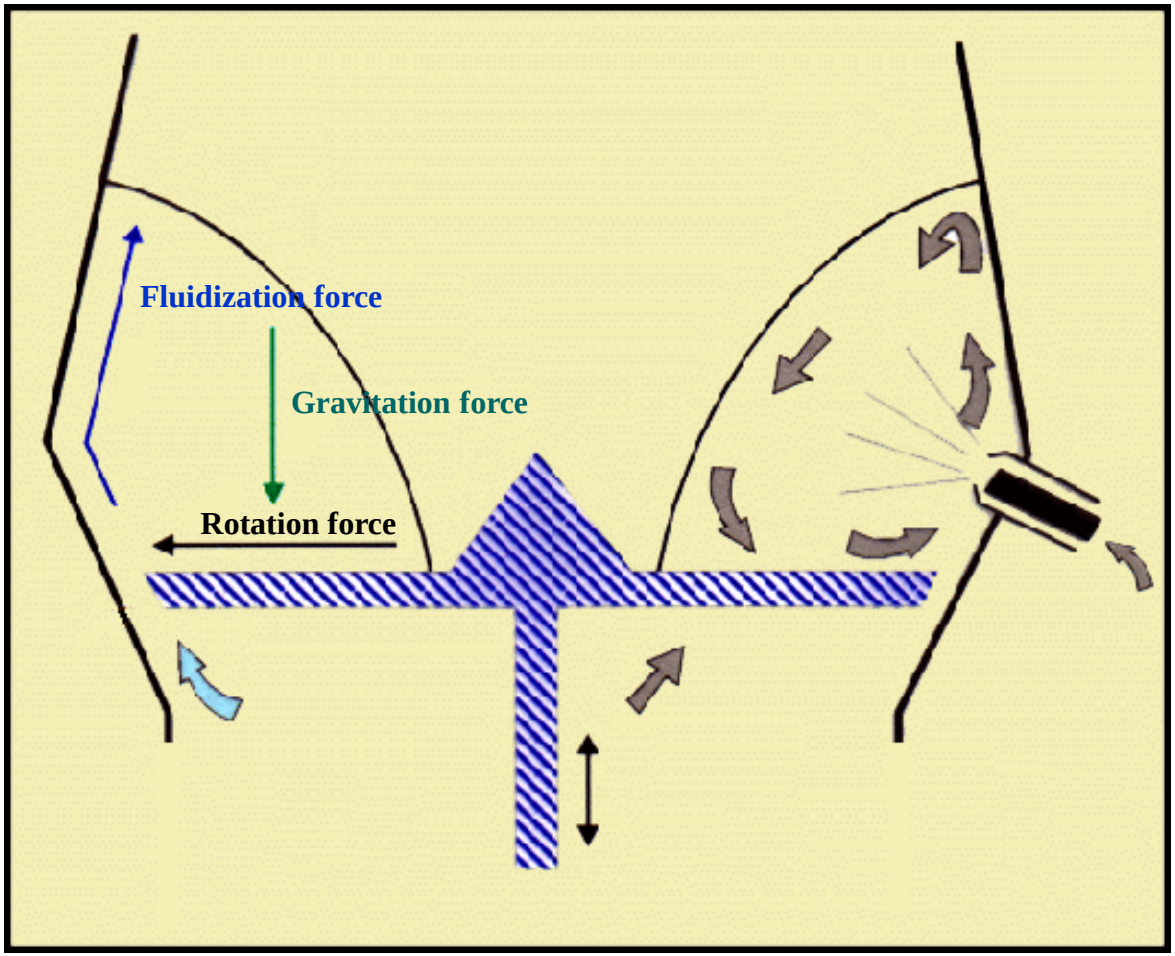
Principle:
Continuous fluid bed granulation,
Bottom Spray

18

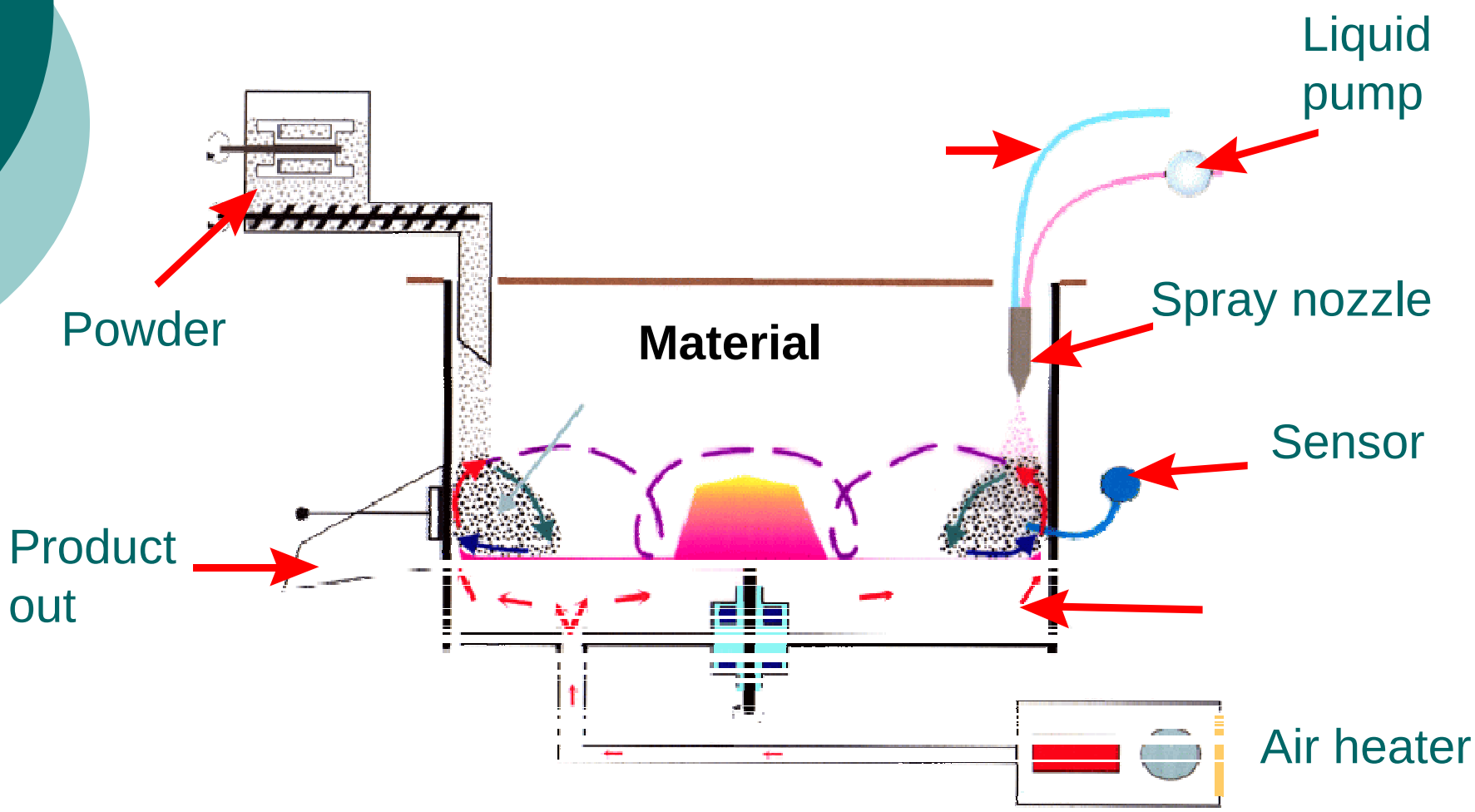
Critical parameters

- Fluidization air flow
  - Determines the homogenity of wetting and the mechanical impact on particles
- Atomizing pressure
  - Determines the drop size and the drying kinetic
- Spray rate
  Temperature
  - Their ratio determines the kinetic of film forming and the speed of particle growth

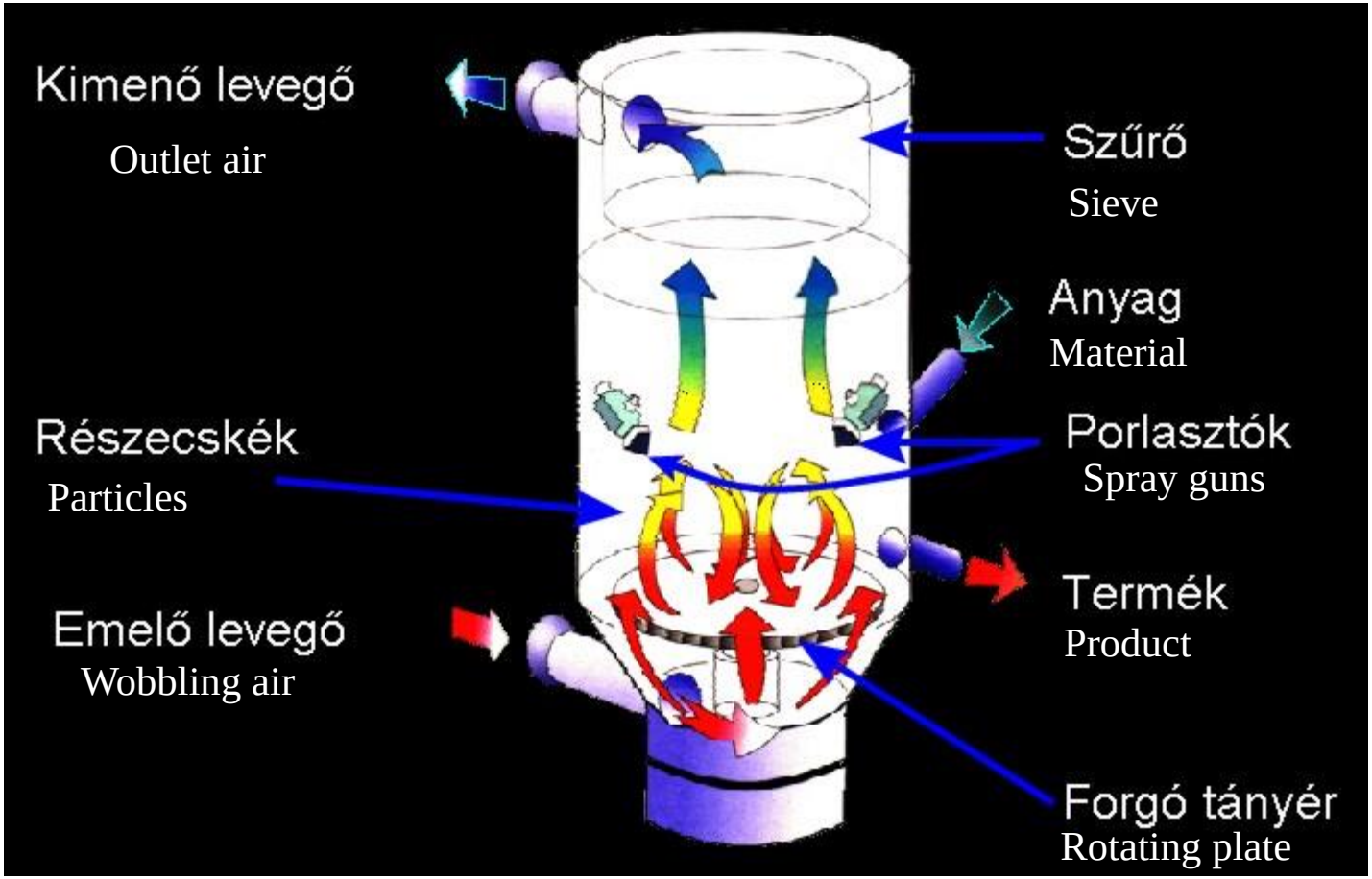
Rotating systems



Rotating systems



„Rotofluid” granulation



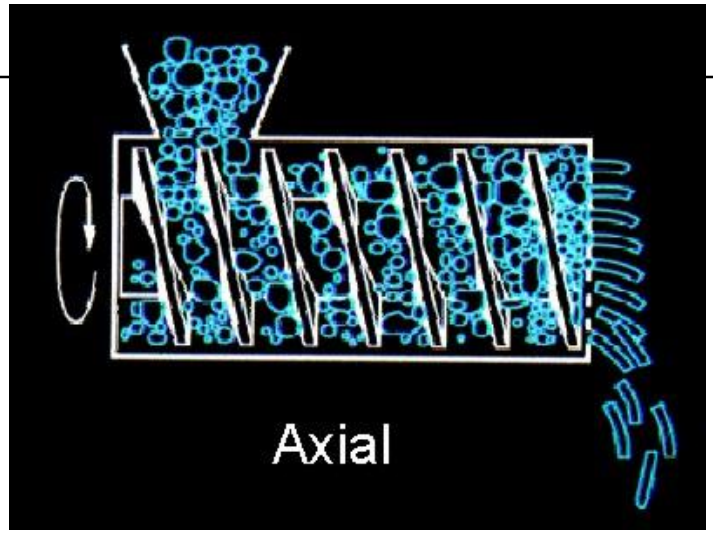
Spir-a-Flow system

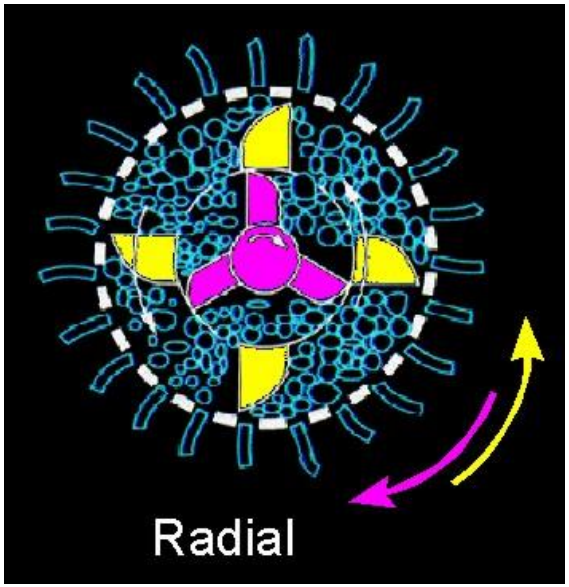
Critical parameters

- Rotor speed
  Fluidization air flow
  - Determines the homogenity of wetting and the shape of the particles
- Atomizing pressure
  - Determines the drop size and the drying kinetic
- Spray rate
  Temperature
  - Their ratio determines the kinetic of film forming and the speed of particle growth

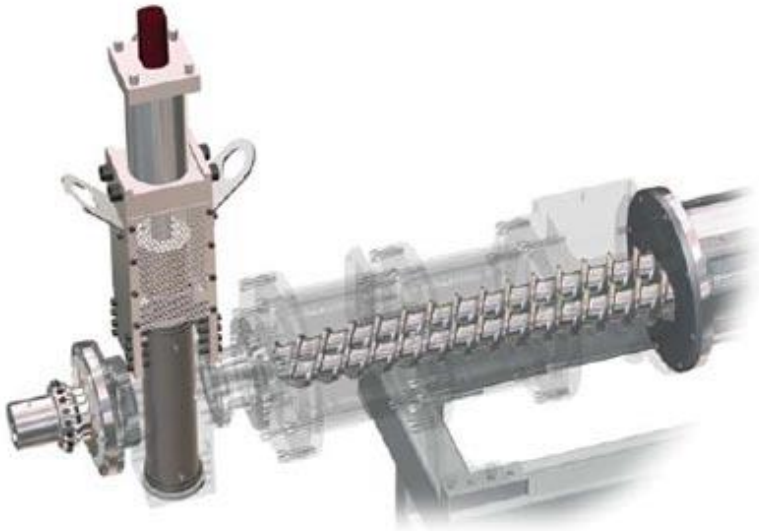
Extrusion

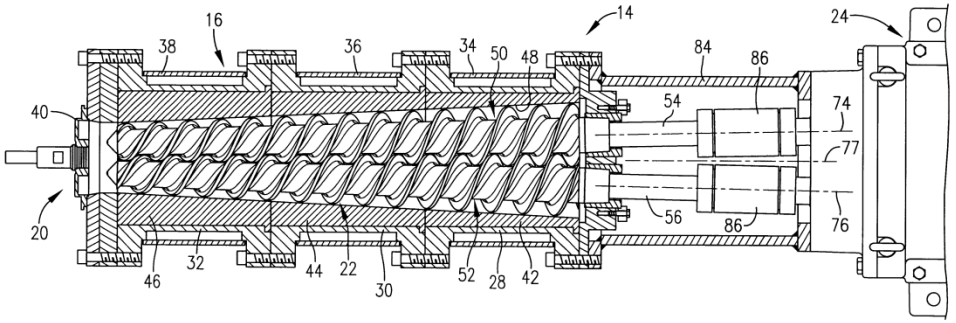
Screw extruders

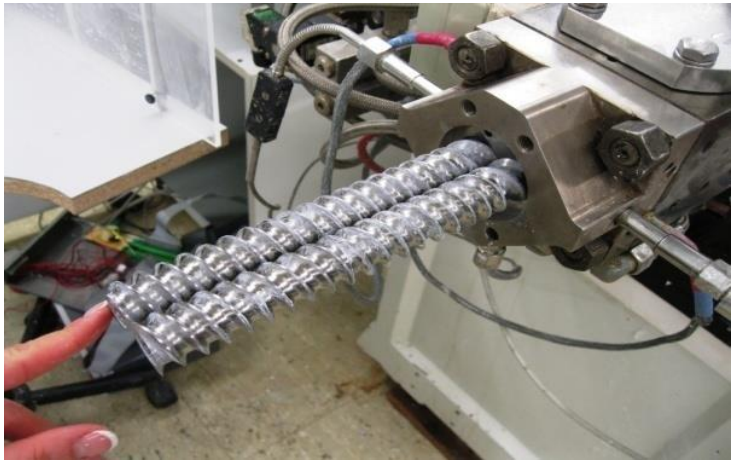


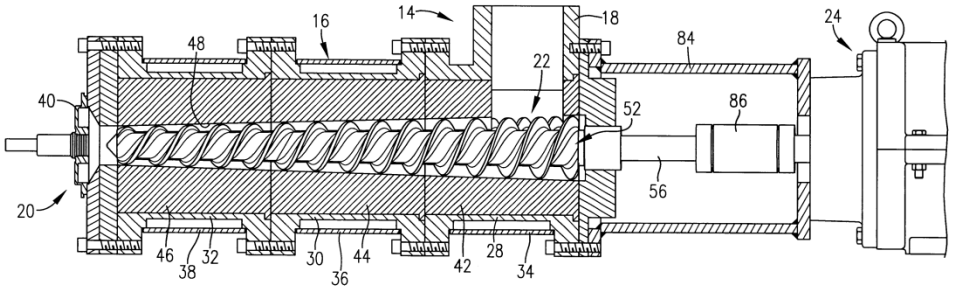


Twin-screw extruders



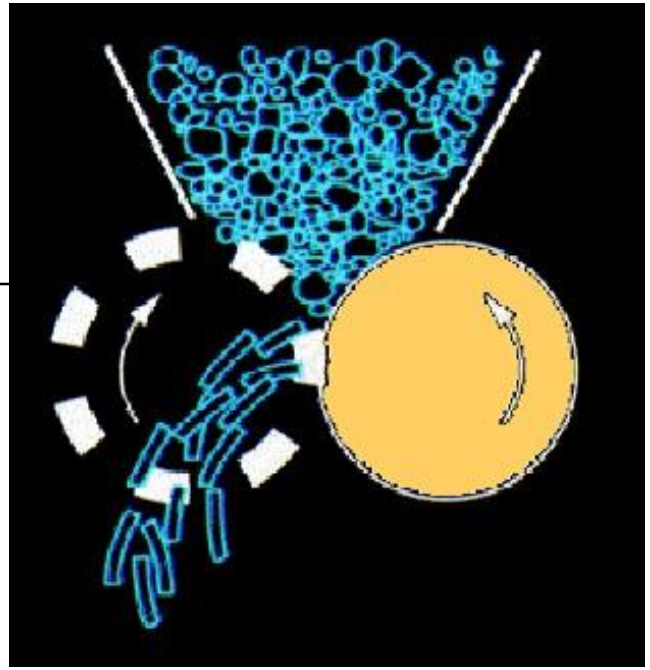


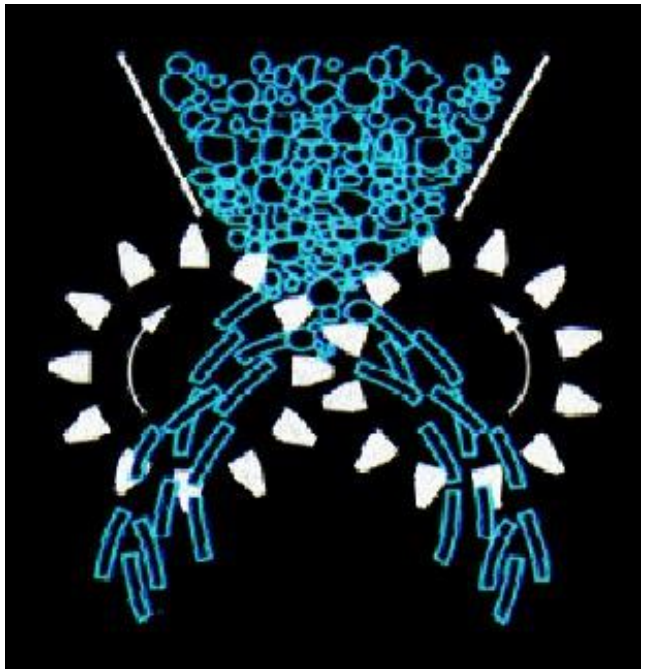




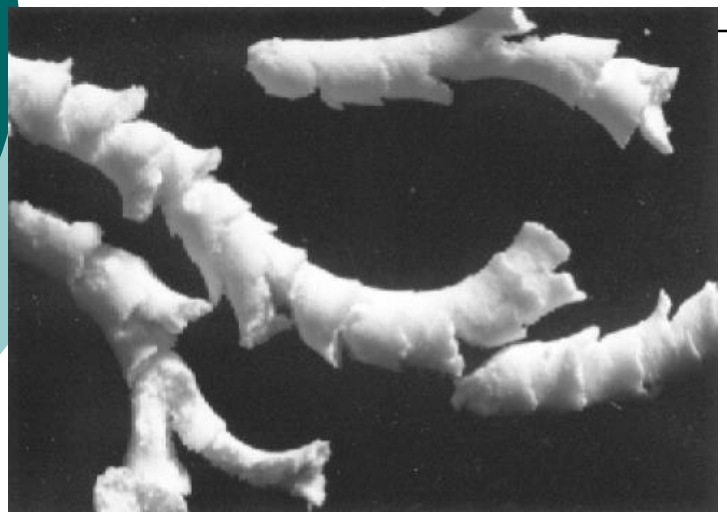
Extrusion –

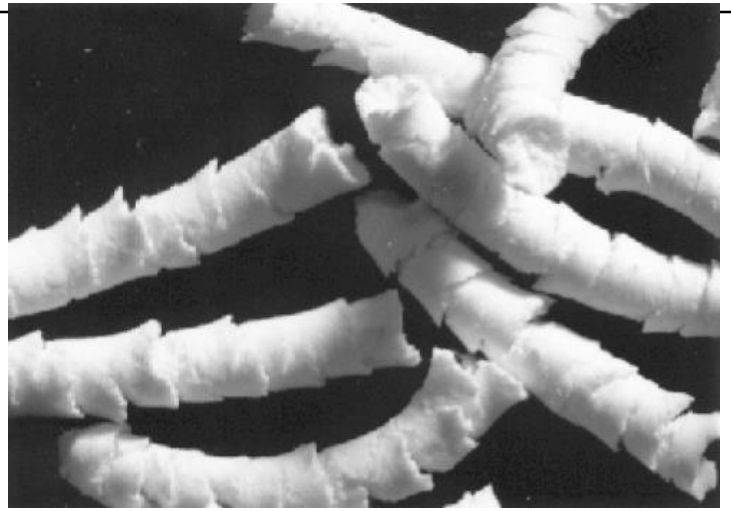
Gravity extruders

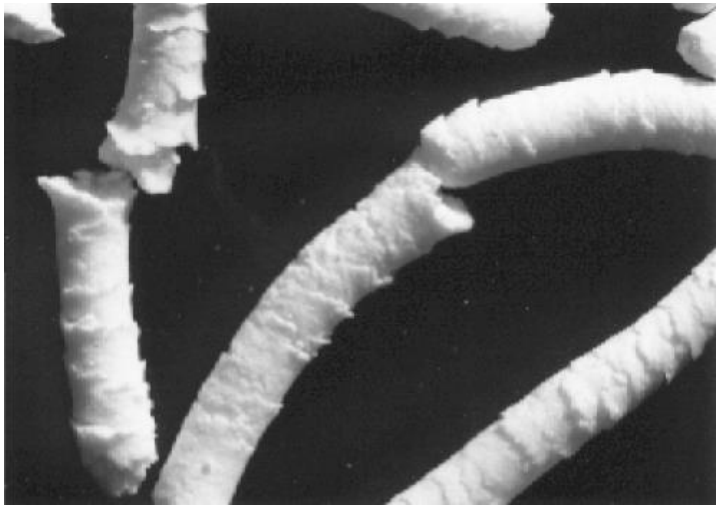


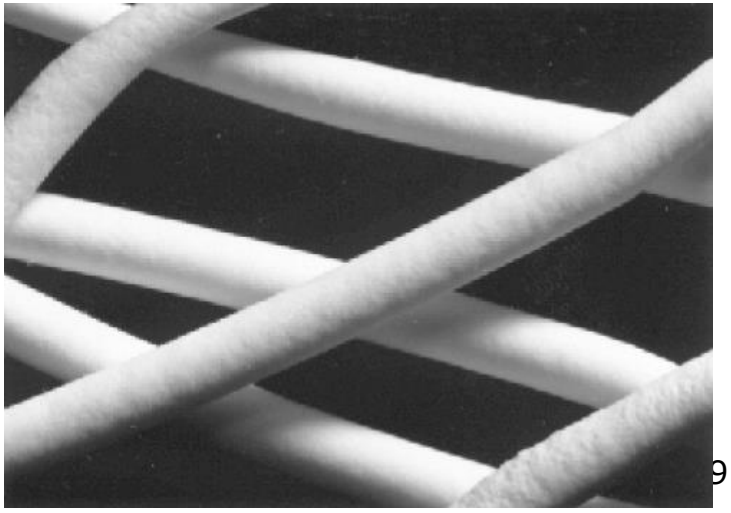


Effect of the humidity content for the quality of the extrudated mass

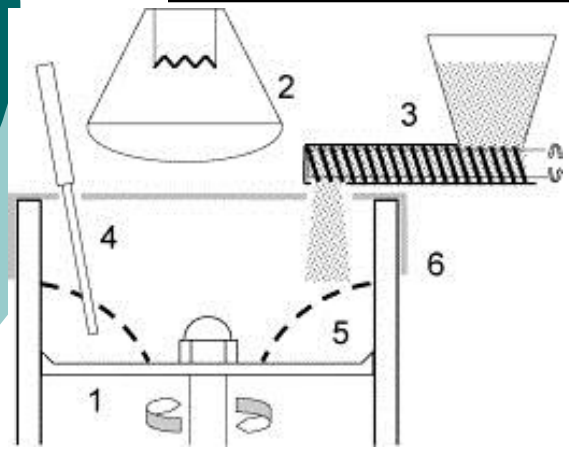


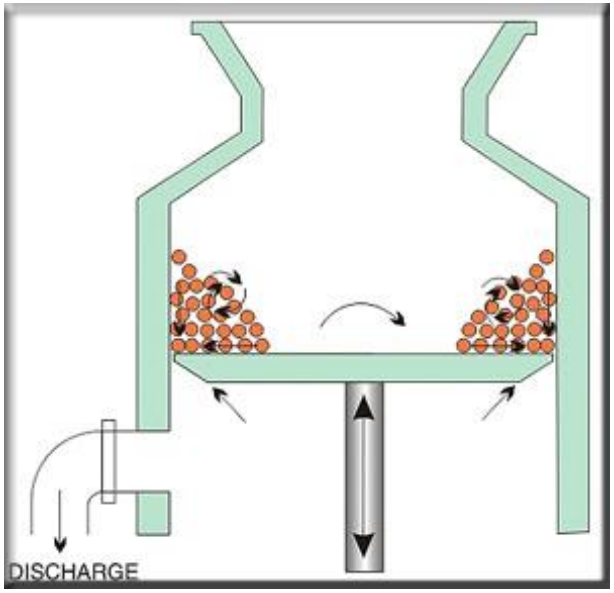


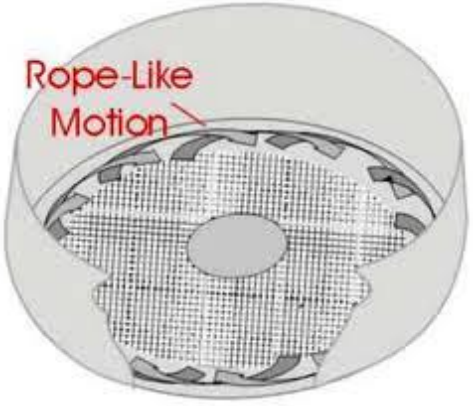




Spheronization



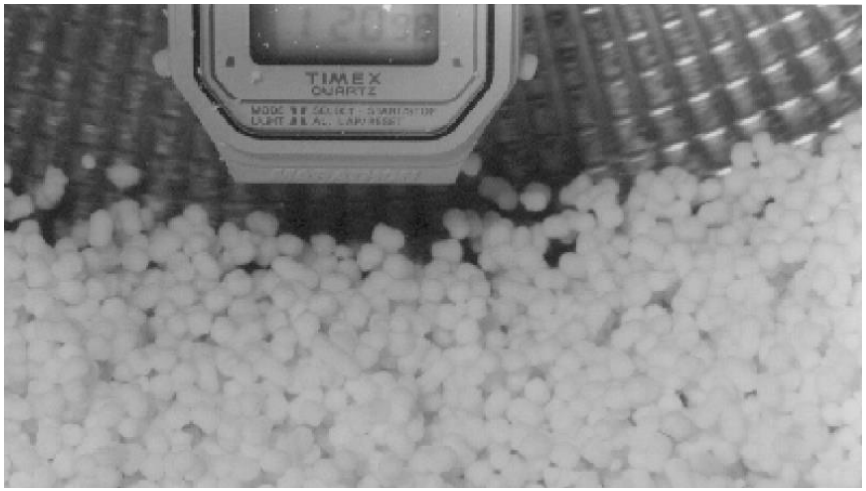




Effect of the spheronizing process

Starting point

End point



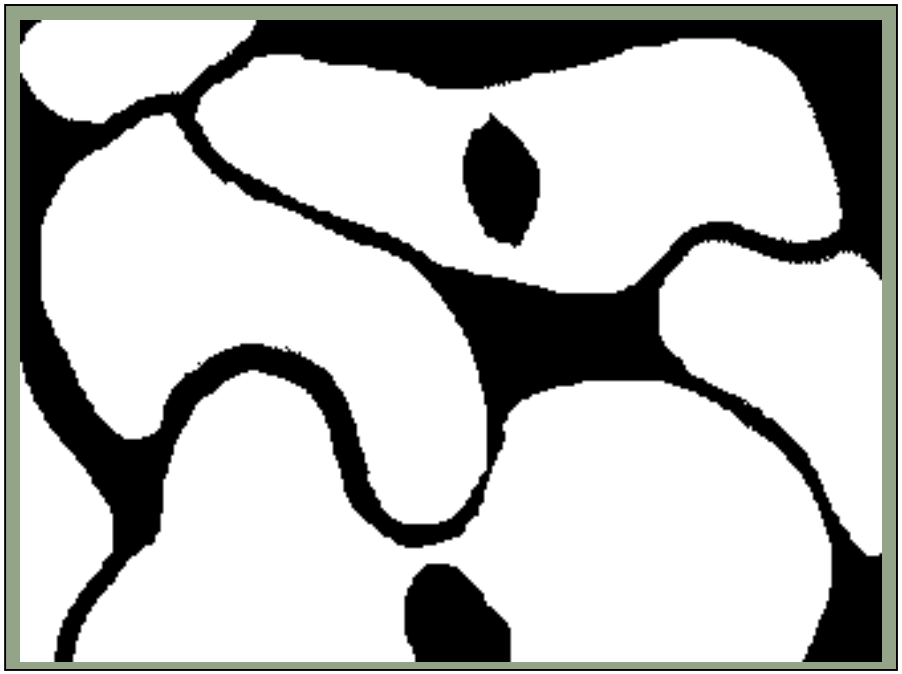
Critical parameters

- Moisture content of the wet mass
  Plasticity of the etruded material
  - Determines the pellet strenght and the product quality

- Speed and time of spheronization
  - Deterimes the shape of the pellets

Dry granulation

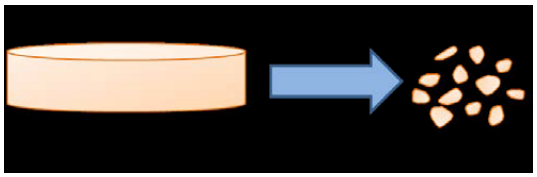
Compression or compaction

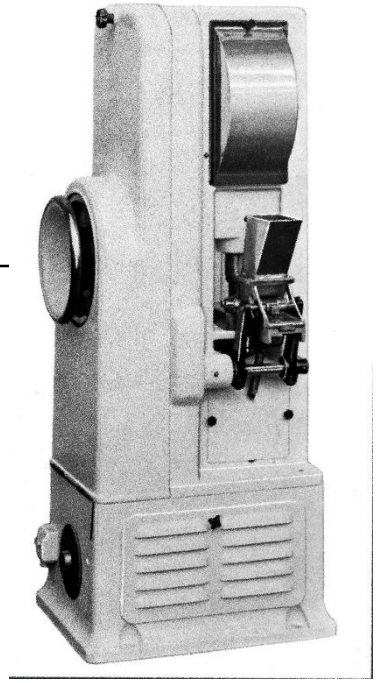


Mechanical interconnection: form-closing bindings can be created

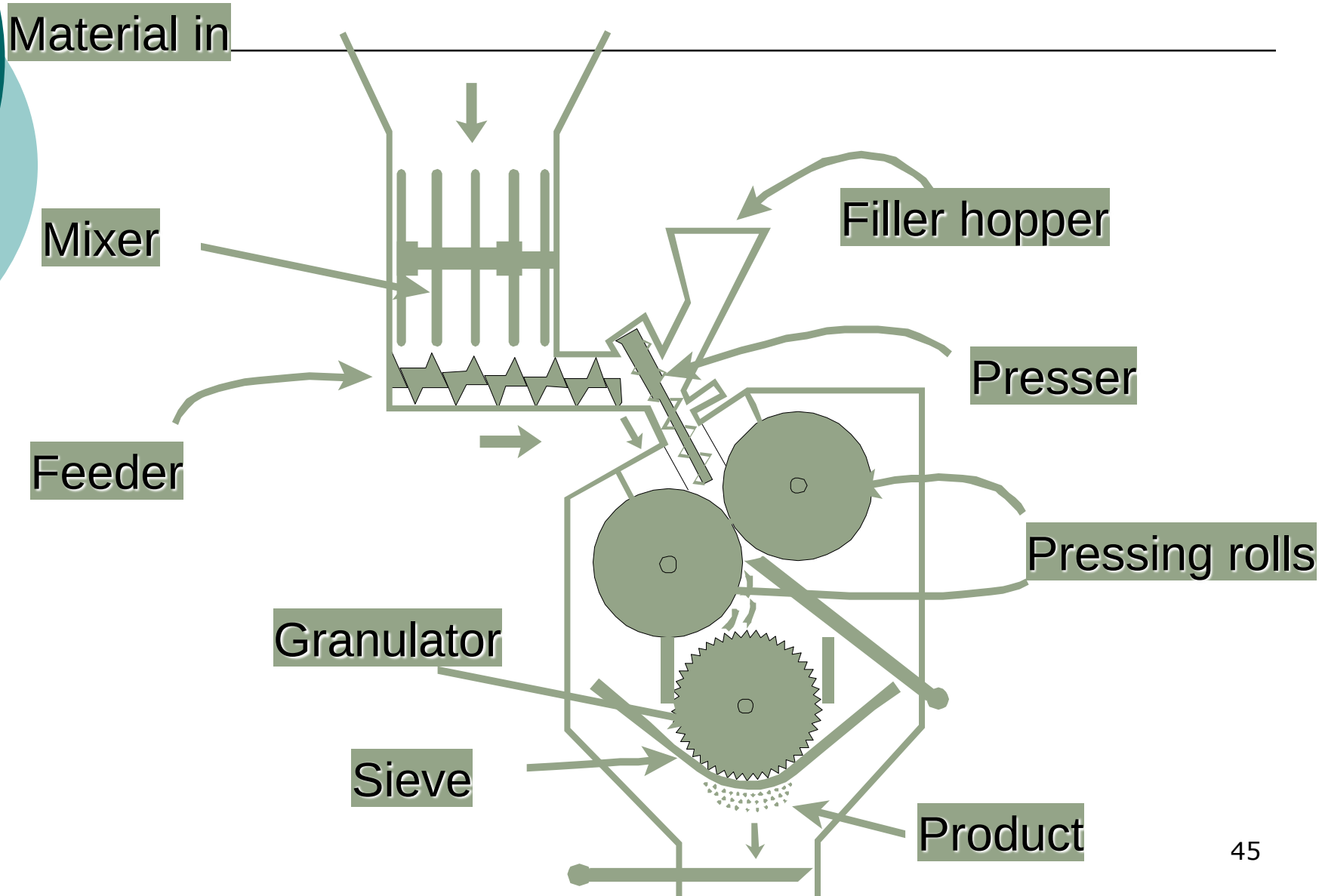
Dry granulation

- Slugging

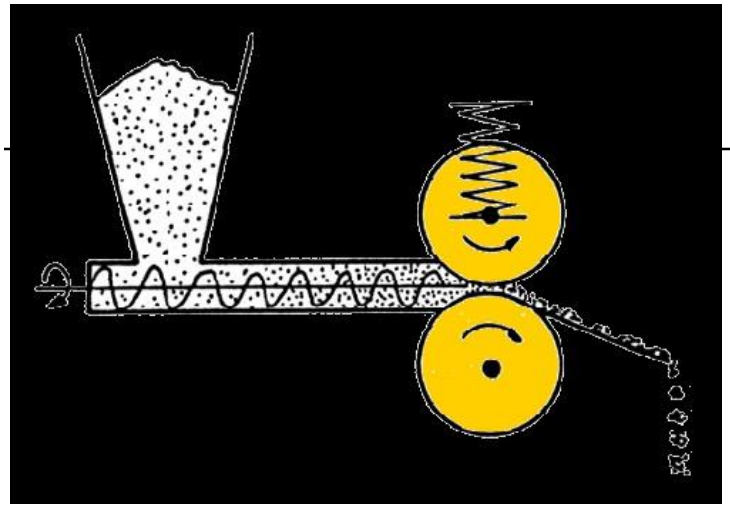


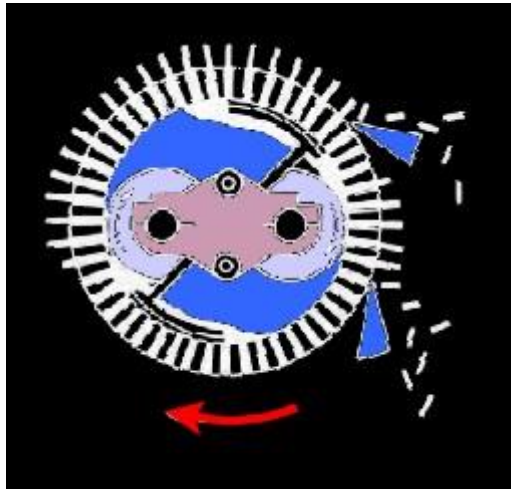


Dry granulator - compactor

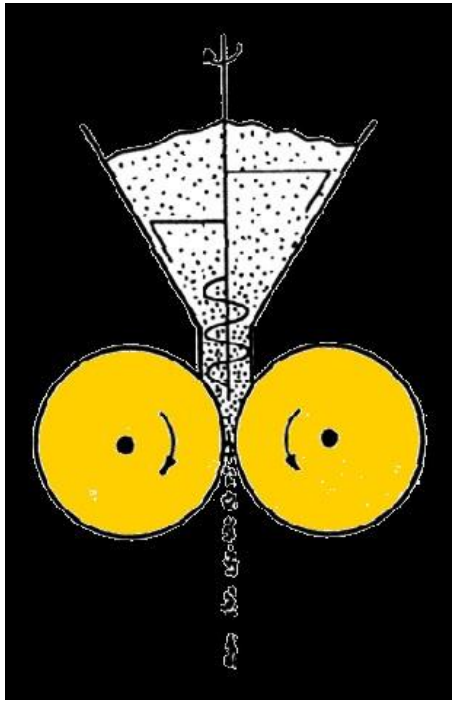


Compactors

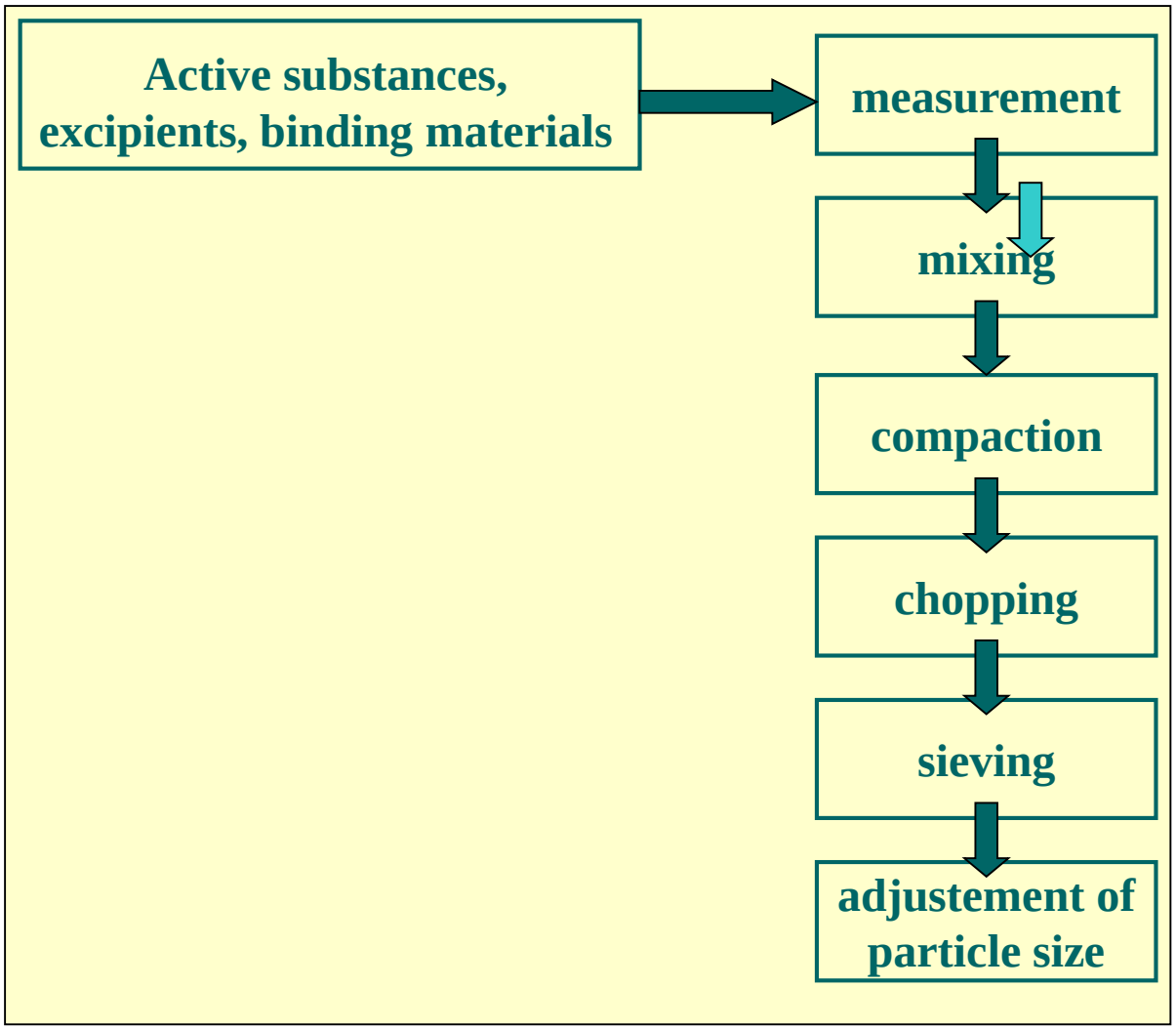




Rotating



Flow chart of dry granulation



Critical parameters

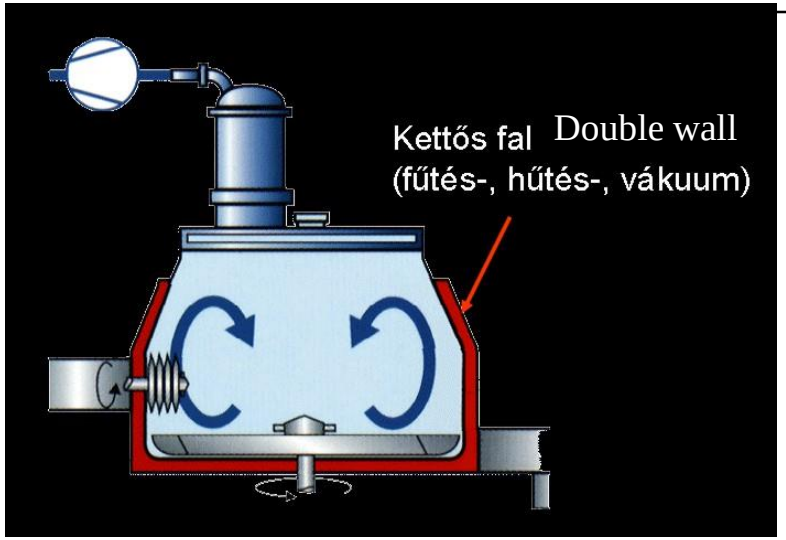
- Distance of the cilinders
- Pressure
- Speed of granulation

Aggregation with melting

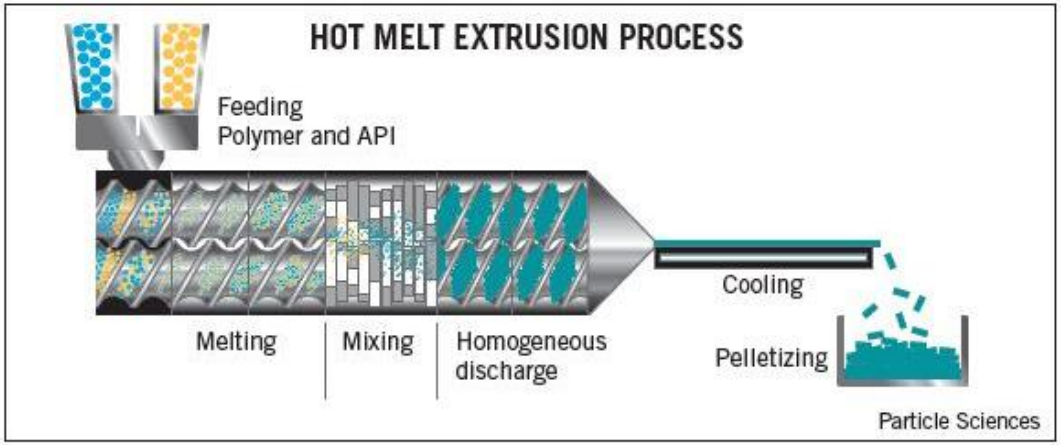
sinter granules

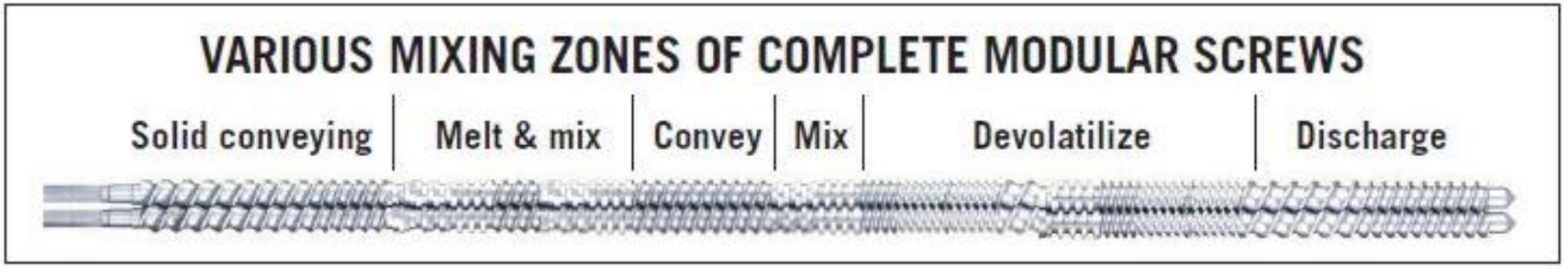
Between particles, molten bridges done by heating can be solidified by cooling. This operation is termed *sintering*, and granules created with this operation are sinter-granules.

Melt granulation – High shear granulation



Hot-melt extrusion

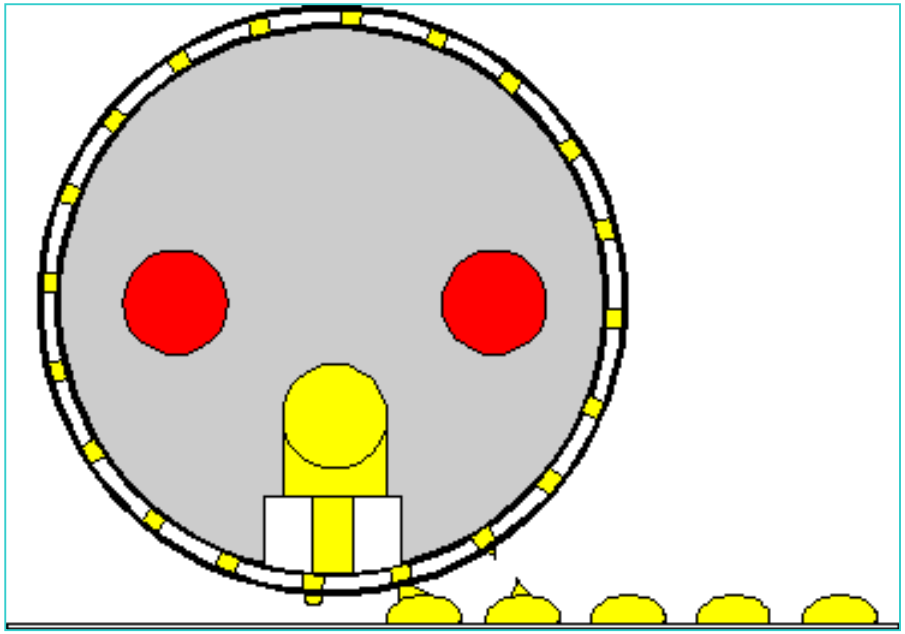




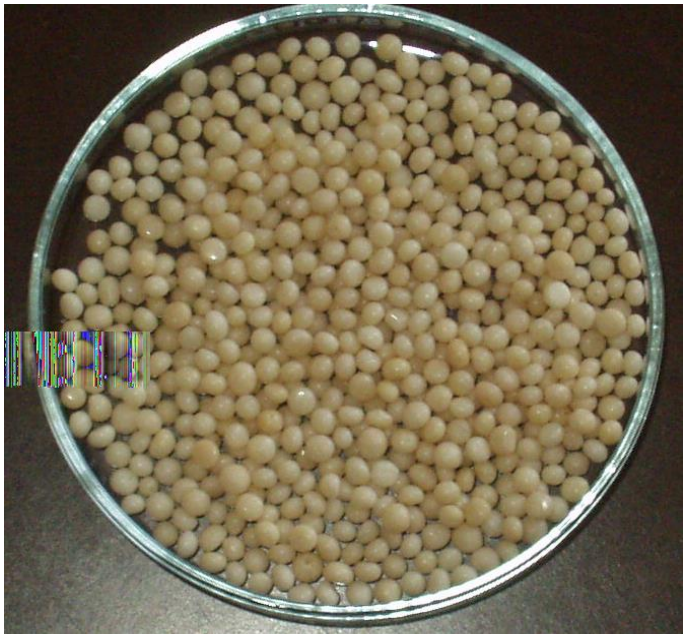
Drop forming methods
Melt confection - Industrial

The principle of the Rotoformer

Rotoform®
(Sandvik process system)
(Sveden)

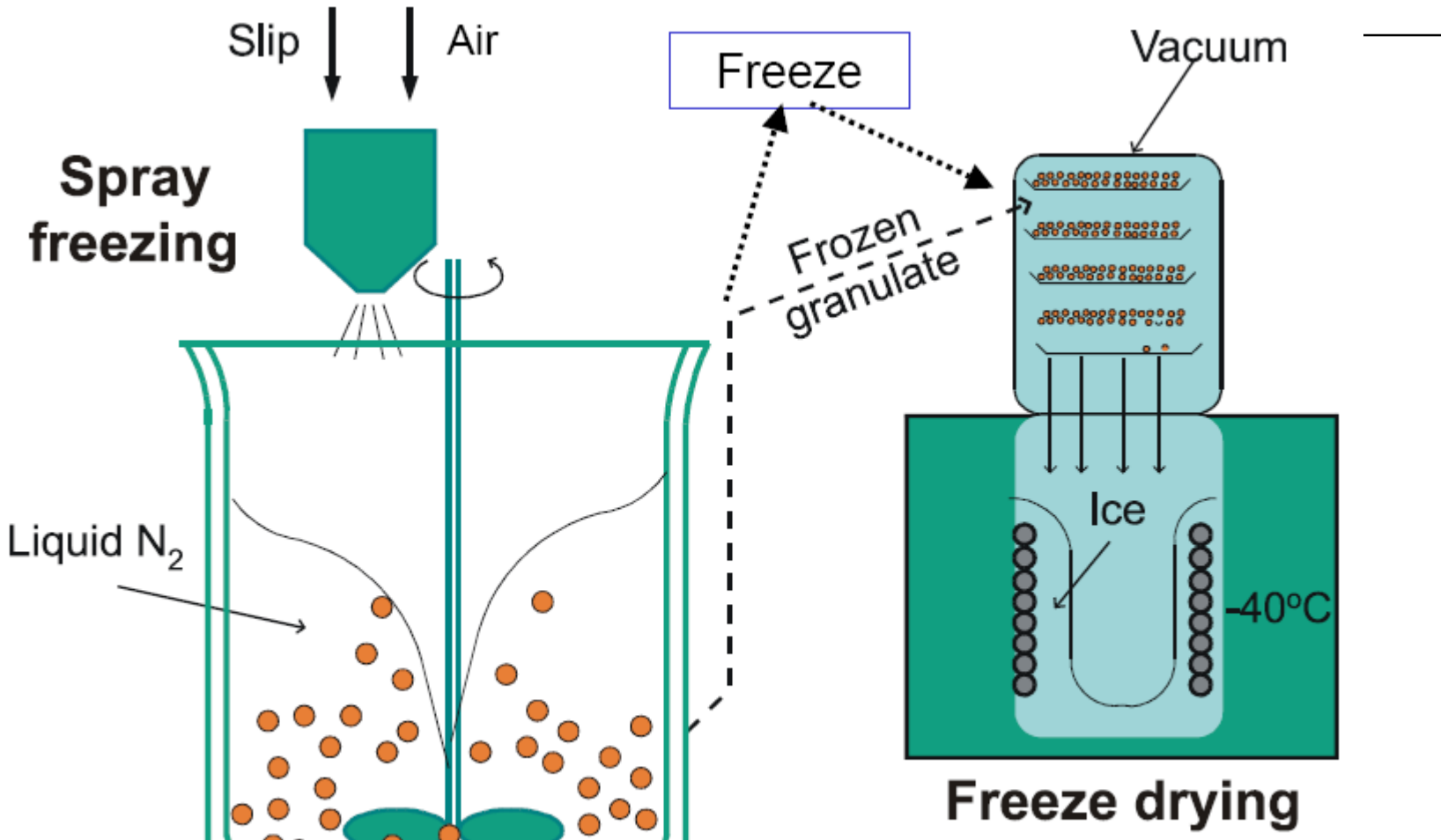


Particles contained Levodopa
diameter: 2.5 ± 0.13 mm

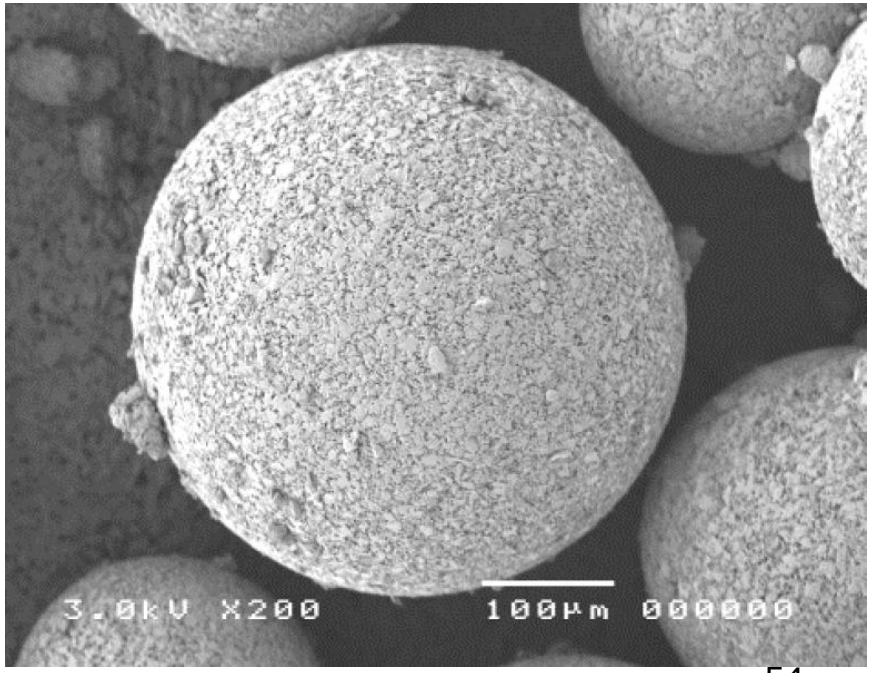


The Rotoformer consists of a heated cylindrical stator – which is supplied with liquid product – and a perforated rotating shell that turns concentrically around the stator, depositing drops of the product across the whole operating width of the steel belt.

Freezing granulation



Granules, prepared by freezing and spraying

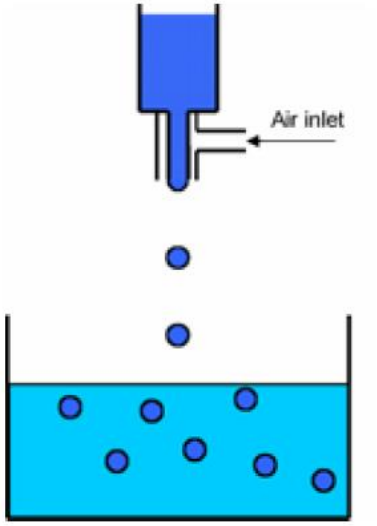


Advantages Drawbacks of the freezing method

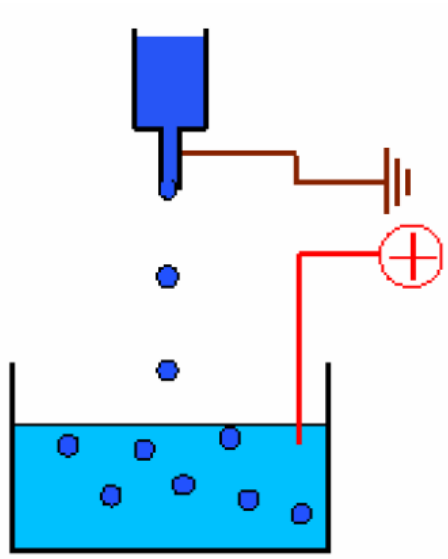
- Controlled density
- No holes inside of the granules
- Same size
- No waste material
- Small quantity
- Easy cleaning

- Two steps
- Solvent material (-20 °C, +10 °C)
- Low tapped density
- Limited product quantity

Prilling (drop forming)



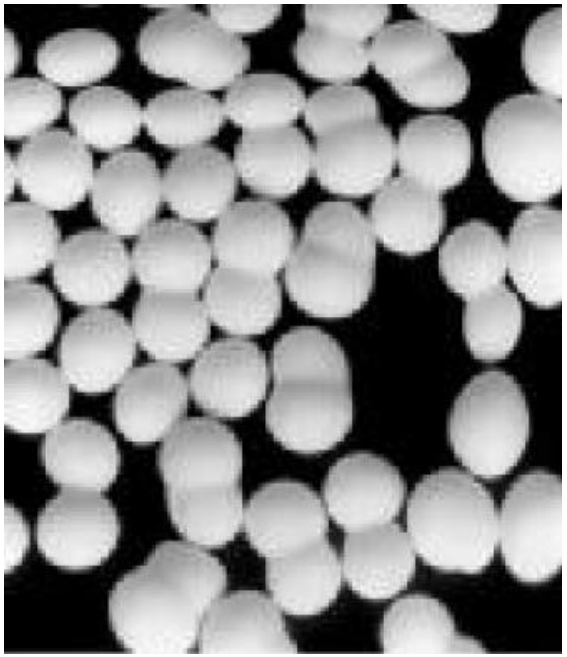
Coaxial air jet



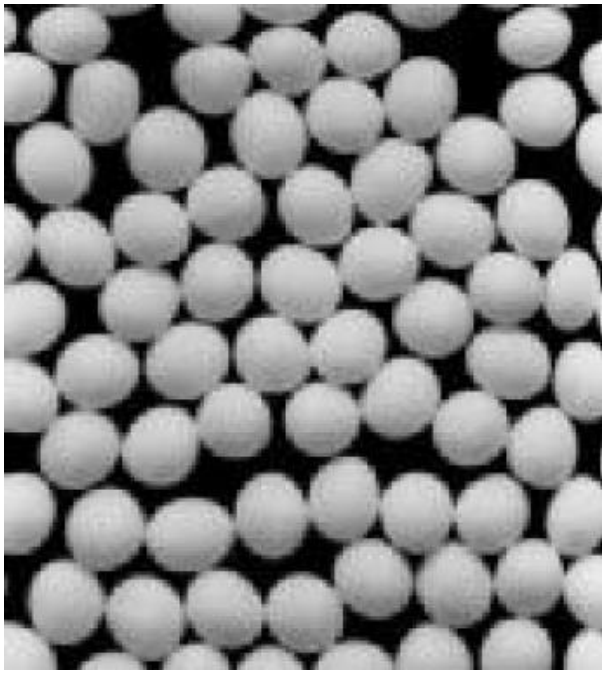
Electrostatic

Effect of the electrostatic charge fot the drop formation

Without



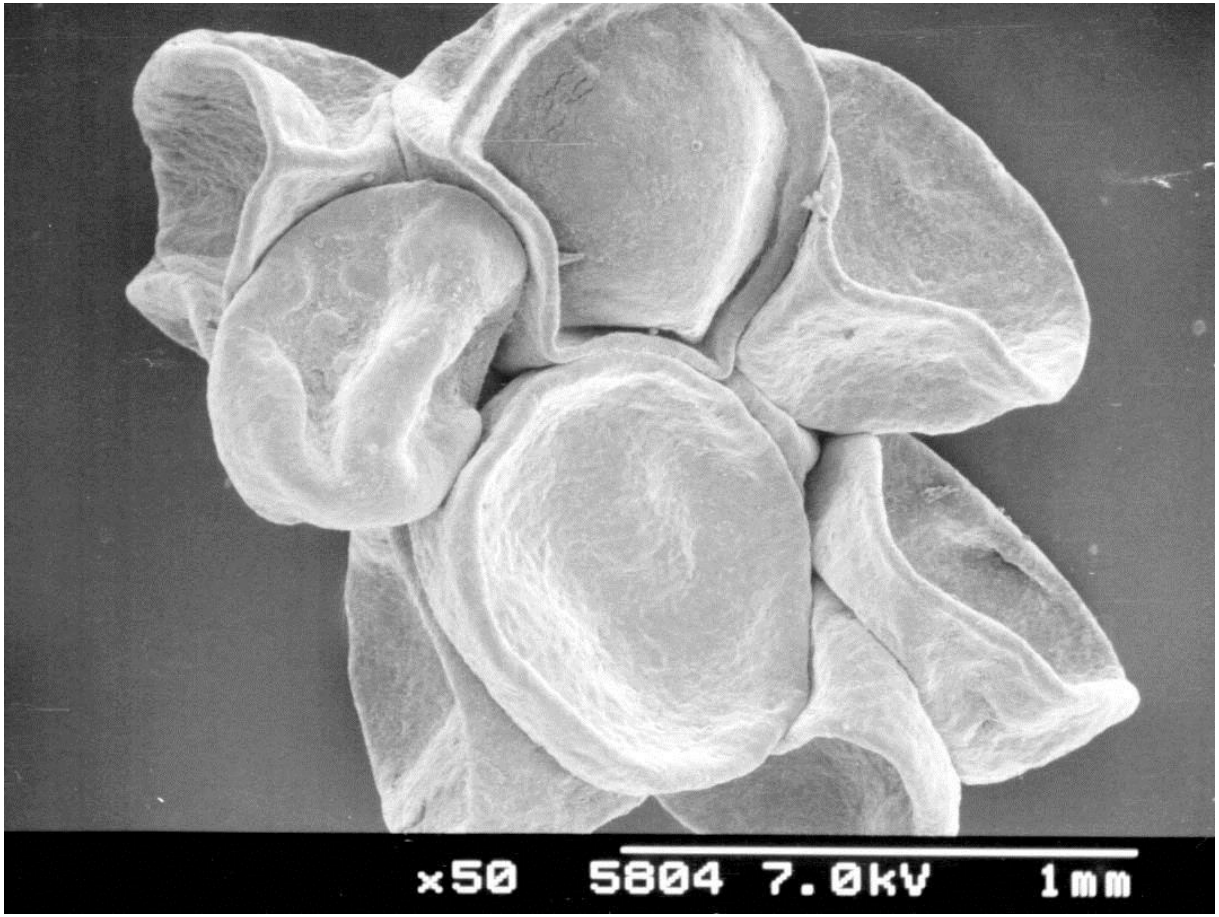
With



Benefits of drop forming

- Uniform size
- Excellent flow properties
- Variable particle size (100 μm-3 mm)
- Sterile preparation
- High efficacy
- Easy scale up (10 g -> n x 100 kg)

THE END



Bouqet of harebell ?